The Exploration of Naturalistically used Ayahuasca and 5-MeO-DMT

Citation for published version (APA):

Uthaug, M. V. (2020). *The Exploration of Naturalistically used Ayahuasca and 5-MeO-DMT: An assessment of their respective Sub-acute and Long-Term effects on Mental Health Related Variables*. [Doctoral Thesis, Maastricht University]. Boekenplan. <https://doi.org/10.26481/dis.20200624mu>

Document status and date:

Published: 01/01/2020

DOI:

[10.26481/dis.20200624mu](https://doi.org/10.26481/dis.20200624mu)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

**The Exploration of Naturalistically used Ayahuasca and 5-MeO-DMT;
An assessment of their respective Sub-acute and Long-Term effects on
Mental Health Related Variables**

© Malin Vedøy Uthaug, 2020

Cover design: Boekenplan

Production: Boekenplan

ISBN: 9789086665082

**The Exploration of Naturalistically used Ayahuasca and 5-MeO-DMT;
An assessment of their respective Sub-acute and Long-Term effects on
Mental Health Related Variables**

DISSERTATION

To obtain the degree of doctor at Maastricht University,

on the authority of Rector Magnificus, Prof dr. Rianne M. Letschert,

in accordance with the decision of the Board of Deans,

To be defended in public on the 24th of June 2020

by

Malin Vedøy Uthaug

Promotor

Prof. dr. J.G. Ramaekers

Co-promoters

Dr. K.P.C Kuypers

Dr. K. van Oorsouw

Assessment Committee

Prof. dr. W.J. Riedel

Prof. dr. T.A.M.J. van Amelsvoort

Prof. dr. A. Blokland

Dr. R. Carhart-Harris

Dr. M. Somers

*Publication of this doctoral dissertation was financially supported by
Prof. Dr. J.G. Ramaekers.*

Du sa jeg alltid har vert så flink å skrive. At jeg skulle bli forfatter og publisere bøker. Kanskje denne doktoravhandlingen er en start. Derfor dedikerer jeg den til deg, kjære Pappa. Jeg elsker deg!

You always said I was good at writing. That I should become a writer and publish books. Perhaps this dissertation is a start. Hence why I dedicate to you, Pappa. I love you!

Table of Contents

Chapter 1 - General introduction.....	7
Chapter 2 - Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution	33
Chapter 3 - Mind or matter? A placebo-controlled study of the effects of ayahuasca ingestion on mental health of participants in a naturalistic, neo-shamanic setting.	61
Chapter 4 - A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness related capacities, and a decrement of psychopathological symptoms	87
Chapter 5 - Prospective examination of synthetic 5-methoxy-N,N-dimethyltryptamine inhalation: effects on salivary IL-6, cortisol levels, affect, and non-judgement	119
Chapter 6 - A comparison of reactivation experiences following vaporization and intramuscular injection (IM) of synthetic 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting.....	153
Chapter 7 - General discussion.....	177
Valorisation addendum.....	195
Summary	203
Samenvatting.....	209
Resumen	215
Souhrn	221
Oppsummering	227
References	233
Acknowledgements	267
Afterwords.....	275
Curriculum Vitae (CV).....	281
Publications	283

Chapter 1 - General introduction

Background

In 2017, it was estimated that around 970 million people worldwide were affected by mental health related disorders (World-Health-Organization, 2012, 2017). As this number continues to rise, it is anticipated that the mood related disorder, depression, will be the second leading cause of impaired functioning world-wide by 2020 (World-Health-Organization, 2001), and the largest contributor to disease burden universally by 2030 (World-Health-Organization, 2009). Mood-related disorders such as depression show a complex ethology where genetic, environmental and social variables play a role in their occurrence (Elder & Mosack, 2011; Lau & Eley, 2010; Wittchen et al., 2011). Left untreated, they are known to have profound impact on individuals causing (social) functional impairment, and lost work productivity (Kupferberg, Bicks, & Hasler, 2016; Simon, 2003), as well as increased risk of suicide (Sher, Oquendo, & Mann, 2001). This can also have serious implications on a societal level by increasing use of health services, that in turn can cause a great global economic burden (Kessler et al., 2009; Simon, 2003; World-Health-Organization, 2009).

Conventional, first-line treatments in Western society for individuals affected by mood-related disorders is a type of psychotherapy like Cognitive Behavioral Therapy (CBT) (Fenn & Byrne, 2013) and/or a type of pharmacotherapy such as for example mood stabilizing and antidepressants medication like serotonin selective reuptake inhibitors (SSRIs) (Stahl, 1998) (Brambilla, Perez, Barale, Schettini, & Soares, 2003; R. Duman, 2002; Sanacora, Zarate, Krystal, & Manji, 2008). Both interventions are considered

to be a ‘top down’ approach, which means they are acting on cognition and the ‘thinking brain’ (i.e., the explicit mind) to bring about change in well-being (J. Beck, 2011; Brambilla et al., 2003; R. Duman, 2002; Fenn & Byrne, 2013; Peter A Levine & Frederick, 1997; Sanacora et al., 2008). While CBT exerts its action by targeting several psychological constructs such as attachment, emotional regulation, conditioning and insights (Lambert, 2011), SSRIs work on a molecular level to increase serotonin in the brain (Artigas, Nutt, & Shelton, 2002; Stahl, 1998). Although CBT and SSRIs have shown to reduce the symptoms of mood-related disorders such as affect (i.e. depression, anxiety and stress), while increasing adaptive functioning (Lambert, 2011), they seem to be less able to effectively resolve the disorder (Kuyken, Watkins, & Beck, 2005; Peter A Levine & Frederick, 1997; Moncrieff, 2007; Turner & Rosenthal, 2008). In fact, even though SSRIs exert their initial pharmacological action within hours, they require prolonged administration before significant clinical improvements can occur (Celada, Puig, Amargós-Bosch, Adell, & Artigas, 2004). As for CBT (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012), it appears that its effectiveness has been overstated in the literature (G. Parker, Roy, & Eysers, 2003), and that it is rather associated with preventative effects of distress rather than full remission (Collins & Dozois, 2008; Gloaguen, Cottraux, Cucherat, & Blackburn, 1998). This implies that attempts to find a treatment to attain full remission of mood-related disorders remains largely unsuccessful (Hengartner, 2017; Hengartner, Angst, & Rössler, 2018; Moncrieff, 2007). The lack of an effective treatment for mood-related disorders is concerning as persisting effects not only increase distress of individuals, but may also lead to increased risk of suicidal behavior, medical and psychiatric comorbidities and increased burden of illness (Jick, Kaye, & Jick, 2004;

McIntyre & O'Donovan, 2004). All things considered; the world is in dire need for a novel treatment option for mood-related disorders.

In response to the obstructed development of a novel treatment option, there has in the last two decades been a renewed scientific interest to the idea of treating several mental health related disorders with alternative pharmacotherapies (i.e the treatment of a disorder or disease with medication). The following part of this dissertation will first focus on introducing such an alternative pharmacotherapy, namely ketamine infusion. After this, a brief introduction to psychedelics, the psychedelic substance psilocybin and psychedelic assisted psychotherapy (PAP) will follow. Finally, the background of two other psychedelics, such as ayahuasca and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), which is the central focus of this thesis, will be presented before the methods, aims, and studies conducted as part of this dissertation is outlined.

The search for a novel treatment option for mood-related disorders

Ketamine

Efforts have been made to find novel pharmacotherapies for mood-related disorders. In fact, the anesthetic and analgesic agent, ketamine (ketamine hydrochloride), an N-methyl-D-aspartate (NMDA) receptor antagonist, is gaining ground as a promising treatment for depression (Abdallah, Sanacora, Duman, & Krystal, 2015). In fact, recently the esketamine (spravato), as nasal spray containing ketamine, has been approved by the The Food and Drug Administration (FDA) for use in treatment-resistant depression (Canady, 2019).

As for previous research on the topic, Berman and colleagues (2000) found that low (sub-anesthetic) doses of ketamine administered intravenously (IV) reduced depression symptoms within 4 hours of administration in severely treatment-resistant depressed patients. Later on, in a placebo-controlled study including 17 treatment-resistant patients with Major Depressive Disorder (MDD) (Zarate et al., 2006), it was found that depressive symptoms halved in 71% of the participants within 24 hours of ketamine administration (0.5mg/kg IV infusion over 40 minutes). This response was sustained for the 1-week follow-up in approximately one-third of the participants. These findings were sensational as the same participants showed no significant change in symptoms following placebo treatment. Ten years later, the antidepressant effects of ketamine were demonstrated in patients diagnosed with bipolar disorder, and patients with depressive symptoms who did not respond to antidepressants or electroconvulsive therapy (Diazgranados et al., 2010; Ibrahim et al., 2011). Recent research shows that there are rapid and longer-term antidepressant effects of *repeated* ketamine administrations compared to a *single* administration (Murrough et al., 2013; Shiroma et al., 2014).

In sum, current research demonstrates ketamine's rapid onset, and persistent efficacy with limited dosing which makes it a superior and attractive alternative pharmacotherapy for mood-related disorders like depression. However, next to ketamine, there are other substances showing a similar potential. Such substances are psychedelics, substances that alter perception and mood and affect numerous cognitive processes (Nichols, 2016). A prototypical example of a psychoactive substance is *4-phosphoryloxy-N,N-dimethyltryptamine*, better known as psilocybin, which will be introduced at greater length later. However, before that, a brief introduction to psychedelics and the mechanisms in which they exert their (therapeutic) effects is in place.

Psychedelics

The word psychedelic means mind-manifesting, and was coined in the late 1950's by Dr. Humphry Osmond in communication with the author Aldous Huxley (Osmond, 1957). Psilocybin, lysergic-acid-diethylamide (LSD), N,N-dimethyltryptamine (DMT), and 3,4,5-trimethoxyphenethylamine (mescaline) are all examples of 'classic' psychedelic substances known to produce a broad diversity of acute subjective effects in perceptual, emotional and cognitive domains (Nichols, 2016; Swanson, 2018). Additionally, it is also known that the overall effects produced by psychedelics are largely dependent on *set and setting* (Robin L Carhart-Harris et al., 2018; Hartogsohn, 2016, 2017). While the former refers to the mental expectation, the latter refers to environment in which the substance is taken in (Robin L Carhart-Harris et al., 2018; Hartogsohn, 2016, 2017).

Psychedelics are distinct to other substances due to their unique ability to evoke changes in the sense of self, ego, body image and personal meaning (Matthew M Nour, Lisa Evans, David Nutt, & Robin L Carhart-Harris, 2016; Swanson, 2018). They are especially known to evoke the experience of the mystical which has been reported to include sacredness, transcendence of time and space, positive mood, ineffability and noetic quality, in addition to a sense of unity (Walter Norman Pahnke, 1963; Stace, 1962). Sense of unity is known to be internal or external (Walter N Pahnke & Richards, 1966; Stace, 1962). The latter is the experience in which the subject-object dichotomy, the division between self and outer world, dissolves. The former is an experience which all normal sense impressions cease and one experiences a selfless state, also known as ego dissolution, defined as the experience of a compromised sense of 'self' (Robin L Carhart-Harris, Muthukumaraswamy, et al., 2016;

Milliere, 2017; Matthew M Nour et al., 2016). Notably, the occurrence of “mystical-type” experiences and ego dissolution have been found to predict betterment in mental health related outcomes (Barsuglia, Davis, & Palmer, 2017a; Bogenschutz et al., 2015; Garcia-Romeu, R Griffiths, & W Johnson, 2014; Griffiths et al., 2011; Griffiths, Richards, Johnson, McCann, & Jesse, 2008; Johnson, Garcia-Romeu, & Griffiths, 2017; Klavetter & Mogar, 1967; Kurland, Grof, Pahnke, & Goodman, 1972; MacLean, Johnson, & Griffiths, 2011; Matthew M Nour et al., 2016; O'Reilly & Funk, 1964; Walter N Pahnke, Kurland, Unger, Savage, & Grof, 1970; Richards, 2015; Leor Roseman, David J. Nutt, & Robin L. Carhart-Harris, 2018b; S. Ross et al., 2016).

Despite evoking the experience of the mystical and ego dissolution, psychedelics are known to exert their (therapeutic) effects through their unique receptor affinities that affect neurotransmission and in turn modulate brain activity and so too neuroplasticity (De Gregorio, Enns, Nuñez, Posa, & Gobbi, 2018; Nichols, 2016). Moreover, the effects following ingestion of psychedelics can be interpreted from the Bayesian and free-energy minimization perspectives (R. Carhart-Harris & Friston, 2019; Robin L Carhart-Harris & Friston, 2010; Friston, 2010). From this point of view the brain is viewed as a machine which makes predictions about the world, and updating them based on experience (Friston et al., 2013) - much like a scientific experiment. Essentially, an inference is made based on prior knowledge and then modified or updated based on what is experienced (Fletcher & Frith, 2009).

In their recent theory titled ***RE**laxed **B**eliefs **U**nder *p***S**ychedelics (REBUS)*, Carhart-Harris and Friston (2019) suggest that psychedelics relax the weight

of the brain's top-down prediction-making, and increase the weight of the bottom-up sense information. In turn, bottom-up information has more influence on the conscious experience, and so too the configuration of the brain's hierarchy overall. Essentially, psychedelics do so by relaxing the default mode network (Robin L Carhart-Harris et al., 2012; Robin L Carhart-Harris & Friston, 2010; Robin Lester Carhart-Harris et al., 2014; Robin L Carhart-Harris et al., 2017; Ciesla & Roberts, 2007; Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010; Hamilton, Farmer, Fogelman, & Gotlib, 2015; Hamilton et al., 2011; Hilt & Pollak, 2012; Nolen-Hoeksema, 2000; Park, Goodyer, & Teasdale, 2004), through activation of the serotonin receptors, and disruption of α - and β -wave patterns, which seem to cultivate top-down expectations through the brain (and are correlated with default mode network activity) (R. Carhart-Harris & Friston, 2019; Robin L Carhart-Harris et al., 2012; Robin Lester Carhart-Harris et al., 2014; Lebedev et al., 2015; Tagliazucchi et al., 2016). With this in mind, and the fact that mood disorders like depression, anxiety, stress as well as addictions are associated with too rigid thought patterns (Brinker & Dozois, 2009; Ciesla & Roberts, 2007; Park et al., 2004; Quello, Brady, & Sonne, 2005), increased activity in the default mode network (Buckner, Andrews-Hanna, & Schacter, 2008; Hamilton et al., 2015; Hamilton et al., 2011; Öngür et al., 2010; Sheline et al., 2009; Zhao et al., 2007; Zhu et al., 2012), and consequently excessive rumination (Brinker & Dozois, 2009; Ciesla & Roberts, 2007; Cooney et al., 2010; Nolen-Hoeksema, 2000; Park et al., 2004), it follows that new information cannot (easily) revise the existing story of how things are. This is because strong priors suppress the new info before it can update anything.

By ingesting psychedelic substance, and through their aforementioned effects, there occurs a disturbance of ego-functions and so too the hierarchy

of the brain which allows for bottom-up processing to occur, and new beliefs can form (R. Carhart-Harris & Friston, 2019; Robin L Carhart-Harris et al., 2012; Robin Lester Carhart-Harris et al., 2014; Lebedev et al., 2015; Tagliazucchi et al., 2016). Through the altering of functional connectivity in the brain (Robin L Carhart-Harris et al., 2012; Robin Lester Carhart-Harris et al., 2014; Lebedev et al., 2015; Frederic Sampedro et al., 2017; Tagliazucchi et al., 2016), psychedelics have been linked to improvement in mindfulness related capacities (Millière, Carhart-Harris, Roseman, Trautwein, & Berkovich-Ohana, 2018; Joaquim Soler et al., 2016). Betterment in mindfulness related capacities has in turn has been significantly associated with improved symptoms of affect in mood-related disorders (Coffey & Hartman, 2008; Hilt & Pollak, 2012; Schroevers & Brandsma, 2010). Moreover, mindfulness is also known to prevent relapse in mood disorders (Breslin, Zack, & McMain, 2002), to be a useful tool in developing emotion regulation skills (Linehan, 1993), facilitate acceptance and change processes (Hayes & Wilson, 2003; Strosahl & Wilson, 1999), and important for skill training in affective and interpersonal regulation (Cloitre, Koenen, Cohen, & Han, 2002). The use of mindfulness as an intervention for mood disorders (Coffey & Hartman, 2008; Hilt & Pollak, 2012; Schroevers & Brandsma, 2010), post-traumatic stress (PTSD), and addiction looks promising as it could theoretically break the behavioral loop of avoidance and increase attention and purposeful behavior that is often a deficit in those individuals with trauma histories (Cloitre et al., 2002).

Taken together, besides evoking a psychedelic experience, psychedelics may through their unique receptor affinities, and ability to disrupt the configuration of the brain's hierarchy, evoke betterment in mental health related variables. However, more research is warranted to deepen the

knowledge about the mechanisms under which psychedelics exert their effects. Now, a brief introduction to the psychedelic substance psilocybin and psychedelic assisted therapy (PAT) will follow.

Psilocybin

Psilocybin is a naturally occurring psychoactive substance produced in more than 200 species of mushrooms (Passie, Seifert, Schneider, & Emrich, 2002). The effects of psilocybin are thought, like other psychedelics, to be mediated via binding to serotonergic (5-HT) 2 receptors, primarily 5-hydroxytryptamine 2A (5-HT_{2A}) receptors (Nichols, 2016; Tylš, Páleníček, & Horáček, 2014).

Previous research demonstrated that administration of psilocybin to (10 mg per oral (p.o.), followed 1 week later by a second dose (25 mg, p.o.) reduced depressive symptoms in 12 participants with treatment-resistant unipolar depression assessed at one week and at three months after treatment (Robin L Carhart-Harris, Bolstridge, et al., 2016). Findings demonstrated that psilocybin was well tolerated by all participants, and that no serious or unexpected adverse events occurred. Overall, this study, despite the lack of a control group, demonstrates the feasibility, safety, and efficacy of psilocybin in treatment-resistant unipolar depression when administered along with psychological support (Robin L Carhart-Harris, Bolstridge, et al., 2016). In another study by Griffiths and colleagues (2016), 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety received psilocybin (22 or 30mg/70 kg, p.o.). Results demonstrated a substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer up to the 6-month follow-up compared to psilocybin (1 or 3 mg/70kg). In addition, it was shown that the psilocybin (22-30 mg/70kg)-induced

mystical-type experience mediated the therapeutic outcomes. To conclude this section, research suggests that psilocybin may hold a therapeutic potential in the treatment of mood-related disorders like depression.

Psychedelic-assisted Psychotherapy (PAP)

Although scientific research points to psilocybin's efficacy in treatment of mental health related disorders, it is important to highlight that there appears to be more to treatment but a stand-alone pharmacological intervention (i.e. alternative pharmacotherapy). Instead, psilocybin and other psychedelics could potentially be used in a therapeutic setting as *catalysts* to bring about betterment in mood-related symptoms as part of Psychedelic-assisted Psychotherapy (PAP) where psychedelics is part of elaborated psychotherapy programs (Schenberg, 2018). Essentially, in PAP, a therapist, or therapy team would meet with the patient prior to their session with the psychedelic substance to psychologically prepare them. Then the therapist or therapy team will monitor the patient throughout the psychedelic effects, and help them process their experience afterwards (i.e., integration). This model has proven not only significantly effective, but also with large effect sizes (Schenberg, 2018; Thomas, Malcolm, & Lastra, 2017) making it a possible novel treatment option to the existing pharmacological (i.e. SSRIs), and psychological treatments (i.e. CBT) (Grinspoon & Doblin, 2001; Mithoefer, Grob, & Brewerton, 2016).

Besides psilocybin, there are other psychedelics too which may show a similar potential as an adjunct to therapy in treatment of mood-related disorders. Such psychedelics include ayahuasca and 5-MeO-DMT. As these substances are the central part of this dissertation, it follows that the next section is a lengthier introduction to both substances.

Ayahuasca

Background

Ayahuasca is a psychedelic plant tea from the Amazon basin (D. J. McKenna, 2004) where some tribes like the Shipibos refer to it as the “*Drink of the Soul*” (Campos, 2011). However, it is argued that the Spaniards forced another definition upon it because for them ayahuasca seemed like a satanic ritual. Nowadays ayahuasca is worldwide a Quechuan word, which translates into “*vine of the soul or spirits*” or “*vine of the dead*” (Janine Tatjana Schmid, 2012). The earliest accounts of its existence can be found in Richard Spruce’s book “*Notes of a Botanist on the Amazon and Andes*” from 1908 (Spruce, 2014).

Ayahuasca has historically been used by shamans in the Amazon-region (Brazil, Ecuador, Colombia and Peru) to communicate with spirits, to have magical experiences, for rites of initiation, and for healing rituals, commonly referred to as “shamanism” (Brito, Neves, & Oberlaender, 1996; Krippner, 2000; Dennis J McKenna, 2004; Townsend, 2004). The social and cultural function of these shamanic ayahuasca practices has been extensively explored in anthropological literature (Schultes, 1957), which emphasizes how these practices produce social cohesion, reinforce psycho-spiritual culture and communal bonds, and generally aid the community in practices of ritual, healing and divination (Schultes, 1957).

The oral use of ayahuasca, is suggested to date back to more than three thousand years (Furst, 1976; Narby, 1999). However, the validity of this claim has been called into question due to the absence of concrete archaeological evidence (Beyer, 2012). Nevertheless, the use of ayahuasca is an integral part of the social and ontological structure of the culture in the

Amazon basin. Here, it is not only used in a ritualistic setting, but also used as part of a ritualistic sacrament (Tupper, 2008), as part of the Santo Daime church founded in 1930 (Tupper, 2008), and the União do Vegetal (UDV) founded in 1961 (MacRae, 2004).

The principles and techniques of traditional shamanic rituals where ayahuasca is used, have in the 20th century spread beyond its native habitat, and been adopted into the Western contemporary society as a new and modern shamanism commonly known as *neo-shamanism* (Leor Roseman et al., 2018b; Townsend, 2004). Neo-shamanism is considered to be a manifestation of a counter-reaction to the Cartesian split of the material and non-material, in other words modernity (Braun, 2010). This split of the material and non-material is suggested to be, in shamanic terms, soul loss at a cultural level described as a “*pervasive feeling of anomie and cultural disintegration*” (M. Berman, 1981). Ayahuasca is believed to facilitate healing for this through the facilitation of contact with the non-material world (M. Berman, 1981; Noel, 1997; Von Stuckard, 2002). At the current time, ayahuasca is commonly sought after by an increasing number of Westerners because of its holistic healing approach to psychological problems, addressing both the spiritual dimension of healing, along with the physical (Fotiou, 2012; Kavenská & Simonová, 2015; Michael Winkelman, 2005). Frequently mentioned benefits of ayahuasca use include self-knowledge, change in the way one relates to oneself, spiritual development, improved interpersonal relations, overcoming mental and physical problems, and gaining a new perspective on life (Kavenská & Simonová, 2015).

Pharmacology of ayahuasca

The psychotropic effects of the brew ayahuasca are reported to be due to the cocktail of its alkaloids, and correspond with the experiences induced by other psychedelics such as psilocybin (D. J. McKenna, 2004). Ayahuasca is most commonly prepared from the *Psychotria viridis* bush that contains the serotonergic 2A receptor agonist N,N-dimethyltryptamine (DMT), as well as the *Banisteriopsis caapi* (*B. caapi*) containing β -carboline alkaloids such as harmine, harmaline and tetrahydroharmine (THH) (F. Palhano-Fontes et al., 2015; J. Riba et al., 2001). While harmine and harmaline inhibit the action of monoamine oxidase enzyme (MAO) (Godinho, Silva, & Kawashima, 2017), tetrahydroharmine acts as a weak reuptake inhibitor of serotonin, and as a weak MAO-inhibitor, (Godinho et al., 2017). In short, the β -carbolines are potent reversible inhibitors of MAO, an enzyme that normally breaks down DMT. With this action, the DMT (in the ayahuasca brew) can reach the central nervous system for a prolonged period resulting in the psychedelic effects, starting between 30 and 60 minutes post-administration (D. J. McKenna, 2004), reaching maximum intensity between 60 to 120 minutes, and lasting up to 6 hours after administration (J. Riba et al., 2001).

Regarding dose, McKenna and his colleagues (1998) highlighted that a typical dose of ayahuasca is 100 ml, while others have reported 200 ml (Rivier & Lindgren, 1972). Concerning the concentrations of alkaloids reported in ayahuasca, McKenna et al. (McKenna, 1998) found that in a 100 ml dose of various Peruvian preparations of ayahuasca, there was a total of 728 mg total alkaloid. Here, 467 mg was harmine, 160 mg was THH, 41 mg was harmaline, while 60 mg was DMT. In another study, Rivier and Lindgren (Rivier & Lindgren, 1972) it was found that in 200 ml dose of ayahuasca, there was an

average of 30 mg of harmine, 10 mg THH, and 25 mg DMT. In a study by Callaway and colleagues (1996), it was reported that a typical dose of ayahuasca used by the UDV (100 ml) contained 24 mg of DMT, 107 mg of THH, 20 mg of harmaline and 170 mg of harmine.

Previous research of ayahuasca

The prevalence of ayahuasca use worldwide in (non)western societies, as well as its (anecdotal) effects on mental well-being sparked scientific interest (Ede Frecska, Petra Bokor, & Michael Winkelman, 2016). Today, scientific evidence suggests that ayahuasca may hold therapeutic potential as a treatment tool for mental health-related disorder (Ede Frecska et al., 2016).

According to Frecska and colleagues (2016), the therapeutic mechanism of action is best understood from a bio-psycho-socio-spiritual model. With regard to biology, a study by de Lima Osório and colleagues (2011) suggests that harmine and other substances present in ayahuasca might have antidepressant-like effects in the central nervous system of (healthy) animals and patients. Furthermore, Morales-García and colleagues (2017) investigated the effect of the main alkaloids presented in the *B. caapi*, and the harmine metabolite harmol, and their ability to stimulate adult neurogenesis in vitro. It was concluded that modulation of brain plasticity by these alkaloids might contribute to the antidepressant effects of ayahuasca. With regard to the social aspect, as ayahuasca is ingested in groups, it brings forth a sense of social support which is crucial in recovery of many mental health related illnesses (Ede Frecska et al., 2016). On a spiritual level, ayahuasca is known to induce experiences beyond the normal state of consciousness such as mystical experiences and/or ego dissolution which in turn have shown to mediate betterment in for example depression (Ede Frecska et al., 2016;

Griffiths et al., 2011). Additionally, research in healthy individuals who have had ayahuasca, suggests that spiritual insights, changed worldviews, and a new more positive orientation towards life are common outcomes post-ingestion (José Carlos Bouso et al., 2012; Brito et al., 1996; John H Halpern, Andrea R Sherwood, Torsten Passie, Kimberly C Blackwell, & A James Rutenber, 2008).

Concerning mental health, a study by Santos et al. (2007) investigated the effects of ayahuasca on several psychiatric measures of anxiety, panic-like behavior, and hopelessness in members of the Santo Daime. Findings demonstrate that during intoxication, participants scored lower on scales assessing panic- and hopelessness-related states. Additionally, ayahuasca did not modify state- or trait-anxiety. In another study by Trichter and colleagues (2009), it was shown that participants were able to experience and examine unconscious and unexpressed affect such as for example sadness, anger and joy after ingesting ayahuasca. Furthermore, 50% of participants reported experiencing personal reflections about their past, and insights about their attitude and belief.

Today, there are a number of naturalistic ‘field’ studies suggesting a positive impact of ayahuasca on mental functioning, suggesting that ayahuasca may hold therapeutic potential as a treatment for mental health related disorders (Ede Frecska et al., 2016). With regard to psychology, studies have indicated that in healthy individuals, the use of ayahuasca is related to acute enhancement of flexible thinking (K. Kuypers et al., 2016), and increased mindfulness-related capacities (Joaquim Soler et al., 2016). In people with mental health problems, the use of ayahuasca has been associated with the recovery from eating disorders (Lafrance et al., 2017), the enhancement of

emotion dysregulation in individuals with border-line like traits (Domínguez-Clavé et al., 2018), and also evoked betterment in symptoms of depression (Flávia de L Osório et al., 2015; Rafael Faria Sanches et al., 2016).

Finally, a very recent randomized placebo-controlled trial demonstrated the rapid antidepressant effects of a single dose of ayahuasca (1 ml/kg of placebo or ayahuasca adjusted to contain 0.36 mg/kg of DMT). on treatment-resistant depression (N=29), relative to placebo (Palhano-Fontes et al., 2019). Changes in depression severity as assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating scale at baseline, and at 1, 2, and 7 days after dosing showed significant antidepressant effects of ayahuasca when compared with placebo at all time points. MADRS scores were significantly lower in the ayahuasca group compared with placebo at day 1 and day 2. Between-group effect sizes increased from day 1 to day 7. Response rates were high for both groups at day 1 and day 2, and significantly higher in the ayahuasca group at day 7. Remission rate showed a trend toward significance at day 7 (36% *versus* 7%). Overall, this study serves as supporting evidence for the safety, and therapeutic value of ayahuasca when administered in an appropriate setting. Of note, the psychotherapeutic effect of ayahuasca depends on the level of integration between the insights gained during the experience and everyday life (Frecska, Bokor & Winkelman, 2016). To conclude, although the abovementioned research suggests a therapeutic potential for ayahuasca in the treatment of mental health related disorders, more research is warranted.

5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)

Background

5-methoxy-dimethyltryptamine (5-MeO-DMT) is an analogue of N,N-

dimethyltryptamine (DMT), one of the main active ingredients of ayahuasca (Araújo, Carvalho, de Lourdes Bastos, De Pinho, & Carvalho, 2015). 5-MeO-DMT was initially isolated from the bark of the plant *Dictyoloma incanescens* (Pachter 1959), but can also be found in the milky-white secretion (i.e., bufotoxin) produced in the skin and the parotid glands of *Incilius alvarius* toad, more commonly referred to as the Bufo Alvarius toad (Weil & Davis, 1994). 5-MeO-DMT can also be prepared synthetically (Hoshino & Shimodaira, 1936; Szabo, 2015; Szabo, Kovacs, Frecska, & Rajnavolgyi, 2014).

5-MeO-DMT has been acclaimed to be used historically and contemporary in the form of plant-based snuffs known as *yopo*, by shamans using crafted pipes, in Brazil, Venezuela, Colombia, Ecuador and Peru (De, 1974; Grossa, Delle Monache, Ferrari, & Marini-Bettolo, 1975; Torres, 1996). However, the main alkaloid in mature seeds species used for this snuff is in fact bufotenine, not 5-MeO-DMT (Alvares Pereira, 1957; Chagnon, Le Quesne, & Cook, 1971; de Smet & Rivier, 1987; Fellows & Bell, 1971; Fish, Johnson, & Horning, 1955; Giesbrecht, 1960; Holmstedt & Lindgren, 1979; Iacobucci & Rúveda, 1964; Paris, A, & Etchepare, 1967; Rendón, 1984; Schultes, Holmstedt, Lindgren, & Rivier, 1977; Stromberg, 1954; Torres, 1996; Yamasato, Kawanishi, Kato, & Hashimoto, 1972). Instead, the toad secretion (i.e., bufotoxin) from the *Incilius alvarius* toad, an amphibia living only in the Sonoran Desert, is known to contain a remarkable amount of 5-MeO-DMT. This secretion is produced in the skin and the parotid glands of toad and serves as a defensive mechanism against predators (Erspamer, Vitali, Roseghini, & Cei, 1967; Hutchinson & Savitzky, 2004). Since a toad yields about 0.25-0.50 gram of dried secretion from a “milking session”, with a 5-MeO-DMT

content of up to 15% (Erspamer et al., 1967), a single toad may generate 75 mg of 5-MeO-DMT in its secretion.

Some anecdotal reports suggest that the toad secretion from the *Incilius alvarius* toad may have been used historically by indigenous peoples in the southwestern territory of the USA and northern Mexico (Weil and Davis 1994). Nevertheless, since the purpose of these ancient practices have not been fully clarified, the evidence of 5-MeO-DMT use as a ‘medicine’ (in a similar way to ayahuasca) is lacking. It can therefore not be ruled out that the present use of toad secretion is of more recent origin. For instance, 5-MeO-DMT has been utilized for spiritual purposes as a religious sacrament in the rituals of the USA based Christian “Church of the Tree of Life” (Gottlieb, 1996). This is likely due to the publication of the pamphlet titled “*Bufo alvarius; The Psychedelic Toad of the Sonoran Desert*” by Albert Most in the 1980’s (Most, 1984) which discloses on how to milk the toad and smoke its secretion.

Pharmacology of 5-MeO-DMT

5-MeO-DMT acts as a serotonin agonist on both the 5-HT_{1A} and 5-HT_{2A/C} receptor agonist (Krebs-Thomson, Ruiz, Masten, Buell, & Geyer, 2006; Ott, 2001; Ray, 2010; H.-W. Shen, Jiang, & Yu, 2011; H. W. Shen, Jiang, Winter, & Yu, 2010). However, similar to DMT and 5-Methoxy-*N,N*-diisopropyltryptamine (5-MeO-DiPT), 5-MeO-DMT appears to have a higher affinity for the 5-HT_{1A} receptor and also inhibits the reuptake of 5-HT (Fantegrossi et al., 2006; Nagai, Nonaka, & Kamimura, 2007; Rabin, Regina, Doat, & Winter, 2002; Sadzot et al., 1989; Spencer, Glaser, & Traber, 1987; Winter, 2009). This is a mechanism of action that is somewhat different from tryptamines like psilocybin which has an affinity for the 5-HT_{2A} receptor

(McKenna, Repke, Lo, & Peroutka, 1990). The affinity 5-MeO-DMT exert on the 5-HT-1a receptor might have some additional anxiolytic and antidepressant effects (Jiang, Shen, & Yu, 2015), however the effects of its high affinity to the sigma-1 receptor is still unclear (Szabo et al., 2014).

Although previous research by Davis and colleagues (2018) suggests that 5-MeO-DMT has a good safety profile and low addiction liability in humans (A. K. Davis, J. P. Barsuglia, R. Lancelotta, R. M. Grant, & E. Renn, 2018), adverse effects has occurred following ingestion of the substance. However, it is noteworthy that these events have been connected to poor facilitation and lack of (medical) screening by two underground facilitators in particular ("5-MeO-DMT malpractice; Open Letter Concerning Abuses by Octavio Rettig and Gerry Sandoval," 2019). These events have been addressed in an open letter to both facilitators online.

5-MeO-DMT is known to be orally inactive as it is metabolized by MAO enzymes in the gut and liver (H. W. Shen et al., 2010), and therefore it is usually administered via inhalation of smoke or vapor, and less common via intravenous, intramuscular, rectal, sublingual, or intranasal application (Alan K Davis, Joseph P Barsuglia, Rafael Lancelotta, Robert M Grant, & Elise Renn, 2018a; Metzner, 2013; Ott, 2001; Weil & Davis, 1994). Present anecdotal reports of 5-MeO-DMT use describe inhalation (i.e., smoking or vaporizing) as a common mean of consumption. In fact, 5-MeO-DMT when inhaled, is known to be psychoactive in humans at doses as low as 3-5 mg (of pure substance) and produces a psychedelic experience within 10-15 seconds potentially last up to 20-40 minutes (Weil & Davis, 1994).

Effects following ingestion of 5-MeO-DMT are known to include a diversity of subjective effects including auditory, visual, and time perception

distortions, and emotional experiences, as well as memory impairment that vary depending on dose and route of administration (Ott, 2001; Shulgin & Shulgin, 1997a). Moreover, in addition to 5-MeO-DMT being molecularly different to DMT, individuals under the influence of 5-MeO-DMT often report a sense of oneness with the universe which is analogous to the experience of ego dissolution (Matthew M Nour et al., 2016; Uthaug, Lancelotta, Szabo, Davis, et al., 2019; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, & Kuchař, 2019), as well as the experience of eternity, and surrender (Barsuglia et al., 2017a; Joseph Peter Barsuglia et al., 2018; Germann, 2019; Hesselink, 2018). This is in contrast to DMT, which is known to evoke particularly vivid and complex imagery, e.g. visions of faces and/or “entities” that appear to communicate with them (Strassman, 1992).

Previous research on 5-MeO-DMT

Compared to ayahuasca and psilocybin, there are less scientific research on the effects of 5-MeO-DMT on psychological and biological processes. Nevertheless, Szabo and colleagues (2014) demonstrated for the first time the immunomodulatory potential of DMT and 5-MeO-DMT on human monocyte-derived dendritic cell functions via the sigma-1 receptor. It was concluded that both DMT and 5-MeO-DMT could both be harnessed for the pharmacological treatment of autoimmune diseases and chronic inflammatory conditions of the central nervous system or peripheral tissues (for example intestines). Essentially, the findings point to a new biological role for dimethyltryptamines, which may act as systemic endogenous regulators of inflammation and immune homeostasis through the sigma-1 receptor.

In a different study, by using shotgun mass spectrometry, Dakic and colleagues (2017) explored the proteomic differences induced by 5-MeO-DMT on human cerebral organoids. Fourteen percent of the 6,728 identified proteins were differentially expressed in 5-MeO-DMT-treated cerebral organoids. In silico analysis reinforced previously reported anti-inflammatory actions of 5-MeO-DMT, and revealed modulatory effects on proteins associated with long-term potentiation, the formation of dendritic spines, including those involved in cellular protrusion formation, microtubule dynamics, and cytoskeletal reorganization (Dakic, Nascimento, Sartore, de Moraes Maciel, de Araujo, et al., 2017). In sum, these data offer the first insight about molecular alterations caused by 5-MeO-DMT in human cerebral organoids.

With regard to 5-MeO-DMT research in humans, patterns of use, motivations for consumption, subjective effects, and potential benefits and consequences associated with 5-MeO-DMT use were examined using a web-based survey (N=515) by Davis and colleagues (2018). Findings revealed that respondents consumed 5-MeO-DMT infrequently ($\leq$ once/year), for spiritual exploration, and had used less than four times in their lifetime. The majority (90%) reported moderate-to-strong mystical-type experiences (ineffability, timelessness, awe/amazement, experience of pure being/awareness), and relatively fewer (37%) experienced very slight challenging experiences. Less than half (39%) reported repeated consumption during the same session, and very few reported drug craving/desire (8%), or legal (1%), medical (1%), or psychiatric (1%) problems related to use. Of note, respondents who reported a psychiatric disorder mentioned that 5-MeO-DMT had helped them to reduce their symptoms of anxiety (69%), depression (77%), and post-traumatic stress (79%), or to effectively deal with alcoholism (66%) and drug use disorder

(60%). In another study, it was demonstrated that improvements in symptoms of depression and anxiety was associated with greater intensity of mystical experiences and higher ratings of the spiritual significance and personal meaning of the 5-MeO-DMT experience (Alan K Davis, So, Lancelotta, Barsuglia, & Griffiths, 2019a).

It is important to highlight that there are some who report experiencing “after-effects” following 5-MeO-DMT ingestion. In fact, anecdotal reports on online forums and Facebook support groups indicate that in certain cases, especially with vaporization (5-Hive, 2018a, 2018b), naturalistic use of 5-MeO-DMT is associated with the incidence of a complex and not well understood phenomenon that has been termed *reactivation*. *Reactivation* refers to the re-experiencing of some of the effects induced by 5-MeO-DMT intake at some point after the drug’s acute effects have worn off. From that description, reactivations could be analogous to the LSD flashback phenomenon referred to as “*a re-experiencing of certain elements of the drug induced state after the drug’s effects have worn off and a relative period of normalcy has been experienced*” (Heaton, 1975; Heaton & Victor, 1976; Matefy, Hayes, & Hirsch, 1978; Matefy & Krall, 1974). At the current time no scientific research can explain why reactivations occur, nevertheless precipitating triggers of reactivations tend to be smoking marijuana, falling asleep, states of deep relaxation, deep meditation and certain smells and sounds that remind individuals of their experience (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). Moreover, recent unpublished reports from an online survey on the patterns of use of 5-MeO-DMT indicate that prevalence rates of reactivations (which lasts for 1-2 weeks) are as high as 72% in a subset of respondents using 5-MeO-DMT in a structured ritualized setting (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). However, up to 96% of these

users report their reactivation as being a positive or neutral experience, and only 3% report their reactivation experiences as being negative (Alan K Davis et al., 2018a; Ortiz Bernal, 2019).

Finally, in an observational study by Barsuglia and colleagues (2018), data was obtained from 20 individuals who were administered 5-MeO-DMT as part of a psycho-spiritual retreat program in Mexico. All participants inhaled vaporized toad secretion which is known to contain high concentrations of 5-MeO-DMT. They all received a ‘low dose’ (50 mg of bufotoxin, estimated 5-MeO-DMT content 5-7 mg), and completed the Mystical Experience Questionnaire (MEQ30) approximately 4–6 h after their session. Findings showed that the majority (75%) had “a complete mystical experience” ($\geq 60\%$ on all MEQ30 subscales). Interestingly, compared to a prior laboratory-based psilocybin study, the administration of vaporized 5-MeO-DMT reliably occasioned complete mystical experiences in 75% of individuals and was similar in intensity to high dose psilocybin administered in a laboratory setting. Given that strong mystical experiences are suggested to be predictive of long-term positive treatment outcomes in depression (Griffiths et al., 2016) as well as substance use disorder (Garcia-Romeu, Griffiths, & Johnson, 2015; Johnson, Garcia-Romeu, & Griffiths, 2017), and taking into consideration the fact that 5-MeO-DMT has been documented to reliably induce a comparable mystical experience in naturalistic settings in a much shorter timespan than psilocybin (Joseph Peter Barsuglia et al., 2018), it follows that 5-MeO-DMT may be a viable short-acting alternative for long(er)-acting psychedelic substances, and that further research of its effects in humans is highly warranted.

This thesis

Though more research is warranted, previous research suggests that both ayahuasca and 5-MeO-DMT have a promising therapeutic potential. Unfortunately, the current illegality status of psychedelics makes it rather difficult to conduct further clinical (placebo-controlled) studies (Nutt, King, & Nichols, 2013). Ergo, a naturalistic observational research approach, which is used in the studies presented in this thesis becomes favorable. Naturalistic observational research is characterized by observations and assessments made in individuals who voluntarily consume these substances in a naturalistic setting. This research design allows for further assessment of the effects of psychedelics such as ayahuasca and 5-MeO-DMT, without having to administer them themselves as a researcher (in a lab). Despite the obvious drawbacks of the design, such as the lack of control for possible influencing non-pharmacological variables (i.e., subjectivity bias of both researcher and participant, group dynamics, expectation, suggestibility, as well as personal ['set'] and contextual ['setting'] factors), the strength of the naturalistic design is that researchers can generate valuable input for potential placebo-controlled clinical trials.

Aims of this dissertation

The research summarized in this dissertation sought to investigate the effects of both ayahuasca and 5-MeO-DMT on mental health-related variables such as affect (depression, anxiety and stress), mindfulness related capacities (observing, describing, awareness, non-judgement, and non-reactance), empathy, creativity, and subjective well-being. The main objective motivating this dissertation was to explore whether ingestion of ayahuasca and 5-MeO-DMT is related to the improvement in the aforementioned mental

health variables. Secondly, this dissertation aimed to assess whether the magnitude of the psychedelic experience (for example mystical experiences and experience with ego dissolution) induced by ayahuasca and 5-MeO-DMT was correlated with changes in the mental health related variables. It was expected that ayahuasca and 5-MeO-DMT would demonstrate a similar therapeutic potential as psilocybin by evoking a rapid and persistent betterment in mental health related variables, correlated with the intensity ratings of the psychedelic experience.

While **Chapter 2** to **6** describe the various research of both ayahuasca and 5-MeO-DMT effects on various mental health related variables, **Chapter 7** discusses and integrates the main findings of the studies illustrated in the experimental chapters of the dissertation.

Specifically, **Chapter 2** describes a within-subject study on the effects of ayahuasca on affect and cognitive thinking style. Participants (N=57) were examined at several time points (before, immediately after, and 4-weeks) following an ayahuasca ceremony in Colombia and Netherlands.

Chapter 3 report the findings of placebo-controlled, within-subject study. This study aimed to test the role of non-pharmacological factors such as expectation (mind), and pharmacological factors (matter) related to ayahuasca in self-reported effects by participants (N=30). Assessments were made in participant before and after ingestion of ayahuasca in a neo-shamanic, naturalistic setting, in various locations in Europe (The Netherlands, Spain and Germany).

Chapter 4 outlines a within-subject study assessing the sub-acute and long-term effects of vaporized toad secretion from the parotid glands of the *Incilius alvarius* toad containing 5-MeO-DMT on affect and cognition in humans

(N=42). Assessments were made before and after (up to 4 weeks) ingestion in participants of sessions hosted by underground facilitators in various locations in Europe (The Netherlands, Spain and the Czech Republic).

Chapter 5 presents the immunomodulatory potential of inhalation of vaporized synthetic 5-MeO-DMT. Assessment were made through the collection and analysis of salivary samples, as well as subjective measures before and after ingestion of synthetic 5-MeO-DMT from participants (N=11) in a naturalistic setting in Prague, the Czech Republic.

Chapter 6 highlights the findings of an online survey-study (N=27) designed to further explore the anecdotally reported phenomenon of *reactivation* which has been defined as “*flashback to part(s) of the experience*”, and to compare the effects and experiences of 5-MeO-DMT through two different administration routes (vaporization or intramuscular injection [IM]) retrospectively.

Finally, **Chapter 7** discusses and integrates the main findings of the studies illustrated in the experimental chapters of the dissertation. Clinical implications and recommendations for future research are provided.

Chapter 2 - Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution

Uthaug, M. V., Van Oorsouw, K., Kuypers, K. P. C., Van Boxtel, M., Broers, N. J., Mason, N. L., ... & Ramaekers, J. G. (2018). *Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution. Psychopharmacology, 235(10), 2979-2989.*

Abstract

Rationale: Ayahuasca is a psychotropic plant tea from South America used for religious purposes by indigenous people of the Amazon. Increasing evidence indicates that ayahuasca may have therapeutic potential in the treatment of mental health disorders and can enhance mindfulness-related capacities. Most research so far has focused on acute and sub-acute effects of ayahuasca on mental health-related parameters and less on long-term effects.

Objectives: The present study aimed to assess sub-acute and long-term effects of ayahuasca on well-being and cognitive thinking style. The second objective was to assess whether sub-acute and long-term effects of ayahuasca depend on the degree of ego dissolution that was experienced after consumption of ayahuasca.

Results: Ayahuasca ceremony attendants (N=57) in the Netherlands and Colombia were assessed using questionnaires before, the day after, and 4 weeks following the ritual.

Results: Relative to baseline, ratings of depression and stress significantly decreased after the ayahuasca ceremony and these changes persisted for 4 weeks. Likewise, convergent thinking improved post-ayahuasca ceremony up until the 4 weeks follow-up. Satisfaction with life and several aspects of mindfulness increased the day after the ceremony, but these changes failed to reach significance 4 weeks after. Changes in affect, satisfaction with life, and mindfulness were significantly correlated to the level of ego dissolution experienced during the ayahuasca ceremony and were unrelated to previous experience with ayahuasca.

Conclusion: It is concluded that ayahuasca produces sub-acute and long-term improvements in affect and cognitive thinking style in non-pathological users. These data highlight the therapeutic potential of ayahuasca in the treatment of mental health disorders, such as depression.

Introduction

Ayahuasca is a psychotropic plant tea from South America used for healing purposes by indigenous people of the Amazon (J. T. Schmid, 2012). It is known under various names like *yage*, *caapi*, *natem*, *mihi*, *dapa*, *daime* or *hoasca*. Ayahuasca is prepared from the *Psychotria viridis* bush that contains the serotonergic 2A receptor agonist N,N-dimethyltryptamine (DMT) and the *Banisteriopsis caapi* liana that contains β -carboline alkaloids such as harmine, harmaline and tetrahydroharmine (F. Palhano-Fontes et al., 2015; J. Riba et al., 2001). The β -carboline alkaloids inhibit the action of monoamine oxidase (MAO) that is responsible for breaking down DMT (Godinho et al., 2017). The inhibition of MAO allows DMT to reach the central nervous system for a prolonged period of time, causing intense alterations in sensory integration and awareness (J. Riba et al., 2001). The psychotropic effects of ayahuasca correspond with those induced by other psychedelics such as LSD, mescaline, and psilocybin (D. J. McKenna, 2004). Psychotropic effects of ayahuasca start between 30 and 60 minutes post-administration, reaching maximum intensity between 60 to 120 minutes, and can last up to 4 hours after administration (J. Riba et al., 2001).

The acclaimed benefits of ayahuasca are both spiritual and psychotherapeutic (Trichter, 2010) and may be due to a symbiotic action between pharmacology and an altered state of consciousness (Re, Palma, Martins, & Simões, 2016). Interviews with healthy ayahuasca users suggest that ayahuasca elicits spiritual insights, changed worldviews, and a new, more positive orientation towards life (J. C. Bouso et al., 2012; Grob et al., 1996; J. H. Halpern, A. R. Sherwood, T. Passie, K. C. Blackwell, & A. J. Ruttenber, 2008). Adolescents who regularly consume ayahuasca show less signs of anxiety, are more

optimistic, self-confident, insistent, and emotionally mature than their peers (Da Silveira et al., 2005). Taken together, evidence suggests that ayahuasca may be a useful additive to psychotherapy to promote personal reflection and insights about attitude and belief (S. Trichter, J. Klimo, & S. Krippner, 2009). The efficacy of this approach, however, depends on how well insights gained during the ayahuasca experience are integrated into everyday life (E. Frecska, P. Bokor, & M. Winkelman, 2016).

There is also evidence that ayahuasca affects thinking style. For example, the acute intake of ayahuasca led to significant increase in two facets of the Five Facets Mindfulness Questionnaire, i.e., non-judgement and non-reactivity (J. Soler et al., 2016). This suggests that ayahuasca may foster acceptance of thoughts and feelings experienced by the individual, which may be therapeutic for individuals who experience persistent negative thoughts. Increased acceptance of thoughts and feelings might have therapeutic benefits for patients with for example depression by allowing them to not judge or react to for example rumination. Furthermore, it has been demonstrated that ayahuasca acutely increases creative, divergent thinking while decreasing convergent thinking (K. P. Kuypers et al., 2016). The former represents a style of thinking whereby new ideas can be generated in a context in which more than one solution is correct, whereas the latter refers to a style of thinking where there is only one optimal solution to a problem. Interestingly, changes in divergent thinking help to strengthen psychological flexibility and allow adaptive coping styles (Forgeard & Eichner, 2014). Imaging studies have shown that enhanced mindfulness capabilities are associated with increased functional brain connectivity (F. Sampedro et al., 2017; A. Viol, Palhano-Fontes, Onias, de Araujo, & Viswanathan, 2017).

Most research on ayahuasca has focused on acute and sub-acute effects on subjective well-being. However, there are also indications that effects of ayahuasca last far beyond the (sub)acute phase. Previous research demonstrated that a single oral dose of ayahuasca decreased depressive symptoms in three females as measured by the Hamilton Rating Scale for Depression Scale (HAM-D) (F. De Lima Osório et al., 2011). Depressive symptoms decreased by 79% on day one after intake and remained at 66% below their baseline 2 weeks after intake. More recently, 17 patients who received an oral dose of ayahuasca (2.2 mL/kg) showed a significant reduction in depressive symptoms within a day following treatment which was still present 21 day later (R. F. Sanches et al., 2016). This suggests that ayahuasca has fast acting antidepressant properties that can last for up to three weeks. It has also been suggested that long-term therapeutic impact of psychedelics in part depends on the quality of psychedelic experience such as the occurrence of a profound psychological insight or the experience of ego-dissolution (L. Roseman, Nutt, & Carhart-Harris, 2017).

The present study aimed to assess whether administration of ayahuasca produces long-lasting changes on affect and creativity. The second objective was to assess whether the acute and long-term effects of ayahuasca depend on the degree of ego dissolution that was experienced during the ceremony. In the current study we predicted that participants' self-reported mindfulness and life satisfaction and, creative divergent thinking, would increase after the ayahuasca ceremony as compared to baseline. Moreover, we expected that symptoms of depression, anxiety, and stress-related symptoms would decrease after ayahuasca intake as compared to baseline. We furthermore expected that ayahuasca-induced changes would still be present four weeks after the ceremony as compared to baseline. Finally, we expected that positive

changes in the dependent variables would be correlated with subjective ratings of ego-dissolution.

Methods

Participants

Data were collected at ayahuasca-ceremonies at different locations in Colombia (N=27) and The Netherlands (N=30). On site, participants of the ayahuasca-ceremony were invited to enter the study. Exclusion criteria included non-fluency in Spanish, Dutch or English. A total of 57 participants from either location consented after goals and methods of the study were explained. This study was approved by the standing Ethical Review Committee. Participation was voluntary and no incentives to participate were provided. The participants were not affiliated to any ayahuasca religion (e.g. União do Vegetal, or Santo Daime).

Group 1: The Dutch sample

Thirty volunteers were included at several ayahuasca ceremonies in the Netherlands (40% males and 60% females). Most participants were from Europe (93.3%) while the rest of the participants were from Asia (3.3%) and North America (3.3%). Their motivation for ayahuasca use included ‘understanding myself’ (73.3%), ‘solving issues’ (20%), and ‘curiosity’ (6.7%). The highest completed level of education was higher vocational education (70%), high school (16.7%), a scientific education (10%), or elementary school (3.3%). None of the participants were currently on any medication that could have affected their ayahuasca intake. In total, 13 participants reported they had no previous experience with ayahuasca (43.3%). Twenty participants (66.7%) reported having had experience with other entheogenic drugs in the past, whereas 10 participants (33.3%) reported

they had no experience with other entheogenic drugs. Finally, 23 participants reported they were not diagnosed with any mental health disorder (76.7%), 3 participants reported they suffered from depression (10%), one participant reported anxiety (3.3%), 2 participants reported personality disorders (6.6%) and one participant reported to suffer from addiction (3.3%).

Group 2: The Colombian sample

Twenty-seven volunteers (33.3% males, 66.7% females) from several locations in Colombia (Bogota, Bucaramanga, and Cali) completed the test battery. Most participants were from South America (70.4%) while the rest of participants were from Africa (11.1%), and North America (18.5%). Their reported motivation for ayahuasca use included understanding myself (40.7%), solving issues (18.5%), curiosity (3.7%), and other (37.0%). Most of the participants held a scientific degree (88.9 %), while others held a high school degree (11.1%). None of the participants were currently on any medication that could affect their ayahuasca intake. In total, 11 participants reported they had no experience with ayahuasca (40.7%). Nineteen participants (70.4%) reported having had experience with other entheogenic drugs in the past. Regarding mental health disorders, 15 participants reported they were not diagnosed with any mental health disorder (55.6%), 4 participants reported they suffered from depression (14.8%), 2 participants suffered from anxiety (7.4%), the rest of the participants did not answer this question.

Study procedure

In this observational study assessments were taken during 3 separate sessions: at baseline, the day after and 4 weeks after the ayahuasca ceremony. In total, 57 participants completed the session pre, and post ayahuasca, and 31

participants completed the 4 weeks follow-up. Attendants of the ceremony received an introduction of the research aims and were asked whether they would like to participate and signed the informed consent. They completed a 30-minute test battery consisting of questionnaires, and a psychometric test at baseline prior to the ceremony. All ayahuasca ceremonies were conducted during the night. The test battery was repeated once again on-site when the participants woke up the next day. In addition, participants also completed an ego-dissolution questionnaire. The follow-up ayahuasca assessment at 4 weeks after the ceremony was administered through an online survey created in Qualtrics.

Setting

Group 1: The Dutch sample

The ayahuasca ceremonies in the Netherlands were held in a tipi outside, or in a big hotel-room. The goal of the ceremony was to relieve psychological or physical issues, increase well-being or to gain personal insights. In each ceremony there were at least 2, or more experienced ayahuasca facilitators with a background in healing and/or coaching. Personal intakes were done by a naturopathic doctor that screened participants for their motivation, medicine use and medical and psychological history. Participants on antidepressant medication, or with an anxiety disorder were not allowed to participate.

Group 2: The Colombian sample

The ayahuasca brew in Colombia was taken in a secluded location in the rainforest on top of a mountain, or in the courtyard of an eco-village. Participants arrived at the location in the evening and remained in a dimly lit ceremonial building called *maloca*, used for ayahuasca ceremonies. The

ceremonies were primarily arranged to facilitate personal healing and development, while also being part of the culture in South America. The shamans would provide support for participants if they were going through a challenging time during the ceremony. The shaman screened participants prior to the ceremony and would not allow participants on antidepressants, or those with a mental health disorder to participate.

In both countries, the ceremonies were held by experienced shamans with a background in healing with plant medicines, trained in the Amazon during the ceremony. The shaman and the organizers would sing *icaros* (this is the term that is commonly used to describe the medicine songs performed in these ceremonies) and play instruments (i. e guitar, drums, flute). Furthermore, the shaman in Netherlands, and the shaman in Colombia both provided participants with preparatory instructions (e.g., dietary preparation). Dietary preparation included; not eating (red) meat and foods containing salt, sugar or fats reduce tyramine levels in the body. Lower tyramine levels reduce side effects like increased cardiovascular activity, nausea and headaches that can be caused by the MAO-Inhibitor in the brew. Additional advice was not to subject oneself to stress (e.g. watching violent TV-programs, news), and sexual intercourse to conserve energy, calm the mind, and to increase mindful introspection, which, according to Amazonian tradition improves the healing effects of the plant medicine and will reduce purging and negative side effects of the medicine.

Ayahwasca samples

In total, 4 ayahuasca samples were obtained (two from Colombia, and two from The Netherlands). The alkaloid concentrations of the ayahuasca preparations were determined after dilution using high performance liquid

chromatography-electrospray ionization-time-of-flight mass spectrometry (HPLC-TOF MS) which was calibrated with pure reference substances of N,N-dimethyltryptamine (DMT; Cerilliant, Round Rock TX, US), harmine and harmaline (Aldrich Chemistry, St. Louis MO, US). From the alkaloid concentrations it was determined, that a 200-ml portion of Netherlands 1 contained 371.6 mg of DMT, 485.5 mg of harmine and 892 mg of harmaline; a 200-ml portion of Netherlands 2 contained 915.4 mg of DMT, 971.8 mg of harmine and 38.1 mg; a 200 ml portion of Colombia 1 contained 189.4 mg of DMT, 1261.7 mg of harmine and 69.8 mg of harmaline and a 200 ml portion of Colombia 2 contained 500.5 mg of DMT, 827.4 mg of harmine and 57.4 mg of harmaline.

Measures

Picture Concept Task (PCT)

A creativity task known as the Picture Concept Task (PCT) with non-verbal stimuli was used (K. P. Kuypers et al., 2016). The PCT was composed of stimuli from the Wechsler Preschool and Primary Scale of Intelligence and the Wechsler Intelligence Scale for Children. Each stimulus contains between 4 and 12 color pictures shown in two or three rows. The participants are instructed to find an association between one of the pictures of each row. They are asked to provide the correct solution as there is only one correct answer. The correct answers are taken as the dependent measure of convergent thinking. To assess divergent thinking, participants were asked to provide as many alternative associations as possible by sticking to the rule; 1 item per row. This is the regular instruction included in measures of divergent thinking, and it is used to calculate several parameters, i.e., originality, fluency, and the ratio of both, which reflect quantity and quality of divergent

thinking. Fluency is defined as the number of alternative associations. Originality is calculated by evaluating the originality of the alternative association relative to those provided by all other participants in a session. Alternative answers that were uniquely reported by a single participant received an originality score of 2. Answers that were shared with a single participant were valued as 1, and answers that were shared by 3 or more participants were rated as zero. Mean originality (creativity) scores and ratio originality scores, weighed for fluency (originality/fluency) were used as measures of divergent thinking. Three parallel versions of the PCT were used at baseline and the two follow-up measures after the ceremony to avoid learning effects. Each parallel version consisting of 17 stimuli were shown, and participants had 30 seconds per stimulus.

Subjective measures

The test battery in addition included four questionnaires, the Depression, Anxiety, and Stress Scale-21 (DASS-21), the Satisfaction with Life Scale (SWLS), the Five Facets Mindfulness Questionnaire (FFMQ), and the Ego Dissolution Inventory (EDI).

Depression, Anxiety, and Stress Scale

The Depression, Anxiety, and Stress Scale (DASS-21) is a shorter version of the originally 42-item long self-report questionnaire (J. D. Henry & J. R. Crawford, 2005). Sample items for each subscale include the following; “I couldn’t seem to experience any positive feeling at all”, “I was aware of dryness of my mouth”, and “I found it hard to wind down”, respectively. The purpose of this scale is to measure constructs of depression, anxiety, and stress. The participants responded by rating the concordance with each statement from 0 (did not apply to me at all) to 3 (applied to me very much,

or most of the time). The subscale scores for depression, anxiety and stress are calculated by summing the scores for the relevant items, multiplied by 2, given that the original DASS has 42 questions. In this study, the English version of the scale was used, in addition to a validated version translated into Spanish, and Dutch. The total scale of the English DASS-21 had a coefficient alpha of .93. Subscale coefficient alphas were also high ($\alpha_{\text{depression}} = .88$; $\alpha_{\text{anxiety}} = .82$; $\alpha_{\text{stress}} = .90$). The total scale of the Spanish version of the DASS-21 had a Cronbach alpha coefficient of .96. Cronbach alpha of the Dutch version was .95 (Daza, Novy, Stanley, & Averill, 2002; Wardenaar, Wanders, Jeronimus, & al, 2017).

Satisfaction with Life Scale

The Satisfaction with Life Scale (SWLS) is a 5-item self-report scale) (E. Diener, R. A. Emmons, R. J. Larsen, & S. Griffin, 1985). Sample items include: *“In most ways my life is close to my ideal”* and *“So far I have gotten the important things I want in life”*. The purpose of the scale is to assess someone’s satisfaction with life. The items are answered on a Likert-scale ranging from 1 *“Strongly disagree”* to 7 *“Strongly agree”*. The total score is obtained by summarizing the ratings from each item and ranges between 5 to 35, with higher scores indicating a greater life satisfaction. The scale has good psychometric properties. The original SWLS in English has a Cronbach’s alpha of .87, and was used in addition to a validated translation in Spanish with a Cronbach’s alpha coefficient of .88, and a Dutch translation with a Cronbach’s alpha coefficient of .85 (Beuningen, 2012; Vazquez, Duque, & Hervas, 2013).

Five Facets Mindfulness Questionnaire

The Five Facets Mindfulness Questionnaire (FFMQ) is a 39 item self-report questionnaire (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006) assessing five different factors 1) Observe: noticing experience that are both internal and external such as for example thoughts and emotions, e.g., *“When I’m walking, I deliberately notice the sensations of my body moving”*; 2) Describe: describing internal experiences, e.g., *“I’m good at finding words to describe my feelings”*; 3) Acting with awareness: focus on the present activity, e.g., *“When I do things, my mind wanders off and I’m easily distracted”*; 4) Non-judgment: not evaluating the present experience, e.g., *“I criticize myself for having irrational or inappropriate emotions”*; 5) Non-reaction: allowing thoughts and feelings to come without acting or reacting upon them, e.g., *“I perceive my feelings and emotions without having to react to them”*. The purpose of this scale is to obtain an understanding of an individual’s mindfulness-related capacities. The participants answered the FFMQ by rating the concordance with each statement on a 5-point Likert-scale that ranges from 1 (never true) to 5 (very often or always true). The total FFMQ score is obtained by adding the subscale scores. The scale has shown good internal consistency. Cronbach’s alpha was α non-reaction = .75, α non-judgement = .87, α describe = .91, α observe = .83 and α awareness = .87. In this study, the original English version of the FFMQ was used in addition to a validated translation in Spanish and Dutch. The Cronbach’s alpha for the Spanish translation ranges from .80 to .91 (Cebolla et al., 2012). Cronbach’s alpha for the Dutch translation ranges from .74-.90 (Veehof, Peter, Taal, Westerhof, & Bohlmeijer, 2011).

Ego Dissolution Inventory

The Ego Dissolution Inventory (EDI) is an 8-item self-report scale that assesses the participant's experience of ego dissolution (M. M. Nour, L. Evans, D. Nutt, & R. L. Carhart-Harris, 2016). Sample items for the scale includes the following: "*I experienced a dissolution of my "self" or ego*" and "*I felt at one with the universe*". The purpose of this scale is to acquire a better understanding of the experiences the participants had about ego dissolution during the ayahuasca ceremony. The participants answered the scale with endpoints of either 0 = "*No, not more than usually*" or 100 = "*Yes I experience this completely/entirely*". The EDI is scored by calculating the mean of all the 8 items (range 0-100). The higher the total score, the stronger the experience of ego dissolution. In this study the original English version of the EDI was used in addition to a non-validated Spanish and Dutch version.

Statistical Analyses

Data was analyzed with the Statistical Package for the Social Sciences (SPSS). We carried out linear mixed model analysis that included Session (3 levels: baseline, 1 day after ayahuasca and 4 weeks after ayahuasca) as the within subject factor, Country (2 levels: Colombia and The Netherlands) as between group factor, and the Session x Country interaction. The covariance structure was chosen according to best fit and could vary across outcome variables. Different covariance structures used included compound symmetry heterogeneous (CSH) as well as first lag autoregressive (AR1) structures. Significant main effects of Session and Session x Country were followed by separate contrasts between baseline and follow-up session with Bonferroni adjustments for multiple comparisons. For outcome parameters showing a significant main effect of Session a 2nd mixed model analyses were conducted

with Session (2 levels, baseline and the day after) and Experience with ayahuasca (2 levels, yes or no) as main factors, to determine whether the sub-acute response to the ayahuasca ceremony differed between participants who experienced ayahuasca before or who had no previous experience. Pearson's correlations were carried out to investigate the association between the level of ego dissolution during the ayahuasca ceremony and changes in outcome measures over time relative to baseline.

Results

Overall, 57 participants completed parts of the test battery at baseline and during the day after the ceremony. A total of 31 participants also completed parts of the online test battery at 4 weeks after the ayahuasca ceremony.

Picture Concept Test

The mixed model analysis revealed a significant main effect of Session ($F_{2, 43.8} = 7.06$; $p = .002$) on convergent thinking. Separate contrasts revealed that the number of correct solutions increased after the ayahuasca ceremony, as compared to baseline. The increment in convergent thinking on the day after the ceremony approached significance ($p = .09$) and reached full significance 4 weeks after ($p = .003$). Convergent thinking was not affected by Country or Session x Country. None of the divergent thinking parameters were affected by any of the main factors or their interaction. Mean (SE) performance on the convergent correct and divergent assignment as a function of time after ayahuasca is shown in Figure 1.

Figure 1. Mean (SE) total correct solutions (convergent thinking) and the ratio between originality and fluency (divergent thinking) as a function of time after ayahuasca (* = $p < .05$).

Subjective measures

DASS-21

Mixed model analysis revealed main effects of Session on stress ($F_{2, 72.6} = 7.3$; $p = .001$) and depression ($F_{2, 78.9} = 7.1$; $p = .001$). Separate contrast revealed that subjective ratings of stress and depression decreased on the day after the ayahuasca ceremony ($p = .006$ and $p = .001$, respectively) and as well at 4 weeks after ($p = .002$ and $p = .013$, respectively). See Figure 2.

There was also a main effect of Country indicating lower stress ($F_{1, 52.3} = 17.3$; $p = .001$) and depression ($F_{1, 46} = 16.4$; $p = .001$) scores in the Colombian sample as compared to the Dutch sample. The interaction between Session and Country did not reach significance for stress and depression score. Anxiety ratings were not affected by any of the main factors.

SWLS

Mixed model analyses revealed a main effect of Session ($F_{2, 46.4} = 3.7$; $p = .031$). Contrasts showed that satisfaction with life significantly increased the day after the ayahuasca ceremony ($p = 0.027$) but not 4 weeks later, as compared to baseline. See Figure 3. Satisfaction with life ratings were significantly higher in the Colombian sample as compared to the Dutch sample ($F_{1, 51.6} = 20.4$; $p = .001$). There was no interaction between Session and Country.

Depression, Anxiety, Stress Scales (DASS)

Figure 2. Mean (SE) subjective ratings of stress, depression and anxiety as a function of time after ayahuasca (* = $p < .05$).

Figure 3. Mean (SE) subjective ratings of satisfaction with life and 5 dimensions of mindfulness as assessed with the FFMQ as a function of time after ayahuasca (* = $p < .05$).

FFMQ

Main effects of Session reached significance on 4 mindfulness parameters: i.e. observe ($F_{2, 69.4} = 4.3$; $p=.018$), non-judge ($F_{2, 68.4} = 4.4$; $p=.016$), aware ($F_{2, 60.4} = 5.5$; $p=.006$) and non-reaction ($F_{2, 75.7} = 3.4$; $p=.038$). Describe was not affected by Session. Separate contrasts revealed improvements in observe ($p=0.15$), non-judge ($p=.012$) and aware ($p=.004$) on the day after the ayahuasca ceremony as compared to baseline. Comparisons between FFMQ measures after 4 weeks and baseline revealed no significant differences. See Figure 3. Ratings of aware were significantly higher in the Colombian sample as compared to the Dutch sample ($F_{1, 57.7}=8.6$; $p=.005$). There were no differences between Countries for other FFMQ parameters and interactions between Session and Country never reached significance.

EDI

Mean (SD) ego dissolution rating was 60 (27.3). Overall, total EDI rating varied between 0 (no dissolution) and 100 (maximal dissolution). On the day following the ayahuasca ceremony, EDI scores were negatively correlated to DASS ratings of stress ($r=-.42$; $p=.007$) and depression ($r=-.31$; $p=.001$) and positively correlated to FFMQ ratings of awareness ($r=.39$; $p=.003$), non-judgement ($r=.36$; $p=.007$), non-reactivity ($r=.39$; $p=.003$) as well as satisfaction with life ($r=.37$; $p=.007$). Subjective ratings at 4 weeks after the ceremony did not correlate with EDI, except for non-reactivity ($r=.39$; $p=.028$). Scatterplots showing the negative relation between EDI and ratings of stress and depression on day 1 are shown in Figure 4. EDI did not correlate with the PCT parameter of convergent thinking.

Figure 4. Pearson correlation between ego dissolution and subjective stress (upper panel) and between ego dissolution and depression ratings (lower panel) on the day after the ayahuasca ceremony.

Experience with ayahuasca

The sub-acute effect of ayahuasca did not differ between participants with no (N=24) or previous experience (N=33) with ayahuasca for any of the above outcome parameters that were significant affected by a main effect of Session. There were no main effects of Experience and Session x Experience.

Discussion

The primary aim of the present study was to assess sub-acute and long-term impact of ayahuasca use on affect and cognitive thinking style. A total of 57 visitors of ayahuasca ceremonies in Colombia and The Netherlands consented to participate in this observational study and were asked to complete subjective questionnaires and a creative thinking task prior to an ayahuasca ceremony, the day after and about 4 weeks later. Baseline and sub-acute assessments were conducted on-site whereas the 4-week follow-up was conducted online. The 4-week follow-up was completed by about 54% of the participants. Relative to baseline, ratings of depression and stress significantly decreased after the ayahuasca ceremony and these changes persisted for at least 4 weeks. Likewise, convergent thinking improved after the ayahuasca ceremony even at the 4 weeks follow-up. Satisfaction with life and several aspects of mindfulness increased the day after the ceremony, but these changes failed to reach significance 4 weeks after. Changes in affect, satisfaction with life and mindfulness were significantly related to the level of ego dissolution experienced during the ayahuasca ceremony.

Subjective ratings of stress and depression significantly decreased by 36% and 46% respectively during the day after the ayahuasca ceremony. Ratings of stress and depression remained significantly lower throughout the following month, suggesting that a single ayahuasca ceremony can bring

about changes in affect that last for a prolonged period. Antidepressant properties of ayahuasca are not unexpected given that ayahuasca brews contain β -carboline alkaloids that act as MAO-A inhibitors which are known for their antidepressant actions (Finberg & Rabey, 2016). Sub-acute reductions in depressive symptoms have been reported previously in first time (Barbosa, Giglio, & Dalgallarrondo, 2005) and regular ayahuasca users (J. C. Bouso et al., 2012). A pilot, open-label trial in 6 patients suffering from recurrent or major depressive disorder however showed significant reductions of up to 82% in depressive scores between baseline and 1, 7 and 21 days after intake of a single ayahuasca dose (F. de L. Osório et al., 2015). These data were recently replicated in a larger open-label trial that involved 17 depressed patients (R. F. Sanches et al., 2016). Together these studies support the notion that single doses of ayahuasca can reduce symptomatology in depressed patients as well as in a broad spectrum of users who display non-pathological levels of depression and that such changes persist over a prolonged period.

The mechanism underlying the long-term effects of ayahuasca on affect is presently unknown. Animal studies suggest that *Banisteriopsis caapi* preparations produce antidepressant activity through hippocampal neurogenesis (Farzin & Mansouri, 2006; Fortunato et al., 2010). A recent study demonstrated that harmine, tetrahydroharmine and harmaline, the three main alkaloids present in the *Banisteriopsis caapi* stimulate adult neurogenesis in vitro using hippocampal progenitor cells from adult mice (Morales-Garcia et al., 2017). Neurogenesis has also been suggested to underlie the acute and long-term antidepressant properties of other psychedelic compounds such as ketamine (R.S. Duman & Aghajanian, 2012; Ma et al., 2017) and psilocybin (Catlow, Song, Paredes, Kirstein, & Sanchez-

Ramos, 2013; Idell et al., 2017). Neurogenesis and synaptic plasticity may play a crucial role in how neural circuits regulate their excitability and connectivity and may link the neurobiology of depression to the therapeutic effects of glutamatergic drugs such as ketamine (C. G. Abdallah et al., 2015). In that respect it is of interest that changes in glutamate transmission following ayahuasca ceremonies have been associated to improvements in certain aspect of mindfulness as well (F. Sampedro et al., 2017).

Ayahuasca also produced significant sub-acute improvements in subjective ratings of mindfulness and satisfaction with life. Subjects felt that they were more non-judgmental, acted with more awareness and were more observant on the day following ayahuasca. Similar findings have been reported in an observational study that compared aspects of mindfulness before and 24 hours after an ayahuasca ceremony using the same FFMQ questionnaire (J. Soler et al., 2016). In the present study, ratings of mindfulness and satisfaction with life increased by 5-8%, relative to baseline. On average, similar increments in mindfulness were obtained at 4 weeks after the ayahuasca ceremony, but this time these no longer achieved statistical significance. It should be noted that ayahuasca induced changes in mindfulness were much smaller than changes in symptoms of depression and stress. Consequently, the loss of statistical power caused by the drop in the response rate at the 4-weeks follow-up may have affected the probability of detecting changes as assessed with the FFMQ and SWL more than those assessed with the DASS, because changes in the former were small.

Exposure to the ayahuasca ceremony also increased convergent thinking as assessed with the Picture Concept Task. The number of correctly detected associations increased with 9% sub-acutely and with 29% at the 4 weeks

follow-up. At the latter time point, the increase in cognitive performance also reached statistical significance. The PCT task has previously been used in an observational ayahuasca study to show that the brew increases performance at the divergent, creative thinking assignment but decreases performance in convergent thinking assignments (Kuypers et al., 2016). Data from these studies however are not necessarily conflicting. In the latter study, PCT performance was assessed during the acute phase of the ayahuasca experience (i.e. 2 hours after intake), whereas in the present study PCT performance was assessed sub-acutely and a month after the ceremony. It is conceivable that divergent, flexible thinking will improve during the acute psychedelic, modified state of consciousness that ayahuasca produces but not thereafter. Convergent thinking may not prosper during a psychedelic experience, but may improve afterwards because it relies on mindfulness capabilities such as acting with awareness that contribute to optimization of cognitive functioning (Lebudaa, Zabelinab, & Karwowskia, 2015). Increments in convergent thinking may therefore coincide with improvements in mindfulness that were observed in the present sample of ayahuasca users.

It might be argued that post-ayahuasca changes in affect and thinking style that were observed in the present study are not related to a pharmacological effect of ayahuasca but due to uncontrolled confounders such as psychological expectations of participants prior to and after the ayahuasca ceremony. For example, participants may have been more stressed in anticipation of the ayahuasca ceremony which would explain why stress levels are higher at baseline, prior to the ceremony. Ideally, one would need to include a placebo group to control for the potential bias of expectation. This however is often impossible in observational studies that aim to assess the influence of ayahuasca in naturalistic environments. Yet, there are several

strong indicators in the present study that suggest that changes in affect and thinking were directly related to the intake of ayahuasca. First, it was demonstrated that improvements in affect and cognition were significantly correlated with the strengths of ego dissolution during the ayahuasca experience. Higher ratings of ego dissolutions were associated with stronger reductions in symptoms of depression and stress and with improvements in mindfulness and satisfaction with life. This strongly suggests that changes in mood and thinking were intrinsically related to the actual ayahuasca experience. Second, anxiety levels were very low during baseline and follow-up sessions, which suggest that anxiety levels in anticipation of the ayahuasca ceremony were negligible. Finally, improvements in affect and cognition occurred independent of the previous ayahuasca experience of participants. The aforementioned rules out the possibility that changes were only apparent in first time users who might be overly stressed by the novelty of the ayahuasca experience.

In sum, this study presents supporting evidence for sub-acute and long-term improvements in affect and cognitive thinking style in non-pathological participants of ayahuasca ceremonies. Moreover, it was shown that improvements in affect and mindfulness are larger in participants who experience strong levels of ego dissolution during the acute phase of ayahuasca exposure. These data highlight the therapeutic potential of ayahuasca in the treatment of mental health disorders, such as depression.

Chapter 3 - Mind or matter? A placebo-controlled study of the effects of ayahuasca ingestion on mental health of participants in a naturalistic, neo-shamanic setting.

Abstract

Rationale: Ayahuasca is a plant concoction containing N,N-dimethyltryptamine (DMT) and certain β -carboline alkaloids from South America. Previous research in naturalistic settings has suggested that ingestion of ayahuasca can improve mental health and well-being, however these studies were not placebo controlled and did not control for the possibility of expectation bias.

Objectives: This naturalistic observational study was designed to assess whether mental health changes were produced by ayahuasca (matter), or by set (mind).

Methods: Assessments were made at pre and post-ayahuasca sessions in 30 participants of ayahuasca retreats of naturalistic, neo-shamanic origin hosted in The Netherlands, Spain and Germany. Participants were randomized into two treatment groups that ingested capsules containing ayahuasca (N=14) or placebo (N=16).

Results: Analysis revealed a main effect of Session on symptoms of depression, anxiety and stress. Compared to baseline, symptoms reduced in both groups after the ceremony, independent of treatment. There was a main Treatment x Session interaction on implicit emotional empathy, indicating that ayahuasca increased emotional empathy to negative stimuli.

Conclusion: The current findings suggest that subjective improvements in mental health of participants of naturalistic ayahuasca ceremonies can be driven by non-pharmacological factors such as expectations and intentions (mind-set). Yet, objective measures of empathy also revealed improvements that were solely observed after the pharmacological treatment with ayahuasca

(matter). These findings stress the importance of placebo-controlled designs in psychedelic research and the need to further explore the contribution of non-pharmacological factors to the psychedelic experience.

Introduction

Ayahuasca is a plant concoction originally used by shamans in the Amazon-region for communication with spirits, magical experiences, rites of initiation, and healing rituals. This practice is commonly referred to as “shamanism” (Brito et al., 1996; Krippner, 2000; Dennis J McKenna, 2004; Townsend, 2004). The concoction is prepared by cooking leafs from the *Psychotria viridis* bush and the liana from *Banisteriopsis caapi*. These respectively contain the serotonergic 2A receptor agonist N,N-dimethyltryptamine (DMT), and β -carboline alkaloids such as harmine, harmaline, and tetrahydroharmine. Of note, the β -carboline alkaloids function as monoamine oxidase inhibitors (MAOI) allowing DMT to reach the central nervous system for a prolonged period of time. This leads to intense alterations in perception and sensory integration, and the induction of a spiritual, entheogenic state of consciousness (Dennis J McKenna, 2004; Fernanda Palhano-Fontes et al., 2015; Jordi Riba et al., 2001; Tupper, 2008).

The principles and techniques of traditional shamanic rituals where ayahuasca has been used historically, have recently spread beyond its native habitat, and have subsequently become adopted by the Western contemporary society as a new and modern shamanism commonly known as *neo-shamanism*. At present, ayahuasca is sought after by an increasing number of Westerners for spiritual and physical healing in naturalistic settings, and for various other reasons such as spiritual enlightenment, self-actualization, and the search for mystical experiences (Fotiou, 2012; Uthaug et al., 2018; Michael Winkelman, 2005). The prevalence of ayahuasca use worldwide in (non)western societies, as well as its (anecdotal) effects on mental wellbeing sparked scientific interest (Ede Frecska et al., 2016). Today, there are a number of naturalistic

‘field’ studies suggesting a positive impact of ayahuasca on mental functioning, suggesting that ayahuasca may hold therapeutic potential as a treatment for mental health related disorders (Ede Frecska et al., 2016). Specifically, such studies have indicated that in healthy individuals, the use of ayahuasca is related to acute enhancement of flexible thinking (K. Kuypers et al., 2016) improvement in affect and cognition (Uthaug et al., 2018) and increased mindfulness-related capacities (Joaquim Soler et al., 2016). In people with mental health problems the use of ayahuasca has been associated with the recovery from eating disorders (Lafrance et al., 2017), the enhancement of emotion dysregulation in individuals with border-line like traits (Domínguez-Clavé et al., 2018).

Nevertheless, none of these explorative field studies have controlled for the possibility of the placebo effect, thereby introducing the possibility that changes observed in these studies could be attributed to factors other than the pharmacological agent ayahuasca. Non-pharmacological factors that have been recognized to have an impact on the behavioral and psychological effects of psychedelics, include set and setting (Hartogsohn, 2016). The latter refers to the context in which the ceremony takes place including all sensory modes (e.g., auditory: music, visual: tactile), while the former refers to the intentions, mood state and expectations of the individual partaking in an ayahuasca ritual (Hartogsohn, 2014, 2016, 2017; Kaelen et al., 2018; Lawn, Hallak, Crippa, Santos, et al., 2017; Leary, Litwin, & Metzner, 1963; Shewan, Dalgarno, & Reith, 2000). Since individual intentions and expectations of spiritual healing are thought to play a prominent role in ayahuasca ceremonies they are made explicit in group discussions prior to drinking ayahuasca, and they are further evaluated after the experience during integrative group sessions (Adamson & Metzner, 1988). Moreover, group dynamics before,

during, and after the ceremony are controlled and guided by facilitators or hosts who aim to maximize the setting in which the ceremony takes place (Adamson & Metzner, 1988; Blewett, 1970; Trope et al., 2019). Of note, this may make the participant prone to the effects of suggestibility which might amplify the subjective effects (R. Carhart-Harris et al., 2015).

In order to understand the role of expectation (set) on behavioral and psychological effects observed after participation in an ayahuasca ceremony, a naturalistic, placebo-controlled, observational study was set up to address this knowledge gap. The aim of the present study was to assess the role of ayahuasca as well as ‘non-pharmacological factors’ in an ayahuasca ceremony on mental health related variables (empathy and affect) of participants who engaged in naturalistic, neo-shamanic group sessions at ayahuasca retreats before and after they received ayahuasca or placebo. We hypothesized that the non-pharmacological factors (i.e. mind-set), would impact both ‘treatment’ groups; whereas pharmacological effects (i.e. matter) would only be observable in the ayahuasca group.

Methods

We visited 6 ayahuasca retreats, hosted by a single organization, all taking place at several locations in Europe (The Netherlands, Spain and Germany). The ayahuasca ceremonies were all structured in the same way. The organizers promoted the dates of their ayahuasca ceremonies online and attracted on average 15-25 participants per event. Most of the participants of the retreat were one-time visitors with no or limited previous experience with ayahuasca. A small number of retreat participants were more experienced and member of an “ayahuasca school” linked to the host organization. These people were in training to become facilitators of ayahuasca ceremonies and

as part of their training, aimed to deepen their experience with altered states of consciousness. Only ‘school-members’ were invited to partake in the present study.

The students exposed themselves repeatedly to ayahuasca ceremonies of the host organization. Most of the time they drank ayahuasca while participating, but on some occasions, they were requested by the organizers to not drink ayahuasca in order to be able to observe the ceremony from the perspective of a facilitator. We invited these students to participate in a single-blind, placebo-controlled study, in which the organizers offered the students ayahuasca or an ayahuasca-placebo. If they consented, they received capsules containing either freeze-dried ayahuasca or a placebo substance. The substance was provided and administered by the ceremony organizers.

Ayahuasca students were invited to enter the study after they registered at the retreat. Inclusion criteria to participate included fluency in English, aged over 18, and written consent. Participation was voluntary and no incentives to participate were provided. After inclusion, study participants completed a 30 min test battery prior to the ayahuasca session, which served as the baseline measurement, and in the morning of next day, after the ceremony. This study was approved by the Local Standing Ethical Committee in Maastricht, the Netherlands.

Randomization and dose

Ayahuasca students were randomly assigned by the host organization to receive either ayahuasca (N=14) or placebo (N=16) from one of the facilitators of the retreat, and in the presence of a member of the research team. Additionally, both the facilitators that were present during the administration of ayahuasca and the subsequent ceremony, as well as the

study participants, were blind to the actual treatments. Study participants and facilitators were debriefed the next day, after the test session, about the content of the capsule they received. Study participants received 7 capsules with the option of taking 3 additional ones as a booster. These capsules contained either freeze-dried ayahuasca or a placebo mixture that contained a mix of the following ingredients; coco powder, vitamins (unspecified), turmeric powder, quinoa, traces of coffee, and potato flour. Three ayahuasca capsules were collected in order to determine the concentration of alkaloids afterwards.

During one of the ceremonies, no capsules were offered. Instead a drink mixture was administered which was either regular ayahuasca tea or a placebo drink including coffee, coco powder, and balsamic vinegar; the latter was added to better mimic the authentic ayahuasca taste.

Ayahuasca

The alkaloid concentrations in the ayahuasca capsules were determined after dissolution in 25 mL of water using high-performance liquid chromatography-electrospray ionization-time-of-flight mass spectrometry (HPLC-TOF MS) which was calibrated with pure reference substances of *N,N*-dimethyltryptamine (DMT; Cerilliant, Round Rock TX, US), harmine and harmaline (Aldrich Chemistry, St. Louis MO, US). Weight of ayahuasca capsules and concentrations of DMT and harmalines are shown in Table 1. Doses per individual subject are shown in Table 2.

	Capsule weight	Ingredients	DMT	Harmine	Harmaline
	(mg)	(mg)	(mg/g)	(mg/g)	(mg/g)
Capsule 1	579.6	475.9	3.7	10.6	0.7
Capsule 2	703.8	599.6	3.8	10.5	0.7
Capsule 3	679.4	579.2	3.4	9.2	0.6
Mean±SD	654.3±65.8	551.6±66.3	3.6±0.2	10.1±0.8	0.7±0.1

Table 1. *Weights of ayahuasca capsules and their ingredients, concentrations and doses of DMT, harmine and harmalines per capsules.*

PPT	Number of capsuels	DMT	Harmine (mg)	Harmaline (mg)	EDI (%)	Correct guess of condition (facilitator)	Correct guess of condition (participant)
Placebo condition							
1	10	-	-	-	7.3%	No	No
2	10	-	-	-	5.2%	Yes	Yes
3	10	-	-	-	6.2%	Yes	No
7	2 cups	-	-	-	59.4%	Yes	No
8	2 cups	-	-	-	69.0%	Yes	Yes
11	10	-	-	-	—	Yes	Yes
13	7	-	-	-	21.5%	Yes	Yes
14	10	-	-	-	—	Yes	Yes
17	10	-	-	-	59.0%	Yes	No
18	10	-	-	-	66.1%	-	Yes
20	7	-	-	-	71.6%	Yes	Yes
24	10	-	-	-	17.9%	Yes	Yes
25	7	-	-	-	2.5%	Yes	Yes
27	10	-	-	-	20.0%	Yes	No
28	10	-	-	-	21.3%	Yes	Yes
30	10	-	-	-	2.4%	Yes	Yes
Mean±SD					30.7±27.5%		

PPT	Numbers of capsuels	DMT	Harmine (mg)	Harmaline (mg)	EDI (%)	Correct guess of condition (facilitator)	Correct guess of condition (participant)
Ayahuasca condition							
4	7	25.5	70.5	4.6	7.7%	No	
5	10	36.4	100.7	6.5	14.8%	Yes	
6	7	25.5	70.5	4.6	36.2%	No	
9	1 cup	ND	ND	ND	36.9%	No	
10	1 cup	ND	ND	ND	40.0%	Yes	
12	10	36.4	100.7	6.5	93.8%	No	
15	10	36.4	100.7	6.5	0.0%	No	
16	10	36.4	100.7	6.5	20.0%	No	
19	10	36.4	100.7	6.5	36.3%	-	
21	10	36.4	100.7	6.5	12.5%	Yes	
22	10	36.4	100.7	6.5	44.3%	Yes	
23	10	36.4	100.7	6.5	46.3%	Yes	
26	10	36.4	100.7	6.5	17.4%	No	
29	7	25.5	70.5	4.6	47.5%	No	
4	7	25.5	70.5	4.6	7.7%	No	
5	10	36.4	100.7	6.5	14.8%	Yes	
Mean±SD					32.4± 23.5%		
Total correct guesses						5 of 14	8 of 14

Table 2. Summary of the number of capsules per participant as well as the doses of DMT, harmine and harmaline, the level of ego dissolution and the individual and total (correct) treatment guesses of the facilitators and participants.

Setting of the retreat

The team of facilitators consisted of people with different educational backgrounds such as non-clinical psychology, medicine, dance and circus

training, lawyers, and regular office workers. The facilitators assisting on the session, and the travelling shaman differed per location though all adhered to the methodology of the naturalistic, neo-shamanic retreats, and had previous experience with ayahuasca.

After the registration of the participants was completed by one of the facilitators, all participants of the retreat were welcomed to the room where the session would take place during the night. Here, they were all welcomed by the facilitators of the retreat as well as a travelling shaman, briefed about the schedule for the following three days, and invited to share their motivations and expectations for attending. The room where the ayahuasca session took place had a mattress on the floor for each of the participants to lay on throughout the session. There was also a plastic bucket available for each of the participant in case purging occurred.

During the session, a travelling shaman from the Amazon region was present, and at least 2 facilitators from the organization were present in the room together with the ayahuasca student and other participants. As a rule of thumb, there was 1 facilitator per 7 participants. In addition, some students of the “ayahuasca school” were given the opportunity to help during the session as part of their training.

Throughout the session, the shaman and the facilitators were sitting in front of the room guiding the session (playing music, singing, or giving instructions), while also being ready and alert to give individuals support if needed. The structure of the session would largely depend on the shaman and the dynamic of the group.

An assistant of the organizing team was present at the beginning of the session and distributed the capsules or drink to the students to ensure that neither the

facilitator, shaman, nor the participant knew which student was assigned to which condition (ayahuasca or placebo). Finally, once the session reached its completion in the early morning-hours the following day, the participants would go to sleep in the session-room, or in their dorms.

Test battery

The test battery consisted of a demographic section, the multifaceted empathy test (MET), and five questionnaires: the Ego Dissolution Inventory (EDI), the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), the Depression, Anxiety, and Stress Scale (DASS-21), the Brief Symptom Inventory 18 (BSI-18), and the Five Facets Mindfulness Questionnaire (FFMQ-39). All the material was provided in English. All the measures were filled out twice, i.e., at baseline and post-session except from the EDI that was only filled out once, post-session, to assess the psychedelic experience in retrospect.

Empathy

Multifaceted Empathy Test

The MET consists of 40 pictures of people in various emotional states, with 50% being positive and 50% negative (Dziobek et al., 2008). To assess cognitive empathy (CE), participants were asked to select the emotion word, out of four words, that matched the depicted emotion. To assess emotional empathy (EE), participants were asked to rate on a scale from 1 to 9 ‘how aroused does this picture make you feel’ (implicit EE) and ‘how concerned do you feel for this person’ (explicit EE). The number of correctly classified pictures (CE) and the implicit EE and explicit EE ratings per valence and averaged across valences were used as dependent variables. Previous

validity and reliability analysis of the MET have shown to be in the good to highly satisfactory range (Dziobek et al., 2008), and previous studies have found it to be sensitive to the effects of psychedelics (Hysek et al., 2013; Kuypers et al., 2014; Kuypers, Dolder, Ramaekers, & Liechti, 2017; Mason, Mischler, Uthaug, & Kuypers, 2019a; Pokorny, Preller, Komater, Dziobek, & Vollenweider, 2017; Preller et al., 2015).

The psychedelic experience

Ego Dissolution Inventory

The EDI is an 8-item self-report scale that assesses the participant's experience of ego dissolution, with excellent internal consistency (Cronbach's $\alpha = .93$) (Matthew M Nour et al., 2016). The participants responses their experience by making a mark on a line that ranged from “*No, not more than usual*” (0 %) to “*Yes I experience this completely/entirely*” (100 %). The total EDI is scored by calculating the mean percentage of all the 8 items and ranges between 0 to 100 %. The higher the total score, the stronger the experience of ego dissolution.

5-Dimensional Altered States of Consciousness Rating Scale

The 5D-ASC is a 94-item self-report scale that assesses the participants' alterations from normal waking consciousness with a Cronbach's α range between 0.88-0.95 (Adolf Dittrich, 1998; A Dittrich, Lamparter, & Maurer, 2010; Studerus, Gamma, & Vollenweider, 2010). The participant is asked to make a vertical mark on the line below each statement to rate to what extent the statements applied to their experience in retrospect (i.e., from 0 % “*No, not more than usually*” to 100% “*Yes, more than usually*”), and the score ranges from 0 to 100%. The 5D-ASC measures 11 subscales; *experience of*

unity spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery, audio-visual synesthesia and changed meaning of perception. Moreover, the 5D-ASC measures 5 key-dimensions which include oceanic boundlessness that identifies mystical-type experiences, and has been compared with the “heaven” aspect of Huxley’s mescaline account (Adolf Dittrich, 1998), anxious ego dissociation, visual restructuralization, auditory alterations, and reduction of vigilance.

Subjective effects

Depression, Anxiety and Stress Scale 21

The DASS-21 is the shorter version of the original self-report questionnaire Depression, Anxiety, Stress Scale 42 with a Cronbach’s alpha of 0.93 (Julie D Henry & John R Crawford, 2005). The purpose of the DASS-21 scale is to measure constructs of depression, anxiety and stress ranging from 0 (normal) to 42 (extremely severe). The participants responded by rating the concordance with each statement from 0 “*Did not apply to me at all*” to 3 “*Applied to me very much, or most of the time*”. The sub-scale scores for depression ($\alpha = .88$) with a range from normal = 0 to extreme severe = 28+, anxiety ($\alpha = .82$) with a range from normal = 0 to extreme severe = 20+ and stress ($\alpha = .90$), with a range from normal = 0 to extreme severe = 34+, that are calculated by summing the scores for the relevant items to the characteristic being measured (Julie D Henry & John R Crawford, 2005). As the original DASS has 42 questions, the sum of the DASS-21 is multiplied by 2 to ascertain the comparable scores.

Brief Symptom Inventory 18

The BSI-18 is a self-report scale which contains subscales on somatization, depression, and anxiety (Derogatis 2001). Participants were asked to rate a list of issues people can experience on a 5-point Likert scale ranging from 0 “None at all” to 4 “Extremely”. The BSI-18 is a reliable instrument for the assessment of psychological distress in both clinical and general populations with strong internal consistency and a the Cronbach’s alpha (α) of each sub-scale from the validated English version was as follows; somatization = .82, depression = .87, anxiety = .84 (Franke et al. 2017), and scores range from 0 to 24.

Five Facets Mindfulness Questionnaire 15

The FFMQ-15 is a 15-item self-report questionnaire which measures five different factors; 1) Observe: noticing experience that are both internal and external such as thoughts and emotions; 2) Describe: describing internal experiences; 3) Acting with awareness: focus on the present activity; 4) Non-judgment: not evaluating or judging the present experience; 5) Non-reaction: allowing thoughts and feelings to come without acting or reacting upon them (Baer et al. 2006)(Gu et al., 2016). The purpose of this scale is to obtain an understanding of an individual’s mindfulness related capacities. The participants answered the FFMQ by rating the concordance with each statement on a 5-point Likert-scale that ranges from 1 “never true” to 5 “very often or always true”. The sub-scale scores are obtained by adding the relevant items for each of the five facets. Facet scores range from 8–40, except for the non-reactivity facet, which ranges from 7–35. The original scale has shown good internal consistency, and the Cronbach’s alpha (α) of

each sub-scale was; non-reaction = .77, non-judgement = .78, describe = .83, observe = .69 and awareness = .70 (Baer et al., 2006).

Statistical analysis

The statistical analysis was conducted in IBM SPSS Statistics 24 ("IBM SPSS Statistics for Windows," 2016) using a mixed model ANOVA that included a within subject factor Session (two levels: baseline and post-session), a between subject factor Groups (two levels: ayahuasca or placebo), and their interaction. Pearson's correlations were carried out to investigate the association between the ratings of ego dissolution and altered states of consciousness during the session and changes in outcome measures over time relative to baseline. To be able to conduct correlational analyses on the relative change over time, change scores were calculated for the dependent variables by extracting the mean score of the pre-measure from the post-measure. Change scores were correlated with post-measures of ego dissolution (EDI) and of Altered states of consciousness (5D-ASC dimensions). The alpha criterion level of significant was set at $p = .05$.

Results

Participants

There was no statistical difference between demographics (age, origin, education, previous experience with ayahuasca and other psychedelics, alcohol and cigarette use, contemplative practice, mental health related disorder, and motivation) of participants in each group. Overall, 12 participants were male, and 18 were female, with a mean (SD) age of 40.18 (10.10). Most participants were from Europe (N=28), while the rest was either from North America (N=1) or Asia (N=1). Furthermore, 11 participants held a bachelor's degree while the rest held a high school diploma (N=10), a master's (N=2) or a PhD (N=2). All participants reported previous

experience with ayahuasca. Overall, the participants in the group had on average tried ayahuasca 23.7 times ($SD=15.58$). Additionally, most participants ($N=27$) had previous experience with other substances (e.g. THC, LSD, psilocybin). Fourteen participants reported that they use alcohol, while 11 participants reported that they smoke, and 20 participants reported having a contemplative practice (e.g. meditation, yoga, prayer). Most participants ($N=24$) reported that they had relatives suffering from a mental disorder, but only one participant reported that the relative had a confirmed diagnosis of a mental health related disorder and received treatment. Finally, the participants declared motivation to ingest ayahuasca during this school retreat, besides partaking in the training to become a facilitator for the company, included the following; understand myself ($N=25$), resolve problems ($N=19$), curiosity ($N=11$), other ($N=16$).

Single-blind guess

In the ayahuasca group, 8 out of 14 participants (57.1%) correctly guessed which condition they were assigned to, whereas the facilitators only guessed correctly in 5 out of 14 cases (38.5%). In the placebo group 11 participants out of 16 (68.7%) guessed correctly which condition they were assigned to and the facilitator guessed correctly in 14 out 16 cases (93.3%), see Table 1.

Subjective effects and MET

Mixed model ANOVA revealed significant main effects of Session on ratings of stress ($F_{1, 26} = 8.278$; $p = .008$, Cohen's $D = 0.54$), depression ($F_{1, 26} = 6.518$; $p = .017$, Cohen's $D = 0.66$) as assessed by the DASS-21, and on anxiety symptoms as assessed by BSI-18 ($F_{1, 26} = 5.125$; $p = .032$, Cohen's $D = 0.41$). This indicates that ratings of stress, depression and anxiety were lower after the ceremony as compared to baseline, independent of Treatment group. Furthermore, a significant interaction between Treatment and Session was observed for the measure of implicit arousal to negative stimuli ratings

on the MET ($F_{1, 16} = 5.111$; $p = .038$, Cohen's $d = 0.14$), indicating that ayahuasca increased emotional empathy to negative stimuli, and placebo did not. Mean (SE) affect ratings and implicit arousal levels in both Treatment groups are shown in Figure 1. None of the FFMQ measures were affected by Session or Treatment.

Figure 1. Mean ratings (SE) of stress (A) and depression (B), as assessed by DASS-21, as well as anxiety (C), as assessed by the BSI-18), and implicit arousal to negative stimuli (D), as assessed by MET. Statistical significance is indicated with *.

The psychedelic experience

There were no group differences between ratings of the total ego dissolution ratings. Post-session EDI ratings varied between 0 % (no dissolution) to 100

% (maximal dissolution). The overall mean (SD) rating of the experience of ego dissolution as assessed by the EDI was 32.39% (23.50) in the ayahuasca group and 30.66% (27.54) in the placebo group. Individual and mean ratings of EDI are given in Table 1.

Mean ratings on 5D-ASC dimensions varied between 10%-27% in the ayahuasca group, and between 6-23% in the placebo group. Furthermore, mean ratings on the 5D-ASC subscales varied between 11-34% in the ayahuasca group, and 4-21% in the placebo group. None of the 5D-ASC ratings significantly differed between groups. Mean ratings of 5D-ASC dimensions and subscales are given in Figure 2.

Figure 2. Mean ratings (SD) of the experience of altered states of consciousness as assessed by 5D-ASC (from 0-100%) sub-scales (right) and dimensions (left) per group (ayahuasca and placebo).

Correlational analysis

Ayahuasca group

There were no significant correlations between subjective ratings of ego dissolution, and 5D-ASC ratings, with change scores on the objective measure of emotional empathy (implicit arousal to negative stimuli) and subjective ratings of depression, stress and anxiety.

Placebo group

There were no significant correlations between subjective ratings of the experience with ego dissolution and change scores of depression, stress and anxiety. A negative correlation between change scores of depression and auditory alterations, as assessed with the 5D-ASC dimensions, ($r = -.680$, $p = .007$). Furthermore, there was a negative correlation between change scores of stress and oceanic boundlessness ($r = -.579$, $p = .030$), anxious ego dissolution ($r = -.683$, $p = .007$), visual restructuralization ($r = -.551$, $p = .041$), auditory alterations ($r = -.918$, $p = .000$). Moreover, there was a negative correlation between anxiety, and oceanic boundlessness ($r = -.779$, $p = .001$, $N = 14$), anxious ego dissolution ($r = -.704$, $p = .005$, $n = 14$), auditory alterations ($r = -.556$, $p = .039$, $N = 14$), and reduction of vigilance ($r = -.561$, $p = .037$).

5D-subscales revealed a negative correlation between changes in depression (as assessed by the DASS-21) and impaired control cognition ($r = -.701$, $p = .005$) and between stress and impaired control cognition ($r = -.704$, $p = .005$). Additionally, there was a negative correlation between change scores of anxiety and experience of unity ($r = -.763$, $p = .001$), disembodiment ($r = -.599$,

$p = .024$), impaired control and cognition ($r = -.654$, $p = .011$), anxiety ($r = -.710$, $p = .004$), and changed meaning and perception ($r = -.732$, $p = .003$).

Discussion

The primary objective of the present study was to assess the separate contribution of ayahuasca (matter), and non-pharmacological factors, such as set (mind), on perceived subjective effects in participants of neo-shamanic, naturalistic ayahuasca ceremonies, and either received ayahuasca or placebo. In order to monitor whether subjects and ceremony facilitators were blind to the treatment randomization we asked them to guess the treatment after the experience. Overall, 57.1% and 68.7% of the participants in the ayahuasca and placebo group respectively, correctly guessed to which condition they were assigned. Facilitators guessed correctly in 38,5% and 93,3% of cases in the ayahuasca and placebo group respectively. This suggests that only a moderate number of participants, just above chance level, correctly guessed which condition they had been assigned to. Guesses of facilitators was below chance level in the ayahuasca group, but fairly accurate in the placebo group. Overall, these data indicate that it was not overly evident for study participants whether they were assigned to ayahuasca or placebo.

Distinguishing ayahuasca from placebo may have been particularly difficult since mean ratings of ego dissolution and psychedelic experience were similar in both groups. The mean subjective ratings of the experience of ego dissolution, was relatively low in the ayahuasca group as well as in the placebo group (32.4%, and 30.7%, respectively). Moreover, subjective ratings of altered states of consciousness as assessed by the 5D-ASC dimensions and sub-scales were also relatively low in both groups. This is in contrast to previous research on ayahuasca which demonstrated that

ingestion of the brew in a naturalistic setting induced a moderate experience of ego dissolution (Uthaug et al., 2018). A major explanation for this difference is that the dose of alkaloids (DMT, harmine, harmaline) was lower in the present study than that which was reported in a former study by the first author (Uthaug et al., 2018). Another possible explanation for the low ratings of the psychedelic experience could be that the participants knew there was a possibility for them to receive placebo, and thus their expectancy may be lowered because of the “risk of getting a placebo”, resulting in lowered ratings of the psychedelic experience (Colloca, 2014). Together, ratings of the psychedelic experience in the present study indicate that participants in both groups experienced altered states of consciousness during the ceremony, and that the strength of the experience was mild to moderate.

Subjective ratings of symptoms of depression, stress and anxiety were significantly less after the ceremony as compared to baseline, across both treatment groups. These positive changes in mental health did not significantly differ between participants in the ayahuasca and placebo group which suggests a primary, contributory role for non-pharmacological factors. Non-pharmacological factors such as expectation, preparation and intention (mind-set can shape the response to hallucinogens (Hartogsohn, 2014, 2017). Expectations are built from previous experience with the substance, and on general knowledge of its effects on affect and well-being (Haijen et al., 2018; Laska & Sunshine, 1973; Metzner, Litwin, & Weil, 1965). Participants in the study had extensive previous experiences with ayahuasca and may have developed personal sets of expectation and intentions. Repeated participation in ayahuasca ceremonies might stimulate learned associations with enhanced well-being, that are memorized and experienced even when assigned to a placebo group. Similar mechanism have been proposed to explain the strength

placebo effects in a wide range of medical patient groups (Colloca, 2014; Haour, 2005).

Additionally, it is known that expectancies are modelled through verbal suggestions and instructions (Bartels et al., 2014; Kirsch, 1985, 2004; Martin-Pichora, Mankovsky-Arnold, & Katz, 2011; Van Oorsouw & Merckelbach, 2007). For example, in a study by Van Oorsouw and Merckelbach (2007), it was investigated whether positive ("memory-enhancing") and negative ("memory-impairing") placebos may enhance and undermine, respectively, memory of a film fragment. Specifically, it was found that the positive placebo group, memory was better than that of participants who received negative placebos or control participants. Participants in the negative placebo group made more distortion errors than participants in the positive placebo or control group. In the context of the present study, one might speculate that (repeated) suggestion of the positive mental health effects of ayahuasca, by either peers, or facilitator(s) throughout the ceremony, may have stimulated some of the positive changes in mental health parameters that were observed after the ceremony.

Likewise, the setting of the ceremony, such as the physical, social, and cultural environment may alter the mental experience of a pharmacological agent (Hartogsohn, 2014). Ceremonies included in the present study were always conducted in a supportive group environment which may very well have impacted the participants' overall experience in a positive way, and may have contributed to the improvements in affect (Adamson & Metzner, 1988). Additionally, previous research has demonstrated that psychedelics, like LSD, can enhance suggestibility by temporarily suspending the drive to maintain control of one's mind and environment (R. Carhart-Harris et al.,

2015). This finding suggests that individuals can become unusually open and receptive to social group dynamics that take place during an ayahuasca ceremony and right after during integration sessions to support mental healing (Baker, 2005).

The present study however also provided evidence for a pharmacological induced change in mental state. Participants that were assigned to the ayahuasca group displayed a significant increase in arousal to negative emotions that was not observed in the placebo group. This increase in empathic emotion was assessed with the MET which is an objective, computerized assessment that might be less susceptible to the influence of non-pharmacological factors. Similar findings have been reported in naturalistic studies on other psychedelics such as psilocybin, albeit in the absence of a placebo control group (Mason et al., 2019a). Overall, the present finding is important as low level empathy has been found in stress-related psychopathologies like depression, anxiety disorders, and post-traumatic stress disorder (PTSD) (S. R. Chamberlain, N. A. Fineberg, A. D. Blackwell, T. W. Robbins, & B. J. Sahakian, 2006; A. M. Cusi, G. M. Macqueen, R. R. Spreng, & M. C. McKinnon, 2011; U. S. Donges et al., 2005; Lee & Orsillo, 2014; Morrison et al., 2016; G. Nietlisbach, Maercker, Rossler, & Haker, 2010; Palm & Follette, 2011; M. Parlar et al., 2014). Treatments that increase empathy may be very relevant for patients that suffer from mood disorders. Core features of mood disorders include repetitive and rigid patterns of negative and compulsive thoughts, together with social difficulties and impaired empathetic abilities (Aldao, Nolen-Hoeksema, & Schweizer, 2010; A. T. Beck, 1967; R. G. Dos Santos et al., 2016; Morrison et al., 2016; G. Nietlisbach & Maercker, 2009; Todd, Forstmann, Burgmer, Brooks, & Galinsky, 2015). The lack of empathy is particularly evident in depression

and has been suggested to contribute or underlie a wide range of symptoms of depression (A.M. Cusi et al., 2011; U. S. Donges et al., 2005).

A correlational analysis between measures of the psychedelics experience and subjective ratings of affect, demonstrated that ratings of altered states of consciousness were negatively related to changes in subjective rating of affect in the placebo group, but not the treatment group. This suggests that the magnitude of symptom reduction is related to the strength of the psychedelic experience. It is not entirely clear why that association was found in the placebo group only and not in the ayahuasca group. Previous studies in naturalistic settings have reported similar associations between strength of the psychedelic experience and the magnitude of subjective mental health changes following the use of ayahuasca (Uthaug et al., 2018) and 5-MeO-DMT (Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019). The fact that the magnitude of the psychedelic experience and sample sizes were relatively low in the present study may have been a complicating factor.

The present study has limitations. Participants were very experienced users of ayahuasca which makes it rather likely that expectancy effects contributed strongly to outcome measures in both groups. Expectancy effects may be much less in novel ayahuasca users, who therefore may be more susceptible to the pharmacological impacts of ayahuasca. Future studies should also investigate the impact of pharmacological and non-pharmacological factors on the ayahuasca experience of novel users. Another limitation is the limited sample size which restricts the generalizability of the data.

In sum, the current findings demonstrate that subjective improvements in mental health of participants in naturalistic ayahuasca ceremonies can be

driven by non-pharmacological factors such as expectations and intentions that define their mind-set. Yet, objective measures of empathy also revealed improvements that were solely observed after the pharmacological treatment with ayahuasca (matter). The present findings warrant further research into the non-pharmacological factors contributing to the mental health effects following ingestion of ayahuasca as well as other psychedelics ingested in a ritualistic (neo-shamanic) settings.

Chapter 4 - A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness related capacities, and a decrement of psychopathological symptoms

Uthaug, M. V., Lancelotta, R., van Oorsouw, K., Kuypers, K. P. C., Mason, N., Rak, J., ... & Páleníček, T. (2019). A single inhalation of vapor from dried toad secretion containing 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms. Psychopharmacology, 236(9), 2653-2666.

Abstract

Rationale: 5-methoxydimethyltryptamine (hereinafter referred to as 5-MeO-DMT) is a psychedelic substance found in the secretion from the parotid glands of the Bufo Alvarius toad. Inhalation of vapor from toad secretion containing 5-MeO-DMT has become popular in naturalistic settings as a treatment of mental health problems, or as a means for spiritual exploration. However, knowledge of the effects of 5-MeO-DMT in humans is limited.

Objectives: The first objective of this study was to assess sub-acute and long-term effects of inhaling vapor from dried toad secretion containing 5-MeO-DMT on affect and cognition. The second objective was to assess whether any changes was associated with the psychedelic experience.

Methods: Assessments at baseline, within 24 hours, and 4 weeks following intake were made in 42 individuals who inhaled vapor from dried toad secretion at several European locations.

Results: Relative to baseline, ratings of satisfaction with life and convergent thinking significantly increased right after intake and were maintained at follow-up 4 weeks later. Ratings of mindfulness also increased over time and reached statistical significance at 4 weeks. Ratings of depression, anxiety and stress decreased after the session, and reached significance at 4 weeks. Participants that experienced high levels of ego dissolution or oceanic boundlessness during the session displayed higher ratings of satisfaction with life and lower ratings of depression and stress.

Conclusion: A single inhalation of vapor from dried toad secretion containing 5-MeO-DMT produces sub-acute and long-term changes in affect and cognition in volunteers. These results warrant exploratory research into therapeutic applications of 5-MeO-DMT.

Introduction

5-methoxy-dimethyltryptamine (5-MeO-DMT) is a potent, fast-acting, psychedelic substance, which acts as a serotonin 5-HT-1-A/5-HT-2A/C receptor agonist (Krebs-Thomson et al., 2006; Ray, 2010; H. W. Shen et al., 2010). The psychedelic substance 5-MeO-DMT was initially isolated from the bark of the plant *Dictyoloma incanescens* (Pachter 1959), and has also been found in the milky-white secretion produced in the skin and the parotid glands of the Bufo Alvarius toad, also known by the scientific name *Incilius alvarius*, and more commonly referred to as the “Colorado river toad” or “Sonoran desert toad”. Besides 5-MeO-DMT, the secretion of Bufo Alvarius also contains 5-hydroxy-N,N-dimethyltryptamine, the closely related O-demethylated analog of 5-MeO-DMT, commonly known as bufotenine. Moreover, the toad secretion also contains several cardioactive agents like bufagins, various catecholamines such as epinephrine and norepinephrine, and non-cardioactive sterols such as cholesterol, provitamin D, gamma sitosterol and ergosterol (Chen and Kovaříková 1967). Since a toad yields about 0.25-.50 gram of dried secretion from a “milking session”, with a 5-MeO-DMT content of up to 15% (Erspamer et al., 1967), a single toad may generate 75 mg of 5-MeO-DMT in its secretion, that when smoked, is already psychoactive in humans at doses as low as 3-5 milligrams (Weil & Davis, 1994). Users have reported that the psychedelic effects of 5-MeO-DMT are more potent and more intense as compared to other psychedelics (Barsuglia, Davis, & Palmer, 2017b; Joseph Peter Barsuglia et al., 2018; Alan K Davis, Joseph P Barsuglia, Rafael Lancelotta, Robert M Grant, & Elise Renn, 2018b). A single inhalation of vaporized dried toad secretion produces a psychedelic experience within 15 seconds (Weil and Davis 1994), and may last up to 20-40 minutes (Ott 2001).

Some reports suggest that the secretion of the *Bufo Alvarius* toad may have been used historically by indigenous peoples in the southwestern territory of the USA and northern Mexico (Weil and Davis 1994). However, the purpose of these ancient practices has not been fully clarified, and evidence of use as a medicine is scarce. Therefore, it cannot be ruled out that the present use of toad secretion is of more recent origin.

A recent survey among users of 5-MeO-DMT (toad, synthetic or plant derived) indicated that most respondents used 5-MeO-DMT for spiritual exploration and reported mystical-type experiences of moderate-to-high intensity (Davis et al. 2018). Interestingly, those respondents who reported a psychiatric disorder mentioned that 5-MeO-DMT had helped them reduce their symptoms of anxiety, depression and post-traumatic stress, or to effectively deal with alcoholism and drug abuse (Alan K Davis et al., 2018b; A. K. Davis, So, Lancelotta, Barsuglia, & Griffiths, In Press). The potential mental health benefits of 5-MeO-DMT have not been studied in humans but might be similar to those that have been reported for ayahuasca, an Amazonian plant preparation that contains the closely-related psychedelic compound, N,N-dimethyltryptamine (DMT). The potential of ayahuasca to rapidly and persistently reduce symptoms of depression has been shown in a range of open-label studies (De Lima Osório et al. 2011; Sanches et al. 2016), and was recently confirmed in a randomized placebo-controlled clinical trial in patients suffering from treatment-resistant depression (Palhano-Fontes et al. 2018). Moreover, in vitro studies have recently provided evidence of anti-inflammatory, neuroregenerative and anti-addictive effects induced by 5-MeO-DMT (Dakic et al. 2017; Szabo et al. 2014). Overall, these findings support a potential role for 5-MeO-DMT as a therapeutic tool.

The present study was conducted to obtain initial data on the effects of 5-MeO-DMT on mental health related functions such as affect and cognition. We visited several locations in three European countries, where people would inhale vapor from dried toad secretion containing 5-MeO-DMT. Our primary objective was to assess whether inhaling the vapor produces any sub-acute and/or long-lasting improvements in measures of affect and cognition. We expected that symptoms of affect, such as depression, anxiety, stress and somatization reported by participants at baseline would be ameliorated by use of the vapor from dried toad secretion containing 5-MeO-DMT through means of inhalation, and that measures of, cognition, such as creative thinking and mindfulness related capacities, would improve. We also expected that such changes would persist over time and would still be measurable at 4 weeks after intake. As a secondary objective, we aimed to determine whether the sub-acute and long-term effects of inhaling the vapor from the 5-MeO-DMT-rich toad secretion mental health measures were related to certain aspects of the acute psychedelic state, such as ego dissolution and other subjective experiences that characterize the altered state of consciousness. The rationale for studying these associations is based on results reported in other studies, that have demonstrated a direct association between the beneficial effects of psychedelic tryptamines such as psilocybin (Garcia-Romeu et al. 2014; Roseman et al. 2017), the DMT-containing brew ayahuasca (Uthaug et al. 2018), and the ability of these drugs to induce mystical experiences and ego dissolution during the acute psychedelic phase.

Methods

Participants

We recruited our sample from three different countries in Europe (Czech Republic (N=25), Spain (N=10), and The Netherlands (N=7). In all three

locations, participants inhaled vapor from dried toad secretion containing 5-MeO-DMT. Participants were invited to enter the study on site. Overall, 75 participants agreed to participate in the study at baseline. Of those, 42 participants completed the test battery both before inhalation of the vapor from dried toad secretion containing 5-MeO-DMT (baseline), and within 24 hours, while only 24 completed the test battery at the third and final assessment 4 weeks after intake. Most participants were from Europe (N = 34 [81%]) while the rest of participants were from Asia (N = 2 [4.8%]), Australia (N = 2 [4.8%]), South America (N = 3 [7.1%]) and North America (N = 1 [2.4%]). Sixty percent of the sample were males, and 40% females. Mean age for the entire group was 38 years (SE= .80). Furthermore, their motivation to inhale vapor from dried toad secretion containing 5-MeO-DMT included increasing self-understanding (N = 18[42.9%]), solving personal problems (N = 5[11.9%]), the combination of both (N=1 [4.2%]) and other (N = 18 [42.9%]) reasons. A listing of these “*other*” motivations or reasons to inhale vapor from dried toad secretion containing 5-MeO-DMT is given in Table 1.

In regard to education level, most participants had completed high school (N=14 [33.3%]), a similar percentage had obtained a bachelor’s degree (N=13[31%]), a Master’s degree (N=11[26.2%]), and a lower proportion held a PhD (N=3[7.1%]). One participant had only completed elementary school (N=1[2.4%]). In total, 15 participants reported having had no previous experience with 5-MeO-DMT (whether this was toad, synthetic or plant was unspecified), while the majority (92.9 %) had experience with other psychedelics (e.g. LSD, Psilocybin etc.). In regards to mental health status as per self-reports, 32 (76.2 %) of the participants reported having no mental health disorder, 1 (2.4%) participant reported having depression, 1 (2.4%)

participant reported having a personality disorder, and 1 (2.4%) participant reporting having another mental health disorder not included on the administered list. Furthermore, 4 (9.4%) participants reported having anxiety, while 3 (7.1%) participants reported addiction. As per the nature of this observational study, participants which attended the session to inhale vapor from dried toad secretion containing 5-MeO-DMT were included in the study if they met the inclusion criteria (fluent in either Spanish, Czech, Dutch, or English, were over 18 years of age, and gave their written informed consent). The study was approved by the Ethical Review Committee for Psychology and Neuroscience (ERCPN), from Maastricht University, Maastricht, The Netherlands. Participation was voluntary and no incentives, monetary or otherwise, were offered in exchange for participation.

Setting

The sessions in the Czech Republic, and The Netherlands were conducted in the open, e.g., in a garden or in nature at a secluded location, whereas the session in Spain were held inside in a tipi or a rented house (as these sessions took place in winter).

The goal of the sessions was to relieve individuals from psychological and physiological issues, increase their well-being, and facilitate personal insights/personal healing. The facilitator was often assisted by another person, either with a background in coaching (i.e a person trained in supporting clients in achieving a specific goal through providing training and guidance), or a person with no (clinical) background in psychology or in psychedelic assisted therapy at all. These individuals (with or without background) had previous experience with 5-MeO-DMT (if this was toad, synthetic form or plant was not specified), and got involved at the sessions

out of personal interest. Participants on antidepressant medications or suffering from a mental health disorder such as schizophrenia, other psychoses, or cardiovascular illnesses were not allowed to participate in the sessions by the facilitator or the assistants. Yet it is important to highlight that many facilitators and their assistants lacked the clinical expertise to identify and exclude participants with contraindications.

The facilitator or their assistants provided participants with preparatory instructions prior to the session. Dietary preparation included not eating (red) meat and foods containing high levels of salt, or sugar. Additional advice was to avoid stress, calm the mind, increase mindful introspection, focus on their intention, and abstain from alcohol and other substances to reduce purging and other adverse events that might arise from combining the use of multiple medications (polypharmacy) with the inhalation of vapor from dried toad secretion containing 5-MeO-DMT. In each session, a facilitator administered the vapor by placing the dried toad secretion in a glass pipe, and then heating it up using a torch lighter. During administration of the vapor from dried toad secretion containing 5-MeO-DMT, the participant remained either standing or laying down on the ground or floor. The participant was instructed to inhale as much of the vapor as possible, and to hold it in for some seconds before exhaling. The assistants remained on site after the session to assist in the integration process of the experience if this was deemed necessary and/or requested by the participant. The facilitator would chant (*Cantos de Haaco Camaac*, healing shamanic chants), and/or play various musical instruments (rattle, drums, flute) during the experience of the participants.

Understanding myself (42.9%)

Solving problems (11,9%)

All the above (2.4%)

Other motivations (42.9%)

- *Seeking something that I don't know*
- *Heal myself, transform myself, accept myself, improve myself*
- *Awakening*
- *Medicine, new dose*
- *To get back to myself, to heal, to be on good terms with myself*
- *To get the experience I have been searching for*
- *To heal my soul*
- *To reconnect and professional potential in my work*
- *My own research*
- *To get closer to my core existence*
- *Grow spiritually*
- *To connect with all that is, transcendence, downloading universal knowledge and understanding of self*
- *I want to learn how to support others*
- *I want to love myself more. Understand the purpose of my life, my mission.*
- *To reconnect*
- *Whatever the medicine wants to show me in this moment.*
- *Information for me and for the outside. New neuronal connections*

Table 1. Listings of motivations for participants for inhaling vapor from dried toad secretion containing 5-MeO-DMT).

Study procedure

The nature of the study was essentially observational and involved three consecutive assessments: a baseline assessment prior to inhalation of vapor from dried toad secretion containing 5-MeO-DMT, a second assessment conducted within 24h post the session, and a follow-up assessment at 4 weeks after. Individuals who were at the location to inhale the vapor from dried toad secretion containing 5-MeO-DMT received a detailed explanation of the research aims and were invited to sign the informed consent in order to participate in the study. They completed a 30-minute test battery consisting of questionnaires and a psychometric test prior to the session that were used as baseline measures. The test battery was administered again on-site after the acute effects of the vapor from dried toad secretion containing 5-MeO-DMT had disappeared, or within the following 24-hours through an online survey created in Qualtrics. The follow-up assessment at 4 weeks after intake was administered online, also through Qualtrics.

Samples

It is worth noting that none of the session facilitators weighed the dose of dried toad secretion that they administered in the glass pipe, but instead relied on visual inspection when preparing the individual dosages. We therefore do not know the actual doses of dried toad secretion that were given during sessions to each participant. Some facilitators reported to administered around 20-30 mg of dried toad secretion, while others reported to administer up to 100 mg to 120 mg. We did however obtain five samples of the dried *Bufo Alvarius* toad secretion to identify the compounds that it contained. These samples were analyzed for the presence of the following tryptamines;

N-Methyltryptamine (NMT), *N,N*-Dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), 5-hydroxy-dimethyltryptamine (bufotenin, 5-HO-DMT), *N,N*-diethyltryptamine (DET), 5-Hydroxy-*N*-methyltryptamine (N-Methylserotonin, NMe-5HT) and steroid lactones (Bufogenin, Bufotalidin), tryptophols (5-Methoxytryptophol, 5-MeO-tryptophol), 5-Hydroxytryptophol (5-HO-tryptophol), and 5-Methoxy-3-indoleacetic acid (5-MIAA).

The availability of different compounds in the toad secretion in milligrams (in case of tryptamines calculated to weight of freebase) per 1 gram of dried toad secretion in each of these samples is given in Table 2.

Sample	5-MeO-DMT	5-HO-DMT	DMT	NMT	DET	NMe-5HT	Bufogenin	Bufotalidin	5-MeO-Tryptophol	5-HO-Tryptophol	5-MIAA
[mg/g]								[µg / g]			
1	265.9	0.642	0.016	N.D.	<LOQ	0.028	<LOQ	<LOQ	0.696	N.D.	N.D.
2	203.6	0.600	0.032	N.D.	<LOQ	0.014	0.005	<LOQ	2.357	N.D.	N.D.
3	274.3	1.179	0.029	N.D.	<LOQ	0.050	0.013	<LOQ	1.307	N.D.	N.D.
4	283.3	3.530	0.022	N.D.	<LOQ	0.171	0.011	<LOQ	0.997	N.D.	N.D.
5	307.3	1.436	0.041	N.D.	0.415	0.064	0.008	<LOQ	3.053	N.D.	N.D.

Table 2. Overview of compound concentrations in milligrams or micrograms per 1 gram of secretion) in samples of dried secretion from the *Bufo Alvarius* toad. ND = not determined. <LOQ = under limit of quantification.

Test battery

The test battery consisted of six questionnaires; The Ego Dissolution Inventory (EDI), the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), the Satisfaction with Life Scale (SWL), the Depression, Anxiety, Stress Scale-21 (DASS-21), the Five Facets Mindfulness

Questionnaire (FFMQ-15), the Brief Symptom Inventory-18 (BSI-18). The BSI instrument overlaps with the DASS-21 but offers the additional sub-measure of somatization, which is why it was selected. In addition, a computerized version of the Picture Concept Test (PCT) was administered. It is worth noting that the EDI and 5D-ASC were administered only once and had to be filled out within 24 hours after the session to measure the intensity of the acute effects of the inhalation of vapor from dried toad secretion containing 5-MeO-DMT.

Ego Dissolution Inventory

EDI is an 8-item self-report scale that assesses the participant's experience of ego dissolution (Nour et al. 2016). The participants answered the scale with making a mark on a line from either "*No, not more than usually*" (0%) to "*Yes I experience this completely/entirely*" (100 %). The EDI is scored by calculating the mean percentage of all the 8 items. The higher the total score, the stronger the experience of ego dissolution. The internal consistency of the EDI is excellent with a Cronbach's alpha (α) of .93. In this study, the original English version of the EDI was used or non-validated, non-formal, translations in Czech, Spanish, and Dutch.

5-Dimensional Altered States of Consciousness Rating Scale

The 5D-ASC is a 94-item self-report scale that assesses the participants' alterations from normal waking consciousness (Studerus et al. 2010). The participant is asked to make a vertical mark on the 10 cm line below each statement to rate to what extent the statements applied to their experience in retrospect from "*No, not more than usually*" to "*Yes, more than usually*". The 5D-ASC contains the 11 subscales *experience of unity, spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition,*

anxiety, complex imagery, elementary imagery, audio-visual synesthesia and changed meaning of percepts. In addition, we compiled the key dimensions of “*oceanic boundlessness*” which is one of the five key dimensions of the scale with a Cronbach’s alpha (α) of .95 that identifies mystical-type experiences, and has been compared with the “heaven” aspect of Huxley’s mescaline account (Adolf Dittrich, 1998). Information about the four remaining dimensions *anxious ego dissociation, visual restructuralization, auditory alterations*, and finally *reduction of vigilance* can be found in the referenced article. In this study, the original English version of the 5D-ASC was used in addition to non-validated, non-formal translation in Czech, Spanish, and Dutch made by our team. Internal consistencies across subscales in the Dutch, Czech and Spanish population were .94, .83 and .94 respectively.

The following questionnaires and computerized test were distributed at baseline, within 24 hours and at the 4-week follow up.

Satisfaction with Life Scale

SWL is a 5-item self-report scale (Diener et al. 1985). The purpose of the scale is to assess someone’s subjective satisfaction with life. The items are answered on a Likert-scale ranging from 1 “*Strongly disagree*” to 7 “*Strongly agree*”. The total score is obtained by summarizing points on each item. Scores can range from 5 to 35 points, indicating a greater life satisfaction with higher scores. The scale has good psychometric properties. The original SWL in English has a Cronbach’s alpha (α) of .87 and was used in addition to a validated translation in Spanish with a Cronbach’s alpha (α) of .88, and a validated translation in Dutch with a Cronbach’s alpha (α) of .85 (Beuningen

2012; Vazquez et al. 2013). Finally, a non-validated translation of the questionnaire in Czech was obtained and used by the research team.

Depression, Anxiety, and Stress Scale 21

DASS-21 is the shorter version of the original self-report questionnaire Depression, Anxiety, Stress Scale 42 (Henry and Crawford 2005). The purpose of this scale is to measure constructs of depression, anxiety, and stress. The participants responded by rating the concordance with each statement from 0 “*Did not apply to me at all*” to 3 “*Applied to me very much, or most of the time*”. The sub-scale scores for depression, anxiety and stress are calculated by summing the scores for the relevant items. The original DASS has 42 questions. To have the comparable scores, the sum of the DASS-21 is multiplied by 2. The total scale of the DASS-21 had a Cronbach’s alpha (α) of .93. In this study, the English version of the scale was used or validated translations into Spanish, Czech and Dutch. The Cronbach’s alpha (α) of the Spanish, Dutch and Czech versions are .96, .95, and .87, respectively (Daza et al. 2002; Kučera et al. 2018; Wardenaar et al. 2017).

Five Facets Mindfulness Questionnaire-15

This measure is a short form of the 39-item FFMQ (Baer et al. 2006). The FFMQ-15 is a self-report questionnaire which measures five different factors; 1) Observe: noticing experience that are both internal and external such as thoughts and emotions; 2) Describe: describing internal experiences; 3) Acting with awareness: focus on the present activity; 4) Non-judgment: not evaluating or judging the present experience; 5) Non-reaction: allowing thoughts and feelings to come without acting or reacting upon them (Gu et al., 2016). The purpose of this scale is to obtain an understanding of an individual’s mindfulness related capacities. The participants answered the

FFMQ-15 by rating the concordance with each statement on a 5-point Likert-scale that ranges from 1 “*never true*” to 5 “*very often or always true*”. The total FFMQ-15 score is obtained by adding all the sub-scale scores. The original scale has shown good internal consistency, and the Cronbach’s alpha (α) of each sub-scale was; non-reaction = .77, non-judgement = .78, describe = .83, observe = .69 and awareness = .70 (Baer et al., 2006). The original English version of the FFMQ-15 was used in addition to non-validated, non-formal translations in Spanish, Dutch, and Czech. Internal consistencies across sub-scales in the Dutch, Czech and Spanish population were .66, .63 and .61 respectively.

Brief Symptom Inventory 18

The Brief Symptom Inventory 18 (BSI-18) is a self-report scale which contains subscales on somatization, depression, and anxiety (Derogatis 2001). Participants were asked to rate a list of issues people can experience on a 5-point Likert scale ranging from 0 “*None at all*” to 4 “*Extremely*”. The BSI-18 is a reliable instrument for the assessment of psychological distress in both clinical and general populations with strong internal consistency and a the Cronbach’s alpha (α) of each sub-scale from the validated English version was as follows; somatization = .82, depression = .87, anxiety = .84 (Franke et al. 2017). In this study, the original English version of the BSI-18 or non-validated, non-formal translations in Spanish, Dutch, and Czech was used. Internal consistencies across sub-scales in the Dutch, Czech and Spanish population were .85, .85 and .83 respectively.

Picture concept Task (PCT)

A creativity task with non-verbal stimuli was used, i.e. the PCT (Kuypers et al. 2016). The PCT was composed of stimuli from the Wechsler Preschool

and Primary Scale of Intelligence and the Wechsler Intelligence Scale for Children. Each stimulus contains between 4 and 12 color pictures shown in two or three rows. The participants are instructed to find an association between one of the pictures of each row. They are asked to provide the correct solution as there is only one correct answer. The correct answers are taken as the dependent measure of convergent thinking. To assess divergent thinking, participants were asked to provide as many alternative associations as possible by sticking to the rule; 1 item per row. This is the regular instruction included in measures of divergent thinking, and it is used to calculate several parameters, i.e., originality, fluency, and the ratio of both, which reflect quantity and quality of divergent thinking. Fluency is defined as the number of alternative associations. Originality is calculated by evaluating the originality of the alternative association relative to those provided by all other participants in a session. Alternative answers that were uniquely reported by a single participant received an originality score of 2. Answers that were shared with a single participant were valued as 1, and answers that were shared by 3 or more participants were rated as zero. Mean originality (creativity) scores and ratio originality scores, weighed for fluency (originality/fluency) were used as measures of divergent thinking. Three parallel versions of the PCT were used at baseline and the two follow-up measures after the session to avoid learning effects. Each parallel version consisting of 17 stimuli were shown, and participants had 30 seconds per stimulus.

Statistical analysis

A repeated measures ANOVA using a linear mixed model analysis with Session (3 levels) as the within subject factor and Country (3 levels) as

between group factor was conducted. Fixed main effects included Session, Country, and Session x Country, using the maximum likelihood method. Covariance structure was chosen according to best fit and included compound symmetry heterogeneous (CSH) as well as autoregressive (AR1) structures. Significant main effects of Session and Session x Country were followed by separate contrasts between baseline and follow-up sessions with Bonferroni adjustments for multiple comparisons. The alpha level of significance was set at 0.05. Pearson's correlations were carried out to investigate association between the level of ego dissolution and the experience of altered states of consciousness during the acute effects induced by inhalation of the vapor from dried toad secretion containing 5-MeO-DMT and changes in outcome measures. *Hedges g* was calculated to estimate effect sizes of significant mental health changes between sessions. The data was analyzed with the Statistical Package for the Social Sciences (SPSS).

Results

Overall, 75 participants agreed to participate in the study at baseline. Of those, 42 participants completed the test battery both before inhalation of the vapor from dried toad secretion containing 5-MeO-DMT (baseline), and within 24 hours, while only 24 completed the test battery at the third and final assessment 4 weeks after intake.

Psychedelic experience

EDI

Mean (SE) ego dissolution rating was 74.24 (3.99). Overall, total EDI rating varied between 0 (no dissolution) and 100 (maximal dissolution). About 20% of the sample rated their level of ego-dissolution in the lower range between 0-60 on the EDI scale. The remainder of the sample achieved high levels of

ego dissolution that ranged from 60-100 on the EDI scale. The distribution of EDI ratings is shown in Figure 1.

Figure 1. Mean ratings (range 0-100%) of the psychedelic experience as assessed with the 5D-ASC subscales after inhalation of vapor from dried toad secretion containing 5-MeO-DMT as well as frequency distributions of ego dissolution and oceanic boundlessness ratings (lower panels).

5D-ASC

Mean rating of the psychedelic experience induced after inhalation of the vapor from dried toad secretion containing 5-MeO-DMT on the 11 subscales of the 5D-ASC is shown in Figure 1. Rating of blissful state, spiritual experience and experience of unity are top three rated sub-scales. These

subscales are also important contributors to the key-dimension oceanic boundlessness. The mean (SE) rating of oceanic boundlessness was 65.8 % (3.35). About 30% of the sample rated their level of oceanic boundlessness in the lower range between 0-60%. The remainder of the sample achieved high levels of oceanic boundlessness that ranged from 60-100% on the 5D-ASC scale. A frequency distribution of rating of oceanic boundlessness is shown in Figure 1.

Affect and cognition

SWL

Mixed model analyses revealed a main effect of Session ($F_{2,44.12} = 5.941$; $p = .005$). Contrasts showed that satisfaction with life significantly increased within 24 hours following the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT ($p = .022$; Hedges $g = 0.29$) and persisted 4 weeks later ($p = .012$; Hedges $g = 0.41$), as compared to baseline. Mean (SE) satisfaction with life before and after inhalation of the vapor is shown in Figure 2.

DASS-21

Mixed model analysis revealed main effects of Session on depression ($F_{2,55.943} = 4.348$; $p = .018$), anxiety ($F_{2,55.033} = 8.875$; $p < .001$) and stress ($F_{2,51.874} = 6.225$; $p = .004$), the three sub-scales of the DASS-21. Separate contrast revealed that subjective ratings of depression, anxiety, and stress decreased within 24 hours following the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT, but failed to reach significance until 4 weeks later ($p = .015$, Hedges $g = 0.79$; $p < .001$, Hedges $g = 0.69$; $p = .003$, Hedges $g = 0.66$ respectively). See Figure 3.

Figure 2 Mean (SE) satisfaction with life before and after inhalation of vapor from dried toad secretion containing 5-MeO-DMT (* = $p < .05$).

Figure 3. Mean (SE) correct responses (PCT), subjective ratings of mindfulness (FFMQ-15) depression, anxiety (DASS-21 and BSI-18), stress (DASS-21) and somatization (BSI-18) as a function of time after inhalation of vapor from dried toad secretion containing 5-MeO-DMT (* = $p < .05$).

FFMQ-15

Main effects of Session reached significance on two mindfulness parameters: i.e. non-judgement ($F_{2,49.299} = 5.27$; $p = .008$), and awareness ($F_{2, 47.42} = 3.28$; $p = .046$). Separate contrasts revealed improvements in non-judgement ($p = .009$; Hedges $g = 0.64$) and awareness ($p = .042$; Hedges $g = 0.12$) 4 weeks after the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT as compared to baseline. Sub-acute assessments of mindfulness

however did not significantly differ from baseline. See Figure 3. Furthermore, there were no significant differences between Session or Countries for the other FFMQ parameters, and interactions between Session and Country only reached significance on awareness ($F_{4,47.54} = 4.63$; $p = .003$). The interactions suggested that changes in awareness were higher in the Dutch and Spanish sample.

BSI-18

Mixed model analyses revealed a main effect of Session on depression ($F_{2,53.088} = 4.014$; $p = .024$), anxiety ($F_{2,46.778} = 5.020$; $p = .011$) and somatization ($F_{2,60.811} = 4.640$; $p = .013$). In addition, the analysis showed a main effect of Country for somatization ($F_{2,37.134} = 3.909$; $p = .029$). Separate contrasts revealed that subjective ratings of depression, anxiety, and somatization decreased within 24 hours of the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT, but failed to reach significance until 4 weeks later ($p = .023$, Hedges $g = 0.65$; $p = .009$, Hedges $g = 0.81$; $p = .011$, Hedges $g = 0.85$, respectively). See Figure 3. Furthermore, the changes in subjective ratings of somatizations were significantly higher in the Czech sample ($M = 2.41$, $SE = .33$) as compared to the Spanish sample ($M = .73$, $SE = .50$; $p = .025$), but not the Dutch sample. There was no interaction between Session and Country.

Picture Concept Test

The mixed model analysis revealed a significant main effect of Session ($F_{2, 31.609} = 5.34$; $p = .010$) and Country ($F_{2, 31.76} = 4.50$; $p = .019$) on convergent thinking. Separate contrasts revealed that the number of correct solutions increased significantly after the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT sub-acutely ($p = .021$; Hedges $g = 0.66$), and

4 weeks later ($p=.002$; Hedges $g=1.32$), as compared to baseline. See Figure 3. The mean (SE) convergent thinking scores were significantly higher ($p=.003$) in the Dutch 12.6 (0.5); and Czech sample 11.1 (0.6) as compared to the Spanish sample 9.4 (.7). There was no interaction between Session and Country. Finally, none of the divergent thinking parameters were affected by any of the main factors or their interaction.

Correlations

EDI

Sub-acutely following the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT, EDI scores were positively correlated with changes in satisfaction with life as measured by the SWL ($r = .357$, $p=.026$), negatively correlated with DASS-21 ratings of stress ($r=-.46$; $p=.003$) depression as measured by BSI-18 ($r = -.378$, $p=.016$) and convergent thinking as assessed with the PCT ($r=-.374$; $p=.046$). EDI did not correlate with any changes measured at 4 weeks. See Figure 4.

5D-ASC

Ratings of oceanic boundless were positively correlated to rating of SWL ($r=.43$, $p=.007$) and negatively correlated with scores of convergent thinking ($r = -.37$; $p=.046$) during the day following the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT. There were no correlations between ratings of oceanic boundlessness and rating of affect or cognitive measures at 4 weeks after the session.

Figure 4. Pearson correlations between satisfaction with life and ego dissolution / oceanic boundlessness (upper panel), between correct responses in the PCT and ego dissolution/ oceanic boundlessness (middle panel) and between ego dissolution and stress and depression ratings (lower panel) on the day after inhalation of vapor from dried toad secretion containing 5-MeO-DMT).

Discussion

The primary aim of the present study was to assess sub-acute, and long-term impact of the inhalation of vapor from dried toad secretion containing 5-MeO-DMT from the *Bufo Alvarius* toad on psychological affect and cognition. A total of 42 participants completed (parts of) the test battery at baseline and after the session, while 24 participants completed the test battery 4 weeks after intake. Relative to baseline, ratings on satisfaction with life and convergent thinking significantly increased right after and over 4 subsequent weeks. Likewise, subjective ratings of non-judgement and awareness also increased over time and reached significance at 4 weeks. Ratings of depression, anxiety and stress as assessed with DASS-21 or BSI-18 questionnaires decreased on the day after the session and reached significance at 4 weeks. Ratings of depression, stress and convergent thinking on the day after the session were negatively correlated with levels of ego dissolution or oceanic boundlessness that were rated after the session. Scores on satisfaction with life the day after the session were positively correlated with scores on ego dissolution and oceanic boundlessness.

Inhalation of the vapor from dried toad secretion containing 5-MeO-DMT produced sub-acute, and long-term improvements in subjective ratings of satisfaction with life, depression, anxiety, and stress. Relative to baseline, ratings of satisfaction with life significantly increased between 7 and 11% immediately after the session as well as 4 weeks after. Reductions in DASS ratings of depression (18%), anxiety (39%) and stress (27%) were evident right after the session and kept decreasing to 68%, 56% and 48% respectively after 4 weeks, at which point the decrements reached statistical significance. BSI-18 ratings of depression, anxiety and somatization indicated a similar pattern of improvement. Overall, this suggests that a single dose of vapor from

dried toad secretion containing 5-MeO-DMT can bring about changes in affect and cognition that last for a prolonged period of time. Similar findings have been reported for 5-MeO-DMT and other related tryptamines. For example, in a recent survey, the use of 5-MeO-DMT in a naturalistic setting was associated with unintended improvement in depression and anxiety (A. K. Davis et al., In Press). Additionally, consumers of ayahuasca, a brew containing N,N-dimethyltryptamine (DMT) displayed significant reductions in ratings of depression and stress that persisted for 4 weeks after intake (Uthaug et al, 2018). Likewise, high-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life in cancer patients (Griffiths et al. 2016). The authors reported that at the 6-month follow-up, these changes were maintained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety (Griffiths et al. 2016).

Notably, increased neurogenesis has been suggested as a central mechanism to underlie instant and long-term antidepressant properties of psychedelic compounds such as ketamine (Duman and Aghajanian 2012; Ma et al. 2017) and psilocybin (Catlow et al. 2013; Idell et al. 2017). Neurogenesis and synaptic plasticity may play a crucial role in how neural circuits regulate their excitability and connectivity and may link the neurobiology of depression to the therapeutic effects of glutamatergic drugs such as ketamine (Abdallah et al. 2015). In that respect, it is of interest that changes in glutamate transmission following ayahuasca use have been associated with improvements in certain aspect of mindfulness as well (Sampedro et al. 2017). Alternatively, it has been proposed that therapeutic improvements in affect following the use of psychedelics might be mediated through sigma-1

receptor (S1R). The endogenous ligands for the S1R include neurosteroids and natural tryptamines, such DMT and 5-MeO-DMT. Research suggests that both DMT, and 5-MeO-DMT modulate innate and adaptive inflammatory responses through the sigma-1 receptor of dendritic cells (Szabo et al. 2014), which in turn might improve the etiology and symptomatology of neuropsychiatric diseases, such as depression.

Inhalation of vapor from dried toad secretion containing 5-MeO-DMT increased convergent thinking as assessed with the Picture Concept Task by 20 and 37% within 24-hours, and 4 weeks after the session. The PCT task has previously been used in two observational ayahuasca studies to show that the brew increases divergent performance during the acute psychedelic state (Kuypers et al. 2016), but improves convergent thinking up until 4 weeks after the psychedelic experience (Uthaug et al, 2018). Likewise, the present data also suggests that the main impact of vapor from dried toad secretion containing 5-MeO-DMT on creativity is to improve convergent thinking following the psychedelic experience. However, in the present study, convergent thinking was also negatively correlated to subjective ratings of ego dissolution and oceanic boundlessness on the day after the session after the session. This suggests that convergent thinking was poor in participants that reported a strong psychedelic experience and that the overall increase in convergent thinking relative to baseline may not be related to inhaling vapor but to another factor. For example, it cannot be overlooked that improvements in convergent thinking performance resulted from practice or learning effects that can arise from repeated performance of the same task over time. We attempted to minimize learning effects by administering parallel versions of the PCT at each time point, but the present study lacks a proper control group to evaluate the effectiveness of this precautionary measure. Alternatively, it

can also not be overlooked that the overall improvement in convergent thinking after the session relates to improvements in mindfulness capabilities, such as acting with awareness, that contribute to optimization of cognitive functioning (Lebudaa and Karwowskia 2015). Long-term increases in convergent thinking may therefore coincide with improvements in mindfulness that were observed in the present sample of people inhaling vapor from dried toad secretion containing 5-MeO-DMT. In fact, inhalation of the vapor induced long-term improvements in two mindfulness parameters (e.g. non-judgement and awareness) as measured by the FFMQ-15. Similar findings have been reported in an observational study that compared aspects of mindfulness before, and 24 hours after an ayahuasca session using the long version of the FFMQ questionnaire (Soler et al. 2016).

Moreover, most participants had a strong psychedelic experience as measured by the EDI and 5D-ASC and scored high on ratings of ego dissolution, as well as on the composite factor oceanic boundlessness. This is in line with previous findings about 5-MeO-DMT's ability to induce strong mystical experiences (Joseph Peter Barsuglia et al., 2018). Additionally, close inspection of the frequency distribution of ratings of ego dissolution and oceanic boundlessness demonstrated that 20-30% of the participants of the present study only had a low to medium psychedelic experience. This variability in psychedelic experience may have been caused by differences in doses administered at ceremonies, inhalation techniques, and the actual concentration of 5-MeO-DMT in the secretion from the *Bufo Alvarius* toad used by different facilitators. Analysis of the five samples of dried secretion from the *Bufo Alvarius* toad revealed that about 25-30% of the dried secretion consisted of the primary component 5-MeO-DMT. Samples also presented (very) low amounts of additional tryptamines such as bufotenine (0.08 -

0.18%), DMT and N-methylserotonin (0.01-0.03%). Differences in tryptamine concentration observed in the dried toad secretion samples might very well affect the strength of the psychedelic experience, particularly when facilitators offer doses that span a wide range (i.e. 30-120mg) as during sessions in the present study. Participants that inhaled vapor from a 30 mg dose of dried toad secretion may have received about 7.5-9mg of 5-MeO-DMT whereas those that received a 120mg dose of dried toad secretion may have inhaled up to 30-36 mg of 5-MeO-DMT. However, these estimates could also be lower as drug delivery may not have been complete due to individual differences in inhalation techniques, drug metabolism and compound ratio following heating or when doses were only partially inhaled (Evans & Relling, 1999; Hadidi, Güzey, & Idle, 1999; H. W. Shen et al., 2010; Yu et al., 2003). Nevertheless, it has become clear from the visits to the session(s) where vapor from dried toad secretion containing 5-MeO-DMT was administered, that dose(s) are not standardized and vary between facilitators. This is likely the one of the main reasons why the psychedelic experience of ego dissolution and oceanic boundlessness differed between the participants.

It could be argued that the changes in affect and cognition that were observed in the present study are not related to a pharmacological effect from the inhalation of vapor from dried toad secretion containing 5-MeO-DMT, but rather due to uncontrolled confounders such as expectations of participants prior to, and after the session. It is conceivable that participants were psychologically distressed in anticipation of the session, which would explain why subjective stress as rated with the BSI-18 and DASS-21 were higher at baseline, prior to the session. Though a contributing role of expectation cannot be completely ruled out, there is also good evidence to suggest that

changes in affect and cognition observed in the present study were related to the actual psychedelic experience. Correlational analysis demonstrated that ratings of satisfaction with life were positively correlated to levels of ego dissolution and oceanic boundlessness, whereas ratings of stress and depression were negatively correlated to the level of ego dissolution. This indicates that the magnitude of mental health changes that were observed after the session were directly associated with the strength of the actual psychedelic experience caused by inhalation of the vapor from dried toad secretion containing 5-MeO-DMT. This finding is in line with previous studies on psychedelics such as psilocybin and ayahuasca that have shown that stronger psychedelic experiences are associated with larger changes in therapeutic outcome measures (Bogenschutz et al. 2015; Griffiths et al. 2016; Roseman et al. 2017; Ross et al. 2016; Uthaug et al. 2018).

Several limitations of the present study should be taken into account, the main one being the lack of a proper control group. Thus, the present findings can therefore only be taken as a preliminary indication of the impact of inhaling vapor from dried toad secretion containing 5-MeO-DMT on mental health parameters. Placebo controlled, randomized clinical trials are needed to replicate the current findings and to control for non-pharmacological factors that could explain the current findings as well. A second limitation is that about 40% (N=33) of the volunteers that gave consent (N=75) to participate in the current did not complete any measures after the ceremony. Of those that completed assessments the day after the ceremony (N=42), 50% did not complete the follow-up assessment at 4 weeks after the session. Their reasons for not completing the assessments are unknown but potentially could be driven by disappointments that emerged over the experience. Most participants listed either “*understanding myself*” or “*solving problems*” as

their motivation for attending the sessions. Other motivations included self-development, the search for a spiritual experience or spiritual healing and curiosity. It is unknown whether the experience from inhaling vapor from dried toad secretion containing 5-MeO-DMT fulfilled the expectations and motivations of all participants. Mental challenges following a 5-MeO-DMT experience have been reported and can include feelings of grief, anxiety, panic, or paranoia (Barsuglia et al. 2017; Davis et al. 2018). Resurfacing of these experiences can occur even weeks after the experience (Sandoval 2006) and may lead to psychological difficulties, particularly in the absence of counseling (Johnson et al. 2008). The possibility thus exists that participants that did not fill out the follow-up measures did not do so because they experienced a negative after-effect. In that case, their lack of responding would strongly bias the current findings. In this light, the fact that facilitators in the field often do not provide professional psychological counselling during and after the sessions is particularly worrisome. Structured counselling sessions during the acute psychedelic experience with additional sessions before and after would potentially increase the ability of users to integrate their experience with the vapor from dried toad secretion containing 5-MeO-DMT, increase our understanding of positive and negative outcomes of exposure to the vapor and reduce the number of volunteers lost to follow-up.

Additionally, as the use of vapor from dried toad secretion containing 5-MeO-DMT through means of inhalation increases there are several ethical and ecological considerations worth highlighting. The International Union for Conservation of Nature (IUCN) red list of threatened species at present does not classify the *Bufo Alvarius* toads as an endangered species. The classification dates back however to an assessment of the toad population in 2004 (Hammerson G and G. 2004). Increasing popularity of inhalation of

vapor at underground ceremonies, and acknowledgement of its therapeutic potential may however affect the stability of the toad population in the long run. The increasing demand for the vapor will disturb the ecological equilibrium of the toads through invasion of habitat, excessive milking, amphibian-trafficking and black-market dynamics (PsychedelicsToday 2018). Harassment of the Bufo Alvarius toad however can be easily prevented by using synthetic 5-MeO-DMT instead of vapor from dried toad secretion containing 5-MeO-DMT. Switching to synthetic 5-MeO-DMT offers the advantage that it does not contain a cocktail of different compounds, can be produced and dosed in a standardized manner, and is therefore much safer to use in naturalistic as well as controlled research settings.

Despite the limitations of this study, the results underscore the effects of 5-MeO-DMT, the main active ingredient in the secretion from the Bufo Alvarius toad, on mental health in humans. This study suggests that a single administration of vapor from toad secretion containing 5-MeO-DMT produces, rapid and persistent improvements in satisfaction with life, mindfulness and psychopathological symptoms, and that these changes are associated to the strength of the psychedelic experience. These results provide evidence supporting further research examining the potential therapeutic effect of 5-MeO-DMT.

Chapter 5 - Prospective examination of synthetic 5-methoxy-N,N-dimethyltryptamine inhalation: effects on salivary IL-6, cortisol levels, affect, and non-judgement

Uthaug, M. V., Lancelotta, R., Szabo, A., Davis, A. K., Riba, J., & Ramaekers, J. G. (2019). *Prospective examination of synthetic 5-methoxy-N, N-dimethyltryptamine inhalation: effects on salivary IL-6, cortisol levels, affect, and non-judgment. Psychopharmacology, 1-13.*

Abstract

Rationale: *5-methoxy-N,N-dimethyltryptamine* is a psychotropic substance found in various plant and animal species and is synthetically produced. *5-methoxy-N,N-dimethyltryptamine* is used in naturalistic settings for spiritual exploration, recreation, or to address negative affect and mood problems. However, scientific knowledge on the effects of *5-methoxy-N,N-dimethyltryptamine* in humans is scarce.

Objectives: The first objective was to assess the effects of inhalation of vaporized synthetic *5-methoxy-N,N-dimethyltryptamine* on neuroendocrine markers. The second objective was to assess effects of the substance on affect and mindfulness. In addition, we assessed whether ratings of subjective measures were associated with changes in stress biomarkers (i.e. cortisol) and immune response (i.e. IL-6, CRP, IL-1 β), as well as the acute psychedelic experience.

Methods: Assessments (baseline, immediately post-session, and 7-days follow-up) were made in 11 participants. Salivary samples were collected at baseline and post-session and analyzed by high-sensitivity enzyme-linked immunosorbent assay (ELISA).

Results: *5-methoxy-N,N-dimethyltryptamine* significantly increased cortisol levels and decreased IL-6 concentrations in saliva immediately post-session. These changes were not correlated to ratings of mental health or the psychedelic experience. Relative to baseline, ratings of non-judgement significantly increased, and ratings of depression decreased immediately post-session and at follow-up. Ratings of anxiety and stress decreased from baseline to 7-day follow-up. Participant ratings of the psychedelic experience

correlated negatively with ratings of affect and positively with ratings of non-judgement.

Conclusion: Inhalation of vaporized synthetic *5-methoxy-N,N-dimethyltryptamine* produced significant changes in inflammatory markers, improved affect, and non-judgement in volunteers. Future research should examine the effect of *5-methoxy-N,N-dimethyltryptamine* with healthy volunteers in a controlled laboratory setting.

Introduction

Tryptamine psychedelics such as psilocybin are known to alter perception, mood, and a host of cognitive processes (Nichols, 2004) and have been indicated for the treatment of mood disorders (Robin L Carhart-Harris et al., 2018; Griffiths, Richards, McCann, & Jesse, 2006; Aline Viol et al., 2019). Additionally, classical serotonergic hallucinogens such as LSD or psilocybin are considered physiologically safe, and do not produce dependence or addiction (Nichols, 2004). A similar potential might exist for the short-acting tryptamine *5-methoxy-N,N-dimethyltryptamine* (5-MeO-DMT).

5-MeO-DMT was first synthesized in 1936 (Hoshino & Shimodaira, 1936), but can also be found naturally in plants such as the *Dictyoloma incanescens* (Pachter, Zacharias, & Ribeiro, 1959), or in the milky-white secretion, also known as bufotoxin, which is produced in the skin and the parotid glands of the *Incilius alvarius* toad, also known as *Bufo alvarius* (Weil & Davis, 1994). A recent lab analysis revealed that about 25-30% of the bufotoxin, used in a naturalistic setting, consisted of the primary component 5-MeO-DMT, as well as (very) low amounts of additional tryptamines such as bufotenine (0.08 - 0.18%), DMT and N-methylserotonin (0.01-0.03%) (Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019).

5-MeO-DMT acts as a serotonin 5-HT_{1A}/5-HT_{2A} receptor agonist (H.-W. Shen, Jiang, C Winter, & Yu, 2010), and is reported to be psychoactive in humans in doses as low as 3-5 milligrams of pure substance when vaporized (Weil & Davis, 1994). 5-MeO-DMT induces a diversity of subjective effects, including auditory, visual, and time perception distortions, emotional

experiences, and memory impairment that vary depending on the dose and route of administration (Ott, 2001; Shulgin & Shulgin, 1997b). In fact, low doses of 5-MeO-DMT (bufotoxin source 50mg, estimated 5-MeO-DMT content 5-7mg) appear to occasion mystical experiences of similar intensity to high-dose psilocybin (Joseph P Barsuglia et al., 2018), but with a much shorter duration of action.

Nevertheless, from a recent survey among users in the general population it appears that 5-MeO-DMT has an acceptable physiological safety profile in naturalistic settings (Alan K Davis et al., 2018b; Alan K Davis, So, Lancelotta, Barsuglia, & Griffiths, 2019b), as well as a low addiction liability (Alan K Davis et al., 2018b). Adverse responses include mental challenges such as feelings of grief, anxiety, panic, or paranoia (Barsuglia et al., 2017b; Alan K Davis et al., 2018b). Resurfacing of these experiences can occur even weeks after the experience and may lead to psychological difficulties, particularly in the absence of counseling (Johnson, Hendricks, Barrett, & Griffiths, 2019).

At the present time, 5-MeO-DMT has become popular in naturalistic settings as a means for spiritual exploration, recreation, or as a way to increase affect or relieve problems associated with mental health (Alan K Davis et al., 2018b). Unpublished reports of 5-MeO-DMT use describe inhalation, smoking, or vaporizing as a common route of consumption (Erowid, n.d). Interestingly, people who reported having had a psychiatric condition described that following the use of 5-MeO-DMT they experienced improvement in depression (77%), anxiety (69%), post-traumatic stress disorder (79%) and substance use disorders (60%) (Alan K Davis et al., 2018b). A recent field study (Uthaug, Lancelotta, van Oorsouw, Kuypers,

Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019) replicated such reports and showed that a single inhalation of vapor from dried toad secretion containing 5-MeO-DMT produces sub-acute and long-term improvements in affect and cognition in 42 undiagnosed participants in naturalistic ceremonies.

The aforementioned research underpins a potential role for 5-MeO-DMT as a therapeutic tool which may be similar to ayahuasca, an Amazonian plant preparation that contains the closely-related psychedelic compound DMT (Palhano-Fontes et al., 2018; Uthaug et al., 2018). The potential of ayahuasca to rapidly and persistently reduce symptoms of depression has been shown in a range of open-label studies (Flávia de Lima Osório et al., 2011; Rafael Faria Sanches et al., 2016), and was confirmed in a randomized placebo-controlled clinical trial in patients suffering from treatment-resistant depression (Palhano-Fontes et al., 2018). DMT and 5-MeO-DMT have also been shown to exert potent anti-inflammatory effects through the modulation of innate and adaptive immune processes (Szabo, 2015; Szabo et al., 2014). Moreover, *in vitro* studies have recently provided evidence of anti-inflammatory, neuroregenerative and anti-addictive effects induced by 5-MeO-DMT (Dakic, Nascimento, Sartore, de Moraes Maciel, Araujo, et al., 2017). In addition, 5-MeO-DMT has been demonstrated to affect neurogenesis, which may contribute to the known antidepressant properties of DMT-derived compounds (Lima, Moulin, Lintzmaier, & Leão, 2018). The potential *in vivo* anti-inflammatory effects of psychedelic tryptamines may open up novel vistas in the treatment of a wide range of diseases including, but not limited to various autoimmune and neurodegenerative disorders (Szabo, 2015). Furthermore, according to the immune hypothesis of psychiatric diseases, therapeutic control of peripheral and brain inflammation could offer novel, important tools in the treatment of severe mental and mood disorders, such as

major depression (Khandaker et al., 2015; Miller & Raison, 2016). Thus, therapeutic inflammatory modulation by serotonergic tryptamines (e.g. 5-MeO-DMT) may represent new and effective treatment modalities in a broad spectrum of clinical pathologies.

The present study was conducted to prospectively assess the effects of 5-MeO-DMT on stress and inflammatory immune functions in users that participated in naturalistic 5-MeO-DMT sessions. A secondary aim was to assess the effects of 5-MeO-DMT on depression, anxiety, stress, mindfulness, and satisfaction with life. A third aim was to determine whether changes in mental health variables were related to the intensity of the psychedelic experience and changes in the stress and immune system response. We expected that symptoms of depression, anxiety, and stress would decrease, and ratings of satisfaction with life would increase, from before to after inhalation of vaporized synthetic 5-MeO-DMT. Whether mental health changes produced by tryptamines are also associated with changes in stress and immune response is presently unknown. However, we hypothesized that salivary stress and immune biomarkers would allow further exploration of the association between anti-inflammatory (Szabo, 2015; Szabo et al., 2014), and mental health effects related to the inhalation of 5-MeO-DMT (Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019).

Methods

For this observational study, we visited a location in Prague, The Czech Republic where people inhaled vapor from synthetic 5-MeO-DMT administered by a facilitator in individualized, one-on-one sessions. Participants were invited to enter the current study when they first contacted

the facilitator to sign up for the session and gave their written informed consent on location prior to drug administration.

A total of 11 participants were approached and consented to participate in the research. These individuals completed baseline and a post-session assessment on location while 10 participants also completed an online follow-up assessment 7 days after intake through Qualtrics, a web-based survey tool to conduct survey research. Exclusion criteria included non-fluency in English, taking (any) medication and age < 18 years. None of the participants were excluded based on these criteria. Participation was voluntary, and no incentives to participate were provided. The study was approved by the Ethical Review Committee Psychology and Neuroscience (ERCPN), in Maastricht, the Netherlands.

Most participants were from Europe (N = 8) and the rest of the participants were from North America (N=3). There were eight males and three females. Mean age of the entire group was 33 years of age (SD=8.59). Participants had obtained a university bachelor's degree (N = 6), a master's degree (N=4) or completed a trade school (N=1). All participants reported having previous experience with psychedelic substances. In total, 9 participants reported having had no previous experience with 5-MeO-DMT, while 2 participants reported having had 5-MeO-DMT on 3 and 5 previous occasions, respectively. The participants motivations to use 5-MeO-DMT included "to understand myself" (N = 2), "out of curiosity" (N=2), "solve problems" (N=1), "to understand myself and solve problems" (N=2), "to understand myself and out of curiosity" (N=1), "to understand myself, solve problems and out of curiosity" (N=2), and finally "to understand myself" and "other", namely "explore possibilities" (N=1). Several participants reported to have

not used any substances the past 7 days (N=4), others reported having used alcohol (N=3), cannabis (N=2), alcohol and cannabis (N=1), alcohol and 3,4-methylenedioxymethamphetamine (MDMA) (N=1). No participant reported having received a diagnosis of mental health disorder from a clinician. However, 4 participants reported past problems related to depression (N=1), depression and anxiety (N=1), depression, anxiety, and Post Traumatic Stress Disorder (PTSD) (N=1), and other (N=1).

Setting of the sessions

The sessions for each participant were held at a yoga studio in Prague in the Czech Republic. The facilitator was male, trained in Holotropic Breathwork, a practice that uses breathing and other elements to putatively allow access to non-ordinary states of consciousness (Grof and Grof, 2010), and had been facilitating sessions using 5-MeO-DMT for about two years.

A total of 18 potential participants were screened by the facilitator, however only 11 of them was invited to the session. The facilitator screened all participants for previous experience with “journey work” (history and context of psychedelic substance use), mental health history, general substance use history, medical history, social history, and their ability to access integration resources. Participants taking any psychiatric medications, with histories of psychosis, personality disorders, severe depression, severe PTSD, or with any cardiovascular disorders were screened out. However, the facilitator did not have formal clinical training to identify and exclude participants with contraindications, thus these decisions rely heavily on self-report of the potential participant.

Prior to the session, in addition to collecting a questionnaire, the facilitator held a video chat or a phone session with all participants to talk more about

the participants intentions and to better assess if the 5-MeO-DMT session would be a good fit for them. The facilitator sent out an email to all participants giving preparatory instructions and details about how the session would be structured. Preparatory instructions included encouraging participants to arrive 30 minutes early to complete study questionnaires. Moreover, the participants were advised to refrain from drinking a lot of anything, to have some snacks rather than a large meal in the hours leading up to their session, and to abstain from any mind-altering substances (i.e alcohol, cannabis, and other medicines they habitually take). Additionally, they were recommended to engage in mindfulness activities prior to the sessions. Finally, they were advised to bring a water bottle and to wear/bring loose clothing for the session.

All participants were required to attend an informational meeting which took place in Prague a few days prior to the start of the sessions. This gave participants an opportunity to meet the facilitator, and to ask him any additional questions about the experience.

In each 5-MeO-DMT session, the only individuals in the room were the facilitator, the participant, and the second author who was taking notes throughout the session on weight of dose, duration of session, frequency of dosing, and phenomenological occurrences.

The room had a mattress on the floor with sheets and pillows for the participant to sit on while the facilitator sat at the front of the room and the second author sat at the back of the room, out of view of the participants. In each session, the facilitator established a conversational connection by asking how the participants slept, how they were feeling, and how their day had gone before starting to talk about how the session would be run. The facilitator

talked about the use of sound in the session and explained that he would be playing a sound called “*Om of the Goddess*” by Jo St. Clair as an auditory focus during the peak experience of the session. Then the facilitator asked participants to let go of all previous expectations and previous experiences to better stay focused in the present moment of what they were about to experience. After explaining how the experience could feel phenomenologically, the facilitator explained that after administering the 5-MeO-DMT vapor from the glass pipe, he would lower the participant onto their back so that they could relax and “fully receive the experience”.

The facilitator took a varied dosing approach for each participant. The decision about dosing was based on a combination of the experience of the practitioner and his knowledge of standard practice (5Hive, 2019), and previously published dosing ranges producing dissociations (Metzner, 2013). The facilitator would ask participants how they approach the unknown using the metaphor of getting into a lake. If the participant said that they preferred being fully immersed right away as in diving into the lake, then the facilitator would go directly into a “full release dose” (between 12-23 mg). If, however, the participant said that they prefer to go gradually into the lake to test the water, then the facilitator would give a smaller “handshake dose” (between 3-6 mg), and gradually increase the dose in one, two or three steps until they reached the “full release dose.”.

On our request, the facilitator would weigh the dose before administration using a scale, My Weigh Gemprow 300, calibrated to measure in grams, down to one thousandth of a gram (0.001), and dose recordings were made by the second author. A summary of dose regimens for each participant is given in Table 1.

Participant	Dose 1 (in mg)	Dose 2 (in mg)	Dose 3 (in mg)	Dose 4 (in mg)	Sum of dose (in mg)	Average duration of inhalation (in seconds)	Average duration of breath held (in seconds)	EDI score (in %)
1	6	17	21		44	44.3	25.5	11.88
2	6	19			25	23.5	23.5	68.13
3	7	15	23		45	25.7	10.3	67.5
4	4.60	6	9	12	31.6	31.3	24.5	72.75
5	18				18	15	10	53.13
6	21				21	30	20	76.25
7	17				17	30	34	100
8	3	6	9	14	32	23	15.5	0
9	6	19	23		48	27.7	15.7	50
10	5	14	21		40	27.7	15.3	35.63
11	18	19	24		61	32	6.3	35

Table 1. An overview of mean ratings of ego dissolution (0-100%), the weighed individual dose(s) of synthetic 5-MeO-DMT per participant in milligrams, as well as the average duration of inhalation of vaporized synthetic 5-MeO-DMT and breath held (in seconds).

At around 20 minutes after the last dose, and when the participant was no longer experiencing acute drug effects, the participant and the facilitator would talk about the experience. These conversations were recorded by the facilitator with permission of the participants. Once the conversation reached its conclusion, the participant would leave the room and meet with the other researcher to complete psychometric, and another biometric data collection of saliva. A week after the session, the facilitator would send all participants

an e-mail with an audio recording of their conversations, and to let them know that integration support is available for them if necessary, through an audio or video call. In addition, the facilitator linked them with other resources helpful on the topic of integration such as the online forum “5Hive” and other Facebook groups devoted to integration. Finally, he also reminded the participants to fill out the online follow-up questionnaire for psychometric data and provided them with a link to the survey in his e-mail.

Study procedure

In this naturalistic observational study, assessments were taken at baseline, immediately post-session, and at 7 days in participants who inhaled vapor from synthetic 5-MeO-DMT. On location, prior and after their session, participants completed a 15-minute test-battery consisting of a demographic section, questionnaires assessing mental health related factors (depression, anxiety, stress, satisfaction with life and mindfulness related capacities). In addition, two salivary samples were collected, one 30 minutes before the participant session (baseline), and post-session (within 1-1.5 hours after the session ended). Saliva samples were collected in Saliva Collection Aid (SCA) tubes (Salimetrics, Carlsbad, CA, USA), immediately stored, and transported on dry ice. Finally, 10 out of 11 participants completed the 7-day follow up assessments, which included mental health measures as distributed at baseline and post-session, as well as questions related to the overall experience.

Subjective measures of mental health

The test battery consisted of five questionnaires in their original language English; the Depression, Anxiety and Stress Scale 21 (DASS-21), the Satisfaction With Life Scale (SWL), the Five Facets Mindfulness Questionnaire (FFMQ-39), the Ego Dissolution Inventory (EDI), and the 5-

Dimensional Altered States of Consciousness Rating Scale (5D-ASC). EDI and 5D-ASC were distributed after the session to assess the experience in retrospect.

EDI

EDI is an 8-item self-report scale that assesses the participant's experience of ego dissolution, with excellent internal consistency (Cronbach's $\alpha = .909$) (Matthew M Nour et al., 2016). The participants answered the scale with making a mark on a line from either "*No, not more than usually*" (0 %) to "*Yes I experience this completely/entirely*" (100 %). The total EDI is scored by calculating the mean percentage of all the 8 items. The higher the total score, the stronger the experience of ego dissolution.

5D-ASC

The 5D-ASC is a 94-item self-report scale that assesses the participants' alterations from normal waking consciousness with an excellent internal consistency (Cronbach's $\alpha = .953$) (Adolf Dittrich, 1998; A Dittrich et al., 2010; Studerus et al., 2010). The participant is asked to make a vertical mark on the line below each statement to rate to what extent the statements applied to their experience in retrospect (i.e from 0 % "*No, not more than usually*" to 100% "*Yes, more than usually*"). The 5D-ASC measures 11 subscales; *experience of unity spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery, audio-visual synesthesia and changed meaning of perception* and five key dimensions; *oceanic boundlessness, anxious ego dissociation, visual restructuralization, auditory alterations, and finally reduction of vigilance*. Moreover, the 5D-ASC measures 5 key-dimensions which include oceanic boundlessness that identifies mystical-type

experiences, and has been compared with the “heaven” aspect of Huxley’s mescaline account (Adolf Dittrich, 1998) anxious ego dissociation, visual restructuralization, auditory alterations, and reduction of vigilance

DASS-21

DASS-21 is the shorter version of the original self-report questionnaire Depression, Anxiety, Stress Scale 42 with excellent internal consistency (Cronbach’s $\alpha = .918$) (Julie D Henry & John R Crawford, 2005). The purpose of the DASS-21 scale is to measure constructs of depression, anxiety and stress ranging from 0 (normal) to 42 (extremely severe). The participants responded by rating the concordance with each statement from 0 “*Did not apply to me at all*” to 3 “*Applied to me very much, or most of the time*”. The sub-scale scores for depression ($\alpha = .88$), anxiety ($\alpha = .82$), and stress ($\alpha = .90$) are calculated by summing the scores for the relevant items to the characteristic being measured (Julie D Henry & John R Crawford, 2005). As the original DASS has 42 questions, the sum of the DASS-21 is multiplied by 2 to ascertain the comparable scores.

SWL

SWL is a 5-item self-report scale, assessing someone’s subjective satisfaction with life with a good internal consistency (Cronbach’s $\alpha = .814$) (ED Diener, Robert A Emmons, Randy J Larsen, & Sharon Griffin, 1985; Pavot & Diener, 2009). The SWL has possible score-range of 5 to 35, with 5-9 indicating an extreme dissatisfaction with life, while scores between 31-35 indicating the respondent is extremely satisfied. The items are answered on a Likert-scale ranging from 1 “*Strongly disagree*” to 7 “*Strongly agree*”. The total score is obtained by adding points on each item.

FFMQ-39

FFMQ is a 39 item self-report scale with an excellent internal consistency (Cronbach's $\alpha = .936$) (Baer et al., 2006) and measures the following five facets of mindfulness related capacities; 1) Observe: noticing experience that are both internal and external such as thoughts and emotions; 2) Describe: describing internal experiences; 3) Acting with awareness: focus on the present activity; 4) Non-judgment: not evaluating or judging the present experience ; 5) Non-reaction: allowing thoughts and feelings to come without acting or reacting upon them. The purpose of this scale is to obtain an understanding of an individual's mindfulness related capacities. The participants answered the FFMQ by rating the concordance with each statement on a 5-point Likert-scale that ranges from 1 "*never true*" to 5 "*very often or always true*". Facet scores were computed by summing the scores on the individual items. Facet scores range from 8 to 40 (except for the non-reactivity facet, which ranges from 7 to 35), with higher scores indicating more mindfulness.

Analysis of saliva samples

All saliva samples (2-3 mL/sample) were assayed for cortisol, IL-6, CRP, and IL-1 β using high-sensitivity ELISA kits following the manufacturer's recommended protocol (Salimetrics). The test volume was 25 μ L, with a range of standards from 0.012 – 3.000 ug/dL (cortisol), 0 – 100 pg/mL (IL-6), 93.75 pg/mL – 3000 pg/mL (CRP), 3.13 pg/mL – 200 pg/mL (IL-1 β), and the assays had a lower limit of sensitivity of 0.007 ug/dL (cortisol), 0.07 pg/mL (IL-6), 10 pg/mL (CRP), and < 0.037 pg/mL (IL-1 β). Samples were thawed, and immediately centrifuged at 3000 rpm for 15 minutes to remove mucins, and diluted 1:2 (cortisol, IL-6, IL-1 β) or 1:10 (CRP) prior to assay.

All samples were measured in duplicates, and the average of the duplicates was used in the statistical analyses. The intra- and inter-assay coefficients of variation were less than 10% and 15%, respectively. Absorbance measurements were carried out using a Synergy HT microplate reader (Bio-Tek Instruments, Winooski, VT, USA) at 450 nm.

Statistical analysis

A repeated measures ANOVA using a linear mixed model analysis with Session, the assessment point, (3 levels; baseline, post- session and follow-up) as the within subject factor was conducted. Fixed main effects included Session, using the maximum likelihood method. Covariance structure was chosen according to best fit and included compound symmetry heterogeneous (CSH), unstructured correlations (UNR), as well as heterogeneous first-order autoregression (AR1) structures. Significant main effects of Session were followed by separate least significant difference (LSD) contrasts between baseline and follow-up session. The alpha level of significance was set at 0.05. Pearson's correlations were carried out to investigate the association between the level of ego dissolution, and the experience of altered states of consciousness with subjective measures of affect and cognition. In addition to investigating the association between any of the psychometric data, and the saliva ELISA data, Cohen's d was calculated to estimate effect sizes of significant mental health changes between baseline and post sessions, and Hedges' g was calculated to estimate effect sizes of significant mental health changes between baseline and follow-up sessions. Eta square scores (η_p^2) were calculated to estimate effect sizes of significant mental health changes between sessions. The data was analyzed with the Statistical Package for the Social Sciences 24.0 (SPSS) ("IBM SPSS Statistics for Windows," 2016).

For the statistical analysis of saliva ELISA data, two groups (“baseline”, [collected 30 minutes before the participants session], and another one “immediately post-session” [collected within 1-1.5 hours after their session ended], where the samples of each participants were paired up) were compared with Student's t-test. Data analyses were performed using GraphPad Prism version 8.00 for Windows (GraphPad, 2019) (GraphPad Software Inc., La Jolla, CA, USA, www.graphpad.com). Differences were considered to be statistically significant at $p < 0.05$.

Results

Dose

During their individual session with 5-MeO-DMT, 3 participants had 1 dose of 5-MeO-DMT, 1 participant had 2 doses, 5 participants had 3 doses, and 2 participants had 4 doses. The doses varied by participant, and ranged from 3 to 24 mg. The summed total doses varied between 17 mg and 61 mg. Doses were administered between 8 and 25 minutes apart, and additional doses were given only when discernible effects of the previous dose had diminished. For an overview of dose(s), and inhalation time, see Table 1.

Adverse reactions

Notably, 45.5% (N=5) of the sample reported adverse effects post-session. 1 participant reported feeling “scared and confused”, 1 participant reported “feeling anger, joy love and fear”, 1 participant vomited shortly after intake, 1 participant expressed “feeling a little shock on the first try, but nothing bad”, and finally 1 participant reported feeling that their throat was scratching from smoking.

On the 7-day follow-up, 27.3 % (N=3) of the sample reported adverse effects in the days following the session. One participant reported some affect and

somatic tension in muscles, one participant reported difficulties sleeping (insomnia), and finally, one participant reported experiencing somatic tension in muscles, in the 7 days following their session.

The psychedelic experience

EDI

Overall, the mean (SD) ratings of EDI was 51.84 % (29.49). A frequency distribution of the EDI ratings is shown in Figure 1. EDI scores per individual are shown in Table 1.

5D-ASC

The mean (SD) ratings of the experience of altered states of consciousness as rated by the 5 dimensions of the 5D-ASC, were; *oceanic boundlessness* = 46.88 % (30.11), *anxious ego dissociation* = 23.83 % (15.80), *visual restructuralization* = 27.16 % (22.76), *auditory alterations* = 14.39 % (14.37), and finally *reduction of vigilance* = 22.34 % (8.61). Furthermore, the mean (SD) rating of the experience of altered states of consciousness as rated by the 11 sub-scales of the 5D-ASC, ranging from 0 % to 100 % are shown in Figure 1. The top three rated subscales were *experience of unity* 53.82 % (36.25), *blissful state* 51.35 % (38.94) and *disembodiment* 49.58 % (30.84).

Figure 1. Frequency distribution of the experience of ego dissolution as assessed by the EDI post-session after inhalation of vaporized synthetic 5-MeO-DMT (left panel). Mean ratings (range 0-100%) of the psychedelic experience as assessed with the 5D ASC subscales (upper right panel), and dimensions (lower right panel) after inhalation of vaporized synthetic 5-MeO-DMT.

Stress and inflammatory markers

Mean difference in (SD) cortisol, CRP, IL-6 and IL-1 β salivary concentrations are shown in Figure 2. Inhalation of vaporized synthetic 5-MeO-DMT resulted in significant increase in the levels of salivary cortisol (mean difference, MD = 0.21 μ g/dL; $p < 0.001$), and significant decrease of salivary IL-6 (MD = 3.51 pg/mL; $p < 0.001$). Inhalation of vaporized synthetic 5-MeO-DMT did not produce statistically significant changes in salivary CRP and IL-1 β .

The normal/physiological range of the monitored biomarkers in saliva are the following: CRP: <3 ng/mL; cortisol: 0.15-0.65 µg/dL; IL-1β: 50-200 pg/mL; IL-6: 5-25 pg/mL (Desai & Mathews, 2014). Baseline levels of all investigated biomarkers were in the physiological range in case of each participant, see Figure 2.

Subjective measures of affect and cognition

Overall, main effects of session reached significance on anxiety (as assessed by DASS-21) ($F_{2, 19.380} = 6.023$; $p = .009$, $\eta_p^2 = 0.38$), depression (as assessed by DASS-21) ($F_{2, 9.979} = 8.104$; $p = .008$, $\eta_p^2 = 0.18$), and non-judgement (as assessed by FFMQ) ($F_{2, 10.182} = 14.018$; $p = .001$, $\eta_p^2 = 0.45$), while approaching significance in stress (as assessed by DASS-21) ($F_{2, 20.355} = 3.070$; $p = .068$, $\eta_p^2 = 0.21$), see Figure 3.

Separate contrasts between baseline and measures immediate post-session revealed a significant reduction in depression ratings ($p = .049$, Cohen's $d = 0.31$), and a significant increase in non-judgement ($p = .017$, Cohen's $d = 0.36$). Separate contrasts between baseline and the 7-day follow up revealed a reduction in stress ($p = .043$, Hedge's $g = 0.67$), anxiety ($p = .010$, Hedge's $g = 0.40$) and non-judgement ($p = .001$, Hedges' $g = 0.51$). Moreover, there was a reduction in depression ratings which approached significance at 7-days follow up ($p = .073$, Hedges' $g = 0.30$).

Figure 2. Effect of 5-MeO-DMT on salivary neuroendocrine and immune markers.

Saliva samples were collected before (baseline) and 1-1,5 h after (post) the inhalation of vaporized synthetic 5-MeO-DMT and were analysed by ELISA. Results are shown as mean $\pm$ SEM. Asterisks (****) represent p values < 0.001 ; n.s. means no statistical significance.

Figure 3. Mean (SE) ratings of anxiety (upper left panel), depression (upper right panel) and stress (bottom right panel) as assessed by DASS-21 (upper panel), and ratings of non-judgement (lower left panel) as measured by FFMQ-39. Before (0), post-session (1) and 7 days after (7) inhalation of vaporized synthetic 5-MeO-DMT, (* $p < .05$).

Correlations

Dose

No significant correlations were found between the total dose and measures of the psychedelics experience, salivary biomarker and subjective measures of affect and cognition. All correlations were very low and ranged from $r = -.499$ to $r = .240$.

Salivary biomarkers and the psychedelic experience

There was no correlation between mean difference in salivary cortisol and IL-6 (between baseline and immediate post-session) and the ratings of the psychedelic experience (as assessed with EDI and 5D-ASC post-session). Nevertheless, there was a negative correlation between salivary IL-1 β and the experience with ego dissolution ($r = -.679$; $p = .022$) and experience of unity ($r = -.622$; $p = .041$). A negative correlation was also found between salivary CRP and oceanic boundlessness ($r = -.769$; $p = .006$), anxious ego dissolution ($r = -.755$; $p = .007$), and auditory alterations ($r = -.671$; $p = .024$), experience of unity ($r = -.722$; $p = .012$), spiritual experience ($r = -.720$; $p = .012$), blissful state ($r = -.767$; $p = .006$), insightfulness ($r = -.778$; $p = .005$), disembodiment ($r = -.659$; $p = .028$) and elementary imagery ($r = -.670$; $p = .024$). Additionally, there was a positive correlation between salivary CRP and anxiety scores ($r = .664$; $p = .026$).

Salivary biomarkers and subjective measures

There was no correlation between changes in salivary cortisol and IL-6 and ratings of subjective measures between baseline or post-session. However, there was a negative correlation between salivary CRP and awareness ($r = -.714$; $p = .014$) and non-judgement ($r = -.720$; $p = .012$), and a negative correlation between salivary IL-1 β and satisfaction with life ($r = -.874$; $p = .000$), and a positive correlation with depression ($r = .637$; $p = .023$).

The psychedelic experience and subjective measures

Post ratings of the psychedelic experience (as assessed by EDI and 5D-ASC) were correlated with post and follow up session ratings of non-judgement (as assessed by FFMQ), depression, anxiety and stress (as assessed by DASS-

21), and satisfaction with life (as assessed with SWL). For an overview of correlations between the experience of ego dissolution and subjective measures post session and 7-Day follow-up see Figure 4. For an overview of correlations between 5D-ASC ratings and subjective measures see, Table 2 (post-session) and Table 3 (7-Day follow-up).

Figure 4. Pearson's correlations between ego dissolution and affect and non-judgement ratings post-session (upper panel), as well as affect and non-judgement ratings at follow up (lower panel) after inhalation of vaporized synthetic 5-MeO-DMT.

Table 2. An overview of Pearson's correlations between the psychedelic experience as assessed by EDI, 5D-ASC (dimensions and subscales) and subjective measures (FFMQ, DASS-21, and SWL), at post session. * $p = < .05$, ** $p = < .01$.

Table 3. An overview of Pearson's correlations between the psychedelic experience as assessed by EDI, 5D-ASC (dimensions and subscales) and subjective measures (FFMQ, DASS-21, and SWL), at 7-Day follow-up. * $p < .05$, ** $p < .01$.

Discussion

Participants reported moderate levels of ego dissolution and altered states of consciousness during the psychedelic experience as measured by the EDI and 5D-ASC. These ratings are qualitatively similar but lower in magnitude than reported after inhalation of vaporized toad secretion containing 5-MeO-DMT from the *Incilius alvarius* toad (Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019).

Inhalation of vaporized synthetic 5-MeO-DMT primarily induced experience of unity, a blissful state and elementary imagery whereas inhalation of vaporized toad secretion induced experience of unity, spiritual experience and a blissful state (Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019). However, in the latter study the magnitude of ratings was 20-30% higher than in the current study. Likewise, the percentage of individuals that achieved maximum ego dissolution was higher as compared to the present study. These differences in the magnitude of the psychedelic experiences observed may be related to that fact that the sample size in this study was 4 times smaller or to differences in dose. There is little information about 5-MeO-DMT doses that are administered at naturalistic ceremonies, but in the current study we were fortunately able to weigh doses before administration. The total dose administered to participants varied widely between 15-61 mg and depended largely on personal desires of the participant. However, the magnitude of their psychedelic experience was not significantly correlated the total dose of 5-MeO-DMT that participants received. The current data thus seems to suggest that any dose of 5-MeO-DMT can elicit a psychedelic experience but at an unpredictable magnitude. Other factors causing individual differences may have co-influenced the strength of the experience such as actual drug concentrations in blood, drug metabolism, openness to the psychedelic experience, inhalation technique, or levels of dissociation in the nervous system. In the present study, one participant placed great efforts in resisting the psychedelic experience mentally during 4 subsequent dose sessions and eventually reported minimal levels of altered states of consciousness.

Five participants (45.5%) reported adverse effects during the session, and three participants (27.3%) reported adverse effects during the days following

intake. Adverse events included physical distress and feelings of anger, fear, panic and sadness. Similar percentages and types of adverse events have been reported in a recent survey among 515 users of 5-MeO-DMT (Alan K Davis et al., 2018b) where 37% of the responders reported challenging psychological and physical experiences, and 40%- 60% of respondents reported physical distress or feelings of fear, grief, insanity, isolation and death. The intensity of these experiences by survey responders however were rated as very small. This suggests that adverse events from the psychedelic experience are tolerable but challenging and occur in a sizeable fraction of 5-MeO-DMT users.

Because classic serotonergic psychedelics have been shown to modulate immune responses by downregulating inflammatory processes through 5-HT₂ and sigma-1 receptors (Nau Jr et al., 2014; Nau Jr, Yu, Martin, & Nichols, 2013; Szabo et al., 2014), we hypothesized that the administration of vaporized synthetic 5-MeO-DMT would alter the levels of inflammatory cytokines and the neuroendocrine-immune regulator cortisol. Interestingly, out of the four salivary biomarkers monitored in this study, only cortisol and IL-6 levels were affected by 5-MeO-DMT administration, see Figure 2. Cortisol has been widely known to be strongly induced by physical and psychological stress and has an important role in acute stress adaptation, as well as in restoring homeostasis following stressful events (Malarkey & Mills, 2007). Modulation of 5-HT₂ receptors by peak dose(s) of 5-MeO-DMT may represent or mimic an intense neuroendocrine stress-like state, thus our results showing elevated levels of salivary cortisol are not surprising given the fast-action of inhaled tryptamines, and are in good agreement with the literature regarding their fast-acting, stress-mimicking neuromodulatory effects on human physiology (Do Yup Lee & Choi, 2015).

We also found that IL-6 was affected by 5-MeO-DMT administration. IL-6 is an important inflammatory cytokine that is released in the early phase of infections and essential in immune defense, but is also involved in pathological autoinflammatory processes (Jones & Jenkins, 2018). Pharmacological manipulation of IL-6 secretion or the IL-6 trans-signaling pathway may offer us novel possibilities for the therapy of autoimmune diseases, infections, as well as new generation vaccine design (Garbers, Heink, Korn, & Rose-John, 2018). Cortisol and other glucocorticoids are known to rapidly suppress inflammation and have been widely used in the therapy of acute and chronic inflammatory states (Gleeson et al., 2011). Thus, the observed decrease in salivary IL-6 levels may be the direct consequence of increased cortisol secretion independent of any psycho-neuroimmune feedback effects, or 5-HT_{2A} and sigma-1 receptor modulatory actions of 5-MeO-DMT. Furthermore, the *in vivo* biological half-life of IL-6 is approximately 2 hours (Baran et al., 2018), which may explain the observed, relatively low, effect size of IL-6 modulation by 5-MeO-DMT (Figure 2B). Since salivary and plasma concentrations of the evaluated biomarkers are closely correlated, at least within the context of inflammatory and stress markers, saliva has been suggested as a potential qualitative surrogate for plasma in biomarker studies (La Fratta et al., 2018). Although the sample and effect sizes are low, our results suggest a possible anti-inflammatory effect of 5-MeO-DMT in humans. These findings warrant further investigation into the potential systemic anti-inflammatory effects of 5-MeO-DMT and other DMT analogs.

Although there was no correlation between salivary cortisol and IL-6 and subjective measures and the psychedelic experience post-session or at follow up, we observed an inverse correlation between CRP levels and both

awareness, non-judgement, and several 5D-ASC dimensions post-session, with a positive correlation between anxiety ratings as rated per the 5D-ASC. At follow up there was a correlation between CRP levels and both awareness and nonjudgment. Moreover, we also observed an inverse correlation between IL-1 β and satisfaction with life and ratings of ego dissolution, and a positive correlation with depression and 5D-ASC ratings, post-session. A negative correlation was found between IL-1 β and description and satisfaction with life, and a positive correlation with stress at follow-up. CRP is considered a reliable biomarker of systemic inflammation, and inflammatory states. In psychoneuroimmunology and biological psychiatry, inflammation has been tightly linked to neurocognitive processes and behavioral traits (Bauer & Teixeira, 2018; Raison & Miller, 2011). Systemic inflammation can greatly influence mood, cognitive processing, and psychosocial functioning. For example, it has been shown that inflammatory challenge can increase self-reported feelings of social disconnection and self-awareness (Eisenberger, Inagaki, Mashal, & Irwin, 2010; Moieni, Irwin, Jevtic, Breen, & Eisenberger, 2015). Our CRP-awareness and CRP-non-judgement correlation results are in line with previous findings showing an inverse correlation between CRP levels and psychological parameters (Asakura et al., 2015). Although inhalation of 5-MeO-DMT did not alter CRP levels significantly, CRP is an acute phase protein which production is under the direct control of IL-6, and both have been linked to neuropsychological regulatory processes within the context of inflammation (Del Giudice & Gangestad, 2018). We hypothesize that the observed subacute effect of 5-MeO-DMT on salivary IL-6 may also be expanded to significant changes in circulating CRP levels in the long run. Thus, the involvement of the IL-6-

CRP-brain axis in the biopsychological effects of 5-MeO-DMT administration in human warrants future research.

Inhalation of vaporized synthetic 5-MeO-DMT produced significant improvements in mindfulness rating of non-judgement and reduced symptoms of depression directly after the session as well as at the 7-day follow-up. Moreover, inhalation of 5-MeO-DMT reduced symptoms of anxiety and stress from baseline which reached significance at the 7-day follow-up. It should be highlighted that the ratings in affect (depression, anxiety and stress) were subtle which introduces the possibility that the reduction in affect can be interpreted as betterment in well-being. However, the present findings are in line with previous research on use of synthetic 5-MeO-DMT in ceremonial settings (Alan K Davis et al., 2019b), as well as a naturalistic observational study investigating the effects following use of toad secretion containing 5-MeO-DMT (Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019). Additionally, prior research showed that consumers of ayahuasca displayed significant reductions in ratings of depression and stress that persisted for 4 weeks after intake (Uthaug et al., 2018). Likewise, high-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life in cancer patients (Griffiths et al., 2016). The authors reported that at the 6-month follow-up, these changes were maintained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety (Griffiths et al., 2016). Finally, another study that compared aspects of mindfulness before, and 24 hours after an ayahuasca session, found that ayahuasca increased mindfulness related capacities such as non-judgement and non-reaction following intake (Joaquim Soler et al., 2016). With this in

mind, the present result suggests that inhalation of vapor from synthetic 5-MeO-DMT can bring about improvements in affect and aspects of mindfulness that might alleviate symptoms of mood disorders (Baer, 2003). These data suggest suggests that clinical research examining the potential therapeutic effect of 5-MeO-DMT is warranted.

Changes in the ratings of subjective measures that were observed in the present study are not necessarily related to a pharmacological effect of 5-MeO-DMT, but could have resulted from uncontrolled variables such as response expectancy of the participants prior to and after the session or the set and setting of drug administration (Robin L Carhart-Harris et al., 2018; Hartogsohn, 2016). Yet, the finding that the strength of actual psychedelic experience was positively correlated to changes in non-judgement and negatively correlated with symptoms of depression, stress and anxiety strongly suggest that the inhalation of 5-MeO-DMT contributed to changes in these subjective measures. This finding is in line with previous studies on psilocybin, ayahuasca and toad secretion have shown that stronger psychedelic experiences are associated with larger changes in subjective health outcomes (Bogenschutz et al., 2015; Griffiths et al., 2006; Leor Roseman, David J Nutt, & Robin L Carhart-Harris, 2018a; A. Ross & Thomas, 2010; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, Kuchař, et al., 2019; Uthaug et al., 2018). Still, the present findings is not without limitations. In fact, the small sample size, the possibility that volunteers were biased and thus responded in a socially desirable manner as well as the lack of a placebo control group limit the generalizability of the data. The present study should be replicated in a larger sample under experimental, placebo-controlled conditions for a final confirmation.

In conclusion, this prospective study in volunteers showed that inhalation of vaporized synthetic 5-MeO-DMT induced rapid changes in inflammatory markers and produced improvements in affect and non-judgement that lasted for 7 days. The present findings warrant further investigation into anti-inflammatory and mental health effects of synthetic 5-MeO-DMT in clinical trials.

Chapter 6 - A comparison of reactivation experiences following vaporization and intramuscular injection (IM) of synthetic 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting

Uthaug, M. V., Lancelotta, R., Bernal, A. O., Davis, A. K., & Ramaekers, J. G. (2020). A comparison of reactivation experiences following vaporization and intramuscular injection (IM) of synthetic 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting. Journal of Psychedelic Studies, 1(aop), 1-10.

Abstract

Rationale: Previous research suggests a therapeutic potential of *5-methoxy-N,N-dimethyltryptamine* (5-MeO-DMT). However, online anecdotal reports have described a phenomenon following cessation of the acute effects of 5-MeO-DMT use which has been termed *reactivation* (i.e., re-experiencing [“flashback”]). To date, no research has investigated whether different routes of administration may confer different reactivation rates, effects and experiences.

Objectives: We aimed to assess whether intramuscular injection (IM) and vaporization of 5-MeO-DMT conferred different reactivation rates, changes in satisfaction with life as well as ratings of the experience with ego dissolution and the mystical.

Methods: Using internet-based advertisements, 27 respondents ($M_{\text{age}}=32$. $SD=1.40$; males=18; North America=19) completed an online-based survey.

Results: Of the 14 participants in the IM group, 3 (21%) reported reactivations; in contrast, of the 13 participants in the vaporization group, 9 (69%) reported reactivations. Redosing occurred more frequently in the vaporization group (1-6 times with 3-35mg of 5-MeO-DMT), relative to the IM group (1-2 times with 5-10 mg of 5-MeO-DMT). All participants in the IM group experienced release of physical tension, compared to 8 participants in the vaporization group. in the IM group reported longer time of onset of acute effects (between 1-3 [N=6] and 4-6 minutes [N=6]), relative to the vaporization group where the majority (N=11) reported a rapid onset of 1-50 seconds.

Conclusion: Findings suggest that compared to vaporization, the IM route of administering 5-MeO-DMT is associated with lower and less doses, lower frequencies of reporting reactivation, a higher frequency of physical tension release, and longer onset of acute effects.

Introduction

The serotonin 5-HT_{1A}/5-HT_{2A} receptor agonist 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a lesser known psychedelic substance (Hoshino & Shimodaira, 1936; H.-W. Shen et al., 2010; Szabo, 2015), and can be found naturally in plants and the secretion (i.e. bufotoxin) from the *Incilius alvarius* toads skin and parotid gland (Pachter et al., 1959; Weil & Davis, 1994). 5-MeO-DMT is known to be orally inactive as it is metabolized by monoamine oxidase (MAO) enzymes in the gut and liver (H.-W. Shen et al., 2010). Therefore, 5-MeO-DMT is usually administered parenterally, most commonly via inhalation of smoke or vapor, and less commonly via intravenous, intramuscular, rectal, sublingual, or intranasal application (Alan K Davis et al., 2018a; Weil & Davis, 1994). Interestingly, previous research demonstrate that inhalation of 5-MeO-DMT is known to evoke a rapid onset of psychedelics effects within seconds which can last for 15-20 min (Weil & Davis, 1994), with subjective effects described as ‘*being shot out of a canon*’ (Oroc, 2009). This contrasts with intramuscular injection (IM) which is anecdotally reported to be more subtle, with a slower onset and a more gradual return from the psychedelic experience (5-Hive, 2017; InnerExplorer, 2017a, 2017b, 2017c). It is worth highlighting that although IM is known to place an additional burden on manufacturing a sterile product, Sherwood and colleagues (2019) identified IM as the most favorable route of administration 5-MeO-DMT for the following reasons; it avoids first pass metabolism, has high bioavailability, precise control of dosage, and evokes a gentle onset with slightly longer duration of effects. This contrasts with vaporization which, although avoids first pass metabolism, is a more accepted and easier way of administration, induces a rapid onset of effects through a much more complex drug delivery and finally make it challenging to control dose.

Recently, use of 5-MeO-DMT has become increasingly popular in naturalistic settings as a means for spiritual exploration, and is associated with enhanced well-being (Alan K Davis et al., 2018a; Alan K Davis et al., 2019a; Uthaug, Lancelotta, Szabo, Riba, & Ramaekers, 2019; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, & Kuchař, 2019). Although many people claim benefits from the use of 5-MeO-DMT, there are some who report experiencing “after-effects” following 5-MeO-DMT ingestion. In fact, anecdotal reports on online forums and Facebook support groups indicate that in certain cases, especially with vaporization (5-Hive, 2018a, 2018b), naturalistic use of 5-MeO-DMT is associated with the incidence of a complex and not well understood phenomenon that has been termed *reactivation*, referred to as the re-experiencing of some of the effects induced by 5-MeO-DMT intake at some point after the drug’s acute effects have worn off. From that description, reactivations could be analogous to the LSD flashback phenomenon referred to as “*a re-experiencing of certain elements of the drug induced state after the drug’s effects have worn off and a relative period of normalcy has been experienced*” (Heaton, 1975; Heaton & Victor, 1976; Matefy et al., 1978; Matefy & Krall, 1974). Nevertheless, it is worth highlighting that at the current time no scientific research can explain why reactivations (or LSD flashbacks) occur.

Recent unpublished reports from an online survey on the patterns of use of 5-MeO-DMT indicate that prevalence rates of reactivations (which lasts for 1-2 weeks) are as high as 72% in a subset of respondents using 5-MeO-DMT in a structured ritualized setting (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). However, up to 96% of these users report their reactivation as being a positive or neutral experience, and only 3% report their reactivation experiences as being negative (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). However,

with regard to reactivation following 5-MeO-DMT, participants of the recent survey study reported that common precipitating triggers of reactivations tend to be smoking marijuana, falling asleep, states of deep relaxation, deep meditation and certain smells and sounds that remind individuals of their experience (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). Although both reactivations and flashbacks are a recurrence of the users acute psychedelic experience(s), and triggered by similar factors (i.e relaxation), LSD flashbacks can occur for up to several years (Abraham, 1983), and more often are rated as a negative experience (Naditch & Fenwick, 1977). This is in contrast to 5-MeO-DMT reactivations which are reported to occur for 1-2 weeks, and more frequently rated to have a positive or neutral valence (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). Nevertheless, one's experience of a reactivation is likely dependent on the context within which it occurs, and it is likely that the reactivation data from the ceremonial group is influenced by the fact that the group provides robust support for preparation and integration of 5-MeO-DMT experiences which could explain the positive valence of these retrospective reports.

To date, although reactivation is commonly reported following use of 5-MeO-DMT through vaporization (5-Hive, 2018a, 2018b), no research has investigated whether different routes of administration may confer different reactivation rates, effects and experiences. Thus, the present study employed an internet-based survey to investigate and compare the phenomenon of reactivation, as well as other effects and experiences of synthetic 5-MeO-DMT after vaporization and IM. Specifically, the first objective of the present study was to assess the prevalence of reactivations (i.e., “*flashbacks/re-experiencing [parts of] the experience*”) following vaporization and IM of 5-MeO-DMT in the natural environment. The second objective was to examine

whether there were differences in the following characteristics of one's synthetic 5-MeO-DMT experience as a function of the route of administration: redosing, time of onset of acute effects, release of physical tension, satisfaction with life, and ratings of the experience with the mystical and ego dissolution. We expected that as per anecdotal reports, reactivations following use of vaporization would follow (5-Hive, 2018a, 2018b). Moreover, as IM is anecdotally known to induce a similar 5-MeO-DMT experience to vaporization, but with a more slower onset and gradual return from the psychedelic experience (5Hive 2017; InnerExplorer, 2017a; b; c), we expected that ratings of satisfaction with life as well as the ratings of the experience with the mystical and ego dissolution would not differ between the two routes of administration.

Methods

From November 2018 through June 2019 we posted written recruitment advertisements on different Facebook group pages related to 5-MeO-DMT, in addition to using snowball recruiting via messages and other websites. All recruitment advertisements contained information regarding the purpose of the study, the estimated amount of time required to complete the survey (approximately 10-15 minutes), and the anonymity of completing the survey. Upon clicking on any of our links to the survey in the advertisements, potential respondents were sent to the secure survey site (hosted by Qualtrics), where they viewed the informed consent document which repeated the purpose of the study and described eligibility criteria (being at least 18 years old, able to read and understand English, and having used synthetic 5-MeO-DMT at least once in their lifetime through either administration routes). No personal identifying information was collected in the survey.

A total of 50 participants began the survey. Of these, twenty-two participants were excluded because they did not out complete the entire survey, and 1 participant was excluded due to reported non-synthetic 5-MeO-DMT. Thus, the final sample was comprised of 27 participants, 14 participants in the IM group and 13 participants in the vaporization group. Participation was voluntary, and no incentives to participate were provided. All study procedures were approved by the Ethical Review Committee Psychology and Neuroscience (ERCPN), in Maastricht, the Netherlands.

5-MeO-DMT survey

We used a prior published 5-MeO-DMT survey (Alan K Davis et al., 2018a), and former naturalistic observational research on the effects of psilocybin, ayahuasca and 5-MeO-DMT (Mason, Mischler, Uthaug, & Kuypers, 2019b; Uthaug, Lancelotta, Szabo, Riba, et al., 2019; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, & Kuchař, 2019; Uthaug et al., 2018) as basis to inform the current survey. We began the survey by describing the two common types of administration routes of 5-MeO-DMT, namely: vaporization and IM. Then we asked the participants to write about their experience in a way that did not reveal their identity. Other questions asked about demographics (age, gender, origin, previous experience with psychedelics and 5-MeO-DMT), redose, onset of experience, and finally release of physical tension during and after the session. Finally, to get a better understanding of the subjective experiences between the two administration routes, we encouraged those who had experience with both administration routes to write a comparison of the two.

Reactivation

The survey also included items that asked whether participants had had a reactivation which we defined as “*flashbacks/re-experiencing [parts of] the experience*”, and if so, when and during what activity did the reactivation occur.

Subjective Measures

The survey also included three validated measures assessing the experience with ego dissolution, mystical experience and satisfaction with life;

Ego Dissolution Inventory (EDI)

EDI is an 8-item self-report scale that assesses the participant’s experience of ego dissolution, (Matthew M Nour et al., 2016). The participants answered the scale with making a mark on a line from either “*No, not more than usually*” (0 %) to “*Yes I experience this completely/entirely*” (100 %). The total EDI is scored by calculating the mean percentage of all the 8 items, and ranges from 0-100%. The scale has demonstrated sensitivity in assessing the experience of ego dissolution following ingestion of ayahuasca (Uthaug et al., 2018), and 5-MeO-DMT (Uthaug, Lancelotta, Szabo, Riba, et al., 2019; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, & Kuchař, 2019) in a naturalistic setting. The internal consistency of the total scale in the current sample was good (Cronbach’s alpha = .87).

Mystical Experience Questionnaire 30 items (MEQ-30)

MEQ is a 30 item self-report scale of mystical experience (Barrett, Johnson, & Griffiths, 2015; MacLean, Leoutsakos, Johnson, & Griffiths, 2012). The scale has four factors (mystical [which includes unitive experiences, noetic quality, and sacredness], positive mood, transcendence of time/space, and

ineffability) described in (Barrett et al., 2015). Each item was rated on a six-point scale (0 = none, not at all; 1 = so slight cannot decide; 2 = slight; 3 = moderate; 4 = strong [equivalent in degree to any previous strong experience]; and 5 = extreme [more than ever before in my life and stronger than 4]). Scores ranged from 0-100%. Higher scores indicate stronger mystical experiences. A “complete mystical experience” is counted when $\geq 60\%$ of the max possible score is endorsed on all four MEQ subscales. The MEQ30 has demonstrated sensitivity in assessing the effects of a range of psychedelic compounds, including LSD (Schmid & Liechti, 2018), MDMA (Lyvers & Meester, 2012), psilocybin (Barrett et al., 2015), ayahuasca (Schenberg, Tofoli, Rezinovsky, & SILVEIRA, 2017), and 5-MeO-DMT (Barsuglia et al., 2017a; Joseph Peter Barsuglia et al., 2018; Alan K Davis et al., 2018a). The internal consistency of the total scale in the current sample was excellent (Cronbach’s alpha = .96).

Satisfaction with Life (SWL)

SWL is a 5-item self-report scale, assessing someone’s subjective satisfaction with life (ED Diener et al., 1985; Pavot & Diener, 2009). The SWL has possible score-range of 5 to 35, with 5-9 indicating an extreme dissatisfaction with life, while scores between 31-35 indicating the respondent is extremely satisfied. The total score is obtained by adding points on each item. The scale has demonstrated sensitivity to assess satisfaction with life in participants who consumed ayahuasca (Uthaug et al., 2018), psilocybin (Mason et al., 2019b) and 5-MeO-DMT (Uthaug, Lancelotta, Szabo, Riba, et al., 2019; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, & Kuchař, 2019). The internal consistency of the total scale in the current sample was excellent (Cronbach’s alpha = .91).

Statistical analysis

First, frequency counts and a descriptive analysis was performed. Then, a Pearson's Chi-Square and t-test analysis was conducted to assess the similarities and/or differences between the reported demographics and subjective experiences using either administration routes. The alpha level of significance was set at 0.05. Phi was calculated to estimate effect sizes of significant frequency differences in outcome measures between administration routes. The data was analyzed with the Statistical Package for the Social Sciences 24.0 (SPSS 24) (SPSS, 2016).

Results

Sample characteristics

There were no significant group differences concerning their reported demographics (age, gender, origin, previous experience with psychedelics). Across both groups, the mean age of the 27 participants was 32 years of age (SE = 1.40). Out of those 18 were males, 7 females. Furthermore, 1 participant preferred not to report their gender, and 1 participant reported that his/her gender was not listed. Most participants were from North America (N=19), while the rest was from Europe (N=7), and Australia (N=1). Many participants had previous experience with psychedelics; i.e. psilocybin (N=25), LSD (N=22), ayahuasca (N=16), mescaline (N=16), DMT (N=14), 2C-B (N=14), ketamine (N=12), others (N=12), and iboga (N=2), while all (N=27) had previous experience with 5-MeO-DMT through either toad secretion from *Incilius alvarius*, synthetic- or plant form.

Acute effects of 5-MeO-DMT

All participants in the IM group reported that they experienced a relief of physical tension (N=14). This was significantly different from the vaporization group where only 8 out of 13 reported a relief of physical tension, (Pearson's Chi-Square = 6.608, Phi = .489, $p = .016$), see Table 2.

Onset of effects of 5-MeO-DMT

Most participants of the vaporization group reported that it took about 1-50 seconds (N= 11) for the acute effect to start after vaporizing the substance. This was significantly different from the time of onset of acute effects reported in the IM group where participants reported that it took 1-3 minutes (6 out of 14 participants) and 4-6 minutes (6 out of 14 participants) for the acute effects to start after IM (Pearson's Chi-Square = 13.305, Phi = .703, $p = .001$), see Table 2.

Redosing

It should be noted that five participants from the vaporization group reported they were unsure or did not know the weight of the dose they were administered during their session. For an overview of dosing schedules as reported by the participants, see Table 1. Moreover, redosing occurred significantly more frequently in the vaporization group (8 out of 13 participants, who overall received from 1 to 6 doses ranging from 3-35mg, compared to the participants in the IM group (2 out of 14 participants) who received 1-2 doses ranging from 5-10 mg, (Pearson's Chi-Square = 6.454, Phi = .489, $p = .018$), see Table 2.

	Intramuscular injection (N = 14)	Vaporisation (N = 13)	Pearson's Chi-Square	p	Phi
Redosing			6.45	.018	.489
Yes	2	8			
No	12	5			
Total	14	13			
Time of onset			13.35	.001	.703
1-50 seconds	2	11			
1-3 minutes	6	1			
4-6 minutes	6	1			
Total	14	13			
Reactivation			6.23	.021	.481
Yes	3	9			
No	11	4			
Total	14	13			
Relief of physical tension			6.60	.016	.495
Yes	14	8			
No	-	5			
Total	14	13			

Table 1. An overview of the differences between the two administration routes with regard to redosing, time of onset, reactivation and relief of physical tension.

PPT	Dose 1 (in mg)	Dose 2 (in mg)	Dose 3 (in mg)	Dose 4 (in mg)	Dose 5 (in mg)	Dose 6 (in mg)	Total doses (N)	Redose	EDI (%)
------------	---------------------------	-------------------------------	---------------------------	---------------------------	---------------------------	---------------------------	--------------------------------	---------------	----------------

INTRAMUSCULAR INJECTION (IM)

1	5	10					2	Yes	20,75
3	7						1	No	62,5
6	5						1	No	66,13
7	5						1	No	34,5
8	10						1	No	83,5
9	5						1	No	72,5
10	5						1	No	13,75
11	5						1	No	72,13
15	5						1	No	87,5
17	5						1	No	22,38
18	5						1	No	42,63
25	5	5	5	5	5		5	Yes	43,88
26	5						1	No	81,25
27	5						1	No	40,88

PPT	Dose 1 (in mg)	Dose 2 (in mg)	Dose 3 (in mg)	Dose 4 (in mg)	Dose 5 (in mg)	Dose 6 (in mg)	Total doses (N)	Redose	EDI (%)
-----	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-----------------------	--------	---------

VAPORIZATION

2	3	6	9	14			4	Yes	0
4	6	19					2	Yes	79,5
5	7	15	23				3	Yes	60,63
12	3	3	6	6	9	12	6	Yes	20,63
13	-	-					2	Yes	62,5
14	-						1	No	22,63
16	13						1	No	62
19	15	15					2	Yes	76,13
20	-						1	No	42,88
21	-	-					2	Yes	75,88
22	3						1	No	17,88
23	-						1	No	93,75
24	20	35					2	Yes	62,88

Table 2. An overview of reported dose information and ratings of the experience of ego dissolution (as assessed by EDI) per participant, per group.

Reactivation

Participants in the vaporization group reported significantly more frequent occurrences of reactivation (N=9) following ingestion compared to participants in the intramuscular injection group where 3 out of 14 participants reported having a reactivation, (Pearson's Chi-Square = 6.238,

$\Phi = .481$, $p = .021$), see Table 2. In the vaporization group 1 (7.7%) participant reported that reactivations occurred “during the day”, 1 (7.7%) “during the afternoon”, 2 (15.4%) “during the night”, 4 (30.8%) “other times”. Additionally, 1 (7.7%) participant reported that the reactivation occurred “during meditation”, 1 (7.7%) “when trying to sleep”, 1 (7.7%) “during sleep” and 5 (38.5%) participants reported “other activities”, see Table 3. Concerning the IM group, 1 (7.1%) participant reported that reactivations occurred “during the morning”, and 2 (14%) “other times”. Furthermore, 3 (21.4%) reported “other activities”, See table 3

Subjective measures of (acute) effects of 5-MeO-DMT

It should be noted that there was no significant difference between the groups concerning the scores of SWL, as well as EDI, and MEQ.

Satisfaction with Life

The mean (SE) ratings of the satisfaction with life scale, ranging from 0 to 35 was 25.35 (1.57) for the IM group, and 23.23 (2.34) for the vaporization group.

EDI

The mean (SE) ratings of EDI, ranging from 0 % to 100 %, was 53.16% (6.68) for IM group, and 52.09% (7.94) for vaporization group.

MEQ-30

The mean (SE) ratings of the total score of the MEQ-30, ranging from 0 % to 100 %, was 65.47% (4.70) for the IM group, and 57.43 % (6.95) for vaporization group. Moreover, the mean (SE) ratings of the different subscales of the MEQ-30 (i.e transcendence, positive mood, ineffability, and mystical), also ranging from 0 % to 100 % was 41.90 % (4.40), 74.28% (4.90),

43.57 % (1.99), and 67.04 % (6.16) for the IM group, and 50.25% (4.42), 59.23% (7.61), 35.64% (3.81) and 56.82% (9.25) for vaporization group.

Vaporization (N = 13)			
When	N (%)	Activity	N (%)
<i>During the morning</i>	-	<i>During meditation</i>	1 (7.7%)
<i>During the day</i>	1 (7.7%)	<i>When trying to sleep</i>	1 (7.7%)
<i>During the afternoon</i>	1 (7.7%)	<i>During sleep</i>	1 (7.7%)
<i>During the night</i>	2 (15.4%)	<i>Other activity</i>	5 (38.5%)
<i>Other times</i>	4 (30.8%)		
Intramuscular injection (N = 14)			
When	N	Activity	N
<i>During the morning</i>	1(7.1%)	<i>During meditation</i>	-
<i>During the day</i>	-	<i>When trying to sleep</i>	-
<i>During the afternoon</i>	-	<i>During sleep</i>	-
<i>During the night</i>	-	<i>Other activity</i>	3 (21.4%)
<i>Other times</i>	2 (14%)		

Table 3. *An overview of when and during what activity the reactivation occurred, from each group.*

Discussion

This study sought to investigate the prevalence of reactivations (i.e., “*flashbacks/re-experiencing [parts of] the experience*”) following vaporization and IM of synthetic 5-MeO-DMT in a naturalistic environment.

The second objective was to examine whether there were differences in the following characteristics of participants' synthetic 5-MeO-DMT experience as a function of the route of administration: redosing, time of onset of acute effects, release of physical tension, satisfaction with life, and ratings of the experience with the mystical and ego dissolution.

This study yielded some important findings. Firstly, participants in the vaporization group reported significantly more occurrences of reactivation compared to participants in the IM group. As previously stated, reactivations are said to be analogous to LSD, but are different in the sense that they are not long-lasting, and mostly rated as a positive or neutral experience (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). Although there is currently no scientific explanation as to why reactivations occur, nor why they are triggered, there are reasons to suspect that they are triggered by different activities of relaxation (Alan K Davis et al., 2018a; Ortiz Bernal, 2019). Additionally, non-pharmacological factors such as expectation, preparation and intention (set) are known to shape the response to psychedelics (Hartogsohn, 2014, 2016, 2017). Specifically expectations are built from previous experience with the psychedelic substance, and on general knowledge of its effects on affect and well-being (Haijen et al., 2018; Laska & Sunshine, 1973; Metzner et al., 1965), and modelled through verbal suggestions and instructions (Bartels et al., 2014; Kirsch, 1985, 2004; Martin-Pichora et al., 2011; Van Oorsouw & Merckelbach, 2007). With this in mind, and the fact that all participants had previous experience with 5-MeO-DMT, together with the many anecdotal reports available online of 5-MeO-DMT experiences, it is plausible that participants from either group formed different expectations of the reactivation phenomenon based on anecdotal reports online (5-Hive, 2017, 2018a, 2018b; InnerExplorer, 2017a, 2017b,

2017c). All in all, the present findings demonstrate that reactivations occur more frequently following use of 5-MeO-DMT through means of vaporization.

Secondly, relief of physical tension occurred significantly more often in the IM group (14/14 participants) relative to the vaporization group (8/13 participants). A possible explanation for this is the context in which the 5-MeO-DMT was taken in (Robin L Carhart-Harris et al., 2018; Hartogsohn, 2016). One can speculate whether the facilitator who guided the session was doing so in a way that allowed for, and encouraged the participant to connect with their body, and so too their emotions. Perhaps, some of the facilitators have focused more on the physical experience of 5-MeO-DMT whereas other may have focused on the mental experience. Unfortunately, we do not know the settings in which both formulations of 5-MeO-DMT were taken or whether and how these may differ between both formulations, if at all. It follows that further research of the specific setting around naturalistic use of 5-MeO-DMT, in addition to instructions and guidelines from the facilitator is warranted. Another possibility is that relief of physical tension is simply related to the route of administration. IM may evoke more muscle activation than vaporization, which could produce a larger relief of physical tension when the drug is cleared from the body (Legrand et al., 2019). Either way, relief of physical tension following 5-MeO-DMT through IM can be relevant to further investigate. Especially as Somatic Experiencing (SE), an experimental therapy approach developed by Dr. Peter Levine (2012), aimed at focusing on the client's perceived body sensations to bring about resolution of symptoms of mood related disorders is gaining scientific attention, and shows to positively impact people with mood disorders, especially Post-Traumatic Stress Disorder (PTSD) (Andersen, Lahav, Ellegaard, &

Manniche, 2017; Brom et al., 2017; Gupta, 2013; Heller & Heller, 2004; Peter Alan Levine, 1976; Peter A Levine, 2010; Peter A Levine & Frederick, 1997; C. Parker, Doctor, & Selvam, 2008; Payne, Levine, & Crane-Godreau, 2015; Whitehouse & Heller, 2008; Winblad, Changaris, & Stein, 2018). Notably, SE is also an essential part of the current protocol of MDMA in treatment for PTSD run by the The Multidisciplinary Association for Psychedelic Studies (MAPS) (Annie Mithoefer et al., 2013). Taken together, the result of the present study suggests that that release of physical tension that felt therapeutic (analogues to somatic release) occurred more frequently following IM compared to vaporization.

The reported time of onset of the acute effects was significantly slower in the IM group (i.e 1-3 and 4-6 minutes) compared to the vaporization group (1-50 seconds). This is consistent with previous research, demonstrating that onset of effects depend on administration route of 5-MeO-DMT, and occur more rapidly following vaporization (H.-W. Shen et al., 2010; Weil & Davis, 1994). Generally, the present study demonstrates that participants who had 5-MeO-DMT through IM experienced that the time of onset of effects was much slower than those in the vaporization group.

The present findings indicate that dose-ranges were larger in the group that used 5-MeO-DMT through vaporization (3-35 mg), compared to the IM group (5-10mg), and that redosing occurred significantly more frequently in people that vaporized 5-MeO-DMT (N=8) than in people that used 5-MeO-DMT through IM (N=2). A possible explanation for this may be related to the fact that the vaporization route of administration engenders an experience that lasts, on the average, 15-20 minutes (Weil & Davis, 1994), whereas the IM produces an experience that can extend well past 40-60 minutes (5-Hive,

2017; InnerExplorer, 2017a, 2017b, 2017c). One could speculate that individuals who are having the extended experience afforded by IM may feel a stronger sense of completion, or therapeutic closure at the end of the session that leaves them feeling a re-dose is not necessary, whereas those partaking of the substance via the vaporization route are left feeling their process is inconclusive, leading them to re-dose more often. However, this warrants further research. In sum, these results demonstrate that doses are larger, and that redosing occurs more often when people vaporize 5-MeO-DMT, compared to those who received 5-MeO-DMT through IM. no significant difference between the ratings of the psychedelic experience (as assessed by EDI and MEQ-30) or satisfaction with life in retrospect of the experience between the two groups. As per previous research, 5-MeO-DMT through either administration route generated an experience of ego dissolution, mystical experience and satisfaction with life like that of previous (naturalistic) research (Barsuglia et al., 2017a; Alan K Davis et al., 2018a; Uthaug, Lancelotta, Szabo, Riba, et al., 2019; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, & Kuchař, 2019). Specifically, EDI scores as well as total of MEQ-30 for both groups was moderately high, and in line with previous research assessing the psychedelic experience following use of ayahuasca (Uthaug et al., 2018) and 5-MeO-DMT (Barsuglia et al., 2017a; Joseph Peter Barsuglia et al., 2018), and has been shown to be an important factor for therapeutic effect (Leor Roseman et al., 2018b). As previously stated, both groups reported similar ratings of satisfaction with life (as assessed by SWL). The findings of average to high scores of SWL are consistent with previous studies reporting psychological changes after psychedelic use (Garcia-Romeu et al., 2014; Lawn, Hallak, Crippa, Dos Santos, et al., 2017; Mason et al., 2019b; Uthaug,

Lancelotta, Szabo, Riba, et al., 2019; Uthaug, Lancelotta, van Oorsouw, Kuypers, Mason, Rak, Šuláková, Jurok, Maryška, & Kuchař, 2019; Uthaug et al., 2018). Taken together, the present findings suggest that 5-MeO-DMT, through either administration route, evoked similar ratings of experiences of ego dissolution and mystical experiences as well scores of satisfaction with life.

This study is not without limitations. Limitations include the lack of a placebo-control, and control for non-pharmacological factors such as for example ‘set’ and ‘setting’. Furthermore, the respondents may have been inclined to report positive associations due to having a favorable view on the substance which in turn could have biased the results. The use of self-report measures is another limitation as participants are subject to retrospective recall bias (Coughlin, 1990). Moreover, there is no assurance that 5-MeO-DMT was consumed by the participants as no samples were collected for confirmation. Finally, this substance is illegal in most countries, thus participants who chose to fill out the online survey may not be representative of the overall group of users.

Though the findings of the present study are not conclusive, they add to the current clinical considerations of 5-MeO-DMT through IM by Sherwood and colleagues (2019). In sum, the present findings suggest there are no significant differences in subjective experiences of ego dissolution, mystical experience and satisfaction with life between groups that used 5-MeO-DMT through vaporization or IM. However, it was found that IM may not require a high dose, or many re-doses, compared to vaporization. Additionally, IM evoked the phenomenon of reactivations less frequently, had a slower onset of acute effects, and had a strong potential to bring about release of physical

tension (analogues to somatic release). Further research is warranted on the therapeutic effects of 5-MeO-DMT, especially through IM, as well as the topic of reactivation and somatic experiencing.

Chapter 7 - General discussion

Aims of this thesis

The research described in this dissertation investigated the effects of the psychedelic substances ayahuasca and 5-MeO-DMT on mental health-related variables such as affect, mindfulness, well-being, empathy, and creativity. The main objective motivating this dissertation was to explore whether ingestion of ayahuasca and 5-MeO-DMT was related to the improvement in affect, mindfulness, well-being, empathy and creativity. Secondly, this dissertation aimed to assess whether the magnitude of the psychedelic experience induced by ayahuasca and 5-MeO-DMT was correlated with changes in the mental health related variables. It was expected that ayahuasca and 5-MeO-DMT would demonstrate a similar therapeutic potential as psilocybin, evoking a rapid and persistent betterment in mental health related variables, correlated with the intensity ratings of the psychedelic experience.

Main findings of this dissertation

Ayahuasca and 5-MeO-DMT use in a naturalistic setting is associated with persisting betterment in mental health related variables

The research described in this thesis (**Chapters 2-6**) yielded some important and novel findings. First, use of ayahuasca or 5-MeO-DMT in a naturalistic setting was associated with persisting betterment in several mental health related variables for up to 4-weeks. Additionally, it was found that the improvement in mental health related variables was correlated with retrospective self-ratings of ego dissolution (EDI) and psychedelic experience (5D-ASC) experienced during the acute effects of either psychedelic. These

findings are not only in line with the expectation, but also in line with previous studies on ayahuasca and 5-MeO-DMT effects, in both naturalistic and lab settings, showing improvement in affect, creativity, and well-being (Alan K Davis et al., 2018a; Alan K Davis et al., 2019a; De Gregorio et al., 2018; Rafael G dos Santos et al., 2016; K. Kuypers et al., 2016; Flávia de L Osório et al., 2015; Palhano-Fontes et al., 2019; Rafael Faria Sanches et al., 2016), correlated by the ratings of a (profound) psychedelic experience, which has shown to be can be predictive of betterment in mental health induced by psychedelics (Leor Roseman et al., 2018b).

Although the studies in the present thesis were conducted in healthy participants, it is noteworthy that even in this population improvement is demonstrable on processes that are disturbed in patients suffering from mood-related disorders like depression, anxiety, and stress (Brinker & Dozois, 2009; Ciesla & Roberts, 2007; Park et al., 2004; Quello et al., 2005).

It is especially important to highlight the longevity of these effects. In fact, as seen in the studies of this dissertation **Chapter 2-6**, it appears that effects lasted beyond the session (up to 4 weeks) in which ayahuasca or 5-MeO-DMT was ingested. These findings are important as it points to the possibility of these substances to induce more than symptoms management in mood-related disorders which makes them an attractive novel treatment option to conduct further research on.

As previously stated in the introductory chapter (**Chapter 1**) of this dissertation, psychedelics are known to exert their (therapeutic) effects through various mechanisms. Such mechanisms include firstly their unique receptor affinities that affect neurotransmission and their ability to modulate brain activity and so too neuroplasticity (De Gregorio et al., 2018; Nichols,

2016), in addition to their ability to induce the experience of the mystical as well as ego dissolution, which has been linked to betterment in mental health related symptoms (Barsuglia et al., 2017a; Bogenschutz et al., 2015; Garcia-Romeu et al., 2014; Griffiths et al., 2011; Griffiths et al., 2008; Johnson et al., 2017; Klavetter & Mogar, 1967; Kurland et al., 1972; MacLean et al., 2011; Matthew M Nour et al., 2016; O'Reilly & Funk, 1964; Walter N Pahnke et al., 1970; Richards, 2015; Leor Roseman et al., 2018b; S. Ross et al., 2016). Furthermore, psychedelics appears to have the ability to disrupt the configuration of the brain's hierarchy (2019) (Robin L Carhart-Harris et al., 2012; Robin Lester Carhart-Harris et al., 2014; Lebedev et al., 2015; Frederic Sampedro et al., 2017; Tagliazucchi et al., 2016). Especially by reducing the activity the default mode network (Robin L Carhart-Harris et al., 2012; Robin L Carhart-Harris & Friston, 2010; Robin Lester Carhart-Harris et al., 2014; Robin L Carhart-Harris et al., 2017; Ciesla & Roberts, 2007; Cooney et al., 2010; Hamilton et al., 2015; Hamilton et al., 2011; Hilt & Pollak, 2012; Nolen-Hoeksema, 2000; Park et al., 2004), which has been linked to the behaviour of excessive rumination (Brinker & Dozois, 2009; Ciesla & Roberts, 2007; Cooney et al., 2010; Nolen-Hoeksema, 2000; Park et al., 2004). Essentially, by reducing the activity in the default mode network, an increase in mindfulness related capacities is evoked (Millière et al., 2018; Joaquim Soler et al., 2016), an improvement in symptoms of affect in mood-related disorders has been demonstrated to occur (Coffey & Hartman, 2008; Hilt & Pollak, 2012; Schroevers & Brandsma, 2010). Although the studies in this dissertation not explicitly study the activity of the default mode network, the questionnaires did assess symptoms of affect and mindfulness related capacities. As seen in the studies **Chapter 2-6**, there was an improvement in both affect and mindfulness, as well as other variables post ingestion of

ayahuasca and 5-MeO-DMT. Moreover, considering the recent REBUS model by Carhart-Harris and Friston (2019), and previous work on the effects of psychedelics on the brain, it is reasonable to assume that through ingesting either ayahuasca or 5-MeO-DMT, the activity in the participants default mode network was reduced. One can presume that this in turn allowed for bottom-up information to have more influence on the conscious experience of the participants and could very likely account for the reported betterment in mental health related variables (R. Carhart-Harris & Friston, 2019). Whats more is that findings also illustrate betterment in several mental health related variables following ingestion. In sum, the present findings of this dissertation illustrate that ayahuasca and 5-MeO-DMT use in a naturalistic setting is associated with persisting betterment in mental health related variables

Non-pharmacological factors play a role in betterment of mental health related variables following use of ayahuasca in a neo-shamanic, naturalistic setting

The findings of the study described in **Chapter 3** suggests that the reduction in symptoms of affect (depression, anxiety and stress) demonstrated after partaking in an ayahuasca ceremony cannot solely be attributed to the pharmacological effect of ayahuasca. On the contrary, this study shows that placebo in a social setting can induce betterment in symptoms of affect, and well-being. This introduces the possibility that the effects of ayahuasca (as well as other psychedelics ingested in a ritualistic setting) may be (in part) attributable to the placebo effect.

In psychedelic research the placebo response is explained through two mechanisms being expectation and learning (Benedetti, 2014). Firstly, it is known that expectations, preparation and intention ('mind-set') shape the

response to psychedelics (Hartogsohn, 2014, 2017), and that expectations are built from previous experience with the psychedelic substance, and on general knowledge of its effects on affect and well-being (Haijen et al., 2018; Laska & Sunshine, 1973; Metzner et al., 1965). As participants in the study (**Chapter 3**) had extensive previous experiences with ayahuasca, on average 23.7 times, as well as other (psychedelic) substances (N=30), it is reasonable to assume that the participants may have developed personal sets of expectation and intentions. Secondly, their repeated participation in ayahuasca ceremonies might also have stimulated the learning of associating the ceremony and ayahuasca with enhanced well-being that is memorized and experienced, even when taking a placebo.

The placebo effect is not uncommon in clinical research with conventional treatments in patients and similar mechanisms have been proposed to explain the strength of placebo effects (Colloca, 2014; Haour, 2005). Additionally, it is known that expectancies are modelled through verbal suggestions and instructions (Bartels et al., 2014; Kirsch, 1985, 2004; Martin-Pichora et al., 2011; Van Oorsouw & Merckelbach, 2007). For example, in a study by Van Oorsouw and Merckelbach (2007), it was investigated whether positive ("memory-enhancing") and negative ("memory-impairing") placebos may enhance and undermine, respectively, memory of a film fragment. Specifically, it was found that memory performance of the positive placebo group, was better than that of participants who received negative placebos, or control participants. Furthermore, a recent study highlights how healthcare providers' behavior and cognitive mind-sets can affect clinical interactions, and thus provide evidence for a socially transmitted placebo effect (Chen et al., 2019).

In the context of the study described in **Chapter 3**, one might speculate that (repeated) attendance of a ayahuasca ceremony, making these participants experienced users and not novel users, in addition to suggestions of the positive mental health effects of ayahuasca, by either peers, or facilitator(s) throughout the ceremony, may have stimulated some of the positive changes in mental health parameters that were observed after the ceremony. Likewise, the setting of the ceremony, such as the physical, social, and cultural environment is known to alter the mental experience of a pharmacological agent (Hartogsohn, 2014). Ceremonies included in the study in **Chapter 3** were always conducted in a supportive group environment which may very well have impacted the participants' overall experience in a positive way, and may have contributed to the improvements in affect (Adamson & Metzner, 1988). Previous research has demonstrated that psychedelics, like LSD, can enhance suggestibility by temporarily suspending the drive to maintain control over one's mind and environment (R. Carhart-Harris et al., 2015). This finding suggests that individuals can become unusually open and receptive to social group dynamics that take place during an ayahuasca ceremony and right after during integration sessions to support mental healing (Baker, 2005).

Taken together, the present findings underscore that non-pharmacological factors play a role in betterment of mental health related variables following use of ayahuasca in a neo-shamanic, naturalistic setting.

The immunomodulatory potential of 5-MeO-DMT through downregulation of cytokine IL-6

The study described in **Chapter 5** demonstrated 5-MeO-DMT-induced changes in two of the four assessed salivary biomarkers. Specifically, cortisol

levels significantly increased while IL-6 concentrations decreased immediately post-session while not affecting CRP and IL-1 β .

Cortisol, a steroid stress hormone, plays an important role in acute stress adaptation, and the restoration of homeostasis following stressful events (Malarkey & Mills, 2007). Although speculative, modulation of 5-HT₂ receptors by peak dose(s) of 5-MeO-DMT, might mimic an intense neuroendocrine stress-like state as suggested by previous studies on other psychedelics (dos Santos et al., 2011; Galvão et al., 2018; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Kyzar, Nichols, Gainetdinov, Nichols, & Kalueff, 2017; Schmid et al., 2015; Szabo & Frecska, 2016) and MDMA (Harris, Baggott, Mendelson, Mendelson, & Jones, 2002; Parrott, Lock, Adnum, & Thome, 2013; Parrott et al., 2014). Nevertheless, these findings are in good agreement with the literature regarding their fast-acting, stress-mimicking, neuromodulatory effects on human physiology (Do Yup Lee & Choi, 2015).

IL-6 is an important inflammatory cytokine that is released in the early phase of infections and essential in immune defense, but is also involved in pathological auto-inflammatory processes (Jones & Jenkins, 2018). Pharmacological manipulation of IL-6 secretion or the IL-6 trans-signaling pathway may offer novel possibilities for new generation vaccine design, therapy of infections, as well as autoimmune diseases (Garbers et al., 2018). In fact, there are anecdotal evidence suggesting that psychedelics have been used to treat for example Lyme disease and juvenile arthritis (Kagan, 2019).

Cortisol and other glucocorticoids are known to rapidly suppress inflammation and have been widely used in the therapy of acute and chronic inflammatory states (Gleeson et al., 2011). Thus, the observed decrease in

salivary IL-6 levels may be the direct consequence of increased cortisol secretion independent of any psycho-neuroimmune feedback effects, or 5-HT_{2A} and sigma-1 receptor modulatory actions of 5-MeO-DMT. Furthermore, the in vivo biological half-life of IL-6 is approximately 2 hours (Baran et al., 2018), and saliva samples were taken approx. 2-2.5 hours post-administration during the sessions. This may explain the observed, relatively low, effect size of IL-6 modulation by 5-MeO-DMT. Since salivary and plasma concentrations of the evaluated biomarkers are closely correlated, at least within the context of inflammatory and stress markers, saliva has been suggested as a potential qualitative surrogate for plasma in biomarker studies (La Fratta et al., 2018).

Although there was no correlation between salivary cortisol and IL-6 and subjective measures, and the psychedelic experience post-session, or at follow up, we observed an inverse correlation between CRP (C-reactive protein, a typical inflammatory marker in mammals that is produced by the liver as a response to circulating IL-6) levels and both awareness, non-judgement, and several 5D-ASC dimensions post-session, with a positive correlation between anxiety ratings on the 5D-ASC. At follow up there was a negative correlation between CRP levels and both awareness and nonjudgment indicating that higher levels of this stable inflammatory marker are negatively associated with higher cortical functioning, which corroborates the findings of others (reviewed in Raison & Miller, 2011). Moreover, we also observed an inverse correlation between IL-1 β and satisfaction with life and ratings of ego dissolution, however, the statistical power of our analysis (due to low sample numbers) is too low so we are unable to draw reliable inferences from the data. A negative correlation was found between IL-1 β

and description and satisfaction with life, and a positive correlation with stress at follow-up.

As mentioned above, CRP is considered a reliable biomarker of systemic inflammation, and inflammatory states. In psychoneuroimmunology and biological psychiatry, inflammation has been tightly linked to neurocognitive processes and behavioral traits (Bauer & Teixeira, 2018; Raison & Miller, 2011). Systemic inflammation can greatly influence mood, cognitive processing, and psychosocial functioning. For example, it has been shown that inflammatory challenge can increase self-reported feelings of social disconnection and self-awareness (Eisenberger et al., 2010; Moieni et al., 2015). The correlation results CRP-awareness and CRP-non-judgement are in line with previous findings showing an inverse correlation between CRP levels and psychological parameters (Asakura et al., 2015). Although inhalation of 5-MeO-DMT did not alter CRP levels significantly, CRP is an acute phase protein which production is under the direct control of IL-6, and both have been linked to neuropsychological regulatory processes within the context of inflammation (Del Giudice & Gangestad, 2018). One can speculate whether the observed sub-acute effect of 5-MeO-DMT on salivary IL-6 may also be expanded to significant changes in circulating CRP levels long-term. This hypothesis can be tested by measuring serum/plasma or salivary CRP levels several hours to several days post-administration. All things considered; the findings show the immunomodulatory potential of 5-MeO-DMT through downregulation of cytokine IL-6

Intramuscular injection as another possible administration route of 5-MeO-DMT

Another important finding of this dissertation includes further information about the effects and experiences evoked by 5-MeO-DMT through different routes of administration (i.e., vaporization and intramuscular injection [IM]) (5-Hive, 2017, 2018a, 2018b; Bartels et al., 2014; Haijen et al., 2018; Hartogsohn, 2014, 2017; InnerExplorer, 2017a, 2017b, 2017c; Kirsch, 1985, 2004; Laska & Sunshine, 1973; Martin-Pichora et al., 2011; Metzner et al., 1965; Van Oorsouw & Merckelbach, 2007). Specifically, the findings in **Chapter 6** indicate that there was no significant difference in effects and experiences of 5-MeO-DMT when administered through vaporization or IM. However, the results suggest that IM evoked the phenomenon of reactivations less frequently, induced a slower onset of acute effects, and had a strong potential to bring about release of physical tension (analogues to somatic release). As previously stated, expectations, preparation and intention ('mind-set') shape the response to psychedelics (Hartogsohn, 2014, 2017). It is therefore reasonable to assume that non-pharmacological factors such as expectation have played a role in the experience and post-session effects of the participants. It is plausible that participants in this study had different expectations based on their previous knowledge which could likely be derived from the various trip reports online available for both vaporization and IM. Furthermore, expectancies are known to be modelled through verbal suggestions and instructions (Bartels et al., 2014; Kirsch, 1985, 2004; Martin-Pichora et al., 2011; Van Oorsouw & Merckelbach, 2007). Thus, one could speculate whether the suggestions and instructions by the facilitator, could have also played a part in shaping their expectations which may have predicted the post-effects.

Although these study findings are not conclusive, they nevertheless add to the current clinical considerations of 5-MeO-DMT through IM by Sherwood and colleagues (2019). In essence, while the IM route of administration places an additional burden on the manufacturing of a sterile product, it has been identified as the most favorable route of administration 5-MeO-DMT for the following reasons: it avoids first-pass metabolism, has a high bioavailability, it allows for precise control of dosage, and evokes a gentle onset with a slightly longer duration of effects. To summarize, while future research is warranted, it is noteworthy that 5-MeO-DMT administered IM produced the phenomenon of reactivations less frequently, had a slower onset of acute effects, and had a strong potential to bring about release of physical tension (analogues to somatic release).

Save a toad, use a chemist

This dissertation also included the results of the analysis of five samples of dried secretion containing 5-MeO-DMT from the *Incilius alvarius* toad (**Chapter 4**) used at the various locations of assessments. The findings suggest that the main compound found in the toad secretion is 5-MeO-DMT (200-300 mg 5-MeO-DMT per dried gram). However, future research should conduct a vapor analysis to determine whether 5-MeO-DMT remains the main compound of the vapor which is inhaled by users. This present study finding has implications beyond the scope of this dissertation which is worth shedding light on.

As a matter of fact, the use of toad secretion as means of obtaining 5-MeO-DMT comes with several ethical and ecological considerations worth mentioning. These considerations were outlined in an article by the author of this dissertation titled “*The Ethical and Ecological Considerations of*

Inhaling Bufotoxins from Incilius Alvarius” (Uthaug, 2018). It highlights that the *Incilius alvarius* toad is not yet classified as endangered on the International Union for Conservation of Nature (IUCN) red list of threatened species, however this classification dates back to an assessment of the toad population in 2004 (Hammerson & Santos-Barrera, 2004). Thus, it is plausible that the increasing popularity of inhalation of 5-MeO-DMT vapor from dried toad secretion in underground ceremonies, may very well affect the stability of the toad population in the long run. It is likely that the increasing demand for the vapor will disturb the ecological equilibrium of the toads through the invasion of habitat, excessive milking, amphibian trafficking, and black-market dynamics ("Psychedelic Today's 5-MeO-DMT Course," 2018; Wake & Vredenburg, 2008). However, the harassment of the *Incilius alvarius* toad can be easily prevented by using synthetic 5-MeO-DMT. Switching from using toad secretion to synthetic 5-MeO-DMT is suggested for the following reasons; with toad secretion one can never know the exact ratio of the alkaloids. In other words, one can never be hundred percent sure that there are as high concentrations of 5-MeO-DMT in the secretions as illustrated in the sample analysis in this dissertation, or if it contains a cocktail of other bufotoxins with a different alkaloid ratio. Thus, obtaining a synthetic alternative is better regarding safety, as well as for effective and precise measure of dose. Furthermore, toad secretion appears to not be very different from synthetic 5-MeO-DMT in the sense that it evokes a similar trend of persisting effects as shown in **Chapters 4, 5 and 6** of this dissertation. Furthermore, it will be much easier for researchers to re-schedule and legalize a pure substance for medical use than a complex bufotoxin. In summary, although the analysis of the samples of toad secretion demonstrates that there is a high content of 5-MeO-DMT, it is advised that when one wants

to use this substance one should opt for the synthetic variant of 5-MeO-DMT for ethical, ecological and safety reasons.

Drawbacks related to use of longer-acting versus short-acting psychedelics

Despite the promising results from the studies in this dissertation, there are certain logistical drawbacks with the use of long(er)-acting psychedelic such as psilocybin in a Psychedelic Assisted Psychotherapy (PAP) context that need to be considered. Essentially, an experience with psilocybin could last up to 4-6 hours which trained psychotherapists acting as guides are meant to supervise (Johnson, Richards, & Griffiths, 2008; Riba et al., 2003). In addition, the participant is required to partake in several preparation sessions prior to the experience and subsequently a number of integration sessions (Johnson et al., 2008). The consequence is both time and cost consuming. This could pose logistical and financial hurdles to making this type of novel therapy broadly available in an accessible way to the many individuals in need (Johnson et al., 2017). It follows that 5-MeO-DMT might be a viable alternative to these longer-acting psychedelics which can bypass some of the logistical constraints with potentially comparable therapeutic effects. However, further clinical research is warranted before 5-MeO-DMT can be approved as a treatment tool alongside psychotherapy for mood-related disorders.

Limitations

It should be noted that the studies outlined in this dissertation are not without limitations. Firstly, concerning the studies on ayahuasca in **Chapter 2** and **Chapter 3**, as assessments were made in experienced psychedelic users it is plausible that participants reported effects are due to conditioned learning and

expectancy. Secondly, given the evidence of the role of set and setting in the positive effects of a ceremony, provided by the study in **Chapter 3**, it can be inferred that the effects shown in **Chapter 2-6** cannot integrally be ascribed to pharmacological factors alone but rather to the synergy between pharmacology and context (Fotiou, 2012; MacRae, 2004; M. J. Winkelman, 2014).

Suggestions for future research

Although ‘set’ and ‘setting’ are always mentioned as crucial ‘shapers’ of the psychedelic experience, their exact roles are not structurally investigated which warrants further research. With regard to ayahuasca ceremonies, such ‘shapers’ include for example whistling (Katz & De Rios, 1971), *icaros* (a South American indigenous colloquialism for magic song) (Bustos, 2008), purging (Fotiou & Gearin, 2019), social function (Andritzky, 1989), and finally diet (Fotiou, 2012; M Winkelman, 2007). The latter is especially interesting as there are growing evidence in support of the therapeutic effects of the human gut microbiome and probiotics on the symptoms of psychopathologies (Axling et al., 2012; Cryan & Dinan, 2012; Foster, Rinaman, & Cryan, 2017; H. Jiang et al., 2015; Liu & Zhu, 2018; Naseribafrouei et al., 2014; Pizarro & de la Torre, 2018; Rudzki & Szulc, 2018; Shondelmyer, Knight, Sanivarapu, Ogino, & Vanamala, 2018; Steenbergen, Sellaro, van Hemert, Bosch, & Colzato, 2015; Sylvia & Demas, 2018; Zheng et al., 2016). Research suggest that there is an interaction between the gut and brain (Cryan & Dinan, 2012; Galland, 2014; O’Mahony, Clarke, Borre, Dinan, & Cryan, 2015; Sylvia & Demas, 2018), and that diet can reverse the decrease in brain-derived neurotrophic factor (BDNF) levels, while decreasing the volume of limbic brain regions such as the

hippocampus, amygdala and prefrontal cortex which are associated with mood disorders (Bremner et al., 2000; C. Duman, Schlesinger, Russell, & Duman, 2004; Ronald S Duman, 2004a, 2004b, 2005; Greenwood et al., 2003; Martinsen, 1990; Mattson, 2005; Saylam, Üçerler, Kitiş, Ozand, & Gönül, 2006; Sheline, 2003; Sheline, Gado, & Kraemer, 2003; Sheline, Wang, Gado, Csernansky, & Vannier, 1996).

Traditions that use ayahuasca are known to have a holistic view on healing that differs from that in the Western society (Fotiou, 2012; Fotiou & Gearin, 2019). Specifically, ayahuasca users are not solely using ayahuasca to heal their mind, but also spirit and body (Fotiou, 2012). The latter is especially important, and call attention to what has been known since the hay-days of psychotherapy; the body cannot be left out of therapy (Payne et al., 2015). There exist several studies pointing to the effectiveness of bringing focus to the body in a therapy setting. One way of doing so is through Somatic Experiencing (SE), an alternative form of therapy coined by Dr. Peter Levine (P. Levine, 2012; Peter Alan Levine, 1976; Peter A Levine, 2010; Peter A Levine & Frederick, 1997) aimed at focusing on the client's perceived body sensations to bring about resolution of symptoms of mood-related disorders is gaining scientific attention, and shows to positively impact betterment in mood disorders, especially Post-Traumatic Stress Disorder (PTSD) (Andersen et al., 2017; Brom et al., 2017; Gupta, 2013; Heller & Heller, 2004; Leitch, Vanslyke, & Allen, 2009; P. Levine, 2012; C. Parker et al., 2008; Payne et al., 2015; Winblad et al., 2018). Another way of bringing attention to the body is through Holotropic Breathwork (HB) (Grof & Grof, 2010). HB are usually conducted in groups using a combination of accelerated breathing, evocative music, and a technique of bodywork to release bioenergetic and emotional blocks (Holmes, Morris, Clance, & Putney, 1996). Both techniques

warrant further investigation in order to assess their effectiveness and may also be helpful to study to better design a new novel treatment option using psychedelics for mood disorders.

Regarding 5-MeO-DMT, as there is little information about the specific non-pharmacological factors that make up the setting where this substance is ingested, future research should carry out further assessments in this area. Moreover, as the current literature on the topic is relatively scarce in comparison to that of ayahuasca and psilocybin, it follows that future research should also employ other assessment methods besides questionnaires and biomedical samples, such as brain imaging as per previous work by Carhart-Harris and colleagues (Robin L Carhart-Harris et al., 2012; Robin L Carhart-Harris et al., 2017). Assessing the effects of 5-MeO-DMT on brain activity is important as it allows to understand the effects of the psychedelic substance better and can be useful for exploring different aspects of human consciousness.

Concerning immunology, although the sample and effect sizes are low, findings of **Chapter 5** suggest possible anti-inflammatory effects of 5-MeO-DMT in humans through downregulation of IL-6. These findings warrant further investigation into the potential systemic anti-inflammatory effects of 5-MeO-DMT and other DMT analogs and their impact on mood-related disorders associated with an elevated levels of IL-6, such as for example major depressive disorder (MDD) or post-traumatic stress disorder (Carpenter, Heninger, Malison, Tyrka, & Price, 2004; Frommberger et al., 1997; Hiles, Baker, de Malmanche, & Attia, 2012; Karlović, Serretti, Vrkić, Martinac, & Marčinko, 2012; Kunz et al., 2011; Maes et al., 1999; Schaefer, Schmidt, Neumer, Scholler, & Schwarz, 2002; Valkanova, Ebmeier, & Allan,

2013). From the molecular biomedical point of view, several studies point to a causal relationship between inflammatory clinical conditions, certain cytokine-based therapies and depression (Jones KA et al. 2013 *Mol Cell Neurosci* 53:52-62.). For example, cancer and HIV patients who receive cytokine therapy are prone to develop cognitive and neurovegetative symptoms of depression (Anisman H et al. 2007 *J Neuroimmunol* 186:45-53; Pavol MA et al. 1995 *Neurology* 45:947-50.). Well-known comorbidities with depression have been documented in cases of rheumatoid arthritis, cardiovascular disease, or myocardial infarction where the patients exhibit elevated levels of inflammatory markers (Halaris A. 2009 *Int Angiol* 28:92-9; Johnson AK et al. 2006 *J Physiol Pharmacol* 57 Suppl 11:5-29; Dinan TG. 2009 *Curr Opin Psychiatry* 22:32-36.). Furthermore, antidepressant therapies, such as SSRIs, tricyclics, electroconvulsive shock therapy have been reported to reduce inflammatory markers (Dinan TG. 2009 *Curr Opin Psychiatry* 22:32-36; Jones KA et al. 2013 *Mol Cell Neurosci* 53:52-62.). The symptoms of depression caused by interferon-alpha therapy is also responsive to treatment with SSRIs but antidepressants have only a minor restoring effect on the balance of HPA axis function (Hernandez ME et al. 2008 *Eur Neuropsychopharmacol* 18:917-924.). It is also important to note that expression profiling of serum samples and monocytes from patients with major depression and bipolar disorder revealed common regulatory changes, increased levels of inflammatory markers including IL-1 β , IL-6, TNF- α cytokines and C-reactive protein (CRP) (Goldstein BI et al. 2009 *J Clin Psychiatry* 70:1078-1090.). Inflammatory processes and dysregulated immune functions have also been linked to psychotic disorders, e.g. the pathophysiology of schizophrenia (Khandaker GM et al. 2015 *Lancet Psychiatry* 2:258-270.). To understand the potential mechanisms and

therapeutic implications of these findings, a more integrative approach in modern medicine is required including clinical studies of anti-inflammatory therapies in mental and mood disorders, as well as testing the psychotherapeutic and neuropsychological effects of (potentially anti-inflammatory) serotonergic tryptamines in various settings.

Finally, although further research is warranted and welcomed on both ayahuasca and 5-MeO-DMT, it is clear that in order to make any psychedelic substance available to be used as an adjunct to Psychedelic Assisted Psychotherapy, they will have to gain approval by the Food and Drug Administration (FDA) (Lipsky & Sharp, 2001). Such approval would only be granted if the substance shows clinical benefit that outweighs the risks of use. Thus, it is especially important that further clinical assessments of ayahuasca and 5-MeO-DMT be carried out.

Conclusion

The aim of this dissertation was to further enhance the scientific knowledge on the effects induced by ayahuasca and 5-MeO-DMT in healthy participants in order to further assess their potential as novel treatment for mood-related disorders. The overall findings of the present dissertation indicate that use of both ayahuasca and 5-MeO-DMT evoke a betterment in mental health related variables, which in turn is correlated with intensity ratings of the psychedelic experience. However, findings are in no way conclusive, and warrants further clinical assessments, as well as research on the influence of non-pharmacological factors.

Valorisation addendum

This section addresses the impact and relevance of the studies described in this dissertation. Outlined are the way these studies are relevant to society, which target group can benefit, and how research findings have been disseminated.

Societal relevance

I would like to start this section by reconnecting with the background-section in **Chapter 1** of this dissertation. Here, the prevalence of mental health related disorders was highlighted, and the implications it can have on the individual and society if left untreated. Moreover, it was highlighted that both conventional first-line treatments in Western societies for individuals affected by mood-related disorders (i.e CBT and SSRIs), appears to be less able to effectively resolve the disorder (Kuyken et al., 2005; Peter A Levine & Frederick, 1997; Moncrieff, 2007; Turner & Rosenthal, 2008). This implies that attempts to find a treatment to achieve full remission of mood-related disorders remains largely unsuccessful (Hengartner, 2017; Hengartner et al., 2018; Moncrieff, 2007). Nevertheless, as the current dissertation demonstrates, psychedelic substances like ayahuasca and 5-MeO-DMT used in a naturalistic setting is associated with a decrease in symptoms of affect, an increase in mindfulness-related capacities, creativity, empathy and well-being, moderated by the ratings of the psychedelic experience. The evidence of persisting positive effects on mood, wellbeing and cognition, following ayahuasca and 5-MeO-DMT ceremonies are crucial because impaired mood, deficits in mindfulness, as well as creative, flexible thinking, are hallmark symptoms in mood-related disorders such as depression, anxiety, and post-

traumatic stress disorder (PTSD) (Samuel R Chamberlain, Naomi A Fineberg, Andrew D Blackwell, Trevor W Robbins, & Barbara J Sahakian, 2006; A. M. Cusi, G. M. MacQueen, R. N. Spreng, & M. C. McKinnon, 2011; U.-S. Donges et al., 2005; Lee & Orsillo, 2014; Morrison et al., 2016; Gabriela Nietlisbach, Maercker, Rösler, & Haker, 2010; Palm & Follette, 2011; Melissa Parlar et al., 2014).

Moreover, findings reveal that the long-term improvements of mindfulness-related capacities are not only limited to mindfulness-related practices such as meditation and yoga. Interestingly, increased mindfulness-related capacities could be beneficial in a therapeutic setting as it could prevent relapse in mood-related disorders (Breslin et al., 2002). Mindfulness has also shown to be a useful tool to develop emotion regulation skills (Linehan, 1993), and can facilitate acceptance and change processes (Hayes & Wilson, 2003; Strosahl & Wilson, 1999). Additionally, mindfulness is important for skill training in affective and interpersonal regulation prior to exposure (Cloitre et al., 2002). In sum, the use of mindfulness as an intervention for both post-traumatic stress disorder (PTSD), and addiction could theoretically break the behavioral loop in those individuals with a history of trauma and/or addiction (Cloitre et al., 2002).

Additionally, previous research demonstrates that a reduction in creative and empathic skills in populations where social interactions and subjective well-being are compromised. (A. T. Beck, 1967; Neumann et al., 2011). The enhancement of convergent thinking evoked post ayahuasca and 5-MeO-DMT use could reverse this and help to improve people's cognitive, emotional, and interpersonal capabilities. The enhancement of divergent

thinking is important in cognitive therapy as it can help strengthen psychological flexibility and adapt coping styles.

How would a treatment for mood-related disorders with psychedelics look like?

As per the introduction of this thesis (**Chapter 1**), although research points to both ketamine and psilocybin's efficacy in treatment of mental health related disorders, there appears to be more to treatment but a stand-alone pharmacological intervention (i.e alternative pharmacotherapy). Therefore, psychedelics such as ayahuasca and 5-MeO-DMT could potentially be used in a therapeutic setting as *catalysts* to bring about betterment in mood-related symptoms as part of Psychedelic-assisted Psychotherapy (PAP) (Schenberg, 2018). However, as we see per findings in **Chapter 3**, there are several non-pharmacological factors to account for with ayahuasca, and that its effect on the mental health related variables seem to be a result of the synergy between pharmacology and the context rather than pharmacology alone. This may make it problematic to use ayahuasca in a PAP-setting, unless the context is specifically altered to include the various other factors that makes up the context of an "ayahuasca-setting". However, as there are many ayahuasca ceremonies worldwide, and therefore many different contexts, there is exist not only one ayahuasca-setting but many. 5-MeO-DMT on the other hand is not tied up to any specific lineage or traditions. Consequently it may be easier to implement 5-MeO-DMT into a PAP setting similar to that outlined in the protocol for MDMA for PTSD (Mithoefer, Designee, Doblin, & Emerson, 2008). Nevertheless, specific adjustments is advised to be made, and one can presume that those would largely depend on future assessments of 5-MeO-DMT and the settings it shows to be effective in. It also appears that

regulations with regard to settings it is taken in is highly warranted due to the number of adverse effects associated with underground ceremonial settings ("5-MeO-DMT malpractice; Open Letter Concerning Abuses by Octavio Rettig and Gerry Sandoval," 2019). Thus, it is highly advised that 5-MeO-DMT is used in a structured, such as for example a PAP-setting, where a therapist, or therapy team would meet with the patient prior to their trip to psychologically prepare them, monitors them throughout their trip, and then helps them process their experience afterwards (i.e., integration).

Finally, as former research suggests, there are more targets besides the brain to focus on to bring about betterment in mood-related disorders. Consequently, it is strongly suggested that a novel treatment for mood-related disorders should not be developed yet as another a treatment or pharmacological intervention solely targeting the mind. Instead, there are reasons to believe that a holistic approach will be favorable. In fact, previous research on immunology, diet and brain-derived neurotrophic factor, and their connection with mood-related disorders demonstrate that the development and persisting symptoms of mood disorders appears to not to be the result of one process, but of a **whole** process.

Target groups

The findings discussed in this dissertation are relevant to multiple target groups. Firstly, the current findings are relevant to patients with various mood-related disorders. Secondly, the current findings are relevant for therapists working in the area of mental health. Thirdly, researchers in the field of psychedelics can use the knowledge of the present studies to base the design of placebo-controlled research on ayahuasca and 5-MeO-DMT. Moreover, the information in this dissertation can better guide other

researchers on how to go about their future research on psychedelics. Fourthly, the results of the studies summarized in this dissertation can inform organizations in the planning of potential clinical trials of ayahuasca and/or 5-MeO-DMT. Finally, the current findings are also interesting to the general population and (potential) drug users who would like to be further informed about the psychedelic substances such as ayahuasca and 5-MeO-DMT.

Dissemination and impact

One of the goals of this thesis was to assess (persisting) effects of ayahuasca and 5-MeO-DMT in humans, and to further translate the findings into practical applications of the effects following ingestion. The author of this dissertation has taken various efforts to ensure that the knowledge gained from these studies are spread across different target groups. Moreover, the five studies summarized in this dissertation have been published in or submitted to several international peer-reviewed journal to share the findings with the international research community. Worthy of note is that the study described in **Chapter 4**, on the effect of toad secretion containing 5-MeO-DMT on mental health related variables, was downloaded **120 000 times** after its publication (information retrieved on the 14th of February 2020). In addition, most of the research findings have been presented at various international conferences;

- September/October 2017 - the International Transpersonal Conference, Prague, The Czech Republic; poster presentation; “*Acute and Long-term Effects of Ayahuasca on Affect and Cognitive Thinking style*”.

- June 2018 - Beyond Psychedelic Conference in Prague, The Czech Republic – oral presentation: “*In-vivo Effects of Toad Venom (5-MeO-DMT) on Affect and Thinking Style*”;
<https://slideslive.com/38908677/invivo-effects-of-toad-venom-5meodmt-on-affect-andthinking-style>
- August 2019 – Breaking Convention 2019, in London, UK – oral presentation: “*Prospective Examination of Synthetic 5-Methoxy-N,N-dimethyltryptamine Inhalation: Effects on Salivary IL-6, Cortisol levels, Affect and Non-judgement*”;
<https://www.youtube.com/watch?v=URSqxFOcaas&t=373s>
- September 2019 – Insight Conference 2019, in Berlin, Germany – oral presentation:
“*The comparison of effects and experiences following either vaporization or intramuscular injection of synthetic 5-methoxy-N,N-dimethyltryptamine in a naturalistic setting*”;
<https://www.youtube.com/watch?v=opsWlr0MIu8&feature=share>

The research findings of various studies have also been discussed in podcasts and webinars.

- March.2018 - Webinar for Emma Sofia about Ayahuasca and 5-MeO-DMT, Oslo, Norway;
https://www.youtube.com/watch?v=hTTurLoK_78
- March 2018 - Psychedelics Today, USA – Podcast “*Ayahuasca ceremonies and 5-MeO-DMT*”;
<http://www.psychedelictoday.com/2018/03/21/malin-vedoy-uthaug-exploring-ayahuascaceremonies-and-5-meo-dmt/>

The future goal is to continue dissemination of the research findings through (inter)national journal publications, (inter)national conference visits, websites, in addition to the communication of research findings by means of workshops and public debates, presentations and podcasts in order to provide a more interactive atmosphere, and to help keep the scientific community as well as the general public informed and up to date about the topic.

Finally, it is important to highlight that a collective multidisciplinary effort is necessary at a global level considering the many people that are suffering unnecessarily from mood-related disorders. A collaboration amongst scientists from different backgrounds and disciplines is highly warranted to determine further translational value of psychedelics, as well as ayahuasca and 5-MeO-DMT. Besides more science, a collective effort is warranted to bring about further education and information around the topic of psychedelics to the general public, and so too politicians to bring about destigmatization, as well as policy change allowing for betterment in opportunities for the use of psychedelics in treatment of mood-related disorders. A way to go about such behavioral change on a societal level can perhaps be further investigated using Intervention Mapping (Bartholomew, Parcel, & Kok, 1998; Kok, Schaalma, Ruiter, Van Empelen, & Brug, 2004).

Summary

Chapter 1 sketches the need for a novel treatment option for mood-related disorders. It was highlighted that efforts to find such a treatment option have been made through research on both ketamine as well as the psychedelic substance psilocybin. Moreover, previous research highlights that other psychedelics such as ayahuasca and 5-methoxy-dimethyltryptamine (5-MeO-DMT) are worthy of further investigation. However, as the legal status of psychedelic substances worldwide makes it rather difficult to conduct (clinical) research, several naturalistic observational studies were designed for this doctoral dissertation to further investigate the effects of both ayahuasca and 5-MeO-DMT on mental health-related variables. The studies described in **Chapter 2-3** investigated the pharmacological and non-pharmacological impact of ayahuasca ingested in a naturalistic, (neo)shamanic setting. The studies in the following **Chapters 4-6** investigated the effects of 5-MeO-DMT on psychological and biomedical processes in humans.

Specifically, the within-subject study in **Chapter 2** examined the post-acute and longer-term effects of ayahuasca in users in Colombia and the Netherlands (N=57). It was hypothesized that ayahuasca would evoke betterment in mental health related symptoms, and that changes would correlate with the degree of ego dissolution evoked by the psychedelic experience. Assessments were made before, the day after, and 4-weeks after the ayahuasca ceremony and included a test-battery designed to assess symptoms of affect, well-being, mindfulness related capacities and creativity. Relative to baseline, there was a significant reduction in self-reported levels

of depression and stress that persisted for 4-weeks. Additionally, convergent thinking improved post-ayahuasca up until 4-weeks follow-up. Satisfaction with life and several mindfulness related capacities improved the day after the ceremony but failed to reach significance 4 weeks after. Moreover, changes in affect, satisfaction with life, and mindfulness were correlated with the level of ego dissolution experienced during ayahuasca, and unrelated to previous experience with ayahuasca. Thus, it was concluded that ayahuasca produces sub-acute and long-term improvements in affect and cognitive thinking style in non-pathological users.

The placebo-controlled, within-subject study in **Chapter 3** explored whether the post-session effects on mental health related variables (affect, cognition and empathy) were pharmacologically produced by ayahuasca (matter), or due to set (mind). Assessments were made pre and post-ayahuasca ingestion in participants of ayahuasca retreats of naturalistic, neo-shamanic origin hosted in The Netherlands, Spain and Germany. Assessments involved the distribution of a test-battery including standardized measures of affect and cognition as well as an objective task of empathy. Participants were randomized into two treatment groups that ingested capsules containing ayahuasca (N=14) or placebo (N=16). It was predicted that that ‘set’ and ‘setting’ would impact both groups, while the pharmacological effects of ayahuasca would be most prominent in the group that received ayahuasca. Results suggest that participants overall reported low ratings of the experience of ego dissolution and altered states of consciousness in retrospect of the session. Moreover, relative to baseline, a repeated measure analysis revealed that betterment of depression, stress, and anxiety symptoms were related to non-pharmacological factors of the ceremony, while an increase in implicit arousal to negative stimuli (emotional empathy) was pharmacologically

related to ayahuasca. It was concluded that subjective improvements in affect (depression, anxiety and stress) of participants of naturalistic ayahuasca ceremonies can be driven by non-pharmacological factors such as expectations and intentions (mind-set). Furthermore, improvement in implicit arousal to negative stimuli (empathy) was related to the pharmacological treatment with ayahuasca (matter).

The within-subject study in **Chapter 4** sought to investigate the sub-acute and long-term effects of the inhalation of vapor from dried toad secretion containing 5-MeO-DMT. Assessments were made before, after the session, and 4 weeks later in users (N=42) at various European locations (Spain, The Netherlands and Czech Republic) through the distribution of a questionnaire designed to assess symptoms of affect, mindfulness and cognition. It was expected that symptoms of affect, such as depression, anxiety, stress and somatization reported by participants at baseline would be ameliorated by use of the vapor from dried toad secretion containing 5-MeO-DMT through means of inhalation, and that measures of, cognition, such as creative thinking and mindfulness related capacities, would improve. It was expected that such changes would persist over time and would still be measurable at 4 weeks after intake. Relative to baseline, ratings of satisfaction with life and convergent thinking significantly increased right after intake and were maintained at follow-up 4 weeks later. Ratings of mindfulness also increased over time and reached statistical significance at 4 weeks. Ratings of depression, anxiety and stress decreased after the session, and reached significance at 4 weeks. Participants that experienced high levels of ego dissolution or oceanic boundlessness during the session displayed higher ratings of satisfaction with life and lower ratings of depression and stress. All in all, this study suggests that a single inhalation of vapor from toad secretion

containing 5-MeO-DMT produces, rapid and persistent improvements in satisfaction with life, mindfulness and psychopathological symptoms, and that these changes are associated to the strength of the psychedelic experience.

The within-subject study in **Chapter 5** assessed the effects of synthetic 5-MeO-DMT inhalation on salivary biomarkers, as well as mental health related variables such as affect and mindfulness. Eleven participants were assessed using a test-battery before, immediately post-session, and 7 days following a session where they inhaled vapor of synthetic 5-MeO-DMT at location in Prague, The Czech Republic. Additionally, salivary samples were collected before and within 2 hours of their session. It was predicted that symptoms of depression, anxiety, and stress would decrease, and ratings of satisfaction with life would increase, from before to after inhalation of vaporized synthetic 5-MeO-DMT. It was found that inhalation of synthetic 5-MeO-DMT vapor significantly increased cortisol levels and decreased IL-6 concentrations in saliva immediately post-session. These changes were not correlated to ratings of mental health or the psychedelic experience. Relative to baseline, ratings of non-judgement significantly increased, and ratings of depression decreased immediately post-session and at follow-up. Ratings of anxiety and stress decreased from baseline to 7-day follow-up. Participant ratings of the psychedelic experience correlated negatively with ratings of affect and positively with ratings of non-judgement. Taken together, it was concluded that inhalation of vaporized synthetic *5-MeO-DMT* produced significant changes in inflammatory markers, improved affect, and non-judgement in volunteers.

The within-subject study described in **chapter 6** aimed to assess whether intramuscular injection (IM) and vaporization of 5-MeO-DMT induced different reactivation rates (flashback), changes in satisfaction with life, as well as ratings of the experience with ego dissolution and the mystical experience. An assessment was made using an online-survey designed to explore the effects of 5-MeO-DMT in retrospect of the 5-MeO-DMT experience of 27 individuals ($M_{age}=32$. $SD=1.40$; males=18; North America=19) who had either vaporized (N=13) or intramuscularly injected (N=14) 5-MeO-DMT. There was no significant difference between either group regarding demographics or subjective measures. Of the 14 participants in the IM group, 3 (21%) reported reactivations; in contrast, of the 13 participants in the vaporization group, 9 (69%) reported reactivations. Redosing (more than 1 dose) occurred more frequently in the vaporization group (N=8) (1-6 times with 3-35mg of 5-MeO-DMT), relative to the IM group (N=2) (1-5 times with 5-10 mg of 5-MeO-DMT). All participants in the IM group experienced release of physical tension, compared to 8 participants in the vaporization group. Participants in the IM group reported longer time of onset of acute effects (between 1-3 [N=6] and 4-6 minutes [N=6]), relative to the vaporization group where the majority (N=11) reported a rapid onset of 1-50 seconds. It was concluded that compared to vaporization, the IM route of administering 5-MeO-DMT is associated with lower and less doses, lower frequencies of reporting reactivation, a higher frequency of physical tension release, and longer onset of acute effects.

Finally, in **Chapter 7** the key findings of all the studies are discussed in a broader perspective, and implications as well as recommendations for future research is provided. The studies presented in this dissertation give direction to future placebo-controlled research with ayahuasca and 5-MeO-DMT and

endorses studies into their potential as a novel treatment method of mood-related disorders.

Samenvatting

Hoofdstuk 1 schetst de noodzaak van een nieuwe behandelingsmogelijkheid voor stemmingsgerelateerde aandoeningen. Momenteel wordt veel onderzoek verricht naar de dissociatieve stof ketamine en de psychedelische stof psilocybine voor de behandeling van depressie. Een beperkt aantal studies suggereert dat andere psychedelica zoals ayahuasca en 5-methoxydimethyltryptamine (5-MeO-DMT) ook interessant kunnen zijn voor therapeutische toepassing. Echter, omdat de wettelijke status van psychedelische stoffen wereldwijd het vrij moeilijk maakt om gecontroleerd (klinisch) onderzoek te doen met deze stoffen, werd in dit proefschrift uitgeweken naar naturalistische observatiestudies om de effecten van zowel ayahuasca als 5-MeO-DMT op mentale gezondheidsgelateerde variabelen nader te onderzoeken. De studies die worden beschreven in **hoofdstuk 2-3** onderzochten de farmacologische en niet-farmacologische invloed van ayahuasca gebruik in een naturalistische, (neo)sjamanistische setting op psychologisch welbevinden en welzijn. De studies die worden beschreven in **hoofdstukken 4-6** onderzochten de effecten van 5-MeO-DMT op psychologisch welbevinden en welzijn bij de mens.

In **hoofdstuk 2** werd gekeken naar de post-acute en lange termijn effecten van ayahuasca bij gebruikers in Colombia en Nederland (N=57). De hypothese was dat ayahuasca een vermindering van mentale gezondheidsklachten zou veroorzaken, en dat deze veranderingen zouden correleren met de mate van 'ego-dissolutie' die de psychedelische ervaring oproept. De metingen vonden plaats voor, de dag na en 4 weken na de ayahuasca-ceremonie en bevatte een testbatterij die ontworpen was om affect,

welzijn, mindfulness-gerelateerde capaciteiten en creativiteit te beoordelen. Ten opzichte van baseline was er een significante vermindering van zelf gerapporteerde symptomen van depressie en stress die 4 weken lang aanhield. Bovendien verbeterde het convergente denken tot aan 4 weken na ayahuasca gebruik. Tevredenheid met het leven en verschillende mindfulness gerelateerde capaciteiten verbeterden de dag na de ceremonie. Bovendien waren veranderingen in affect, tevredenheid met het leven en mindfulness gecorreleerd met de mate van 'ego-dissolutie' die werd ervaren tijdens de ayahuasca ceremonie . Er werd geconcludeerd dat ayahuasca subacute en lange termijn verbeteringen in affect en cognitieve denkstijl oplevert bij niet-pathologische gebruikers.

De placebo-gecontroleerde, naturalistische studie in **hoofdstuk 3** onderzocht of de post-ayahuasca effecten op gezondheidsgerelateerde variabelen (affect, cognitie en empathie) farmacologisch worden veroorzaakt door ayahuasca, of te wijten zijn aan verwachtingen bij de deelnemers aan ayahuasca ceremonies. Metingen vonden plaats voor en na het innemen van ayahuasca bij deelnemers aan naturalistische, neo-shamanistische ayahuasca ceremonies in Nederland, Spanje en Duitsland. De metingen bestonden uit subjectieve metingen van welbevinden en een objectieve meting van van empathie. De deelnemers werden gerandomiseerd over twee behandelingsgroepen die capsules met ayahuasca (N=14) of placebo (N=16) innamen. Er werd voorspeld dat 'set' en 'setting' beide groepen zou beïnvloeden, terwijl de farmacologische effecten van ayahuasca het meest prominent aanwezig zouden zijn in de groep die ayahuasca kreeg. De resultaten suggereerden een milde toename in 'ego-dissolutie' in beide groepen. Bovendien bleek dat ten opzichte van baseline dat verbetering van depressie, stress en angstsymptomen vooral gerelateerd waren aan niet-farmacologische factoren

van de ceremonie, terwijl een toename in impliciete reacties op negatieve prikkels (emotionele empathie) enkel gerelateerd was aan het gebruik van ayahuasca. Geconcludeerd werd dat subjectieve verbeteringen in affect (depressie, angst en stress) van deelnemers aan ayahuasca ceremonies kunnen worden gedreven door niet-farmacologische factoren zoals verwachtingen en intenties. Verder was de verbetering in emotionele empathie gerelateerd aan de farmacologische behandeling met ayahuasca.

In het onderzoek in **hoofdstuk 4** werd getracht de subacute en lange termijn effecten van inhalatie van damp van gedroogd paddengif dat 5-MeO-DMT bevat, te onderzoeken. Voor, direct na de inhalatie en 4 weken later werden bij gebruikers (N=42) in verschillende Europese locaties (Spanje, Nederland en Tsjechië) metingen verricht door middel van een vragenlijst om affect, mindfulness en cognitie te beoordelen. De verwachting was dat de symptomen van depressie, angst, stress en somatisatie die door de deelnemers tijdens baseline werden gerapporteerd, zouden afnemen na inhalatie van het gedroogde paddengif en dat creatief denken en mindfulness-gerelateerde capaciteiten, zouden verbeteren. De verwachting was dat dergelijke veranderingen zouden aanhouden en 4 weken na inname nog steeds meetbaar zouden zijn. Ten opzichte van baseline nam de tevredenheid met het leven en het convergente denken direct na de inname en 4 weken later toe. Subjectieve beoordelingen van mindfulness namen ook toe en bereikten een statistische significantie na 4 weken. Symptomen van depressie, angst en stress daalden na de sessie en bereikten significantie na 4 weken. Deelnemers die een sterke mate van ‘ego-dissolutie’ ervoeren tijdens de sessie vertoonden een grotere toename in tevredenheid met het leven en een grotere afname van depressie en stress. Al met al suggereert deze studie dat paddengif met 5-MeO-DMT een snelle en aanhoudende verbetering veroorzaakt in psychologisch

welbevinden en welzijn en dat deze veranderingen samenhangen met de intensiteit van de psychedelische ervaring.

In de naturalistische studie in **hoofdstuk 5** werden de effecten van synthetische 5-MeO-DMT inhalatie op biomarkers van het immuunsysteem beoordeeld, evenals de invloed op gezondheidsgelateerde variabelen zoals affect en mindfulness. Elf deelnemers werden beoordeeld met behulp van een testbatterij voor, direct na de sessie en 7 dagen later, waarbij ze damp van synthetische 5-MeO-DMT inhaleerden op een locatie in Praag, Tsjechië. Daarnaast werden er vooraf en binnen 2 uur na de sessie speekselmonsters verzameld. Er werd voorspeld dat de symptomen van depressie, angst en stress zouden afnemen en dat de tevredenheid over het leven zou toenemen, na het inhaleren synthetische 5-MeO-DMT. Uit de resultaten bleek dat inhalatie van synthetische 5-MeO-DMT damp de cortisolspiegels significant verhoogde en dat de IL-6 concentraties in het speeksel onmiddellijk na de sessie afnamen. Deze veranderingen waren niet gecorreleerd met veranderingen in geestelijke gezondheid of de psychedelische ervaring. Ten opzichte van baseline, steeg mindfulness van de deelnemers en verminderden de symptomen van depressie direct na de sessie en na 7 dagen. Symptomen van angst en stress daalden significant na 7 dagen. De intensiteit van de psychedelische ervaring correleerde negatief met de verandering in affect en positief met beoordelingen van mindfulness. Er werd geconcludeerd dat inhalatie van synthetische 5-MeO-DMT damp significante veranderingen in biomarkers van ontstekingsprocessen veroorzaakte, en een verbetering van affect and mindfulness.

De survey studie beschreven in **hoofdstuk 6** had tot doel te beoordelen of intramusculaire injectie (IM) en inhalatie van 5-MeO-DMT damp tot

verschillende ‘reactivatie’ frequenties (flashback) zou leiden, en tot verschillen in tevredenheid met het leven, ego-dissolutie en mystieke ervaringen. Middels een online-enquête werden de effecten van 5-MeO-DMT onderzocht bij 27 personen die 5-MeO-DMT gebruikten via inhalatie (N = 13) of via een intramusculaire injectie (N = 14). Er was geen significant verschil tussen beide groepen wat betreft demografie of subjectieve metingen van welbevinden. Van de 14 deelnemers in de intramusculaire groep meldden 3 (21%) personen reactiveringen. Van de 13 deelnemers in de verdampingsgroep daarentegen meldden 9 (69%) personen reactiveringen. Herdosering (meer dan 1 dosis) kwam vaker voor in de verdampingsgroep (N=8) (1-6 keer met 3-35mg van 5-MeO-DMT), ten opzichte van de intramusculaire groep (N=2) (1-5 keer met 5-10 mg van 5-MeO-DMT). Alle deelnemers in de intramusculaire groep rapporteerden vrijkomen van fysieke spanning, vergeleken met 8 deelnemers in de verdampingsgroep. Deelnemers in de intramusculaire groep rapporteerden een latere start van acute effecten (tussen 1-3 [N=6] en 4-6 minuten [N=6]), ten opzichte van de verdampingsgroep waar de meerderheid (N=11) een snelle start van 1-50 seconden meldde. Geconcludeerd werd dat in vergelijking met inhalatie, de intramusculaire route voor het toedienen van 5-MeO-DMT geassocieerd is met een lagere dosering, minder toedieningen, minder reactivaties, meer (vrijgave van) fysieke spanning en een later begin van acute effecten.

Tot slot worden in **hoofdstuk 7** de belangrijkste bevindingen van alle studies in een breder perspectief besproken en worden de implicaties en aanbevelingen voor toekomstig onderzoek gegeven. De studies die in dit proefschrift worden gepresenteerd geven richting aan toekomstig placebo gecontroleerd onderzoek met ayahuasca en 5-MeO-DMT en ondersteunen

studies naar hun potentieel als een nieuwe behandelingsmethode voor stemmingsgerelateerde aandoeningen.

Resumen

El **capítulo 1** esboza la necesidad de nuevas opciones de tratamiento para trastornos relacionados con el estado de ánimo y salud mental. Se destacó que esfuerzos para encontrar dichas opciones de tratamiento se han realizado a través de investigaciones con ketamina, así como con la sustancia psicodélica psilocibina. Además, investigaciones previas destacan que otros psicodélicos como la ayahuasca y la 5-metoxi-N,N-dimetiltriptamina (5-MeO-DMT) son dignos de investigación más a fondo. Sin embargo, dado que el estado legal de las sustancias psicodélicas en todo el mundo dificulta la realización de investigaciones (clínicas), para esta tesis doctoral se diseñaron varios estudios de observación naturalística para investigar más a fondo los efectos de la ayahuasca y la 5-MeO-DMT en variables relacionadas con la salud mental. Los estudios aquí descritos en los **Capítulos 2-3** investigaron los impactos farmacológicos y no-farmacológicos de la ayahuasca ingerida en un contexto neo (chamánico) de manera naturalística. Los siguientes estudios en los **Capítulos 4-6** investigaron los efectos de la 5-MeO-DMT en procesos psicológicos y biomédicos en humanos.

Específicamente, el estudio de análisis intra-individual en **el capítulo 2** examinó los cambios post-agudos y efectos a largo plazo en personas que utilizan la ayahuasca en Colombia y en los Países Bajos (N=57). Se planteó la hipótesis de que la ayahuasca evocaría mejora en síntomas relacionados con salud mental, y que los cambios se correlacionarían con el grado de disolución del ego producido por la experiencia psicodélica. Las evaluaciones fueron realizadas antes, el día después y 4 semanas después de la ceremonia de ayahuasca e incluyeron una batería de pruebas diseñada para evaluar

síntomas de afecto, bienestar, capacidades relacionadas con la atención plena y la creatividad. Relativo a la línea de base hubo una reducción significativa en los niveles auto-reportados de depresión y estrés que persistieron por 4 semanas. Además, el pensamiento convergente mejoró después de la ayahuasca y se mantuvo hasta las 4 semanas de seguimiento. La satisfacción con la vida y varias capacidades relacionadas con la atención plena mejoraron el día después de la ceremonia, pero no alcanzaron importancia 4 semanas después. Así mismo, los cambios en el afecto, la satisfacción con la vida y la atención plena se correlacionaron con el nivel de disolución del ego experimentado durante la ayahuasca, y esto no se relaciona a la experiencia previa con la ayahuasca. Con esto, se concluyó que la ayahuasca produce mejoras sub-agudas y a largo plazo en el estilo de pensamiento afectivo y cognitivo en usuarios no-patológicos.

El estudio controlado con placebo y con análisis intra-individual en el **Capítulo 3** exploró si los efectos sobre las variables relacionadas con salud mental (afecto, cognición y empatía) posteriores a la sesión fueron producidos farmacológicamente por la ayahuasca (materia), o si fue debido al estado de ánimo (mente). Las evaluaciones fueron realizadas antes y después de la ingesta de ayahuasca en participantes de retiros neo-chamánicos que se realizaron en Los Países Bajos, España y Alemania de manera naturalística. Las evaluaciones consistieron en la distribución de una batería de pruebas que incluye medidas estandarizadas de afecto y cognición, así como como tarea objetiva de empatía. Los participantes fueron asignados de manera aleatoria a dos grupos de tratamientos que ingirieron cápsulas que contenían ayahuasca (N=14) o placebo (N=16). Se predijo que ese “set” and “setting” (que se refiere al estado mental de la persona (set) y al entorno físico (setting)) afectarían a ambos grupos, mientras que los efectos farmacológicos de la

ayahuasca serían más prominentes en el grupo que recibió la ayahuasca. Los resultados sugieren que los participantes en general reportaron bajas calificaciones de la experiencia de disolución del ego y estados alterados de conciencia en retrospectiva de la sesión. Además, relativo al inicio, un análisis de medidas repetidas reveló que el mejoramiento de los síntomas de depresión, estrés y ansiedad estaban relacionados con factores no farmacológicos de la ceremonia, mientras que un aumento en la excitación implícita a estímulos negativos (empatía emocional) estaba farmacológicamente relacionado a la ayahuasca. Se concluyó que las mejoras subjetivas en el afecto (depresión, ansiedad y estrés) de los participantes de ceremonias naturalísticas de ayahuasca pueden ser impulsados por factores no-farmacológicos como las expectativas y las intenciones (mentalidad). Además, la mejora en la excitación implícita a los estímulos negativos (empatía) se relacionó con el tratamiento farmacológico con ayahuasca (materia).

El estudio de análisis intra-individual en el **Capítulo 4** buscó investigar los efectos sub-agudos y a largo plazo de la inhalación de vapor de las secreciones de sapo secas que contienen 5-MeO-DMT. Las evaluaciones se realizaron antes, después de la sesión y 4 semanas después en usuarios (N=42) en varios lugares de Europa (España, Países Bajos y Republica Checa) mediante la distribución de un cuestionario diseñado para evaluar los síntomas de afecto, atención plena y cognición. Se esperaba que los síntomas de afecto, como la depresión, ansiedad, estrés y somatización reportada por los participantes al inicio del estudio serían ameliorados por el uso (inhalación) del vapor de la secreción de sapo que contiene 5-MeO-DMT, y que las medidas de cognición, como pensamiento creativo y capacidades relacionadas con la atención plena mejorarían. Se esperaba que dichos cambios persistirían hasta 4 semanas

después de la ingesta. Relativo a la línea de base, las calificaciones de satisfacción con la vida y el pensamiento convergente aumentaron significativamente después de la ingesta y se mantuvieron en el seguimiento 4 semanas mas tarde. Las calificaciones de atención plena también aumentaron con el tiempo y alcanzaron significación estadística a las 4 semanas. Las calificaciones de depresión, ansiedad y estrés disminuyeron después de la sesión y alcanzaron significación a las 4 semanas. Los participantes que experimentaron altos niveles de disolución del ego o de ilimitación oceánica durante la sesión mostraron calificaciones más altas de satisfacción con la vida y calificaciones más bajas de depresión y estrés. En general, este estudio sugiere que una sola inhalación de la secreción de sapo que contiene 5-MeO-DMT produce mejoras rápidas y persistentes en la satisfacción de vida, la atención plena y los síntomas psicopatológicos, y que estos cambios están asociados con la intensidad de la experiencia psicodélica.

El estudio de análisis intra-individual en el **Capítulo 5** evaluó los efectos de la inhalación de 5-MeO-DMT sintético en biomarcadores salivales, así como en variables relacionadas con la salud mental como el afecto y la atención plena. Once participantes fueron evaluados utilizando una batería de pruebas antes, inmediatamente después y 7 días después de la sesión donde inhalaron el vapor de 5-MeO-DMT sintético en ubicaciones en Praga, Republica Checa. Además, se recogieron muestras salivales antes y dentro de las 2 horas después de la sesión. Se predijo que los síntomas de depresión, ansiedad y estrés disminuirían, y las calificaciones de satisfacción con la vida aumentarían, desde antes hasta después de la inhalación de 5-MeO-DMT sintético vaporizado. Se encontró que la inhalación de vapor de 5-MeO-DMT sintético aumentó los niveles de cortisol y disminuyó las concentraciones de IL-6 en la saliva inmediatamente después de la sesión. Estos cambios no

estuvieron correlacionados a calificaciones de salud mental o de la experiencia psicodélica. Relativo al inicio del estudio, calificaciones de no juzgar aumentaron significativamente. Las calificaciones de depresión disminuyeron inmediatamente después de la sesión y se mantuvieron en el seguimiento. Las calificaciones de ansiedad y estrés disminuyeron del inicio hasta el seguimiento 7 días después. Las calificaciones de los participantes sobre la experiencia psicodélica se correlacionaron negativamente con las calificaciones de afecto y positivamente con las calificaciones de no juzgar. Tomando todo esto en conjunto, se concluyó que la inhalación de 5-MeO-DMT sintético vaporizado produjo cambios significativos en marcadores inflamatorios, mejora de afecto y actitud de no juzgar en los voluntarios.

El estudio de análisis intra-individual descrito en el **Capítulo 6** tuvo como objetivo evaluar si la inyección intramuscular (IM) y la vaporización de 5-MeO-DMT inducen diferentes tasas de reactivación (flashback), cambios en la satisfacción con la vida, así como calificaciones de la experiencia de disolución del ego y la experiencia mística. Se realizó una evaluación utilizando una encuesta en línea que fue diseñada para explorar los efectos en retrospectiva de la experiencia con 5-MeO-DMT en 27 individuos ($M_{\text{edad}}=32$. $DS=1.40$; hombres=18; América del Norte=19) que habían vaporizado ($N=13$) o utilizado 5-MeO-DMT a través de inyección IM ($N=14$). No hubo diferencias demográficas significativas entre los grupos o las medidas subjetivas. De los 14 participantes en el grupo IM, 3 (21%) reportaron reactivaciones; en contraste, de los 13 participantes en el grupo de vaporización, 9 (69%) reportaron reactivaciones. La repetición de dosis (más de una dosis) se produjo con mayor frecuencia en el grupo de vaporización ($N=8$) (1-6 veces con 3-35mg de 5-MeO-DMT), en relación con el grupo IM ($N=2$) (1-5 veces con 5-10 mg de 5-MeO-DMT). Todos los participantes en

el grupo IM experimentaron liberación de tensión física, en comparación con 8 participantes en el grupo de vaporización. Los participantes en el grupo IM reportaron un mayor tiempo para la aparición de los efectos agudos (entre 1-3 [N=6] y 4-6 minutos [N=6]), en relación con el grupo de vaporización donde la mayoría (N=11) reportó un inicio rápido de 1-50 segundos. Se concluyó que, comparado con la vaporización, la ruta de administración con inyección IM de 5-MeO-DMT está asociada a menos dosis, dosis más bajas, menor frecuencia de experiencias de reactivación, mayor frecuencia de liberación de tensión física y un inicio mas demorado de los efectos agudos.

Finalmente, en el **Capítulo 7**, se discuten hallazgos clave de todos los estudios desde una perspectiva mas amplia, y se brindan implicaciones y recomendaciones para futuras investigaciones. Los estudios presentados en esta disertación dan dirección a futuras investigaciones de ayahuasca y 5-MeO-DMT controladas con placebo y respaldan los estudios sobre su potencial como un nuevo método para el tratamiento de trastornos relacionados con el estado de ánimo y la salud mental.

Souhrn

Kapitola 1 nastiňuje potřebu najít nový druh léčby poruch souvisejících s náladou. Bylo zdůrazněno, že snahy o nalezení takovéto léčby byly realizovány prostřednictvím výzkumu jak ketaminu, tak psychedelické látky psilocybinu. Předchozí výzkum navíc naznačuje, že další psychedelika, jako jsou ayahuasca a 5-methoxy-dimethyltryptamin (5-MeO-DMT), jsou hodny dalšího výzkumu. Nicméně právní status psychedelických látek na celém světě ztěžuje provádění (klinického) výzkumu, a proto bylo pro tuto doktorskou disertační práci navrženo několik naturalistických observačních studií tak, aby bylo možné dále zkoumat účinky jak ayahuascy, tak 5-MeO-DMT na duševní zdraví. Studie popsané v **kapitole 2-3** zkoumaly farmakologický a nefarmakologický dopad ayahuascy požití v naturalistickém (neo)šamanském prostředí. Studie v následujících **kapitolách 4-6** zkoumaly účinky 5-MeO-DMT na psychologické a biomedicínské procesy u lidí.

Konkrétně pak studie v rámci **kapitoly 2** zkoumala post-akutní a dlouhodobé účinky ayahuascy na uživatele v Kolumbii a Nizozemsku ($N = 57$). Předpokládalo se, že ayahuasca vyvolá zlepšení příznaků souvisejících s duševním zdravím a že změny budou korelovat se stupněm rozpuštění ega vyvolaného psychedelickou zkušeností. Hodnocení bylo provedeno před, den po a 4 týdny po obřadu a zahrnovalo testovací baterii navrženou k posouzení faktorů jako afekt (příznaky související s depresí, úzkostí a stresem), duševní pohoda, schopnost všímavosti (mindfulness) a kreativita. Ve srovnání s výchozím stavem došlo k významnému snížení úrovně deprese a stresu, které přetrvávalo 4 týdny. Navíc se zlepšilo také konvergentní myšlení až na dobu

4 týdnů po obřadu. Spokojenost se životem a schopnosti všímavosti se zlepšily den po obřadu, ale zlepšení nepřetrvalo v dalších 4 následujících týdnech. Změny v oblasti afektu, spokojenosti se životem a všímavosti korelovaly s úrovní rozpuštění ega, k němuž došlo během obřadu s ayahuascou, a nesouvisely s předchozími zkušenostmi s ayahuascou. Dospělo se tedy k závěru, že ayahuasca způsobuje u nepatologických uživatelů subakutní a dlouhodobé zlepšení afektu a kognitivního myšlení.

V placebem kontrolované studii v rámci **kapitoly 3** se zkoumalo, zda účinky na duševní zdraví (afekt, poznání a empatii) po ukončení obřadu byly farmakologicky vyvolány ayahuascou (hmota) nebo byly vyvolány prostředím (mysl). Zhodnocení byla provedena před a po požití ayahuascy u účastníků naturalistických rituálů neo-šamanského původu, které se odehrávaly v Nizozemsku, Španělsku a Německu. Hodnocení zahrnovalo distribuci testovací baterie včetně standardizovaného měření afektu, kognice, a také objektivní měření empatie. Účastníci byli náhodně rozdělení do dvou léčebných skupin, které požívaly buď kapsle obsahující ayahuascu (N = 14) nebo placebo (N = 16). Předpokládalo se, že prostředí bude mít dopad na obě skupiny, zatímco farmakologické účinky ayahuascy by byly nejvýznamnější ve skupině, která požila ayahuascu. Výsledky naznačují, že retrospektivně účastníci celkově uváděli nízkou úroveň zkušenosti s rozpuštěním ega a změněných stavů vědomí. Navíc, ve srovnání s výchozím stavem, analýza opakovaných měření odhalila, že zlepšení deprese, stresu a symptomů úzkosti souviselo s nefarmakologickými faktory obřadu, zatímco zvýšení implicitní aktivity na negativní podněty (emoční empatie) bylo farmakologicky spojeno s ayahuascou. Dospělo se k závěru, že subjektivní zlepšení afektu (deprese, úzkost a stres) účastníků naturalistických obřadů ayahuascy mohou být způsobeny nefarmakologickými faktory, jako jsou očekávání a úmysly

(nastavení mysli, mind-set). Zlepšení implicitní aktivace na negativní podněty (empatie) souviselo s farmakologickou léčbou ayahuascou (hmota).

Studie v rámci **kapitoly 4** se snažila prozkoumat subakutní a dlouhodobé účinky inhalace par ze sušeného sekretu ropuch obsahujících 5-MeO-DMT. Hodnocení byla provedena před, po podání a o 4 týdny později u uživatelů ($N = 42$) v různých evropských lokalitách (Španělsko, Nizozemsko a Česká republika) prostřednictvím distribuce dotazníku určeného k posouzení afektu, všímavosti (mindfulness) a kognice. Očekávalo se, že symptomy afektu, jako je deprese, úzkost, stres a somatizace uváděné účastníky na začátku studie, by se zmírnily po inhalaci par ze sušeného sekretu ropuchy obsahující 5-MeO-DMT, a zlepšilo by se i kreativní myšlení a schopnosti všímavosti (mindfulness). Očekávalo se, že tyto změny budou přetrvávat v čase a budou stále měřitelné i 4 týdny po užití. Ve srovnání s výchozím stavem se míra spokojenosti se životem a konvergentní myšlení významně zlepšily hned po užití a tento stav přetrvával i o 4 týdny později. Míra všímavosti (mindfulness) se časem také zvyšovala a dosáhla statistické významnosti za 4 týdny. Míra deprese, úzkosti a stresu se po užití snížila a dosáhla významnosti během 4 týdnů. Účastníci, kteří během relace zažili vysokou úroveň rozpuštění ega nebo pocitu neomezenosti oceánů, vykazovali vyšší míru spokojenosti se životem a nižší míru deprese a stresu. Celkově tato studie naznačuje, že jediná inhalace par ze sekretu ropuchy obsahující 5-MeO-DMT vede k rychlému a trvalému zlepšování spokojenosti se životem, všímavosti a psychopatologických symptomů a že tyto změny jsou spojeny se silou psychedelických prožitků.

Studie v rámci **kapitoly 5** hodnotila účinky inhalace syntetické molekuly 5-MeO-DMT na biomarkery slin, jakož i faktory související s duševním

zdravím, jako je afekt a všímavost (mindfulness). Jedenáct účastníků bylo hodnoceno pomocí testovací baterie před, bezprostředně po relaci a 7 dní po relaci, kdy vdechovali páry syntetického 5-MeO-DMT v Praze (Česká republika). Dále pak byly odebrány vzorky slin před a do 2 hodin od inhalace. Bylo předpokládáno, že dojde k poklesu příznaků deprese, úzkosti a stresu a míra spokojenosti se životem se bude zvyšovat následně po inhalaci syntetického 5-MeO-DMT. Bylo zjištěno, že inhalace par syntetického 5-MeO-DMT významně zvýšila hladinu kortizolu a snížila koncentrace IL-6 ve slinách okamžitě po inhalaci. Tyto změny nesouvisely s hodnocením duševního zdraví ani psychedelickým prožitkem. Ve srovnání s výchozím stavem se schopnost nesoudit významně zvýšila a míra deprese klesla okamžitě po relaci a také doby následné kontroly. Míra úzkosti a stresu se snížila z výchozí hodnoty do doby 7 dnů po relaci. Hodnocení účastníků psychedelického prožitku korelovala negativně s mírou afektu a pozitivně s mírou schopnosti nesoudit. Dospělo se k závěru, že inhalace par syntetické 5-MeO-DMT způsobila u dobrovolníků významné změny v zánětlivých markerech, zlepšila afekt a schopnost nesoudit.

Cílem studie popsané v **kapitole 6** bylo posoudit, zda intramuskulární injekce (IM) a odpařování 5-MeO-DMT vyvolaly různé rychlosti reaktivace (flashback), změny spokojenosti se životem, a také míru zkušenosti s rozpuštěním ega a mystickou zkušenost. Hodnocení bylo provedeno pomocí online průzkumu, jehož cílem bylo retrospektivně prozkoumat účinky 5-MeO-DMT u 27 jedinců ($M_{\text{age}} = 32$. $SD = 1,40$; muži = 18; Severní Amerika = 19), kteří užili 5-MeO-DMT buď ve formě páry ($N = 13$) nebo intramuskulární injekce ($N = 14$). Mezi skupinami nebyl žádný významný rozdíl, pokud jde o demografii nebo subjektivní faktory. Ze 14 účastníků ve skupině IM, 3 osoby (21%) uvedli reaktivaci; na rozdíl od 13 účastníků ve

skupině, která užívala páru, uvedlo reaktivaci 9 osob (69%). Více dávek se vyskytovalo častěji ve skupině, která inhalovala (N = 8) (1-6 krát s 3-35 mg 5-MeO-DMT), ve srovnání se skupinou IM (N = 2) (1-5 krát s 5 až 10 mg 5-MeO-DMT). Všichni účastníci ve skupině IM zažili uvolnění fyzického napětí ve srovnání s 8 účastníky ve skupině, která inhalovala. Účastníci ve skupině IM uvedli delší dobu nástupu akutních účinků (mezi 1-3 [N = 6] a 4-6 minutami [N = 6]), ve srovnání k inhalační skupině, kde většina (N = 11) uvedla rychlý nástup 1-50 sekund. Dospělo se k závěru, že ve srovnání s odpařováním je IM způsob podávání 5-MeO-DMT spojen s nižšími a menšími dávkami, nižšími frekvencemi hlášení reaktivity, vyšší frekvencí uvolňování fyzického napětí a delším nástupem akutních účinků.

Na závěr v **kapitole 7** jsou klíčová zjištění všech studií diskutována v širší perspektivě a jsou uvedeny důsledky a doporučení pro budoucí výzkum. Studie prezentované v této disertační práci směřují k budoucímu placebem kontrolovanému výzkumu s ayahuascou a 5-MeO-DMT a potvrzují potenciál nové metody léčby poruch souvisejících s náladou.

Oppsummering

Kapittel 1 skisserer behovet for et nytt behandlingsalternativ for stemningslidelser som for eksempel depresjon, og beskriver forskningen på ketamin og det psykedeliske stoffet psilocybin som et slikt behandlingsalternativ. Det fremgår også av tidligere forskning at andre psykedelika, som ayahuasca og 5-metoksy-dimetyltryptamin (5-MeO-DMT) er verdt å undersøke nærmere. Ettersom den juridiske statusen til psykedeliske stoffer over hele verden gjør det vanskelig å utføre (klinisk) forskning, ble det for denne doktorgradsavhandlingen designet flere naturalistiske observasjonsstudier for å undersøke effektene av både ayahuasca og 5-MeO-DMT på utfallsmål relatert til psykisk helse. Studiene beskrevet i **kapittel 2-3** undersøkte den farmakologiske og ikke-farmakologiske virkningen av ayahuasca inntatt i en naturalistisk (ny)sjamanistisk setting. Studiene i de påfølgende **kapitlene 4-6** undersøkte effekten av 5-MeO-DMT på psykologiske og biomedisinske prosesser hos mennesker.

Spesifikt undersøkte den pre-post test studien beskrevet i **kapittel 2** de post akutte og langsiktige effektene av ayahuasca hos brukere i Colombia og Nederland (N = 57). Det ble antatt at ayahuasca ville fremkalle bedring av psykiske symptomer, og at endringer ville korrelere med graden av egooppløsning (ego dissolution) fremkalt av den psykedeliske opplevelsen. Undersøkelser ble gjort før, dagen etter og 4 uker etter ayahuasca-seremonien og inkluderte et testbatteri designet for å vurdere følgende symptomer: affekt, velvære, mindfulness-relaterte egenskaper og kreativitet. Man så en betydelig reduksjon i selvrapporterte nivåer av depresjon og stress sammenlignet med

før seremonien, som vedvarte i 4 uker. I tillegg ble konvergent tenking forbedret etter ayahuasca-seremonien frem til oppfølgingen etter 4 uker. Tilfredshet med livet og flere mindfulness-relaterte egenskaper var forbedret dagen etter seremonien, men endringen var ikke statistisk signifikant etter 4 uker. Endringer i affekt, tilfredshet med livet og mindfulness var dessuten korrelert med nivået av egooppløsning opplevd under påvirkning av ayahuasca, og var uavhengig av tidligere erfaring med ayahuasca. Vi konkluderte med at ayahuasca gir subakutte og langsiktige forbedringer i affekter og kognitiv tenkestil hos friske rekreasjonsbrukere.

Den placebo-kontrollerte pre-post test studien beskrevet i **kapittel 3** undersøkte om effektene på psykologiske utfallsmål (affekt [depresjon, angst og stress symptomer], kognisjon og empati) ble farmakologisk produsert av ayahuasca, eller på grunn av deltakerens innstilling og holdning. Vurderinger ble gjort før og etter ayahuasca-inntak hos deltakere på ayahuasca-retreats av nysjamanistisk opprinnelse, som ble holdt i Nederland, Spania og Tyskland. Undersøkelser involverte distribusjon av et testbatteri som inkluderte standardiserte målinger av affekt og kognisjon, samt en objektiv undersøkelse av empati. Deltakerne ble randomisert i to behandlingsgrupper som inntok kapsler som inneholdt ayahuasca (N = 14) eller placebo (N = 16). Det ble spådd at "set" (deltakerens tankesett) og "setting" (omgivelsene) ville påvirke begge gruppene, mens de farmakologiske effektene av ayahuasca ville være mest fremtredende i gruppen som fikk ayahuasca. Resultatene antyder at deltakerne samlet sett rapporterte lave nivåer av opplevd egoløsning og endrede bevissthetstilstander retrospektivt. En gjentatt analyse viste at bedring av affekt i forhold til utgangsverdien var relatert til ikke-farmakologiske faktorer ved seremonien, mens en økning i implisitt aktivering av negativ stimuli (emosjonell empati) var relatert til

farmakologiske faktorer (ayahuasca). Det ble konkludert med at subjektive forbedringer av affekter hos deltakere på naturalistiske ayahuasca-seremonier kan være drevet av ikke-farmakologiske faktorer som forventninger og intensjoner (tankesett). Videre var forbedring i implisitt aktivering av negative stimuli (empati) relatert til den farmakologiske behandlingen med ayahuasca.

Den pre-post test studien beskrevet i **kapittel 4** prøvde å undersøke de subakutte og langsiktige effektene av inhalering av damp fra tørket paddesekret fra *Incilius Alvarius* (bedre kjent som *Bufo Alvarius*) som inneholdt 5-MeO-DMT. Vurderinger ble gjort før, etter økten, og 4 uker senere hos deltakerne (N = 42) på forskjellige steder i Europa (Spania, Nederland og Tsjekkia) gjennom distribusjon av et spørreskjema designet for å vurdere symptomer på affekter, mindfulness og kognisjon. Det var forventet at affektive symptomer (depresjon, angst og stress), og somatisering rapportert av deltakere ved baseline ville forbedres ved inhalasjon av dampen fra tørket paddesekret inneholdende 5-MeO-DMT, og at kognitive utfallsmål, for eksempel kreativ tenking og mindfulness-relaterte egenskaper, ville forbedre seg. Det var forventet at slike endringer ville vedvare over tid og fremdeles være målbare 4 uker etter inntak. I forhold til utgangsverdien ble det sett en betydelig økning av tilfredshet med livet og konvergent tenking rett etter inntak og effekten ble opprettholdt ved oppfølging 4 uker senere. Mål på mindfulness økte også over tid og nådde statistisk signifikans etter 4 uker. Mål av depresjon, angst og stress ble redusert etter økten, og nådde statistisk signifikans etter 4 uker. Deltakere som opplevde høye nivåer av egooppløsning eller oceanisk grenseløshet (oceanic boundlessness) under økten, rapporterte høyere verdier av tilfredshet med livet og lavere verdier av depresjon og stress. Alt i alt antyder denne studien at én enkelt inhalasjon av

damp fra paddesekret inneholdende 5-MeO-DMT gir raske og vedvarende forbedringer i tilfredshet med livet, mindfulness og affekter, og at disse endringene er assosiert med intensiteten av den psykedeliske opplevelsen.

Den pre-post test studien beskrevet i **kapittel 5** vurderte effektene av syntetisk 5-MeO-DMT-inhalasjon på biomarkører i spytt, så vel som psykologiske utfallsmål på affekt og mindfulness. Elleve deltagere ble vurdert ved hjelp av et testbatteri før, umiddelbart etter økten og 7 dager etter en økt der de inhalerte damp av syntetisk 5-MeO-DMT på et sted i Praha, Tsjekkia. I tillegg ble spyttprøver samlet før og innen 2 timer etter økten. Det var forventet at inhalering av fordampet, syntetisk 5-MeO-DMT ville føre til reduserte symptomer på depresjon, angst og stress, samt økt livstilfredshet. Det ble funnet at inhalering av syntetisk 5-MeO-DMT-damp økte kortisolnivået betydelig og reduserte IL-6-konsentrasjoner i spytt umiddelbart etter økten. Disse endringene var ikke korrelert med psykologiske utfallsmål eller intensiteten av den psykedeliske opplevelsen. I forhold til utgangsverdien økte vurderingene av ikke-dømmingen (non-judgement) av tanker og opplevelser som oppstår betydelig, og mål på depresjon ble redusert umiddelbart etter økten og videre ved oppfølging. Mål på angst og stress gikk ned fra utgangsverdien til oppfølgingen etter 7 dager. Mål på intensiteten av den psykedeliske opplevelsen korrelerte negativt med mål på affekt og positivt med mål på ikke-dømming. Vi konkluderte med at inhalering av fordampet, syntetisk 5-MeO-DMT ga betydelige forandringer i inflammatoriske markører, forbedret affekt og ikke-dømming hos deltakerne.

Den pre-post test studien beskrevet i **kapittel 6** hadde som mål å vurdere om intramuskulær (IM) injeksjon og fordampning (vaporization) av 5-MeO-DMT induserte forskjellige “reaktivering”, eller gjenopplevelse av

opplevelsen med 5-MeO-DMT (reactivation), endringer i tilfredshet med livet, samt mål på graden av egooppløsning og den mystiske opplevelsen. Ved hjelp av en online-undersøkelse designet for å utforske den retrospektive effekten av 5-MeO-DMT hos 27 individer (M alder = 32. SD = 1,40; menn = 18; Nord-Amerika = 19) som enten hadde inntatt fordampet (N=13) eller intramuskulært injisert (N=14) 5-MeO-DMT. Det var ingen signifikante demografiske forskjeller mellom gruppene eller subjektive effekter av egoløsning og tilfredsstillhet med livet. Av 14 deltakere i IM-gruppen rapporterte 3 (21%) om reaktivering; mens av 13 deltakere i fordampingsgruppen rapporterte 9 (69%) om reaktivering. Redosering (mer enn 1 dose) skjedde oftere i fordampingsgruppen (N=8) (1-6 ganger med 3-35 mg 5-MeO-DMT) enn i IM-gruppen (N=2) (1-5 ganger med 5-10 mg 5-MeO-DMT). Alle deltakerne i IM-gruppen opplevde forløsning av kroppslige spenninger (somatic experiencing), sammenlignet med 8 deltakere i fordampingsgruppen. Deltakere i IM-gruppen rapporterte om lengre tid før de akutte effektene slo inn (mellom 1-3 [N=6] og 4-6 minutter [N=6]), relativt til fordampingsgruppen der majoriteten (N=1) rapporterte om hurtig innsettende effekt på 1-50 sekunder. Vi konkluderte med at, sammenlignet med fordamping, er intramuskulært administrert 5-MeO-DMT assosiert med lavere og mindre doser, lavere hyppighet av reaktivering, en høyere grad av forløsning av kroppslige spenninger og lengre tid før akutte effekter slår inn.

Til slutt, i **kapittel 7**, diskuteres de viktigste funnene fra alle studiene i et bredere perspektiv, deres betydning, samt gis anbefalinger for fremtidig forskning. Studiene som presenteres i denne avhandlingen baner vei for fremtidig placebo-kontrollert forskning med ayahuasca og 5-MeO-DMT og støtter studier om deres potensial som en ny behandlingsmetode for stemningslidelser.

References

- 5-Hive. (2017). So You Want To Intramuscularly Administer 5-MeO-DMT HCl (or other salt) Retrieved from <https://forums.5meodmt.org/index.php?topic=50533.0>
- 5-Hive. (2018a). Integration. Retrieved from <https://forums.5meodmt.org/index.php?topic=50714.msg55384>
- 5-Hive. (2018b). Post-experience struggles/issues. Retrieved from <https://forums.5meodmt.org/index.php?topic=50754.0>
- 5-MeO-DMT malpractice; Open Letter Concerning Abuses by Octavio Rettig and Gerry Sandoval. (2019). Retrieved from <https://5-meo-dmt-malpractice.org/open-letter-concerning-abuses-by-octavio-rettig-and-gerry-sandoval/>
- 5Hive. (2019, 2018). BEST PRACTICES from The Conclave. Retrieved from <https://forums.5meodmt.org/index.php?topic=50729.0>
- Abdallah, C. G., Salas, R., Jackowski, A., Baldwin, P., Sato, J. R., & Mathew, S. J. (2015). Hippocampal volume and the rapid antidepressant effect of ketamine. *J Psychopharmacol*, 29(5), 591-595. doi:10.1177/0269881114544776
- Abdallah, C. G., Sanacora, G., Duman, R. S., & Krystal, J. H. (2015). Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics. *Annual review of medicine*, 66, 509-523.
- Abraham, H. D. (1983). Visual phenomenology of the LSD flashback. *Archives of general psychiatry*, 40(8), 884-889.
- Adamson, S., & Metzner, R. (1988). The nature of the MDMA experience and its role in healing, psychotherapy and spiritual practice. *ReVision*, 10(4), 59-72.
- Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical psychology review*, 30(2), 217-237.
- Alvares Pereira, N. (1957). Obtenção da bufotenina das sementes de Piptadenia peregrina Benth. *Revista Brasileira da Farmácia*, 38, 139-142.
- Andersen, T. E., Lahav, Y., Ellegaard, H., & Manniche, C. (2017). A randomized controlled trial of brief somatic experiencing for chronic low back pain and comorbid post-traumatic stress disorder symptoms. *European journal of psychotraumatology*, 8(1), 1331108.
- Andritzky, W. (1989). Sociopsychotherapeutic functions of ayahuasca healing in Amazonia. *Journal of psychoactive drugs*, 21(1), 77-89.

- Annie Mithoefer, B., Jerome, L., Ruse, J., Doblin, R., Gibson, E., & Marcela Ot'alora, G. (2013). A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder.
- Araújo, A. M., Carvalho, F., de Lourdes Bastos, M., De Pinho, P. G., & Carvalho, M. (2015). The hallucinogenic world of tryptamines: an updated review. *Archives of Toxicology*, 89(8), 1151-1173.
- Artigas, F., Nutt, D. J., & Shelton, R. (2002). Mechanism of action of antidepressants. *Psychopharmacology bulletin*, 36, 123-132.
- Asakura, T., Funatsu, Y., Ishii, M., Namkoong, H., Yagi, K., Suzuki, S., . . . Uwamino, Y. (2015). Health-related quality of life is inversely correlated with C-reactive protein and age in Mycobacterium avium complex lung disease: a cross-sectional analysis of 235 patients. *Respiratory research*, 16(1), 145.
- Axling, U., Olsson, C., Xu, J., Fernandez, C., Larsson, S., Ström, K., . . . Berger, K. (2012). Green tea powder and Lactobacillus plantarum affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6J mice. *Nutrition & metabolism*, 9(1), 105.
- Baer, R. A. (2003). Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clinical Psychology: Science and Practice*, 10(2), 125-143.
- Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment*, 13(1), 27-45.
- Baker, J. R. (2005). Psychedelic sacraments. *Journal of psychoactive drugs*, 37(2), 179-187.
- Baran, P., Hansen, S., Waetzig, G. H., Akbarzadeh, M., Lamertz, L., Huber, H. J., . . . Scheller, J. (2018). The balance of interleukin (IL)-6, IL-6 soluble IL-6 receptor (sIL-6R), and IL-6 sIL-6R sgp130 complexes allows simultaneous classic and trans-signaling. *Journal of Biological Chemistry*, 293(18), 6762-6775.
- Barbosa, P. C. R., Giglio, J. S., & Dalgallarrondo, P. (2005). Altered states of consciousness and short-term psychological after-effects induced by the first time ritual use of ayahuasca in an urban context in Brazil. *Journal of psychoactive drugs*, 37(2), 193-201.
- Barrett, F. S., Johnson, M. W., & Griffiths, R. R. (2015). Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. *Journal of Psychopharmacology*, 29(11), 1182-1190.
- Barsuglia, J., Davis, A., & Palmer, R. (2017a). Characterization of mystical experiences occasioned by 5-MeO-DMT-containing toad bufotoxin and comparison with prior psilocybin studies. *Psychedelic Sci*, 23.
- Barsuglia, J., Davis, A., & Palmer, R. (2017b). Characterization of mystical experiences occasioned by 5-MeO-DMT-containing toad bufotoxin and comparison with prior psilocybin studies. *Psychedelic Science*, 23.

- Barsuglia, J. P., Davis, A. K., Palmer, R., Lancelotta, R., Windham-Herman, A. M., Peterson, K., . . . Griffiths, R. R. (2018). Intensity of mystical experiences occasioned by 5-MeO-DMT and comparison with a prior psilocybin study. *Frontiers in psychology*, 9, 2459.
- Barsuglia, J. P., Polanco, M., Palmer, R., Malcolm, B. J., Kelmendi, B., & Calvey, T. (2018). A case report SPECT study and theoretical rationale for the sequential administration of ibogaine and 5-MeO-DMT in the treatment of alcohol use disorder. *Progress in brain research*, 242, 121-158.
- Bartels, D. J., van Laarhoven, A. I., Haverkamp, E. A., Wilder-Smith, O. H., Donders, A. R. T., van Middendorp, H., . . . Evers, A. W. (2014). Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PloS one*, 9(3), e91727.
- Bartholomew, L. K., Parcel, G. S., & Kok, G. (1998). Intervention mapping: a process for developing theory and evidence-based health education programs. *Health education & behavior*, 25(5), 545-563.
- Bauer, M. E., & Teixeira, A. L. (2018). Inflammation in psychiatric disorders: what comes first? *Annals of the New York academy of sciences*.
- Beck, A. T. (1967). *Depression: Clinical, experimental, and theoretical aspects*: University of Pennsylvania Press.
- Beck, J. (2011). *Cognitive behavior therapy: Basics and beyond*. New York, NY: Guilford Press.
- Benedetti, F. (2014). Placebo effects: from the neurobiological paradigm to translational implications. *Neuron*, 84(3), 623-637.
- Berman, M. (1981). *The reenchantment of the world*: Cornell University Press.
- Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological psychiatry*, 47(4), 351-354.
- Beuningen, J. (2012). The Satisfactin With Life Scale Examining Construct Validity. *Statistics Netherlands*, 201209, 3-23.
- Beyer, S. (2012). On the Origins of Ayahuasca. In (Vol. 2019).
- Blewett, D. (1970). The psychedelics and group therapy. *Aaronson, B. y H. Osmond*.
- Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P. C. R., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *Journal of Psychopharmacology*, 29(3), 289-299.
- Bouso, J. C., González, D., Fondevila, S., Cutchet, M., Fernández, X., Barbosa, P. C. R., & al., e. (2012). Personality, psychopathology, life attitudes and neuropsychological performance among ritual users of Ayahuasca: a longitudinal study. *PloS one*, 7(8), e42421.
- Bouso, J. C., González, D., Fondevila, S., Cutchet, M., Fernández, X., Barbosa, P. C. R., . . . Fábregas, J. M. (2012). Personality, psychopathology, life attitudes

- and neuropsychological performance among ritual users of ayahuasca: a longitudinal study. *PloS one*, 7(8), e42421.
- Brambilla, P., Perez, J., Barale, F., Schettini, G., & Soares, J. (2003). GABAergic dysfunction in mood disorders. *Molecular psychiatry*, 8(8), 721.
- Braun, S. B. (2010). *Neo-shamanism as a healing system: Enchanted healing in a modern world*: The University of Utah.
- Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L., & Charney, D. S. (2000). Hippocampal volume reduction in major depression. *American Journal of Psychiatry*, 157(1), 115-118.
- Breslin, F. C., Zack, M., & McMains, S. (2002). An information-processing analysis of mindfulness: Implications for relapse prevention in the treatment of substance abuse. *Clinical Psychology: Science and Practice*, 9(3), 275-299.
- Brinker, J. K., & Dozois, D. J. (2009). Ruminative thought style and depressed mood. *Journal of clinical psychology*, 65(1), 1-19.
- Brito, G. S., Neves, E. S., & Oberlaender, G. (1996). Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. *The Journal of Nervous & Mental Disease*, 184(2), 86-94.
- Brom, D., Stokar, Y., Lawi, C., Nuriel-Porat, V., Ziv, Y., Lerner, K., & Ross, G. (2017). Somatic experiencing for posttraumatic stress disorder: a randomized controlled outcome study. *Journal of traumatic stress*, 30(3), 304-312.
- Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease.
- Bustos, S. (2008). *The healing power of the icaros: a phenomenological study of ayahuasca experiences*: California Institute of Integral Studies.
- Callaway, J. C., Raymon, L. P., Hearn, W. L., McKenna, D. J., Grob, C. S., Brito, G. S., & Mash, D. C. (1996). Quantitation of N, N-dimethyltryptamine and harmala alkaloids in human plasma after oral dosing with ayahuasca. *Journal of analytical toxicology*, 20(6), 492-497.
- Campos, D. J. (2011). The Shaman and Ayahuasca. *Trans. Alberto Roman. Studio City, California: Divine Arts*.
- Canady, V. A. (2019). FDA panel endorses ketamine nasal spray for depression. *Mental Health Weekly*, 29(8), 6-7.
- Carhart-Harris, R., & Friston, K. (2019). REBUS and the anarchic brain: toward a unified model of the brain action of psychedelics. *Pharmacological reviews*, 71(3), 316-344.
- Carhart-Harris, R., Kaelen, M., Whalley, M., Bolstridge, M., Feilding, A., & Nutt, D. (2015). LSD enhances suggestibility in healthy volunteers. *Psychopharmacology*, 232(4), 785-794.
- Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., . . . Feilding, A. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*, 3(7), 619-627.

- Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., . . . Murphy, K. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences*, 109(6), 2138-2143.
- Carhart-Harris, R. L., & Friston, K. J. (2010). The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. *Brain*, 133(4), 1265-1283.
- Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., . . . Nutt, D. (2014). The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in human neuroscience*, 8, 20.
- Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., . . . Orban, C. (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences*, 113(17), 4853-4858.
- Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., . . . Murphy, K. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific reports*, 7(1), 13187.
- Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., & Kaelen, M. (2018). Psychedelics and the essential importance of context. *Journal of Psychopharmacology*, 32(7), 725-731.
- Carpenter, L. L., Heninger, G. R., Malison, R. T., Tyrka, A. R., & Price, L. H. (2004). Cerebrospinal fluid interleukin (IL)-6 in unipolar major depression. *Journal of affective disorders*, 79(1-3), 285-289.
- Catlow, B. J., Song, S., Paredes, D. A., Kirstein, C. L., & Sanchez-Ramos, J. (2013). Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning. *Exp Brain Res*, 228(4), 481-491. doi:10.1007/s00221-013-3579-0
- Cebolla, A., García-Palacios, A., Soler, J., Guillen, V., Baños, R., & Botella, C. (2012). Psychometric properties of the Spanish validation of the Five Facets of Mindfulness Questionnaire (FFMQ). *The European Journal of Psychiatry*, 26(2), 118-126.
- Celada, P., Puig, M. V., Amargós-Bosch, M., Adell, A., & Artigas, F. (2004). The therapeutic role of 5-HT_{1A} and 5-HT_{2A} receptors in depression. *Journal of Psychiatry and Neuroscience*, 29(4), 252.
- Chagnon, N. A., Le Quesne, P., & Cook, J. M. (1971). Yanomamo hallucinogens: anthropological, botanical, and chemical findings. *Current Anthropology*, 12(1), 72-74.
- Chamberlain, S. R., Fineberg, N. A., Blackwell, A. D., Robbins, T. W., & Sahakian, B. J. (2006). Motor inhibition and cognitive flexibility in obsessive-compulsive

- disorder and trichotillomania. *Am J Psychiatry*, 163(7), 1282-1284.
doi:10.1176/appi.ajp.163.7.1282
- Chamberlain, S. R., Fineberg, N. A., Blackwell, A. D., Robbins, T. W., & Sahakian, B. J. (2006). Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *American Journal of Psychiatry*, 163(7), 1282-1284.
- Chen, P.-H. A., Cheong, J. H., Jolly, E., Elhence, H., Wager, T. D., & Chang, L. J. (2019). Socially transmitted placebo effects. *Nature human behaviour*, 1-11.
- Ciesla, J. A., & Roberts, J. E. (2007). Rumination, negative cognition, and their interactive effects on depressed mood. *Emotion*, 7(3), 555.
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and interpersonal regulation followed by exposure: a phase-based treatment for PTSD related to childhood abuse. *Journal of consulting and clinical psychology*, 70(5), 1067.
- Coffey, K. A., & Hartman, M. (2008). Mechanisms of action in the inverse relationship between mindfulness and psychological distress. *Complementary health practice review*, 13(2), 79-91.
- Collins, K. A., & Dozois, D. J. (2008). What are the active ingredients in preventative interventions for depression? *Clinical Psychology: Science and Practice*, 15(4), 313-330.
- Colloca, L. (2014). Placebo, nocebo, and learning mechanisms. In *Placebo* (pp. 17-35): Springer.
- Cooney, R. E., Joormann, J., Eugène, F., Dennis, E. L., & Gotlib, I. H. (2010). Neural correlates of rumination in depression. *Cognitive, Affective, & Behavioral Neuroscience*, 10(4), 470-478.
- Coughlin, S. S. (1990). Recall bias in epidemiologic studies. *Journal of clinical epidemiology*, 43(1), 87-91.
- Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nature reviews neuroscience*, 13(10), 701.
- Cusi, A. M., MacQueen, G. M., Spreng, R. N., & McKinnon, M. C. (2011). Altered empathic responding in major depressive disorder: relation to symptom severity, illness burden, and psychosocial outcome. *Psychiatry research*, 188(2), 231-236.
- Cusi, A. M., MacQueen, G. M., Spreng, R. R., & McKinnon, M. C. (2011). Altered empathic responding in major depressive disorder: relation to symptom severity, illness burden, and psychosocial outcome. *Psychiatry Res*, 188(2), 231-236. doi:10.1016/j.psychres.2011.04.013
- Da Silveira, D. X., Grob, C. S., de Rios, M. D., Lopez, E., Alonso, L. K., Tacla, C., & Doering-Silveira, E. (2005). Ayahuasca in adolescence: a preliminary psychiatric assessment. *Journal of psychoactive drugs*, 37(2), 129-133.

- Dakic, V., Nascimento, J. M., Sartore, R. C., de Moraes Maciel, R., Araujo, D. B., Ribeiro, S., . . . Rehen, S. K. (2017). Short term changes in the proteome of human cerebral organoids induced by 5-MeO-DMT. *Scientific reports*, 7(1), 12863.
- Dakic, V., Nascimento, J. M., Sartore, R. C., de Moraes Maciel, R., de Araujo, D. B., Ribeiro, S., . . . Rehen, S. K. (2017). Short term changes in the proteome of human cerebral organoids induced by 5-MeO-DMT. *Scientific reports*, 7(1), 12863.
- Davis, A. K., Barsuglia, J. P., Lancelotta, R., Grant, R. M., & Renn, E. (2018). The epidemiology of 5-methoxy- N, N-dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption. *J Psychopharmacol*, 32(7), 779-792.
doi:10.1177/0269881118769063
- Davis, A. K., Barsuglia, J. P., Lancelotta, R., Grant, R. M., & Renn, E. (2018a). The epidemiology of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) use: benefits, consequences, patterns of use, subjective effects, and reasons for consumption. *Journal of Psychopharmacology*, 32(7), 779-792.
- Davis, A. K., Barsuglia, J. P., Lancelotta, R., Grant, R. M., & Renn, E. (2018b). The epidemiology of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption. *Journal of Psychopharmacology*, 0269881118769063.
- Davis, A. K., So, S., Lancelotta, R., Barsuglia, J. P., & Griffiths, R. R. (2019a). 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *The American journal of drug and alcohol abuse*, 45(2), 161-169.
- Davis, A. K., So, S., Lancelotta, R., Barsuglia, J. P., & Griffiths, R. R. (2019b). 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *The American journal of drug and alcohol abuse*, 1-9.
- Davis, A. K., So, S., Lancelotta, R., Barsuglia, J. P., & Griffiths, R. R. (In Press). 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT) used in a naturalistic setting is associated with unintended improvements in depression and anxiety. *The American journal of drug and alcohol abuse*.
doi:10.1080/00952990.2018.1545024
- Daza, P., Novy, D. M., Stanley, M. A., & Averill, P. (2002). The depression anxiety stress scale-21: Spanish translation and validation with a Hispanic sample. *Journal of psychopathology and Behavioral Assessment*, 24(3), 195-205.
- De Gregorio, D., Enns, J. P., Nuñez, N. A., Posa, L., & Gobbi, G. (2018). d-Lysergic acid diethylamide, psilocybin, and other classic hallucinogens: mechanism of action and potential therapeutic applications in mood disorders. In *Progress in brain research* (Vol. 242, pp. 69-96): Elsevier.

- De, J. B. (1974). On the alkaloid composition of the snuff drug yopo from upper Orinoco (Venezuela). *Il Farmaco; edizione scientifica*, 29(8), 574-578.
- de Lima Osório, F., de Macedo, L. R. H., de Sousa, J. P. M., Pinto, J. P., Quevedo, J., de Souza Crippa, J. A., & Hallak, J. E. C. (2011). The therapeutic potential of harmine and ayahuasca in depression: Evidence from exploratory animal and human studies. *The ethnopharmacology of ayahuasca*, 75-85.
- De Lima Osório, F., De Macedo, L. R. H., De Sousa, J. P. M., Pinto, J. P., Quevedo, J., de Souza Crippa, J. A., & Hallak, J. E. C. (2011). The therapeutic potential of harmine and ayahuasca in depression: Evidence from exploratory animal and human studies. *The Ethnopharmacology of Ayahuasca*, 75-86.
- de Smet, P. A., & Rivier, L. (1987). Intoxicating parica seeds of the Brazilian Maué Indians. *Economic Botany*, 41(1), 12-16.
- Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain, behavior, and immunity*, 70, 61-75.
- Desai, G. S., & Mathews, S. T. (2014). Saliva as a non-invasive diagnostic tool for inflammation and insulin-resistance. *World journal of diabetes*, 5(6), 730.
- Diazgranados, N., Ibrahim, L., Brutsche, N. E., Newberg, A., Kronstein, P., Khalife, S., . . . Salvatore, G. (2010). A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of general psychiatry*, 67(8), 793-802.
- Diener, E., Emmons, R. A., Larsen, R. J., & Griffin, S. (1985). The satisfaction with life scale. *Journal of personality assessment*, 49(1), 71-75.
- Diener, E., Emmons, R. A., Larsen, R. J., & Griffin, S. (1985). The Satisfaction With Life Scale. *J Pers Assess*, 49(1), 71-75. doi:10.1207/s15327752jpa4901_13
- Dittrich, A. (1998). The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry*, 31(S 2), 80-84.
- Dittrich, A., Lamparter, D., & Maurer, M. (2010). 5D-ASC: Questionnaire for the assessment of altered states of consciousness. *A short introduction. Zurich, Switzerland: PSIN PLUS*.
- Do Yup Lee, E. K., & Choi, M. H. (2015). Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. *BMB reports*, 48(4), 209.
- Domínguez-Clavé, E., Soler, J., Pascual, J. C., Elices, M., Franquesa, A., Valle, M., . . . Riba, J. (2018). Ayahuasca improves emotion dysregulation in a community sample and in individuals with borderline-like traits. *Psychopharmacology*, 1-8.
- Donges, U.-S., Kersting, A., Dannlowski, U., Lalee-Mentzel, J., Arolt, V., & Suslow, T. (2005). Reduced awareness of others' emotions in unipolar depressed patients. *The Journal of nervous and mental disease*, 193(5), 331-337.
- Donges, U. S., Kersting, A., Dannlowski, U., Lalee-Mentzel, J., Arolt, V., & Suslow, T. (2005). Reduced awareness of others' emotions in unipolar depressed patients. *J Nerv Ment Dis*, 193(5), 331-337.

- dos Santos, R. G., Osorio, F. L., Crippa, J. A. S., Riba, J., Zuardi, A. W., & Hallak, J. E. (2016). Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): a systematic review of clinical trials published in the last 25 years. *Therapeutic advances in psychopharmacology*, 6(3), 193-213.
- Dos Santos, R. G., Osório, F. L., Crippa, J. A. S., Riba, J., Zuardi, A. W., & Hallak, J. E. C. (2016). Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): a systematic review of clinical trials published in the last 25 years. *Ther Adv Psychopharmacol*, 6(3), 193-213. doi:10.1177/2045125316638008
- dos Santos, R. G., Valle, M., Bouso, J. C., Nomdedéu, J. F., Rodríguez-Espinosa, J., McIlhenny, E. H., . . . Riba, J. (2011). Autonomic, neuroendocrine, and immunological effects of ayahuasca: a comparative study with d-amphetamine. *Journal of clinical psychopharmacology*, 31(6), 717-726.
- Duman, C., Schlesinger, L., Russell, D., & Duman, R. (2004). *Inhibition of MAPK kinase produces depressive effects and blocks effects of antidepressant drugs and physical exercise*. Paper presented at the Soc Neurosci Abstr.
- Duman, R. (2002). Synaptic plasticity and mood disorders. *Molecular psychiatry*, 7(S1), S29.
- Duman, R. S. (2004a). Neural plasticity: consequences of stress and actions of antidepressant treatment. *Dialogues in clinical neuroscience*, 6(2), 157.
- Duman, R. S. (2004b). Role of neurotrophic factors in the etiology and treatment of mood disorders. *Neuromolecular medicine*, 5(1), 11-25.
- Duman, R. S. (2005). Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. *Neurobiology of aging*, 26(1), 88-93.
- Duman, R. S., & Aghajanian, G. K. (2012). Synaptic dysfunction in depression: potential therapeutic targets. *science*, 338(6103), 68-72.
- Dziobek, I., Rogers, K., Fleck, S., Bahnemann, M., Heekeren, H. R., Wolf, O. T., & Convit, A. (2008). Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET). *Journal of autism and developmental disorders*, 38(3), 464-473.
- Eisenberger, N. I., Inagaki, T. K., Mashal, N. M., & Irwin, M. R. (2010). Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain, behavior, and immunity*, 24(4), 558-563.
- Elder, B. L., & Mosack, V. (2011). Genetics of depression: an overview of the current science. *Issues in mental health nursing*, 32(4), 192-202.
- Erowid. (n.d). Timeline Retrieved from https://erowid.org/chemicals/5meo_dmt/5meo_dmt_timeline.php
- Ersparmer, V., Vitali, T., Roseghini, M., & Cei, J. M. (1967). 5-Methoxy and 5-hydroxyindoles in the skin of *Bufo alvarius*. *Biochemical pharmacology*, 16(7), 1149-1164.

- Evans, W. E., & Relling, M. V. (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. *science*, 286(5439), 487-491.
- Fantegrossi, W., Harrington, A., Kiessel, C., Eckler, J., Rabin, R., Winter, J., . . . Woods, J. (2006). Hallucinogen-like actions of 5-methoxy-N, N-diisopropyltryptamine in mice and rats. *Pharmacology Biochemistry and Behavior*, 83(1), 122-129.
- Farzin, D., & Mansouri, N. (2006). Antidepressant-like effect of harmaline and other beta-carbolines in the mouse forced swim test. *Eur Neuropsychopharmacol*, 16(5), 324-328. doi:10.1016/j.euroneuro.2005.08.005
- Fellows, L. E., & Bell, E. (1971). Indole metabolism in *Piptadenia peregrina*. *Phytochemistry*, 10(9), 2083-2091.
- Fenn, K., & Byrne, M. (2013). The key principles of cognitive behavioural therapy. *InnovAiT*, 6(9), 579-585.
- Finberg, J. P., & Rabey, J. M. (2016). Inhibitors of MAO-A and MAO-B in Psychiatry and Neurology. *Front Pharmacol*, 7, 340. doi:10.3389/fphar.2016.00340
- Fish, M., Johnson, N., & Horning, E. C. (1955). *Piptadenia* alkaloids. Indole bases of *P. peregrina* (L.) Benth. and related species. *Journal of the American Chemical Society*, 77(22), 5892-5895.
- Fletcher, P. C., & Frith, C. D. (2009). Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nature reviews neuroscience*, 10(1), 48.
- Forgeard, M. J., & Eichner, K. V. (2014). for Positive Interventions. *The Wiley Blackwell handbook of positive psychological interventions*, 137.
- Fortunato, J. J., Reus, G. Z., Kirsch, T. R., Stringari, R. B., Fries, G. R., Kapczinski, F., . . . Quevedo, J. (2010). Effects of beta-carboline harmine on behavioral and physiological parameters observed in the chronic mild stress model: further evidence of antidepressant properties. *Brain Res Bull*, 81(4-5), 491-496. doi:10.1016/j.brainresbull.2009.09.008
- Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: regulation by the microbiome. *Neurobiology of stress*, 7, 124-136.
- Fotiou, E. (2012). Working with “La Medicina”: Elements of Healing in Contemporary Ayahuasca Rituals. *Anthropology of Consciousness*, 23(1), 6-27.
- Fotiou, E., & Gearin, A. K. (2019). Purging and the body in the therapeutic use of ayahuasca. *Social Science & Medicine*, 239, 112532.
- Frecka, E., Bokor, P., & Winkelman, M. (2016). The Therapeutic Potentials of Ayahuasca: Possible Effects against Various Diseases of Civilization. *Front Pharmacol*, 7, 35. doi:10.3389/fphar.2016.00035
- Frecka, E., Bokor, P., & Winkelman, M. (2016). The therapeutic potentials of ayahuasca: possible effects against various diseases of civilization. *Frontiers in pharmacology*, 7, 35.

- Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature reviews neuroscience*, 11(2), 127.
- Friston, K., Schwartenbeck, P., FitzGerald, T., Moutoussis, M., Behrens, T., & Dolan, R. J. (2013). The anatomy of choice: active inference and agency. *Frontiers in human neuroscience*, 7, 598.
- Frommberger, U. H., Bauer, J., Haselbauer, P., Fräulin, A., Riemann, D., & Berger, M. (1997). Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. *European archives of psychiatry and clinical neuroscience*, 247(4), 228-233.
- Furst, P. T. (1976). *Hallucinogens and culture*: Chandler & Sharp Pub.
- Galland, L. (2014). The gut microbiome and the brain. *Journal of medicinal food*, 17(12), 1261-1272.
- Galvão, A. C. M., Almeida, R. N., Silva, E. S., Freire, F. A. M., Palhano-Fontes, F., Onias, H., . . . Lobão-Soares, B. (2018). Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. *Frontiers in psychiatry*, 9, 185.
- Garbers, C., Heink, S., Korn, T., & Rose-John, S. (2018). Interleukin-6: designing specific therapeutics for a complex cytokine. *Nature reviews Drug discovery*.
- Garcia-Romeu, A., R Griffiths, R., & W Johnson, M. (2014). Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. *Current drug abuse reviews*, 7(3), 157-164.
- Germann, C. B. (2019). 5-methoxy-N, N-dimethyltryptamine: An ego-dissolving endogenous neurochemical catalyst of creativity. *bioRxiv*, 578435.
- Giesbrecht, A. (1960). Sobre a ocorrência de bufotenina em semente de *Piptadenia falcata*, Benth. *Anais da AssociaCdo Brasileira da Quimica*, 19, 117-119.
- Gleeson, M., Bishop, N. C., Stensel, D. J., Lindley, M. R., Mastana, S. S., & Nimmo, M. A. (2011). The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Reviews Immunology*, 11(9), 607.
- Gloaguen, V., Cottraux, J., Cucherat, M., & Blackburn, I.-M. (1998). A meta-analysis of the effects of cognitive therapy in depressed patients. *Journal of affective disorders*, 49(1), 59-72.
- Godinho, A. F., Silva, M. C., & Kawashima, J. D. (2017). Ayahuasca Modifies Amphetamine Self Ingestion and Modifies Anxiety and Locomotor Activity in Adolescent Rats. *Electronic Journal of Biology*, 13(2).
- Gottlieb, A. (1996). *Legal highs: a concise encyclopedia of legal herbs and chemicals with psychoactive properties*: Counter Culture.
- GraphPad, S. I. (2019). GraphPad Prism version 8.0.0 for Windows GraphPad Software, Inc, San Diego, California USA

Retrieved from www.graphpad.com

- Greenwood, B. N., Foley, T. E., Day, H. E., Campisi, J., Hammack, S. H., Campeau, S., . . . Fleshner, M. (2003). Freewheel running prevents learned helplessness/behavioral depression: role of dorsal raphe serotonergic neurons. *Journal of Neuroscience*, 23(7), 2889-2898.
- Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., . . . Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, 30(12), 1181-1197.
- Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R. (2011). Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology*, 218(4), 649-665.
- Griffiths, R. R., Richards, W. A., Johnson, M. W., McCann, U. D., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology*, 22(6), 621-632.
- Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology*, 187(3), 268-283.
- Grinspoon, L., & Doblin, R. (2001). Psychedelics as catalysts of insight-oriented psychotherapy. *Social Research*, 68(3), 677.
- Grob, C. S., McKenna, D. J., Callaway, J. C., Brito, G. S., Neves, E. S., Oberlander, G., & al., e. (1996). Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. *The Journal of Nervous and Mental Disease*. *Journal of Nervous and Mental Disorders*, 184(2), 86-94.
- Grof, S., & Grof, C. (2010). Holotropic breathwork. *Albany, NY: State University of New York*.
- Grossa, D., Delle Monache, F., Ferrari, F., & Marini-Bettolo, G. (1975). New observations on the alkaloid composition of hallucinogenic snuff drugs yopo and epéna. *Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti*, 58(4), 605-607.
- Gu, J., Strauss, C., Crane, C., Barnhofer, T., Karl, A., Cavanagh, K., & Kuyken, W. (2016). Examining the factor structure of the 39-item and 15-item versions of the Five Facet Mindfulness Questionnaire before and after mindfulness-based cognitive therapy for people with recurrent depression. *Psychological Assessment*, 28(7), 791.
- Gupta, M. A. (2013). Review of somatic symptoms in post-traumatic stress disorder. *International Review of Psychiatry*, 25(1), 86-99.

- Hadidi, H., Güzey, C., & Idle, J. (1999). Pharmacogenetics and toxicological consequences of human drug oxidation and reduction. *General and Applied Toxicology*. Basingstoke: Macmillan Reference, 215-250.
- Haijen, E. C., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., . . . Lorenz, R. (2018). Predicting responses to psychedelics: a prospective study. *Frontiers in pharmacology*, 9, 897.
- Halpern, J. H., Sherwood, A. R., Passie, T., Blackwell, K. C., & Ruttenber, A. J. (2008). Evidence of health and safety in American members of a religion who use a hallucinogenic sacrament. *Medical Science Monitor*, 14(8), SR15-SR22.
- Halpern, J. H., Sherwood, A. R., Passie, T., Blackwell, K. C., & Ruttenber, A. J. (2008). Evidence of health and safety in American members of a religion who use a hallucinogenic sacrament. *Medical Science Monitor*, 14(8). doi:10.12659/MSM.908931
- Hamilton, J. P., Farmer, M., Fogelman, P., & Gotlib, I. H. (2015). Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. *Biological psychiatry*, 78(4), 224-230.
- Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biological psychiatry*, 70(4), 327-333.
- Hammerson, G., & Santos-Barrera, G. (2004). *Incilius alvarius*. The IUCN Red List of Threatened Species. Retrieved from <http://dx.doi.org/10.2305/IUCN.UK.2004.RLTS.T54567A11152901.en>
- Haour, F. (2005). Mechanisms of the placebo effect and of conditioning. *Neuroimmunomodulation*, 12(4), 195-200.
- Harris, D. S., Baggott, M., Mendelson, J. H., Mendelson, J. E., & Jones, R. T. (2002). Subjective and hormonal effects of 3, 4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology*, 162(4), 396-405.
- Hartogsohn, I. (2014). *The Psycho-social Construction of LSD: How Set and Setting Shaped the American Psychedelic Experience 1950-1970*: Bar Ilan University.
- Hartogsohn, I. (2016). Set and setting, psychedelics and the placebo response: an extra-pharmacological perspective on psychopharmacology. *Journal of Psychopharmacology*, 30(12), 1259-1267.
- Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law*, 3, 2050324516683325.
- Hasler, F., Grimberg, U., Benz, M. A., Huber, T., & Vollenweider, F. X. (2004). Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology*, 172(2), 145-156.

- Hayes, S. C., & Wilson, K. G. (2003). Mindfulness: Method and process. *Clinical Psychology: Science and Practice*, 10(2), 161-165.
- Heaton, R. K. (1975). Subject expectancy and environmental factors as determinants of psychedelic flashback experiences. *The Journal of nervous and mental disease*, 161(3), 157-165.
- Heaton, R. K., & Victor, R. G. (1976). Personality characteristics associated with psychedelic flashbacks in natural and experimental settings. *Journal of abnormal psychology*, 85(1), 83.
- Heller, D. P., & Heller, L. (2004). Somatic experiencing in the treatment of automobile accident trauma. *US Association for Body Psycho-Therapy Journal*, 3 (2), 42-52.
- Hengartner, M. P. (2017). Methodological flaws, conflicts of interest, and scientific fallacies: implications for the evaluation of antidepressants' efficacy and harm. *Frontiers in psychiatry*, 8, 275.
- Hengartner, M. P., Angst, J., & Rössler, W. (2018). Antidepressant use prospectively relates to a poorer long-term outcome of depression: results from a prospective community cohort study over 30 years. *Psychother Psychosom*, 87(3), 181-183.
- Henry, J. D., & Crawford, J. R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. *Br J Clin Psychol*, 44(Pt 2), 227-239. doi:10.1348/014466505X29657
- Henry, J. D., & Crawford, J. R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *British journal of clinical psychology*, 44(2), 227-239.
- Hesselink, J. M. K. (2018). Transformative Psychopharmacology: the Case of 5-methoxy-n, n-dimethyltryptamine. *International Journal of Psychotherapy Practice and Research*, 1(3), 9.
- Hiles, S. A., Baker, A. L., de Malmanche, T., & Attia, J. (2012). A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. *Brain, behavior, and immunity*, 26(7), 1180-1188.
- Hilt, L. M., & Pollak, S. D. (2012). Getting out of rumination: Comparison of three brief interventions in a sample of youth. *Journal of abnormal child psychology*, 40(7), 1157-1165.
- Hofmann, S. G., Asnaani, A., Vonk, I. J., Sawyer, A. T., & Fang, A. (2012). The efficacy of cognitive behavioral therapy: A review of meta-analyses. *Cognitive therapy and research*, 36(5), 427-440.
- Holmes, S. W., Morris, R., Clance, P. R., & Putney, R. T. (1996). Holotropic breathwork: An experiential approach to psychotherapy. *Psychotherapy: Theory, Research, Practice, Training*, 33(1), 114.

- Holmstedt, B., & Lindgren, J.-E. (1979). Chemical constituents and pharmacology of South American snuffs. *Ethnopharmacologic search for psychoactive drugs*(1645), 339-373.
- Hoshino, T., & Shimodaira, K. (1936). Über die synthese des bufotenin-methyl-äthers (5-methoxy-n-dimethyl-tryptamin) und bufotenins (synthesen in der indol-gruppe. XV). *Bulletin of the Chemical Society of Japan*, 11(3), 221-224.
- Hutchinson, D. A., & Savitzky, A. H. (2004). Vasculature of the parotoid glands of four species of toads (Bufonidae: Bufo). *Journal of Morphology*, 260(2), 247-254.
- Hysek, C. M., Schmid, Y., Simmler, L. D., Domes, G., Heinrichs, M., Eisenegger, C., . . . Liechti, M. E. (2013). MDMA enhances emotional empathy and prosocial behavior. *Social cognitive and affective neuroscience*, 9(11), 1645-1652.
- Iacobucci, G. A., & Rúveda, E. A. (1964). Bases derived from tryptamine in Argentine Piptadenia species. *Phytochemistry*, 3(3), 465-467.
- . IBM SPSS Statistics for Windows. (2016). Armonk, NY: IBM Corp.
- Ibrahim, L., Diazgranados, N., Luckenbaugh, D. A., Machado-Vieira, R., Baumann, J., Mallinger, A. G., & Zarate Jr, C. A. (2011). Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 35(4), 1155-1159.
- Idell, R. D., Florova, G., Komissarov, A. A., Shetty, S., Girard, R. B., & Idell, S. (2017). The fibrinolytic system: A new target for treatment of depression with psychedelics. *Medical Hypotheses*, 100, 46-53.
- InnerExplorer. (2017a). "Defining Intramuscular Dosage Range: An Experience with 5-MeO-DMT (exp109250)". Retrieved from <https://erowid.org/experiences/exp.php?ID=109250>
- InnerExplorer. (2017b). "The Drop Rejoining the Ocean: An Experience with 5-MeO-DMT (exp109223)". . Retrieved from <https://erowid.org/experiences/exp.php?ID=109223>
- InnerExplorer. (2017c). "Intramuscular Dosage Range Follow-Up: An Experience with 5-MeO-DMT (exp109810)". . Retrieved from <https://erowid.org/experiences/exp.php?ID=109810>
- Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., . . . Shi, J. (2015). Altered fecal microbiota composition in patients with major depressive disorder. *Brain, behavior, and immunity*, 48, 186-194.
- Jiang, X.-L., Shen, H.-W., & Yu, A.-M. (2015). Potentiation of 5-methoxy-N, N-dimethyltryptamine-induced hyperthermia by harmaline and the involvement of activation of 5-HT1A and 5-HT2A receptors. *Neuropharmacology*, 89, 342-351.

- Jick, H., Kaye, J. A., & Jick, S. S. (2004). Antidepressants and the risk of suicidal behaviors. *Jama*, 292(3), 338-343.
- Johnson, M. W., Garcia-Romeu, A., & Griffiths, R. R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. *The American journal of drug and alcohol abuse*, 43(1), 55-60.
- Johnson, M. W., Hendricks, P. S., Barrett, F., & Griffiths, R. R. (2019). Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. *Pharmacology and Therapeutics*.
- Johnson, M. W., Richards, W. A., & Griffiths, R. R. (2008). Human hallucinogen research: guidelines for safety. *Journal of Psychopharmacology*, 22(6), 603-620.
- Jones, S. A., & Jenkins, B. J. (2018). Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. *Nature reviews immunology*, 1.
- Kaelen, M., Giribaldi, B., Raine, J., Evans, L., Timmerman, C., Rodriguez, N., . . . Carhart-Harris, R. (2018). The hidden therapist: evidence for a central role of music in psychedelic therapy. *Psychopharmacology*, 235(2), 505-519.
- Kagan, W. (2019). The Science and Healing Benefits of Psychedelics Retrieved from <https://www.chronogram.com/hudsonvalley/the-science-and-healing-benefits-of-psychedelics/Content?oid=8992305>
- Karlović, D., Serretti, A., Vrkić, N., Martinac, M., & Marčinko, D. (2012). Serum concentrations of CRP, IL-6, TNF- α and cortisol in major depressive disorder with melancholic or atypical features. *Psychiatry research*, 198(1), 74-80.
- Katz, F., & De Rios, M. D. (1971). Hallucinogenic music: An analysis of the role of whistling in Peruvian ayahuasca healing sessions. *The Journal of American Folklore*, 84(333), 320-327.
- Kavenská, V., & Simonová, H. (2015). Ayahuasca tourism: Participants in shamanic rituals and their personality styles, motivation, benefits and risks. *Journal of psychoactive drugs*, 47(5), 351-359.
- Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., . . . Wang, P. S. (2009). The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiology and Psychiatric Sciences*, 18(1), 23-33.
- Khandaker, G. M., Cousins, L., Deakin, J., Lennox, B. R., Yolken, R., & Jones, P. B. (2015). Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *The Lancet Psychiatry*, 2(3), 258-270.
- Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American Psychologist*, 40(11), 1189.
- Kirsch, I. (2004). Conditioning, expectancy, and the placebo effect: comment on Stewart-Williams and Podd (2004).

- Klavetter, R. E., & Mogar, R. E. (1967). Peak experiences: Investigation of their relationship to psychedelic therapy and self-actualization. *Journal of Humanistic Psychology*, 7(2), 171-177.
- Kok, G., Schaalma, H., Ruiter, R. A., Van Empelen, P., & Brug, J. (2004). Intervention mapping: protocol for applying health psychology theory to prevention programmes. *Journal of health psychology*, 9(1), 85-98.
- Krebs-Thomson, K., Ruiz, E. M., Masten, V., Buell, M., & Geyer, M. A. (2006). The roles of 5-HT 1A and 5-HT 2 receptors in the effects of 5-MeO-DMT on locomotor activity and prepulse inhibition in rats. *Psychopharmacology*, 189(3), 319-329.
- Krippner, S. (2000). The epistemology and technologies of shamanic states of consciousness. *Journal of Consciousness Studies*, 7(11-12), 93-118.
- Kunz, M., Ceresér, K. M., Goi, P. D., Fries, G. R., Teixeira, A. L., Fernandes, B. S., . . . Gama, C. S. (2011). Serum levels of IL-6, IL-10 and TNF- α in patients with bipolar disorder and schizophrenia: differences in pro-and anti-inflammatory balance. *Revista brasileira de psiquiatria*, 33(3), 268-274.
- Kupferberg, A., Bicks, L., & Hasler, G. (2016). Social functioning in major depressive disorder. *Neuroscience & Biobehavioral Reviews*, 69, 313-332.
- Kurland, A. A., Grof, S., Pahnke, W. N., & Goodman, L. E. (1972). Psychedelic drug assisted psychotherapy in patients with terminal cancer. *Journal of Thanatology*.
- Kuyken, W., Watkins, E., & Beck, A. T. (2005). Cognitive-behavior therapy for mood disorders.
- Kuypers, K., Riba, J., de la Fuente Revenga, M., Barker, S., Theunissen, E., & Ramaekers, J. (2016). Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology*, 233(18), 3395-3403.
- Kuypers, K. P., de la Torre, R., Farre, M., Yubero-Lahoz, S., Dziobek, I., Van den Bos, W., & Ramaekers, J. G. (2014). No evidence that MDMA-induced enhancement of emotional empathy is related to peripheral oxytocin levels or 5-HT1a receptor activation. *PloS one*, 9(6), e100719.
- Kuypers, K. P., Dolder, P. C., Ramaekers, J. G., & Liechti, M. E. (2017). Multifaceted empathy of healthy volunteers after single doses of MDMA: a pooled sample of placebo-controlled studies. *Journal of Psychopharmacology*, 31(5), 589-598.
- Kuypers, K. P., Riba, J., de la Fuente Revenga, M., Barker, S., Theunissen, E. L., & Ramaekers, J. G. (2016). Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology (Berl)*, 233(18), 3395-3403. doi:10.1007/s00213-016-4377-8
- Kyzar, E. J., Nichols, C. D., Gainetdinov, R. R., Nichols, D. E., & Kalueff, A. V. (2017). Psychedelic drugs in biomedicine. *Trends in pharmacological sciences*, 38(11), 992-1005.

- La Fratta, I., Tatangelo, R., Campagna, G., Rizzuto, A., Franceschelli, S., Ferrone, A., . . . Felaco, M. (2018). The plasmatic and salivary levels of IL-1 β , IL-18 and IL-6 are associated to emotional difference during stress in young male. *Scientific reports*, 8(1), 3031.
- Lafrance, A., Loizaga-Velder, A., Fletcher, J., Renelli, M., Files, N., & Tupper, K. W. (2017). Nourishing the spirit: exploratory research on ayahuasca experiences along the continuum of recovery from eating disorders. *Journal of psychoactive drugs*, 49(5), 427-435.
- Lambert, M. J. (2011). Psychotherapy research and its achievements.
- Laska, E., & Sunshine, A. (1973). Anticipation of Analgesia, a placebo effect. *Headache: The Journal of Head and Face Pain*, 13(1), 1-11.
- Lau, J. Y. F., & Eley, T. C. (2010). The Genetics of Mood Disorders. *Annual Review of Clinical Psychology*, 6(1), 313-337.
doi:10.1146/annurev.clinpsy.121208.131308
- Lawn, W., Hallak, J. E., Crippa, J. A., Dos Santos, R., Porffy, L., Barratt, M. J., . . . Morgan, C. J. (2017). Well-being, problematic alcohol consumption and acute subjective drug effects in past-year ayahuasca users: a large, international, self-selecting online survey. *Scientific reports*, 7(1), 15201.
- Lawn, W., Hallak, J. E., Crippa, J. A., Santos, R., Porffy, L., Barratt, M. J., . . . Morgan, C. J. (2017). Well-being, problematic alcohol consumption and acute subjective drug effects in past-year ayahuasca users: a large, international, self-selecting online survey. *Scientific reports*, 7(1), 15201.
- Leary, T., Litwin, G. H., & Metzner, R. (1963). Reactions to psilocybin administered in a supportive environment. *Journal of Nervous and Mental Disease*.
- Lebedev, A. V., Lövdén, M., Rosenthal, G., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2015). Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. *Human brain mapping*, 36(8), 3137-3153.
- Lebudaa, I., Zabelinab, D. L., & Karwowskia, M. (2015). Mind full of ideas: A meta-analysis of the mindfulness–creativity link. *Personality and Individual Differences*, 93, 22-26.
- Lee, J. K., & Orsillo, S. M. (2014). Investigating cognitive flexibility as a potential mechanism of mindfulness in Generalized Anxiety Disorder. *Journal of Behavior Therapy and Experimental Psychiatry*, 45(1), 208-216.
doi:<https://doi.org/10.1016/j.jbtep.2013.10.008>
- Legrand, G., Guiguet-Auclair, C., Viennet, H., Aumeran, C., Reynaud, D., Badrikian, L., & Debost-Legrand, A. (2019). Nurses' practices in the preparation and administration of intramuscular injections in mental health: A cross-sectional study. *Journal of clinical nursing*.
- Leitch, M. L., Vanslyke, J., & Allen, M. (2009). Somatic experiencing treatment with social service workers following Hurricanes Katrina and Rita. *Social Work*, 54(1), 9-18.
- Levine, P. (2012). Somatic experiencing. In.

- Levine, P. A. (1976). *Accumulated stress, reserve capacity, and disease*. University of California, Berkeley,
- Levine, P. A. (2010). *In an unspoken voice: How the body releases trauma and restores goodness*: North Atlantic Books.
- Levine, P. A., & Frederick, A. (1997). *Waking the tiger: Healing trauma: The innate capacity to transform overwhelming experiences*: North Atlantic Books.
- Lima, R. V., Moulin, T., Lintzmaier, L. P., & Leão, R. N. (2018). A single dose of 5-MeO-DMT stimulates cell proliferation, neuronal survivability, morphological and functional changes in adult mice ventral dentate gyrus. *Frontiers in molecular neuroscience*, 11, 312.
- Linehan, M. M. (1993). *Skills training manual for treating borderline personality disorder*: Guilford Press.
- Lipsky, M. S., & Sharp, L. K. (2001). From idea to market: the drug approval process. *The Journal of the American Board of Family Practice*, 14(5), 362-367.
- Liu, L., & Zhu, G. (2018). Gut–brain axis and mood disorder. *Frontiers in psychiatry*, 9, 223.
- Lyvers, M., & Meester, M. (2012). Illicit use of LSD or psilocybin, but not MDMA or nonpsychedelic drugs, is associated with mystical experiences in a dose-dependent manner. *Journal of psychoactive drugs*, 44(5), 410-417.
- Ma, Z., Zang, T., Birnbaum, S. G., Wang, Z., Johnson, J. E., Zhang, C. L., & Parada, L. F. (2017). TrkB dependent adult hippocampal progenitor differentiation mediates sustained ketamine antidepressant response.
- MacLean, K. A., Johnson, M. W., & Griffiths, R. R. (2011). Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *Journal of Psychopharmacology*, 25(11), 1453-1461.
- MacLean, K. A., Leoutsakos, J. M. S., Johnson, M. W., & Griffiths, R. R. (2012). Factor analysis of the mystical experience questionnaire: a study of experiences occasioned by the hallucinogen psilocybin. *Journal for the scientific study of religion*, 51(4), 721-737.
- MacRae, E. (2004). The ritual use of ayahuasca by three Brazilian religions. *Drug use and cultural contexts beyond the West*. London: Free Association Books, 27-45.
- Maes, M., Lin, A.-h., Delmeire, L., Van Gastel, A., Kenis, G., De Jongh, R., & Bosmans, E. (1999). Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. *Biological psychiatry*, 45(7), 833-839.
- Malarkey, W. B., & Mills, P. J. (2007). Endocrinology: the active partner in PNI research. *Brain, behavior, and immunity*, 21(2), 161-168.

- Martin-Pichora, A. L., Mankovsky-Arnold, T. D., & Katz, J. (2011). Implicit versus explicit associative learning and experimentally induced placebo hypoalgesia. *Journal of pain research*, 4, 67.
- Martinsen, E. W. (1990). Benefits of exercise for the treatment of depression. *Sports medicine*, 9(6), 380-389.
- Mason, N. L., Mischler, E., Uthaug, M. V., & Kuypers, K. P. (2019a). Sub-Acute Effects of Psilocybin on Empathy, Creative Thinking, and Subjective Well-Being. *Journal of psychoactive drugs*, 1-12.
- Mason, N. L., Mischler, E., Uthaug, M. V., & Kuypers, K. P. (2019b). Sub-acute effects of psilocybin on empathy, creative thinking, and subjective well-being. *Journal of psychoactive drugs*, 51(2), 123-134.
- Matefy, R. E., Hayes, C., & Hirsch, J. (1978). Psychedelic drug flashbacks: subjective reports and biographical data. *Addictive behaviors*, 3(3-4), 165-178.
- Matefy, R. E., & Krall, R. G. (1974). An initial investigation of the psychedelic drug flashback phenomena. *Journal of consulting and clinical psychology*, 42(6), 854.
- Mattson, M. P. (2005). Energy intake, meal frequency, and health: a neurobiological perspective. *Annu. Rev. Nutr.*, 25, 237-260.
- McIntyre, R. S., & O'Donovan, C. (2004). The human cost of not achieving full remission in depression. *Canadian Journal of Psychiatry*, 49(1), 10-16.
- McKenna, D. J. (1998). Ayahuasca: An ethnopharmacologic history. In.
- McKenna, D. J. (2004). Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. *Pharmacology & therapeutics*, 102(2), 111-129.
- McKenna, D. J. (2004). Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. *Pharmacol Ther*, 102(2), 111-129. doi:10.1016/j.pharmthera.2004.03.002
- McKenna, D. J., Repke, D. B., Lo, L., & Peroutka, S. J. (1990). Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. *Neuropharmacology*, 29(3), 193-198.
- Metzner, R. (2013). *The Toad and the Jaguar: a Field Report of Underground Research on a Visionary Medicine: Bufo alvarius and 5-Methoxy-dimethyltryptamine*: Regent Press.
- Metzner, R., Litwin, G., & Weil, G. (1965). *The relation of expectation and mood to psilocybin reactions: a questionnaire study*.
- Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature reviews immunology*, 16(1), 22.
- Milliere, R. (2017). Looking for the self: phenomenology, neurophysiology and philosophical significance of drug-induced ego dissolution. *Frontiers in human neuroscience*, 11, 245.

- Millière, R., Carhart-Harris, R. L., Roseman, L., Trautwein, F.-M., & Berkovich-Ohana, A. (2018). Psychedelics, meditation, and self-consciousness. *Frontiers in psychology*, 9.
- Mithoefer, M. C., Designe, S., Doblin, R., & Emerson, A. (2008). A manual for MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder.
- Mithoefer, M. C., Grob, C. S., & Brewerton, T. D. (2016). Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. *The Lancet Psychiatry*, 3(5), 481-488.
- Moieni, M., Irwin, M. R., Jevtic, I., Breen, E. C., & Eisenberger, N. I. (2015). Inflammation impairs social cognitive processing: a randomized controlled trial of endotoxin. *Brain, behavior, and immunity*, 48, 132-138.
- Moncrieff, J. (2007). Are antidepressants as effective as claimed? No, they are not effective at all. *The Canadian Journal of Psychiatry*, 52(2), 96-97.
- Morales-García, J. A., de la Fuente Revenga, M., Alonso-Gil, S., Rodríguez-Franco, M. I., Feilding, A., Perez-Castillo, A., & Riba, J. (2017). The alkaloids of Banisteriopsis caapi, the plant source of the Amazonian hallucinogen Ayahuasca, stimulate adult neurogenesis in vitro. *Scientific reports*, 7(1), 5309.
- Morales-Garcia, J. A., Echeverry-Alzate, V., Alonso-Gil, S., Sanz-SanCristobal, M., Lopez-Moreno, J. A., Gil, C., . . . Perez-Castillo, A. (2017). Phosphodiesterase7 Inhibition Activates Adult Neurogenesis in Hippocampus and Subventricular Zone In Vitro and In Vivo. *Stem Cells*, 35(2), 458-472. doi:10.1002/stem.2480
- Morrison, A. S., Mateen, M. A., Brozovich, F. A., Zaki, J., Goldin, P. R., Heimberg, R. G., & Gross, J. J. (2016). Empathy for Positive and Negative Emotions in Social Anxiety Disorder. *Behaviour research and therapy*, 87, 232-242. doi:10.1016/j.brat.2016.10.005
- Most, A. (1984). *Bufo alvarius: The psychedelic toad of the Sonoran desert*: Venom Press.
- Murrough, J. W., Perez, A. M., Pillemer, S., Stern, J., Parides, M. K., aan het Rot, M., . . . Iosifescu, D. V. (2013). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biological psychiatry*, 74(4), 250-256.
- Naditch, M. P., & Fenwick, S. (1977). LSD flashbacks and ego functioning. *Journal of abnormal psychology*, 86(4), 352.
- Nagai, F., Nonaka, R., & Kamimura, K. S. H. (2007). The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. *European journal of pharmacology*, 559(2-3), 132-137.
- Narby, J. (1999). *The cosmic serpent*: Penguin.

- Naseribafrouei, A., Hestad, K., Avershina, E., Sekelja, M., Linløkken, A., Wilson, R., & Rudi, K. (2014). Correlation between the human fecal microbiota and depression. *Neurogastroenterology & Motility*, 26(8), 1155-1162.
- Nau Jr, F., Miller, J., Saravia, J., Ahlert, T., Yu, B., Happel, K. I., . . . Nichols, C. D. (2014). Serotonin 5-HT₂ receptor activation prevents allergic asthma in a mouse model. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 308(2), L191-L198.
- Nau Jr, F., Yu, B., Martin, D., & Nichols, C. D. (2013). Serotonin 5-HT_{2A} receptor activation blocks TNF- α mediated inflammation in vivo. *PLoS one*, 8(10), e75426.
- Neumann, M., Edelhäuser, F., Tauschel, D., Fischer, M. R., Wirtz, M., Woopen, C., . . . Scheffer, C. (2011). Empathy decline and its reasons: a systematic review of studies with medical students and residents. *Academic medicine*, 86(8), 996-1009.
- Nichols, D. E. (2004). Hallucinogens. *Pharmacology & therapeutics*, 101(2), 131-181.
- Nichols, D. E. (2016). Psychedelics. *Pharmacological reviews*, 68(2), 264-355.
- Nietlisbach, G., & Maercker, A. (2009). Social Cognition and Interpersonal Impairments in Trauma Survivors with PTSD. *Journal of Aggression, Maltreatment & Trauma*, 18(4), 382-402.
doi:10.1080/10926770902881489
- Nietlisbach, G., Maercker, A., Rösler, W., & Haker, H. (2010). Are empathic abilities impaired in posttraumatic stress disorder? *Psychological reports*, 106(3), 832-844.
- Nietlisbach, G., Maercker, A., Rossler, W., & Haker, H. (2010). Are empathic abilities impaired in posttraumatic stress disorder? *Psychol Rep*, 106(3), 832-844. doi:10.2466/pr0.106.3.832-844
- Noel, D. C. (1997). *The soul of shamanism: Western fantasies, imaginal realities*: Continuum New York.
- Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of abnormal psychology*, 109(3), 504.
- Nour, M. M., Evans, L., Nutt, D., & Carhart-Harris, R. L. (2016). Ego-Dissolution and Psychedelics: Validation of the Ego-Dissolution Inventory (EDI). *Front Hum Neurosci*, 10, 269. doi:10.3389/fnhum.2016.00269
- Nour, M. M., Evans, L., Nutt, D., & Carhart-Harris, R. L. (2016). Ego-dissolution and psychedelics: validation of the ego-dissolution inventory (EDI). *Frontiers in human neuroscience*, 10, 269.
- Nutt, D. J., King, L. A., & Nichols, D. E. (2013). Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature reviews neuroscience*, 14(8), 577.

- O'Reilly, P., & Funk, A. (1964). LSD in chronic alcoholism. *Canadian Psychiatric Association Journal*, 9(3), 258-261.
- O'Mahony, S. M., Clarke, G., Borre, Y., Dinan, T., & Cryan, J. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural brain research*, 277, 32-48.
- Öngür, D., Lundy, M., Greenhouse, I., Shinn, A. K., Menon, V., Cohen, B. M., & Renshaw, P. F. (2010). Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Research: Neuroimaging*, 183(1), 59-68.
- Oroc, J. (2009). *Tryptamine Palace: 5-MeO-DMT and the Sonoran desert toad*: Simon and Schuster.
- Ortiz Bernal, A. M. (2019). *Reactivations after 5-MeO-DMT use in naturalistic settings: An initial exploratory analysis of the phenomenon's predictors and its emotional valence.*
- Osmond, H. (1957). A review of the clinical effects of psychotomimetic agents. *Annals of the New York academy of sciences*, 66(3), 418-434.
- Osório, F. d. L., Sanches, R. F., Macedo, L. R., Dos Santos, R. G., Maia-de-Oliveira, J. P., Wichert-Ana, L., . . . Hallak, J. E. (2015). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Brazilian Journal of Psychiatry*, 37(1), 13-20.
- Osório, F. d. L., Sanches, R. F., Macedo, L. R., Santos, R. G. d., Maia-de-Oliveira, J. P., Wichert-Ana, L., . . . Hallak, J. E. (2015). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Revista brasileira de psiquiatria*, 37(1), 13-20.
- Ott, J. (2001). Pharmepena-psychonautics: human intranasal, sublingual and oral pharmacology of 5-methoxy-N, N-dimethyl-tryptamine. *Journal of psychoactive drugs*, 33(4), 403-407.
- Pachter, I. J., Zacharias, D. E., & Ribeiro, O. (1959). Indole alkaloids of *Acer saccharinum* (the Silver Maple), *Dictyoloma incanescens*, *Piptadenia colubrina*, and *Mimosa hostilis*. *The Journal of Organic Chemistry*, 24(9), 1285-1287.
- Pahnke, W. N. (1963). *Drugs and mysticism: An analysis of the relationship between psychedelic drugs and the mystical consciousness: A thesis*. Harvard University,
- Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C., & Grof, S. (1970). The experimental use of psychedelic (LSD) psychotherapy. *Jama*, 212(11), 1856-1863.
- Pahnke, W. N., & Richards, W. A. (1966). Implications of LSD and experimental mysticism. *Journal of Religion and Health*, 5(3), 175-208.
- Palhano-Fontes, F., Andrade, K. C., Tofoli, L. F., Santos, A. C., Crippa, J. A., Hallak, J. E., . . . de Araujo, D. B. (2015). The psychedelic state induced by ayahuasca

- modulates the activity and connectivity of the default mode network. *PLoS one*, 10(2), e0118143. doi:10.1371/journal.pone.0118143
- Palhano-Fontes, F., Andrade, K. C., Tofoli, L. F., Santos, A. C., Crippa, J. A. S., Hallak, J. E., . . . de Araujo, D. B. (2015). The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. *PLoS one*, 10(2), e0118143.
- Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., . . . dos Santos, R. G. (2018). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological medicine*, 1-9.
- Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., . . . dos Santos, R. G. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological medicine*, 49(4), 655-663.
- Palm, K. M., & Follette, V. M. (2011). The roles of cognitive flexibility and experiential avoidance in explaining psychological distress in survivors of interpersonal victimization. *Journal of psychopathology and Behavioral Assessment*, 33(1), 79-86.
- Paris, R., A. S., & Etchepare, S. (1967). *SUR LES ALCALOÏDES ET LES FLAVONOÏDES DUNE LÉGUMINEUSE HAÏTI-PIPTADENIA PEREGRINA BENTH. ABSENCE D'ALCALOÏDES CHEZ LE PIPTADENIA AFRIQUANA HOOK F.* Paper presented at the ANNALES PHARMACEUTIQUES FRANÇAISES.
- Park, R. J., Goodyer, I., & Teasdale, J. D. (2004). Effects of induced rumination and distraction on mood and overgeneral autobiographical memory in adolescent major depressive disorder and controls. *Journal of Child Psychology and Psychiatry*, 45(5), 996-1006.
- Parker, C., Doctor, R. M., & Selvam, R. (2008). Somatic therapy treatment effects with tsunami survivors. *Traumatology*, 14(3), 103-109.
- Parker, G., Roy, K., & Eyers, K. (2003). Cognitive behavior therapy for depression? Choose horses for courses. *American Journal of Psychiatry*, 160(5), 825-834.
- Parlar, M., Frewen, P., Nazarov, A., Oremus, C., MacQueen, G., Lanius, R., & McKinnon, M. C. (2014). Alterations in empathic responding among women with posttraumatic stress disorder associated with childhood trauma. *Brain Behav*, 4(3), 381-389. doi:10.1002/brb3.215
- Parlar, M., Frewen, P., Nazarov, A., Oremus, C., MacQueen, G., Lanius, R., & McKinnon, M. C. (2014). Alterations in empathic responding among women with posttraumatic stress disorder associated with childhood trauma. *Brain and behavior*, 4(3), 381-389.
- Parrott, A. C., Lock, J., Adnum, L., & Thome, J. (2013). MDMA can increase cortisol levels by 800% in dance clubbers. *J Psychopharmacol*, 27(1), 113-114.

- Parrott, A. C., Montgomery, C., Wetherell, M. A., Downey, L. A., Stough, C., & Scholey, A. B. (2014). MDMA, cortisol, and heightened stress in recreational ecstasy users. *Behavioural pharmacology*, 25(5 and 6), 458-472.
- Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2002). The pharmacology of psilocybin. *Addiction biology*, 7(4), 357-364.
- Pavot, W., & Diener, E. (2009). Review of the satisfaction with life scale. In *Assessing well-being* (pp. 101-117): Springer.
- Payne, P., Levine, P. A., & Crane-Godreau, M. A. (2015). Somatic experiencing: using interoception and proprioception as core elements of trauma therapy. *Frontiers in psychology*, 6, 93.
- Pizarro, N., & de la Torre, R. (2018). Inter-relationship of the intestinal microbiome, diet, and mental health. *Current Behavioral Neuroscience Reports*, 5(1), 1-12.
- Pokorny, T., Preller, K. H., Kometer, M., Dziobek, I., & Vollenweider, F. X. (2017). Effect of psilocybin on empathy and moral decision-making. *International Journal of Neuropsychopharmacology*, 20(9), 747-757.
- Preller, K., Pokorny, T., Krähenmann, R., Dziobek, I., Stämpfli, P., & Vollenweider, F. (2015). The effect of 5-HT_{2A}/1a agonist treatment on social cognition, empathy, and social decision-making. *European Psychiatry*, 30, 22.
- Psychedelic Today's 5-MeO-DMT Course. (2018). In *Psychedelics Today*.
- Quello, S. B., Brady, K. T., & Sonne, S. C. (2005). Mood disorders and substance use disorder: a complex comorbidity. *Science & Practice Perspectives*, 3(1), 13.
- Rabin, R. A., Regina, M., Doat, M., & Winter, J. (2002). 5-HT_{2A} receptor-stimulated phosphoinositide hydrolysis in the stimulus effects of hallucinogens. *Pharmacology Biochemistry and Behavior*, 72(1-2), 29-37.
- Raison, C. L., & Miller, A. H. (2011). Is depression an inflammatory disorder? *Current psychiatry reports*, 13(6), 467-475.
- Ray, T. S. (2010). Psychedelics and the human receptorome. *PloS one*, 5(2), e9019.
- Re, T., Palma, J., Martins, J. E., & Simões, M. (2016). Transcultural Perspective on Consciousness: Traditional Use of Ayahuasca in Psychiatry in the 21st Century in the Western World. *The Journal of Natural and Social Philosophy*, 12(2), 237.
- Rendón, P. (1984). Obtención de la bufotenina de la semilla de Piptadenia macrocarpa Benth. *Revista Boliviana de Química*, 5(1), 39-43.
- Riba, J., Rodríguez-Fornells, A., Urbano, G., Morte, A., Antonijoan, R., Montero, M., . . . Barbanoj, M. J. (2001). Subjective effects and tolerability of the South American psychoactive beverage Ayahuasca in healthy volunteers. *Psychopharmacology (Berl)*, 154(1), 85-95.
- Riba, J., Rodríguez-Fornells, A., Urbano, G., Morte, A., Antonijoan, R., Montero, M., . . . Barbanoj, M. J. (2001). Subjective effects and tolerability of the

- South American psychoactive beverage Ayahuasca in healthy volunteers. *Psychopharmacology*, 154(1), 85-95.
- Riba, J., Valle, M., Urbano, G., Yritia, M., Morte, A., & Barbanoj, M. J. (2003). Human pharmacology of ayahuasca: subjective and cardiovascular effects, monoamine metabolite excretion, and pharmacokinetics. *Journal of Pharmacology and Experimental Therapeutics*, 306(1), 73-83.
- Richards, W. A. (2015). *Sacred knowledge: Psychedelics and religious experiences*: Columbia University Press.
- Rivier, L., & Lindgren, J.-E. (1972). "Ayahuasca," the South American hallucinogenic drink: An ethnobotanical and chemical investigation. *Economic Botany*, 26(2), 101-129.
- Roseman, L., Nutt, D. J., & Carhart-Harris, R. L. (2017). Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. *Front Pharmacol*, 8, 974. doi:10.3389/fphar.2017.00974
- Roseman, L., Nutt, D. J., & Carhart-Harris, R. L. (2018a). Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. *Frontiers in pharmacology*, 8, 974.
- Roseman, L., Nutt, D. J., & Carhart-Harris, R. L. (2018b). Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. *Frontiers in pharmacology*, 8(974). doi:10.3389/fphar.2017.00974
- Ross, A., & Thomas, S. (2010). The health benefits of yoga and exercise: a review of comparison studies. *The Journal of Alternative and Complementary Medicine*, 16(1), 3-12.
- Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., . . . Babb, J. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of Psychopharmacology*, 30(12), 1165-1180.
- Rudzki, L., & Szulc, A. (2018). "Immune gate" of psychopathology—the role of gut derived immune activation in major psychiatric disorders. *Frontiers in psychiatry*, 9, 205.
- Sadzot, B., Baraban, J. M., Glennon, R. A., Lyon, R. A., Leonhardt, S., Jan, C.-R., & Titeler, M. (1989). Hallucinogenic drug interactions at human brain 5-HT₂ receptors: implications for treating LSD-induced hallucinogenesis. *Psychopharmacology*, 98(4), 495-499.
- Sampedro, F., de la Fuente Revenga, M., Valle, M., Roberto, N., Domínguez-Clavé, E., Elices, M., . . . de Araujo, D. B. (2017). Assessing the psychedelic "after-glow" in ayahuasca users: post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness

- capacities. *International Journal of Neuropsychopharmacology*, 20(9), 698-711.
- Sampedro, F., de la Fuente Revenga, M., Valle, M., Roberto, N., Dominguez-Clave, E., Elices, M., . . . Riba, J. (2017). Assessing the Psychedelic "After-Glow" in Ayahuasca Users: Post-Acute Neurometabolic and Functional Connectivity Changes Are Associated with Enhanced Mindfulness Capacities. *Int J Neuropsychopharmacol*, 20(9), 698-711. doi:10.1093/ijnp/pyx036
- Sanacora, G., Zarate, C. A., Krystal, J. H., & Manji, H. K. (2008). Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nature reviews Drug discovery*, 7(5), 426.
- Sanches, R. F., de Lima Osorio, F., Dos Santos, R. G., Macedo, L. R., Maia-de-Oliveira, J. P., Wichert-Ana, L., . . . Hallak, J. E. (2016). Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression: A SPECT Study. *J Clin Psychopharmacol*, 36(1), 77-81. doi:10.1097/JCP.0000000000000436
- Sanches, R. F., de Lima Osório, F., dos Santos, R. G., Macedo, L. R., Maia-de-Oliveira, J. P., Wichert-Ana, L., . . . Hallak, J. E. (2016). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a SPECT study. *Journal of clinical psychopharmacology*, 36(1), 77-81.
- Santos, R. d., Landeira-Fernandez, J., Strassman, R., Motta, V., & Cruz, A. (2007). Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *Journal of ethnopharmacology*, 112(3), 507-513.
- Saylam, C., Üçerler, H., Kitiş, Ö., Ozand, E., & Gönül, A. S. (2006). Reduced hippocampal volume in drug-free depressed patients. *Surgical and radiologic anatomy*, 28(1), 82-87.
- Schaefer, M., Schmidt, F., Neumer, R., Scholler, G., & Schwarz, M. (2002). Interferon-alpha, cytokines and possible implications for mood disorders. *Bipolar disorders*, 4, 111-113.
- Schenberg, E. E. (2018). Psychedelic-assisted psychotherapy: A paradigm shift in psychiatric research and development. *Frontiers in pharmacology*, 9, 733.
- Schenberg, E. E., Tofoli, L. F., Rezinovsky, D., & SILVEIRA, D. X. D. (2017). Translation and cultural adaptation of the states of consciousness questionnaire (SOCQ) and statistical validation of the mystical experience questionnaire (MEQ30) in brazilian portuguese. *Archives of Clinical Psychiatry (São Paulo)*, 44(1), 1-5.
- Schmid, J. T. (2012). The myth of ayahuasca. *TYPES, EFFICACY AND MYTHS*, 127.
- Schmid, J. T. (2012). THE MYTH OF AYAHUASCA. *International Journal of Religion and Society*, 3(3/4), 257.

- Schmid, Y., Enzler, F., Gasser, P., Grouzmann, E., Preller, K. H., Vollenweider, F. X., . . . Liechti, M. E. (2015). Acute effects of lysergic acid diethylamide in healthy subjects. *Biological psychiatry*, 78(8), 544-553.
- Schmid, Y., & Liechti, M. E. (2018). Long-lasting subjective effects of LSD in normal subjects. *Psychopharmacology*, 235(2), 535-545.
- Schroevers, M. J., & Brandsma, R. (2010). Is learning mindfulness associated with improved affect after mindfulness-based cognitive therapy? *British Journal of Psychology*, 101(1), 95-107.
- Schultes, R. E. (1957). The identity of the malpighiaceae narcotics of South America. *Botanical Museum Leaflets, Harvard University*, 18(1), 1-56.
- Schultes, R. E., Holmstedt, B., Lindgren, J.-E., & Rivier, L. (1977). DE PLANTIS TOXICARIIS E MUNDO NOVO TROPICALE COMMENTATIONES XVIII: Phytochemical examination of Spruce's ethnobotanical collection of *Anadenanthera peregrina*. *Botanical Museum Leaflets, Harvard University*, 25(10), 273-287.
- Sheline, Y. I. (2003). Neuroimaging studies of mood disorder effects on the brain. *Biological psychiatry*, 54(3), 338-352.
- Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., . . . Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, 106(6), 1942-1947.
- Sheline, Y. I., Gado, M. H., & Kraemer, H. C. (2003). Untreated depression and hippocampal volume loss. *American Journal of Psychiatry*, 160(8), 1516-1518.
- Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences*, 93(9), 3908-3913.
- Shen, H.-W., Jiang, X.-L., C Winter, J., & Yu, A.-M. (2010). Psychedelic 5-methoxy-N, N-dimethyltryptamine: metabolism, pharmacokinetics, drug interactions, and pharmacological actions. *Current drug metabolism*, 11(8), 659-666.
- Shen, H.-W., Jiang, X.-L., & Yu, A.-M. (2011). Nonlinear pharmacokinetics of 5-methoxy-N, N-dimethyltryptamine in mice. *Drug Metabolism and Disposition*, 39(7), 1227-1234.
- Shen, H. W., Jiang, X. L., Winter, J. C., & Yu, A. M. (2010). Psychedelic 5-methoxy-N,N-dimethyltryptamine: metabolism, pharmacokinetics, drug interactions, and pharmacological actions. *Curr Drug Metab*, 11(8), 659-666.
- Sher, L., Oquendo, M. A., & Mann, J. J. (2001). Risk of suicide in mood disorders. *Clinical neuroscience research*, 1(5), 337-344.
- Sherwood, A., Kaylo, K., Kargbo, R., Davis, A., Lancelotta, R., Uthaug, M., & Barrow, B. (2019). *CLINICAL CONSIDERATION OF 5-MeO-DMT*. Paper

- presented at the International Forum on Consciousness, Madison, Wisconsin.
- Shewan, D., Dalgarno, P., & Reith, G. (2000). Perceived risk and risk reduction among ecstasy users: the role of drug, set, and setting. *International Journal of Drug Policy*, 10(6), 431-453.
- Shiroma, P. R., Johns, B., Kuskowski, M., Wels, J., Thuras, P., Albott, C. S., & Lim, K. O. (2014). Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *Journal of affective disorders*, 155, 123-129.
- Shondelmyer, K., Knight, R., Sanivarapu, A., Ogino, S., & Vanamala, J. K. (2018). Focus: Nutrition and Food Science: Ancient Thali Diet: Gut Microbiota, Immunity, and Health. *The Yale journal of biology and medicine*, 91(2), 177.
- Shulgin, A., & Shulgin, A. (1997a). *TIHKAL: the continuation*: Transform Press.
- Shulgin, A., & Shulgin, A. (1997b). *TIHKAL: the continuation* (Vol. 546): Transform Press Berkeley.
- Simon, G. E. (2003). Social and economic burden of mood disorders. *Biological psychiatry*, 54(3), 208-215.
- Soler, J., Elices, M., Franquesa, A., Barker, S., Friedlander, P., Feilding, A., . . . Riba, J. (2016). Exploring the therapeutic potential of Ayahuasca: acute intake increases mindfulness-related capacities. *Psychopharmacology*, 233(5), 823-829.
- Soler, J., Elices, M., Franquesa, A., Barker, S., Friedlander, P., Feilding, A., . . . Riba, J. (2016). Exploring the therapeutic potential of Ayahuasca: acute intake increases mindfulness-related capacities. *Psychopharmacology (Berl)*, 233(5), 823-829. doi:10.1007/s00213-015-4162-0
- Spencer, D., Glaser, T., & Traber, J. (1987). Serotonin receptor subtype mediation of the interoceptive discriminative stimuli induced by 5-methoxy-N, N-dimethyltryptamine. *Psychopharmacology*, 93(2), 158-166.
- Spruce, R. (2014). *Notes of a Botanist on the Amazon and Andes* (Vol. 2): Cambridge University Press.
- SPSS, I. (2016). IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.
- Stace, W. T. (1962). *The Teachings of the Mystics: Being Selections from the Great Mystics and Mystical Writings of the World*.
- Stahl, S. M. (1998). Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. *Journal of affective disorders*, 51(3), 215-235.
- Steenbergen, L., Sellaro, R., van Hemert, S., Bosch, J. A., & Colzato, L. S. (2015). A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain, behavior, and immunity*, 48, 258-264.

- Strassman, R. (1992). Subjective effects of DMT and the development of the Hallucinogen Rating Scale. *Newsletter of the Multidisciplinary Association for Psychedelic Studies*, 3(2).
- Stromberg, V. L. (1954). The isolation of bufotenine from *Piptadenia peregrina*. *Journal of the American Chemical Society*, 76(6), 1707-1707.
- Strosahl, K., & Wilson, K. (1999). Acceptance and commitment therapy: an experiential approach to behavior change. New York: Guilford Press.
- Studerus, E., Gamma, A., & Vollenweider, F. X. (2010). Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PloS one*, 5(8), e12412.
- Swanson, L. R. (2018). Unifying theories of psychedelic drug effects. *Frontiers in pharmacology*, 9, 172.
- Sylvia, K. E., & Demas, G. E. (2018). A gut feeling: microbiome-brain-immune interactions modulate social and affective behaviors. *Hormones and behavior*, 99, 41-49.
- Szabo, A. (2015). Psychedelics and immunomodulation: novel approaches and therapeutic opportunities. *Frontiers in immunology*, 6, 358.
- Szabo, A., & Frecska, E. (2016). Dimethyltryptamine (DMT): a biochemical Swiss Army knife in neuroinflammation and neuroprotection? *Neural regeneration research*, 11(3), 396.
- Szabo, A., Kovacs, A., Frecska, E., & Rajnavolgyi, E. (2014). Psychedelic N, N-dimethyltryptamine and 5-methoxy-N, N-dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. *PloS one*, 9(8), e106533.
- Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S. D., Murphy, K., . . . Crossley, N. (2016). Increased global functional connectivity correlates with LSD-induced ego dissolution. *Current Biology*, 26(8), 1043-1050.
- Thomas, K., Malcolm, B., & Lastra, D. (2017). Psilocybin-assisted therapy: a review of a novel treatment for psychiatric disorders. *Journal of psychoactive drugs*, 49(5), 446-455.
- Todd, A. R., Forstmann, M., Burgmer, P., Brooks, A. W., & Galinsky, A. D. (2015). Anxious and egocentric: how specific emotions influence perspective taking. *J Exp Psychol Gen*, 144(2), 374-391. doi:10.1037/xge0000048
- Torres, C. (1996). Status of research on psychoactive snuff powders: A review of the literature. *Jahrbuch für Ethnomedizin und Bewußtseinsforschung*, 5, 15-39.
- Townsend, J. B. (2004). Individualist Religious Movements: Core and Neo-shamanism. *Anthropology of Consciousness*, 15(1), 1-9.
- Trichter, S. (2010). AYAHUASCA BEYOND THE AMAZON THE BENEFITS AND RISKS OF A SPREADING TRADITION. *Journal of Transpersonal Psychology*, 42(2).

- Trichter, S., Klimo, J., & Krippner, S. (2009). Changes in spirituality among ayahuasca ceremony novice participants. *J Psychoactive Drugs*, 41(2), 121-134. doi:10.1080/02791072.2009.10399905
- Trichter, S., Klimo, J., & Krippner, S. (2009). Changes in spirituality among ayahuasca ceremony novice participants. *Journal of psychoactive drugs*, 41(2), 121-134.
- Trope, A., Anderson, B. T., Hooker, A. R., Glick, G., Stauffer, C., & Woolley, J. D. (2019). Psychedelic-Assisted Group Therapy: A Systematic Review. *Journal of psychoactive drugs*, 1-15.
- Tupper, K. W. (2008). The globalization of ayahuasca: Harm reduction or benefit maximization? *International Journal of Drug Policy*, 19(4), 297-303.
- Turner, E. H., & Rosenthal, R. (2008). Efficacy of antidepressants. In: British Medical Journal Publishing Group.
- Tylš, F., Páleníček, T., & Horáček, J. (2014). Psilocybin—summary of knowledge and new perspectives. *European neuropsychopharmacology*, 24(3), 342-356.
- Uthaug, M. (2018). The Ethical and Ecological Considerations of Inhaling Bufotoxins from *Incilius Alvarius*. Retrieved from <https://psychedelictoday.com/2018/10/03/ethics-ecology-bufotoxins/>
- Uthaug, M., Lancelotta, R., Szabo, A., Davis, A., Riba, J., & Ramaekers, J. (2019). *Prospective examination of synthetic 5-methoxy-N,N-dimethyltryptamine inhalation: effects on salivary IL-6, cortisol levels, affect, and non-judgement.*
- Uthaug, M., Lancelotta, R., Szabo, A., Riba, J., & Ramaekers, J. (2019). Prospective examination of synthetic 5-methoxy-N,N-dimethyltryptamine inhalation: effects on salivary IL-6, cortisol levels, affect, and non-judgement. *Psychopharmacology*, 1-13.
- Uthaug, M., Lancelotta, R., van Oorsouw, K., Kuypers, K., Mason, N., Rak, J., . . . Kuchař, M. (2019). A single inhalation of vapor from dried toad secretion containing 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms. *Psychopharmacology*, 1-14.
- Uthaug, M., Lancelotta, R., van Oorsouw, K., Kuypers, K., Mason, N., Rak, J., . . . Ramaekers, J. (2019). A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness related capacities, and a decrement of psychopathological symptoms.
- Uthaug, M., van Oorsouw, K., Kuypers, K., van Boxtel, M., Broers, N., Mason, N., . . . Ramaekers, J. (2018). Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution. *Psychopharmacology*, 235(10), 2979-2989.

- Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *Journal of affective disorders*, 150(3), 736-744.
- Van Oorsouw, K., & Merckelbach, H. (2007). Expectancies and memory for an emotional film fragment: A placebo study. *The American journal of psychology*, 287-301.
- Vazquez, C., Duque, A., & Hervas, G. (2013). Satisfaction with life scale in a representative sample of Spanish adults: validation and normative data. *Span J Psychol*, 16, E82. doi:10.1017/sjp.2013.82
- Veehof, M. M., Peter, M., Taal, E., Westerhof, G. J., & Bohlmeijer, E. T. (2011). Psychometric properties of the Dutch Five Facet Mindfulness Questionnaire (FFMQ) in patients with fibromyalgia. *Clinical rheumatology*, 30(8), 1045-1054.
- Viol, A., Palhano-Fontes, F., Onias, H., de Araujo, D. B., Hövel, P., & Viswanathan, G. M. (2019). Characterizing complex networks using Entropy-degree diagrams: unveiling changes in functional brain connectivity induced by Ayahuasca. *Entropy*, 21(2), 128.
- Viol, A., Palhano-Fontes, F., Onias, H., de Araujo, D. B., & Viswanathan, G. M. (2017). Shannon entropy of brain functional complex networks under the influence of the psychedelic Ayahuasca. *Sci Rep*, 7(7), 73-88.
- Von Stuckard, K. (2002). Reenchanted nature: Modern Western shamanism and nineteenth-century thought. *Journal of the American Academy of Religion*, 70(4), 771-800.
- Wake, D. B., & Vredenburg, V. T. (2008). Are we in the midst of the sixth mass extinction? A view from the world of amphibians. *Proceedings of the National Academy of Sciences*, 105(Supplement 1), 11466-11473.
- Wardenaar, K. J., Wanders, R. B. K., Jeronimus, B. F., & al, e. (2017). The Psychometric Properties of an Internet-Administered Version of the Depression Anxiety and Stress Scales (DASS) in a Sample of Dutch Adults. *Journal of psychopathology and Behavioral Assessment*, 1-16.
- Weil, A. T., & Davis, W. (1994). Bufo alvarius: a potent hallucinogen of animal origin. *Journal of ethnopharmacology*, 41(1-2), 1-8.
- Whitehouse, B., & Heller, D. P. (2008). Heart Rate in Trauma: Patterns Found in Somatic Experiencing and Trauma Resolution. *Biofeedback*, 36(1).
- Winblad, N. E., Changaris, M., & Stein, P. K. (2018). Effect of Somatic Experiencing resiliency-based trauma treatment training on quality of life and psychological health as potential markers of resilience in treating professionals. *Frontiers in Neuroscience*, 12, 70.
- Winkelman, M. (2005). Drug tourism or spiritual healing? Ayahuasca seekers in Amazonia. *Journal of psychoactive drugs*, 37(2), 209-218.

- Winkelman, M. (2007). Shamanic guidelines for psychedelic medicine. *Psychedelic medicine: New evidence for hallucinogenic substances as treatments*, 2, 143-168.
- Winkelman, M. J. (2014). Therapeutic applications of ayahuasca and other sacred medicines. In *The therapeutic use of ayahuasca* (pp. 1-21): Springer.
- Winter, J. (2009). Hallucinogens as discriminative stimuli in animals: LSD, phenethylamines, and tryptamines. *Psychopharmacology*, 203(2), 251-263.
- Wittchen, H.-U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., . . . Faravelli, C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European neuropsychopharmacology*, 21(9), 655-679.
- World-Health-Organization. (2001). *The World Health Report 2001: Mental health: new understanding, new hope*: World Health Organization.
- World-Health-Organization. (2009). *The financial crisis and global health: report of a high-level consultation, Geneva, Switzerland, 19 January 2009*. Retrieved from
- World-Health-Organization. (2012). Depression: A Global Crisis. World Mental Health Day, October 10 2012. *World Federation for Mental Health, Occoquan, Va, USA*.
- World-Health-Organization. (2017). Other Common Mental Disorders: Global Health Estimates. *Geneva: World Health Organization*, 1-24.
- Yamasato, S., Kawanishi, K., Kato, A., & Hashimoto, Y. (1972). Organic bases from Brazilian Piptadenia species. *Phytochemistry*, 11(2), 737-739.
- Yu, A.-M., Idle, J. R., Byrd, L. G., Krausz, K. W., Küpfer, A., & Gonzalez, F. J. (2003). Regeneration of serotonin from 5-methoxytryptamine by polymorphic human CYP2D6. *Pharmacogenetics and Genomics*, 13(3), 173-181.
- Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., . . . Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of general psychiatry*, 63(8), 856-864.
- Zhao, X.-H., Wang, P.-J., Li, C.-B., Hu, Z.-H., Xi, Q., Wu, W.-Y., & Tang, X.-W. (2007). Altered default mode network activity in patient with anxiety disorders: an fMRI study. *European journal of radiology*, 63(3), 373-378.
- Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., . . . Du, X. (2016). Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Molecular psychiatry*, 21(6), 786.
- Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., & Yao, S. (2012). Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naïve major depression patients. *Biological psychiatry*, 71(7), 611-617.

Acknowledgements

Finalizing this doctoral work wouldn't have been possible had my parents not met and my mom birthed me! Thank you, mom and dad, for your unconditional love and support throughout my life!

To my dear sister, Marthe, I miss you dearly, and have missed you for years. I look forward to finding a way back to each other.

To *min kjære*, thank you for everything. The good as well as the bad. I love you. Always have and always will.

To my non-biological sister in Colombia, Yvonne, thank you for entering my life, for your support, and for setting an example on how to live life with love. I love you very much and I look forward to more adventures and collaboration in the future.

To the rest of the Mariño family in Colombia; Querida Mami, Papi y Sergio (Natasha), gracias por ser el puente entre mi yo viejo y mi nuevo yo, por darme la bienvenida durante mi estancia en Colombia para recopilar datos para esta investigación y para aceptarme como su propia hija. Te extraño y te amo a todos. Nos encontraremos de nuevo pronto. Abrazos de La Blanca Adoptada.

To my friend Matej Stepan, thank you for the many life lessons, and the support through the years we have known each other. I am incredibly grateful to you for taking me on the road-trips to Austria, Italy, Slovenia, Switzerland and many other amazing places to help me get a mental break from the PhD work. For the many cookies we shared, for the reggaeton I forcefully, but with good intent, made you listen to in '*El Carro Pequeño*'.
267

For inspiring me repeatedly to be more like Arthur - the character of your first novel and soon to be first feature film. May we always honor the promise we made to one another of always following our dreams.

Throughout my time as a PhD candidate at Maastricht University I have had the privilege of getting to know and work with several different and important people. I would now like to extend my thanks to some of these individuals;

First, to my primary supervisor, Prof. Dr. Johannes Ramaekers (Jan), I want to thank you for your openness and belief in my research ideas, for your patience, time and evaluations during my process of learning. For helping me out financially to cover various research costs, and numerous flights. For being not only a supervisor, but also a great friend who I have come to trust with not only professional but also personal matters. You have always demonstrated a deep and sincere understanding and given me wise advices. Additionally, I want to thank you for believing in my capacities, and for the encouragement of finding a balance between science and practice. I'm still figuring out what that looks like career-wise. Finally, I am, and will always be eternally grateful for the encouragement, thoughts and pep-talks in times I completely crashed. Stay who you are as a person and academic. Any PhD student is lucky to have you as their supervisor!

I want to extend my thanks to my former 2nd supervisor, the excellent ayahuasca researcher Dr. Jordi Riba. Thank you for believing in my project and directing me to Jan's office in 2016. I am thankful for your feedback on the many manuscripts we have co-authored together, for your advice on how to best collect biomedical samples, and for aiding in the study designs. I would like you to know that you always were and still is a research hero of

mine. Your work, originality, and dedication are what inspired me to get on to this quest to begin with. Please come back to the field. You are dearly needed and missed.

To my co-promoter, Dr. Kim van Oorsouw; thank you for the many coffee- and lunch meetings. For the help with setting up various studies, for showing me how to make syntaxes in SPSS, and for helping me through this academic journey and for being a great friend in the process!

To my other co-promoter Dr. Kim Kuypers; thank you for being a badass woman in this field. Your perseverance and dedication to this field, and what you've managed to pull off in this field is admirable. I have felt that things aren't easy as a woman in this field, but you surely give me hope that anything is possible! Keep up the great work - but remember to take care of yourself too!

Besides my supervisors and co-promoters there are two other individuals in the research team at Maastricht I would like to give a special thanks to;

First, I want to extend a big thank you to, soon-to-be-Dr Natasha Mason, for not only being a scientist who I respect and look up to but also being a great colleague and friend. For gifting me a book to remind me that I've earned my place and belong in this field. For the many heart to heart conversations we've had, and for helping each other with data collections. You're already a great scientist and researcher, but I can't wait to see what more awesomeness you'll carry out in the years to come.

Second, Dr. Elizabeth de Sousa Fernandes Perna, thanks for the connection and support we have built for each other both professional and personally! Thank you for letting me sleep over the times I visited Maastricht. For the

pizza party and for the laughs! Remember to always be courageous, no matter what. Also, remember you can always call me!

Furthermore, to Lilian Kloft; it's been an absolute pleasure getting to know you and I am grateful for your support and care – both in research and personally! To Johannes Reckweg, thank you for the many laughs, and for helping me with data collection! I'm so proud of you! Keep up the good work!

In addition to the people mentioned above, I would like to extend my gratitude to Prof. Dr. Stefan Toennes at Goethe-Universitat in Frankfurt for aiding in the writing of various manuscripts, and for carrying out the analysis of various ayahuasca samples for my dissertation work.

Throughout the time as a PhD student I've met many other individuals outside of the faculty which has become not only colleagues but also dear friends. One of these individuals is Rafael Lancelotta, who I eagerly contacted after seeing a YouTube video of him from Breaking Convention 2017 where he presented on the topic of 5-MeO-DMT.

Rafael Lancelotta, aka Rafael Lancelot Merlin The Second, and Cactus; For being someone I look up to, who continue to inspire me, and amaze me as a walking Erowid, and beautiful being on this planet. Cheers to you my friend! Thank you for opening my eyes and making me see things from a different angle, and to realize that ecological and ethical implications of the work is of importance too. Furthermore, thank you for coming all the way to Prague to help with the data collection for the biomedical study, for the many “duct-tape” calls we had over Skype, the conversations, ideas, and especially our friendship which I cherish so dearly. I look forward to the rest of the work we will be doing together, and till the day we stand on the finish line seeing 5-MeO-DMT

with an FDA approval. We are riding a big wave my friend. Hold on tightly. We are not done yet.

To Dr. Attila Szabo; for coming up to me at Beyond Psychedelics conference in Prague to talk with me about a potential collaboration. I assure you; I was the one that was starstruck! Your heart is so big and your help throughout these years have been so much appreciated. I have learned so much from you. I look forward to conducting more research with you in the future! Thank you for believing in me and my capacities when I couldn't see it myself. You have become such a dear friend and I look forward to nourishing that connection further in the years to come.

Thank you to Dr. Alan Kooi Davis for our numerous collaborations, for teaching me the importance of reporting intrinsic values of the sample of the study, instead of ones from the measure validation (haha!). For aiding me in the execution, analysis and writings of the various 5-MeO-DMT projects I've carried out as part of my doctoral dissertation. For our study on Mescaline. For your advices and our growing friendship which has been a great support in the recent times. I hope we get to meet in person soon.

As a large portion of my time as a PhD student was spent in Prague, it goes without saying that the team at The National Institute of Mental Health (NUDZ) is acknowledged as well for their aid in my projects. Thank you to Dr. Tomas Palenicek, for being a great contact and collaborator in Prague. To the rest of the collaborators at NUDZ, Dr. Jakub Rak, Edita, Martin - thank you for aiding in the planning and execution of the biomedical study on 5-MeO-DMT, and for the analysis of the toad secretion as well as biomedical samples.

A special thanks goes to another individual in Prague, my dear 'grandpa', friend and colleague Michael Vancura; I'm so grateful for having had the

privilege of getting to know you. I'm beyond thankful for the many slices of chocolate cake we've shared, for the many talks we've had that I've learned so much from, and the work we've done together on Holotropic Breathwork. I can't wait to visit you in Prague, and to gift you more Troika!

To 'Lanning', thank you for the kindness, hospitality and the belief in my research, and for 'paying your debt' to Stanislav Grof by supporting me and Michael Vancura on the quest of gaining more understanding of the effects of Holotropic Breathwork. Know I still intend to give you something in return, and that I intend to return the favor you gifted me to an individual I meet in the future who are in a similar situation like I was.

A special thanks goes to Andy, the owner of the A Maze in Tchaiovna in Prague, for allowing me to speak about my research and personal experience, and for supporting and giving space to unfiltered opinions and thoughts.

To the many people I've had the privilege of getting to know whilst collecting data in Madrid – thank you! To Olga Martinez, “mi hermana de el triangolo”, thank you for your warmth, your knowledge, for giving me a temporary home whenever I'm in Madrid and for becoming a dear friend.

Other people that I have come to known throughout this research include Ana Maria Bernal Ortiz, who is currently blossoming in the research field. I can't wait to see more of your work! It has been an absolute pleasure connecting with you and I look forward to more of that in the future!

To the team at USONA Inc, especially Tura Patterson, thank you for our connection and our collaboration. I trust and believe that sooner rather than later we will reach our mutual goals together!

To Kyle and Joe for featuring me on Psychedelics Today's podcast, for helping to push me forward, and for having me on the board of advisors – thank you!

To all the facilitators, shamans and neo-shamans - thank you for allowing me to collect data at your session/ceremony!

As special thanks go to Dr. Octavio Rettig who not only gifted me with my first experience with 5-MeO-DMT, and for believing in me and the research, but most importantly for teaching me about the necessity of care and harm-reduction in the sphere of 5-MeO-DMT. May we all learn.

Cheers to the following people who helped me translating the test-batteries into various languages; Marcin Oleszkowicz, Dominika Brychcy, Diana Popa-Cermean, Matej Stepan, Martin Slozil, Yvonne Naranjo Marino, Iva Vukovojac, Eduardo Cerna, Alberto Latorre, and Niklas Knott.

To, Katarina Buglova, Dr. Jakub Rak, Ana Maria Bernal Ortiz, Tor-Morten Kvam, Jørn Kløvfjell Melva, Kristoffer Andersen and Prof. Dr. Johannes Ramaekers for helping with the translation of the summary chapter of my thesis to Czech, Spanish, Norwegian and Dutch – thank you!

A big thanks goes to everybody else who has contributed to the research projects (or my own personal development in the process) in one way or the other!

At the end of this research journey I managed to secure a Research Assistant position at Imperial College in London continuing my research on 5-MeO-DMT under supervision of Dr. Robin Carhart-Harris. Thank you for welcoming me, Robin! It is an honor. Also, thank you Eric Grotefeld for making that possible!

While at Imperial I've also meet (and reconnected) with many other incredible beings and academics. Some of these include Dr. Jack Allocca, Dr. Carl H Smith, soon-to-be Dr. Chris Timmermann, Lisa Luan, Dr. Raphael Milliere, as well as Dr. David Erritzøe. I admire you all, and I know I can learn much from you. I look forward carrying out the research on 5-MeO-DMT together and forward with you! Thank you for becoming my new colleagues and friends.

Finally, if there is one advice I would like to give to anyone who want to embark on a journey towards becoming a (psychedelic) researcher, besides being persistent, open to learning, passionate, critical while staying true to their values, and taking good care of themselves, it is this:

there is always a way, you just have to find it.

Afterwords

April 2020

Champagne! This doctoral dissertation is not only a manifestation of hard work, but also a manifestation of the promise I made to myself in the presence of my friend Matej Stepan at Vaclav Havel airport in Prague in the summer of 2016; *I will become a psychedelic researcher and in doing so, aid in the process of making a novel treatment option available for people with mental health related disorders.*

It is now four years since I did my masters' on ayahuasca, and three years since I started my doctoral research on the effects of ayahuasca and 5-MeO-DMT at Maastricht University. What a ride it has been! Am I happy about this academic accomplishment? *Sure*. But, the academic accomplishment fades in comparison to the personal realizations and development that has occurred. That's what I'm most proud of! Which is also why I created this section, to voice some of my own reflections and insights from the (research) journey.

Essentially, I've struggled with my own mental health stemming from trauma throughout my whole life to some extent or the other. I'm not stating this for you to pity me, instead I just want to be open about it, not hide it away like I've done for too long.

Lately, my mental health got bad. Really bad. Because of the many things that happened in my life as well as in the recent months. Things just built up, then they sort of exploded, and I couldn't cope with it. So, I crashed. Mentally and physically.

The main reason for that is that I've looked for the solution to my struggle in the wrong place. I have been 'searching' for a solution for quite a few years now actually. Through travelling, reading books and lately in psychedelics. But these things were not the solution. Not even one of them. And they never will be. Thinking that they were was an act of bypassing and escaping.

This is not to say that I do not believe in the therapeutic potential of psychedelics, because I do, but I don't believe them to be a "magic bullet" or "quick fix". Instead I believe in their potential as a *catalyst* in the therapeutic process driven by ourselves.

Essentially, I have learned that the solution to mental health struggles is to take responsibility for ourselves, and to go into what is difficult. Not around, but into it, to sit with it and in doing so *find home*. There is comfort in discomfort.

What does 'home' mean? 'Home' to me means me as a whole. 'Home' is the integration of the light and the dark, the white and the black. Home is the grey. 'Finding home' is the process of getting there. This process is not done in an instant. It takes time for it is a deepening spiral of revisiting, processing and integration, in all parts of ourselves - body, mind and spirit.

Additionally, 'finding home' is done in relation to others. Someone once said something along the lines of the following; "*we are created in relationships, and thus we should also heal in relationships*". I don't know who said this, but I nevertheless think it is a key point to mention in this section for it illuminates the importance of the therapeutic relationship in the process of finding home.

Now, what does that look like? To heal in relationship that is? To me, a relationship can be a place where one can ‘feel felt’. In other words, having a moment of ‘*you understand me*’ after having shared something, that has been held in isolation and aloneness, in a safe, open and non-judgmental space. Such a place can be a therapeutic setting with a therapist, or with a family member, a friend or a partner.

I realized that ‘the solution’ to my mental health struggles quite late. Some would say early though as I am *only* 26, nearly 27, years old. But to me it still feels like a lot of years wasted. At least in some way. However, better to realize it sooner rather than later, right? That being said, realizing is one thing - another is taking the appropriate action to back it up, and to feel it – to embody it.

The way I’ve gone about explaining my mental health in the recent time is through the metaphor of a black hole. A black hole that consumed and crushed everything that came close to it, growing bigger and bigger, and darker and darker. This black hole mainly destroyed (parts of) myself, and a relationship with someone I love deeply. Someone who was and still is everything I looked for in a man to share a life with. It hurts. For both of us I believe. That this happened. That I somehow “allowed” that black hole to consume us. That being said, I realize now in retrospect, that it wasn’t *just* my fault. For as Anthony de Mello states, to love is *to see* oneself, as well as the other, and not the picture we’ve painted of ourselves or them.

The heartache, on top of engaging in therapy and bodywork these days to finally integrate those painful parts of myself, to become whole for myself, and make sure that what happened doesn’t happen again, is a lot. But it will

be worth it because even though I may not get a life with him, I will get a life worth living with myself.

I must admit that the process of integration is incredibly overwhelming and scary. It requires a lot of strength and courage to move beyond what is known into the unknown yet somehow still known. I therefore understand very much that people would rather look for a “quick fix”. But I believe we all have what it takes. Deep down.

We all have made mistakes in our life. I know I’ve made quite a few, and these days I am learning bit by bit WHY and HOW I made them. This is part of the integration process. Understanding myself and thus become more aware of those ‘patterns’ I’ve blindly acted upon until this day. In doing so I trust to be prepared to make better decisions for the future, and in doing so – make those previous patterns obsolete.

I don’t believe in the saying that “one has to love oneself before one can be in a relationship”. Instead, I believe that one can become whole alongside a partner. I’ve learned that its possible, but only if we take full responsibility for ourselves.

I also believe that although I’ve made mistakes, they shouldn’t define me or put me in a box that I cannot escape. I believe that we are all work of arts. Every stroke of a brush represents an experience we’ve made. The strokes combined is our own work of art; ourselves. A painting of who we are in that very moment in time. This process of painting and repainting will continue over the course of all our lives until we take our last breath. We are always evolving! If there is evolvment and movement, there is still hope and change in the horizon.

To anyone out there who may feel like a black hole I want you to gift you with the following saying by Stephen Hawking;

"The message of this lecture is that black holes ain't as black as they are painted. They are not the eternal prisons they were once thought. Things can get out of a black hole both on the outside and possibly to another universe. So if you feel you are in a black hole, don't give up – there's a way out"

The good news is that a black hole dies bit by bit due to something called Hawking Radiation: *"The flow of particles of negative energy into the black hole reduces its mass until it disappears completely in a final burst of radiation."*

Do I wish I had this knowledge earlier? *Sure!*

Do I sometimes beat myself up over not knowing before? *Absolutely!*

But, can I accept and love that part of me who was too hurt and/or unable to see? *Yes. I think so.*

Am I there yet? *No. And that is ok. I'm on my way. I'm on my way home. And that's what matters.*

May we all find our way home.

Curriculum Vitae (CV)

Malin Vedøy Uthaug was born in Bergen, Norway in 1993. She moved to Prague after graduating from high school in her hometown in 2012. After obtaining her dual Bachelor's in Psychology from both University of New York in Prague and Empire State College in New York in June 2016, she continued her studies at Maastricht University in The Netherlands. At Maastricht University she obtained her Master of Science in Psychology with specialization Health and Social Psychology in 2017. During her 6-month research internship while studying at Maastricht University, she was based in Bogotá, Colombia. Here she investigated the short-term and long-term effects of the psychedelic brew from the Amazon's called ayahuasca on mental health under supervision of Prof. Dr. Johannes Ramaekers and Dr. Jordi Riba.

After finishing her master's degree, Malin continued working as a PhD candidate at the department of Neuropsychology and Psychopharmacology, at the faculty of Psychology and Neuroscience at Maastricht University. Here she investigated the short-term and long-term effects of primarily ayahuasca and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in naturalistic settings, while simultaneously initiating several other studies on the psychedelic substance mescaline and the breathing practice known as Holotropic Breathwork (HB).

Besides being a researcher investigating psychedelics as a novel treatment option for mood-related disorders and trauma, Malin is also an editor for the '*Journal of Psychedelics Studies*', a board member of the American podcast-show known as '*Psychedelics Today*',

and the co-founder of the *Norwegian Association for Psychedelic Science* (*Norsk Forening for Psykedelisk Vitenskap* [NFPV]: <https://nfpv.no/english>) whose main aim is to educate the general public as well as researchers, and mental health practitioners in Norway about psychedelics.

Malin is currently working as a Research Assistant at The Centre for Psychedelic Research, at Imperial College London, led by Dr. Robin Carhart-Harris. Here she is investigating the effects of 5-MeO-DMT on mental health related variables, brain activity and consciousness in both a naturalistic as well as a lab setting.

Publications

As part of this dissertation

- **Uthaug, M. V.**, Lancelotta, R., Bernal, A. O., Davis, A. K., & Ramaekers, J. G. (2020). A comparison of reactivation experiences following vaporization and intramuscular injection (IM) of synthetic 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting. *Journal of Psychedelic Studies*, 1(aop), 1-10.
- **Uthaug, M. V.**, Lancelotta, R., Szabo, A., Davis, A. K., Riba, J., & Ramaekers, J. G. (2019). Prospective examination of synthetic 5-methoxy-N, N-dimethyltryptamine inhalation: effects on salivary IL-6, cortisol levels, affect, and non-judgment. *Psychopharmacology*, 1-13.
- **Uthaug, M. V.**, Lancelotta, R., van Oorsouw, K., Kuypers, K. P. C., Mason, N., Rak, J., ... & Páleníček, T. (2019). A single inhalation of vapor from dried toad secretion containing 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms. *Psychopharmacology*, 1-14.
- **Uthaug, M. V.**, Van Oorsouw, K., Kuypers, K. P. C., Van Boxtel, M., Broers, N. J., Mason, N. L., ... & Ramaekers, J. G. (2018). Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution. *Psychopharmacology*, 235(10), 2979-2989.

Not as part of this dissertation

- Mason, N. L., Mischler, E., **Uthaug, M. V.**, & Kuypers, K. P. (2019). Sub-acute effects of psilocybin on empathy, creative thinking, and subjective well-being. *Journal of psychoactive drugs*, 51(2), 123-134.