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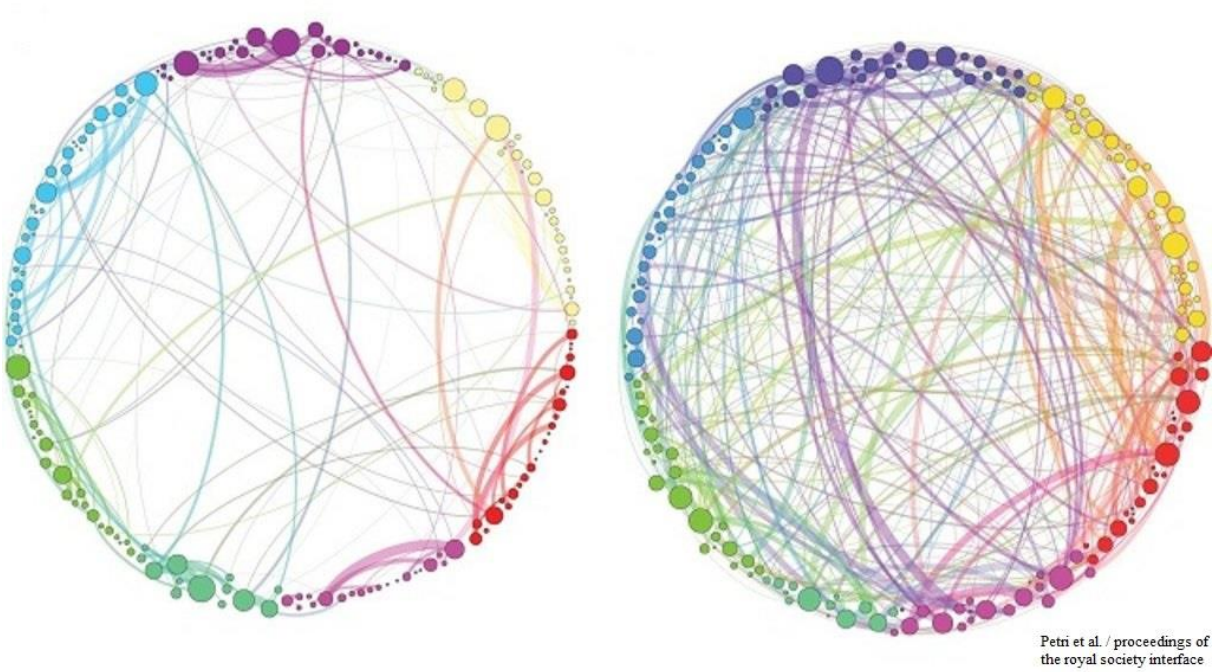

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Introduction

Depression is a serious mental illness affecting over 300 to 350 million people worldwide (WHO, 2018; Cipriani et al., 2018). People suffering from depression experience a wide variety of symptoms, including a depressed mood, loss of interest, and reduced energy.

There are many different therapeutic approaches to treat depression, of which cognitive behavioral therapy (CBT) and the use of antidepressants (e.g. SSRI's) are probably the most prominent. Both seem to be efficacious in alleviating the symptoms of depression (Butler et al., 2006; Driessen & Hollon, 2010; Cipriani et al., 2018). However, a more recent review suggests that the effects of CBT might be overestimated until now (Cuijpers et al., 2013).

Likewise, the exclusive use of antidepressants seems to have some significant effects on alleviating depressive symptoms, but they sometimes seem to improve spontaneously, which happens in particular to placebo responders in antidepressant trials (Cipriani et al., 2018). In addition, trials that were included in the meta-analysis by Cipriani et al. (2018) were of short duration and it usually takes a few weeks for antidepressants to exert their full effect, including any adverse effects. Thus, it can be hard to infer any causality from the use of an antidepressant or a placebo.

Despite these seemingly efficacious resources, the fact remains that 300 to 350 million people worldwide are still depressed. Do they simply lack resources? Are antidepressants not as effective as they seem or do people ordinarily neglect them due to their adverse effects? More importantly, are these the only options for patients when treating depression?

Recently, studies involving the classic psychedelics (i.e. psilocybin, lysergic acid diethylamide, and DMT) are showing tremendous potential in treating people with depression and other disorders like addiction, end-of-life anxiety, and alcoholism (Carhart-Harris et al., 2012; dos Santos et al., 2016; Johnson et al., 2014; Bogenschutz et al., 2015; Griffiths et al., 2016; Ross et al., 2016; Johnson et al., 2017). How is this possible and what are the possible mechanisms behind these psychedelic drugs?

This paper will specifically look at the psychedelic compound *psilocybin cubensis* and its role in alleviating depressive symptoms by offering insight into both qualitative and quantitative mechanisms of therapeutic action. It may further do this, albeit indirectly, to the other classic psychedelics as well, since their overall experience and effect seem quite similar due to their neurochemical structure.

From Disconnection to Connection

Psilocybin cubensis (from the genus *psilocybe*) is a tiny mushroom that contains the naturally occurring psychedelic prodrug *psilocybin* and converts to *psilocin* (4-hydroxy-dimethyltriptamine) in the body when taken orally. It is a serotonin receptor agonist and its psychoactive effects are mediated by serotonin 2A (5-HT2a) receptor agonism. Lastly, psilocybin is non-toxic and non-addictive, and is not associated with drug-seeking behavior (Carhart-Harris et al, 2016).

The following study (Carhart Harris et al., 2016). aimed to investigate the feasibility, safety, and efficacy of psilocybin in patients with unipolar treatment-resistant depression. Participants had depression for an average of 18 years, tried three to eleven different antidepressants, and had up to six courses of psychotherapy.

After only two oral doses of psilocybin (10mg and 20mg), six people (N=20) went into remission while the

symptoms of eleven participants returned, but were hopeful again despite this unfortunate occurrence. The remaining three participants did not respond at all. Next to alleviating symptoms of depression, there were also marked and sustained improvements in anhedonia and anxiety. Finally, psilocybin was well tolerated by all patients and there were no serious or adverse events, thereby proving its feasibility, efficacy, and safety.

Six months later, Watts et al. (2017) conducted a follow-up study where Dr. Rosalind Watts, a clinical psychologist, interviewed all the participants to ask about their (psychedelic) experience that occured during the psilocybin session. Using a thematic analysis to identify the patients' experiences of treatment – and how it compared with previous treatments (i.e. psychotherapy and antidepressants) – she discovered one theme, or spectrum rather, which showed itself as both a poetic and noetic phenomenon in all the participants' interviews: "connection versus disconnection."

Disconnection was inferred from the interview data as follows: "*disconnected from the world, others, self, senses, and trapped in the mind*." Conversely, connection was defined as: "*an intellectual, empathic and embodied closeness to self, others, and world*" and was further subdivided into the following domains: mind, senses, emotions, body, identity, others, and world (Watts, 2017).

One participant said the following about the psilocybin session: "*During the session, I was everybody, unity, one life with six billion faces. I was the one asking for love and giving love. I was swimming in the sea, and the sea was me*." Another individual said: "*Being absolutely connected to myself, to everything in the universe.*" Watts et al. (2017) argue that this strong feeling of connection seems to be a fundamental change process. Thus, connection seems to be a qualitative mechanism of therapeutic action of psilocybin.

The Significance of the Psychedelic Experience

One decade earlier, a small group of scientists led by Dr. Roland Griffiths looked at the acute and persisting effects of psilocybin (Griffiths et al., 2006). They conducted a rigorous double-blind study (N=36) with clinical pharmacology methods to evaluate psilocybin's (30mg/70kg) acute (up to 7 hours) and longer-term (2 months) mood-altering and psychological effects, and compared it to methylphenidate hydrochloride (40mg/70kg). To assess qualitative effects, Griffiths et al. (2006) used three questionnaires for subjective drug effects and two questionnaires for the mystical experience. Two months later, the participants were asked to complete another series of five questionnaires to assess any possible lasting changes in attitude, mood, or behavior as well as possible changes in personalized measures of personality, mood, and spirituality. Concurrently, community observer ratings of participants' attitudes and behavior were being retrieved by telephone as well (see Appendix A: Questionnaires).

Both hallucinogen and mystical experience questionnaires (seven hours after administration) showed significant higher effects when compared to methylphenidate. The former showed alterations in mood, affect, and cognition, consisting of visual pseudo-hallucinations, feelings of transcendence and/or anxiety, and a sense of meaning. The latter provided evidence that 22 of the 36 volunteers had a "complete" mystical experience after psilocybin, while only 4 did after methylphenidate (Griffiths et al., 2006). Two months later, the participants completed the other questionnaires where psilocybin, again, showed significant higher effects than methylphenidate. The results showed great elevations in ratings of positive attitudes, mood, social effects, and behavior (Griffiths et al., 2006). Observer ratings were consistent with these findings.

The authors elaborate on these findings by saying the following about psilocybin and its extraordinary short-term and long-term effects: "*It is remarkable that 67% of the volunteers rated the experience with psilocybin to be either the single most meaningful experience of his or her life or among the top five most meaningful experiences of his or her life. In the comments, the volunteers judged the meaningfulness of the experience to be similar, for example, to the birth of a first child or death of a parent.*" (Griffiths et al., 2006).. Furthermore, participants described the experience, or aspects thereof, as related to "a sense of unity without content" (e.g. pure consciousness) and/or "unity of all things."

Results of Griffiths et al. (2006) seem to suggest that the aforementioned theme of "connection" is being corroborated by themes like: "*a sense of unity*" which looks similar to its definition: "*an intellectual, empathic and embodied closeness to self, others, and world*." Thus, the psychedelic and/or mystical experience might serve as a causal agent, or even as a catalyst, for changes in behavior, mood, attitudes, and personality, since people who indeed had a full mystical experience showed more changes in these domains (Griffiths et al., 2006).

Neural Correlates of the Psychedelic State

Much can be said about the phenomenology of the psychedelic experience and its qualia. But what about effects in the brain? To study this, Carhart-Harris et al. (2012) designed a fMRI protocol (i.e. ASL perfusion and BOLD) to capture the transition from normal waking consciousness to the psychedelic state (N=15). The measurement took place before and after intravenous infusions of placebo and psilocybin. Results showed a significant reduction in blood flow to the thalamus, hypothalamus and anterior and posterior cingulate cortex (ACC and PCC). Moreover, a consistent finding among all the participants was decreased activity in the ACC/medial prefrontal cortex (mPFC). The less activity there was in all of these areas, the more this predicted the intensity of the subjective effects. Thus, the psychedelic experience can be inferred from the deactivation of these brain areas and explains the quantitative mechanisms of psilocybin. But how does this relate to depression?

One possibility concerns the hypothalamus, which plays a major role in the body's response to stress through the hypothalamic-pituitary-adrenal (HPA) axis. It has been suggested that the dysregulation of this particular axis – and the subgenual prefrontal cortex being hyperactive – are frequently being observed in depression (Sudheimer et al., 2015; Hamilton et al., 2015). The mechanisms of psilocybin, and its inhibitory effect on the hypothalamus, could in turn influence regulation of the HPA-axis, which then might alleviate depressive symptoms. This remains highly speculative and requires further investigation, but it might be one other quantitative mechanism.

The Default Mode Network

Another topic involves the Default Mode Network (DMN) and its role in depression (Carhart-Harris et al., 2012; Hamilton et al., 2015; Wise et al., 2017). The DMN comprises the aforementioned posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC), and involves self-referencing and having a sense of self or "ego" (Carhart-Harris et al., 2012). Activity of the DMN is known to be elevated in patients with depression and is normalized after effective treatment (Holtzheimer & Mayberg, in Carhart-Harris et al., 2012). Furthermore, the mPFC and PCC are key nodes in the DMN and are implicated in ruminative cognition, another symptom of depression.

Hamilton et al. (2015) first reported meta-analytic findings that showed increased functional connectivity between the DMN and the subgenual prefrontal cortex (part of the mPFC), which predicts levels of rumination. Two years later, these findings were confirmed by Wise et al. (2017) with fMRI by showing greater connectivity between these two regions in major depression when compared to healthy controls.

The fMRI results from Carhart-Harris et al. (2012) show that psilocybin consistently deactivates the DMN and that deactivations are correlated with the drug's subjective effects. As said, depression involves rumination, and individuals' cognitions can also become rigidly pessimistic. The former is linked with hyperactivity of the mPFC while the latter is linked to deficient 5-HT2A receptors stimulation, particularly in the mPFC region (Carhart-Harris et al., 2012).

As mentioned before in the paragraph about "connection," psilocybin is a 5-HT2A agonist and this corresponds with the suggestion of Carhart-Harris et al. (2012) that there might be a biological mechanism for decreased symptoms in depression: "*decreased mPFC activity via 5-HT2A receptor stimulation*."

Suggestions like these can be further corroborated by fMRI results from Carhart-Harris et al. (2017) who looked at psilocybin's effects in the brain from people with treatment-resistant depression (N=19) by contrasting pre-treatment and post-treatment results. Carthart-Harris et al. (2017) propose a 'reset' therapeutic mechanism of the DMN that will enable a subsequent re-integration and resumption of normal functioning.

In sum, it is plausible to suggest that deactivation of the DMN – and the stimulation of 5-HT2A receptors – will result in the alleviation of depressive symptoms due to less functional connectivity between the mPFC and PCC.

Discussion

Psilocybin cubensis shows much promise as a psychotherapeutic tool when treating people with depression. This paper found the following evidence for psilocybin's effects in depression, where both connection and the significance of the psychedelic experience serve as qualitative mechanisms, and HPA-axis dysregulation and the Default Mode Network are established as quantitative mechanisms.

One might ask if there is a place for psilocybin and the other classic psychedelics in modern psychotherapy. Of course, studies involving psychedelics need to be replicated with rigorous methods and more controlled variables. For instance, Carhart-Harris et al. (2016) was an open-label feasibility trial, which makes it difficult to draw any specific conclusions since there was no control group. However, the subsequent literature presented in this paper (Watts et al., 2017; Carhart-Harris et al., 2012; Carhart-Harris et al., 2017) corroborate the feasibility trial enough to conclude that psilocybin has significant and long-term effects with underlying causal mechanisms that alleviate depression. Currently, a randomised controlled trial involving psilocybin and major depression is in transit (Carhart-Harris et al., 2018), which might account for earlier methodological shortcomings and further elucidate psilocybin's mechanisms and effects.

Finally, a framework of "psychedelic axioms" might be desirable when conducting pychedelic sessions. For instance, axioms like "set and setting", and integration (Fadiman, 2011) all highly influence the course and final destination of a psychedelic session. Other mechanisms, like suggestibility and expectancy (Carhart-Harris et al., 2012; Griffiths et al., 2006), need to be controlled to see in what degree these will have an effect on psilocybin's outcomes. Ideally, researchers and therapists acquire enough insight into psilocybin's clinical utility to make this a feasible, safe, and efficacious treatment option for patients that are suffering from depression.

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Appendix A: Questionnaires

The subjective drug effects were assessed by using the following questionnaires (Griffiths et al., 2006).

- Hallucinogen rating scale
- APZ
- Addiction Research Center Inventory (ARCI)

The mystical experience was assessed by using the following questionnaires (Griffiths et al., 2006).

- The States of Consciousness Questionnaire
- Mysticism Scale

The remaining questionnaires were used after two months to assess any possible lasting changes in attitude, mood, or behavior as well as possible changes in personalized measures of personality, mood, and spirituality:

- Persisting Effects Questionnaire
- Mysticism Scale-Lifetime
- Spiritual Transcendence Scale
- NEO PI-R
- PANAS-X