The Emotional Effects And Therapeutic Potential of Psilocybin for Treatment of Depression

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An exploration of the history of psychedelics, their effects on perception and emotions, and their potential uses in psychotherapy (2461 words)

Background

Ever since Lysergic acid diethylamide (LSD) was first consumed by its creator Albert Hofmann in 1943, psychedelics have played a large role in both the political and the psychological arenas. Two scientists, Woolley and Shaw, were among the first to propose that the neurotransmitter serotonin could have a substantial impact on behavior, proposing that the "neurogenic behaviour of animals can be profoundly influenced by pharmacological agents which interfere with the action of this compound" (Woolley & Shaw, 1954). With the knowledge that LSD was a serotonin agonist, they suggested that the mental changes enacted by LSD "may be the result of an interference with the action of serotonin in the brain" and claimed that serotonin deficiency may lead to schizophrenia (Woolley & Shaw, 1954). This idea that neurotransmitters affect behavior is central to how we view psychological illnesses today.

Most classical psychedelics (such as psilocybin, LSD, and DMT) are agonists of the 5-HT_{2a} serotonin receptor. Agonists bind to the receptor and activate it by having shapes similar to the neurotransmitter the receptor was designed for.

While LSD was synthesized, psilocybin was introduced to popular culture in the United States around 1957 via a *Life* magazine article, though it had been in use for centuries in other parts of the world for religious purposes.

After an initial surge of relatively unorganized and unscientific psychedelic trials during the 1960s, during which LSD gained popularity in the United States among counterculture groups and the government declared it and other classic pyschedelics such as DMT, mescaline, and psyilocybin Schedule I substances under the Controlled Substances Act of 1970 (CSA), which means the drugs (FDA, 1974):

1. have a high potential for abuse
2. have no currently accepted medical use in treatment in the United States
3. have a lack of accepted safety for use of the drugs or other substances under medical supervision

This came after an attempt by the CIA to use LSD as a mind-control drug and mounting concerns about the effects of psychedelics on society.

While there were preliminary studies done on therapeutic uses of psychedelics in the 1950s and 1960s, most were poorly documented and less than ethical. Since the enactment of the CSA, research on psychedelics in the United States has essentially halted. In Europe, however, research on scheduled substances is often less restricted, and in the last decade there has been an attempted resurgence in the study of potential therepeutic uses of psychedelics. Thus, a majority of the psychedelic studies referenced in this paper come from either Switzerland or Germany.

Through examination of the linked history of psychedelics and anti-depressants, the effects of psychedelics, and emotional biases in mood disorders the idea of using psychedelics for treatment of mood disorders emerges as a promising possibility.

Antidepressants

The first classes of antidepressants developed were the monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants (TCAs) which were mildly effective but had deblitiating side effects. (Interestingly, ayahuasca, a psychedelic popular in rituals, is DMT combined with an MAOI.) An effective antidepressant that did not cause potentially deadly somatic side effects with relative frequency was not available until the first selective serotonin reuptake inhibitor (SSRI) was released in 1988 (Ferguson, 2001-02). This class of antidepressants was more selective in targeting specific serotonin receptors in the brain, which led to less side effects. While SSRIs still are not ideal by any means, they have been the most effective and available method of pharmacologically treating depression for a long time.

SSRIs work by blocking the serotonin (5-HT) receptors in the brain in order to prevent the reuptake of the neurotransmitter, leading to an abundance of serotonin in the brain. Stemming from the research of Woolley and Shaw, it is now believed that a lack of serotonin plays a large role in many mood disorders, especially anxiety disorders and depression.

Even though SSRIs have been demonstrated to have less side effects than the accepted alternatives, they still have

many negative effects on users' lives. SSRIs can cause lower quality of sleep, weight gain, long-lasting sexual dysfunction, nausea, anxiety, and even the deadly serotonin syndrome when combined with other drugs (Ferguson, 2001-02). Considering this wide spectrum of negative effects, it would be enormously beneficial to identify a new class of drug that could alleviate mood disorders with less harm to the patient.

It is important to note here that antidepressants diminish the effects of psychedelics that act on the 5-HT_{2a} receptor. This is due to the fact that there are less available serotonin receptors to bind to. There are no official studies confirming this due to the obvious ethical issues of giving psychedelics that can create mental issues to people that need medication to decrease mental issues. However, anecdotal evidence from several drug forums confirms this effect (SKA, 2012; Bran Man, 2009), which, when combined with pharmacological intuition, provides substantial evidence for this interaction.

The interaction of classic psychedelics and SSRIs, while potentially making research more difficult, also provides an interesting hint for future research that antidepressants and psychedelics affect many of the same receptors in the brain.

Psilocybin's Effects

Using the five dimensional altered states of consciouness scale (5D-ASC), a German study set out to determine the psychological and physiological effects of psiolocybin on humans. The 5D-ASC is a widely-utilized scale that allows researchers to measure the effects of psychedelics in participants. The five dimensions are oceanic boundlessness, dread of ego dissolution, visionary restructuralization, auditory alterations, and vigilance reduction. The study claims that psilocybin can be used to help study "neurobiological basis of altered states of consciousness" (Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004). Rises in blood pressure were observed in some subjects, but that was the only mildly concerning somatic effect observed. Interestingly, very low (45 μg/kg of weight) and low doses (115 μg/kg) of psilocybin seem to be valenced in terms of results against medium (215 μg/kg) and high (315 μg/kg) doses, with some subjects unable to distinguish between the two doses in each valence. Psilocybin was found to increase the scores of all 5D-ASC scales, and demonstrated an "excellent linearity" between psilocybin dose and the three core dimensions of oceanic boundlessness (derealization), dread of ego dissolution (anxious dysphoria), and visionary restructuralization (hallucinations), meaning that psilocybin especially alters perception, ego, and affect. Increased inactivity, introversion, and dreaminess were also present in all subjects, with significant dreaminess lasting for at least 24 hours after dose administration (Hasler et al., 2004). The study declares that there is "no cause for concern that [psilocybin] is hazardous with respect to somatic health" (Hasler et al., 2004).

Emotional Biases in Mood Disorders

To determine whether psilocybin can alleviate depression, it is important to describe specific depressive symptoms that could be alleviated. One study found that participants with major depressive disorder and those in a period of remission that had experienced one major depressive episode in their lives demonstrated "significantly greater vigilance to the sad faces than did the NC [non-disordered] participants" without significant variance between the groups (Joormann & Gotlib, 2007), whereas never-disordered participants were much more vigilant in general than the major depressive disorder participants.

Another study revealed similar findings using functional magnetic resonance imaging (fMRI). It found that "amygdala reactivity in depressed patients was increased to masked negative emotional stimuli and decreased to masked positive emotional stimuli" in comparison to a control group (Suslow et al., 2010).

Together, these studies provide ample evidence that depression fundamentally alters the way people process emotional faces and interpret their surroundings.

Psilocybin and Emotion

As previously mentioned, psilocybin generally decreases awareness. However, one study examined the effects of psilocybin on facial processing as compared to the effects of ketamine (a dissociative). The results were fascinating: psilocybin was found to reduce the brain's ability to process negative faces much more than positive ones, whereas the effects with ketamine were very similar across the board (Schmidt, Kometer, Bachmann, Seifritz, & Vollenweider, 2012).

This raises interesting implications for dealing with depression and other mood disorders using SSRIs and other antidepressants. These findings could also act as a window into how (and how well) SSRIs work as treatment for mood disorders. It is certainly plausible that the alteration of emotional facial processing plays a key role in the affective states of people with depression, leading to significant social and practical effects.

Emotional Bias

There are myriad ways in which emotions affect desicion-making and peoples' interpretations of the world.

One particularly relevant study discusses two different types of affective influence on decision-making: that of *expected emotions*, and that of *immediate emotions*. Expected emotions are predictions about the emotional consequences of decisions, i.e. "This will make me happy," while immediate emotions are emotions about the decision that the individual is currently experiencing. Incidental influences, the

emotional state of an individual unrelated to the current decision, also play a role. The study revealed that people rely on emotional processes for decision-making more when they are under pressure or in distress (Loewenstein & Lerner, 2003).

From this, one can extrapolate the consequences of depression on decision-making. People who are clinically depressed will theoretically be more cautious and less confident, as their expected emotions about decisions will usually be more negative than those of non-disordered people. Their immediate emotional state will also be more negative, or they may even feel pressured to make decisions, leading to a fearful immediate emotional state where they rely even more on their emotions to make decisions. Their incidental mood not relating to the particular decision will also have a negative effect on confidence. This cyclical thinking could make it difficult for the depressed person to break out of a depressive episode.

As demonstrated earlier, depressed people demonstrate a significant bias toward negative faces (Joormann & Gotlib, 2007; Suslow et al., 2010). Importantly, Joormann and Gotlib's study also proved that this bias toward negative faces lasts longer than the depressive episode itself. Studies have also found that antidepressants tend to reduce emotional processing of negative faces "short-term treatment with reboxetine [an antidperessant] reduced amygdala activation to subliminal negative facial expressions" (Norbury, Mackay, Cowen, Goodwin, & Harmer, 2007). Reboxetine was also found to *increase* amygdala activation in regards to subliminal positive expressions (Norbury et al., 2007). These effects are not just specific to reboxetine, either. Citalopram was also found to increase positive facial processing biases (Harmer, Shelley, Cowen, & Goodwin, 2014). By pairing these findings with those of Schmidt et al. on psilocybin, one can see that both psilocybin and traditional antidepressants have similar effects on facial processing.

Proposed Studies

There are two studies that could potentially make the therapeutic potential of psilocybin clearer. The first would attempt to prove that a causal link exists between facial processing biases and depression. The second would examine the effects of psilocybin on depressed participants.

The first study is difficult to design. While there is a plethora of studies that prove the emotional facial-processing biases that come with depression, it is difficult to find one that proves the causation of one by the other. Due to the multifaceted nature of complex mood disorders such as depression, it may not be possible to prove that such a link exists. Joormann and Gotlib caution against proclaiming negative facial processing biases as evidence of a vulnerability for the onset of depression. However, they also point out that "the risk of recurrence increases with each depressive episode that is experienced" (Joormann & Gotlib, 2007). Ideally, a study would examine emotional facial processing biases before the onset of depression, during a depressive episode, and after the end of an episode. It is important to note that even if a causal relationship between biased facial processing and depression is not established, facial processing still has been demonstrated to have effects on social support structures of depressed patients and the attempts at recovery (Joormann & Gotlib, 2007).

There are obvious ethical complications with the second study. While psilocybin often has positive lasting effects on a user's mental state with "over 60% of subjects [rating] the [psychedelic] experience as very enriching and over 90% as enriching to at least a medium degree" and several subjects rating the experience as enriching despite undergoing acute anxiety during the experiment (Studerus, Kometer, Hasler, & Vollenweider, 2011), it has significant potential to cause ego dissolution and intense anxiety, particularly at higher doses (Hasler et al., 2004). This is one reason previous studies looking at therapeutic uses for psilocybin have predominately focused on patients with advanced-stage cancer, as many of those participants would find adverse psychological effects potentially caused by psychedelics preferable to debilitating end-of-life anxiety.

One alternative to directly administering psychedelics to depressed patients is to poll past users of psychedelics that were clinically depressed at the time of usage. This certainly has an ethical edge over other methods, but the results have the potential to be skewed due to selection bias, self-reporting, and questionnaire design.

Ideally, a study would measure the level of depression in participants with a psychiatric scale before and after the administration of one average dose of psilocybin compared to a placebo, while also measuring facial processing biases before, during, and after administration of the drug. Finding an ethical way to do this would be the main obstacle in completing this study.

Discussion

From the current body of research, one can infer that psilocybin could potentially be used to alleviate negative facial processing biases, what appears to be a key symptom of depression. These biases affect decision-making and social cirumstances, and SSRIs and psilocybin have been shown to have similar effects on these biases.

The main caveat to the inferred conclusion is that it is difficult to determine if this bias in facial processing is caused by mood or if it causes the mood. The proposed research should help ameliorate this issue, but even if a causal relationship is not determined, it is still possible that psilocybin could be used to help patients recover from depressive episodes.

The majority of this paper has focused on the possibilities of psilocybin as an antidepressant, but there is also research that supports the possible use of psilocybin as a psychother-

apeutic aid. One study found that "participants... reported more vivid and visual recollections under psilocybin" and suggests that psilocybin could be combined with positive memory cues as a treatment for depression to revert pessimistic mindsets (Carhart-Harris et al., 2012). It could also be used as a method of assisting memory recall in a therapeutic setting.

There are also several studies that deal with the therapeutic possibilities of psilocybin already. The drug has especially been used in treatment of existential anxiety in patients with advanced-stage cancer. In one such study, results demonstrated that "psilocybin produces mood-elevating effects that persist after the acute effects of the drug" in terminally ill patients (Grob CS, Danforth AL, Chopra GS, & et al, 2011).

There are certainly ethical obstacles to the administration of psilocybin to depressed patients in a research setting. While one long-term population study of psychedelic users found "no relation between lifetime use of psychedelics and any undesirable past year mental health outcomes, including serious psychological distress, mental health treatment... or symptoms of panic disorder, major depressive episode, mania, social phobia, generalized anxiety disorder, agoraphobia, post-traumatic stress disorder, or non-affective psychosis" (Krebs & Johansen, 2013), it is important to note that the responses in this study were self-reported and the drugs were self-administered outside of a controlled setting. In all valid scientific studies patients are closely monitored by a trained professional during their psychedelic experience.

More research is required before psilocybin can be considered a safe drug with positive therapeutic effects, but psilocybin has nevertheless emerged as a promising, potentially less harmful alternative to the current psychiatric medications used to treat mood disorders.

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