The metaphysics behind pharmacotherapy: treating depression with conventional and psychedelic drugs

La metafísica tras la farmacoterapia: tratando la depresión con fármacos convencionales y psicodélicos

A metafísica tras a farmacoterapia: tratando a depressão com fármacos convencionais e psicodélicos

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ABSTRACT

This paper aims to explore and compare the metaphysical entailments of the conventional psychopharmacological approach in the treatment of depression to those of a psychedelic approach. We will examine the thesis by which knowledge of how drugs act upon us shapes our self-image and our understanding of psychopathology and defend that this process can only take place in a supportive environment. It is commonly claimed that the nature of depression was shaped after the therapeutic success of antidepressants; nevertheless, psychedelic drugs were at least as successful as antidepressants, and they didn't end up having the same power to influence our views. It was possible for first and second-generation antidepressants to influence our views because of a supportive environment, where social, political, economic and even metaphysical issues were at play to create that result. We will compare the unfolding of the two paradigms elicited by these two kinds of drugs, one where pills are seen as magic bullets aimed to restore biochemical balance, and another where drugs are seen as therapeutic tools capable of inducing a

life-changing experience, provided there is an adequate context. We will review different factors that contributed to the establishment of a reductionist paradigm, such as the aspirations of psychiatry and the assumed objectivity of biologically oriented explanations. Finally, we will reflect on the new paradigm that unfolds with contemporary research.

Keywords: Monoamine hypothesis; Therapeutic tool; Experience; Context

RESUMEN

El propósito de este artículo es comparar las implicaciones metafísicas de la aproximación psicofarmacológica convencional al tratamiento de la depresión, con las implicaciones de la aproximación mediante drogas psicodélicas. Examinaremos la tesis según la cual el conocimiento sobre cómo actúan sobre nosotros los fármacos moldea nuestra auto-imagen y nuestra comprensión de la psicopatología –y defenderemos que este proceso sólo ocurrir en un entorno adecuado–. Suele afirmarse que la naturaleza de la depresión fue inferida a partir del éxito terapéutico de los antidepresivos; no obstante, los psicodélicos fueron tan exitosos como los antidepresivos y, en cambio, no ejercieron la misma influencia en nuestra visión. Los antidepresivos de primera y segunda generación pudieron influenciar nuestra mirada porque se encontraban en un entorno propicio para ello. Cuestiones sociales, políticas, económicas e incluso metafísicas entraron en juego para llegar a ese resultado. Compararemos el despliegue de estos dos paradigmas suscitados por sendos fármacos: uno, donde los fármacos son vistos como *fórmulas mágicas* cuya meta es restablecer el equilibrio bioquímico; otro, donde los fármacos son vistos como herramientas terapéuticas capaces de inducir una experiencia capaz de cambiar la vida del paciente, en el contexto apropiado. Revisaremos los factores que contribuyeron al establecimiento de un paradigma reduccionista, tales como las aspiraciones científicas de la psiquiatría y la identificación de las explicaciones biologicistas con el terreno de la objetividad.
Finalmente, reflexionaremos sobre el nuevo paradigma que se abre con la investigación contemporánea.

Palabras clave: Hipótesis monoaminérgica; Herramienta terapéutica; Experiencia; Contexto

RESUMO

Este trabalho tem como objetivo explorar e comparar as implicações metafísicas da abordagem psicofarmacológica convencional no tratamento da depressão com aqueles de uma abordagem psicodélica. Examinaremos a tese segundo a qual o conhecimento de como as drogas agem sobre nós molda nossa auto-imagem e nossa compreensão da psicopatologia, e defenderemos que este processo só pode ocorrer em um quadro favorável. É comumente alegado que a natureza da depressão foi moldada após o sucesso terapêutico dos antidepressivos; no entanto, as drogas psicodélicas eram pelo menos tão bem sucedidas quanto os antidepressivos, e não acabavam tendo o mesmo poder de influenciar nossas opiniões. Era possível que os antidepressivos de primeira e segunda geração influenciassem nossas visões por causa de um quadro favorável, onde questões sociais, políticas, econômicas e até mesmo metafísicas estavam em jogo para chegar a esse resultado. Compararemos o desenvolvimento dos dois paradigmas promovidos por esses dois tipos de drogas, um onde as pílulas são vistas

como *fórmulas mágicas* destinadas a restaurar o equilíbrio bioquímico e outro onde as drogas são vistas como ferramentas terapêuticas capazes de induzir uma experiência transcendental. Revisaremos diversos fatores que contribuíram para o estabelecimento de um paradigma reducionista, como as aspirações da psiquiatria e a suposta objetividade das explicações biologicamente orientadas. Finalmente, refletiremos sobre o novo paradigma que se desenvolve na pesquisa contemporânea.

Palavras clave: Hipótese monoaminérgica; Ferramenta terapêutica; Experiência, Contexto

In the following pages, we will explore and compare the metaphysics behind two different approaches to treating depression: treatment with conventional drugs and with psychedelic ones. By conventional drugs we are referring to those drugs commonly known as first and second-generation antidepressants—having particularly in mind MAOIs, tricyclic drugs and, especially, SSRIs. By psychedelics we are referring to those naturally occurring or chemically designed substances, usually agonists of the serotonin 2A receptor—such as LSD or psilocybin—known for their capability to alter cognition and perception, and more importantly, to induce altered states of consciousness (Baumeister, Barnes, Giaroli & Tracy 2014).

In recent years, scientific interest in the therapeutic potential of psychedelic drugs has risen considerably, although these drugs were already used in psychiatric settings in the later fifties, sixties and earlier seventies—not only to study psychoses, as it is commonly known, because of their alleged *psychotomimetic* properties, but also as therapeutic tools for several ailments, ranging from severe addiction to marital problems. Nowadays much research is again being conducted on psychedelics—or similar substances, such as MDMA—as treatments for different disorders: i.e., MDMA as a treatment for post-traumatic stress, ibogaine and ayahuasca to overcome addiction or LSD to manage the anxiety produced by life-threatening diseases (Kyzar, Nichols, Gainetdinov, Nichols & Kalueff, 2017). While more research needs to be conducted, the preliminary results of all of these studies are more than promising.

Inasmuch as we see research on psychedelics as a growing trend, we believe it is appropriate to address them from a philosophical point of view.

We will examine the thesis by which knowledge of how drugs act upon us shapes our self-image and our understanding of psychopathology—and defend that this process can only take place in a supportive environment. First and second-generation antidepressants played a major role in shaping both depression and our self-image, but that was only possible because the background was set to entertain the kind of simplistic and biologically oriented explanations that could be inferred from their effects.

To explore our topic, we will begin by saying a few words on the recent history of both antidepressants and psychedelics. The key point here is that the development of antidepressants revolves around the idea of restoring a biochemical imbalance, while psychedelics are closely connected with the idea of experience—highlighting also the personal context (*set, setting* and *matrix*). Grounded on this, we will see how two different paradigms unfold: antidepressants conceptualized as *magic bullets;* psychedelics, as *therapeutic tools.*

Magic Bullets and Therapeutic Tools

As Peter Kramer (1993) noted in his famous book, *Listening to Prozac,* drugs have a vast potential to shape how we understand ourselves, perceive others and conceive of psychopathology. That's why if we find out that a substance—as stated for Prozac—has the capability to radically transform our personality, we are inclined to think of ourselves as biologically determined–or, at least, heavily conditioned—and to think of the brain-mind relationship as a reductionist or even an eliminativist one. Notwithstanding, drugs do not speak—and we do not listen to them—in a vacuum: they and we are already situated in a given culture, entrenched on a particular cosmovision and largely influenced by political, social and economic issues.

As it is commonly known, the first so-called antidepressants were discovered by chance in the fifties: the first one, iproniazid—a monoamine oxidase inhibitor—was discovered while used as a treatment for tuberculosis; the second one, imipramine—a tricyclic drug—showed its antidepressant effect while used in psychosis treatment. At that time, it was discovered that iproniazid acts as an inhibitor of the oxidation of monoamines—serotonin and norepinephrine—which means that it leaves more of them available in brain synapses. Later, it was also discovered that imipramine blocks the reuptake of serotonin and norepinephrine—which, in the end, meant equally that more of them were available in the brain. In the sixties, the monoamine hypothesis of depression appeared for the first time. Depression was presented as a deficit of a monoamine, usually serotonin or norepinephrine, or both. The nature and cause of depression, as it also occurred with psychotic disorders, were then inferred from the success of its treatment: if a pill that makes more norepinephrine or serotonin available in the synapses can cure depression, then it should be or be caused by a biochemical imbalance. Finally, other evidence such as “the strategy of tryptophan depletion”—producing a marked reduction in plasma tryptophan and therefore in brain serotonin, impacting negatively in mood—came to support the monoamine theory of depression in favor of a diminished activity of serotonin pathways (Van Praag, 2007).

This paradigm was strongly backed up by the pharmaceutical industry, which embarked on a mission to develop more selective drugs, which gave birth to SSRIs. Actually, the pharmaceutical industry was, and still is, so enthusiastic about the monoamine theory of depression that some have seen in it the creation and exploitation of a big myth, even questioning their alleged efficacy (Kirsch, 2010). Be that as it may, this new kind of drugs, to which Prozac belongs, further supported the view of depression as a biochemical imbalance, given their astonishing success, although they also introduced new philosophical and psychiatric challenges, as we will see further.

Pills were conceptualized as magic bullets aimed at restoring brain biochemistry to normal. Questions of personal meaning or context were often disregarded or, at best, taken into consideration but not seen as the actual causes or the best account for the disorder, which was to be understood in terms of biochemical imbalance. Depression was conceptualized as a discrete entity, naturally separated from other disorders and from the personality core, that's why its treatment was presented as a restoration of the self, the authentic self-free from disorder (Kramer, 1993).

At roughly the same time that the first antidepressant was discovered by chance, psychiatrists were already using psychedelics as therapeutic tools. While *restoration*—both of biochemistry and the self—is the notion around which the conventional psychopharmacological approach revolves, *experience* is the central idea in psychedelic drug use. This view highlights the role of phenomenology and personal meaning in treatment, instead of reducing therapy to the restoration of an abnormal brain or an authentic self, freed from a pathological entity called depression.

When psychedelics were first introduced in psychiatric settings, there were two therapeutic methods: the "psychedelic method", where one high dose usually of LSD or psilocybin was used to lead the subject to a life-changing, mystical, or transcendental experience–an experience so profound that it would lead the subject to a process of continuing growth–and the "psycholytic method", accompanied by psychotherapy—often associated with psychoanalysis–where several increasing doses of LSD were administered in different sessions, the subject being able to gain insight and learn from them (Eisner, 1997). The preference for one or another method depended on the therapist and also on the problem presented by the patient, since psychedelics were used to treat a wide array of conditions. Regardless of the method chosen and the condition treated, experience was the cornerstone. The goal was:

> [t]o produce a unique experience for the patient which is to be so profound and impressive that it changes the patient's own evaluation of his past life

> experiences and consequently may lead him to establish new values and a more realistic frame of reference than had been established before. (Sherwood, Stolaroff & Harman, 1968, p. 96).

To do so, the key was to induce an experience that resembled a mystical one–or transcendental, if preferred, since the experience needn't be a religious one. The usual features of the experience involve (1) a sense of unity or oneness, (2) transcendence of time and space, (3) a deeply felt positive mood, (4) a sense of awesomeness, reverence and wonder, (5) meaningfulness of psychological or philosophical insight and (6) ineffability and paradoxicality (Roseman, Nutt & Carhart-Harris, 2018). However, that state couldn't be achieved only by the effect of the drug: it was a mere catalyst. To account for the mechanism of action, other factors beyond pharmacological ones had to come to play.

In 1958, the World Health Organization defined psychedelics as *nonspecific amplifiers*—meaning that one could administer the same drug, in the same dose, to the same patient and yet obtain very different results depending on the patient's interpersonal and motivational situation. So, in order to fully understand the workings of psychedelics one must not only look to the substance itself, but also to the context that surrounds its use. Soon, several concepts appeared in order to account for the quality of the experience and the therapeutic outcome: *set, setting* and *matrix.* As Timothy Leary, who coined the terms *set* and *setting,* wrote:

> [T]he drug does not produce the transcendent experience. It merely acts as a chemical key—it opens the mind, frees the nervous system of its ordinary patterns and structures. The nature of the experience depends almost entirely on set and setting. Set denotes the preparation of the individual, including his personality structure and his mood at the time. Setting is physical—the weather, the room's atmosphere; social—feelings of persons present towards one

> another; and cultural—prevailing views as to what is real (Leary, Metzner, & Alpert, 1964/2008, p. 3).

Individual intentions are also part of the set and they are crucial to the therapeutic outcome: intentions affect experiences during the session, and the intentions acknowledged and affirmed then affect long-term outcome. Also, in considering long-term outcome one has to keep in mind a concept introduced by the psychedelic pioneer Betty Eisner, the concept of *matrix,* which does not strictly refer to the subject, but to the environment from which the subject comes and to which he or she returns. For the best outcome, this environment has to be supportive and entertain personal change and growth (Eisner, 1997). In conclusion: in the psychedelic paradigm, drugs are only partially responsible for the therapeutic outcome–the environment, the context and the subject's preparation are all necessary elements when giving an account of it. This is far from yielding a reductionist explanation or a biologically oriented one–of course, one can and ought to study the pharmacodynamics of these substances and their biological correlates, but that would only be a part of the explanation and, possibly, not even the most useful one in terms of therapeutic success. It is simply not possible to establish a direct causal relation between drug and outcome.

While antidepressants are usually presented as magic bullets, psychedelics are presented as tools–or *chemical keys,* in Leary's words. That's why it is possible to conceive of conventional antidepressant treatment aside from psychotherapy, but it is impossible to separate psychedelic therapy from some kind of psychotherapy or psychological preparation and integration before and after the experience: it is impossible not to attend to the meaning and the quality of the experience. While it is often hard to integrate psychotherapy and psychopharmacological antidepressant treatment, the very notion of psychedelic or psycholytic therapy involves the psychological realm.

Those critically-oriented would find this appealing, since meaning, environment, and both personal and cultural context would play a major role in psychiatry; on the contrary, those presenting a biomedical orientation would find this a step back in the progress of psychiatry as a branch of medicine, since it would introduce unnecessary subjective elements, making it difficult to find universal explanations and therapies. This isn't a trivial issue. In fact, as Matthew Oram (2014) notes, that could have been the key factor that led psychedelics to be finally banned and considered as devoid of therapeutic utility in the seventies.

Appealing and unappealing paradigms

It is surprising that, given the fact that psychedelics were widely used in psychiatric settings in the later fifties, sixties and earlier seventies—tens of thousands of patients were quite successfully treated with them (Grinspoon & Bakalar, 1979)—they were finally prohibited during the *War on Drugs*. In 1970, psychedelics were included in the Schedule I by the North American Controlled Substances Act, a schedule were there can be found substances which allegedly (a) have a high potential for abuse; (b) have no currently accepted medical use in treatment in the United States; and (c) lack of accepted safety under medical supervision. A year after that, in the Convention on Psychotropic Substances signed in Vienna—and to present date adhered to by 183 parties—psychedelics were prohibited almost worldwide. Regarding the first criterion applied in the schedule, it has to be noted that the meaning of "abuse" is not clarified anywhere and even nowadays continues to be problematic—even more so considering that psychedelics have proved not to cause dependence. With regard to the second and third criteria, we will discuss further some factors that could have led to the consideration that psychedelics are devoid of therapeutic interest. The consequences of this restrictive legislation have been terrible: once a drug has been included in Schedule I, there is no agreed procedure on how to move it to a less restrictive

schedule—besides the fact that scientific research becomes notably difficult, since really hard-to-get permits from governmental agencies are mandatory to carry out research, which also makes it difficult to prove the efficacy and safety of these drugs.

To understand the ban one has to pay attention to social and political issues, as well as economic ones. It is believed that the therapeutic interest in psychedelics diminished as the social alarm grew during the sixties, because of all the social movements that made intense use of drugs; but it is equally important, for example, the fact that in 1966 Sandoz Pharmaceuticals withdrew support for LSD research, making it almost unmarketable and unprofitable.

Furthermore, Mathew Oram (2014) shows how metaphysic considerations also played a role in the prohibition. In 1962, the Harris Drug Amendments were introduced. The aim of the Amendments was that, for a drug to hit the market, its pharmacological efficacy must be proven on controlled trials–and that was accomplished by isolating all extrapharmacological factors that could influence the outcome of the treatment. Those requirements were tailored to biologically oriented treatments, under the model of infectious disease. In other words: in this paradigm there was no place for set, setting and matrix–much less for transcendental experiences. The idea that a drug must prove its efficacy isolated from all extrapharmacological factors simple couldn't work for psychedelics, since, admittedly, their effects where accomplished thanks to all the extrapharmacological factors. Besides, the therapy could not be exactly the same for every patient, neither could a double-blind be strictly maintained, since drug effects are so obvious. In the Amendments, treatments were viewed as purely biological processes–as in the infectious model, where antibiotics had proven to be so successful decades ago. A specific treatment was required for every specific disease–an assumption, by the way, that could well accommodate the monoamine theory of depression and that has been widely supported by the biomedically oriented

psychiatry, where mental disorders are thought to be discrete pathological entities requiring a specific treatment, as we will argue further.

In addition, psychedelic therapists were often reluctant to embark on the design and launch of complex clinical trials and, since they were a novelty, no one knew at first exactly which guidelines were to be followed–an issue that, as we will see, has been considerably solved over time, since double-blind randomized controlled trials have successfully assessed the efficacy and safety of the psychedelic therapy.

In conclusion, this all finally led to the consequence that the evidence supporting the efficacy of psychedelic treatments was not regarded as valid, since it widely rested upon case reports and not upon–what was alleged to be–well-controlled and well-designed clinical trials under a biomedical paradigm. That is why, despite our adherence in this paper to the thesis that drugs have a vast potential to influence the way we conceive of ourselves–often entailing heavy metaphysical assumptions—we also have to acknowledge that they are subject to the *zeitgeist*, which includes already culturally assented views, bureaucratic procedures, economic interests, and so on. That is to say, not all drugs have the same supportive environment to be heard.

Psychiatry's biological orientation

Following this line of thought, we would like now to take a look at the broader context in which the prohibition of psychedelic drugs took place, while antidepressants grew in popularity, becoming even highly promoted drugs. We would like to say a few words on the reputation of psychiatry those days, the establishment of the so-called biomedical model and the impact of diagnostic manuals such as DSMs–all these issues being interlinked and usually creating feedback relations.

It was possible for antidepressants to shape our understanding under a biological light because this kind of understanding was desirable, since it was considered that biological explanations—particularly if backed up by therapeutic success—would

protect psychiatry from criticisms, installing it in the realm of medicine. For psychiatry to be taken seriously and to recover its damaged legitimacy, it was necessary to finally enter the secure field of science, as medicine—the premise being that issues regarding biology belonged to the objective, value-free, and scientific domain, whereas those regarding the mind belonged to a subjective, value-laden, and non-scientific realm.

A crucial cornerstone in this endeavor was the third revision of the *Diagnostic and Statistic Manual of Mental Disorders* (*DSM-III*), from the American Psychiatric Association, which came out in 1980. The DSM-III was presented as an atheoretical manual—meaning it would only present a list of criteria which should be met in order to qualify for a diagnosis, saying nothing about its etiopathology. Nonetheless, the little emphasis put by the manual on the context in which symptoms develop facilitated a reductionist and acontextual view of mental disorders—which, as we already know, fits very well with the image of depression rendered by antidepressants (Horwitz & Wakefield, 2007). The success of the so-called second-generation antidepressants is linked with the release of DSM-III, since it made easy both Major Depressive Disorder diagnosis and antidepressant's prescription.

In order to increase the reliability of diagnosis, a set of operationalized diagnostic criteria were introduced. Solving this problem was relatively easy: it required that, regardless of the school to which therapists belonged, they all adopted the same definitions. The DSM-III was successful in doing that and it became the reference manual both in research environments and in clinical practice. Nonetheless, although reliability was increased, there was—and there still is—a serious problem with the reliability of some diagnoses—actually worsened by DSM-5—as can be seen attending to the category in which we are interested, Major Depressive Disorder, with a kappa of 0.28 (Regier et al., 2013).

As problematic as this is, the state of the validity of psychiatric diagnosis seems even worse. How can we *validate* the theoretical constructs that appear in the DSM? What

does *validate* even mean? By the time DSM-III was written, the most influential work on psychiatric validation was that of Eli Robins and Samuel Guze (1970). In their paper, they proposed five validators which slipped some strong metaphysical assumptions. The first validator, according to them, is clinical description; the second one, laboratory tests; the third validator is the delimitation against other disorders; fourthly, follow-up studies must be carried out to ensure that classifications are correct; and, in fifth and last place, high prevalence of a mental disorder among relatives is also considered to be an indicator of the disorder being the same. According to Robins and Guze, validating a construct is demonstrating its compliance with these standards.

As Kendell and Jablensky (2003) note, this validation process entails a reification of diagnostic categories: diagnostic constructs are no longer useful constructs in clinical practice; they are rather discrete entities that can be identified and delimited in nature. The possibility that, in reality, these natural demarcations might not exist was simply not considered: if diagnostic procedures were improved, then the real entities of the natural world would emerge.

The truth is that this spirit of reification and delimitation has guided both psychiatric and psychopharmacological research—as we have already seen in the novel trial design requirements imposed by the Harris Drug Amendments. Under that model, great efforts have been invested, for example, in sharply differentiating depression from anxiety; but what is becoming more and more obvious is that it is simply not possible: the overlapping of symptoms is indisputable and the current categorial diagnosis system makes comorbidity not the exception in psychiatry, but the norm (Mellor Marsá & Aragona, 2009). Clinical course is highly variable; the genetic vulnerability inheritance is not only given for a disorder, but occurs in families of disorders; and, finally, laboratory studies have not so far yielded a single biomarker for psychiatric disorders (Zachar & Jablensky, 2015). All these problems have led psychiatry to rethink its categorical classification and move towards a dimensional one: instead of assuming

that in the natural world there are discrete entities that correspond to mental disorders, the current approach is shifting towards the hypothesis that we are facing a continuum of symptoms, so that we should be talking about a *spectrum* rather than about categories. Surprisingly, antidepressants have also played a role in this redefinition of the field, since they have proved to be much more than just antidepressants: i. e., SSRIs are used to treat anxiety disorders, obsessive-compulsive disorder, eating disorders, etc. Moreover, they can also affect people considered to be healthy–and, as Kramer noted, their effects on disordered people seem to go often beyond the *restoration* of a previous and more authentic self: they can perform a profound transformation of patients' personalities. All of this erodes that vision of mental disorders as discrete entities clearly separated from each other and from normality.

More nuanced explanations

Now that we are listening to the whole story that antidepressants have to tell us, we are finding out some things that psychedelics already told us: the fact that we can use the same substance to treat different disorders leads us to believe that those disorders have more in common that we thought–that nature's joints aren't there for us to sharply carve on. The same goes for the line that divides pathology from normality: not only those diagnosed with a disorder can be affected by–and possibly benefit from, depending on one's values–antidepressants. Equally, not only disordered people would potentially find benefit from a psychedelic experience.

We've also learned that simple biochemical theories cannot account for the nature of depression. Needless to say, the reductionistic conception of depression as a monoamine deficiency has never gained sufficient scientific support–which, of course, does not imply that serotonin has no role in mood regulation: it does, but the story is not so simplistic and we have not yet come up with all the pieces (Cowen & Browning, 2015). Researchers' hypotheses are now pointing to broader explanations. For

example, the fact that antidepressants take a while to produce recognizable effects has led some researchers to propose a cognitive neuropsychological hypothesis to account for SSRI antidepressant action, based on their ability to produce positive biases in the processing of emotional information (Harmer & Cowen, 2013). Thus, the delay in their action becoming apparent can be explained by the time that this new emotional processing needs to achieve the conscious level–despite acute effects being already present within hours of the first SSRI administration.

SSRIs may interfere with depression's typical focus on negative stimuli, re-biasing automatic emotional processing and enabling a positive interpretation of experience at a conscious emotional level, when given in an appropriate interpersonal environment. This ability to induce an altered, positively-biased, emotional processing may be considered similar to psychedelic drugs' ability. Besides, it is noteworthy that terms such as "interpretation of experience" and "interpersonal environment" are becoming part of the explanation of its mechanism of action. Nonetheless, although SSRIs and psychedelics seem to share some common points regarding the treatment of depression, there are important differences, such as the kind of emotional reprocessing that they seem to induce: antidepressants may induce an emotional moderation or blunting, while psychedelics are considered to induce an emotional release (Carhart-Harris & Goodwin, 2017). Alongside, SSRIs' effects seem to happen bottom-up: they seem to interfere with an automated emotional processing, whose action would finally hit the conscious realm, allowing a more positive interpretation of experience. Instead, the emotional reprocessing induced by psychedelic drugs is immediately available to the subject's (altered) consciousness—to the extent that the therapeutic outcome depends on the quality of the experience and on its integration, as we will see further.

It is also worth mentioning that SSRIs may produce effects on synaptic plasticity—a mechanism which is involved in learning and memory and could account for re-learning processes that SSRIs allegedly trigger. Similarly, several studies also show that

psychedelics enhance neuroplasticity (Kyzar et al., 2017). And, finally, both SSRIs and psychedelics seem to have the ability to modulate the Default Mode Network, downregulating its activity and increasing its connectivity (Baumeister et al., 2014). In fact, this explanation in terms of altered brain connectivity and enhanced plasticity is thought to mark a whole new paradigm—a paradigm where psychedelics seem to have a lot to say. As Nichols, Johnson & Nichols (2017) note, receptor—based pharmacotherapy, focused on neurotransmitters or neuromodulators, seems to deal with components of broader malfunctioning networks. Instead, psychedelics, when administered in supportive contexts, seem to have the unique ability to induce entropic brain activity, radically altering such resting networks and allowing them to *reset,* by reducing their stability, integrity and segregation. Interestingly, studies have correlated experiences of ego dissolution with the disintegration of the Default Mode Network. After this experience, brain networks seem to be rewired in what's considered to be a healthier way (Roseman, Leech, Feilding, Nutt & Carhart-Harris, 2014). This ability of psychedelics to act at a network-level would explain its efficacy in the treatment of different disorders, while helping in the reformulation of the modular image of the mind afflicted by discrete pathological entities. Nowadays, instead of a modular mind afflicted by discrete pathological entities, the idea of brain networks being disrupted and reconnected is more attractive. The metaphor of a brain being reset, pretty much like a computer does, has lately become very popular when picturing psychedelics' mechanism of action. Can we spot here once again the spirit of our time?

As for the mind-brain relationship, emergentism could be the most fruitful paradigm where the mind and its properties are grounded on the brain, but still different from and not reducible to it. That might be why psychedelics can act like *chemical keys*: by altering brain functioning, they allow the emergence of an altered state of mind, but the actual properties of that state cannot be inferred from brain properties.

New trials under a new light

Research on psychedelic therapy is more focused on looking for biological correlates of phenomenological aspects relevant to the therapeutic outcome, than on looking for reductive explanations that can account for a drug's action.

Contemporary research is still guided by most of the principles followed in the sixties: the importance of the set is acknowledged by the fact that the psychedelic therapy still relies on some kind of psychotherapy or psychological preparation for and integration of the experience, and the setting is still carefully taken care of, with much emphasis put, for example, on the music played to guide the experience, which must be adjusted to each patient's needs. Recently, several trials have been conducted to assess the success of psychedelic drugs combined with psychotherapy or psychological support in treating depression. The results are impressive, although we should not ignore the fact that the number of patients involved in them is still small–it could not be otherwise, since psychedelics are still under prohibition, which means that hard-to-get permits from governmental agencies are mandatory to carry out the studies.

In 2016, Carhart-Harris et al. conducted an open-label feasibility study to assess the efficacy of psilocybin in treating treatment-resistant Major Depressive Disorder in 20 patients, proving significant decreases in depressive symptoms for up to 3 months, as well as in anxiety and anhedonia. That same year, two double-blind randomized controlled trials with an active placebo took place (Ross et al., 2016; Griffiths et al. 2016), to assess the efficacy of psilocybin in treating anxiety and depression related to life-threatening cancer in 29 and 51 patients, respectively. Once again, there was a positive outcome, with significantly decreased anxiety and depression, sustained in both trials for up to 6 months in 60-80% of the patients.

Nowadays, new methods are available to design and evaluate trials, making it possible to rigorously assess the efficacy and safety of psychedelic therapy. Nonetheless, we have to highlight the fact that what has to be proved is not the efficacy of the drug itself,

but of the therapy as a whole. Contemporary researchers have learned the lesson: while it is desirable to isolate the effects of the drug as much as possible, they cannot get to the point where the psychedelic method gets compromised.

Experience is still the key factor around which this method revolves and, in fact, profound psychological experiences have been found to be predictors of subsequent psychological health and long-term outcome, and particularly, the kind of experience that has been called “mystical”, “transcendental” or “peak” (Roseman, Nutt & Carhart-Harris, 2018). The occurrence of this kind of experiences during the session mediates long-term positive clinical outcomes, while the occurrence of anxiety and impaired cognition predicts less positive ones. The more profound the experience, the more one feels an *oceanic boundlessness*, characterized by insightfulness, a blissful state, experience of unity and spiritual experience, the better the therapeutic prospects. Furthermore, only those “mystical” or “transcendental” qualities of the experience are linked with positive outcome, meaning that other non-transcendental qualities, such as perceptual changes, are not responsible for improvements in health.

Conclusions

Psychoactive drug effects are a powerful source of evidence regarding our own nature and our comprehension of psychopathology. Notwithstanding, when we *listen to drugs* we might be misled into thinking that we are only hearing their voice, instead of their voice through our cosmovision. When we face evidence we are always looking at it not only through a series of metaphysical assumptions, but also from an entanglement of political, social, bureaucratic, economic, moral, and so on, factors. Now that psychedelic research may be leading the rise of a new paradigm, research on the changing conditions that, after a few decades, are making it possible to finally hear psychedelic drugs’ voice is a task to be undertaken.

Although philosophically it would still be possible to maintain a reductionist or eliminativist view of the mind, the fact is that this metaphysical assumption does not make a good heuristic for those seeking the best therapeutic outcome. Psychedelic therapy cannot be reduced only to its psychopharmacological or biological dimension, and it might be that reducing the effect of antidepressants only to its psychopharmacological dimension could also be a mistake. The notions of set, setting and matrix can be found to be useful also when considering conventional antidepressants: the expectations that a patient has regarding antidepressant use, the establishment of a trust relation with the therapist, and the interpersonal environment are all extrapharmacological factors that can mediate the therapeutic outcome.

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