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Journal of Brain and Neurological Disorders

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Review Article

The Neuroimaging Documentation of Psychedelic Drugs' Effect on the Brain: dmt, lsd, Psilocybin, and Ibogaine as Examples: A Mini Review

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Received Date: 11 April, 2022 | **Accepted Date:** 31 May, 2022 | **Published Date:** 20 June, 2022

Citation: Abdul Wahab Alahmari (2020) The Neuroimaging Documentation of Psychedelic Drugs' Effect on the Brain: dmt, lsd, Psilocybin, and Ibogaine as Examples: A Mini Review. 5(2): DOI: 10.31579/2692-9422/027

Abstract

Many psychedelics drugs are praised on social media platforms like YouTube by non-experts or bias documentaries claiming that these drugs have therapeutic effects on addicted patients or clarity of the mind. The aim of this paper is to collect a neuroimaging documentation of these psychedelics' drugs and their effect on the brain. That can be documented on MRI, CT, or any other imaging modalities.

Keywords: dmt; lsd; psilocybin; ibogaine; neuroimaging; brain effect; addiction

Introduction

Psychedelic drugs are used mostly without medical prescription due to its hallucination effect which is desired by many. But there are many who claim that these hallucogenic drugs can help stop addiction or clear the mind. For example, one YouTube channel and podcast on spotify named "Joe Rogan experience" have been mentioned countless times DMT until the show become so associated with psychedelics. As well, on the same show and others they claim that ibogaine will stop addiction. Since this show have been associated with many conspiracy theories and hosted Alex Jones (another conspiracy theorist) many times, they claim that the United States government have banned ibogaine and ibogaine clinics to allow more drug industry which is not accurate since ibogaine damage the purkinje cells in the cerebellum and it cause a large list of side effects including erectile dysfunction. This paper will take four popular psychedelic drugs and evaluate their effectiveness based on the scientific published literature and provide any published neuroimaging evidences of a change in the brain morphology or function.

There is a contra argument about psychedelics where many advocates say these psychedelics are not harmful when these psychedelics are used with small doses like LSD. But a general rule in drugs that dose need to be increased over time to reach euphoria, hallucination, or whatever is the effect of the used drug. Therefore, the dose control argument can't be used since "under-sensitivity" can developed over time and with more use of the substance and it will lead to overdose eventually. Then the damage can occur due to the overdose.

N, N-dimethyltryptamine (DMT)

Naturally is known as ayahuasca is South America used in rituals and ceremonies. Synthetically is DMT which is mixed with other pharmaceutical materials (i.e. to be activated orally, but it is active alone when administrated intravenous or intramuscular) to make a chemical psychedelic. Both are serotonergic psychedelic and DMT at high doses can cause seizures, respiratory arrest, coma, and serotonin syndrome for patients who use anti-depressants. DMT is dangerous on patients who have schizophrenia. DMT is not addictive, but the user could crave it psychologically. Some users can hurt themselves, while they experience these visual and auditory hallucinations which can see and feel near-death experience (NDE) [1] in their so called "trips". DMT has the lowest side effects among the four psychedelics mentioned in this paper.

Ayahuasca intake showed alter consciousness under fMRI. The posterior cingulate cortex, precuneus, and medial prefrontal cortex are responsible for default mode network which responsible for self-oriented mental activity. The connection between the posterior cingulate cortex and precuneus were affected (i.e. decrease) after ingesting the ayahuasca appeared on the activity map and compared before and after consumption [2]. see (Fig. 1). In another meta-analysis found in multiple studies deactivation of certain regions in the brains because of using DMT ayahuasca, psilocybin, and LSD users mainly in; amygdala, temporal gyrus, and fusiform gyrus on activation likelihood estimation (ALE) meta-analysis of the fMRI. As well, frontal, parietal, and limbic lobes are activated, but the putamen and anterior cingulate are highly activated. The connectivity of the left hemisphere was disturbed. Specifically, the cingulate cortex and inferior temporal gyrus of the left hemisphere.

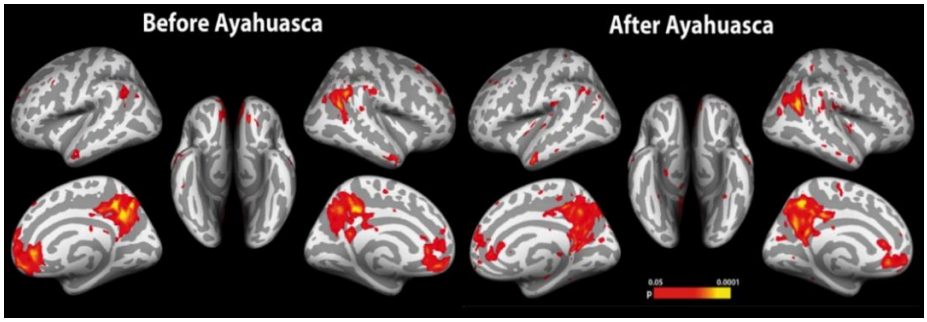

Figure 1: *An ALE fMRI activity map before and after consuming ayahuasca shows left hemisphere disturbed activity especially in the cingulate cortex and inferior temporal gyrus.*

A published study claims to use DMT to treat bipolar depression [3]. Another paper claim to use DMT to treat anxiety and post-traumatic stress disorder (PTSD) [4]. The issue is the first paper is based on a single case and the other paper is based on an experiment on a rat. Furthermore, the effect is not known whether caused by the DMT or by the other material mixed with it which is monoamine oxidase inhibitor (MAOI) which was the shared by other authors [5]. Furthermore, there is a published case report about a case of PTSD after using of DMT [6].

Lysergic acid diethylamide (LSD or ACID)

LSD was first synthesized in 1938 and it was well known in the year 1943 that it can be used as a psychedelic. By the year 1960, it was banned for after been associated with the recreational use. It is a potent serotonergic psychedelic that have been associated with out of body experience (OBE) [7]. It is known from 1967 that LSD cause a chromosomal change or damage [8]. Where others found it to be dangerous for pregnant and at high doses respectively [9,10]. The author of the first paper did not make a very disturbing title for the published paper. According to Dicots et al. (1967), the next author in 1971 made the titles of their paper very disturbing and entitled "LSD and genetic damage" and they made a conclusion that LSD does not affect the chromosomes to capture the attention for their papers. All the mentioned responses in their paper to other papers were "negative reports", "non-confirmed results", "alleged", "undetectable", "we believe", etc. Their paper has been refuted by a later paper in 1978 and LSD damage was proven and detected at high doses [10]. Then Cornwell et al. (2010) published a paper under the title "the myth of "moral panic": an alternative account of LSD prohibition" claiming that the author of the first paper want to make a moral panic regarding LSD which is not accurate [11]. Furthermore, the author used the word "myth" to regard the finding of that paper as not true which is proven in many papers to be not the case [8,9,10]. This shows that there is a pro-psychedelics movement that disregard any scientific empirical evidence which is similar to what these YouTube channels (i.e. Joe Rogan and other similar streams) are preaching daily. The issue is corn well (2010) did not test any patient, conduct an experiment on patients using LSD, or provide any scientific proves, but it was speaking about how papers like LSD was presented in the media. Furthermore, the author used the same technique that he was criticizing by using a "catchy" or "provocative" title which he did worse than the rest of the papers published about LSD. The author made 26 pages long of rambling about mass control which is the favorite topic for people like Alex Jones and Joe Rogan and other conspiracy theorists.

The effect of LSD on chromosomes is well documented. The effect on the brain by LSD using three imaging techniques which are; arterial spin labeling (ALS), blood oxygen level dependent (BOLD), and magnetoencephalography (MEG). The cerebral blood flow (CBF) increased in the visual cortex, increase primary visual cortex (V1) connectivity profile, decrease visual cortex alpha power, and decrease of connectivity between Para hippocampus and retro splenial cortex see (Fig. 2) which correlate with "ego-dissolution" [12]. There is increased resting state functional connectivity (RSFC) between V1 and other cortical and subcortical regions see (Fig. 3). As well, there is a decreased RSFC between Para hippocampus and retro splenial cortex & the posterior cingulate cortex see (Fig. 4). The RSFC increased between Para hippocampus and the medical prefrontal cortex [12].

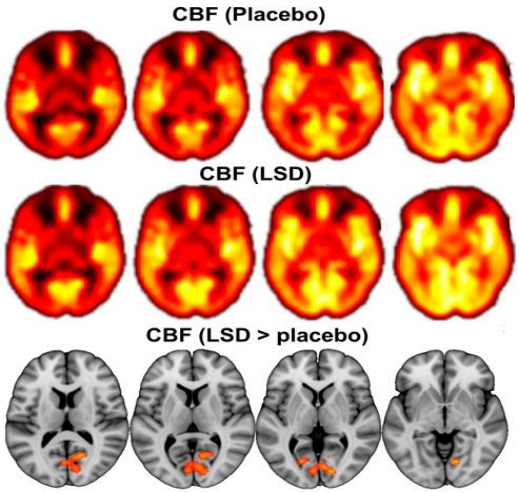

Figure 2: *The CBF map shows increased blood flow (CBF) in LSD more than*

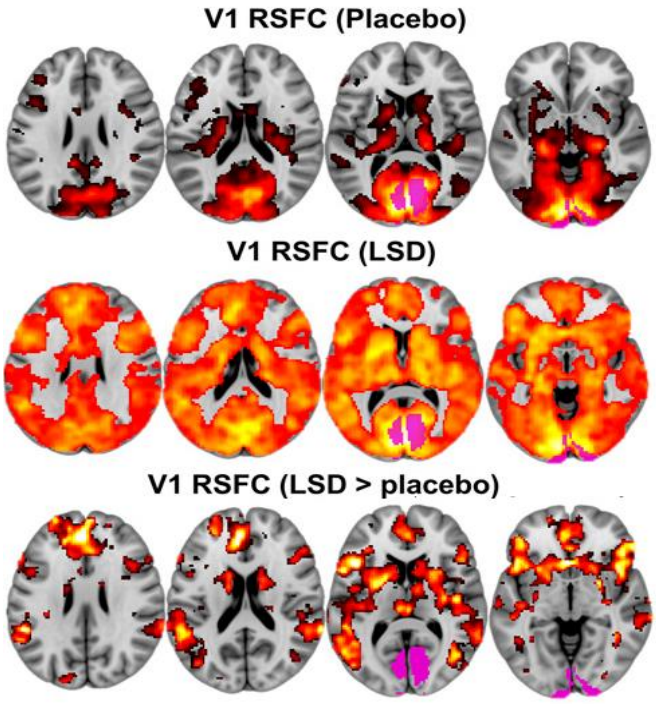

Figure 3: *The RSFC of the primary visual cortex (V1) shows high activity in LSD more than placebo.*

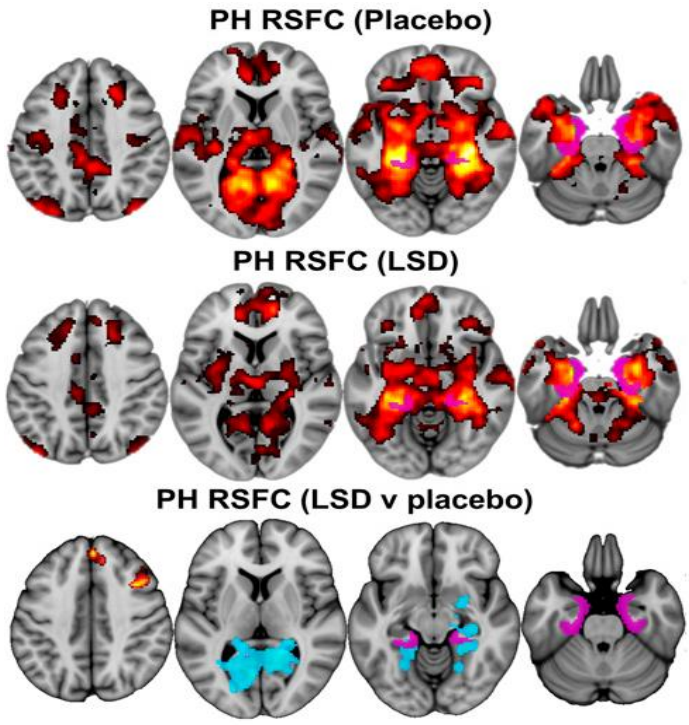

Figure 4: *The RSFC map of the parahippocampus (PH) shows less activity in LSD less than placebo.*

Psilocybin (mushroom)

This psychedelic has been used in rituals and ceremonies for more than 6,000 years and mainly in central America. It is a serotonergic psychedelic like DMT and LSD. This psychedelic mushroom has been tested for potential promising treatment for anxiety, mood disorder, drug addiction & dependency, and depression.

On PET scan, cortical gylocose were increased in patients were given psilocybin compared to patients were given placebo [13]. Both psilocybin and ayahuasca caused decreased of RSFC default-mode network (DMN) on fMRI [2,13].

According to a published study which used a psilocybin to treat depression and monitored by fMRI. A three measurements were taken

before and after using psilocybin which are cerebral blood flow (CBF) and blood oxygen-level dependent (BOLD) resting-state functional connectivity (RSFC). The depression symptoms decreased after the treatment and the fMRI showed decreased CBF in the temporal cortex and specially the amygdala see (Fig. 5). As well, the RSFC was decreased in the parahippocampus and prefrontal cortex. The left Heschl's gyrus, left planum temporale, left precentral gyrus, left superior temporal gyrus, right supramarginal gyrus, left amygdala, and right parietal operculum reached a statistical significance in decreased CBF. The RSFC increased was seen in the default-mode network after the treatment. As well, RSFC increased in ventromedial prefrontal cortex and bilateral inferior lateral parietal cortex. The paper concludes with using psilocybin as "a rest therapeutic for depression" [14]. A high blood flow in the amygdala have been associated with depression [15]. The decrease of depression has been found to be associated with low CBF in the amygdala [14].

The RSFC increased in subgenual anterior cingulate cortex with the posterior cingulate cortex and precuneous after the treatment with psilocybin see (Fig. 6) [**14]**. The RSFC in the ventromedial prefrontal cortex increased, but did not correlate with depression symptoms see (Fig. 7). The RSFC decreased bilaterally in the parahippocampus, but did not correlate with depression symptoms see (Fig. 8) [14]. The RSFC of the amygdala did not change [14].

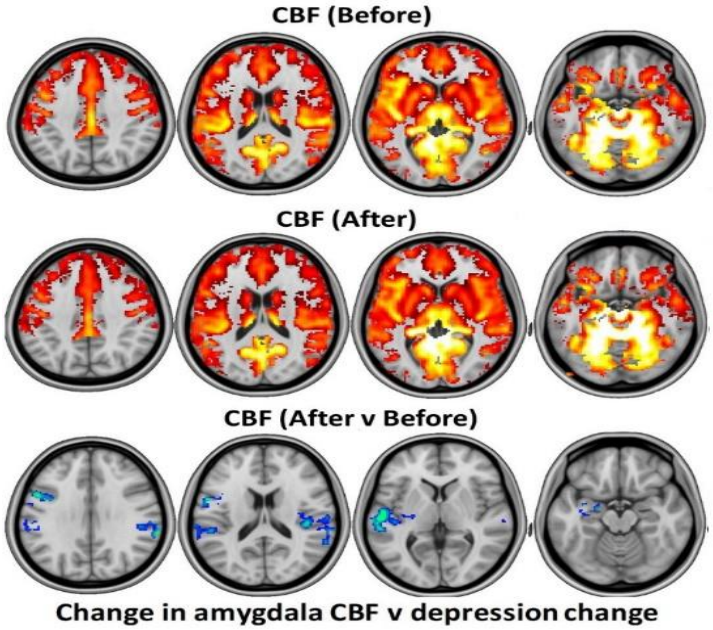

Figure 5: *The change of cerebral blood flow (CBF) in amygdala after the treatment.*

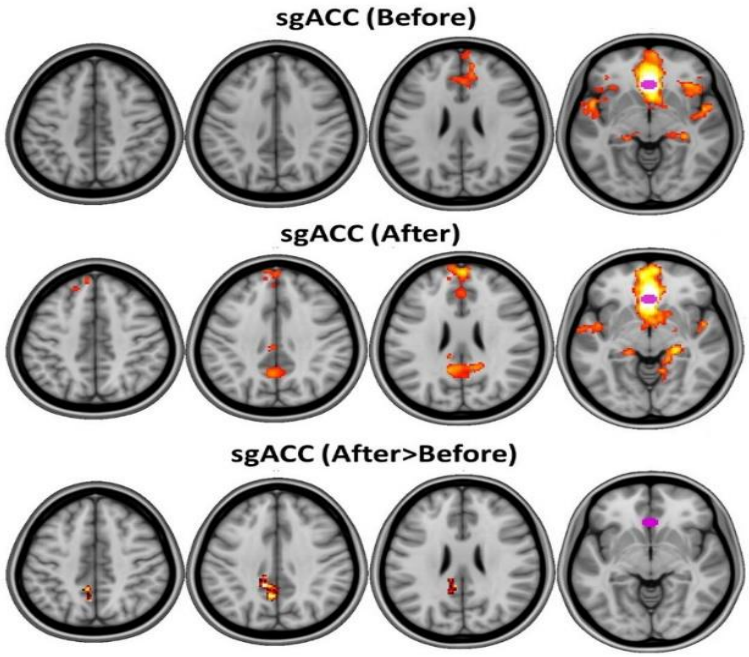

Figure 6: *The RSFC increased in subgenual anterior cingulate cortex (sg ACC) after the treatment.*

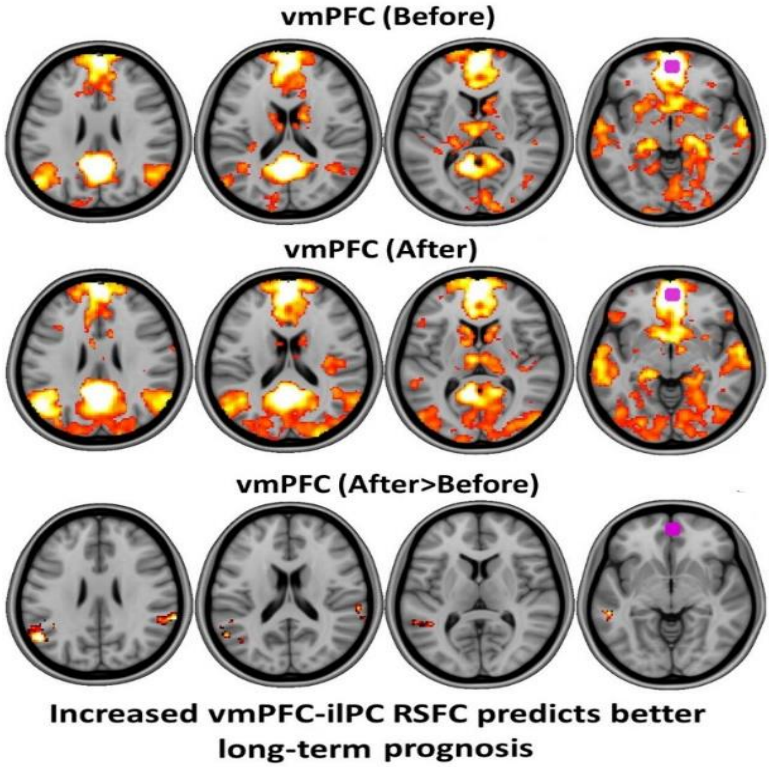

Figure 7: *The RSFC in the ventromedial prefrontal cortex (vmPFC) increased after the treatment, but did not correlate with depression symptoms.*

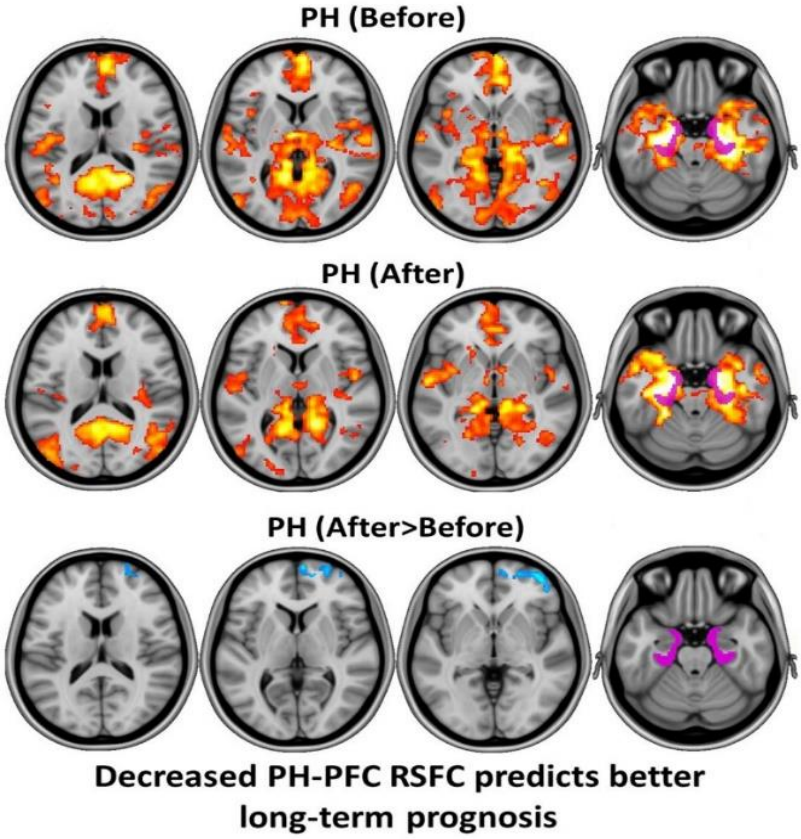

Figure 8: *The RSFC decreased bilaterally in the parahippocampus, but did not correlate with depression symptoms.*

Ibogaine

Chemically is ibogaine and naturally is iboga. It is used to treat addiction and drug dependency. It damages the purkinje cells in the cerebellum on a microscopic level; therefore; the neuroimaging might not be able to show the microscopic damage or change. There is microscopic technique called autoradiography which prepare histology slides then image it in vitro with X-ray. It is called [14]. 2 deoxy glucose method (2-DG) autoradiography which measure local cerebral glucose utilization (LCGU). The glucose level in the brain remains constant under normal physiological circumstances. A published paper measured LCGU in normal rats, ibogaine rats, morphine dependent rats, and morphine dependent & ibogaine treated rats. In ibogaine rats, the ibogaine caused a significant increased LCGU parietal, cingulate, occipital cortices. As well, increased LCGU in the cerebellum. Furthermore, tremorgenic and hallucinogen effect were noticed compared to the control rats. The morphine rats showed a little alteration in the LCGU, but the morphine rats treated with ibogaine showed a global reduction in LCGU in regions as; medial and lateral preoptic areas, cortex of nucleus accumbens, diagonal band nucleus, inferior colliculus, locus coeruleus, and flocculus see (Fig. 9) which does not appear on rats given saline then treated by ibogaine in this experiment [16]. Therefore, these LCGU changes can be linked to the anti-addictive and hallucigenic effect of ibogaine. In an older study, purkinje cells were degenerated in the vermis because of ibogaine [17]. Ibogaine activated astrocyte and microglia which may cause neural injury and degeneration [17].

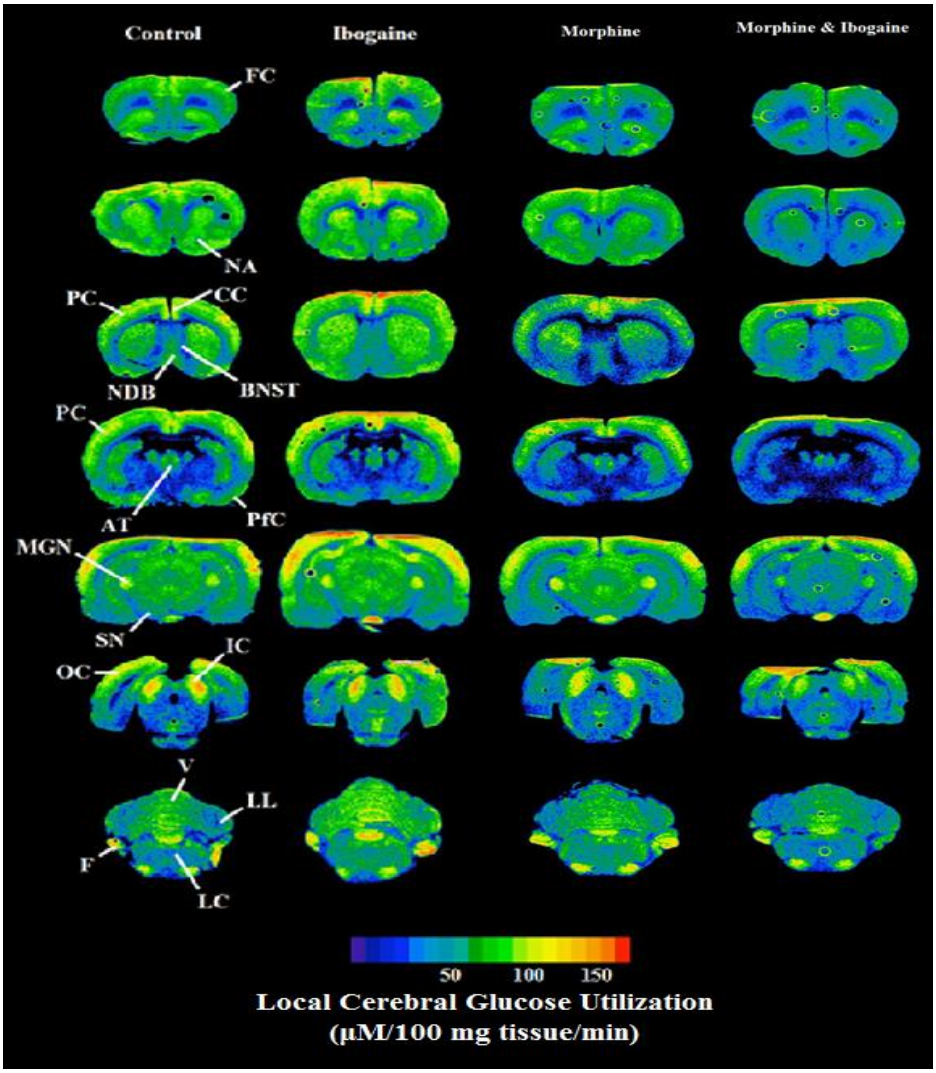

Figure 9: *The effect of ibogaine on local cerebral glucose utilization in a Rat's brain and imaged by autoradiography. From left to right; control rats, ibogaine rats, morphine dependent rats, morphine dependent rats treated with ibogaine. Abbreviations; FC: Frontal Cortex, NA: Nucleus Accumbent, CC: Cingulate Cortex, BNST: Bed Nucleus of Stria Terminalis, NDB: Nucleus of the Diagonal Band, PC: Parietal Cortex, AT: Anterior Thalamus, PfC: Piriform Cortex, MGN: Medial Geniculate Nucleus, SN: Substantia Nigra, OC: Occipital Cortex, IC: Inferior Colliculus, V: Vermis, LL: Lateral Lobe, F: Flocculus, and LC: Locus Coeruleus.*

Discussion

The effect of these psychedelic is shown not to be therapeutic and based on a weak scientific evidence and did not reach at high level. To be used as a treatment, it needs to reach empirical evidence that is observed in a scientific experiment and passes thru many trials.

It has been shown that DMT treat anxiety and post-traumatic stress disorder claim which is based on a single case and the other paper is based on an experiment on a rat. Furthermore, the effect is not known whether caused by the DMT or by MAOI. There is a case report about DMT user developed PTSD after using DMT [6].

The effect of LSD on chromosomes is well known. Furthermore, a systematic review in 2020 was conducted which found 3,668 papers about LSD. After screening, 43 papers where candidates and further screening lead to excluding 32 papers which are not a clinical trial (i.e. case reports and reviews). The rest 11 papers did not confirm modern standards of clinical trials either without a control group or with a non-randomized control group [18]. This shows that LSD need tested and go thru clinical trials at the highest standards first. The study concludes that only four study out of 11 claim a significant effect in the participant life quality, but no clear alcohol abstinence effect [18]. In addition, LSD can cause death at high doses see (Table 1) [19].

Psilocybin claimed to treat anxiety, mood disorder, drug addiction & dependency, and depression. The CBF map showed decrease of blood flow in the amygdala which has been documented to be associated with depression when the amygdala has a high blood flow. But this is not a sufficient evidence to be a treatment. A paper published by Johns Hopkins team in JAMA claim that psilocybin is "efficacious" treating major depressive disorder (MDD) [20]. while their patients still using their medications! The paper is unclear in their methodology and their CONSORT diagram of participant flow is vague. The paper is unclear how many did not continue the treatment and their sample is 24 participant which is very low. And they depend their conclusion on a personal questionnaire and rater evaluation rather than tangible proves. No placebo was given, short period follows up (four weeks), and specific ethnicity participants all of these do not hold water. After that Johns Hopkins University announced a breakthrough based on a 24 participants study!

Ibogaine used mainly to treat addiction, but it can damage the purkinje cells in the cerebellum and cause erectile dysfunction. The effect of the ibogaine in the cerebellum can't be documented on a brain CT scan [21, 22]. There are many cases (i.e. a huge number) published about patients who died after using ibogaine.

Psychedelic type	**Neural damage**	**Therapeutic benefits**	**Over dose can cause death**	**Serious Side Effect**
DMT	N/A	Claims that it can treat bipolar depression and PTSD.	IV might cause death at extreme high doses. Otherwise, lethal dose has not been determined in intramuscular and oral doses.	N/A, the lowest compare to the other.
LSD	Yes	Claims to treat psychosomatic diseases, anxiety, depression, and addiction [18].	Yes, above 14 milligrams per kilogram [19].	Chromosomal damage or change.
Psilocybin	N/A	Claims to be a treatment for anxiety, mood disorder, drug addiction & dependency, and depression and major depressive disorder [20].	Yes, above 280 milligrams per kilogram [21].	Hallucinogen persisting perception disorder (HPPD) from days to years in some cases [22].
Ibogaine	Yes	Claim to treat addiction and drug dependency.	Yes, it will cause cardiac arrest at high doses. Neurotoxicity above 25 milligrams per kilogram [23].	Purkinje cells damage [23].

Table 1: *Psychedelics' effect summary.*

Generally, the activity increased in the cortex and the limbic lobes. Both DMT and psilocybin cause RSFC decreased default-mode network. The reason that DMT and psilocybin has some similarity in their effects, it is probably because they have a similar chemical structure. As well, both LSD and psilocybin cause RSFC decreased in the Para hippocampus see (Table 2).

Psychedelic	**DMT**	**LSD**	**Psilocybin**	**Ibogaine**
Brain areas with increased activity	**ALE fMRI** -Low activation: Frontal, parietal, and limbic lobes. -High activation: Putamen and anterior cingulate.	**CBF** - Visual cortex, and primary visual cortex (V1). - The connectivity between V1 and other cortical and subcortical regions. **RSFC** -V1 and other cortical and subcortical regions.	**PET*** - Cortical glucose. **After treatment RSFC**** - Default-mode network. - Ventromedial prefrontal cortex and bilateral inferior lateral parietal cortex.	**LCGU** - Parietal, cingulate, occipital cortices. - Cerebellum.

		- The connectivity between parahippocampus and the medical prefrontal cortex.	- Subgenual anterior cingulate cortex with the posterior cingulate cortex and precuneous. - Ventromedial prefrontal cortex.	
Brain areas with decreased activity	**ALE fMRI** -The connection between the posterior cingulate cortex and precuneus. -The amygdala, temporal gyrus, and fusiform gyrus. -The cingulate cortex and inferior temporal gyrus of the left hemisphere. **RSFC** - Default-mode network.	**CBF** - Visual cortex alpha power, and the connectivity between parahippocampus and retrosplenial cortex. **RSFC** - The connectivity between parahippocampus and retrosplenial cortex & the posterior cingulate cortex.	**After treatment CBF**** - Temporal cortex and amygdala. - left Heschl's gyrus, left planum temporale, left precentral gyrus, left superior temporal gyrus, right supramarginal gyrus, left amygdala, and right parietal operculum. **After treatment RSFC**** - Parahippo-campus and prefrontal cortex. **RSFC*** - Default-mode network.	**LCGU after treatment***** - Medial and lateral preoptic areas, cortex of nucleus accumbens, diagonal band nucleus, inferior colliculus, locus coeruleus, and flocculus.

* no treatment (i.e. at normal circumstances), ** treatment of depression by psilocybin (a.k.a mushroom), *** after treatment of morphine dependent rats with ibogaine.

Table 2: *Psychedelics activities in the brain.*

Conclusion

The suggestion that psychedelics are proven treatments is not accurate at this time. Most of the reviewed papers about the mentioned four psychedelic point to the other direction. Most of the psychedelics in this paper can caused death at high doses. DMT considered the safest and psilocybin as the most promising psychedelic in this paper to treat depression. At this point none of them is a reliable treatment. Due to the legalization of marijuana in the United States, the culture of legalizing substances is a new trend. Pushing for legalizing psychedelics right now is not based on empirical evidence of their healing power, but based on emotional bases to be used for recreational purposes like what is seen in the documentary movie made by Joe Rogan called "DMT: The spirit molecule 2010". The movie did not show any benefit of DMT except where they claimed to prepare cancer patients for death by giving them DMT. What if the patients had a bad trip and become more anxious from death? Giving DMT to cancer patients to prepare them for death is a weak argument. Furthermore, the documentary asked a mathematician to give his scientific opinion about DMT which shows the bias and lack of credibility. What a mathematician knows about pharmacology, psychology, psychiatry, and neurology? Other treatment should be looked for to treat mental illness like; depression or addiction since a lot of bias can be spotted in psychedelic papers because it became like other polarizing topics such as; abortion or death penalty. As this paper showed many examples of others who ignored the data and preach slogans for political or emotional purposes.

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DOI: 10.31579/ 2642-973X/027