Potential Depression Treatment: Serotonergic Psychedelics Promote Neural Plasticity through Spinogenesis and Synaptogenesis.

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Abstract

Serotonergic psychedelics such as DOI, DMT, and LSD have previously shown potential benefits in regards to depression treatment and other related disorders. This is because of their effects in the brain like increasing prefrontal cortex plasticity which seems to be the fast-acting property of ketamine as an antidepressant currently used for depression treatment. This suggests potential benefits coming from serotonergic psychedelics towards depression treatment, but more research is needed on the structural and functional mechanism of these drugs. Ly et al.'s (2018) study focuses on this by treating mature rat cortical neurons both *in vivo* and *in vitro* with serotonergic psychedelics to explore their effects on spinogenesis and synaptogenesis through super-resolution structured illumination microscopy, which are important in neural plasticity and play a role in depression symptoms, hence its treatment. Spinogenesis and synaptogenesis were both promoted by the different treatments, increasing plasticity, and producing similar results to ketamine, therefore acting as potential future treatments for depression.

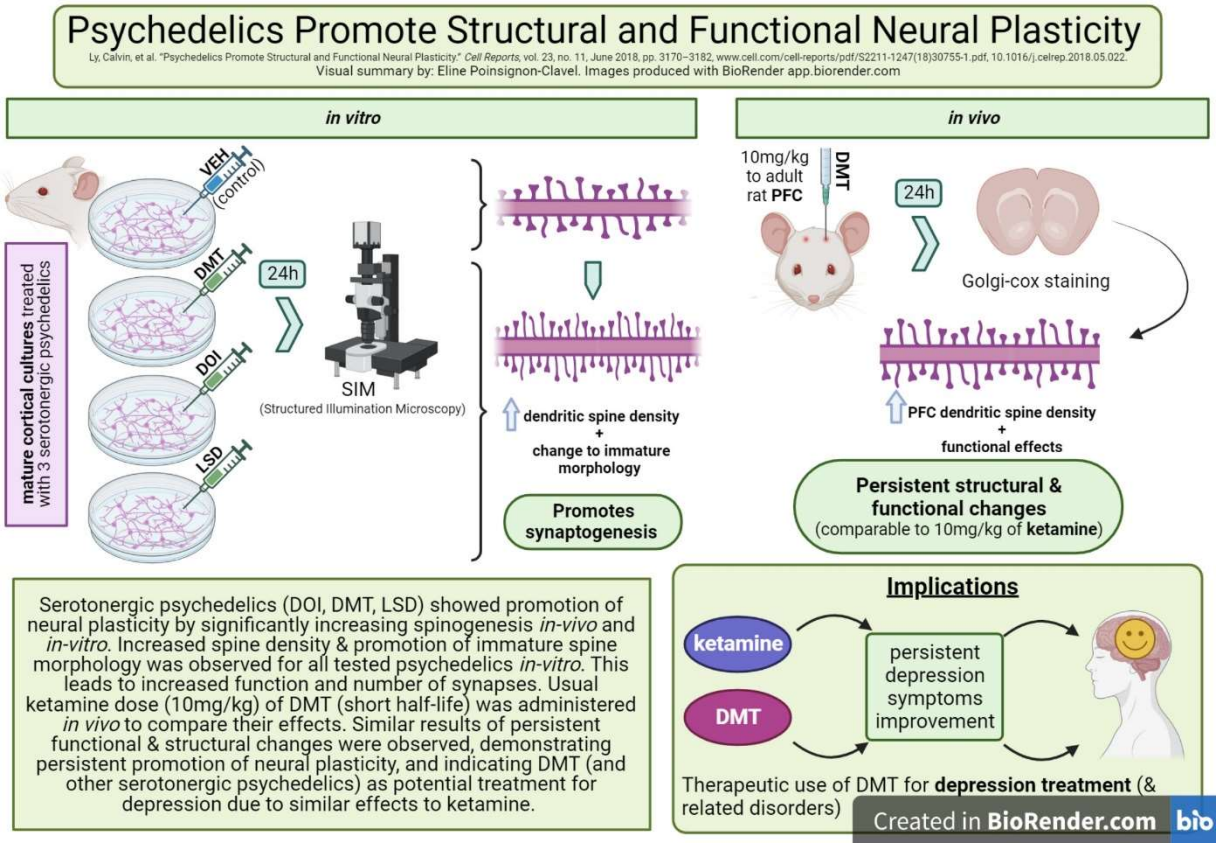

Figure 1: Visual summary of Ly et al. (2018)'s paper, made with BioRender.com

Key words: Psychedelics, neural plasticity, DMT, LSD, DOI, ketamine, synaptogenesis, spinogenesis, prefrontal cortex, depression treatment, super-resolution structured illumination microscopy.

Introduction

Many previous studies have researched the therapeutic use of ketamine, a dissociative anesthetic drug, as treatment for depression due to its rapid antidepressant effects as a N-methyl-D-aspartate receptor antagonist (aan het Rot et al. 2012, Corriger and Pickering 2019). Additionally, serotonergic psychedelics (SPs) such as LSD, psilocybin, or DMT have also shown potential in treating mental health disorders through micro-dosing. Neuroimaging studies have shown functional organization and dynamics changes throughout the whole brain (Girn et al. 2022). Studies on SPs and ketamine are starting to become more prevalent as their use could be very beneficial towards many disorders other than depression such as anxiety disorders, PTSD, or addiction. Furthermore, not all patients benefit from antidepressant drug treatments, and those who do usually do not feel the effects until several weeks of drug taking (Ly et al. 2018). This makes the new research of treatment by SPs and ketamine very interesting and novel as they have been stigmatized as recreational drugs despite being marked as potential drugs considered for neuropsychiatric diseases treatment within the last few years.

Many past studies led to the discovery that neuronal atrophy in the prefrontal cortex (PFC) is the main reason for the pathophysiology of many disorders related to depression, and stress was found to worsen this (Ly et al. 2018). This translates as structural changes like synaptic and dendritic spine loss within the PFC, but these could be counteracted. So far, ketamine seems the most promising for counteracting these changes (Castrén and Antila 2017). Its treatment has demonstrated promotion of dendritic spine growth, increased synthesis of synaptic proteins, as well as stronger responses in synapses on animal models (Autry et al. 2011). Though SPs seem to demonstrate similar antidepressant results as ketamine upon single dose treatments (even on treatment-resistant patients), they still lack research supporting their safety and therapeutic mechanisms (Ly et al. 2018). Ly et al. (2018) therefore reasoned that SPs may work in a similar fashion as ketamine – increasing neural plasticity both functionally and structurally in cortical neurons – which could help deepen the research for depression treatments with psychoplastogens (psychedelics increasing plasticity).

In order to test SPs' functional mechanism in potentially treating depression-related disorders, Ly et al. (2018) conducted experiments both *in vivo* and *in vitro*. The main experiments within this study consisted of treating cortical cultures of mature rats for 24 hours with different SPs which were DMT, LSD, and DOI to measure synaptogenesis through dendritic spine growth, density, and other morphological changes. The second main experiment consisted of taking a closer look at the potential of DMT on spinogenesis and persistency of its benefits by administering it in mature rats' PFC and comparing it to ketamine results from previous studies. The results demonstrated great potential in synaptogenesis promotion from the tested SPs, as well as implications for the use DMT for persistent depression symptoms improvement resembling ketamine treatment.

Major Findings

Spinogenesis and synaptogenesis in rat cortical neurons with DOI, DMT, and LSD treatments *in vitro*

Mature rat cortical cultures were treated with DOI, DMT, and LSD for 24 hours. The three SPs were chosen to each represent a compound from different psychedelic classes (amphetamine, tryptamine, and ergoline). Each treatment showed an increase in spinogenesis by increased dendritic spine density after observing and measuring them with super-resolution structured illumination microscopy (SIM). LSD showed the biggest increase in spine density with almost double of what the control (VEH) showed (figure 2B). Additionally, all treatments showed a change in morphology where an increase in thin and filopodium spines was observed, which are immature spine types, whereas mature types (mushroom) decreased (figure 2C). Synaptogenesis also increased as synaptic density increased, but not the size (figure 2E, F). These findings indicate that all three SPs tested improve synaptic plasticity and counteract the synaptic and dendritic spine changes made by depression as explained in the introduction.

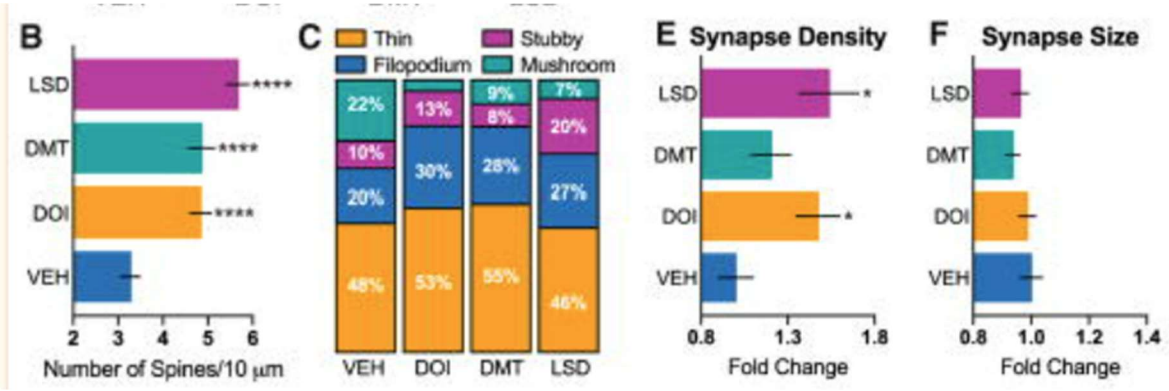

Figure 2: SPs (DOI, DMT, LSD) treatments promote both spinogenesis and synaptogenesis. (Ly et al. 2018)

The findings go against what previous studies have shown regarding DOI effect on cortical neurons (Jones et al. 2009). Ly et al. (2018)'s study also adds to previous studies that such changes are not only feasible by DOI, but also by LSD and DMT.

Spinogenesis in rat PFC with DMT *in vivo*, and comparison with ketamine

Due to inspiring results from the *in vitro* experiment, and past research stating DMT as producing beneficial behavioural results for depression and PTSD in rat models (using 10mg/kg doses for hallucinogenic effects with minimal safety risks) (Carbonaro et al. 2014), Ly et al. (2018) deepened their research *in vivo*. They administered a single 10mg/kg DMT dose in mature rat PFC and assessed its effects on spinogenesis with *ex-vivo* Golgi-Cox staining slices 24 hours later. Results showed increased dendritic spine density in cortical pyramidal neurons (figure 3I) which was comparable to effects from ketamine (figure 3J). They also found that, despite DMT's very short half-life, its structural and functional effects are persistent. These findings are crucial to determine whether DMT could be used as a potential treatment for depression as its effects resemble ketamine's which is already being used as a treatment. They also made sure that the promotion of spinogenesis occurred *in vivo*, and not only *in vitro* to make sure of its potential validity as a treatment. DMT's persistent effects also make it a great contestant for treatment as it makes its benefits last.

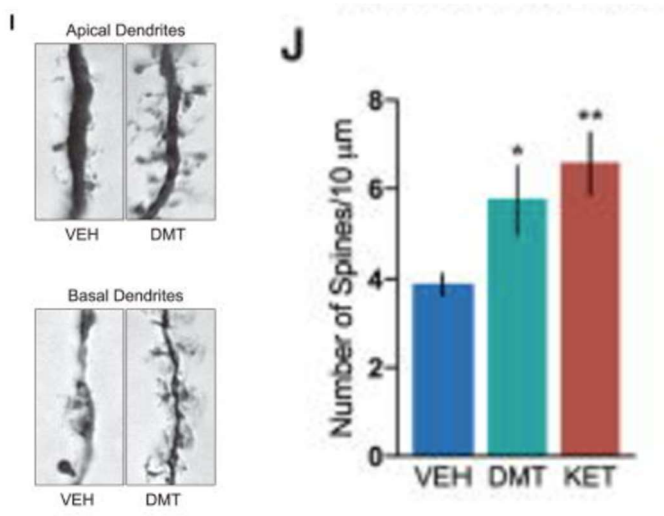

Figure 3: DMT treatment promotes spinogenesis comparatively to ketamine treatment. (Ly et al. 2018)

These findings validate previous research stating that SPs including DMT could be used as depression treatment and leads to increased neuroplasticity (Artin, Zisook, and Ramanathan 2021). This was also the first time that DMT and ketamine effects on spinogenesis were directly compared, filling some gaps in literature.

Conclusion

Ly et al.'s (2018) paper made impactful advancements in the topic of psychedelics in clinical treatments. Their findings on the effects of DOI, DMT, and LSD promoting spinogenesis and synaptogenesis in cortical neurons indicated increased neural plasticity from different psychedelic classes treatments, as well as counteraction against structural changes found in depression patients. Their other findings on DMT's *in vivo* persistent promotion of spinogenesis resembling the effects from ketamine indicated potential for DMT to be further studied as a depression treatment due its similarity with ketamine which is already being used as treatment.

The authors concluded that despite the different molecular target between ketamine and SPs, similar structural plasticity changes resulted from their downstream effects. This novel discovery is important for this field of study as SPs are not associated with addiction from their use, unlike ketamine (Nutt et al. 2010), which could therefore improve the safety of depression treatment. They also concluded that the similar effects they found of the studied SPs to ketamine supported the hypothesis on PFC neurons plasticity being structurally and functionally promoted by the antidepressant and anxiolytic effects of SPs. Their findings also answer a major question made by previous studies about whether psychedelics promote dendritic spine density changes or not (Kyzar et al. 2017), which it did.

Discussion & Critical analysis

Despite Ly et al.'s (2018) study's great advancements, research on SPs effects on other depression symptoms is still necessary, and their potentially harmful hallucinogenic effects on some patients also need to be further studied for increased safety of usage as clinical treatments. More research on their therapeutic mechanism is still required as it is a novel field of research for next-generation neurotherapeutics. Additionally, more research could be done on their other

potential benefits regarding productivity, motivation, and overall happiness which also play a role in depression.

The findings brought up a discrepancy with previous literature on the effects of DOI. Jones et al.'s (2009) study found that DOI treatment on cortical neurons increased dendritic spine size, but not their density, where the opposite held true for Ly et al.'s (2018) findings. This indicates that more research may be necessary to increase the validity of these specific results. This paper only looked at three types of SPs when more could have been included like psilocybin (Vargas et al. 2020). Additionally, other currently studied drugs within this field could have been included, for example, MDMA (Reiff et al. 2020). Lastly, the authors should also repeat the same *in vitro* structural plasticity experiment with neurons exposed to the treatments for a shorter period of time than they did in this paper. This is because the usual exposure to psychedelics in the brain is shorter than 24 hours because of fast metabolism (Ly et al. 2018).

Future directions

To fill in the gaps of this paper regarding the accuracy of treatment length, future studies should focus on a more accurate replication of how the used SPs are metabolised when used for treatment in depression patients. The same *in vitro* experiment would be done using the same SPs (DOI, DMT, LSD) to test synaptogenesis and spinogenesis, but with a shorter treatment length. Mature rat cortical cultures would be treated with each SP for each of their respective metabolism time (instead of 24 hours) in order to get drug-specific results. These would then be assessed with SIM to measure dendritic spine density and synapse density. Outcomes would reveal similar trends as the ones seen in this paper, however, the extent of the promotion of these structural changes would be lesser as they would not be treated for as long, hence not letting the SPs take action for as long so less time for changes to be made. If this is not the case, it may be due to 'saturation' of the SP effects on these particular processes where the improvements observed end up plateauing.

This proposed experiment could be further enhanced by including more currently research drugs for this treatment such as MDMA and psilocybin and proceeding just as described in the previous paragraph. This would allow for a wider range of results with the same aim of better understanding the effects of novel therapeutic use of drugs for depression.

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