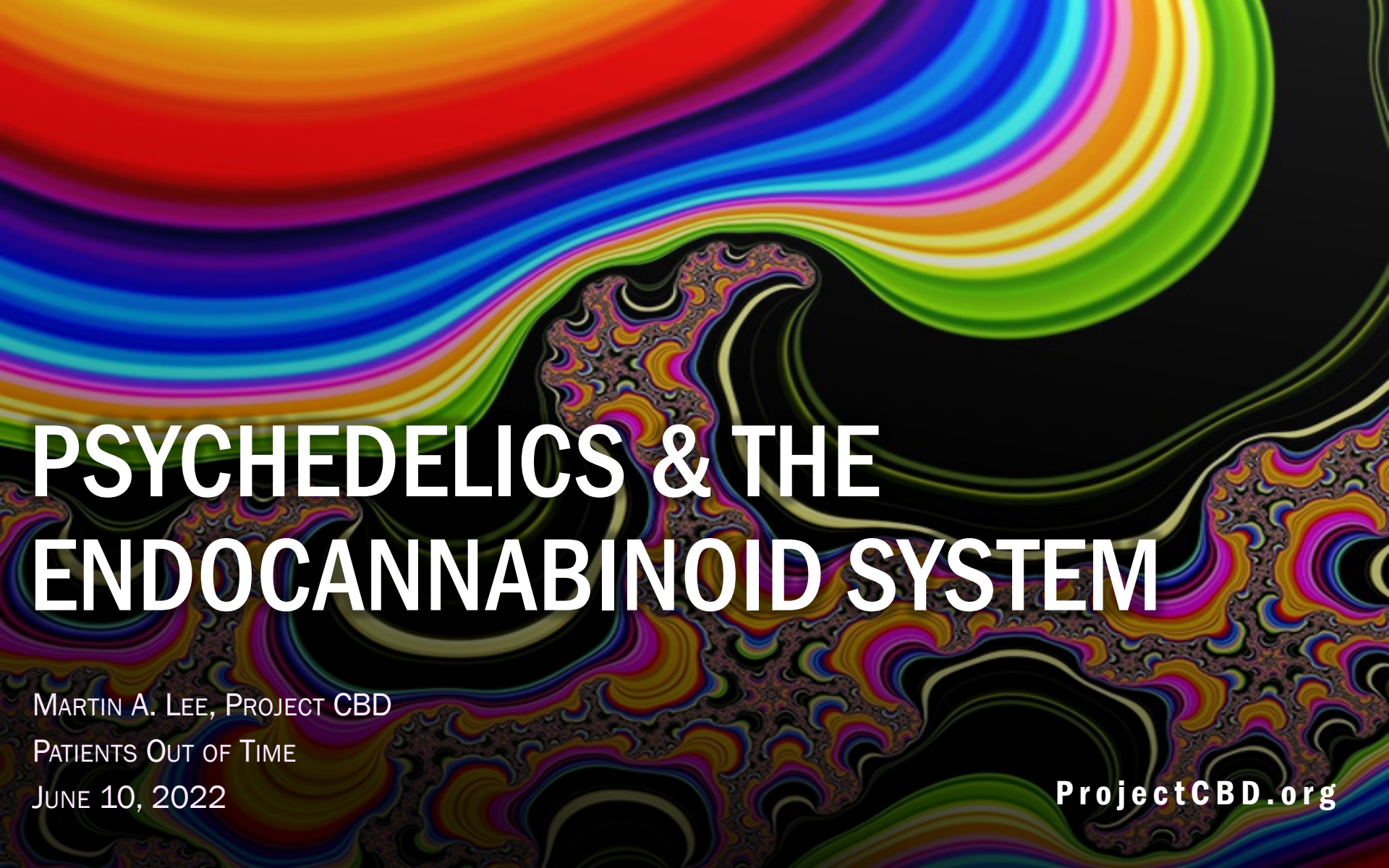


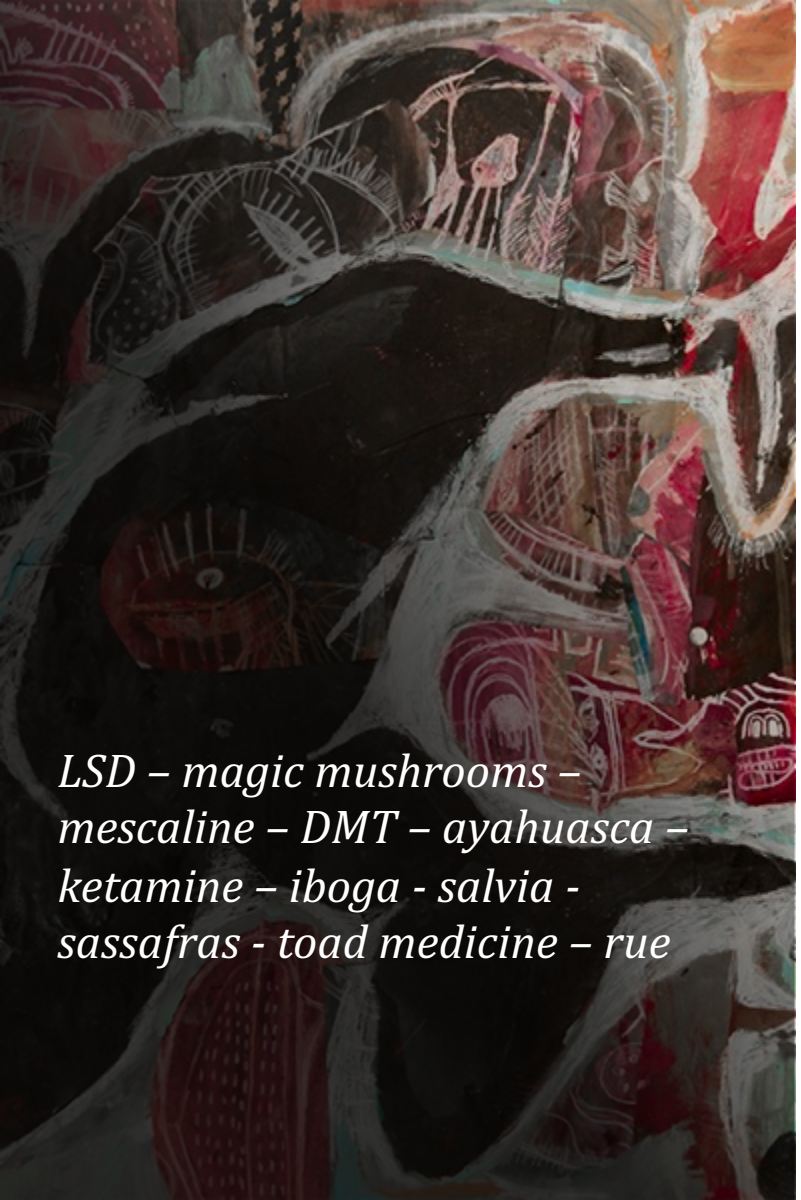
PSYCHEDELICS & THE ENDOCANNABINOID SYSTEM

Martin A. Lee, Project CBD

Patients Out of Time

June 10, 2022

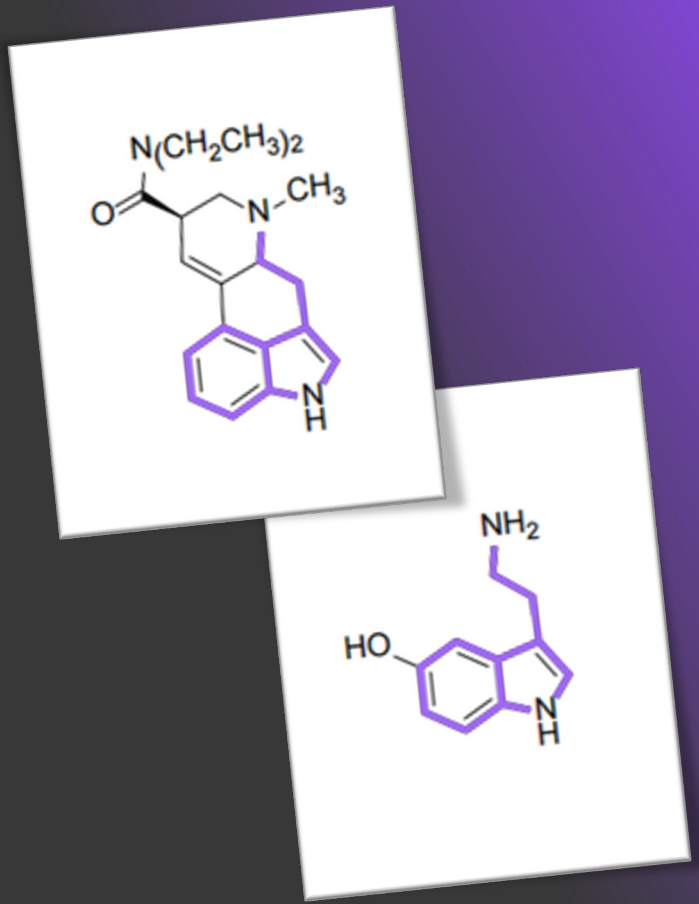
ProjectCBD.org



PSYCHEDELIC DRUG RENAISSANCE

- Renaissance of psychedelic research; trying to emulate MMJ success.
- Parallels: healing without the high.
- Non-hallucinogenic analogs of psychedelic drugs: “pseudo-delics.”
- Psychedelic-assisted therapy: trip seen as essential for transformative breakthrough.

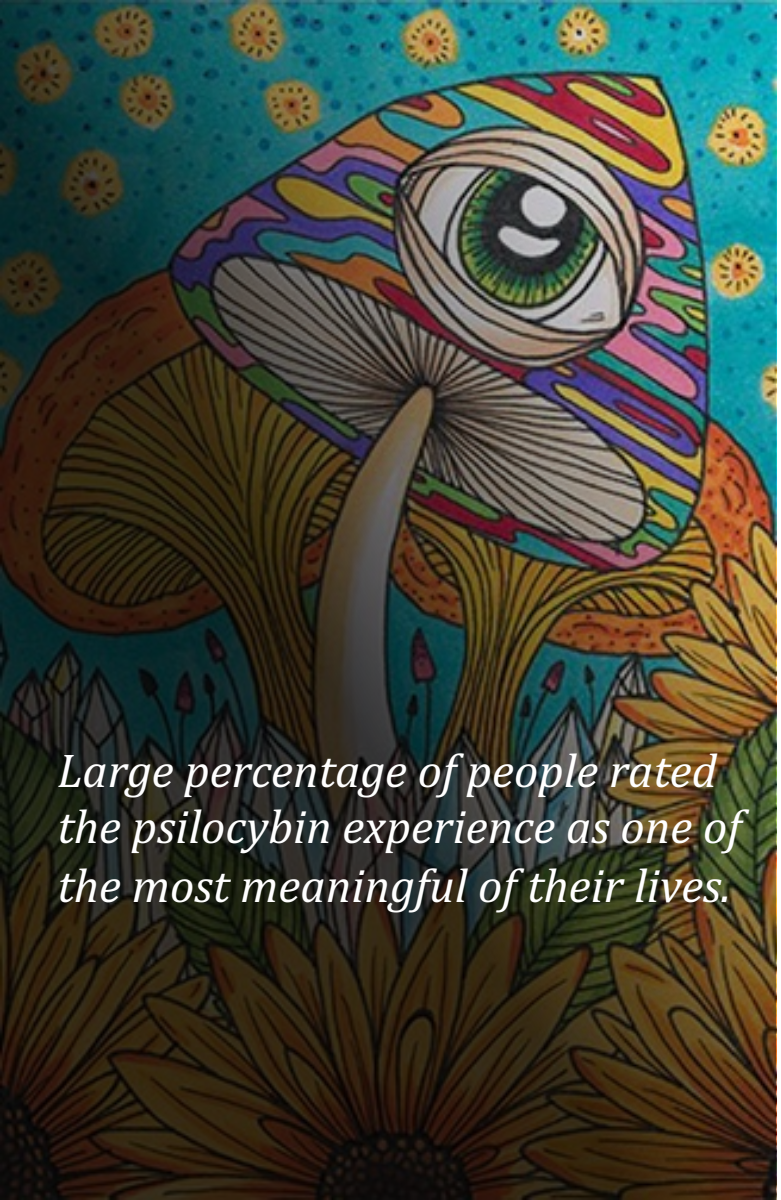
PSYCHEDELIC =
MIND-MANIFESTING



EARLY LSD RESEARCH

- LSD catalyzed entire field of serotonin neuroscience.
- Therapeutic Indications: Substance abuse, trauma, depression.
- 1950s through mid-1960s: More than 1000 clinical papers about LSD and psychedelics, describing 40,000 patients; several international conferences on LSD-assisted therapy.
- 2016: “Meta-analysis of controlled trials has demonstrated a consistent and clinically significant beneficial effect of high-dose LSD.” [1]
- Overall lack of adverse reactions under clinical supervision.

[1] “Classical hallucinogens in the treatment of addictions,” Bogenschutz MP et al, 2016
https://www.ncbi.nlm.nih.gov/pubmed/25784600



PSYCHEDELIC RESEARCH: HIATUS & REVIVAL

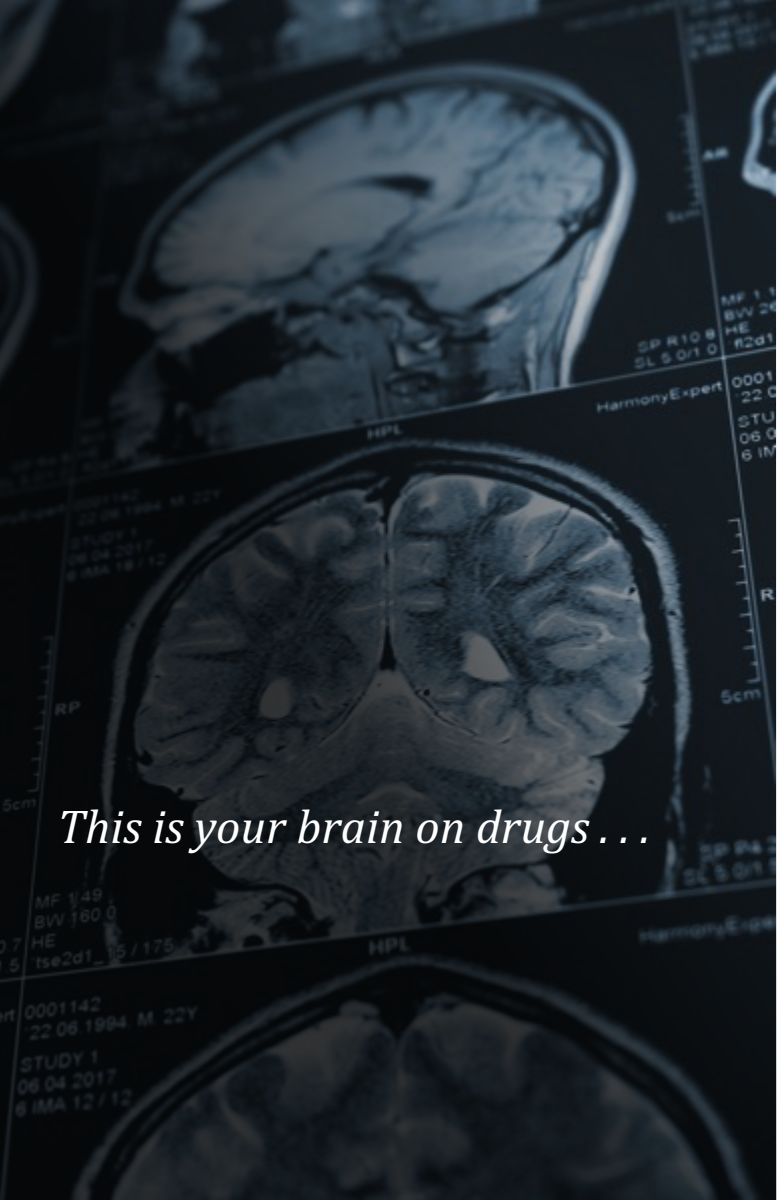
- Research hiatus: a political response to nonmedical use of psychedelics in the 1960s.
- Psilocybin/psilocin research resumes in 1992.
- Two independent, randomized trials showed psilocybin has significant lasting efficacy against cancer-related anxiety and depression.[2]
- A 2011 Johns Hopkins study reported that psychedelics can trigger mystical, quantum leap-type experiences, resulting in sustained positive personality changes.[3]

[2] Grob CS et al, 2011, https://www.ncbi.nlm.nih.gov/pubmed/20819978 and Griffiths RR et al, 2016 https://www.ncbi.nlm.nih.gov/pubmed/27909165
[3] Griffiths RR et al, 2011, https://www.ncbi.nlm.nih.gov/pubmed/21674151

PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION

- Imperial College, 2017: probed neural correlates of psychedelic experience by tracking MRI-measured brain activity changes while under the influence of psilocybin.[4]
- Psilocybin/psilocin “de-synchronizes” Default Mode Network (“neurological basis for the self”): likened to brain “reset” mechanism.
- Efficacious in assisted psychotherapy for treatment-resistant depression. Rapid and long-lasting antidepressant effects in 19 patients. Follow-up study at 6 months found antidepressant and anxiolytic effects of psilocybin were sustained and remained significant.
- 2018: psilocybin fast-tracked by FDA for refractory depression.

[4] Carhart-Harris RL et al, 2017, https://www.ncbi.nlm.nih.gov/pubmed/29030624



This is your brain on drugs . . .

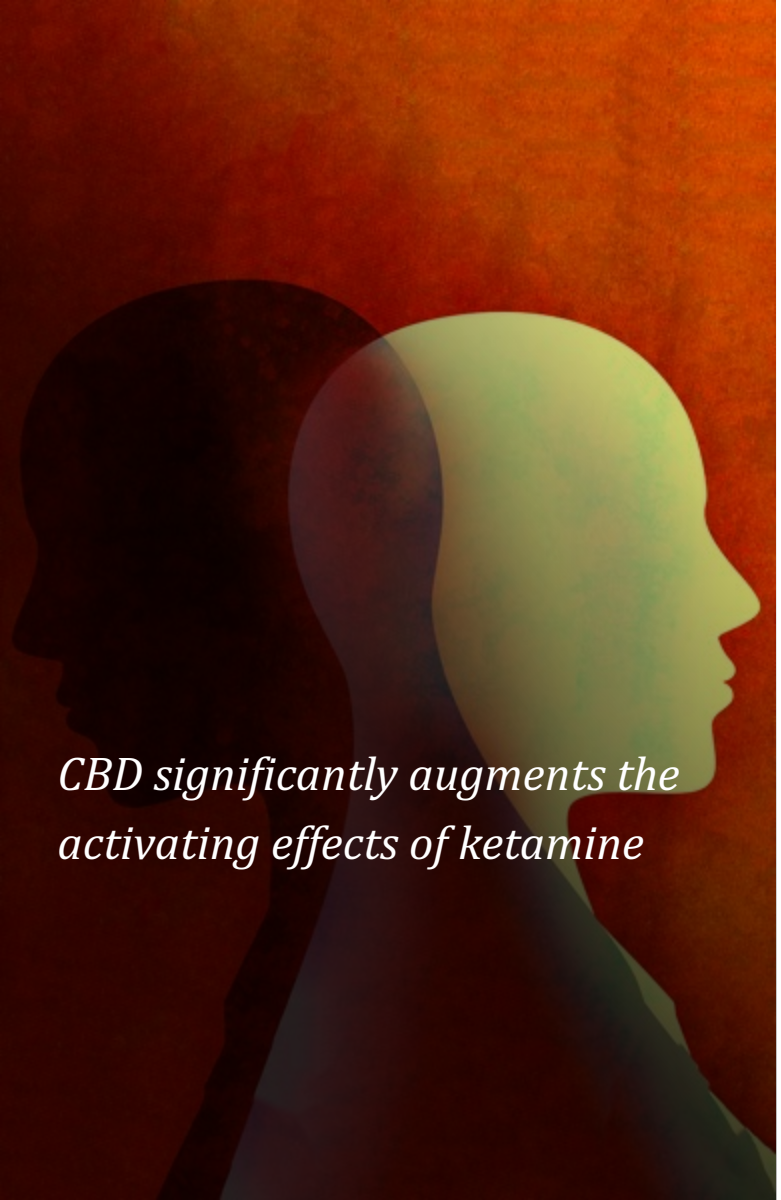
Sci Rep. 2017; 7: 13187.
Published online 2017 Oct 13. doi: 10.1038/s41598-017-13282-7
PMCID: PMC5640601
PMID: 29030624

Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms

Robin L Carhart-Harris,[✉1] Leor Roseman,[1,2] Mark Bolstridge,[1] Lysia Demetriou,[5,6] J Nienke Pannekoek,[1,7] Matthew B Wall,[1,4,5] Mark Tanner,[5] Mendel Kaelen,[1] John McGonigle,[5] Kevin Murphy,[3] Robert Leech,[2] H Valerie Curran,[4] and David J Nutt[1]

Abstract

Psilocybin with psychological support is showing promise as a treatment model in psychiatry but its therapeutic mechanisms are poorly understood. Here, cerebral blood flow (CBF) and blood oxygen-level dependent (BOLD) resting-state functional connectivity (RSFC) were measured with functional magnetic resonance imaging (fMRI) before and after treatment with psilocybin (serotonin agonist) for treatment-resistant depression (TRD). Quality pre and post treatment fMRI data were collected from 16 of 19 patients. Decreased depressive symptoms were observed in all 19 patients at 1-week post-treatment and 47% met criteria for response at 5 weeks. Whole-brain analyses revealed post-treatment decreases in CBF in the temporal cortex, including the amygdala. Decreased amygdala CBF correlated with reduced depressive symptoms. Focusing on a priori selected circuitry for RSFC analyses, increased RSFC was observed *within* the default-mode network (DMN) post-treatment. Increased ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex RSFC was predictive of treatment response at 5-weeks, as was decreased parahippocampal-prefrontal cortex RSFC. These data fill an important knowledge gap regarding the post-treatment brain effects of psilocybin, and are the first in depressed patients. The post-treatment brain changes are different to previously observed acute effects of psilocybin and other 'psychedelics' yet were related to clinical outcomes. A 'reset' therapeutic mechanism is proposed.

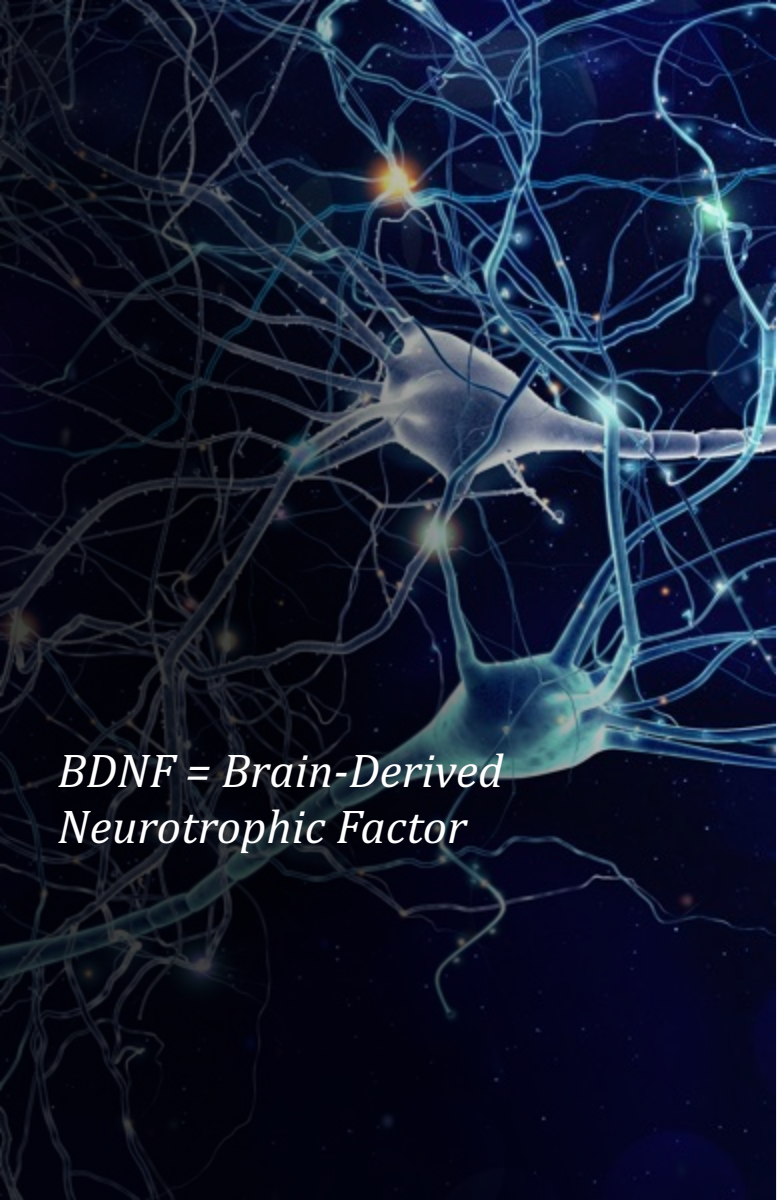


CBD significantly augments the activating effects of ketamine

KETAMINE & THE ECS

- Ketamine, an FDA-approved “dissociative anesthetic,” is administered off-label for refractory depression at ketamine clinics. High doses of ketamine are hallucinogenic.
- Ketamine’s central & peripheral analgesic effects are mediated by ECS.[5]
- 2019, Iranian scientists: “Ketamine induced anti-depressant-like effects in mice: possible involvement of cannabinoid system.”[6]
- Endocannabinoids potentiate the effects of ketamine. So does CBD.
- Ketamine treatment quick acting, doesn’t entail daily dosing, weight gain or libido loss typically associated with anti-depressants.

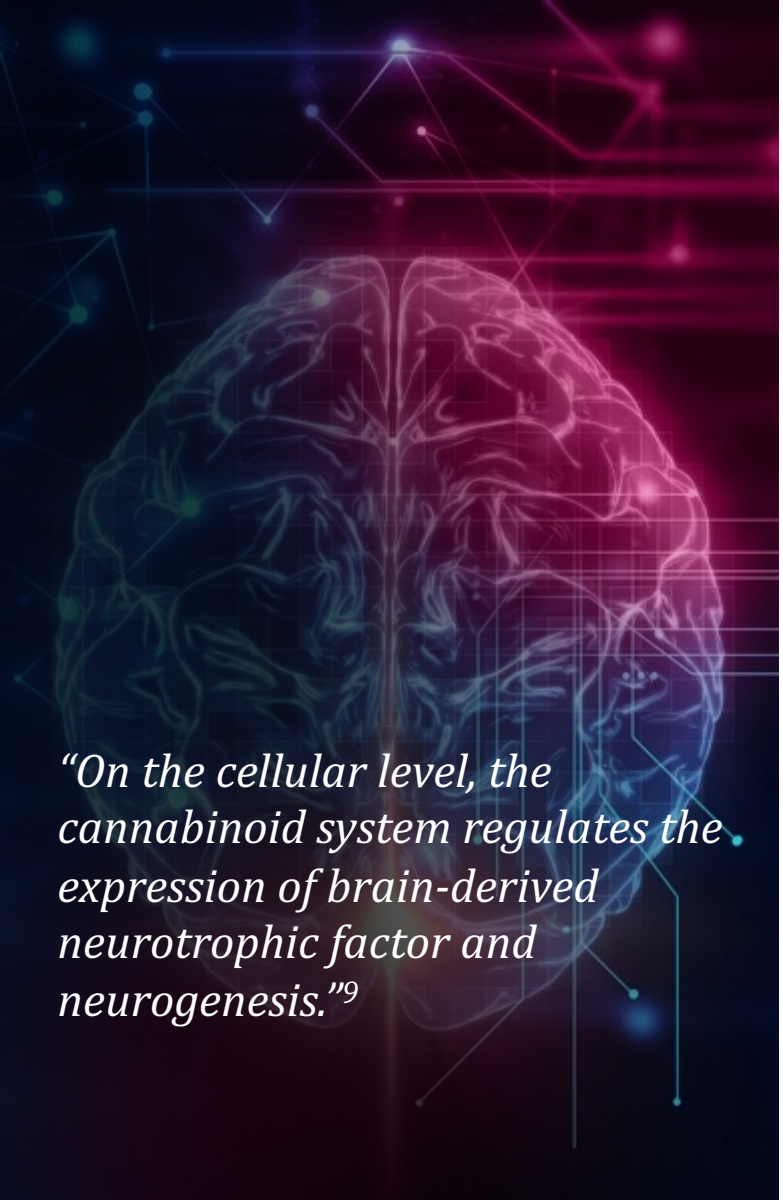
[5] Pacheco DDF et al, 2019 https://www.ncbi.nlm.nih.gov/pubmed/30716423) and Ferreira RCM et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/29247851 Khakpai F et al, 2019,
[6] https://www.ncbi.nlm.nih.gov/pubmed/30970516



KETAMINE, GLUTAMATE & BDNF

- US & Panamanian scientists, 2014: Ketamine blocks a glutamate ion channel, which triggers production of BDNF (brain-derived neurotrophic factor).[7]
- "Fertilizer of the brain" -- role of BDNF in adult neurogenesis, neuroplasticity, and synaptogenesis is the subject of many studies.
- Ketamine's rapid antidepressant effects involve enhanced BDNF-induced neurogenesis & synaptogenesis.
- UC Davis study, 2018: A 10 mg/kg dose of ketamine "produced a robust increase in dendritic spine density in the prefrontal cortex of rats."[8]

[7] Vasquez CE et al, 2014, https://www.ncbi.nlm.nih.gov/pubmed/25277075
[8] Ly C et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/29898390



"On the cellular level, the cannabinoid system regulates the expression of brain-derived neurotrophic factor and neurogenesis."[9]

BDNF & ECS

Front Cell Neurosci. 2018 Nov 28;12:441. doi: 10.3389/fncel.2018.00441. eCollection 2018.

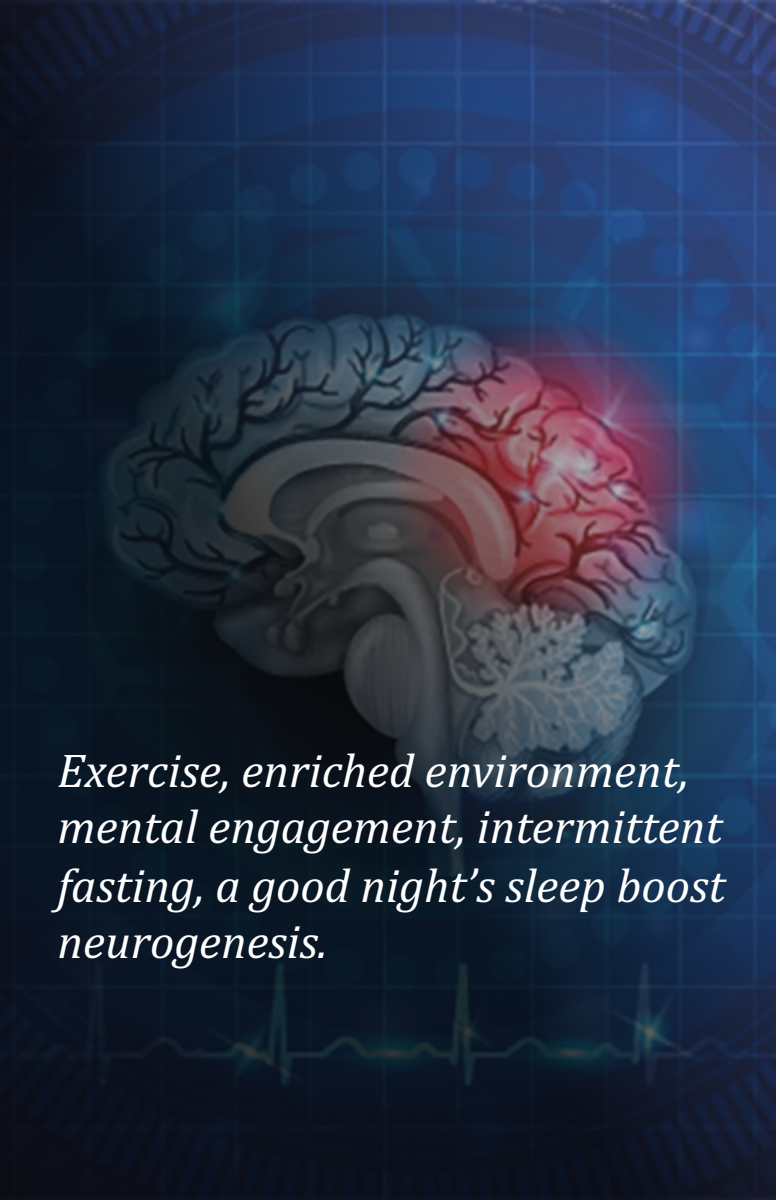
Brain-Derived Neurotrophic Factor (BDNF) Role in Cannabinoid-Mediated Neurogenesis.

Ferreira FF[1,2], Ribeiro FF[1,2], Rodrigues RS[1,2], Sebastião AM[1,2], Xapelli S[1,2].

Abstract

The adult mammalian brain can produce new neurons in a process called adult neurogenesis, which occurs mainly in the subventricular zone (SVZ) and in the hippocampal dentate gyrus (DG). Brain-derived neurotrophic factor (BDNF) signaling and cannabinoid type 1 and 2 receptors (CB1R and CB2R) have been shown to independently modulate neurogenesis, but how they may interact is unknown. We now used SVZ and DG neurosphere cultures from early (P1-3) postnatal rats to study the CB1R and CB2R crosstalk with BDNF in modulating neurogenesis. BDNF promoted an increase in SVZ and DG stemness and cell proliferation, an effect blocked by a CB2R selective antagonist. CB2R selective activation promoted an increase in DG multipotency, which was inhibited by the presence of a BDNF scavenger. CB1R activation induced an increase in SVZ and DG cell proliferation, being both effects dependent on BDNF. Furthermore, SVZ and DG neuronal differentiation was facilitated by CB1R and/or CB2R activation and this effect was blocked by sequestering endogenous BDNF. Conversely, BDNF promoted neuronal differentiation, an effect abrogated in SVZ cells by CB1R or CB2R blockade while in DG cells was inhibited by CB2R blockade. We conclude that endogenous BDNF is crucial for the cannabinoid-mediated effects on SVZ and DG neurogenesis. On the other hand, cannabinoid receptor signaling is also determinant for BDNF actions upon neurogenesis. These findings provide support for an interaction between BDNF and endocannabinoid signaling to control neurogenesis at distinct levels, further contributing to highlight novel mechanisms in the emerging field of brain repair.

[9] Bilkei-Gorzo A, 2012, https://www.ncbi.nlm.nih.gov/pubmed/23108550

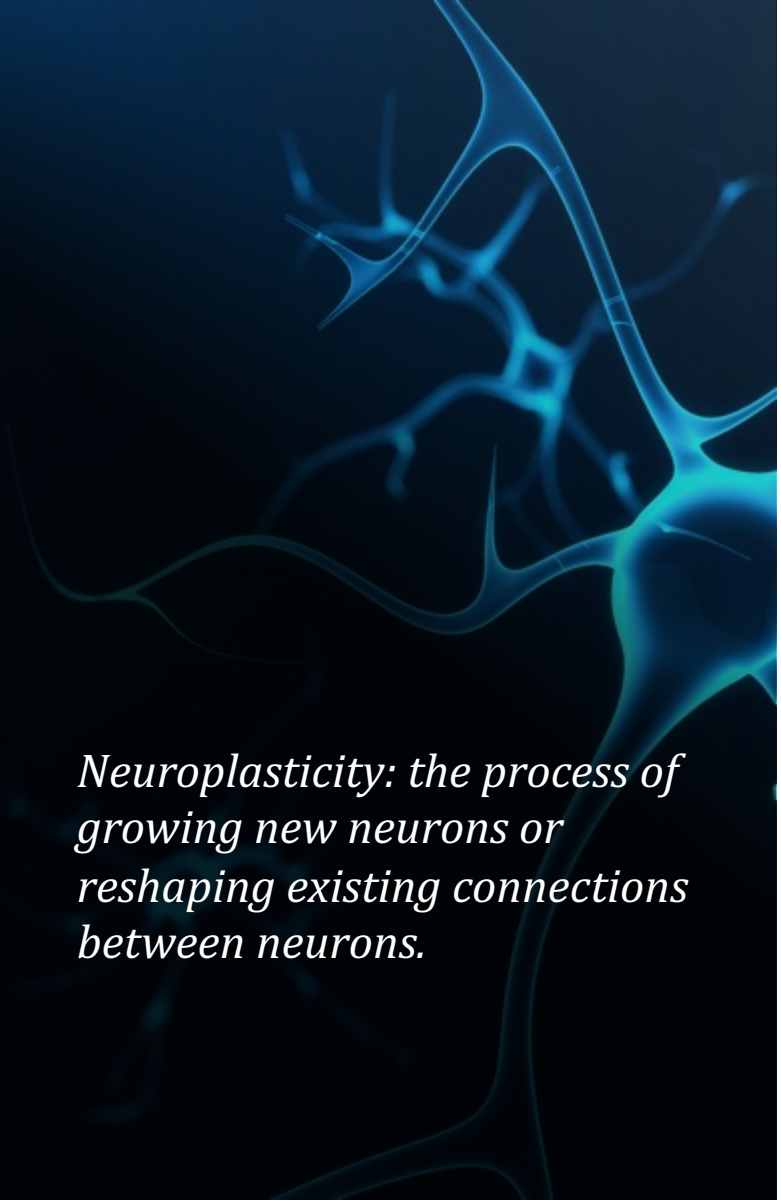


Exercise, enriched environment, mental engagement, intermittent fasting, a good night's sleep boost neurogenesis.

ECS & NEUROGENESIS

- Brazilian researchers, 2018: eCB signaling choreographs embryonic and adult NG[10] and MIT study, 2011: eCB signaling regulates proliferation, migration & integration of stem cells into neuronal circuitry.[11]
- Nature, 2019: Neurogenic activity robust when young, decreases with age. Gradual reduction in new brain cells is linked to cognitive decline, neurodegenerative disease.[12]
- Neurogenic niches in the hippocampus, locus of learning & memory: subgranular zone of dentate gyrus and subventricular zone of lateral ventricles; densely populated with CB receptors.
- Spanish study, 2017: Activation of CB1 receptors stimulates NG. CB2 receptor drives neurogenesis & improves functional outcome after stroke.[13] And pharmacological blockage or genetic KO of CBRs leads to impaired NG. Chronic stress depletes NG. Decreased NG in schizophrenic patients. FAAH inhibition increases NG.[14]

[10] de Oliveira RW, 2019, https://www.ncbi.nlm.nih.gov/pubmed/29764526; [11] Oudin MJ, 2011, https://www.ncbi.nlm.nih.gov/pubmed/21411643 ; [12] Sorrells SF et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/29513649
[13] Bravo-Ferrer I et al, 2017, https://www.ncbi.nlm.nih.gov/pubmed/27899748
[14] Rodrigues RS et al, 2019, https://www.ncbi.nlm.nih.gov/pubmed/30959794

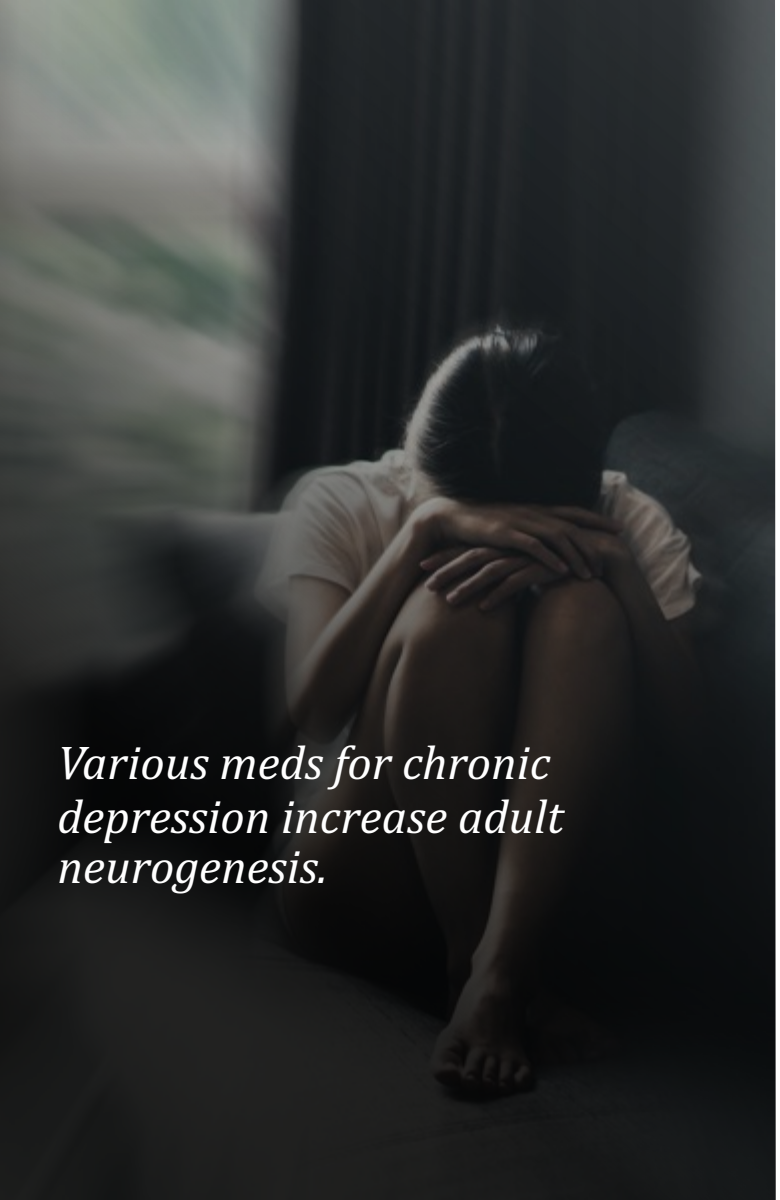


Neuroplasticity: the process of growing new neurons or reshaping existing connections between neurons.

ESC & NEURAL PLASTICITY

- Science, 2007: Endocannabinoid signaling shapes neuronal connectivity, maintains integrity of brain function,[15]
- French study, 2020: eCB signaling facilitates adaptive learning, the brain's ability to make new neural connections, correct abnormalities from chronic stress.[16]
- ECS regulates neural plasticity within hippocampus and throughout much of the brain, including the striatum "where various forms of bidirectional eCB-mediated plasticity occur."[17]
- CB1 receptor mediates changes in synaptic plasticity; CB1R KO mice have reduced dendritic branching in the PFC and motor cortex.

[15] Berghuis P et al 2007, https://www.ncbi.nlm.nih.gov/pubmed/17525344
[16] "BDNF Controls Bidirectional eCB Plasticity at Corticostriatal Synapses," Gangarossa et al 2019, https://www.ncbi.nlm.nih.gov/pubmed/ 31329835



Various meds for chronic depression increase adult neurogenesis.

NEURONAL ATROPHY & DEPRESSION

- Neural plasticity versus dendritic atrophy: neuronal atrophy is a contributing factor to mood and anxiety disorders.
- Loss of dendritic spines in the PFC, a hallmark of depression and neuropsychiatric disease.[17]
- Columbia University study, 2003: The behavioral effects of antidepressant pharmaceuticals are contingent on enhanced hippocampal neurogenesis.[18]
- Facilitation of neurogenesis is a treatment strategy for clinical depression, Alzheimer's, MS, and Parkinson's.

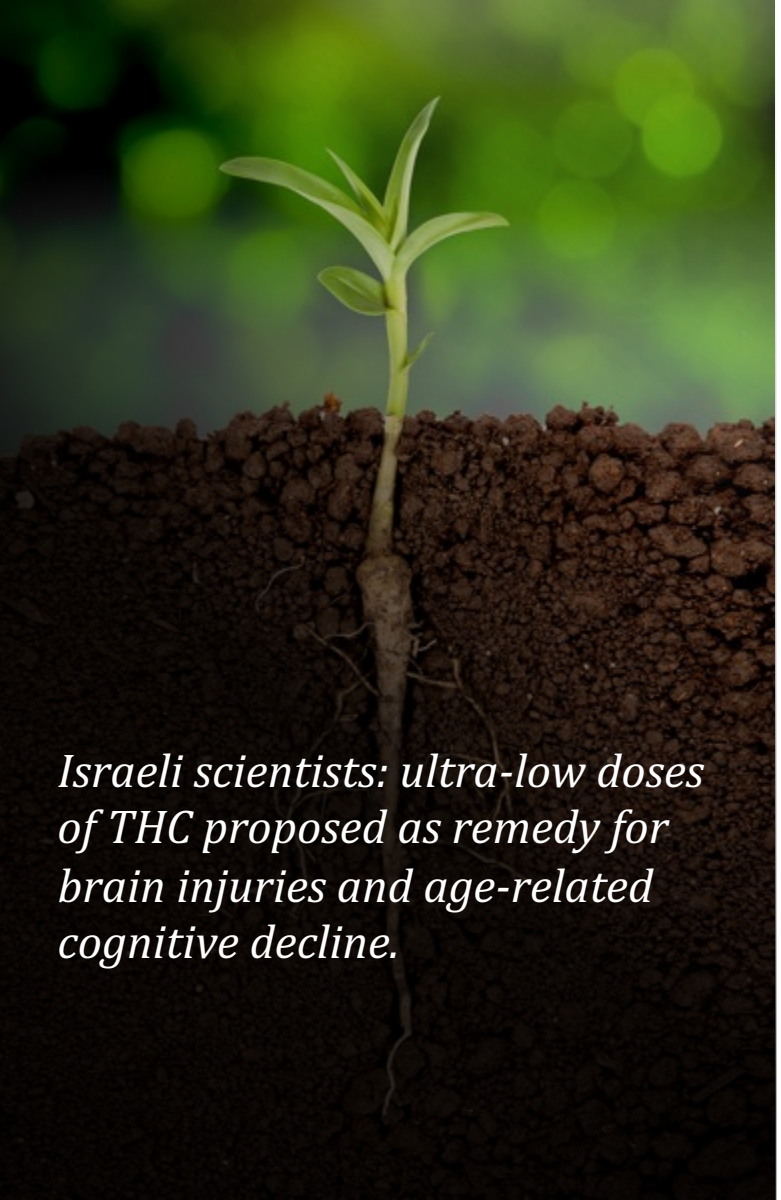
[17] Ly C et al, https://www.ncbi.nlm.nih.gov/pubmed/29898390
[18] Santarelli L et al, 2003, https://www.ncbi.nlm.nih.gov/pubmed/12907793

Depleted adult hippocampal neurogenesis is a key factor in drug addiction etiology.

ALCOHOLISM & NEUROGENESIS

- Spanish scientists: “Substance abuse causes a disruption in the synaptic plasticity of the brain circuits involved in addiction, with the alteration of normal eCB activity playing a prominent role.”[19]
- Chronic alcohol exposure reduces eCB activity and disrupts adult neurogenesis.[20]
- “The ECS [is] one of the most relevant biochemical systems mediating alcohol addiction . . . adult hippocampal neurogenesis is a key factor involved in drug abuse and it may provide a new strategy for the treatment of alcohol addiction and dependence.”[21]

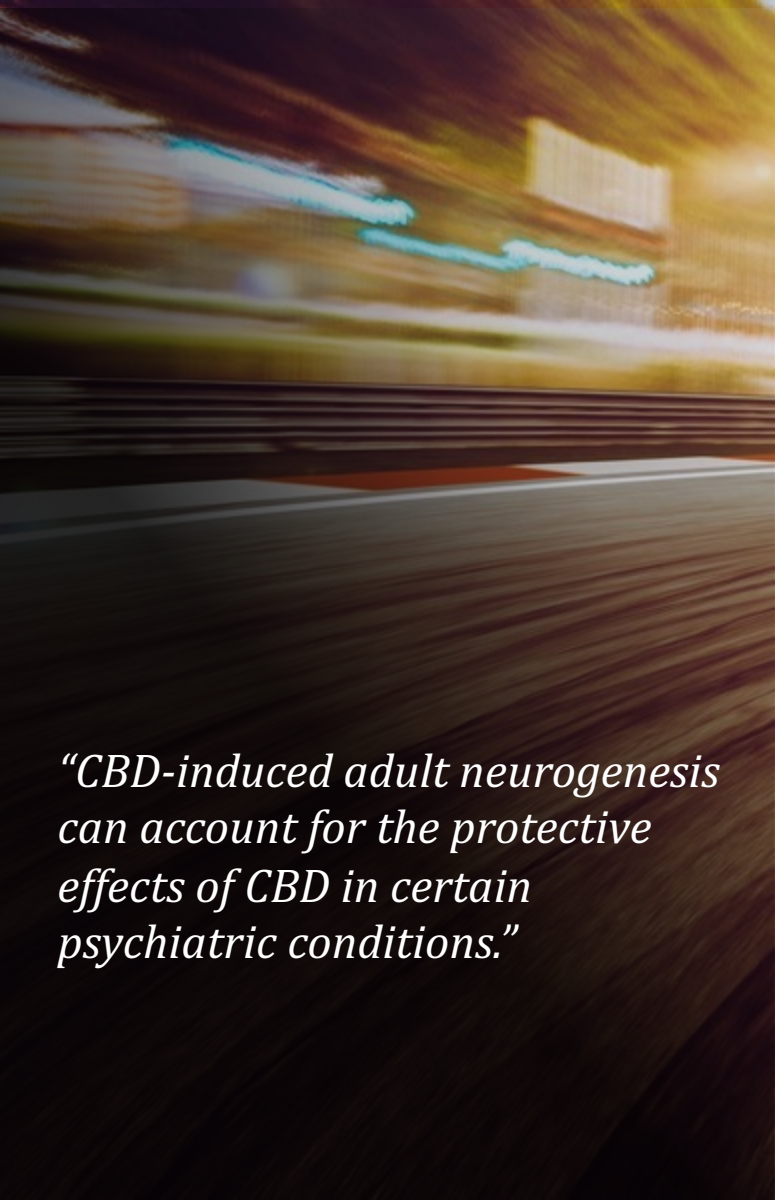
[19] “Fernandez-Espejo E, Nunez-Domonguez L, 2019, https://www.ncbi.nlm.nih.gov/pubmed/30857785
[20] Rivera P et al, 2015, https://www.ncbi.nlm.nih.gov/pubmed/26483633
[21] Alen F et al, 2010, https://www.ncbi.nlm.nih.gov/pubmed/20047713



THC PROMOTES NEUROGENESIS

- Malaysian scientists, 2017: THC enhances neurogenesis in the hippocampus, improving cognitive function of rats.[22]
- Canadian-based researchers: THC stimulates the creation of new brain cells by activating CB1 receptors.[23]
- Portuguese study, 2018: THC administration promotes the upregulation of BDNF gene expression.[24]
- THC enhanced the markers involved in all stages of the neurogenesis mechanism.[25]

[22] Suliman NA et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/ 28933048
[23] Jiang W et al, 2005, https://www.ncbi.nlm.nih.gov/pubmed/16224541
[24] Ferreira FF et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/30546297
[25] Suliman NA et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/28933048



"CBD-induced adult neurogenesis can account for the protective effects of CBD in certain psychiatric conditions."

CBD IS NEUROGENIC

- German scientists: "The pro-neurogenic effects of CBD might explain some of the positive therapeutic features of CBD-based compounds."[26]
- Brazilian & Danish scientists: CBD induces rapid and sustained anti-depressant effects through increased BDNF signaling and synaptogenesis in the hippocampus & PFC.[27]
- CBD activation of PPAR-gamma nuclear receptor is associated with increased neurogenic activity.
- Brazilian & Spanish researchers: CBD attenuates the decrease in hippocampal neurogenesis & dendrite spine density induced by chronic stress.[28]
- Low dose CBD "increased cell proliferation & neurogenesis," higher doses "decreased cell proliferation & neurogenesis."[29]

[26] Wolf SA et al, 2010, https://www.ncbi.nlm.nih.gov/pubmed/20565726
[27] Sales AJ et al, 2019, https://www.ncbi.nlm.nih.gov/pubmed/29869197
[28] Campos AC et al, 2017, https://www.ncbi.nlm.nih.gov/pubmed/28588483
[29] Schiavon AP, et al, 2016, https://www.ncbi.nlm.nih.gov/pubmed/26187374

2018 UC Davis study:
"Psychedelics are capable of robustly increasing neurogenesis and/or synaptogenesis in vitro and in vivo."

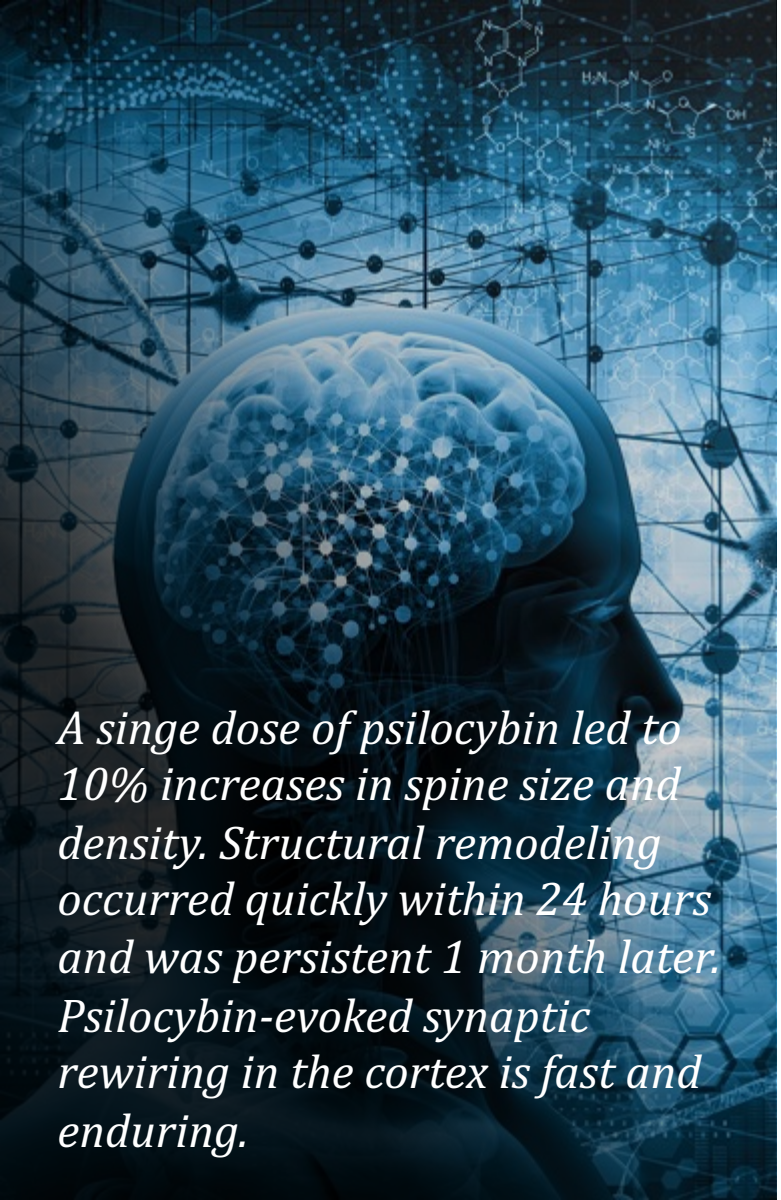
Cell Rep. 2018 Jun 12;23(11):3170-3182. doi: 10.1016/j.celrep.2018.05.022.

Psychedelics Promote Structural and Functional Neural Plasticity.

Ly C[1], Greb AC[1], Cameron LP[2], Wong JM[2], Barragan EV[2], Wilson PC[3], Burbach KF[4], Soltanzadeh Zarandi S[1], Sood A[5], Paddy MR[3], Duim WC[1], Dennis MY[6], McAllister AK[7], Ori-McKenney KM[3], Gray JA[8], Olson DE[9].

Abstract

Atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders. The ability to promote both structural and functional plasticity in the PFC has been hypothesized to underlie the fast-acting antidepressant properties of the dissociative anesthetic ketamine. Here, we report that, like ketamine, serotonergic psychedelics are capable of robustly increasing neuritogenesis and/or spinogenesis both in vitro and in vivo. These changes in neuronal structure are accompanied by increased synapse number and function, as measured by fluorescence microscopy and electrophysiology. The structural changes induced by psychedelics appear to result from stimulation of the TrkB, mTOR, and 5-HT2A signaling pathways and could possibly explain the clinical effectiveness of these compounds. Our results underscore the therapeutic potential of psychedelics and, importantly, identify several lead scaffolds for medicinal chemistry efforts focused on developing plasticity-promoting compounds as safe, effective, and fast-acting treatments for depression and related disorders.



A singe dose of psilocybin led to 10% increases in spine size and density. Structural remodeling occurred quickly within 24 hours and was persistent 1 month later. Psilocybin-evoked synaptic rewiring in the cortex is fast and enduring.

> Neuron. 2021 Aug 18;109(16):2535-2544.e4. doi: 10.1016/j.neuron.2021.06.008. Epub 2021 Jul 5.

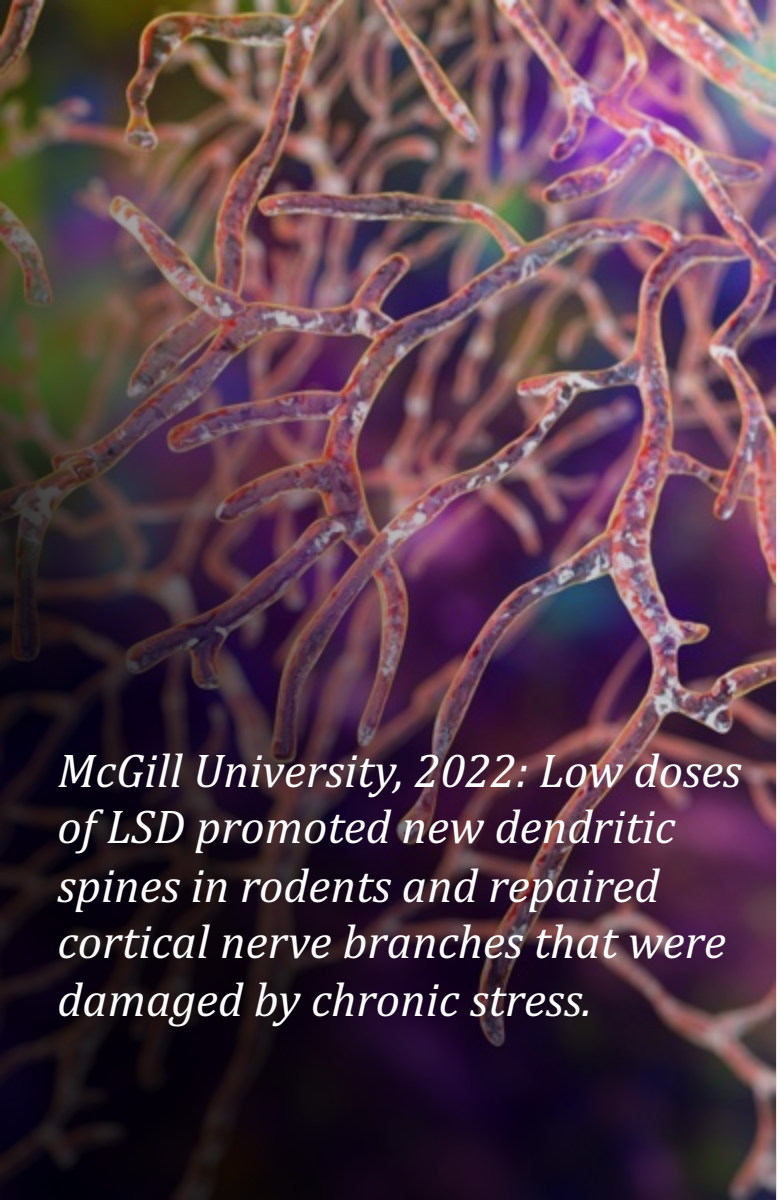
Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo

Ling-Xiao Shao [1], Clara Liao [2], Ian Gregg [1], Pasha A Davoudian [3], Neil K Savalia [3], Kristina Delagarza [1], Alex C Kwan [4]

PMID: 34228959
PMCID: PMC8376772 (available on 2022-08-18)
DOI: 10.1016/j.neuron.2021.06.008

Abstract

Psilocybin is a serotonergic psychedelic with untapped therapeutic potential. There are hints that the use of psychedelics can produce neural adaptations, although the extent and timescale of the impact in a mammalian brain are unknown. In this study, we used chronic two-photon microscopy to image longitudinally the apical dendritic spines of layer 5 pyramidal neurons in the mouse medial frontal cortex. We found that a single dose of psilocybin led to ~10% increases in spine size and density, driven by an elevated spine formation rate. The structural remodeling occurred quickly within 24 h and was persistent 1 month later. Psilocybin also ameliorated stress-related behavioral deficit and elevated excitatory neurotransmission. Overall, the results demonstrate that psilocybin-evoked synaptic rewiring in the cortex is fast and enduring, potentially providing a structural trace for long-term integration of experiences and lasting beneficial actions.



McGill University, 2022: Low doses of LSD promoted new dendritic spines in rodents and repaired cortical nerve branches that were damaged by chronic stress.

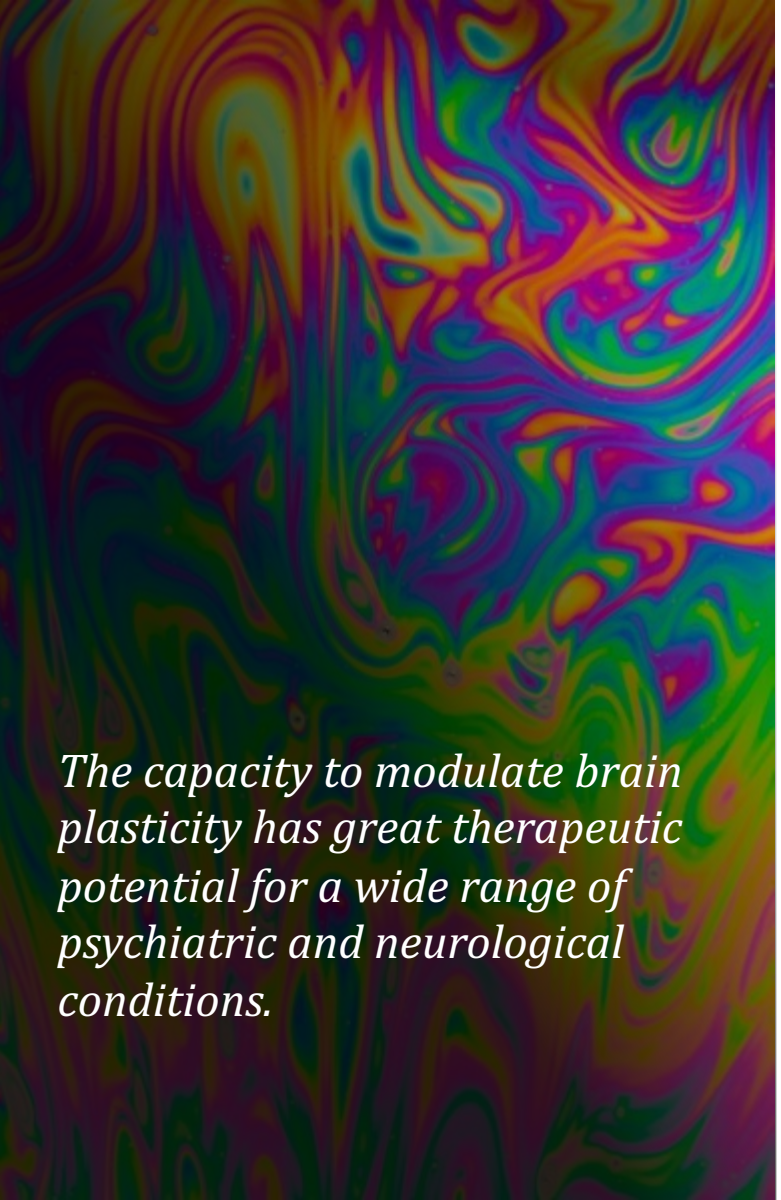
> Neuropsychopharmacology. 2022 May;47(6):1188-1198. doi: 10.1038/s41386-022-01301-9. Epub 2022 Mar 17.

Repeated lysergic acid diethylamide (LSD) reverses stress-induced anxiety-like behavior, cortical synaptogenesis deficits and serotonergic neurotransmission decline

Danilo De Gregorio [1 2], Antonio Inserra [# 1], Justine P Enns [# 1], Athanasios Markopoulos [1], Michael Pileggi [1], Youssef El Rahimy [1], Martha Lopez-Canul [1], Stefano Comai [1 3 2], Gabriella Gobbi [4]

Abstract

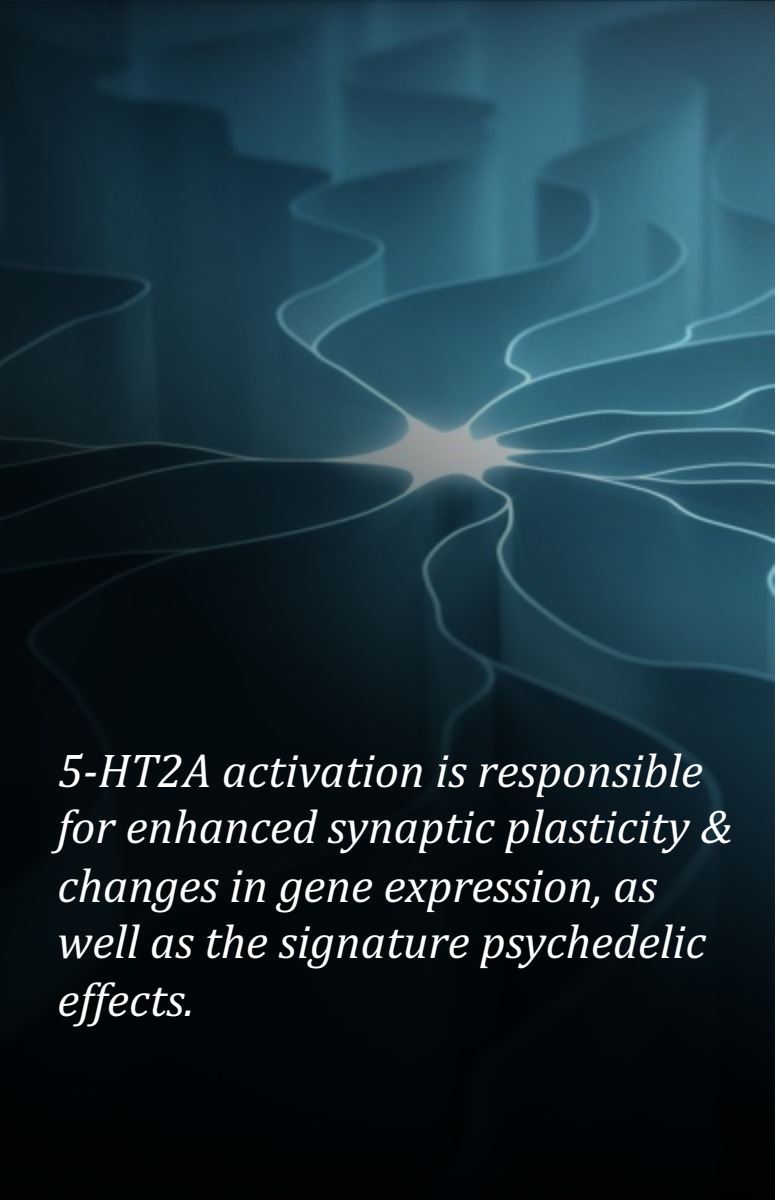
Lysergic acid diethylamide (LSD) is a serotonergic psychedelic compound receiving increasing interest due to putative anxiolytic and antidepressant properties. However, the potential neurobiological mechanisms mediating these effects remain elusive. Employing in vivo electrophysiology, microionthophoresis, behavioral paradigms and morphology assays, we assessed the impact of acute and chronic LSD administration on anxiety-like behavior, on the cortical dendritic spines and on the activity of serotonin (5-HT) neurons originating in the dorsal raphe nucleus (DRN) in male mice exposed to chronic restraint stress. We found that while the acute intraperitoneal (i.p.) administration of LSD (5, 15 and 30 and 60 µg/kg) did not produce any anxiolytic or antidepressant effects in non-stressed mice, the dose of 30 µg/kg (daily for 7 days) prevented the stress-induced anxiety-like behavior and the stress-induced decrease of cortical spine densitiy. Interestingly, while LSD acutely decreased the firing activity of 5-HT neurons, repeated LSD increased their basal firing rate and restored the low 5-HT firing induced by stress. This effect was accompanied by a decreased inhibitory response of 5-HT neurons to microiontophoretic applications of the 5-HT_{1A} agonist 8-OH-DPAT (8-hydroxy-N,N-dipropyl-2-aminotetralin). In conclusion, repeated LSD prevents the exacerbation of anxiety-like behavior following chronic stress exposure, but has no behavioral effects in non-stressed mice. These effects are paralleled by increased cortical spinogenesis and an enhancement of 5-HT neurotransmission which might be due to 5-HT_{1A} receptors desensitization. Increased cortical spine density and enhancement of serotonergic neurotransmission may thus represent a candidate mechanism which mediate the therapeutic effects of serotonergic psychedelics on stress-induced anxiety.



The capacity to modulate brain plasticity has great therapeutic potential for a wide range of psychiatric and neurological conditions.

PSYCHEDELICS ARE NEUROGENIC

- The positive impact of psychedelics on substance abuse and depression is contingent on psychedelic-induced neurogenesis and neural plasticity.
- Serotonergic psychedelics (LSD, psilocybin, mescaline) upregulate BDNF and stimulate enhanced neurogenesis & synaptic plasticity even more so than ketamine.
- Psychedelics promote changes in neural structure and dendritic growth across vertebrate and invertebrate species through an evolutionary conserved mechanism.

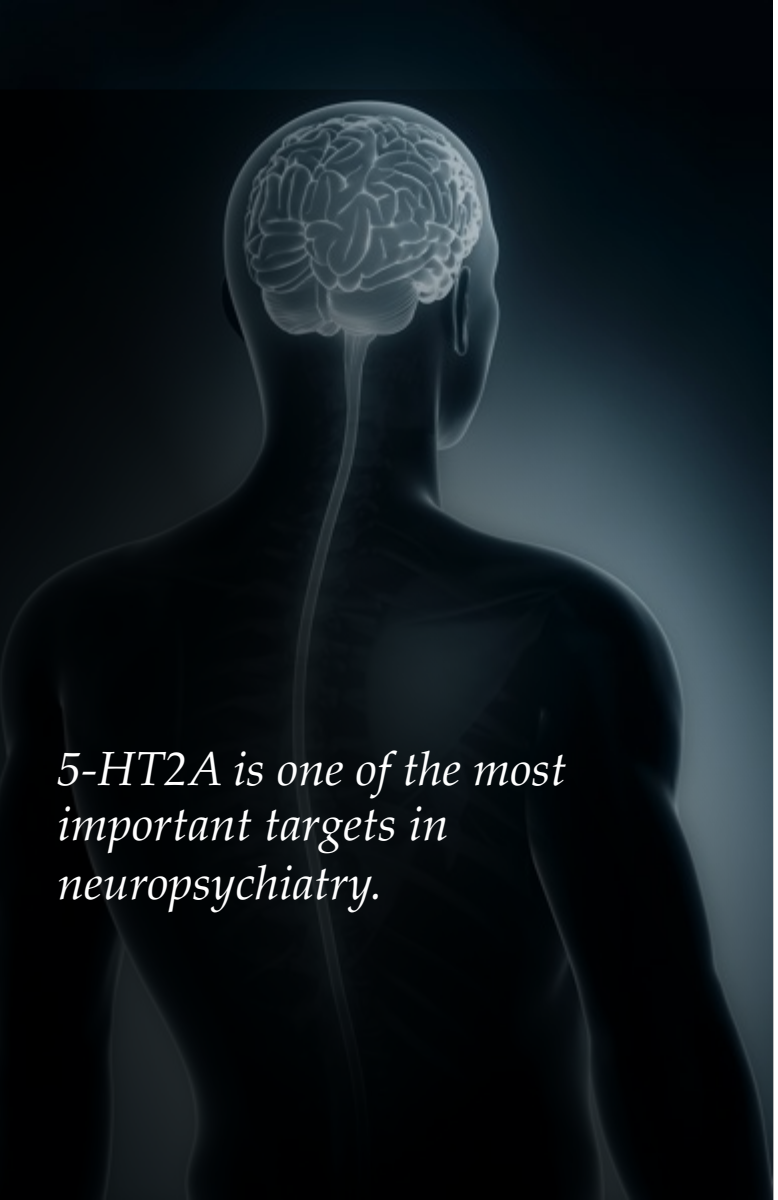


5-HT2A activation is responsible for enhanced synaptic plasticity & changes in gene expression, as well as the signature psychedelic effects.

5-HT2A: PSYCHEDELIC RECEPTOR

- 1998: Franz Vollenweider shows that LSD & psilocybin are potent 5-HT2A receptor agonists. Higher 5-HT2A binding affinity predicts more potent neurogenic & neuroplastic effects.[30]
- 5-HT2A mediates the hallucinogenic as well as the plasticity-inducing effects of psychedelics.
- 5-HT2A receptor antagonist blocks the hallucinogenic effects of LSD and the ability of psychedelics to promote neurogenesis & synaptic plasticity.
- Spanish study, 2018: aberrant 5-HT2A signaling linked to headaches, mood disorders & hallucinations. 5-HT2A receptors dysregulated in the PFC of schizophrenics. [31]

[30] Ly C et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/29898390
[31] Galindo L et al, 2018, https://www.ncbi.nlm.nih.gov/pubmed/29294249

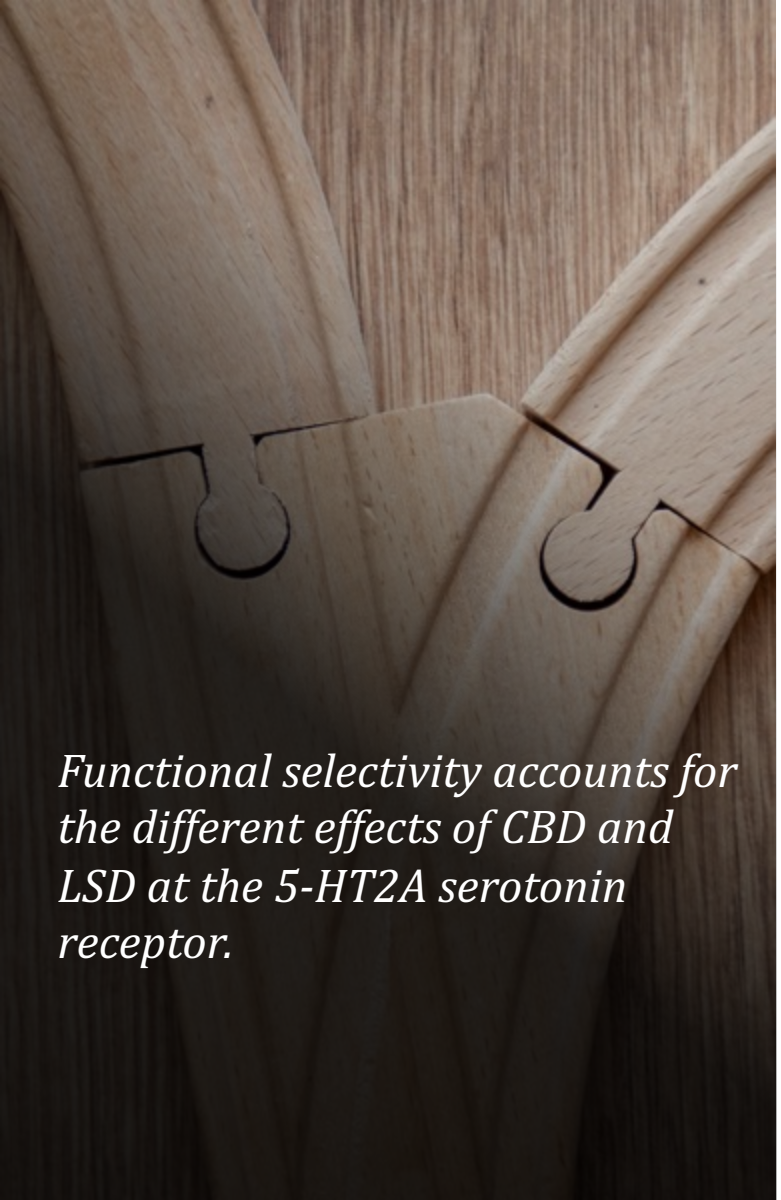


UBIQUITOUS 5-HT2A

- LSU study, 2018: 5-HT2A is the most widely expressed serotonin receptor in brain & body; in nearly every cell type; highest density in neocortex.[32]
- 5-HT2A activation upregulates genes that suppress inflammation.
- 5-HT2A & analgesia: “Spinal 5-HT2A receptor is involved in electroacupuncture inhibition of chronic pain.” (Chinese scientists, 2022) [33]
- CBD binds to several serotonin receptor subtypes, including 5-HT1A and 5-HT2A.

[32] Flanagan TW, Nichols CD, 2018, https://www.ncbi.nlm.nih.gov/pubmed/30102081

[33] Yuan, XC, et al. 2022, https://www.ncbi.nlm.nih.gov/pubmed/35240891



Functional selectivity accounts for the different effects of CBD and LSD at the 5-HT2A serotonin receptor.

FUNCTIONAL SELECTIVITY: LSD, CBD & 5-HT2A

- Russo et al, 2005: CBD active at 5-HT2A "but less so, relative to CBD at 5-HT1A."[33a]
- British scientists, 2015: CBD exhibits reasonable affinity at plausible concentration for 5-HT1A and 5-HT2A receptors.[34]
- LSU study, 2018: Functional selectivity (biased agonism): Different ligands (CBD & LSD) signaling through the same receptor (5-HT2A) can produce distinct physiological responses involving multiple transduction pathways that culminate in similar downstream effects: neurogenesis, neural plasticity.[35]

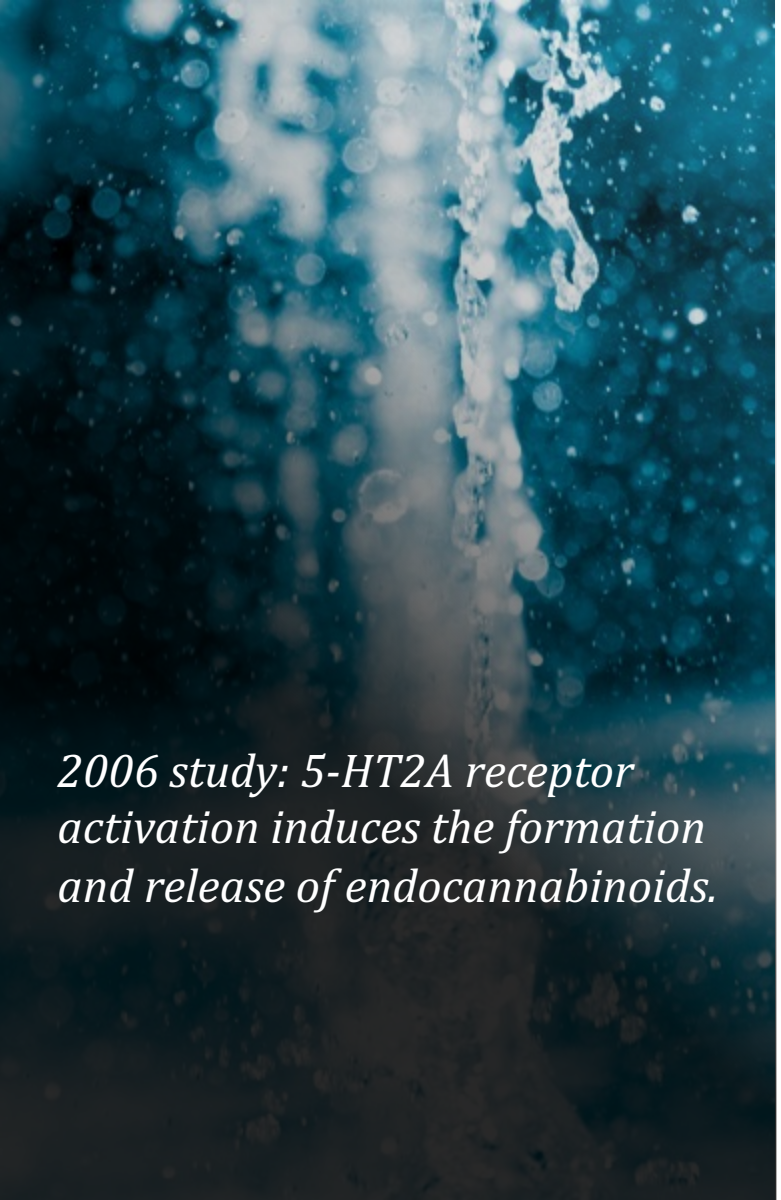
[33a] Russo EB et al, 2005, https://ncbi.nlm.nih.gov/pubmed/16258853
[34] Ibeas Bih C et al, 2015, https://www.ncbi.nlm.nih.gov/pubmed/26264914
[35] Flanagan TW, Nichols CD, 2018, https://www.ncbi.nlm.nih.gov/pubmed/30102081

Functional selectivity makes it possible to tease apart neurogenic signaling from the psychedelic experience.

X-RAY CRYSTALLOGRAPHY & DRUG DESIGN

- Chinese Academy of Sciences crystallography study (2022) reveals different 5-HT2A receptor docking sites.
- Chinese researchers have developed several psychedelic analogs that display antidepressant activity without hallucinogenic effects.
- These “pseudo-delic” compounds activate 5-HT2A’s plasticity-inducing docking site while bypassing or blocking the psychedelic docking site.
- How does 5-HT2A activation convey neurogenic and plasticity-inducing effects?

- Cao, D, Yu, J, Wang, H, et al (Chinese Academy of Sciences), “Structure-based discovery of non-hallucinogenic psychedelic analogs.” *Science*. 2022;375(6579):403-411.



2006 study: 5-HT2A receptor activation induces the formation and release of endocannabinoids.

J Neurochem. 2006 Nov;99(4):1164-75. Epub 2006 Sep 29.

Serotonin 5-HT(2A) receptor activation induces 2-arachidonoylglycerol release through a phospholipase c-dependent mechanism.

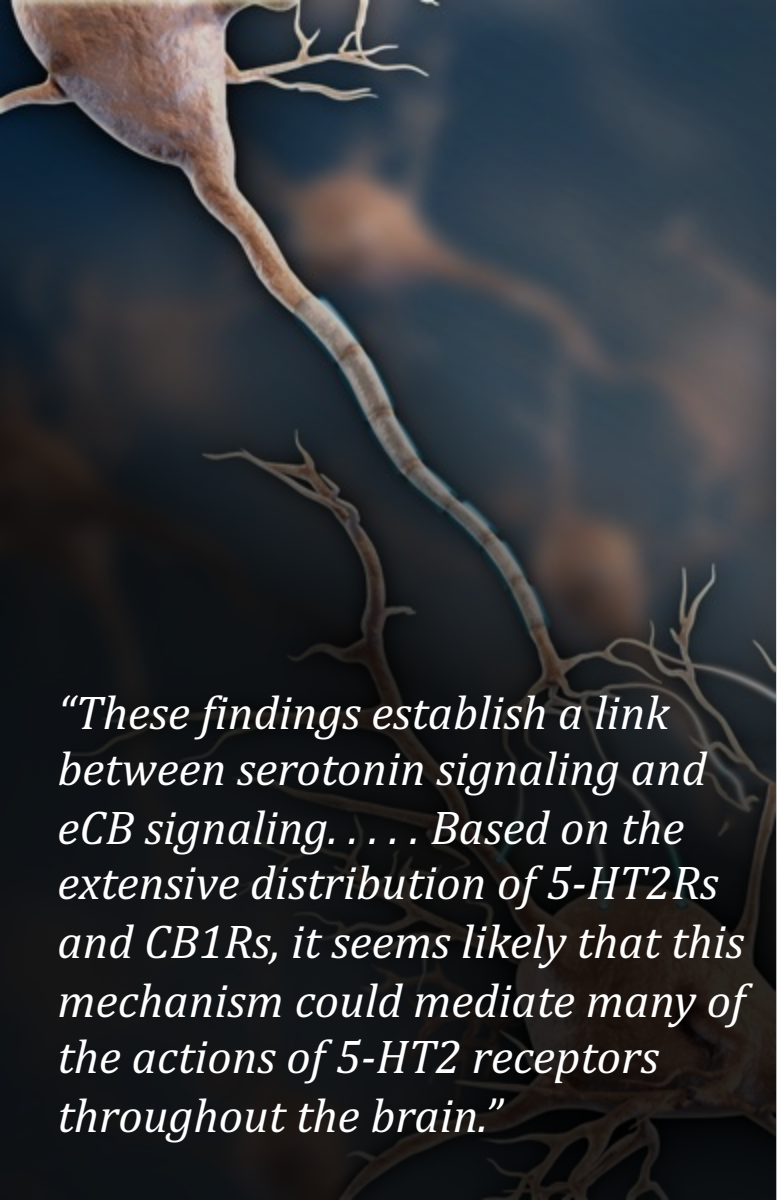
Parrish JC[1], Nichols DE.

Author information

1 Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, Indiana 4790, USA.

Abstract

To date, several studies have demonstrated that phospholipase C-coupled receptors stimulate the production of endocannabinoids, particularly 2-arachidonoylglycerol. There is now evidence that endocannabinoids are involved in phospholipase C-coupled serotonin 5-HT(2A) receptor-mediated behavioral effects in both rats and mice. The main objective of this study was to determine whether activation of the 5-HT(2A) receptor leads to the production and release of the endocannabinoid 2-arachidonoylglycerol. NIH3T3 cells stably expressing the rat 5-HT(2A) receptor were first incubated with [(3)H]-arachidonic acid for 24 h. Following stimulation with 10 mum serotonin, lipids were extracted from the assay medium, separated by thin layer chromatography, and analyzed by liquid scintillation counting. Our results indicate that 5-HT(2A) receptor activation stimulates the formation and release of 2-arachidonoylglycerol. The 5-HT(2A) receptor-dependent release of 2-arachidonoylglycerol was partially dependent on phosphatidylinositol-specific phospholipase C activation. Diacylglycerol produced downstream of 5-HT(2A) receptor-mediated phospholipase D or phosphatidylcholine-specific phospholipase C activation did not appear to contribute to 2-arachidonoylglycerol formation in NIH3T3-5HT(2A) cells. In conclusion, our results support a functional model where neuromodulatory neurotransmitters such as serotonin may act as regulators of endocannabinoid tone at excitatory synapses through the activation of phospholipase C-coupled G-protein coupled receptors.



“These findings establish a link between serotonin signaling and eCB signaling. . . . . Based on the extensive distribution of 5-HT2Rs and CB1Rs, it seems likely that this mechanism could mediate many of the actions of 5-HT2 receptors throughout the brain.”

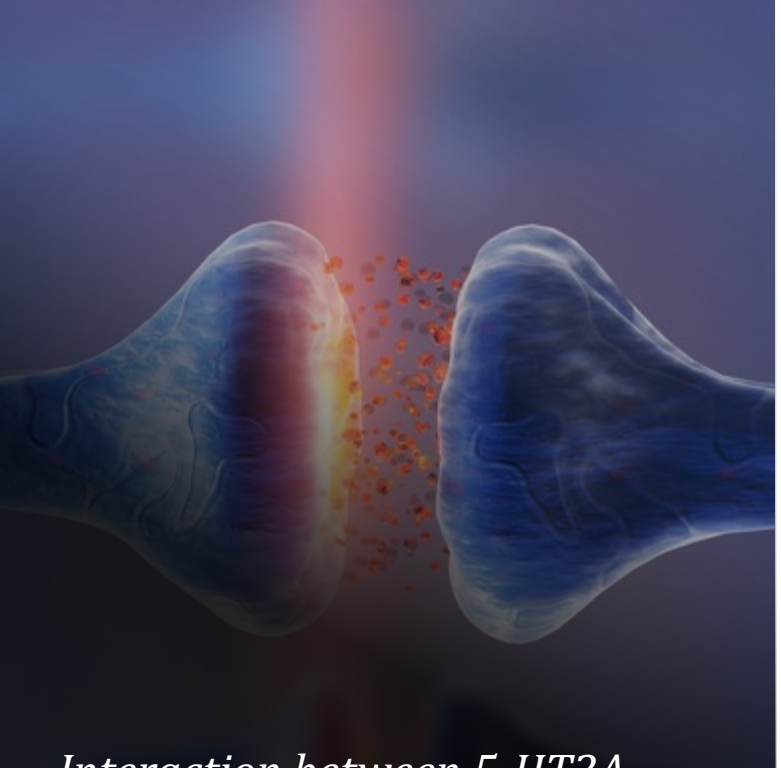
J Neurosci. 2008 Jun 18;28(25):6508-15. doi: 10.1523/JNEUROSCI.0678-08.2008.

Serotonin evokes endocannabinoid release and retrogradely suppresses excitatory synapses.

Best AR[1], Regehr WG.

Abstract

5-HT(2)-type serotonin receptors (5-HT(2)Rs) are widely expressed throughout the brain and mediate many of the modulatory effects of serotonin. It has been thought that postsynaptic 5-HT(2)Rs act primarily by depolarizing neurons and thereby increasing their excitability. However, it is also known that 5-HT(2)Rs are coupled to G(q/11)-type G-proteins and that some other types of G(q/11)-coupled receptors can regulate synapses by evoking endocannabinoid release and activating presynaptic cannabinoid-type 1 receptors (CB(1)Rs). Here, we examine whether activation of 5-HT(2)Rs can regulate synapses through such a mechanism by studying excitatory synapses onto cells in the inferior olive (IO). These cells express 5-HT(2)Rs on their soma and dendrites, and the IO receives extensive serotonergic input. We find that the excitatory synaptic inputs onto IO cells are strongly suppressed by serotonin receptor agonists as well as release of endogenous serotonin. Both 5-HT(2)Rs and 5-HT(1B)Rs contribute to this modulation by decreasing the probability of glutamate release from presynaptic boutons. The suppression by 5-HT(2)Rs is of particular interest because it is prevented by CB(1)R antagonists, and 5-HT(2)Rs are thought to be located only postsynaptically on IO cells. Our results indicate that serotonin activates 5-HT(2)Rs on IO neurons, thereby releasing endocannabinoids that act retrogradely to suppress glutamate release by activating presynaptic CB(1)Rs. These findings establish a link between serotonin signaling and endocannabinoid signaling. Based on the extensive distribution of 5-HT(2)Rs and CB(1)Rs, it seems likely that this mechanism could mediate many of the actions of 5-HT(2)Rs throughout the brain.

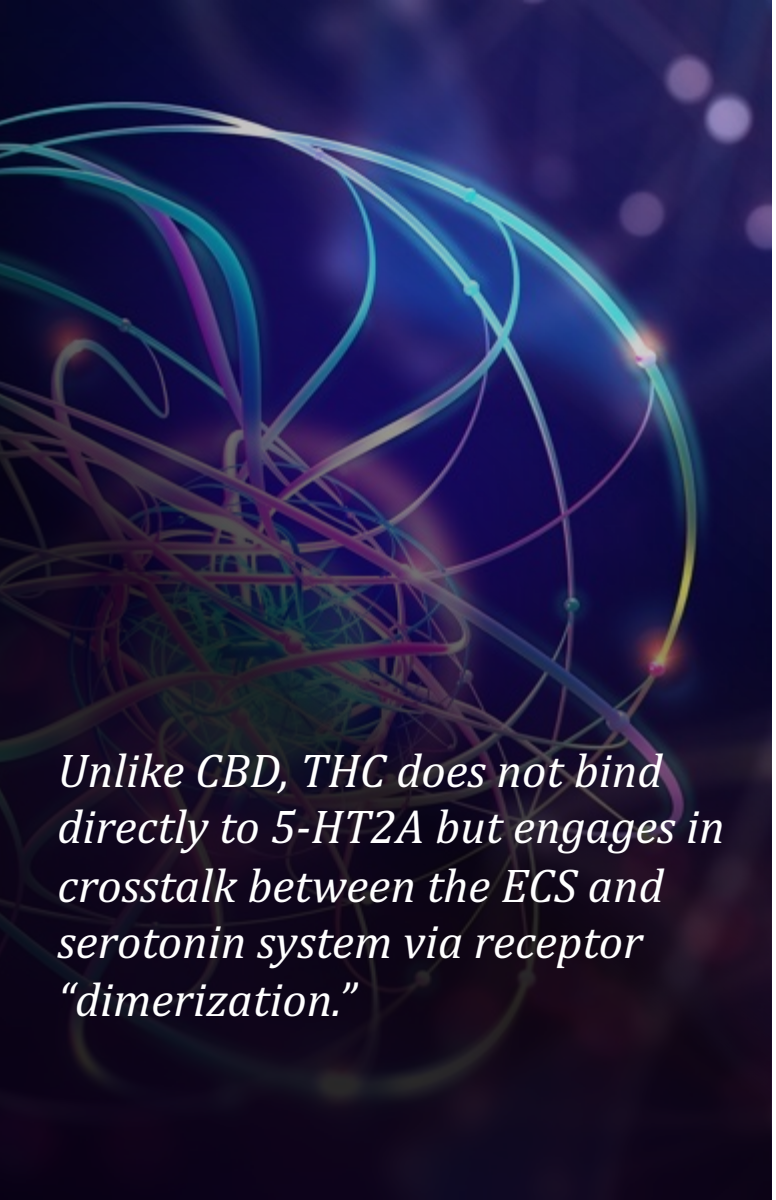


Interaction between 5-HT2A receptors and the endocannabinoid system is fundamental to the neurogenic & antidepressant effects of psychedelic drugs.

5-HT2A & 2AG

- Psychedelics activate the 5-HT2A serotonin receptor, which induces endocannabinoid (2AG) release.
- 2AG binds to CB1 & CB2 receptors, which promotes neuroprotection, neurogenesis, neuroplasticity, dendritic growth & new neural connections.
- Bidirectional regulation: cannabinoid receptor agonists also upregulate & enhance 5-HT2A receptor activity.[36]

[36] Franklin JM, Carrasco GA. 2013, https://www.ncbi.nlm.nih.gov/pubmed/23151877

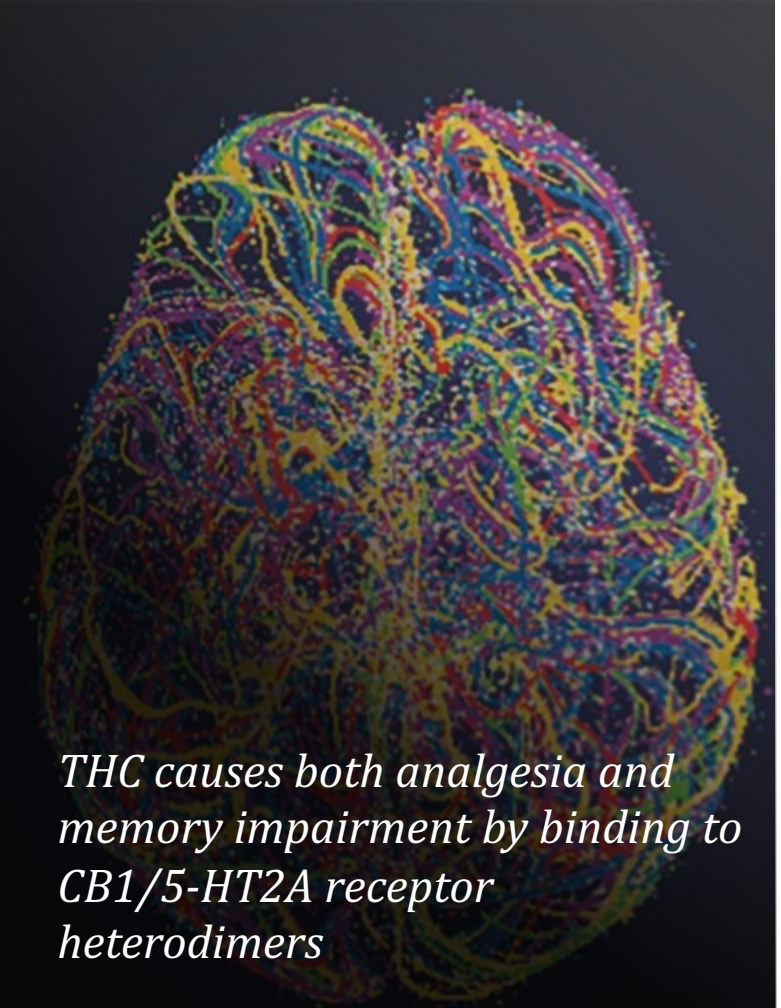


Unlike CBD, THC does not bind directly to 5-HT2A but engages in crosstalk between the ECS and serotonin system via receptor "dimerization."

CB1 & 5-HT2A RECEPTOR DIMERIZATION

- Cannabinoid & serotonin receptors entangle to form novel receptor complexes ("dimers") that can have unique signaling capabilities.
- CB1/5-HT2A conjugates may be implicated in the neurobiological underpinnings of hallucinations caused by high dose THC.
- Turkish study, 2010: CB1/5HT2A heterodimer complexes mediate the painkilling properties of THC, as well as THC's impact on short-term memory.[37]
- Spanish & British researchers, 2015: CB1/5-HT2A receptor heterodimers are "expressed and functionally active in specific brain areas involved in memory impairment."[38]

[37] Seyrek M et al, 2010, https://www.ncbi.nlm.nih.gov/pubmed/20868676
[38] Vinals X et al, 2015, https://www.ncbi.nlm.nih.gov/pubmed/26158621



THC causes both analgesia and memory impairment by binding to CB1/5-HT2A receptor heterodimers

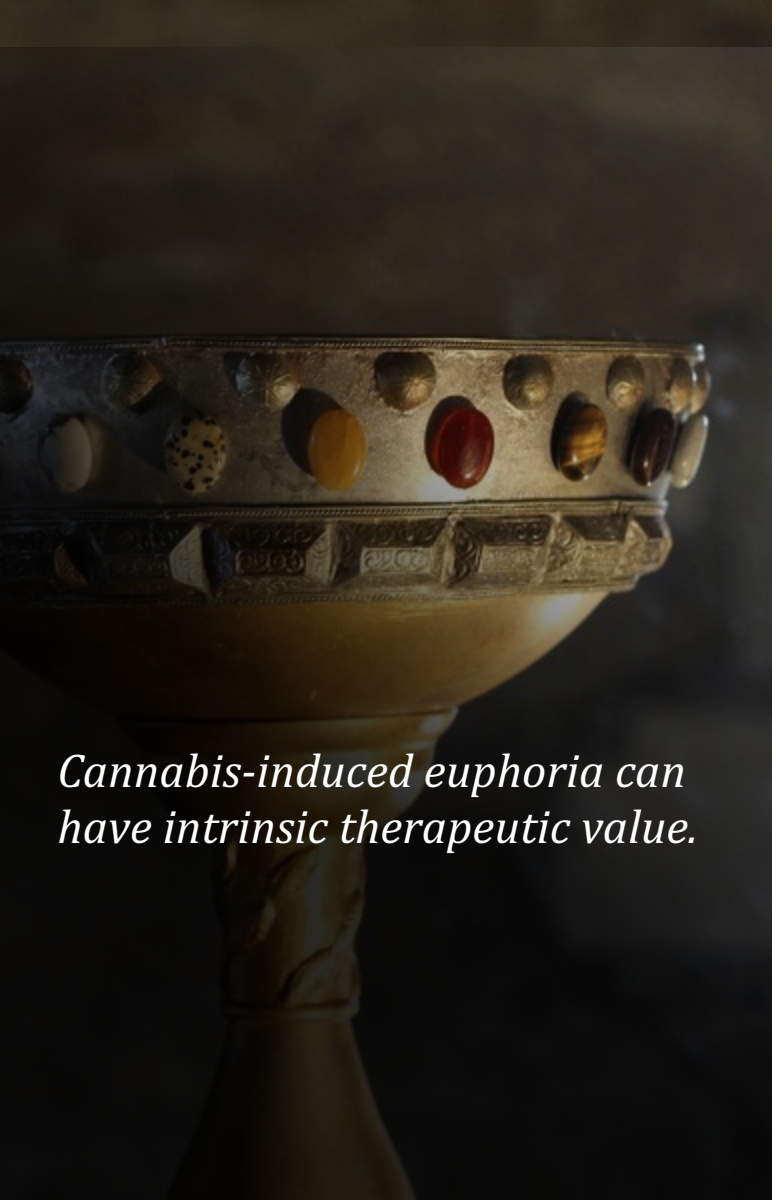
PLoS Biol. 2015 Jul 9;13(7):e1002194. doi: 10.1371/journal.pbio.1002194. eCollection 2015 Jul.

Cognitive Impairment Induced by Delta9-tetrahydrocannabinol Occurs through Heteromers between Cannabinoid CB1 and Serotonin 5-HT2A Receptors

Xavier Viñals [1], Estefanía Moreno [2], Laurence Lanfumey [3], Arnau Cordomí [4], Antoni Pastor [5], Rafael de La Torre [5], Paola Gasperini [6], Gemma Navarro [2], Lesley A Howell [7], Leonardo Pardo [4], Carmen Lluís [2], Enric I Canela [2], Peter J McCormick [6], Rafael Maldonado [1], Patricia Robledo [8]

Abstract

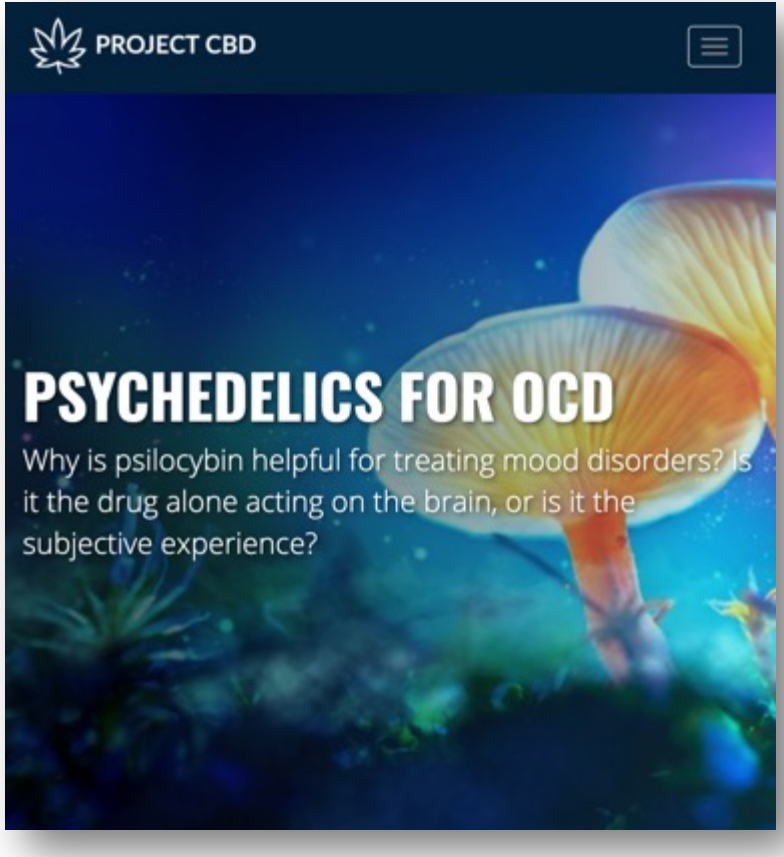
Activation of cannabinoid CB1 receptors (CB1R) by delta9-tetrahydrocannabinol (THC) produces a variety of negative effects with major consequences in cannabis users that constitute important drawbacks for the use of cannabinoids as therapeutic agents. For this reason, there is a tremendous medical interest in harnessing the beneficial effects of THC. Behavioral studies carried out in mice lacking 5-HT2A receptors (5-HT2AR) revealed a remarkable 5-HT2AR-dependent dissociation in the beneficial antinociceptive effects of THC and its detrimental amnesic properties. We found that specific effects of THC such as memory deficits, anxiolytic-like effects, and social interaction are under the control of 5-HT2AR, but its acute hypolocomotor, hypothermic, anxiogenic, and antinociceptive effects are not. In biochemical studies, we show that CB1R and 5-HT2AR form heteromers that are expressed and functionally active in specific brain regions involved in memory impairment. Remarkably, our functional data shows that costimulation of both receptors by agonists reduces cell signaling, antagonist binding to one receptor blocks signaling of the interacting receptor, and heteromer formation leads to a switch in G-protein coupling for 5-HT2AR from Gq to Gi proteins. Synthetic peptides with the sequence of transmembrane helices 5 and 6 of CB1R, fused to a cell-penetrating peptide, were able to disrupt receptor heteromerization in vivo, leading to a selective abrogation of memory impairments caused by exposure to THC. These data reveal a novel molecular mechanism for the functional interaction between CB1R and 5-HT2AR mediating cognitive impairment. CB1R-5-HT2AR heteromers are thus good targets to dissociate the cognitive deficits induced by THC from its beneficial antinociceptive properties.



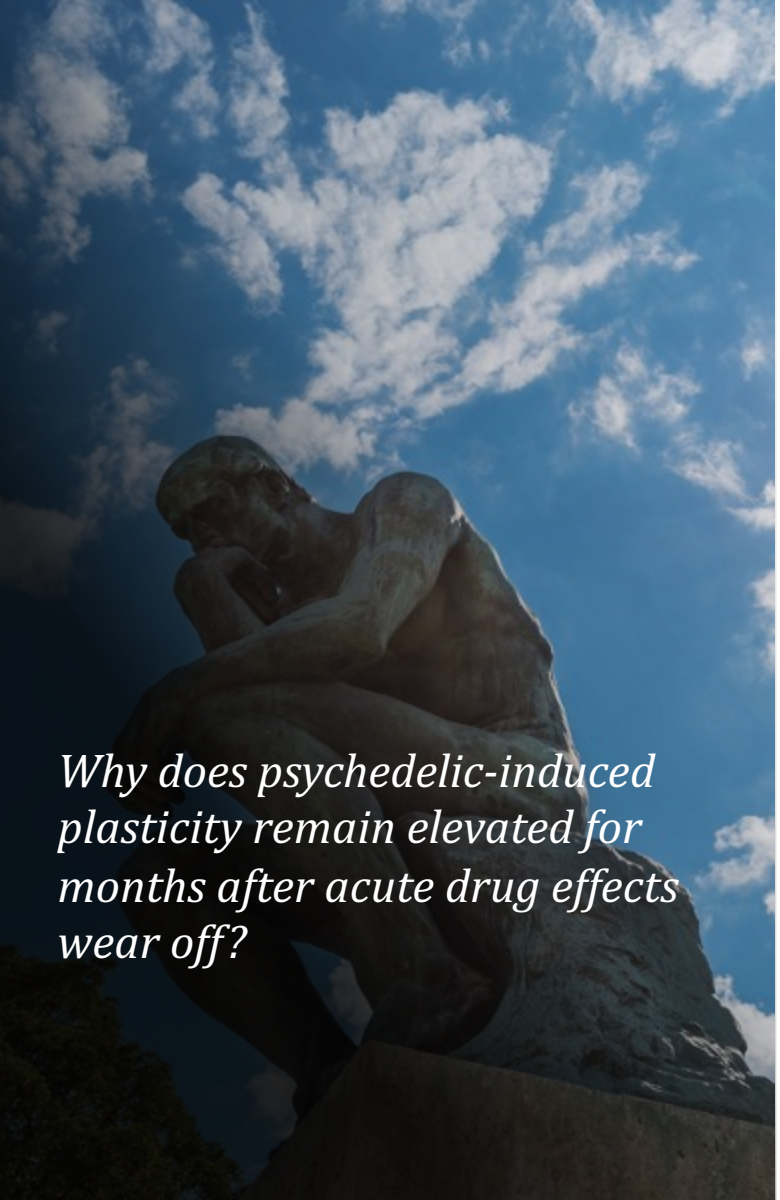
THE HOLY GRAIL

- Researchers are optimizing peptides that modulate 5-HT2A/CB1 receptor signaling in order to amplify THC's painkilling attributes without adversely affecting memory or cognitive function.
- Analgesia without intoxication.
- Ameliorating pain without side effects is the pharmaceutical Holy Grail.
- But is cannabis-induced euphoria always a negative side effect?

HEALING WITHOUT THE TRIP?



- Does tripping have intrinsic therapeutic value, or is it just a colorful distraction? Are hallucinogenic effects necessary for treating depression and other conditions?
- Psilocybin for obsessive-compulsive disorder.
- Is it the drug alone, acting physiologically on the brain, or is it the lived, subjective response engendered by the drug that makes psychedelics so useful for treating mental health disorders?
- With drug company startups keen on developing trip-free knock-offs, this question has major implications for fledgling efforts to medicalize & commercialize psychedelic drugs.



BEYOND CHANGING YOUR BRAIN

- Will a non-hallucinogenic “psychoplastogen” (plasticity-inducing) compound have the same therapeutic efficacy as psilocybin or LSD or ayahuasca? Don’t bet on it.

- A psychedelic experience can precipitate enduring antidepressant effects that may not be accessible without the trip.

- In some cases, tripping is conducive to deep insight that alters mental constructs and how we view the world. When combined with therapy, psychedelics can trigger a state of heightened neuroplasticity that creates a unique window of opportunity for self-realization and healing.

- Psychedelics appear to de-habituate & reset brain circuits, enabling long-term, positive change. But tripping doesn’t just occur in the brain. The dazzling immediacy & experiential density of a psychedelic trip can’t be reduced just to changes in brain activity patterns.

FOR MORE INFORMATION: PROJECTCBD.ORG