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Psychedelics

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COMMENTARY

Peripheral signals, central questions: Examining the relationship between psychedelics and brain-derived neurotrophic factor (BDNF)

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What are the mechanisms through which psychedelics may exert therapeutic effects in psychiatric disorders? There are two approaches to answering this question: first is the identification of novel pathways. Additionally, it would be of interest to determine the effects of psychedelics on mechanisms that already appear to underlie the neurobiology and therapeutics of psychiatric disorders. This commentary highlights a recent article by Shafiee et al. (1) that reported a meta-analysis of the effect of psychedelics on the peripheral levels of brain-derived neurotrophic factor (BDNF).

Certain breakthroughs have succeeded in sparking seismic shifts in our understanding and approach to therapy. From the discovery of antibiotics to the advent of anesthesia, each milestone has reshaped the boundaries of medicine and what we are capable of. The resurgence of psychedelics in treating and preventing psychiatric disorders may represent another such transformative moment.

Although the counterculture movements of the 1960s created a shadow of stigma and prohibition around psychedelics that has lasted for decades, research in recent years has revealed their true therapeutic potential, changing public opinion on these substances. Indeed, if the first antibiotic came from a fungus (genus *Penicillium*), why cannot other medicines also come from fungi?

Psilocybin, found primarily in the mushroom genus *Psilocybe*, is just one of the many psychedelic drugs being researched today. Others include lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), 3,4-methylenedioxymethamphetamine (MDMA), mescaline, and ayahuasca. All these substances have been shown to alter consciousness by interacting with serotonin receptors in the brain. Nevertheless, the molecular mechanisms underlying their therapeutic efficacy remain to be fully understood. Since alterations in brain-derived neurotrophic factor have been observed in various neuropsychiatric disorders as well as in antidepressant treatment, the relationship between psychedelics and BDNF has become a promising topic of research.

BDNF is the most abundant protein within the nerve growth factor (NGF) family, which encompasses NGF itself, along with neurotrophin-3 and neurotrophin-4 (2). Initially recognized for their indispensable roles in regulating the proliferation, movement, development, and survival of cells, neurotrophins continue to be expressed in the mature brain, playing a crucial part in maintaining synaptic flexibility and the overall functionality and longevity of neurons (3).

Depression is associated with structural changes in the brain, including neuron shrinkage and reduced connectivity in critical areas like the hippocampus. This disruption is a crucial factor in depressive symptoms, and antidepressant treatments can counteract these effects. BDNF, a peptide vital for maintaining and forming synaptic connections, is central to this recovery process. Studies indicate that stress and depression can lower BDNF levels in the brain, exacerbating the condition. However, antidepressant treatments, especially rapid-acting ones like ketamine, can quickly elevate BDNF levels, facilitating rapid improvements in mood and cognitive function. This contrasts with traditional antidepressants, which gradually increase BDNF over weeks or months. The significance of BDNF in the brain's response to antidepressants underscores its potentially pivotal role in depression. By boosting BDNF, treatments can reverse the detrimental effects of stress and depression on the brain, offering a path to recovery. Additionally, the interplay between BDNF and other growth factors, like VEGF, highlights the complex but hopeful landscape of depression treatment, where understanding and enhancing BDNF's role could be key to more effective therapies (4).

In February 2024, an article titled "The effect of psychedelics on the level of brain-derived neurotrophic factor: A systematic review and meta-analysis" was published in the *Journal of Psychopharmacology* by Shafiee and colleagues (1). This team of researchers was able to meticulously synthesize all the current information on the relationship between psychedelics and BDNF.

To examine the relationship between psychedelics and BDNF, Shafiee et al. used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This involved performing a systematic search in international databases (Embase, Scopus, Web of Science, and PubMed) to identify every published paper and peer-reviewed randomized clinical trial that evaluated the correlation between psychedelic consumption and BDNF levels. After screening the results and performing a quality assessment of the data using the Cochrane Risk of Bias 2 tool, they were ultimately left with 37 full texts and nine studies. The case and non-case groups were compared using a standardized mean difference (SMD) and 95% confidence interval. A fixed effect model was used in case of low heterogeneity (I^2 value below 25%). Otherwise, a random effect meta-analysis was used.

The meta-analysis, the first of its kind, revealed that the levels of peripheral BDNF in psychedelic users were significantly higher than in non-exposed controls. However, it is essential to note that only DMT was associated with a statistically significant increase in peripheral BDNF levels. There were no significant alterations in peripheral BDNF with the other psychedelic subgroups, such as LSD, psilocybin, and others; also, most of these studies (seven out of nine) reported levels of BDNF in the plasma, while only two studies reported levels of BDNF in the serum.

Peripheral BDNF is 99% stored in platelets, with only a tiny amount of free BDNF in the plasma (5). As a result, serum BDNF levels may be affected by BDNF release from platelets. Serum BDNF also shows greater stability than plasma BDNF, so storage time and temperature conditions after blood sampling must also be considered (6, 7). Indeed, Tsuchimine et al. found no correlation between serum and plasma BDNF, suggesting that they may be independent measures of relevance (6). In addition, sex steroids and menstrual periods have the potential to influence the function and expression of BDNF (8–10). Consequently, levels of BDNF in men and women should be reported separately.

None of the studies in the meta-analysis measured BDNF levels directly in the central nervous system (CNS), representing a challenge in clinical studies. Consequently, the measurement of BDNF in the

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periphery is often used as a proxy. Klein and colleagues examined blood, serum, plasma, and brain-tissue BDNF levels in three mammalian species: rat, pig, and mouse (11). Their data support the view that measures of blood and plasma BDNF levels reflect brain-tissue BDNF levels. Additionally, Pillai et al. demonstrated that there are parallel changes in BDNF levels of both the plasma and cerebrospinal fluid (CSF) in patients who had psychosis (12). This indicates that plasma BDNF levels may reflect brain changes in BDNF. Furthermore, it has been demonstrated that BDNF can cross the blood-brain barrier, further establishing blood and plasma as a proxy for CNS BDNF levels (5).

Though decreased in patients with depression, levels of BDNF are increased in patients with post-traumatic stress disorder. This suggests a compensatory role for BDNF in stress response (13). Moreover, the role of BDNF in neuropsychiatric illnesses is more complex than we thought. This requires further investigation to confirm BDNF's potential role in elucidating the enigmatic neurobiological mechanisms with which psychedelics exert their effects. Another critical piece item to be considered is the fact that BDNF appears to be a vital mediator of the therapeutic response to antidepressants (14, 15). Would BDNF, therefore, be a potential mediator of the antidepressant effects of psychedelics?

To sum it up, this carefully conducted meta-analysis revealed that the levels of peripheral BDNF (mainly sampled from the plasma) were significantly increased in patients who received DMT. Due to the limited number of studies in the other subgroups of psychedelics and factors related to BDNF variability, including serum vs plasma and male vs female, definitive conclusions cannot be drawn yet.

Understanding the neuroprotective mechanisms of psychedelics could have implications for not only psychiatric disorders but also the treatment of neurodegenerative diseases and age-related cognitive decline. Researchers may be able to design more targeted and effective treatments with fewer side effects. Future studies should also observe BDNF levels longitudinally to see how long the effects of psychedelics remain. BDNF levels should also be compared with notes from psychotherapy sessions when available. A standardized classification for psychedelic experiences could assist in confirming the definitive clinical efficacy and safety of psychedelics. This is particularly relevant as various countries begin to approve these substances for the treatment of various psychiatric disorders. As an example, Australia's Therapeutic Goods Administration (TGA) now allows the drugs psilocybin and MDMA to be prescribed by doctors to treat psychiatric conditions, including depression and post-traumatic stress disorder (16).

The revival of psychedelics in psychiatry, the so-called psychedelic renaissance, has come to reflect a broader shift in medicine that is moving away from a reductionist model of treating symptoms and towards a more holistic approach that addresses the root cause of illness. Further research is needed to test the exciting hypothesis that by catalyzing transformative experiences that transcend the confines of ego and identity, psychedelics may offer a unique opportunity to access the deeper layers of the psyche and facilitate healing and the prevention of further distress.

Vivek Seelamneni[1]
[1] *Università Vita-Salute San Raffaele, 20132 Milano MI, Italy*
✉ *e-mail: vivek.seelamneni@gmail.com*

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