Letter

Low Doses of LSD Acutely Increase BDNF Blood Plasma Levels in Healthy Volunteers

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ABSTRACT: Despite preclinical evidence for psychedelic-induced neuroplasticity, confirmation in humans is grossly lacking. Given the increased interest in using low doses of psychedelics for psychiatric indications and the importance of neuroplasticity in the therapeutic response, this placebo-controlled within-subject study investigated the effect of single low doses of LSD (5, 10, and 20 μg) on circulating BDNF levels in healthy volunteers. Blood samples were collected every 2 h over 6 h, and BDNF levels were determined afterward in blood plasma using ELISA. The findings demonstrated an increase in BDNF blood plasma levels at 4 h (5 μg) and 6 h (5 and 20 μg) compared to that for the placebo. The finding that LSD acutely increases BDNF levels warrants studies in patient populations.

KEYWORDS: psychedelics, LSD, neuroplasticity, BDNF, microdosing, placebo-controlled clinical trial
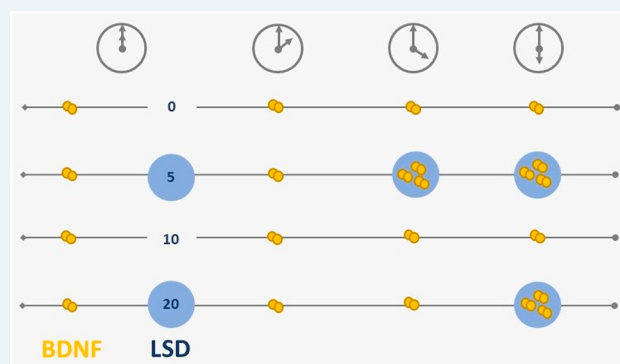
Preclinical research has demonstrated that psychedelic substances, including 2,5-dimethoxy-4-iodoamphetamine (DOI), lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), and psilocybin, as well as alkaloids present in ayahuasca (harmine, tetrahydroharmine, and harmaline) affect neuroplasticity after acute and chronic administration.[1−5] Catlow and colleagues, for example, demonstrated the increased formation of neurons (neurogenesis) in mice' dentate gyrus after an average psilocybin dose of 3.5 μg/35 g bodyweight (intraperitoneal (i.p.)), while this was slightly decreased after a dose of 35 μg/35 g (psilocybin/bodyweight).[6] Interestingly, when repeatedly given i.p. psilocybin four times interspersed with 1 week, a higher dose of 52 μg/35 g (psilocybin/bodyweight) increased neuroplasticity.[2] Chronic administration in rats of twice the ritualistic dose of ayahuasca (150 mL/70 kg bodyweight containing 0.26 mg/kg DMT) for 28 days resulted in increased in brain-derived neurotrophic factor (BDNF) levels in the hippocampus of the female rats, compared to that in control animals.[7]

A recent in vitro study in cultured cortical neurons of animals showed increased formation of new neurites, as expressed by the number of dendritic branches, the total length of the arbors, and formation of synapses, after extended (24 h) treatment with a range of psychedelics like DOI, LSD, and DMT.[1] While these effects were similar across psychedelic classes and the dissociative ketamine, LSD was the most

potent, as shown via neuritogenesis assay.[1] Also in cultured human cortical neurons, the neuro-regenerative effects of DMT[8] and modulation of proteins involved in dendritic spine formation by 5-MeO-DMT have been shown.[9]

In light of the increased scientific interest in using low psychedelic doses,[10] also known as "microdosing",[11] critical preclinical work with DMT has also shown that neuroplastic changes even take place after administration of low DMT doses that are considered to be subhallucinogenic.[1] Examples are morphological changes in the prefrontal cortex of adult rats and functional changes ex vivo.[1] The practice of microdosing entails repeatedly taking low doses, which are usually one-tenth of a recreational dose that causes a psychedelic experience. For LSD, that would, for example, be between 10 and 20 μg.[12]

User claims suggest the effectivity of self-medication with low doses of psychedelics in the treatment of disorders related to neuroplasticity, including depression.[10] Interestingly, depression has been linked with impairments in neuro-

plasticity, and pharmacologically induced symptom improvement is linked with increases in BDNF levels.[13,14] BDNF is highly expressed in limbic brain regions, which are involved in emotional processes, memory, and mood. Notably, Bershad et al. recently demonstrated connectivity changes in the limbic areas after a low dose of LSD (13 μg, tartrate).[15] These biological changes correlated positively with the enhanced mood in healthy volunteers.[15]

Together, these findings add scientific evidence to the idea that LSD in low doses could have therapeutic potential in mood-related disorders.[10] Given the interest in BDNF as a key player in several neurodegenerative and neuropsychiatric disorders[13,16,17] and preclinical data showing psychedelics-induced neuroplasticity even at low doses of psychedelics,[1] the present double-blind, placebo-controlled, within-subject (WS) study aimed to investigate whether LSD base in low doses (0, 5, 10, and 20 μg) affects BDNF plasma levels in healthy volunteers. Blood samples were collected every 2 h over 6 h, and BDNF levels were determined afterward in blood plasma using ELISA.[18] Previously, it has been demonstrated that blood plasma BDNF concentrations reflect mammalian brain-tissue BDNF levels.[19]

RESULTS

Difficulties with the peripheral venous catheter during blood sample collection resulted in missing data. For one participant, no blood samples were collected; for the remaining 23 participants, the percentage of samples over all time points ranged from 6 to 100%. Only five (21.7%) of the participants had a complete data set; therefore, we opted to run the analyses per dose for complete cases (placebo−LSD dose) to be able to perform statistical analyses. In Table 1, the

Table 1. Participant Age and Sex per Complete Within-Placebo-LSD Dose Case

LSD dose (μg)	participants (number)	mean age (SD)	sex (male/female)
5	10	21.5 (3.06)	4:6
10	9	22.89 (2.80)	5:4
20	8	23.75 (2.66)	6:2

demographic details of participants included in the statistical analyses are presented. Four trapezoidal areas under the curves (AUC) for BDNF were calculated for the three LSD doses and placebo; the same procedure was used for LSD concentrations.

Wilcoxon signed-rank (S-R) tests revealed a statistically significant difference between AUC BDNF levels following 5 ug of LSD ($Z = -2.60$, $p = 0.009$, $r = 0.58$, 95% CI [0.11;1.06]) and 20 μg of LSD ($Z = -2.52$, $p = 0.01$, $r = 0.63$, 95% CI [0.09;1.17]) compared to placebo; the difference between AUC BDNF levels after 10 μg of LSD and placebo was not significant ($Z = -1.01$, $p = 0.31$) (Figure 1A). AUC LSD plasma levels for the selection of complete WS cases per dose are shown in Figure 1B for illustrative purposes to show that LSD plasma levels increased with increasing LSD doses.

Wilcoxon S-R tests revealed higher BDNF levels at +4 h after administration of 5 μg of LSD ($Z = -2.80$, $p < 0.01$, $r = 0.63$, 95% CI [0.15; 1.11]) and 10 μg LSD ($Z = -1.95$, $p = 0.05$, $r = 0.46$, 95% CI [−0.04; 0.97]) compared to placebo. Although analysis including the 10 μg dose revealed a statistically significant p value (0.05), the CI included zero, indicating nonsignificance. Tests at +6 h after LSD administration revealed significant effects of 5 μg of LSD ($Z = -2.29$, $p = 0.02$, $r = 0.51$, 95% CI [0.03; 0.99]) and 20 μg of LSD ($Z = -2.52$, $p = 0.01$, $r = 0.63$, 95% CI [0.09; 1.17]) on BDNF levels compared to placebo (Figure 2A−C). Corresponding LSD plasma levels are presented in Figure 2D,E.

Friedman tests investigating BDNF changes in the function of time demonstrated that BDNF plasma levels remained stable in the placebo conditions throughout the test frame. BDNF plasma levels under the LSD conditions showed their highest levels at 4 h after administration of 5 μg of LSD (8.95 ng/mL), and at 6 h after administration of 10 μg of LSD (8.28 ng/mL) and 20 μg of LSD (11 49 ng/mL) (Table 2).

DISCUSSION

This study provides preliminary evidence that low doses of LSD increase BDNF plasma levels in healthy volunteers up to 6 h after administration, suggesting a window of opportunity for a therapeutic response[20,21] and cognitive enhancement[22,23] that might be of use in patient populations. This line of thinking is supported by recent findings with ketamine and ayahuasca (containing the psychedelic DMT) demonstrating increased serum BDNF levels 24 and 48 h after a single (high) dose, respectively, compared to placebo, which was related to fast antidepressant actions.[21,24,25]

Of interest is the different time-course of BDNF levels for the 5 μ and 20 μg doses. While BDNF levels peaked at 4 h for the 5 μg dose, these levels significantly increased 2 h later for the 20 μg dose. Recently, Zhang et al. showed that a

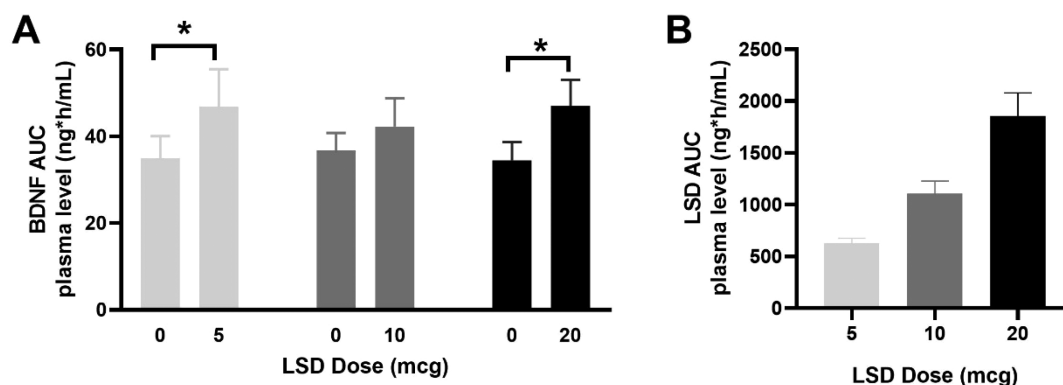**Figure 1.** Total mean AUC (SEM) of BDNF (A) and of LSD (B) plasma levels for complete WS LSD dose-placebo cases. N(5 μg LSD) = 10; N(10 μg LSD) = 9; N(20 μg LSD) = 8. *, statistical significance at $p \leq 0.05$.
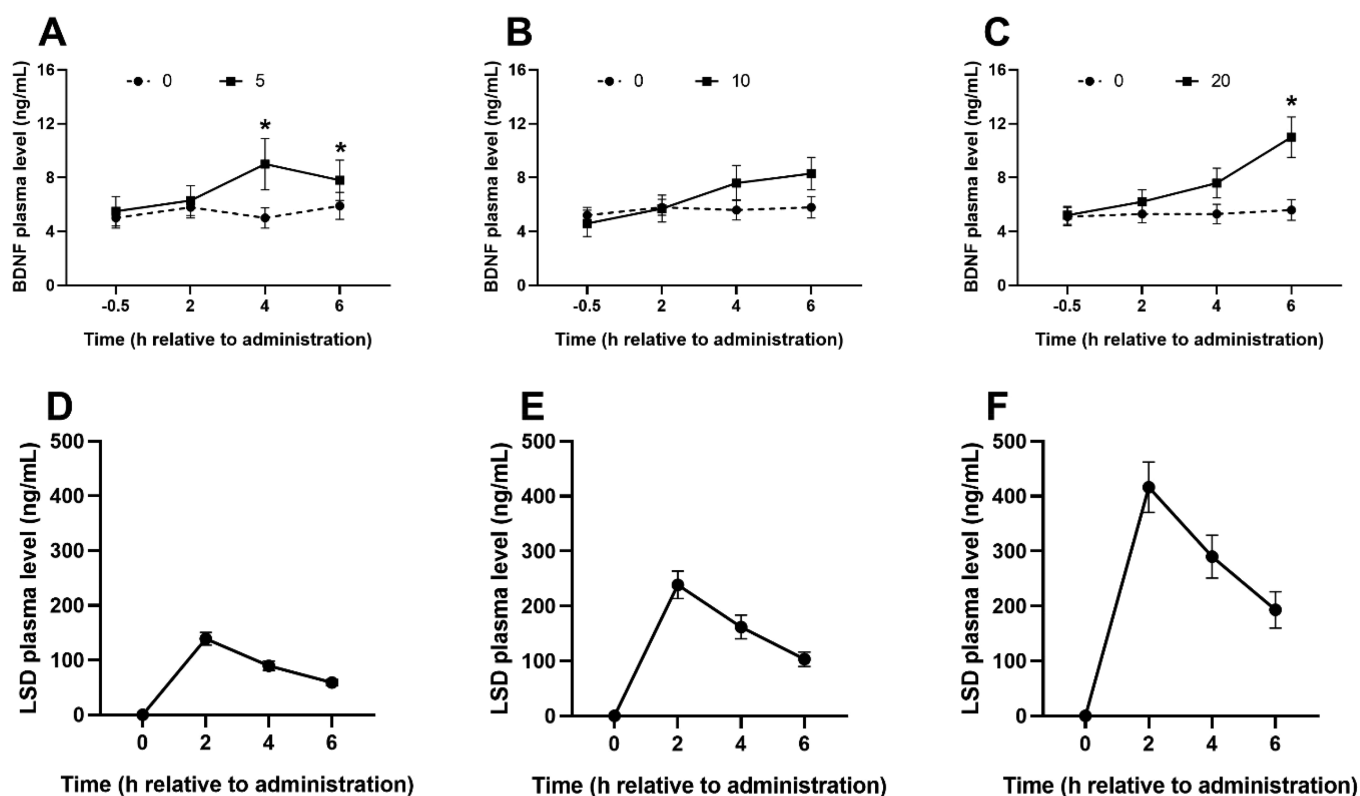
Figure 2. Mean (SEM) BDNF plasma levels for each LSD dose with the corresponding WS placebo condition per time of testing (A−C) and corresponding mean (SEM) LSD plasma levels (D−F). *, statistical significance at $p \leq 0.05$ in A−C; no statistical tests were performed over data in D−F.

Table 2. Friedman Test of Time on BDNF Plasma Levels in the LSD Conditions and Dunn's Pairwise Comparisons

LSD dose (μg)	participants number	Friedman test main time effect			Dunn's pairwise comparisons $(Z(1))^a$				
		$(x^2(3))$	p	effect size Cramer's V	0 h–2 h	0 h–4 h	0 h–6h	2 h–4 h	4 h–6 h
5	10	15.72	<0.01	0.51	1.21	3.64*	2.77*	2.42*	0.87
10	9	13.00	<0.01	0.49	1.09	2.56*	3.29*	1.46	0.73
20	8	19.05	<0.01	0.63	0.77	2.13	4.07*	1.36	1.94

^{a}*, statistical significance at a sequential Bonferroni corrected p value < 0.05.

subanesthetic dose of IV ketamine (10 mg/kg/2h) increased BDNF in the amygdala at 2 h after administration, while 40 mg/kg/2 h did not affect BDNF levels, instead elevating levels of other proteins involved in plasticity (cFos, pERK) in the mPFC and hippocampus.[26] Earlier, they showed that IV ketamine (20 mg/kg/2h) induced a *decrease* in BDNF *plasma* in rats at 2 h after ketamine administration, while 5 mg/kg/2h did not affect the levels.[27] Their findings emphasize that BDNF levels undergo time-dependent changes following ketamine administration that can be influenced by the dose and timing of assay,[26] something that might also explain the absence of effects in our study after dosing with 10 μg of LSD. Looking at the BDNF levels under the 20 μg dose condition suggests that the peak had yet to come. While the multiple assessment points in the present study were a strength, future studies might want to include extra assessment points beyond the 6 h postdrug period, even assessing the next day to understand the time-course of the effect.

While microdosing implies taking repeated doses of a psychedelic for a prolonged time, the present study only assessed the acute effects of a single administration on BDNF levels. Future studies will have to assess the effects of repeated

dosing on neuroplasticity to understand whether or not this practice is beneficial to neuroplasticity. Previous studies investigating the repeated administration of ketamine and classical psychedelics have provided mixed results. Preclinical studies, and studies in ketamine abusers, for example, have shown that long term administration *decreases* the BDNF production in animals and humans.[28,29] However, preclinical studies with repeated administration of high doses of serotonergic psychedelics demonstrated increased neuroplasticity.[27]

Concerning the underlying pathway, previously it was shown that the structural changes induced by psychedelics appear to result from stimulation of the TrkB, mTOR, and 5-HT2A signaling pathways.[30] Ketamine is known to set off a signaling cascade by antagonizing NDMA receptors on presynaptic GABA neurons, resulting in an increased postsynaptic production of BDNF. The intermediate steps are increased presynaptic glutamate release and activation of mTOR pathways.[31−33] Ketamine and LSD might share a final common pathway when it comes to stimulation of BDNF. Future studies might include other proteins as well, to understand the neurobiological pathways underlying neuroplasticity and the

potential (therapeutic) implications of these induced changes. Potential foci might be proteins such as cFos and Perk, implicated in synaptic plasticity and memory formation,[26] as ketamine is known to impact these.

While the present study had a small final sample size due to the difficulty in collecting blood over the 6 h course the participants were in the lab, the strength was the within-subject set up which neutralized the variation in the placebo−LSD comparisons and the multiple measurements after administration. Besides emphasizing the need to sample BDNF beyond the LSD elimination stage, in addition to including behavioral and imaging measures, future studies could focus on similarities between underlying biological pathways of the well-studied ketamine and LSD, as these will contribute to understanding the scope of effects LSD might have, based on ketamine findings. This first evidence of neuroplasticity in humans after low doses of a psychedelic provides a foundation to explore and replicate this finding in patient populations, to understand the therapeutic value of it, if any exists.

■ MATERIALS AND METHODS

Participants were 24 recreational psychedelic users who provided informed consent, fell within the inclusion criteria,[34] and passed medical screening including standard blood chemistry, hematology, and urinalysis before inclusion.

Test days were scheduled with minimally 5 days in between. A test day started at 9:00 AM with a screen for the presence of drugs of abuse in urine and alcohol in the breath, as well as a urine pregnancy test for female participants. When tests were negative, a venous catheter was placed to draw blood. LSD (5, 10, and 20 μg LSD base) was dissolved in 96% ethanol; the placebo consisted of 1 mL of ethanol (96%) without LSD. LSD and placebo were administered orally at 10:00 AM. A dose of 5, 10, and 20 μg LSD base would be equivalent to respectively 6.2, 12.3, and 24.6 μg pure LSD tartrate (1:0.5 without any crystal water). Participants were allocated to unique treatment orders. Blood samples were taken at −0.5 h, +2 h, +4 h, and +6 h relative to drug administration using BD vacutainer heparin tubes spray-coated with lithium heparin. Samples were centrifuged, and plasma was transferred into a clean tube and frozen subsequently at −20 °C until analysis. BDNF determination was assessed using an ELISA kit (Biosensis Mature BDNF Rapid ELISA kit: human, mouse, rat; Thebarton, Australia).[18] Plasma samples were appropriately diluted (1:20), and detection of BDNF was carried out on a precoated mouse monoclonal anti-mature BDNF 96-well plate as described in the manufacturer's protocol. The intra- and interassay coefficients of variation of this assay are below 10% (intra-assay CV 4.29%, interassay CV 7.14%). Samples were analyzed in duplicate, and mean values of respective measurements were calculated and used in statistical analyses. All measurements were done in a blinded fashion. LSD concentrations were determined using ultra-high-performance liquid chromatography/tandem mass spectrometry (UHPLC−MS/MS) as previously described.[35] A different extraction procedure reanalyzed samples with an LSD concentration below 5 pg/mL. In brief, aliquots of 150 μL of plasma were extracted with 450 μL of methanol. The samples were rigorously mixed and subsequently centrifuged. The supernatant was evaporated under a constant stream of nitrogen and resuspended in 200 μL of mobile phases A and B (10:90 v/v). An LLOQ of 2.5 pg/mL was reached by this extraction.

This study is part of a more extensive study, including cognitive, psychological, and physiological parameters which are reported elsewhere.[34] The study adhered to the code of ethics on human experimentation,[36] was approved by the Medical Ethics Committee of the Academic Hospital of Maastricht and Maastricht University, and was registered in the Dutch Clinical Trial register (number: NTR7102 https://www.trialregister.nl/). A permit for obtaining, storing, and administering LSD was obtained from the Dutch Drug Enforcement Administration.

■ STATISTICAL ANALYSIS

Complete WS cases entered statistical analyses performed by the statistical program SPSS (version 25.0). Nonparametric Wilcoxon S-R tests for related samples (placebo−LSD dose) were conducted on BDNF AUC's and BDNF plasma levels at −0.5 h, +2 h, +4 h, and +6 h after dose administration of 5, 10, and 20 μg of LSD. In order to understand at which time points BDNF levels were statistically different, separate Friedman tests per treatment condition were performed, and in the case of a main effect, followed by Dunn's tests for pairwise comparisons including baseline (0 h) versus 2 h, 4 h, and 6 h, as well as 2 h−4 h and 4 h−6 h.

In the case of statistically significant effects at alpha = 0.05, effect sizes and their 95% confidence intervals (95% CI) are given; to that end, (point-biserial) correlations are calculated for Wilcoxon tests where 0.10, 0.24, and 0.37 signify small, moderate, and large effect sizes;[37,38] in case of Friedman tests, Cramer's V was calculated where 0.06, 0.17, and 0.29 signify small, moderate, and large effect sizes.[39] The alpha level was corrected for multiple comparisons with sequential Bonferroni in case of Dunn's tests.

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Author Contributions

N.R.P.W.N., N.L.M., P.C.D., A.F., J.G.R., K.P.C.K. conceptualized the study and wrote the protocol. N.R.P.W.N., F.H., M.E.L., N.V., A.E., K.P.C.K. collected and/or analyzed the data. N.R.P.W.N. and K.P.C.K. wrote the manuscript. All authors contributed to versions leading up to the final manuscript.

Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

5-HT2A	Serotonin 2A receptor
BDNF	Brain-derived neurotrophic factor
CI	Confidence interval
ELISA	Enzyme-linked immunosorbent assay
i.p.	Intraperitoneal
IV	Intraveneous
LSD	D-Lysergic acid diethylamide
mPFC	Medial prefrontal cortex
mTOR	Mammalian target of rapamycin
NMDA	*N*-Methyl-D-aspartate
pERK	Phosphorylation of extracellular signal-regulated kinase
S-R	Signed-rank
WS	Within subject

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