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Subacute effects of a single dose of psilocybin on biomarkers of inflammation in healthy humans: An open-label preliminary investigation

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ABSTRACT

Rationale: Psilocybin is a serotonergic psychedelic that has gained prominent attention recently as a potential therapeutic for neuropsychiatric disorders including Major Depressive Disorder. Pre-clinical and initial studies in humans suggest that serotonin 2A receptor agonists, including serotonergic psychedelics, have anti-inflammatory effects. This may contribute to its therapeutic effects as previous studies indicate a link between neuropsychiatric disorders and inflammatory processes. However, the effect of psilocybin on biomarkers of inflammation has not been evaluated in humans.

Objectives: Investigate the effect of a single dose of psilocybin on peripheral biomarkers of inflammation in healthy humans.

Methods: Blood samples were collected from 16 healthy participants before and one day after the administration of a single oral dose of psilocybin (mean dose: 0.22 mg/kg) and subsequently analyzed for concentrations of high-sensitivity C-reactive protein (hsCRP), tumor-necrosis-factor (TNF) and soluble urokinase plasminogen activator receptor (suPAR). Change in inflammatory markers was evaluated using a paired *t*-test where $p < 0.05$ was considered statistically significant.

Results: We did not observe statistically significant changes in any of the above biomarkers of inflammation (all Cohen's $d \leq 0.31$; all $p \geq 0.23$).

Conclusions: Our data do not support that a single dose of psilocybin reduces biomarkers of inflammation in healthy individuals one day after administration. Nevertheless, we suggest that future studies consider additional markers of inflammation, including markers of neuroinflammation, and evaluate potential anti-inflammatory effects of psilocybin therapy in clinical cohorts where more prominent effects may be observable.

1. Introduction

Over the past decade, psilocybin has emerged as a promising therapeutic for several hard-to-treat neuropsychiatric disorders, including Major Depressive Disorder [1,2], end-of-life anxiety [3], addiction [4], and Obsessive-Compulsive Disorder [5]. In healthy individuals, psilocybin has been shown to increase well-being [6], the core personality trait openness [7], and mindfulness [8]. Interestingly, the above changes appear to have a rapid onset and persist well beyond the acute pharmacological actions.

Mechanisms thought to mediate these lasting effects of psilocybin include changes in distributed brain function, assessed with resting-state connectivity [9], modulation of brain serotonin (5-HT) 2A receptor ($5\text{-HT}_{2A}R$) binding [8] and the acute subjective experience [10]. Recently, anti-inflammatory action within the central nervous system has been proposed as a complementary mechanism that may contribute

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to the observed lasting therapeutic effects of psilocybin [11,12]. This is consistent with evidence linking neuroinflammation in the pathogenesis of depression [13] and other neuropsychiatric disorders [14]. Despite this intriguing and potentially clinically relevant association, anti-inflammatory effects of psilocybin in humans have not been evaluated.

Psilocybin is a substituted indolealkylamine naturally found in mushrooms of the genus *Psilocybe* and a prodrug for psilocin, which interacts with multiple 5-HT receptor subtypes, including 1A, 1D, 2A, and 2C [15]. The psychoactive effects of psilocin are mediated by activation of the cerebral 5-HT_{2A}R [16]. The 5-HT system acts as an important intercellular signaling pathway in the brain, shaping neuronal processes that support emotion, memory and complex behavioral phenotypes [17]. However, approximately 90% of 5-HT in the human body is synthesized in the gastrointestinal tract and subsequently absorbed by circulating platelets, which release 5-HT in target tissue upon their activation, modulating, e.g., intestinal function, vasoconstriction, and platelet aggregation [18]. Several immune cells express 5-HT receptors which, once stimulated by circulating 5-HT, have receptor- and cell type-specific effects on the immune response [19]. In human monocytes, the 5-HT_{2A}R agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) has shown to inhibit lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF) secretion [20]. Accordingly, DOI inhibited *in vivo* TNF-induced expression of cell adhesion, cytokine, and chemokine genes in rat intestines [21], and reduced histological airway inflammation in a mouse model of asthma [22]. Dimethyltryptamine (DMT) and 5-methoxy-dimethyltrytamine (5-MeO-DMT) are potent 5-HT_{2A}R agonists and structural analogues to psilocybin, and have been shown to decrease pro-inflammatory gene expression in human dendritic cells, apparently dependent of σ-opioid receptor activation [23]. A recent study reported reduced concentrations of several pro-inflammatory cytokines in LPS-stimulated human macrophages after treatment with water extracts of different psilocybin-containing mushroom *genera*, although the direct effect of psilocybin in this effect was not specifically characterized [24]. To date, only two studies have investigated the effects of direct 5-HT_{2A}R agonism on circulating cytokines in humans. One study in healthy participants reported decreased salivary interleukin 6 (IL-6) and increased salivary cortisol after inhalation of 5-methoxy-dimethyltryptamine (5-MeO-DMT) [25]. Another study reported decreased levels of circulating C-reactive protein (CRP) in plasma after ingestion of ayahuasca, a brew containing dimethyltryptamine (DMT), in healthy participants and patients with depression [26]. The effects of psilocybin on inflammatory biomarkers in humans have not yet been evaluated.

In this study, we quantified blood levels of three inflammatory biomarkers 1 h before and 23 h after a single oral dose of psilocybin in healthy participants. We examined CRP, an acute-phase reactant routinely measured in the assessment of both innate and adaptive inflammatory responses, applying a high-sensitivity (hs) analysis that is able to discriminate very low blood levels, is used to assess low-grade inflammation, and has been shown to be a risk factor for all-cause mortality [27]. hsCRP has been proposed as a biomarker of central nervous system inflammation in depression, as it correlates both with central inflammatory biomarkers and severity of motivational symptoms of depression [28]. We also evaluated TNF (formerly known as TNF-α), a pro-inflammatory cytokine, which is central to the innate immune response and a relevant peripheral biomarker for central nervous system inflammation [29]. The third biomarker we examined is soluble urokinase plasminogen activator receptor (suPAR), a hydrophilic receptor which promotes immune cell migration and binds urokinase-type plasminogen activator (uPA) [30]. Psilocybin has been hypothesized to upregulate uPA and other profibrinolytic proteins, which counteract inflammation by degrading fibrin and aid neuroplasticity by activating brain-derived neurotrophic factor [31]. suPAR has recently been proposed as a biomarker of chronic low-grade inflammation and predictor of disease [32]. Interestingly, elevated suPAR levels appear to determine future use of antidepressants in blood donors [33]. Here we investigated the effects of psilocybin on blood hsCRP, TNF, and suPAR levels, because they are sensitive biomarkers for low-grade inflammation and seem to correlate with central nervous system inflammation. Consistent with evidence for a general anti-inflammatory effect of 5-HT_{2A}R agonists, we hypothesized that psilocybin would reduce blood levels of hsCRP, TNF, and suPAR.

2. Materials and methods

2.1. Participants

Sixteen healthy participants were recruited through an online survey (demographics are shown in Table 1). Data acquired from these participants were also included in previously published neuroimaging studies unrelated to the topic of this paper, including data from positron emission tomography (PET) and functional magnetic resonance imaging [8,16,34–36]. After receiving a detailed description of the study, participants provided written informed consent and subsequently underwent a screening interview and a medical examination. The medical examination included a blood screening panel, which included CRP, electrolytes, complete blood count, hemoglobin, ferritin, and hepatic and renal panels. Exclusion criteria were: 1) use of psychedelic drugs in the preceding 6 months or other psychotropics (except alcohol) in the preceding month; 2) present or previous primary psychiatric disease (Diagnostic and Statistical Manual of Mental Disorders IV or World Health Organization International Classification of Diseases 10) or in first-degree relatives; 3) present or previous neurological condition/disease, significant somatic condition/disease or intake of drugs suspected to influence test results; 4) non fluent Danish language skills; 5) vision or hearing impairment; 6) previous or present learning disability; 7) pregnancy; 8) breastfeeding; 9) magnetic resonance imaging (MRI) contraindications; 10) alcohol or drug abuse; 11) allergy to test drugs; 12) significant exposure to radiation within the past year (e.g., medical imaging investigations); 13) intake of QT-prolonging medication or electrocardiogram (ECG) results indicative of heart disease; 14) blood donation less than 3 months before project participation; 15) bodyweight less than 50 kg; 16) low plasma ferritin levels (<12 μg/l); 17) age <18.

The study was approved by the Ethics Committee for the Capital Region of Copenhagen (journal identifier: H-16028698, amendments: 56023, 56967, 57974, 59673, 60437, 62255) and Danish Medicines Agency (EudraCT identifier: 2016-004000-61, amendments: 2017014166, 2017082837, 2018023295) and conducted in accordance with the Declaration of Helsinki.

2.2. Psilocybin intervention

Participants were prepared for the psilocybin intervention as described in previous publications [8,16,34] and summarized in the following. After medical examination and prior to psilocybin administration, all participants were informed about the possible effects of psilocybin, including bodily discomfort, changes in perception, and emotional discharge. Participants underwent approximately 1 h long, semi-structured preparatory consultations with the psychologists who later assisted them the intervention. The preparatory consultations

Table 1
Population demographics. N = number, SD = standard deviation.

	N (%)	Mean	SD	Range
Females	6 (37.5%)			
Psychedelic-naive	13 (81.3%)			
Age (years)		30.5	5.97	[24.2; 49.9]
Weight (kg)		79.4	11.3	[58; 105]
Psilocybin dose (mg)		17.4	6.41	[3; 24]
Weight adjusted dose (mg/kg)		0.22	0.08	[0.05; 0.3]

familiarized participants with the assisting psychologists, explored participants personal background and motivations for participation, and presented strategies for promoting a good experience and addressing potential challenging experiences. On the intervention day, participants were requested to be well-rested, to abstain from alcohol the day before and from caffeine in the morning. We screened for drugs of abuse with a urine test (Rapid Response, BTNX Inc., Markham, Canada) and conducted a brief medical examination. Two psychologists acted as guides during the intervention day, while a medical doctor acquainted with specific drug effects was available at all times in case of an acute medical situation. On the day after, participants received post-session integration sessions with one of the assisting psychologists. Further psychological follow-up was offered if needed.

Data included in the present study was collected as part of two related but distinct studies [8,16]. In the first study, psilocybin was administered followed by the acquisition of PET scans during the psychedelic experience (N = 6 of participants included current study). In the second study, 10 participants received psilocybin in a private room, completing other aspects of the study, e.g., brain imaging, independent of the psilocybin session (see Stenbæk et al., 2021 for a detailed description of settings). All participants received psilocybin at around 10:00 a.m. Psilocybin was given orally as a set of 3 mg capsules (e.g., 6 capsules administered for an 18 mg dose), taken with a glass of water. The first study examined a range of doses, all of which induced self-reported perceptual effects (0.05–0.3 mg/kg), whereas doses in the second study were generally higher and aimed to be as close to, without exceeding, a fixed dose (0.2 mg/kg (n = 4) or 0.3 mg/kg (n = 6)). Both studies were performed open-label in part because the primary focus was change in measures of 5-HT_{2A}R PET, which is expensive to acquire and not clearly sensitive to placebo effects.

To quantify and monitor the subjective experience in real-time, subjective drug intensity (SDI) was measured approximately every 20 min, and from the time of drug administration to the end of the session, using a Likert scale (question: "How intense is your experience right now?"; 0 = "not intense at all", 10 = "Very much"). Participants responded orally and the supporting psychologists noted their responses. After acute drug effects had waned, and approximately 6 h after psilocybin administration, participants completed the revised Mystical Experience Questionnaire (MEQ30), which is a 30-item self-reported inventory developed to quantify mystical-type experiences elicited by psilocybin [37].

2.3. Biochemical procedures

Venous blood samples for biomarker analysis were collected approximately 1 h before psilocybin administration and at the same time the next day (i.e. 24 h after first blood sample), to avoid circadian effects on, e.g., TNF levels [38] and for feasibility reasons (the same time participants met for psychological follow-up). Blood samples were collected in sterile EDTA tubes for plasma, and clot activator tubes (both BD Vacutainer) for serum isolation. Whole blood was immediately stored on ice, centrifuged at 2860 rpm (1317 *g*), 4 °C, for 7 min, and the isolates frozen at −80 °C and stored until processed.

hsCRP measures were determined from serum analyzed in one batch on a Cobas 8000 with a c502 module by a latex particle-based immunoassay (LIA) turbidimetry method. Lower detection limit was 0.30 mg/l and upper limit was 20 mg/l. Coefficient of variance was maximum 4% for measurements of approximately 7 mg/l and maximum 7% for lower measures of approximately 0.6 mg/l.

The concentration of TNF in plasma samples (50 μl) was analyzed using Sandwich Enzyme-linked Immunosorbent Assay (ELISA) (eBioscience Diagnostics) according to manufacturer's instructions. The plates were pre-coated with a capture antibody, to which TNF binds. A biotin-conjugated TNF detector antibody was added and recognized by streptavidin horse-radish-peroxidase (HRP). A 3,3′,5,5; -tetramethylbenzidine (TMB) chromogen substrate solution reactive with HRP was added and converted into a blue color in proportion to the amount of bound TNF in the well. A stop solution was added converting the blue color into a yellow color and the absorbance was measured at 450 nm. A standard curve was designed for each plate ranging from 0 to 500 ng/l and absorbances measured was converted into TNF concentrations using standard curve measurements and non-linear regression with $r^2 \geq 0.97$. Lower limit of detection was determined to be 2.3 ng/l.

The serum concentration of suPAR was determined by ELISA according to manufacturer's instruction (suPARnostic, Virogates, Denmark). The standards (ranging from 0.7 to 14.3 μg/l) and the samples were run in singlets. The curve control included on the plate was within the expected range (2.0–3.4 μg/l) with 2.44 μg/l.

2.4. Statistical analysis

Statistical calculations were performed in RStudio (Version 1.1.383 – © 2009–2017 RStudio, Inc.). For each biomarker, a paired, two-sided Student's t-test was performed. Cohen's d was calculated for the *t*-test by dividing the mean of differences by the standard deviation of the differences (i.e., $mean_D/SD_D$). 95% confidence intervals and p-values are reported. Our threshold for statistical significance was set to $p < 0.05$. Linear regression models were applied to evaluate the dose-response relationship between the weight-adjusted psilocybin dose and changes in biomarker concentrations.

Considering our small sample, we performed a bootstrap (1000 resamples with replacement) and permutation test (1000 permutations) to derive non-parametric estimates of confidence intervals and statistical significance. The results were not substantively different from those of parametric tests. For clarity we report results from parametric tests only. We considered to perform statistical analyses with a composite biomarker variable, but refrained from this because of low intercorrelation between the biomarkers (multiple correlation coefficient = 0.11).

3. Results

We did not observe statistically significant changes in blood concentrations of hsCRP, TNF, or suPAR following psilocybin administration (Table 2, Fig. 1, all $p \geq 0.23$). Numerically, hsCRP levels decreased 32% (Cohen's d = −0.31), whereas TNF and suPAR increased 83% (Cohen's d = 0.25) and 5% (Cohen's d = 0.18), respectively.

Linear regression modelling showed no effects of weight adjusted dose ($p \geq 0.22$) on biomarker change (Fig. 2).

The subjective drug intensity (SDI) had a mean peak of 9.7 (range = 8–10) and followed a time-course consistent with previous findings. The Mystical Experience Questionnaire (MEQ30) scores (mean = 3.6, range = 1.9–4.9) indicated a quality of experience typical for psychedelic drug effects (see Stenbæk et al., 2021 for a detailed description of temporal and mystical features of drug effects).

4. Discussion

Our results do not support our hypothesis, that a single dose of psilocybin induces statistically significant changes in blood levels of hsCRP, TNF, or suPAR one day after administration in healthy individuals. Despite these negative findings, this study provides valuable information for future research in the potential immunomodulatory effects of psilocybin.

Although we did not observe a statistically significant effect in our limited sample, it is notable that the magnitude of our observed decrease in hsCRP (32%) following psilocybin is comparable to that reported in a recent study of ayahuasca (32.4% in healthy controls) [26]. This convergence in effect size is encouraging that 5-HT_{2A}R agonism may induce a change in CRP, which would be consistent with *in vitro* and *in vivo* studies reporting that 5-HT_{2A}R stimulation inhibits IL-6 synthesis [22,25], a critical regulator of CRP secretion [39]. Nevertheless, as we will consider in more detail below, our estimated effect size suggests that

Table 2
Effects of psilocybin on inflammatory biomarkers. Blood concentrations of high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor (TNF), and soluble urokinase plasminogen activating receptor (suPAR) before and after psilocybin intervention. SD = standard deviation; 95% CI: 95% confidence interval. Confidence intervals and p-values are for the paired two-sided *t*-test.

	Mean (SD) baseline	Mean (SD) 24 h	Difference	95% CI	P-value	Cohen's D
Total						
hsCRP (mg/l)	1.92 (3.16)	1.30 (1.34)	−0.62	[-0.437; 1.66]	0.233	−0.311
TNF (ng/l)	4.40 (5.76)	8.04 (12.4)	3.64	[-11.3; 4.02]	0.328	0.253
suPAR (µg/l	2.05 (0.498)	2.15 (0.628)	0.1	[-0.385; 0.193]	0.49	0.177
Females						
hsCRP (mg/l)	0.977 (0.579)	0.957 (0.784)	−0.02	[-0.485; 0.525]	0.923	−0.0416
TNF (ng/l)	1.33 (2.15)	9.77 (19.2)	8.44	[-28.6; 11.7]	0.331	0.440
suPAR (µg/l)	2.15 (0.432)	2.13 (0.531)	−0.02	[-0.351; 0.396]	0.884	−0.0629
Males						
hsCRP (mg/l)	2.48 (3.94)	1.51 (1.59)	−0.97	[-0.779; 2.71]	0.242	−0.396
TNF (ng/l)	6.24 (6.53)	6.99 (6.87)	0.75	[-8.41; 6.91]	0.829	0.0702
suPAR (µg/l)	1.99 (0.547)	2.16 (0.707)	0.17	[-0.623; 0.289]	0.428	0.262

a much larger future sample would be required to be sufficiently powered to detect statistically significant effects.

Conversely, TNF levels were numerically increased one day after psilocybin, which is inconsistent with previous studies reporting that DOI, DMT, and 5-MeO-DMT blunt TNF secretion [20,23]. Notably, these compounds have different pharmacological profiles than psilocin, which means that apart from 5-HT_{2A}R-agonism, they act on different receptor types with different affinities. TNF secretion is modulated by multiple 5-HT receptors [19] as well as the σ-opioid receptor [23]; thus, different 5-HT_{2A}R agonists with different receptor binding profiles may have distinct effects on inflammatory markers, making it difficult to compare effects directly.

Another plausible explanation for numerically divergent results might be that the 5-HT_{2A}R shows functional selectivity, which means that different ligands exert differential effects on downstream signaling. Indeed, one study compared 21 different 5-HT_{2A}R agonists and found, that these had different anti-inflammatory potentials, which seemed to be dependent on different downstream pathways, rather than the canonical 5-HT_{2A}R signaling pathway involving calcium mobilization [40].

In female participants there was a statistically non-significant mean change of TNF of 8.44, which numerically is considerably larger than the TNF change in male participants (0.75). The mean change of TNF in females is considerably loaded by one extreme outlier, and would more closely resemble the change seen in males, if the outlier were to be omitted (0.67). Our data do not grant hypotheses on whether biological gender moderates the effects of psilocybin on biomarkers.

Several limitations of our study should be considered. Our sample of 16 participants seems to be small for detecting inflammatory effects. Considering our observed effect on hsCRP (Cohen's d = −0.31), a similar future study would require ~80 participants to be sufficiently statistically powered (type II error, 1-β = 0.8) to detect a significant effect (type I α = 0.05) with a two-sided test. As a preliminary estimate of effect sizes, our current data are informative for future studies. Although our sample size limits the power to rule out small changes, psilocybin presumably did not cause any significant inflammation in our healthy participants. Changes in CRP 24 h after an endotoxin challenge in healthy humans have been reported to be over 50-fold from baseline [41], vastly exceeding our 95% confidence interval for hsCRP (−0.437–1.66 mg/l). As such, our data indicate that psilocybin does not produce the same inflammatory response as a direct inflammatory challenge. This observation can be useful for investigators and clinicians concerned about potential pro-inflammatory effects when administering psilocybin to patients susceptible to inflammation (e.g. autoimmune disorders).

The study was conducted in an open-label design and did not include a placebo group for comparison. Although expectations have shown to significantly influence the subjective experience [42], a recent placebo-controlled study of ayahuasca in healthy participants reported no change in blood levels of CRP in the placebo arm, despite reported subjective experiences [26]; suggesting that placebo-induced subjective experiences are not accompanied by changes in inflammatory marker levels. One meta-analysis examining the anti-inflammatory effects of the placebo arms in studies of rheumatoid arthritis finds significant reductions in CRP, but concludes that these reductions are unlikely to be caused by psychological effects, but rather non-psychological effects, such as regression to the mean (because of high baseline levels) and ongoing treatment-*as*-usual [43]. Although our study participants are healthy, have low baseline levels of inflammatory markers, and do not

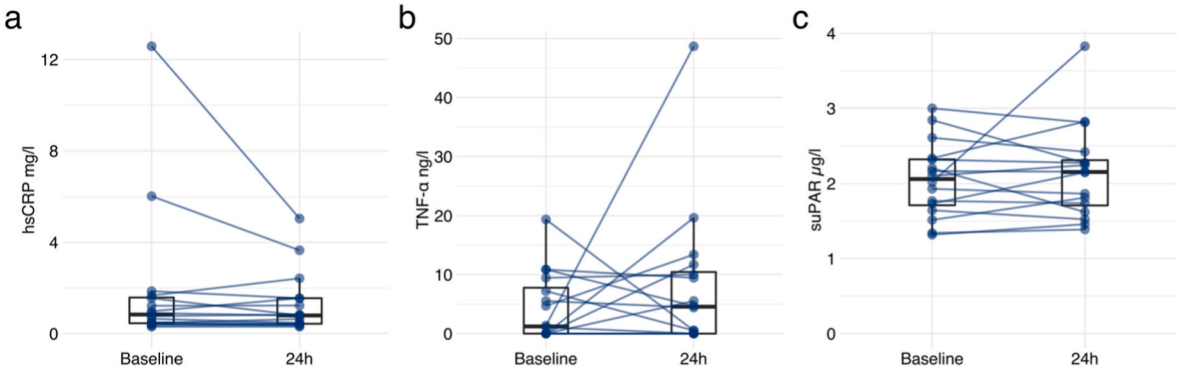

Fig. 1. Effects of psilocybin on inflammatory biomarkers. These combined box- and line-plots show individual blood concentrations of high-sensitivity C-reactive protein (hsCRP) (serum) (a), tumor necrosis factor (TNF) (plasma) (b), and soluble urokinase plasminogen activating factor (suPAR) (serum) (c) at baseline and 24 h after baseline (i.e. 23 h after psilocybin ingestion). Horizontal lines within boxes are medians, lower and upper borders of boxes are lower and upper quartiles, respectively, and whiskers demarcate the extremes (but not outliers exceeding 1.5 times the interquartile range).

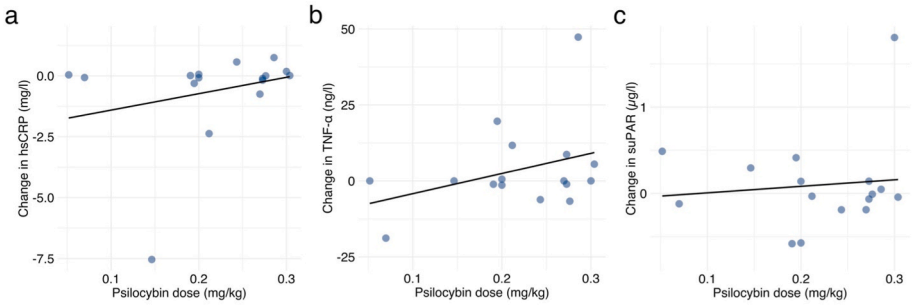

Fig. 2. Dose-response relationships. These plots show the relationship between the individual weight-adjusted psilocybin doses and the changes of high-sensitivity C-reactive protein (hsCRP) (serum) (a), tumor necrosis factor (TNF) (plasma) (b), and soluble urokinase plasminogen activating factor (suPAR) (serum) (c) between baseline and 24 h after baseline.

use any medications, we cannot rule out effects of expectation on our results.

The acquisition of post-intervention blood samples was timed 23 h after psilocybin administration; 24 h after first blood sample to avoid circadian effects on biomarkers, and just after psychological and psychometric follow-up for the convenience of study participants. The lack of multiple post-intervention blood samples may have limited our ability to detect a significant change in inflammatory markers. The examined biomarkers have different rates of recession: blood levels of CRP levels decline within days [41], TNF within hours [44], and suPAR over weeks [45]. Galvão-Coelho and colleagues measured significant reductions in CRP on the second day after ayahuasca ingestion, but did not measure CRP levels at other time points [26]. Although TNF blood levels are expected to decrease within hours after the release has been inhibited, reductions in suPAR blood levels might take days to weeks to be measurable. Our data do not rule out a potential acute decline and subsequent return to baseline of biomarker levels (especially TNF) between blood samples, i.e. within 23 h after psilocybin. Further investigation is needed to resolve the temporal dynamics of inflammatory biomarker concentrations after psilocybin administration (e.g. hours, days, weeks after intervention).

Our current analysis focused on peripheral markers of inflammation; future studies should consider evaluating psilocybin effects on more direct measures of neuroinflammation. For example, cerebrospinal fluid (CSF) concentrations of inflammatory markers might be more sensitive to psilocybin effects. Metabolites of the kynurenine-tryptophan, nitric oxide, and neopterin pathways have been suggested as suitable CSF biomarkers for neuroinflammation [46]. Several novel positron emission tomography (PET) targets (e.g., 18 kDa translocator protein, monoamine oxidase B, and cyclooxygenase-1 and -2) may also provide insight into modulatory effects of psilocybin on neuroinflammation [47]. Taken together, there are prominent opportunities to more clearly establish the effect of psilocybin and other serotonergic psychedelics on neuroinflammatory biomarkers.

Our study examined young and healthy individuals with low baseline levels of inflammatory markers, hindering our ability to detect a psilocybin-induced decrease. Baseline inflammatory marker levels for our participants were largely within previously described ranges for healthy individuals (hsCRP: 0–10 mg/l, 15/16 within this range; TNF: 0–32.2 ng/l, all within this range; suPAR: 1.3–3.6 µg/l, 15/16 within this range) [48–50]. Healthy individuals are nevertheless a relevant study population for delineating biological mechanisms associated with serotonergic psychedelics as they experience the acute psychoactive effects as well as lasting positive effects on mood and personality. Evidence suggests a possible role for 5-HT_{2A}R agonists in the treatment of inflammatory diseases, including autoimmune disorders. As such, it would be informative to directly assess the immunomodulatory effects of psilocybin in a clinical cohort characterized by heightened inflammation. Intriguingly, a study of the antidepressant effects of infliximab, a TNF inhibitor, showed that baseline hsCRP and TNF levels distinguished responders from non-responders [51]. Whether the antidepressant effects of psilocybin therapy [1,2] are dependent on anti-inflammatory action, or even predictable from baseline inflammatory markers, is yet to be determined in populations of depressed patients.

In conclusion, we did not find any statistically significant changes of hsCRP, TNF, or suPAR one day after a single oral dose of psilocybin. This preliminary investigation represents the first evaluation of psilocybin effects on inflammatory markers in humans and might serve as a step stone for further research on psilocybin's potential immunomodulatory effects. Future studies should consider 1) a sample size of ~80; 2) randomized and blinded placebo control; 3) multiple sampling time points; 4) evaluating more direct markers of neuroinflammation; and/or 5) evaluating clinical cohorts.

Author contributions

DRB has contributed to the study design, recruitment of study participants, data collection, data analysis, and has drafted the manuscript. MKM has contributed to the study protocol, data collection, supervision, and has reviewed the final draft. AS has contributed to study design and review of the final draft. SSA has performed laboratory analyses and reviewed the final draft. DSS has contributed to data collection, and review of the final draft. VGF has contributed to study design, supervision, and review of the final draft. BE has contributed to study design, performed laboratory analyses, and reviewed the final draft. JDM has contributed to study design and reviewed the final draft. GMK is the primary investigator, and has contributed to study design and reviewed the final draft. PMF has contributed to the study protocol, data collection, primary supervision and has co-drafted the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vibe G Frojaer reports a relationship with Lundbeck Pharma that includes: speaking and lecture fees. Vibe G Frojaer reports a relationship with SAGE Therapeutics Inc that includes: consulting or advisory. Gitte Moos Knudsen reports a relationship with SAGE Therapeutics Inc that includes: speaking and lecture fees. Gitte Moos Knudsen reports a relationship with Biogen Inc that includes: speaking and lecture fees. Gitte Moos Knudsen reports a relationship with Sanos Bioscience that includes: consulting or advisory.

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