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Psilocybin induces acute and persisting alterations in immune status in healthy volunteers: An experimental, placebo-controlled study

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ABSTRACT

Patients characterized by stress-related disorders such as depression display elevated circulating concentrations of pro-inflammatory cytokines and a hyperactive HPA axis. Psychedelics are demonstrating promising results in treatment of such disorders, however the mechanisms of their therapeutic effects are still unknown. To date the evidence of acute and persisting effects of psychedelics on immune functioning, HPA axis activity in response to stress, and associated psychological outcomes is preliminary. To address this, we conducted a placebo-controlled, parallel group design comprising of 60 healthy participants who received either placebo (n = 30) or 0.17 mg/kg psilocybin (n = 30). Blood samples were taken to assess acute and persisting (7 day) changes in immune status. Seven days' post-administration, participants in each treatment group were further subdivided: 15 underwent a stress induction protocol, and 15 underwent a control protocol. Ultra-high field (7-Tesla) magnetic resonance spectroscopy was used to assess whether acute changes in glutamate or glial activity were associated with changes in immune functioning. Finally, questionnaires assessed persisting self-report changes in mood and social behavior. Psilocybin immediately reduced concentrations of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α), while other inflammatory markers (interleukin (IL)- 1β, IL-6, and C-reactive protein (CRP)) remained unchanged. Seven days later, TNF-α concentrations returned to baseline, while IL-6 and CRP concentrations were persistently reduced in the psilocybin group. Changes in the immune profile were related to acute neurometabolic activity as acute reductions in TNF-α were linked to lower concentrations of glutamate in the hippocampus. Additionally, the more of a reduction in IL-6 and CRP seven days after psilocybin, the more persisting positive mood and social effects participants reported. Regarding the stress response, after a psychosocial stressor, psilocybin did not significantly alter the stress response. Results are discussed in regards to the psychological and therapeutic effects of psilocybin demonstrated in ongoing patient trials.

1. Introduction

Substantial evidence has demonstrated that psychosocial stressors can activate the immune system, initiating inflammatory processes that may underlie certain psychiatric disorders (Szabo and Rajnavolgyi, 2013; Hori and Kim, 2019; Dantzer et al., 2008). An increasing number of studies have demonstrated that patients characterized by stress-related disorders such as depression, addiction, and post-traumatic stress disorder (PTSD) show elevated circulating concentrations of pro-inflammatory cytokines including interleukin (IL)-1α, IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), as well as acute-phase proteins such as C-reactive protein (CRP) (Hori and Kim, 2019; Dantzer et al., 2008; Dowlati et al., 2010; Newton et al., 2014; Baker et al., 2001; Martinez et al., 2018; Fagundes et al., 2013). An inflammatory challenge

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(i.e. an endotoxin derived from *Escherichia coli*) results in the rise of pro-inflammatory cytokines such as IL-6 and TNF-α in plasma and has been found to induce depressive-like behaviors, including social withdrawal/disconnection and depressed mood in both healthy animals (Najjar, 2013) and humans (Moieni et al., 2015). Further evidence suggests that heightened systemic inflammation may also contribute to non-responsiveness to current antidepressant therapies, resulting in treatment resistance (Miller and Raison, 2016; Strawbridge et al., 2015). Overall, evidence supports that pharmacological treatments that decrease pro-inflammatory processes may hold therapeutic value in a wide range of neuropsychiatric diseases (Baumeister et al., 2016).

Serotonin (5-HT)2A agonist drugs, such as the classic psychedelics psilocybin, lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT), ayahuasca (containing DMT), and 5-MeO-DMT, have been found to possess anti-inflammatory properties in preclinical models (for a review see Szabo (Szabo, 2015). In humans, one observational study found that inhalation of 5-methoxy-DMT (5-MeO-DMT) decreased IL-6 concentrations in saliva 1–1.5 h after administration, with no effects on CRP or IL-1β (Uthaug et al., 2020). The strongest evidence of psychedelics' anti-inflammatory processes stems from one clinical study, which found a reduction of CRP, but not IL-6, in both depressed patients and controls, 48 h after administration of ayahuasca compared to baseline (Galvão-Coelho et al., 2020). In depressed patients, reductions in CRP correlated with a reduction in depressive symptoms. Accordingly, a growing number of clinical trials are finding promising results regarding psychedelics' ability to treat a range of psychiatric disorders characterized by aberrant inflammatory profiles, such as (treatment-resistant) depression, addiction, and PTSD (Flanagan and Nichols, 2018; Baumeister et al., 2014; Kuypers, 2019). Taken together, evidence suggests that psychedelics possess systemic anti-inflammatory properties in humans that may contribute to their ability to alleviate (depressive) symptoms. However, the evidence of acute and persisting effects of psychedelic drugs on immune functioning, and their relationship with psychological outcomes such as increased mood and sociability is still preliminary.

If psychedelics' anti-inflammatory mechanisms give rise to symptom alleviation, it is of interest to understand the underlying biological mechanisms. It has been established that pro-inflammatory cytokines play a key role in immune system-to-brain signaling, influencing brain function, mood, and behaviour (Dantzer et al., 2008; Marsland et al., 2017). For example, peripheral cytokines have been found to cross the blood–brain barrier (Dantzer et al., 2008), influencing glutamate transmission (Haroon and Miller, 2016) and inhibiting astrocyte glutamate uptake (Haroon et al., 2017; Akkouh et al., 2020), potentially leading to sustained glutamatergic activity, excitoxicity (Thompson and Szabo, 2020), and impaired synaptic plasticity in areas such as the medial prefrontal cortex and hippocampus. These brain areas are known to regulate stress and emotion (Khairova et al., 2009; Averill et al., 2017), and play a direct role in hypothalamic-pituitary-adrenal (HPA) axis functioning. These neuronal and glial alterations can give rise to large-scale neural network disruptions which may contribute to the pathophysiology of mood disorders (Miller and Raison, 2016; Lee and Giuliani, 2019). Interestingly, changes in glutamatergic transmission have been found to be altered by psychedelic drugs and suggested to play a role in the therapeutic efficacy of these substances in clinical trials (Mason et al., 2020; Vollenweider and Kometer, 2010; Doss et al., 2021; Sampedro et al., 20172017; Nichols and Barker, 2016; van Elk and Yaden, 2022). However, whether such psychedelic-induced changes in glutamatergic or glial activity are associated with alterations in systemic inflammation has yet to be assessed.

Finally, if psychedelics reduce the symptomatology of stress-related disorders, and alter immune signaling, might they also modify an individual's stress response? Indeed, it could be hypothesized that one way in which cytokine concentrations may be reduced is through lowered reactivity to psychosocial stressors. It has been established that psychosocial stressors increase peripheral cytokine concentrations, resulting in inflammation (Hori and Kim, 2019; Fagundes et al., 2013). Thus, a possible explanation for increased inflammation in the aforementioned disorders is a heightened stress response - and/or exposure to extreme stress - potentially in combination with a dysregulated HPA axis (Chen et al., 2017; Bellavance and Rivest, 2014). A one or two-time ingestion of a psychedelic drug has been found to reduce symptomatology of stress-related disorders in clinical populations (Reiff et al., 2020) and decrease feelings of stress in healthy populations (Uthaug et al., 2020; Uthaug et al., 2019; Uthaug, 2018). Nevertheless, it has yet to be objectively and directly demonstrated whether an individual's response to an acute psychosocial stressor is reduced in the days following ingestion of a psychedelic substance.

The aim of the present double-blind, placebo-controlled, parallel-group design was fourfold: the primary aim was to assess the acute and persisting (7 day post) effects of the classic psychedelic psilocybin, on a range of inflammatory markers associated with the prognosis and therapeutic response of stress-related psychiatric disorders, including IL-1β, IL-6, IL-8, and TNF-α, as well as CRP, in healthy subjects. The secondary aim was to assess the acute and persisting effect of psilocybin on the stress response. Acutely, cortisol concentrations were taken as a marker of HPA axis activation. Seven days following treatment administration, participants underwent a stress-induction protocol (Maastricht acute stress test; MAST) or control protocol to assess whether psilocybin reduces stress reactivity. Exploratory aims assessed the hypothesis that psilocybin-induced changes in immune status would be associated with psychosocial functioning (Najjar, 2013; Moieni et al., 2015). Furthermore, acute glutamate and glial activity (concentrations of myo-inositol (mI)) were measured in the medial prefrontal cortex (mPFC) and hippocampus to assess whether acute changes in cytokine concentrations related with neurometabolic activity.

2. Materials and methods

A detailed description of the experimental procedure is provided in the Supplementary Methods and briefly summarized here and Fig. 1.

The study was conducted between July 2017 and June 2018 at Maastricht University, the Netherlands employing a balanced randomized (1:1), placebo-controlled, double-blind, parallel-group design. Sixty healthy participants were recruited, whom met the following criteria: 18–40 years old; previous experience with a psychedelic drug, but not within the past 3 months; normal weight, body mass index between 18 and 28 kg/m2; free from psychotropic medication; good physical health, including absence of major medical, endocrine, and neurological conditions; and written informed consent. Exclusion criteria consisted of: history of drug abuse or addiction; pregnancy or lactation; health issues including hypertension (diastolic $>$ 90 and systolic $>$ 140), cardiac dysfunction, and liver dysfunction; current or history of psychiatric disorders; previous experience of serious side effects to psychedelics; and MRI contraindications. Before inclusion, subjects answered medical questionnaires about their health and drug use, and were screened and examined by a study physician, who checked for general health, conducted a resting ECG, and took blood and urine samples in which hematology, clinical chemistry, urine, and virology analyses were conducted.

Participants were allocated to a treatment condition (0.17 mg/kg psilocybin or placebo, p.o.), and then subsequently to a stress-induction condition (MAST or control). This resulted in 30 participants in the psilocybin condition, with 15 of those participants undergoing the MAST and 15 undergoing the control protocol, and 30 participants in the placebo condition, with 15 of those participants undergoing the MAST and 15 undergoing the control condition. All 4 groups were equivalent in regards to age, sex, and education level. Full demographic information on the sample can be found in Table 1.

Participants visited the lab on three separate occasions. The first visit included a familiarization with testing day procedures. The second visit consisted of the formal testing day, with baseline blood samples

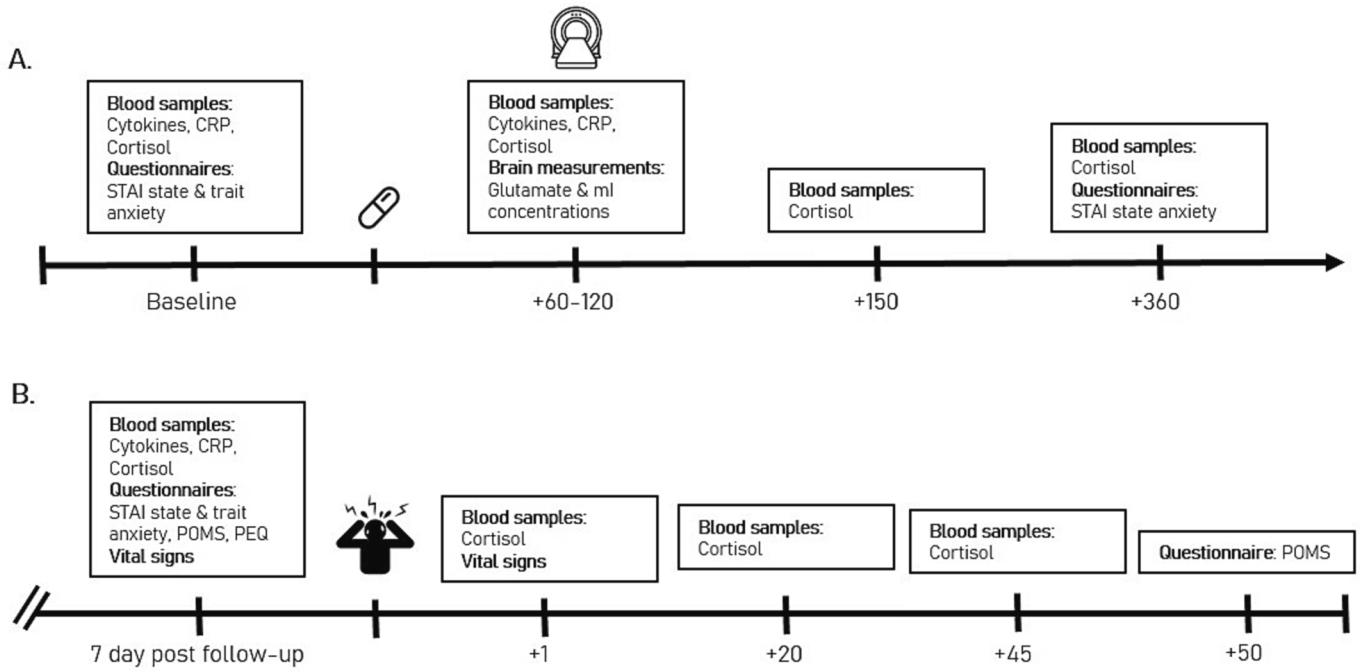

Fig. 1. Experimental timeline. A) testing day 1, including psilocybin or placebo treatment. B) testing day 2, which took place 7 days after testing day 1. Timing is in minutes, relative to the treatment (psilocybin or placebo in A; stress induction or control protocol in B). Note, the STAI is reported on in the supplementary.

Table 1
Mean subject characteristics (SD) and history of drug use for healthy participants in the psilocybin and the placebo condition (N = 60), as previously published in [Mason, Kuypers (Mason et al., 2020).

Variable	Psilocybin	Placebo	Value	*P* value
Sex (male/female), n, total	18/12, 30	17/13, 30	$\chi 2 = 0.07$ ‡	0.79
Age, years	22.73 (2.90)	23.20 (3.65)	$t = -0.55$†	0.60
History of psychedelic use, years	2.92 (2.62)	2.19 (2.55)	$t = 1.04$	0.30
Lifetime psychedelic use, number of occasions	9.53 (16.81)	5.47 (8.24)	$t = 1.09$	0.28
Cannabis consumption, per month	2.67 (3.14)	3.24 (4.91)	$t = -0.47$†	0.64
Alcohol consumption, glasses per week	5.47 (4.78)	5.82 (4.02)	$t = 0.31$†	0.76
Caffeine consumption, glasses per week	10.00 (7.75)	9.38 (8.10)	$t = 0.30$†	0.76
Nicotine consumption, cigarettes per week	3.82 (15.66)	7.67 (15.49)	$t = -0.96$†	0.34

*Significant *P* values; †Independent *t* test; ‡$\chi 2$ test for frequency data.

(baseline), treatment administration (psilocybin or placebo), magnetic resonance spectroscopy (MRS) to assess relative glutamate and myo-inositol (mI) concentrations, and further blood samples (acute). The third testing day took place 7 days after the acute testing day, and included the final blood samples (follow-up), followed by the completion of the stress-induction protocol and physiological (cortisol, blood pressure) and psychological (subjective stress ratings) stress response. Both the formal testing day and the follow-up testing day always started at 9:00am, to allow comparability of cortisol and inflammatory blood samples across testing days.

This study was conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Fortaleza (Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and was approved by the Academic Hospital and University's Medical Ethics committee. All participants were fully informed of all procedures, possible adverse reactions, legal rights and responsibilities, expected benefits, and their right to voluntary termination without consequences. The present data were part of a larger experimental trial (Netherlands Trial Register: NTR6505) of which parts have been previously published (Mason et al., 2020; Mason et al., 2021).

2.1. Immune assays

Venous blood samples were collected before treatment administration (baseline), after treatment administration on the acute testing day (during peak drug effects; 80 min), and 7 days after the acute testing day, to assess the concentrations of IL-1β, IL-6, IL-8, TNF-α, and CRP. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged at 3500 rpm/min and the plasma fraction was isolated and stored at −20 °C until assaying.

Cytokines. The simultaneous determination of IL-1β, IL-6, IL-8, and TNF-α plasma concentrations was performed using bead-based multiplexing technology using a XMAG-Luminex assay (Bio-Rad, Hercules, California, USA) (Bio-Plex Pro Human Cytokine Kit Panel). Briefly, standards, blanks, controls, and the participants' samples were incubated with the suspension of beads covered with antibodies specific for the tested molecules. After the incubation and washing steps, the cocktail of biotinylated detection antibodies was applied, followed by incubation with streptavidin–phycoerythrin solution. The fluorescence signal was read on a BioPlex 200 equipment (Bio-Rad). For further details of the immunoassay, see Table S1 and S2.

C-Reactive protein. CRP concentrations were assessed by a latex-enhanced immunoturbidimetric assay developed to accurately measure CRP concentrations in serum and plasma samples for conventional CRP ranges, using an ABX Pentra 400 Clinical Chemistry analyzer (ABX Horiba, Montpellier, France). Sample volumes were 4ul, analyzed in singles. The CRP assay has a working range from 0.01 mg/dL to 10 mg/dL. Population values have the following thresholds: Low: < 1.0 mg/dL., Average: 1.0–3.0 mg/dL and High: > 3.0 mg/dL. Using internal controls, of 1.11 mg/dL, 5.23 mg/dL and 0.12 mg mg/dL, the CV (%) are 1.02, 2.25 and 3.79 respectively.

2.2. Stress test

The MAST (Smeets et al., 2012) was used at the 7-day follow-up day to induce acute stress. It is a reliable method to induce a strong autonomic, glucocorticoid and subjective stress responses (Quaedflieg et al., 2017). The MAST combines physical stress induction, unpredictability, uncontrollability, and the social-evaluative nature of other stress induction protocols. In short, participants alternated between putting their hand in 2 °C water for a period between 45 and 90 s and doing mental arithmetic (counting back from 2043 in steps of 17) while their faces were recorded and social-evaluative pressure (i.e. negative feedback) was provided by an experimenter unfamiliar to the participant. The control protocol was similar to the experimental protocol with the difference that water was lukewarm (36 °C) and participants had to count from 1 to 25 at their own pace while no social pressure was applied. To determine individuals' responses to the stressor, serum cortisol samples *(see neuroendocrine response)* and vital signs (heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure) were obtained before and following the MAST. Subjective ratings of anxiety were obtained before and after the MAST via the Profile of Moods Scale (POMS)).

2.3. Neuroendocrine response

Acute. As a marker of HPA-axis activation and consequent immunomodulation (Bellavance and Rivest, 2014), acute cortisol concentrations were assessed via venous blood samples, taken before treatment administration (baseline) and after treatment administration on the acute testing day (80, 150, and 360 min post).

In response to the stress test. Seven days post treatment, blood-cortisol was sampled again in response to the stress induction paradigm. This included a baseline sample 5 min before the MAST or control, and then samples 1, 20, and 45 min after the paradigm.

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged at 3500 rpm/min and the plasma fraction was isolated and stored at −20 °C until assaying. The reagent employed for plasma cortisol determination was Elecsys Cortisol II, Roche®. Samples were analyzed with a high-throughput immunochemistry module (Cobas® e801 Module, Roche) using electrochemiluminescence (ECL) technology.

2.4. Subjective measures

Profile of Mood States (POMS). The POMS was used to assess subjective ratings of anxiety in relation to the stress test. The POMS is a self-assessment mood questionnaire with 72 items, rated on a 5-point Likert scale, with 0 being 'not at all' to 4 'extremely'. Participants had to indicate to what extent these items were representative of their mood at that moment in time. Eight mood states are classified and quantified by calculating the sum score of associated items for each mood state, i.e., anxiety (9 items), depression (15 items), anger (12 items), vigor (8 items), fatigue (7 items), confusion (7 items), friendliness (8 items) and elation (6 items). For this study, only the anxiety subscale was considered.

Persisting Effects Questionnaire (PEQ). To assess persisting changes in psychosocial functioning following the treatment administration, the PEQ was completed by participants at the beginning of the follow-up day. It is a 143-item long scale assessing changes in attitudes, moods, behavior, and spiritual experience which participants consider to be due to the experiences they had during the acute testing days (and in comparison to their state before the acute testing day) (Griffiths et al., 2006). Prior research has found that PEQ is sensitive to the prolonged effects of psychedelics, up to one year after ingestion (Schmid and Liechti, 2018). The scale consists of six categories: *attitudes about life* (Number of items (N) = 26), *attitudes about self* (N = 22), *mood changes* (N = 18), *relationships* (N = 18), *behavioral changes* (N = 2), and *spiritual experience* (N = 59). Each category reflected positive and negative changes, resulting in 12 subscales. All items were rated on a 6-point scale (ranging from 0 = *none* to 5 = *extreme*). The scores of the resulting 12 scales (positive and negative scales for each of 5 categories) were assessed by calculating mean (SE) separately for each category (Griffiths et al., 2011).

2.5. MRS acquisition and processing

Single-voxel proton magnetic resonance spectroscopy (MRS) measurements were performed on a MAGNETOM 7 T MR scanner (Siemens Healthineers, Erlangen, Germany). Spectroscopic voxels were placed by a trained operator at the mPFC (voxel size = 25 × 20 × 17 mm3) and the right hippocampus (voxel size = 37 × 15 × 15 mm3). Spectra were acquired with the stimulated echo acquisition mode sequence (TE = 6.0 ms, TR = 5.0 s, 64 averages). Outcome measures for MRS were concentration ratios of glutamate and myo-inositol to total creatine (tCr, creatine + phospho-creatine).

Detailed information regarding image acquisition and MRS quantification is previously published (Mason et al., 2020). Spectroscopy data was analyzed with LCModel version 6.3-1H (see supplement for more information).

2.6. Statistical analyses

Statistical analysis was conducted in IBM SPSS Statistics 25 using a Linear Mixed Models analysis.

For the inflammatory response assessment, the model included Session (baseline, acute, follow-up), Treatment (psilocybin or placebo), and Session × Treatment, with Treatment as fixed effects, Session as repeated effects, and a random intercept. A first order autoregressive covariance structure (AR1) was used. If a significant main effect of Treatment or a significant Session × Treatment was observed, results were interpreted with a simple effects test (e.g. simple slopes).

Due to violations of the assumption of normality (Shapiro wilks), concentration values of IL-6, CRP, and IL-8 were log transformed. One participant's IL-6 values were excluded from analysis due to being an extreme outlier, which persisted even after log transformation (Table S3).

For the assessment of physiological and psychological responses to stress, the AR1 model included Timepoint (Cortisol: baseline, 1, 20, 45 min post stress test; Heart rate/blood pressure: baseline, immediately post stress test; POMS anxiety ratings: baseline and 50 min post stress test), Treatment (psilocybin or placebo), and Stress condition (stress or no stress), Timepoint × Treatment × Stress condition, and Treatment × Stress condition, with Treatment as fixed effects, Timepoint as repeated effects, and a random intercept. If a significant main effect of Treatment or Stress condition, or a significant Timepoint × Treatment × Stress condition or Treatment × Stress condition was observed, results were interpreted with a simple effects test (e.g. simple slopes).

Subscales on the PEQ were compared between the treatment groups using independent samples *t* tests.

Spearman's correlations were conducted to assess the relationship between acute concentrations of neurometabolites and acute changes in inflammatory markers which showed a treatment effect. To assess the potential relationship between changes in inflammatory markers and changes in mood and sociability, a canonical correlation was used, as this approach assesses the relationship between two multivariate data sets, allowing investigation of variables that may have multiple causes and effects, while also reducing the potential of type 1 error (Sherry and Henson, 2005). Variables were separated into two sets; set 1 included the mood and sociability ratings from the PEQ, and set 2 included the inflammatory markers which showed a significant treatment effect. Regarding the latter, baseline change scores were used (e.g. acute TNF-α concentrations – baseline; 7-day post IL-6 concentrations – baseline; 7-day post CRP concentrations – baseline).

Statistical significance was set at a P value of <0.05.

3. Results

3.1. Demographic variables

Demographic information has been previously published elsewhere (Mason et al., 2020; Mason et al., 2021) and briefly summarized here.

The psilocybin group ($n = 30$) and the placebo group ($n = 30$) did not differ in respect to demographic variables, such as sex, age, and drug use history (Table 1).

3.2. Psilocybin reduced inflammatory markers in a time and marker-dependent manner

The primary aim was to assess the acute and persisting (7 day post) effects of psilocybin, on inflammatory markers associated with the prognosis and therapeutic response of stress-related psychiatric disorders, namely TNF-α, IL-6, IL-1β, IL-8, as well as CRP.

TNF-α. Analysis revealed a significant Session × Treatment interaction on TNF-α ($F_{2,\ 76.17} = 3.06$, p = 0.05). Compared to placebo, psilocybin significantly decreased TNF-α concentrations acutely (t = -2.45, df = 84.70, p = 0.016) whereas concentrations 7 days' post-treatment were unaffected (t = -1.50, df = 54.49, p = 0.14) (Fig. 2).

IL-6. Analysis revealed a significant Session × Treatment interaction on IL-6 ($F_{2,\ 92.88} = 3.43$, p = 0.04). Compared to placebo, concentrations acutely did not differ after psilocybin (t = 0.13, df = 86.42, p = 0.89), whereas psilocybin significantly decreased IL-6 concentrations at follow-up (t = -2.044, df = 138.82, p = 0.04) (Fig. 2).

CRP. Analysis revealed a significant Session × Treatment interaction on CRP ($F_{2,\ 85.73} = 6.52$, $p = 0.002$). Compared to placebo, concentrations acutely did not differ after psilocybin ($t = 0.15$, df = 83.46, $p = 0.88$), whereas psilocybin significantly decreased CRP concentrations at follow-up ($t = -2.68$, df = 107.22, $p = 0.01$) (Fig. 2).

IL-1β. There was no significant effect of Treatment on IL-1β ($F_{1,45.06} = 3.70$, p = 0.06) or Session × Treatment interaction ($F_{2,66.58} = 1.33$, p = 0.27) (Table S4).

IL-8. There was no significant effect of Treatment ($F_{1,55.24} = 0.02$, p = 0.87) or Session × Treatment interaction ($F_{2,95.47} = 0.90$, p = 0.41) for IL-8 (Table S4).

3.3. Psilocybin acutely activated the HPA axis, as indicated by increased cortisol concentrations up to 150 min post treatment administration

The secondary aim was to assess the acute and persisting effect of psilocybin on the stress response. Acutely, cortisol concentrations were taken as a marker of HPA axis activation. There was a significant Session × Treatment interaction on cortisol concentrations ($F_{3,\ 109.46} = 9.82$, $p = 0.000$). Compared to placebo, psilocybin acutely increased concentrations from baseline (psilocybin mean(SE): 12.89 (1.44); placebo: 12:01 (1.15)), peaking at 80 min post administration (psilocybin: 17.15 (1.52); placebo: 9.45 (0.71); $t = 5.08$, df = 98.94, $p < 0.001$), and then began to fall at 150 min post administration (psilocybin: 13.98 (1.53); placebo: 8.32 (0.75); $t = 4.09$, df = 133.13, $p = < 0.001$). There were no differences between groups at 360 min post treatment (psilocybin: 8.70 (0.99); placebo: 6.55 (0.57); $t = 1.69$, df = 130.49, $p = 0.09$).

3.4. Psilocybin did not significantly alter the stress response to a psychosocial stressor 7 days post treatment administration

Seven days following treatment administration, participants underwent a stress-induction protocol (MAST) or control protocol to assess whether psilocybin reduces stress reactivity. Stress reactivity was quantified via cortisol concentrations, heart rate and blood pressure, and subjective ratings of anxiety, after participants underwent a stress-induction protocol or control protocol.

Cortisol. Analysis revealed a significant interaction between Treatment × Stress condition × Time on changes in cortisol ($F_{9,89.07} = 5.96$, $p < 0.001$). Irrespective of psilocybin or placebo treatment, individuals in the stress condition had significantly higher increases in cortisol compared to the no-stress test (Table 2). In the psilocybin group, cortisol values were significantly increased during the stress test ($t = 2.19$, df = 74.14, $p = 0.03$), 20 min later ($t = 2.31$, df = 112.90, $p = 0.02$), and 45 min later ($t = 2.32$, df = 117.65, $p = 0.02$), compared to baseline. In the placebo group, cortisol values were significantly increased during the stress test ($t = 3.23$, df = 74.14, $p = 0.002$), 25 min later ($t = 3.88$, df = 112.90, $p < 0.001$), and 45 min later ($t = 4.02$, df = 117.28, $p < 0.001$), compared to baseline (Fig. 3; Table 2).

Blood pressure and heart rate. Analysis revealed a significant

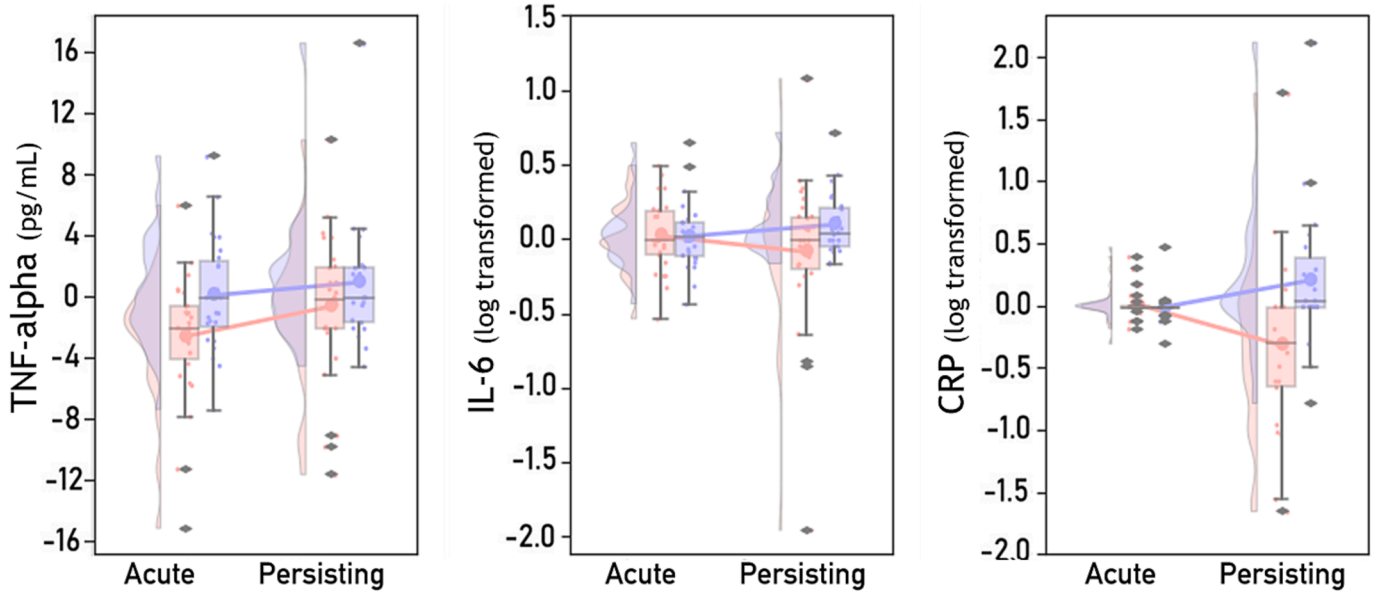

Fig. 2. Raincloud plots displaying concentrations of immune markers (change from baseline) which demonstrated differences between treatment groups. Significant differences were found between groups acutely (TNF-alpha) and 7 days post (IL-6 and CRP). The plot consists of a probability density plot, a boxplot, and raw data points. In the boxplot, the line dividing the box represents the median of the data, the ends represent the upper/lower quartiles, and the extreme lines represent the highest and lowest values excluding outliers. The code for raincloud plot visualization has been adapted from Allen, Poggiali (Allen et al., 2019). Data points are change scores from baseline; CRP and IL-6 are log-transformed scores.

Table 2
Mean (SD) of all outcome variables of the stress test.

Stress condition	Variable	Time relative to stress/control test									
		Pre		During		Post (20 min)		Post (45 min)		Post (50 min)	
		Psilocybin	*Placebo*	*Psilocybin*	*Placebo*	*Psilocybin*	*Placebo*	*Psilocybin*	*Placebo*	*Psilocybin*	*Placebo*
Stress	Cortisol	12.13 (7.01)	10.89 (4.48)	13.09 (7.03)	13.04 (4.65)	12.36 (7.07)	12.93 (4.81)	11.30 (6.33)	11.47 (4.83)		
	Diastolic HR	114.67 (14.61)	112.00 (10.06)	132.28 (21.16)	122.20 (13.18)						
	Systolic HR	67.13 (8.07)	67.93 (6.98)	82.07 (9.69)	77.20 (10.56)						
	BPM	67.20 (11.50)	67.40 (9.87)	66.50 (10.67)	63.07 (12.08)						
	Anxiety	3.13 (2.77)	1.43 (1.15)							2.60 (1.92)	2.57 (1.55)
No stress	Cortisol	16.38 (9.61)	13.18 (6.92)	15.03 (9.35)	12.81 (6.86)	12.51 (8.89)	12.80 (6.00)	11.66 (8.25)	11.15 (6.16)		
	Diastolic HR	116.21 (9.05)	110.33 (12.67)	113.20 (7.03)	109.00 (13.04)						
	Systolic HR	74.43 (6.41)	68.00 (8.51)	70.40 (8.33)	67.93 (7.71)						
	BPM	70.57 (10.40)	67.67 (15.64)	66.60 (8.76)	65.60 (13.82)						
	Anxiety	3.00 (2.95)	3.43 (2.53)							2.73 (2.15)	2.71 (2.61)

interaction between Treatment × Stress condition × Time in diastolic blood pressure ($F_{3,\ 55.16} = 8.40$, $p = 0.000$) and systolic blood pressure ($F_{3,\ 55.51} = 13.25$, $p = 0.000$), but not beats per minute (BPM) ($F_{3,\ 53.74} = 0.54$, $p = 0.66$). In both the group that received the placebo treatment, and the group that received the psilocybin treatment, individuals in the stress condition had significantly higher increases in diastolic (psilocybin: $t = 3.98$, df = 55.17, $p < 0.001$; placebo: $t = 2.51$, df = 54.50, $p = 0.01$) and systolic (psilocybin: $t = 4.46$, df = 55.52, $p < 0.001$; placebo: $t = 2.84$, df = 54.74, $p = 0.01$) blood pressure (Table 2).

Rating of anxiety after the stress test (POMS). Analysis revealed a trending interaction between Treatment × Stress condition × Time in ratings of anxiety 50 min after the stress test ($F_{3,\ 54.00} = 2.35$, $p = 0.08$). Whereas individuals who had received the placebo treatment reported an increase in anxiety following the stress test compared to the control protocol (t = 2.37, df = 54.02, p = 0.02), those who had received the psilocybin treatment did not show any difference in anxiety ratings when comparing responses following the stress test to the control procedure (t = 1.77, df = 79.9, p = 0.81) (Table 2).

3.5. Psilocybin-induced changes in IL-6 and CRP predict persisting positive changes in mood and sociality

An exploratory aim assessed the hypothesis that psilocybin-induced changes in immune status would be associated with psychosocial functioning. First, it was determined that psilocybin induced persisting changes in mood and sociability. Namely, those who received psilocybin had significantly higher ratings of positive mood changes (psilocybin mean (SE): 10.30 (1.90), placebo: 2.27 (0.78); $t(57) = 3.90$, $p < 0.001$, $d = 1.02$) and altruistic/positive social effects (psilocybin: 10.53 (1.84); placebo: 2.37 (1.10); $t(57) = 3.80$, $p < 0.001$, $d = 0.98$) 7 days after psilocybin, compared to the placebo group.

There were no significant changes in negative mood or antisocial/negative social effects (See Table S5 for mean and statistical values for all items on the PEQ).

Next, a canonical correlation analysis was conducted using the three markers of immune functioning (change scores from baseline) as predictors of reported persisting changes in mood and social relationships.

The analysis yielded two functions with squared canonical correlations (R_c^2) of 0.472 and 0.115 for each successive function. The full model across all functions was statistically significant ($F_{6,\ 32.00} = 2.47$, $p = 0.04$), explaining 54% of the variance. From this model, the first function was considered noteworthy, explaining 47.22% of the variance. The dominant contributors to the model were both persisting positive changes in mood and social relationships, whereas the dominant predictors were persisting decreases in IL-6 and CRP (Table 3).

3.6. Psilocybin-induced changes in TNF- α correlate with relative concentrations of glutamate/tCr in the hippocampus

Furthermore, acute glutamate and glial activity (mI) were measured in the medial prefrontal cortex (mPFC) and hippocampus to assess whether acute changes in cytokine concentrations related with neurometabolic activity.

First, it was determined that, compared to placebo, relative glutamate/tCr concentrations were significantly higher in the mPFC (U = 200.50, p = 0.01, d = 0.80) and significantly lower in the hippocampus (U = 163.50, p = 0.03, d = 0.69) after psilocybin. There were no significant treatment differences when comparing concentrations of mI/tCr for the mPFC (U = 346.50, p = 0.95, d = 0) or hippocampus (U = 239.00, p = 0.58, d = 0.13) (See table S6 and S7 for further information, including means and SEs).

In the psilocybin condition, a significant positive correlation was found between acute changes in TNF- α, and acute concentrations of glutamate/tCr in the hippocampus (R = 0.514, $p = 0.006$, n = 27), indicating that after psilocybin, the more of a reduction of TNF- α, the lower the hippocampal glutamate concentrations (Fig. 4). There were no significant correlations between changes in IL-6 and glutamate/tCr concentrations in the mPFC and hippocampus after psilocybin (all $p > 0.15$).

4. Discussion

The present study demonstrates that a single, moderate dose of psilocybin has both acute and persisting effects on the immune profile in healthy volunteers. Psilocybin immediately reduced concentrations of the pro-inflammatory cytokine TNF-α. This effect was specific, as the other assessed inflammatory marker concentrations remained unchanged. Seven days later, TNF-α concentrations returned to baseline while IL-6 and CRP concentrations were reduced after psilocybin, compared to placebo. When investigating whether such changes in the immune profile were related to acute neurometabolic activity, it was found that acute reductions in TNF-α were linked to lower glutamate/

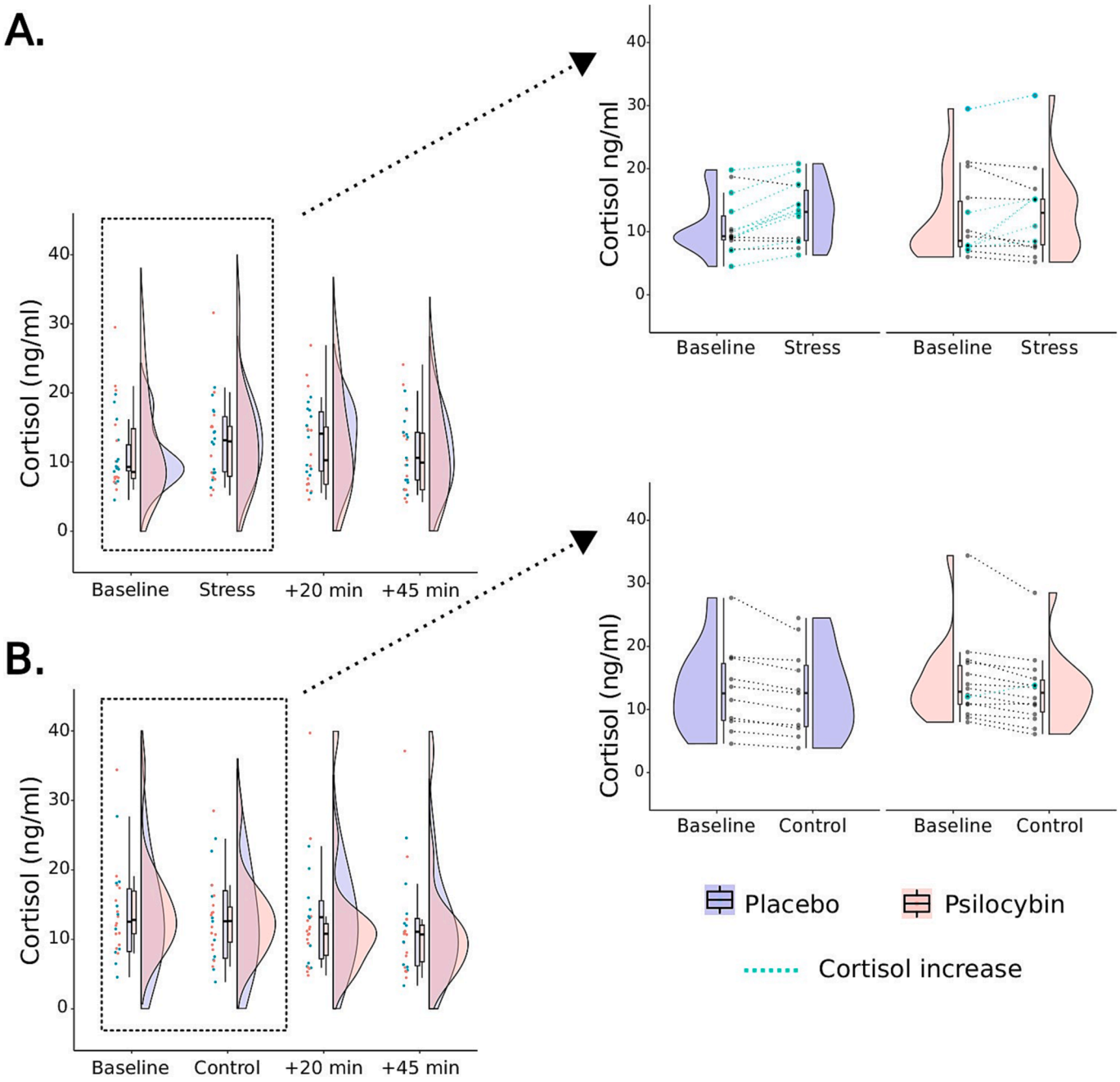

Fig. 3. Neuroendocrine response (cortisol values) before, during, and after the stress (A) or the control (B) protocol, in those who received psilocybin or placebo. The left panel displays the cortisol response across all time points. After the stress condition, both those who received psilocybin or placebo showed a significant increase in cortisol up to 45 min after the stress test. There were no significant changes in cortisol after the control condition. The right panel zooms in, displaying cortisol concentrations before the stress/control protocol and during the stress/control protocol. The connecting lines demonstrate how individual participant's cortisol concentrations changed over these two time points, and are separated by drug treatment condition (placebo or psilocybin). Blue lines indicate a cortisol increase. Although numerically more people in the placebo group showed increased cortisol concentrations after stress compared to psilocybin, the group difference was not significant.

tCr concentrations in the hippocampus, but not to glial activation (mI). When assessing whether changes in the inflammatory response related to persisting changes in psychological outcomes, it was found that the more of a reduction in IL-6 and CRP seven days after psilocybin, the more persisting positive mood and positive social effects participants reported. Regarding the stress response, after a psychosocial stressor, psilocybin did not significantly alter the stress response compared to placebo.

4.1. Acute and persisting effects of psilocybin on the immune profile

The effect of psilocybin on the immune profile of participants was two-fold: 1) acute changes were characterized by significantly decreased plasma concentrations of TNF-α, whereas 2) persisting changes were associated with decreased concentrations of circulating IL-6 and CRP. These changes are consistent with previous *in vitro* and animal *in vivo* studies demonstrating the anti-inflammatory properties of serotonergic psychedelics (Szabo, 2015; Flanagan and Nichols, 2018; Thompson and Szabo, 2020; Nau et al., 2013; Nau et al., 2015; Szabo et al., 2014). TNF-

Table 3
Canonical solution for inflammatory markers predicting persisting positive changes in mood and sociality for Function 1. $r_s > |0.45|$ and $h^2 > 45\%$ are underlined and deemed valuable contributors (for an in depth explanation and interpretation of canonical correlations and associated terminology, the reader is referred to (Sherry and Henson, 2005)).

Variable	Function 1			
	Coef.	r_s	r_s^2 (%)	h^2(%)
Persisting positive changes in mood	0.321	0.962	92.54	92.54
Persisting positive altruistic/positive social effects	0.6960	0.992	94.41	94.41
R_c^2			47.22	
TNF- α acute change	0.336	0.302	9.12	9.12
IL-6 persisting change	-0.402	-0.855	73.10	73.10
CRP persisting change	-0.588	-0.942	88.74	88.74

Note: *Coef* = standardized canonical function coefficient; r_s = structure coefficient; r_s^2 = squared structure coefficient; h^2 = communality coefficient.

α is an early response cytokine and a crucial, integrated part of inflammatory innate immune responses. Its modulation is therefore rapid and falls under tight control (Mizgerd et al., 2001; Cerami, 1992). As the acute, down-regulatory effect of psilocybin on circulating TNF-α was associated with increased concentrations of plasma cortisol (see supplementary results), one possible interpretation is the cortisol-induced modulation of this cytokine. Cortisol is known to be quickly and robustly induced by both psychological and physical stress and has a crucial role in stress adaptation and the restoration of homeostasis following acute stressors (Malarkey and Mills, 2007). Acute doses of psilocybin (Hasler et al., 2004), and its serotonergic psychedelic analogs are known to induce cortisol release in humans (Uthaug et al., 2020), and thus may have a stress-mimicking effect via HPA-axis modulation (Lee et al., 2015). Furthermore, cortisol and related glucocorticoids can rapidly and effectively suppress inflammation and have been used in the clinical therapy of both acute and chronic inflammatory diseases (Gleeson et al., 2011). The observed, prompt decrease in plasma TNF-α might be the direct result of the cortisol peak elicited by psilocybin administration. Another possible interpretation is that psilocybin exerts its anti-inflammatory effects via the 5-HT2A and/or sigma-1 receptors of circulating immune cells and thereby causes rapid changes in blood TNF-α concentrations. Previous preclinical studies with similar psychedelic analogs support this hypothesis (Uthaug et al., 2020; Nau et al., 2013; Nau et al., 2015; Szabo et al., 2014; Nardai, 2020).

IL-6 is a pleiotropic cytokine that has a dominantly pro-inflammatory effect in systemic and tissue-specific immune regulation (Garbers et al., 2018). IL-6 is a direct inducer and regulator of CRP in the liver, and thus blood IL-6 and CRP concentrations are strongly correlated (as also demonstrated in our data, see supplementary results), and CRP is considered an important circulating biomarker of inflammation in clinical practice (Pradhan, 2001). Since cortisol has a short biological half-life, and systemic cortisol-mediated effects normally last only for a couple of hours in humans, persisting decreases in the concentrations of both IL-6 and CRP are unlikely to be mediated by cortisol. Persisting immunomodulation by psilocybin via the 5-HT2A and/or sigma-1 receptors of immune cells offers a plausible explanation for the observed phenomenon and is also consistent with previous reports on the anti-inflammatory capacity of psilocybin and related psychedelic tryptamines, as discussed above (reviewed in (Szabo, 2015; Flanagan and Nichols, 2018). Finally, the persisting anti-inflammatory effects may also be the result of neuro-immunoregulatory feedback loops through HPA-axis modulation that involve cortisol in the acute phase and possibly other neuroendocrine regulators as well as cytokines in the long-run (Malarkey and Mills, 2007; Bonaz et al., 2016).

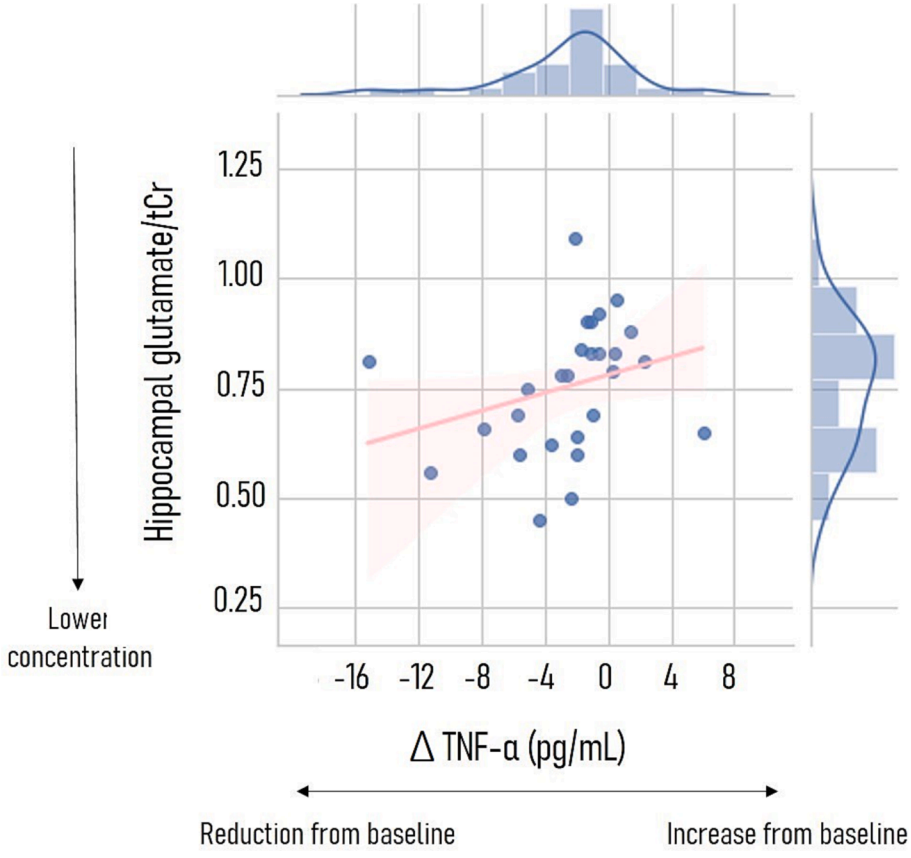

Fig. 4. Scatter plot depicting relationship between acute changes in TNF-α (acute concentrations of TNF- α – baseline concentrations of TNF- α) and acute hippocampal glutamate/tCr concentrations, in the psilocybin condition.

IL-6 and CRP are established, robust markers in subgroups of individuals with major depressive (MDD) and anxiety disorders where elevated concentrations are associated with more severe symptoms and symptom-dynamics (Wium-Andersen et al., 2013; Osimo et al., 2019; Chamberlain et al., 2019; Frommberger et al., 1997; Ting et al., 2020; Hodes et al., 2016). Similar patterns have also been observed in other psychiatry disorders, such as schizophrenia, supporting the subgroup-specific effects of inflammation on brain functions in neuropsychiatric disorders (Sæther et al., 2023). Furthermore, MDD patients that display higher circulating levels of inflammatory cytokines tend to less likely respond to conventional antidepressant treatments (Drevets et al., 2022). Thus, the persisting effect of psilocybin on circulating biomarkers of inflammation may reflect an important biological component of its documented, persistent antidepressant effects (Davis et al., 2021; Carhart-Harris et al., 2021), and suggests a similar mechanism for other tryptamines (Palhano-Fontes et al., 2019; D'Souza et al., 2022).

Relatedly, compared to those who received placebo, 7 days after psilocybin administration, participants reported a range of persisting positive effects which they attributed to psilocybin administration. A relationship was found between persisting reductions in CRP and IL-6, and increases in self-rated positive mood and social effects, two domains which are particularly interesting in relation to immune functioning. Namely, previous experimental work has demonstrated that when healthy participants undergo an inflammatory challenge, they show increases in depressed mood, and report feeling more socially disconnected from others (Moieni et al., 2015; Eisenberger et al., 2010; Reichenberg et al., 2001). Such findings are in line with research which suggests that pro-inflammatory cytokines initiate a "sickness behavior", characterized by social withdrawal, fatigue, anhedonia, and reduced appetite, which is reversible once cytokine concentrations are reduced (Dantzer, 2009; Hart, 1988). Importantly, this cytokine-induced sickness behavior is an innate, adaptive immune system response, thought to facilitate recuperation from illness by conserving energy to combat acute inflammation (Maes et al., 2012). That said, this behavior can also become pathological, for example if it is exaggerated in intensity (cytokines produced in high quantities) or duration (cytokines produced for a longer duration than normal) (Dantzer, 2009). Accordingly, there is growing evidence that disorders such as depression are associated with significant elevations in circulating concentrations of pro-inflammatory cytokines, especially IL-6, as well as CRP (Wium-Andersen et al., 2013; Miller et al., 2009; Mössner et al., 2007). As such, cytokine modulators have been suggested to be novel drugs for depression (Kappelmann et al., 2018; Kappelmann et al., 2021), particularly if patients' baseline inflammatory concentrations are high (Raison et al., 2013). In trying to understand the relationship between inflammation and depressive symptomology, previous work has found that inflammatory-induced feelings of social withdrawal mediate increases in depressive mood during an inflammatory challenge (Eisenberger et al., 2010). Interestingly, it has been repeatedly found that a single administration of a psychedelic drug, like psilocybin, lysergic acid diethylamide (LSD), ayahuasca, or the mixed $5HT_{2A}$ agonist/ monoaminergic releaser 3,4-methylenedioxymethamphetamine (MDMA) induces prosocial effects and increases in feelings of connectedness in both healthy participants (for a review see Preller and Vollenweider (Preller and Vollenweider, 2019) and patients (Watts et al., 2017). These psychedelic-induced prosocial effects have been repeatedly found to relate to persisting (therapeutic) outcomes (Watts et al., 2017; Kiraga et al., 2021; Mason et al., 2019). Finally, the only other study to-date which assessed the relationship between inflammatory markers and persisting psychological effects after psychedelic administration, found that the larger the reduction of CRP, the lower the ratings of depression 48 h after ayahuasca treatment (Galvão-Coelho et al., 2020). Thus taken together, evidence suggests a relationship between immune system functioning, prosocial behavior, and psychological well-being after psychedelic intake, which could account for some of the immediate and persisting therapeutic responses seen in psychedelic-assisted clinical trials. However, limitations inherent to the study design warrant consideration. Our sample consisted of 60 healthy participants who had a previous experience with a psychedelic drug, a sample that is neither wholly generalizable to a clinical, nor to the general, population. That said, in regards to the latter, participants reported very infrequent use of psychedelic and other psychoactive substances (Table 1), and were only eligible for study participation if their last psychedelic use was > 3 months ago. Furthermore, an inherent difficulty of studying substances with such salient subjective effects is maintaining the treatment blind. Thus, it could be suggested that participant recognition of the treatment condition could affect biological and subjective parameters, emphasizing the importance of active placebo conditions or cross-psychotropic comparisons in future trials.

4.2. *Relationship between psilocybin-induced changes in the inflammatory response, and brain neurometabolites*

Our findings about the acute and persistent effects of psilocybin administration on circulating cytokines show both an early-immediate (TNF-α) as well as persisting systemic, anti-inflammatory modulation (IL-6 and CRP). In order to be able to contextualize these results in a psycho-neuroimmunological frame of interpretation, we assessed the relative concentrations of mI and glutamate in several brain areas implicated in stress and emotion regulation, and correlated those which demonstrated a treatment effect with the immune biomarker results.

Myo-inositol is an important marker of glial activation reflecting the inflammatory activity of the immunocompetent cells of the brain: astrocytes and microglia (reactive gliosis) (Chang et al., 2013; Poletti et al., 2020). As mI/tCr concentrations did not display a treatment effect, it is unlikely that glial activation in the mPFC and hippocampus contribute to the psilocybin-altered immune response. Contrarily, psilocybin induced region-dependent alterations in glutamate, thus we correlated glutamate/tCr concentrations with acute (TNF-α) concentrations in relevant areas of the cortex. We found a positive relation between acute TNF-α and glutamate/tCr concentrations in the hippocampus. (Sub)cortical glutamate concentrations and glial activity (especially that of astrocytes) are tightly connected, and inflammation has been shown to influence glutamate neurotransmission in the brain (Haroon et al., 2017). Furthermore, it has also been reported that inflammation and dysregulated glial activation can lead to increased release and abnormal clearance of glutamate in the synaptic space contributing to the pathophysiology of mood disorders, such as MDD (Haroon et al., 2017). Based on our results, we suggest that the observed psilocybin-induced changes in glutamate concentrations, and correlations between TNF-α and glutamate are not glia-dependent, but are likely the result of neuromodulation. According to previous reports, brain TNF-α and glutamate act synergistically and their concentrations are correlated, a phenomenon that has been suggested to be a core mechanism in inflammation-related neurodegenerative processes (Zou and Crews, 2005), thus our findings are complementary by demonstrating that after psilocybin administration, greater reductions of TNF-α were associated with lower hippocampal glutamate concentrations. Thus it is interesting to speculate on, whether a psilocybin-induced decrease of TNF- α may result in reduced hippocampal glutamate concentrations, which could be therapeutically relevant in the case of pathological conditions characterized by excessive (damaging) glutamate release and hippocampal dysfunction (Averill et al., 2017; MacQueen et al., 2003; Olmos and Lladó, 2014).

In sum, our findings show some degree of area-specificity of acute psilocybin effects that are mostly related to the hippocampus via TNF-α and glutamate/tCr. The observed effects are not persistent and, given the absence of mI changes, do not indicate a global, all-encompassing feature with regards to glial cell activation. This might be the consequence of a direct, local effect of psilocybin (in the hippocampal area), or on the other hand, may be an issue of statistical power due to sample numbers. As such, further investigations into the potential acute and

persisting cortical glia-modulatory effects of psilocybin are highly warranted.

4.3. Persisting effects of psilocybin on the stress response

In the current study, stress was induced by the MAST, a test developed to combine both physical and psychological stress components, which activate both the sympatho-adrenal-medullary (SAM) and the HPA axis (Smeets et al., 2012). The SAM is considered the "fast response" to a stressor, acting via direct and fast sympathetic nerve stimulation, which results in secretion of catecholamines such as adrenaline and noradrenaline, and increases in heart rate, blood pressure, and respiration frequency. This quick response helps the body focus its resources, giving rise to the well-known "fight or flight" response (Sharpley, 2009). The second stress response pathway is slower, acting via the HPA axis which commences with the perception of stress (López et al., 1999), resulting in the hypothalamus releasing corticotropin releasing hormone, which triggers excretion of adrenocorticotropic hormones by the pituitary gland, and ultimately promotes release of cortisol in the bloodstream via the adrenal glands (Ulrich-Lai and Herman, 2009). Compared to the no-stress control protocol, the MAST induced significant autonomic responses including increases in systolic and diastolic blood pressure, and increases in cortisol, in both those which received psilocybin, and those that had received placebo. Such findings are in line with previous studies utilizing the MAST in a healthy population (Smeets et al., 2012; Meyer et al., 2013; Quaedflieg et al., 2013; Quaedflieg et al., 2013; Shilton et al., 2017; van Ruitenbeek et al., 2021). Unlike previous studies, this study did not find a significant increase in anxiety ratings between the stress and no stress conditions after the MAST. However it is important to note that in this study, anxiety ratings were measured 50 min after the stress test, a timeframe in which previous studies have shown that participants' anxiety ratings return to baseline (Meyer et al., 2013).

When comparing cortisol and cardiovascular responses on the MAST between the drug treatment groups, there were no significant statistical differences between groups. Contrarily, when inspecting the ratio of participants whose cortisol values increased within the psilocybin-stress and placebo-stress groups, it appeared that less participants in the psilocybin-stress group demonstrated a cortisol response to stress (Fig. 3; T_1: *mean change of 0.96 ng/mL* (psilocybin) vs *2.15 ng/mL* (placebo), respectively). Thus it could be that given the moderate dose of psilocybin and the participant group (healthy volunteers), the sample size per group (N = 15) was too small to detect between-group differences 7 days post administration. Future studies with a larger sample size, and in a clinical population, should investigate whether psychedelics induce persisting changes to the HPA axis, such as HPA axis downregulation. The question is of importance as hyperactivity of the HPA axis, and resultant hypercortisolism, are one of the most consistent biological findings in regards to stress-related disorders (Tafet and Nemeroff, 2020; Arborelius et al., 1999; Nestler et al., 2002).

5. Conclusion

In conclusion, our findings demonstrate a rapid and persisting decrease in cytokine concentrations upon psilocybin administration (Fig. 5). This acute change may contribute to the psychological and therapeutic effects of psilocybin demonstrated in ongoing patient trials. Such rapid effects may be modulated via an acute glutamatergic – TNF- α interaction in the hippocampus, whereas persisting changes in IL-6 and CRP may contribute to reported increases in mood and prosocial behavior.

Additionally, our results do not provide evidence that a moderate dose of psilocybin induces a persisting alteration in the stress response in healthy volunteers. Rather our results could provide preliminary

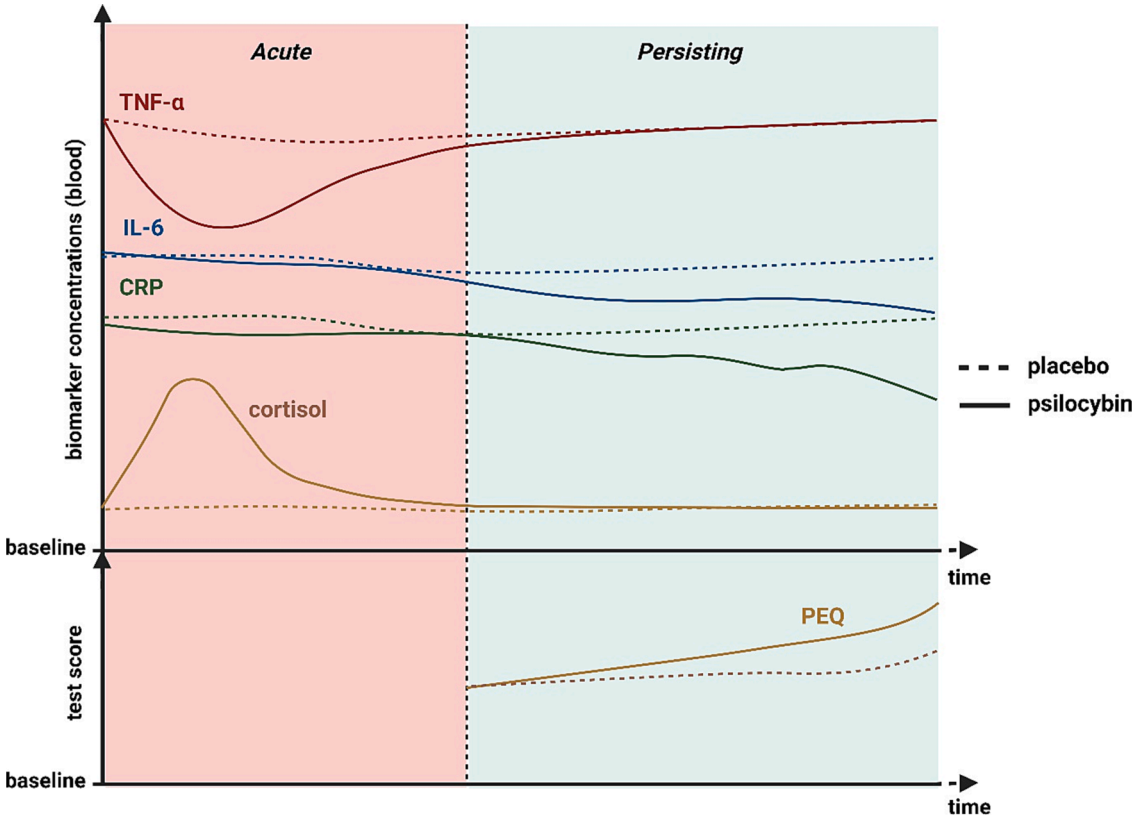

Fig. 5. Pictorial summary of the potential connections between the biological markers assessed in this study (inflammatory and HPA-axis modulation) and the psychological outcomes (PEQ). Not represented is the neuroendocrine response to the stress test, which can be found in Fig. 3.

indication for future studies with a larger (clinical) sample size to further investigate this.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study is part of the Beckley/Maastricht Research Programme. The Beckley Foundation made a financial contribution to the study. The authors report no other relevant funding, and all authors report no potential conflicts of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.09.004.

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