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Lipids and C-reactive protein predict anhedonia and reward circuit functional connectivity responses to anti-cytokine and dopaminergic therapies in patients with depression

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ABSTRACT

Increased inflammation and associated metabolic disturbances have been shown to affect neurotransmitters and brain circuits, contributing to an immunometabolic phenotype of anhedonic depression. To extend our previous findings on relationships between plasma lipids and antidepressant response to anti-cytokine therapy, we explored in secondary analyses whether lipid-related biomarkers similarly predicted change in anhedonia or functional connectivity (FC) in dopamine-rich corticostriatal reward circuitry in medically-stable, depressed patients with a range of inflammation levels (indexed by plasma C-reactive protein [CRP]) who were administered inflammation-targeted therapies. Relationships were examined between baseline lipids (plasma cholesterols, triglycerides and non-esterified fatty acids) and reduction of anhedonia symptoms in Study 1 ($n = 60$) after three infusions of infliximab or placebo and change in resting-state FC in Study 2 ($n = 31$) after acute, within-subject challenge with levodopa (L-DOPA) and placebo. A treatment by inflammation interaction revealed lower anhedonia after infliximab versus placebo ($F[1,49] = 5.5$, $p < 0.05$) in patients with, but not without, CRP>3 mg/L ($n = 27$). A composite score of lipid-related biomarkers (with increasing values reflecting higher concentrations) also precited anhedonia response (post-treatment minus baseline) to infliximab ($r = -0.46$, $p < 0.05$) but not placebo ($r = 0.14$, $p = 0.56$). Lipid scores similarly predicted CRP-related increases in reward circuit FC after L-DOPA ($r = 0.53$, $p < 0.01$) but not placebo ($r = 0.20$, $p = 0.34$). Responses to infliximab and L-DOPA were strongest in patients with versus without clinically elevated CRP (>3 mg/L) and/or cholesterol (>150 mg/dL)($p < 0.05$). Results highlight a role for dyslipidemia in immunometabolic depression, biomarkers of which, together with CRP, have potential to classify patients indicated for therapies that block inflammation or its effects on neurotransmitters like dopamine.

1. Introduction

Inflammation and its effects on the brain are thought to contribute to major depressive disorder (MDD) and particularly symptoms of anhedonia in the ~30–50 % of patients with higher levels of peripheral inflammatory cytokines and acute phase reactants like C-reactive protein (CRP) [1–3]. While adiposity and associated metabolic disturbances are known drivers of systemic inflammation [4], inflammatory cytokines also promote disease processes such as dyslipidemia and insulin resistance [5,6]. Recent evidence suggests these bidirectional relationships between inflammation and metabolic disturbances may jointly contribute to the brain and behavioral pathophysiology that defines a subgroup of patients with an immunometabolic phenotype of depression [7,8]. As both increased inflammation and metabolic disturbances have been associated with reduced responsiveness to conventional antidepressant therapies [9–12], better understanding the role of immune and metabolic interactions in depression may open new avenues for therapeutic strategies that can be targeted to patients with this

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immunometabolic phenotype [13,14].

In terms of potential mechanisms, robust clinical and laboratory animal evidence has established that administration of inflammatory stimuli impacts dopamine release and the neural activation of reward-relevant basal ganglia and prefrontal regions, and induces motivational deficits and anhedonia, a core and disabling symptom of depression [15,16]. Our recent data also contributes to a growing literature showing relationships between endogenous elevations in circulating inflammatory markers in patients with MDD and other psychiatric disorders and alterations in brain structure and function [17], including in key striatal and prefrontal regions involved in reward processing and effortful behavior [18–23]. For example, we showed that plasma concentrations of CRP (as well as inflammatory cytokines and their soluble receptors) in medically-stable MDD patients negatively corelated with functional connectivity (FC) in dopamine-rich cortico-striatal reward circuitry using resting-state functional magnetic resonance imaging (fMRI) [20]. Lower FC in a ventral striatum (VS) to ventromedial prefrontal cortex (vmPFC) reward circuit was in turn associated with higher symptoms of anhedonia, as assessed by a subscale of the Inventory of Depressive Symptomatology-Self Report (IDS-SR). These relationships between CRP, reward circuit FC and anhedonia persisted in both data-driven whole-brain and targeted seed-to-region of interest (ROI) analyses [20,22]. Similarly, metabolic challenges including high fat meals and lipid solutions also affected dopamine release and neural activity in reward-relevant brain regions [24–26], and evidence of dyslipidemia associated with low cortical and subcortical cerebral blood flow and FC in patients with depression [27,28].

Regarding therapeutic strategies, we and others have studied depressed patients with a range of CRP concentrations and variable evidence of metabolic disturbance to determine whether those with higher inflammatory or metabolic biomarkers exhibit preferential brain or behavioral responses to anti-cytokine or dopaminergic therapies [29–33]. For example, inhibition of tumor necrosis factor (TNF) signaling with infliximab reduced overall depressive symptom severity versus placebo in treatment resistant depressed (TRD) patients with higher levels of baseline plasma CRP and other inflammatory markers, with maximum effect at CRP >5 mg/L [29]. Consistent with more recent reports of greater efficacy for reduced anhedonia than overall depression severity after ani-cytokine therapy in depressed patients [30,32], the symptom most improved by infliximab in TRD patients with high CRP was related to anhedonia, item #7 (work and activities) on the Hamilton Depression Rating Scale (HAM-D) [29]. Analysis of gene expression signatures in infliximab-responders showed that baseline transcripts predictive of a subsequent antidepressant response to infliximab were not only related to inflammation and TNF-signaling, but also to cholesterol and glucose metabolism [34]. These findings were validated by assessment of circulating biomarkers whereby plasma lipids (cholesterols, triglycerides, and non-esterified fatty acids [NEFA]), and to some extent measures of glucose metabolism, predicted the antidepressant response to infliximab [33]. Interestingly, plasma lipids were lower after infliximab versus placebo in TRD patients with higher CRP, and infliximab modified expression of metabolic-related gene transcripts in responders [33,34]. These data suggest that dysregulation of cholesterol metabolism and high plasma lipids are predictive of and possibly involved in the antidepressant response to infliximab in TRD patients with increased inflammation.

In addition to inhibiting inflammation, this immunometabolic phenotype of depression may benefit from therapies that reverse the effects of inflammation and metabolic dysfunction on brain neurotransmitters like dopamine [12,15]. Accordingly, we have found evidence of low synthesis and release of striatal dopamine in both patients and laboratory animals administered inflammatory cytokines [35,36], which was reversed by the dopamine precursor, levodopa (L-DOPA) [37]. We also recently studied medically stable MDD patients with a range of CRP concentrations to determine whether those with higher inflammation, presumed to have lower dopamine availably, would respond to acute challenge with L-DOPA by increased FC in reward circuitry. Indeed, L-DOPA increased FC in a VS-vmPFC reward circuit in patients with CRP > but not ≤2 mg/L, with the strongest effects in patients with CRP >3 mg/L [38]. Relationships between FC and change in hedonic capacity, as determined by the Snaith-Hamilton Pleasure Scale (SHAPS) used as a momentary assessment, also showed a treatment by CRP interaction whereby higher VS-vmPFC FC after L-DOPA related to improvements in anhedonia [38]. The findings support the ideas that MDD patients with higher CRP have lower dopamine availability, and that FC in reward circuitry may serve as a brain biomarker for assessing response to novel therapies in depressed patients with increased inflammation. Whether the FC response to L-DOPA relates to lipid biomarkers of metabolic disturbance, or whether depressed patients with higher CRP and lipids have special benefit from treatments targeting inflammation or its effects on the brain, has not been investigated.

Herein, and consistent with prior reports [30,32], we first explored whether anti-cytokine therapy with infliximab reduced symptoms of anhedonia versus placebo, and at a lower CRP cut-point than for overall depression severity (>3 mg/L versus >5 mg/L), as assessed by the subscale from the IDS-SR in patients with TRD (n = 60; Study 1). Total, low and non-high-density lipoprotein (LDL, non-HDL) cholesterol, triglycerides, and NEFA (but not HDL cholesterol) were associated with the overall antidepressant response to infliximab when controlling for covariates [33]. Therefore, relationships between the anhedonia response to infliximab versus placebo and these lipids at baseline were examined using a composite score method that captures the contribution of multiple related metabolic or inflammatory markers [2,39–41]. In Study 2, we similarly explored whether plasma lipid scores predicted reward circuit FC responses to challenge with L-DOPA versus placebo previously shown to be modified by plasma CRP concentrations in a randomized, within-in subject cross-over challenge in MDD patients (n = 31; Study 2). Finally, how the presence or absence of clinically significant elevations in CRP and/or cholesterol related to anhedonia and FC responses was also examined. We hypothesized that lipid biomarkers would be associated with both reduced symptoms of anhedonia and increased reward circuit FC after infliximab and L-DOPA, respectively, and that patients with elevations in CRP and lipid biomarkers would have the strongest responses. This work contributes to our understanding of the pathophysiology of and biomarkers to identify patients with an immunometabolic phenotype of anhedonic depression that might benefit from appropriately targeted therapies.

2. Methods

2.1. Participants and procedures

Both studies enrolled adult (18–65 years) male and female outpatients with a primary diagnosis of MDD (or bipolar disorder current episode depressed) experiencing a current MD episode without psychosis, as determined by Structured Clinical Interview for DSM criteria (see **Supplement**). All subjects were medically stable per medical history, physical exam, and laboratory testing. No patients tested for drugs of abuse at screening or study visits, and none took medications affecting the immune system. See **Supplement** for details.

Study 1: Sixty variably medicated participants with TRD, defined as non-responsive to antidepressant treatment per a score ≥2 on the Massachusetts General Hospital Staging (MGH-S) method in the current episode, underwent blood sampling and behavioral assessments as part of a randomized, double-blind study of infliximab versus placebo (n = 30/group) as previously described. See **Supplement** and reports of inflammatory and metabolic predictors of overall depression severity response to infliximab versus placebo for details [29,33,34]. Patients recruited to have a range of inflammation levels defined by screening CRP concentrations were stratified based on > versus ≤2 mg/L (reflecting the middle of the moderate risk category for CRP, 1–3 mg/L per American Heart Association [AHA] guidelines) [42] and randomized

to receive three infusions of infliximab (5 mg/kg) or matched placebo in saline at baseline, 2 weeks, and 6 weeks of a 12-week trial. Symptoms of anhedonia were assessed at baseline and at weekly or bi-weekly follow-up safety or clinical assessment visits for 12 weeks after the first infusion of infliximab or placebo (see Fig. 1A).

Study 2: Thirty-one participants with available and analyzable resting-state fMRI scans both before and after acute challenge with L-DOPA and placebo administered on separate study visits were included to examine FC in VS-vmPFC reward circuitry as previously described [38]. Patients were recruited to have a range of inflammation levels from low to high as distributed across mean plasma CRP concentrations of 0–1, >1–2, >2–3, and >3 mg/L (~25 %/group). All subjects were free of psychotropic medications. No participants were removed from antidepressants for the purposes of this study. Patients underwent fMRI before and after acute challenge with L-DOPA (250 mg with 25–50 mg carbidopa; see **Supplement** for details) and identically encapsulated placebo administered on separate visits spaced ~1-week apart using a double-blind, randomized, cross-over design [38].

The studies were registered with ClinicalTrials.gov (Study 1: NCT00463580; Study 2: NCT02513485) and shared as NIMH Data Archive #2540 (Study 2). All procedures were approved *a priori* by the Institutional Review Board of Emory University. All participants

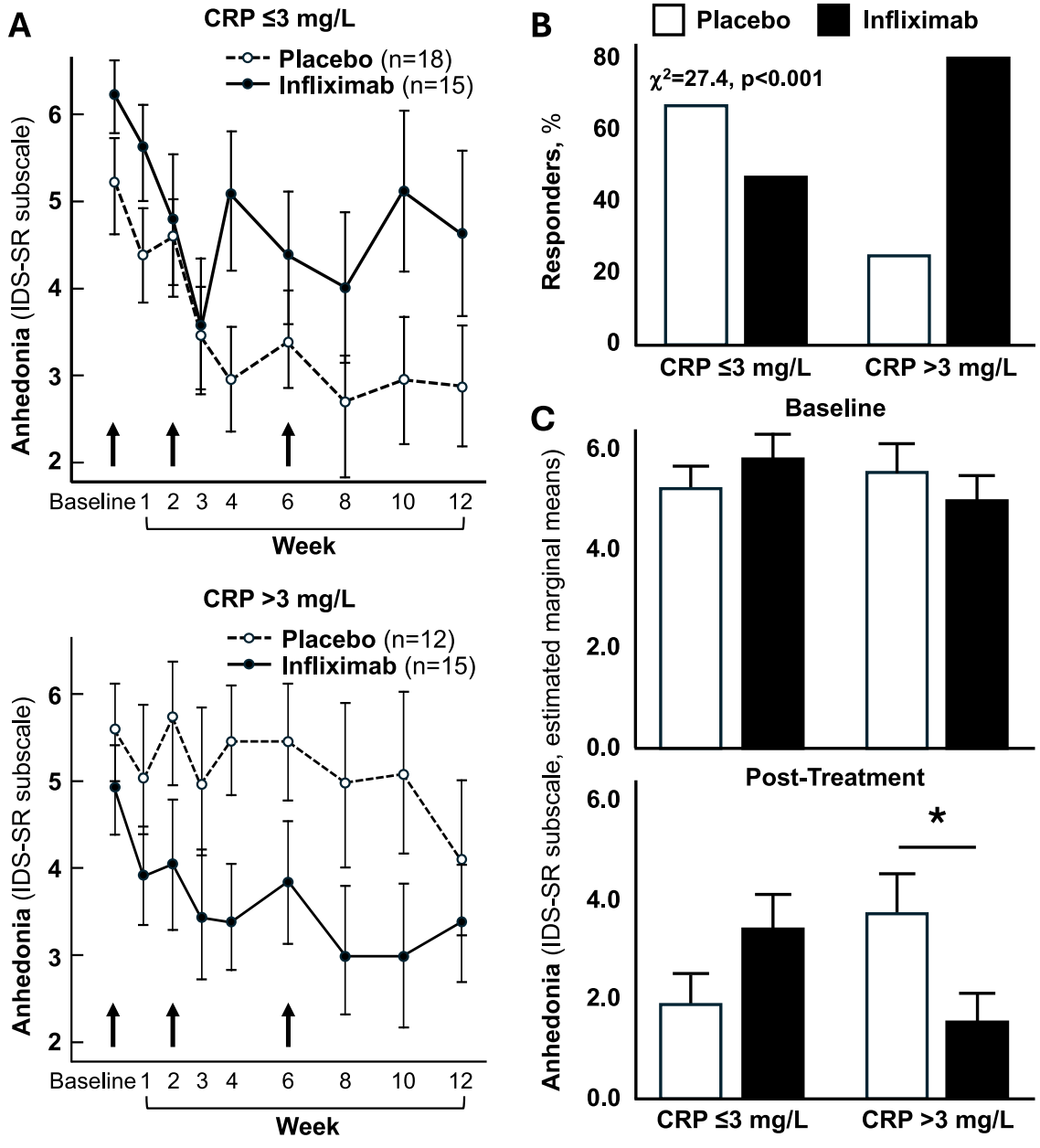

Fig. 1. The anhedonia response to infliximab versus placebo and role of baseline plasma CRP levels in TRD patients (Study 1). Anhedonia scores across time as a function of treatment and baseline plasma CRP level (>3 versus ≤3 mg/L, n = 60; **A**) revealed early symptom reduction followed by attenuation of anhedonia response ~2–4 weeks after each infusion (baseline, week 2 and week 6, black arrows). This pattern was most prominent in patients with CRP >3 mg/L receiving infliximab, and this group showed the highest anhedonia response rate (≥50 % reduction in symptoms at any time during the study from baseline) ($p < 0.01$; **B**). A treatment by inflammation interaction also revealed lower anhedonia scores (maximal response at any time during the study) after infliximab versus placebo only in patients with >3 mg/L CRP ($p < 0.05$; **C**, lower panel), with no difference in anhedonia scores at baseline (upper panel). *$p < 0.05$, Bonferroni correction controlling for covariates.

provided written informed consent.

2.2. Blood collection

Whole blood was collected into EDTA-containing vacutainer tubes through indwelling catheters after participants had at least 30 min of rest. Plasma was obtained by centrifugation at 1000×*g* for 10 min at 4 °C, aliquoted into siliconized polypropylene tubes, and stored at −80 °C until assay. Blood for lipid biomarkers was collected ~3 h from the patient's last food intake (~3pm ± 1 h) during an inpatient baseline study visit for Study 1, and after an overnight fast (~10am ± 2 h) during a baseline visit ~1 week prior to the first study visit for Study 2.

2.3. Measurement of CRP and lipid biomarkers

High sensitivity (hs)-CRP was measured by immunoturbidimetric methods as described [29,38]. Lipid-related biomarkers (total, LDL, and non-HDL cholesterols, triglycerides, and NEFA) were measured in the Biomarker Core Lab of the Atlanta Research and Education Foundation using enzymatic methods reagents from Sekisui Diagnostics (Exton, PA) implemented on the AU480 chemistry analyzer (Beckman Coulter) as described [33,43]. Mean inter- and intra-assay coefficients of variation were reliably <10 %. Non-normal markers were natural log transformed (non-HDL, triglycerides and NEFA for Study 1; triglycerides for Study 2). To examine the shared contribution of all lipid-related metabolic markers to relationships with anhedonia and FC responses, a lipid composite score was created for each study as the sum of Z-scores of all markers, a common method for examining the contribution of multiple related metabolic or inflammatory markers [2,39–41]. Because Z scores center the mean of each marker at 0 ± 1 (mean, SD), thus classifying each participant as having "higher" (above 0) or "lower" (below 0) levels of each marker, when combined into a composite score (as the sum of Z scores for each marker) it can be used as a continuous variable for comparison with other variables [2](see Fig. S1 for the contribution of each individual marker to composite scores above or below the median). The lipid composite scores for both studies were normally distributed and passed tests of normality.

2.4. Anhedonia

For Study 1, symptoms of anhedonia were assessed using a 3-item Anhedonia Subscale from the IDS-SR [44] previously shown to be associated with inflammation and its effects on corticostriatal reward circuitry [2,20,22]. This subscale included items 8 *response of mood to good or desired events*, 19 *general interest in people and activities*, and 21 *capacity for pleasure* each scored on a scale of 0–3. As with our prior work assessing the effects of infliximab versus placebo on depression severity, including the original trial results [29], response (post-treatment minus baseline) was defined as the maximum reduction in anhedonia symptom severity at any timepoint during the study versus baseline [29,33,34]. Anhedonia response was used either as a continuous variable (see Statistical analyses) or to calculate rate of response as defined by ≥ 50 % reduction in anhedonia scores versus baseline [29,33,34]. Complementary results for the last anhedonia assessment were also reported.

2.5. Reward circuit FC

Imaging data were acquired at Emory's Center for Systems Imaging on a Siemens Prisma 3T scanner and 64-channel head coil as previously described [38]. Briefly, a T1-weighted, magnetization prepared rapid gradient echo (MPRAGE) sequence was obtained at 1 mm^3 resolution. Wakeful resting-state fMRI images were acquired by 2D gradient-echo EPI BOLD (see **Supplement**) both before and after L-DOPA or placebo administration using phase-encoding directions of opposite polarity (anterior-posterior) for distortion correction over ~10 min [45]. Data were analyzed with standard preprocessing protocols in AFNI (http://afni.nimh.nih.gov/; see **Supplement**). Resting BOLD time series were additionally processed to minimize artifacts from head motion, respiration, cardiac pulsation, and hardware using ANATICOR method [46] via motion/outlier censoring (aka scrubbing), nuisance regression, and band pass filtering (0.009Hz < f < 0.08Hz; see **Supplement** for signal censoring). Individuals' 4D fMRI data were spatially normalized into standard Montreal Neurological Institute (MNI) space. Left-VS (see **Supplement** for justification) to vmPFC FC was assessed using a targeted, *a priori* seed-to-ROI approach. Subject-level Fisher's normalized Z-scores were extracted for FC between a 3 mm^3 radius spherical seed centered on left-VS (including nucleus accumbens) [47] and vmPFC ROI previously associated with neural activation to receipt of reward in neuroimaging meta-analysis [48] and used in our previous work [20,22,38,40,41]. This unbiased, targeted approach was chosen to increase rigor, reproducibility, and potential application of results to future trials (see **Supplement**) [38].

2.6. Statistics

Patient characteristics were summarized using mean and standard deviation (SD) for continuous and percent for categorical variables. Analyses were conducted with and without clinical and demographic covariates that may influence relationships between inflammatory or metabolic markers and brain and behavioral responses (age, sex, race, and body mass index [BMI]). To establish relationships between CRP or lipid biomarkers and change in anhedonia symptoms that were independent of depression severity, baseline Hamilton Depression Rating Scale (HAM-D) scores were controlled in Study 1, as well as use of psychotropic (n = 37) and cholesterol (n = 10) medications (which were absent in Study 2). Study 2 also controlled for study-specific variables (e.g., treatment order, carbidopa dose; see **Supplement** for details).

Analyses for Study 1 first examined the effects of infliximab and placebo (treatment) on symptoms of anhedonia over time using a general linear model (GLM) with repeated measures on time (baseline and all post-treatment assessments). Data were summarized as mean (± SEM) as a function of treatment and baseline CRP > versus ≤3 mg/L to visualize the pattern of anhedonia response by inflammation level. Based on the revealed response pattern and prior analyses of the primary study outcomes [29,33,34], response at any time during the study was calculated using an intent-to-treat approach [29], and examined first in relation to response rate (≥50 % reduction in symptom severity from baseline) as a function of treatment and CRP level by logistic regression with likelihood ratio tests. Between-subject effects of treatment and inflammation (CRP level) on anhedonia symptoms (maximal response at any time as a continuous variable) was also examined using a general linear model (GLM) with repeated measures on time (baseline and post-treatment).

To determine whether baseline lipid biomarkers predicted the change in anhedonia scores, the anhedonia response (maximal response as anytime during the study minus baseline) was calculated. Relationship of this anhedonia response was first examined in relation to treatment and CRP level with GLM. Post-hoc comparisons with Bonferroni correction were used to interpret GLM results. Linear regression models were used to examine relationships between baseline lipid biomarkers (lipid composite scores) and anhedonia responses to infliximab or placebo (Study 1) and reward circuit FC response to L-DOPA and placebo (Study 2). To determine whether relationships between the lipid biomarkers and anhedonia and FC responses differed for infliximab or L-DOPA versus placebo, interaction terms (lipid composite score X treatment) were examined in multivariate models including the composite scores and treatment, in addition to comparison of slopes (beta coefficients) for each independent treatment [49] to examine moderation. See **Supplement** for details. Individual lipid markers were explored in linear models containing covariates to determine whether common markers predicted both anhedonia and FC responses. Participants were then grouped based on presence or absence of CRP >3 mg/L and/or total

cholesterol >150 mg/dL (reflecting higher than optimal cholesterol levels according to AHA guidelines) [50] and their anhedonia and FC responses to infliximab or L-DOPA were compared by GLM. Between-subjects contrasts were also used to compare responses of patients with elevations of one or both biomarkers to responses of patients without either CRP >3 mg/L or cholesterol >150 mg/dL. All tests of significance were two-tailed with $\alpha < 0.05$, conducted in IBM SPSS Statistics 29.

3. Results

Baseline sociodemographic, clinical, and biomarker data for 60 patients randomly assigned to infliximab or placebo (n = 30 per group) in Study 1 as described [29] are shown in Table 1. There were no significant differences between groups for demographic or clinical variables, including baseline anhedonia scores. Biomarkers of cholesterol metabolism were available from 52 subjects (n = 26 per group). Because baseline cholesterols and triglycerides were higher in patients assigned to placebo, Z-scores for each lipid biomarker were calculated separately for each group. This standardized each marker to 0 ± 1 (mean, SD) for both the infliximab and placebo-treated groups prior to creating the lipid composite score. Similar results obtained from Z-scores created from the entire group are reported in the **Supplemental Results**. All analyses also controlled for demographic and clinical covariates that, even if not significantly different, may contribute to or confound relationships between biomarkers and behavior. Biomarkers of cholesterol metabolism were available from all 31 patients with rsFC available both before and after placebo and L-DOPA administered ~1 week apart in randomized order as described [38] for Study 2 and per Table 2.

3.1. Anhedonia response to infliximab in study 1: role of higher CRP

Of the 60 patients randomly assigned to infliximab or placebo, 27 (45 %) had baseline CRP concentrations >3 mg/L (see Table S1 for participant data by CRP level). All 60 patients received at least one infusion followed by at least one follow-up visit, and 27 in the infliximab group and 28 in the placebo group completed all 3 infusions. Five participants in the infliximab group dropped out prior to the end of the study (due to scheduling conflicts or were lost to follow-up), three of which received only one infusion. Two participants in the placebo group received only 2 infusions (both due to medical or psychiatric complications), and 1 of these participants dropped out at that time. Thus, 90 % of patients completed all 12 weeks of the trial (29 in the placebo group and 25 in the infliximab group) [29], and 6 of these study completers were missing anhedonia data from at least one timepoint during the study.

Table 1
Demographic, clinical, and baseline biomarker characteristics of TRD patients receiving infliximab or placebo infusions.

Study 1	Infliximab (n = 30)	Placebo (n = 30)	P-value
Sex, female	20 [66.7 %]	20 [66.7 %]	1.00
Race			
Caucasian	23 [76.7 %]	23 [76.7 %]	0.81
African American	6 [20.0 %]	5 [16.7 %]	
Other	1 [3.3 %]	2 [6.7 %]	
Age	42.5 [8.2]	44.3 [9.4]	0.42
BMI	31.2 [6.9]	32.7 [8.0]	0.44
BL CRP (mg/L)	6.3 [8.9]	5.4 [8.2]	0.69
BL HAM-D-17	24.1 [4.0]	23.6 [3.8]	0.60
BL Anhedonia	5.6 [1.8]	5.2 [1.9]	0.49
Bipolar Disorder	3 [10.0 %]	6 [20.0 %]	0.17
Psychotropic medication	16 [53.3 %]	21 [70.0 %]	0.18
Cholesterol medication	4 [13.3 %]	6 [20.0 %]	0.49
BL Total Cholesterol (mg/dL)$^{+}$	146.3 [31.6]	169.5 [36.4]	0.02
BL LDL (mg/dL)$^{+}$	95.6 [28.0]	104.6 [28.6]	0.26
BL non-HDL (mg/dL)$^{+}$	109.1 [30.7]	128.2 [35.9]	0.05
BL Triglycerides (mg/dL)$^{+}$	79.6 [40.0]	121.3 [67.6]	0.01
BL NEFA (mg/dL)$^{+}$	0.3 [0.1]	0.4 [0.3]	0.04

Results expressed as n [percent] or mean [SD]. BL: baseline; BMI: body mass index; CRP: C-reactive protein; HAM-D-17: 17-item Hamilton Depression Rating Scale; LDL: low-density lipoprotein cholesterol; non-HDL: non-high-density lipoprotein cholesterol; NEFA: non-esterified fatty acids; TRD: treatment-resistant depression. $^{+}$n = 26/group.

Table 2
Demographic, clinical, and biomarker characteristics of MDD patients receiving acute L-DOPA and placebo ~1 week apart in randomized order as a pharmacological fMRI challenge.

Study 2	MDD Patients (n = 31)
Sex, Female	21 (67.7 %)
Race	
Caucasian	20 [64.5 %]
African American	9 [29.0 %]
Other	2 [6.5 %]
Age	37.0 [11.4]
BMI	28.4 [5.9]
BL CRP	2.7 [3.3]
BL HAMD-17	21.8 [3.8]
BL Anhedonia	4.3 [1.9]
BL Total Cholesterol (mg/dL)	163.2 [26.0]
BL LDL (mg/dL)	106.2 [17.9]
BL non-HDL (mg/dL)	113.8 [19.9]
BL Triglycerides (mg/dL)	38.1 [17.6]
BL NEFA (mg/dL)	0.5 [0.2]

Results expressed as n [percent] or mean [SD]. BL: baseline; BMI: body mass index; CRP: C-reactive protein; HAM-D-17: 17-item Hamilton Depression Rating Scale; LDL: low-density lipoprotein cholesterol; L-DOPA: levodopa; non-HDL: non-high-density lipoprotein cholesterol; MDD: major depressive disorder; NEFA: non-esterified fatty acids.

When considering the effect of treatment (infliximab or placebo) on anhedonia scores over time in 48 patients (26 placebo, 22 infliximab) with data available at all timepoints, there was a main effect of time ($F[8,46] = 6.42$, $p < 0.001$) but no main effect of treatment or a time-by-treatment interaction (both $p > 0.35$) in models with or without covariates. Interestingly, plotting anhedonia scores available across time from all 60 participants as a function of treatment and baseline plasma CRP level (>3 versus ≤3 mg/L; Fig. 1A) revealed early symptom reduction followed by attenuation of anhedonia response ~2–4 weeks after each infusion (baseline, week 2 and week 6, black arrows). This pattern was most prominent in patients with CRP >3 mg/L receiving infliximab, but also seen in patients with CRP ≤3 mg/L receiving placebo (the preferred treatments for patients in either CRP group, respectively). Based on this pattern of symptom reduction with respect to timing of infusions, and consistent with prior analysis of response rates for the primary study outcome of depression symptom severity [29,33,34], the rate of anhedonia response at any time during the study (≥50 % reduction in symptoms severity from baseline) was calculated and revealed a treatment by CRP interaction when considering either CRP level ($\chi^2 = 9.72$, $p < 0.01$) (Fig. 1B) or CRP as a continuous variable ($\chi^2 = 8.38$, $p < 0.01$) in models including covariates. A similar trend was observed for rate of response at the final assessment (see Fig. S2). Of the infliximab responders with CRP >3 mg/L, >80 % had an initial response (≥50 % reduction in symptoms severity) in the early phase of the study (between weeks 1 and 3) when participants received two infusions spaced by 2 weeks. Of the early responders, >70 % maintained this response at later phases of the study (weeks 6–12). Of patients with CRP ≤3 mg/L that responded to placebo (the preferred treatment in the lower inflammation patients), >70 % similarly responded early in the study (between weeks 1 and 3) and >65 % of early responders maintained their response later in the study (weeks 6–12).

A higher response rate to infliximab versus placebo in patients wit h CRP >3 mg/L was further supported by a between-subject CRP level by treatment interaction for anhedonia scores (maximal response at any time during the study as a continuous variable; $F[1,56] = 6.11$, $p =$

0.017, Fig. 1C, lower panel). This interaction remained significant when controlling for age, sex, race, BMI, baseline HAM-D scores, and use of cholesterol or psychiatric medications ($F[1,49] = 5.46$, $p = 0.024$), and a similar trend was observed when considering anhedonia scores at the final assessment ($F[1,49] = 2.98$, $p = 0.091$). Post-hoc testing revealed significantly lower anhedonia scores after infliximab versus placebo ($p < 0.05$) in patients with >3 mg/L CRP (Fig. 1C, lower panel), with no significant treatment difference in patients with ≤3 mg/L CRP ($p = 0.136$). Baseline anhedonia did not differ as a function of treatment group or CRP level (all $p > 0.236$; Fig. 1C, top panel). Of note, a CRP level by treatment interaction was also observed for post-treatment anhedonia scores when controlling for baseline anhedonia ($F[1,48] = 4.85$, $p < 0.05$), and was similar when using CRP as a continuous variable with a CRP by treatment interaction term ($F[1,48] = 3.38$, $p = 0.072$).

3.2. Relationship between lipid-related biomarkers and anhedonia response to infliximab in study 1

To determine whether baseline lipid biomarkers predicted the change in anhedonia scores, the anhedonia response (maximal response as anytime during the study minus baseline) was calculated and first examined in relation to CRP level. A trend for treatment by CRP interaction effects on the change in anhedonia scores (response at any time minus baseline, $p = 0.090$ when controlling for covariates) was observed, which was significant when removing one patient assigned to infliximab who did not report any anhedonia symptoms at baseline or during the study ($F[1,48] = 4.09$, $p < 0.05$; Fig. 2A). Post-hoc testing revealed a statistical trend for a greater response to infliximab versus placebo in patients with CRP >3 mg/L ($p = 0.052$). The lipid composite score at baseline did not significantly correlate with the anhedonia response (change in anhedonia scores: post-treatment minus baseline) in all patients ($r = -0.23$, $df = 50$, $p = 0.098$). A statistically significant interaction between treatment and the lipid composite score was not observed in the whole group ($r = -0.20$, $df = 41$, $p = 0.202$), but this was significant when removing the 10 patients that were taking cholesterol medications ($r = -0.35$, $df = 33$, $p < 0.05$), in models controlling for covariates (Table S2). Interestingly, lipid biomarkers were negatively associated with the anhedonia response (with higher baseline lipids predicting a greater reduction in anhedonia symptoms) only in patients treated with infliximab ($r = -0.44$, $df = 24$, $p < 0.05$), with no significant relationship observed after placebo ($r = -0.04$, $df = 24$, $p = 0.836$) in the group as whole. The relationship between baseline lipid biomarkers and the anhedonia response in patients treated with infliximab persisted when controlling for age, sex, race, BMI, baseline HAM-D scores, and use of cholesterol or psychiatric medications ($r = -0.46$, $df = 17$, $p < 0.05$; Fig. 2B). A significant difference between beta coefficients (± standard error) (see Table S2) was observed for relationships between lipid biomarkers and the anhedonia response in patients treated with infliximab versus placebo when controlling for covariates (-0.28 ± 0.13 versus 0.15 ± 0.26, $t = -2.1$, $df = 50$, $p < 0.05$).

3.3. Relationship between lipid-related biomarkers and reward circuit FC response to acute L-DOPA challenge in study 2

The reward circuit response to L-DOPA and placebo was calculated as change in resting-state VS-vmPFC FC using a seed to ROI targeted FC approach (see Fig. 3A and section 2.5). The lipid composite score at baseline significantly correlated with the FC response (post-treatment minus baseline) irrespective of treatment ($r = 0.28$, $df = 60$, $p = 0.027$). This relationship was improved when controlling for treatment as well as study-related and demographic variables ($r = 0.37$, $df = 53$, $p = 0.006$), and there was no treatment by lipid score interaction ($r = 0.06$, $df = 52$, $p = 0.686$). Similar to the relationship between lipid scores and the anhedonia response to infliximab, baseline lipid biomarkers significantly predicted the FC response only to L-DOPA ($r = 0.53$, $df = 23$, $p = 0.007$ controlling for covariates; Fig. 3B) but not placebo ($r = 0.20$, $df = 23$, $p = 0.341$). A significant difference was also observed for the beta coefficients (see Table S3) for relationships between the lipid composite score and response to L-DOPA versus response to placebo (0.04 ± 0.01 versus 0.01 ± 0.01, $t = 2.3$, $df = 30$, $p < 0.05$).

3.4. Individual lipid-related biomarkers and response to infliximab and L-DOPA: role of higher CRP

As individual lipid-related biomarkers could not be included together in multiple linear regression models due to variance inflation

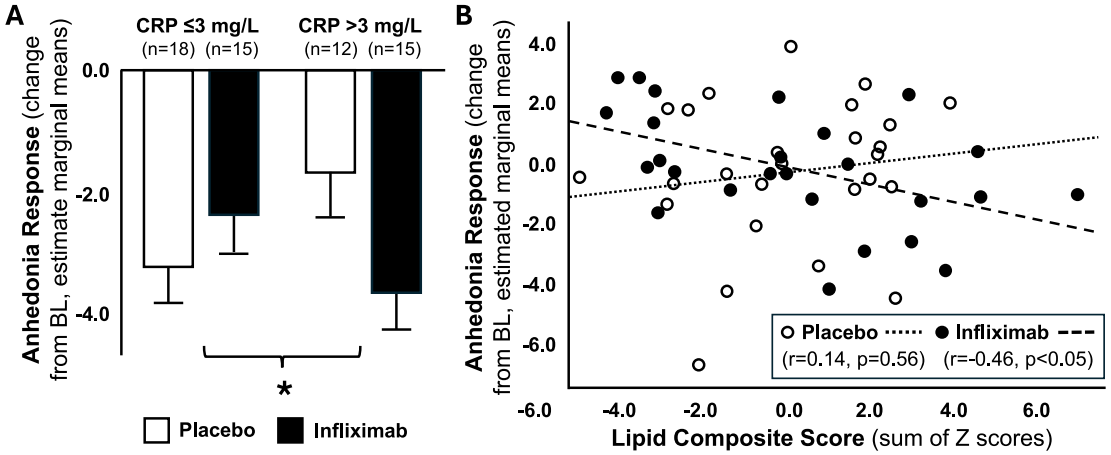

Fig. 2. Plasma lipid biomarkers at baseline predicted the anhedonia response to infliximab but not placebo in TRD patients (Study 1). A treatment by CRP interaction effect on the change in anhedonia scores (response at any time minus baseline) was observed when removing one patient assigned to infliximab that did not report any anhedonia symptoms ($n = 59$, $p < 0.05$; **A**), with a trend for greater response to infliximab versus placebo in patients with CRP >3 mg/L ($p = 0.052$). A composite score for lipid-related biomarkers was created as the sum of Z-scores for baseline concentrations of total, LDL and non-HDL cholesterol, triglycerides, and NEFA with increasing values reflecting greater concentrations of these markers (see Fig. S1). This lipid composite score negatively associated with the change in anhedonia scores (response at any time minus BL) to infliximab ($r = -0.46$, $p < 0.05$ controlling for covariates; **C**) but not placebo ($r = 0.14$, $p = 0.56$), $n = 26$/group. Data are presented as estimated marginal means (± standard error) controlling for covariates. *$p < 0.05$. BL: baseline; CRP: C-reactive protein; non-HDL: non-high-density lipoprotein; LDL: low-density lipoprotein; NEFA: non-esterified fatty acids; TRD: treatment-resistant depression.

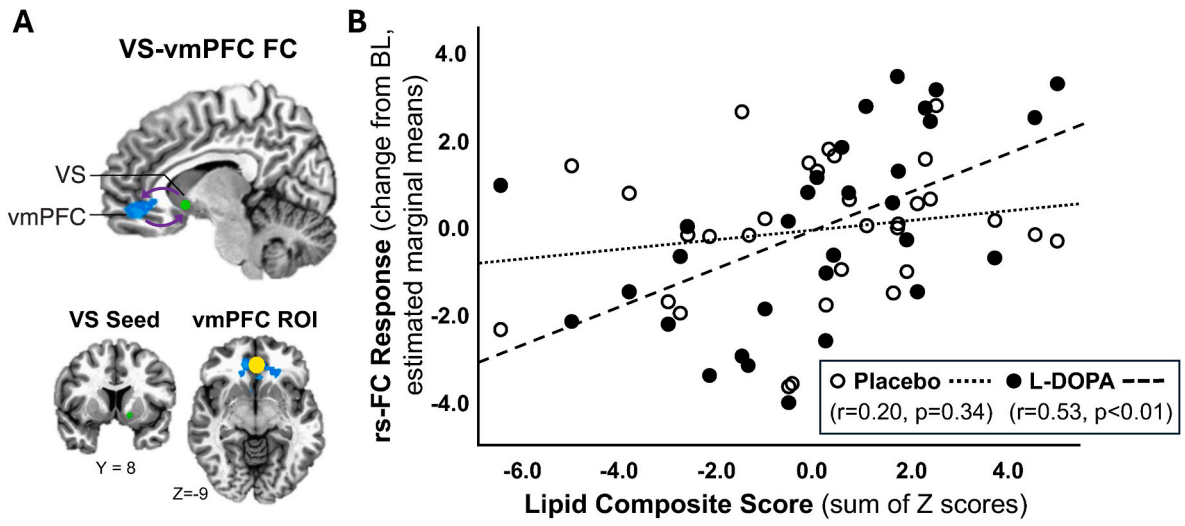

Fig. 3. Baseline plasma lipid biomarkers predicted inflammation-associated changes in FC in reward circuitry after acute challenge with levodopa but not placebo in MDD (Study 2). Resting-state FC between a seed in left VS (green) and ROI in vmPFC (yellow), shown overlayed on a vmPFC cluster identified to have reduced FC with left VS in association with higher CRP in MDD in our prior voxel-wise analyses (blue-cyan) [20](**A**), was increased by L-DOPA versus placebo in patients with higher CRP [38]. A composite score for lipid-related biomarkers (sum of Z-scores for total, LDL and non-HDL cholesterol, triglycerides, and NEFA) positively associated with the VS-vmPFC FC response to L-DOPA (post-treatment minus baseline; n = 31; r = 0.53, p < 0.01 controlling for covariates; **B**) but not placebo (r = 0.20, p = 0.34). BL: baseline; FC: functional connectivity; non-HDL: non-high-density lipoprotein; LDL: low-density lipoprotein; L-DOPA: levodopa; MDD: major depressive disorder; NEFA: non-esterified fatty acids; vmPFC: ventromedial prefrontal cortex; VS: ventral striatum.

(factors >10), relationships between individual markers and study outcomes were explored in models containing covariates to see whether common markers predicted both anhedonia and FC responses. For Study 1, while all markers exhibited negative relationships with the anhedonia response to infliximab (r values ranging from −0.30 to −0.48; higher lipid markers predicting greater symptom reduction), only total cholesterol was statistically significant (p < 0.05; Table S4). For Study 2, all markers except NEFA showed statistically significant positive correlations with the reward circuit FC response to L-DOPA (r = 0.42–0.47, all p < 0.05; Table S4).

As both anhedonia and FC responses were predicted by total cholesterol at baseline, the combined effect of biomarkers of lipid metabolism and inflammation was further explored by assigning patients to one of three categories based on the presence or absence of clinically-relevant elevations in cholesterol (>150 mg/dL) [50] and/or CRP (>3 mg/L) [42] as: 1) lower levels of both markers, 2) higher levels of at least one marker, and 3) higher levels of both markers. For Study 1, there was a main effect of group assignment on the anhedonia response to infliximab ($F[2,23] = 3.86$, $p < 0.05$). Consistent with post-hoc tests with Bonferroni correction, contrasts showed significantly greater reductions in anhedonia symptoms in patients with one or two versus no elevated biomarkers ($p < 0.05$, asterisks in Fig. 4A). While the main effect remained significant when controlling for all covariates except for age and BMI, contrasts were significant for patients with higher levels of one biomarker when controlling for age and BMI ($p < 0.05$, cross in Fig. 4A), and for patients with higher levels of both markers when controlling for age but not BMI. For study 2, the main effect of group assignment on the FC response to L-DOPA was only significant when controlling for covariates ($F[2,22] = 3.5$, $p < 0.05$). While post-hoc tests with Bonferroni comparison showed only a statistical trend for those with two compared to no elevated biomarkers ($p = 0.05$), contrasts reveled higher FC responses in patients with one or two versus no biomarkers elevated when controlling for covariates ($p < 0.05$, crosses in Fig. 4B).

4. Discussion

Herein, we found that inflammation-related anhedonia and reward circuit FC responses to anti-inflammatory or neurotransmitter targeted therapies, infliximab and L-DOPA respectively, in patients with depression were similarly predicted by baseline concentrations of lipid-related biomarkers. Indeed, a composite score of the same lipids (cholesterols, triglycerides and NEFA) that predicted the antidepressant response to infliximab in our prior work [33] were related to change in anhedonia symptoms after infliximab. Anhedonia was only significantly reduced compared to placebo in patients with CRP > versus ≤3 mg/L, consistent with improved SHAPS scores after infliximab in bipolar depressed patients with evidence of high inflammation and/or metabolic disturbance [30] or anti-IL-6 with sirukamab in depressed patients with CRP >3 mg/L [32]. We similarly found that plasma lipid scores predicted reward circuit FC responses to challenge with L-DOPA versus placebo previously shown to depend on concentrations of plasma CRP in MDD patients [38]. Finally, potential joint contributions of inflammation and metabolic processes were supported by evidence that patients with both ele vated CRP and higher levels of cholesterol were most responsive to treatments that inhibit inflammation or dopaminergic therapies like L-DOPA.

Notably, our results indicate future use of combined CRP and lipid biomarkers to identify depressed patients that may benefit from therapies targeting inflammation or its effects on the brain. Findings that both markers similarly predicted anhedonia responses to infliximab in TRD and reward circuit FC responses to L-DOPA in MDD indicate a shared pathophysiology of immune and metabolic alterations in these patients. These results also suggest common mechanisms of action of anti-cytokine and dopaminergic therapies on reward pathways in patients with immunometabolic depression. Inflammatory cytokines and associated oxidative stress signals are thought to affect the availability and release of striatal dopamine, in part through limiting its synthetic precursors like L-DOPA [15]. While metabolic changes including higher circulating lipids may have direct effects on the brain [27,28], metabolic disturbances including aspects of dyslipidemia are known activators of peripheral immunes cells that drive systemic inflammation [4]. Therefore, reduced peripheral inflammation by anti-cytokine therapies like infliximab in patients with both higher CRP and high lipids may reverse the impact of metabolism-induced cytokine release on the brain to subsequently improve dopamine and reward circuit function as a mechanism of reduced symptoms of anhedonia. In our recent studies enrolling depressed patients with higher CRP to receive sub-chronic

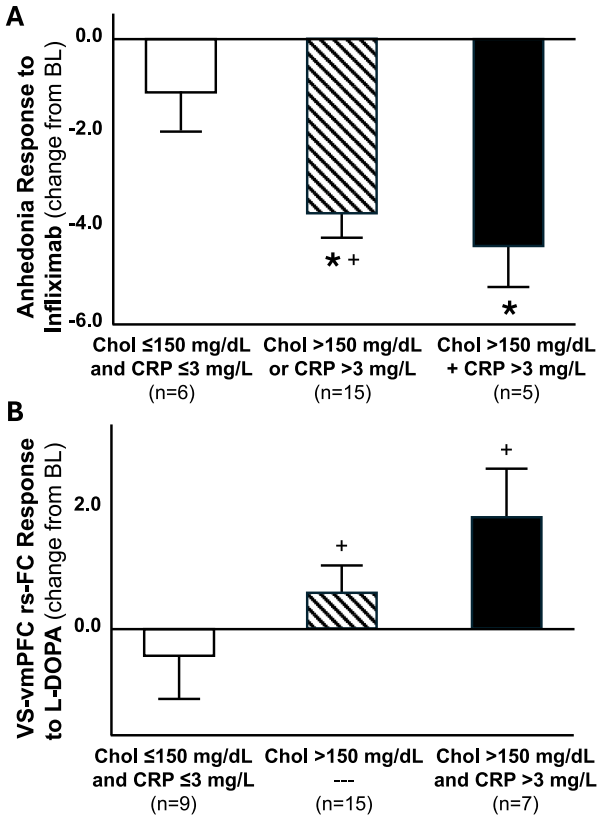

Fig. 4. Patients with higher baseline CRP and/or cholesterol had greater anhedonia and reward circuit FC responses to infliximab and L-DOPA, respectively. Anhedonia and resting-state VS-vmPFC FC responses (post-treatment minus baseline) to infliximab (Study 1; **A**) and L-DOPA (Study 2; **B**), respectively, were greater in patients with clinically significant elevations in at least one biomarker, CRP (>3 mg/L) and/or total cholesterol (>150 mg/dL), versus those with no elevated biomarkers. Note: all patients in Study 2 with CRP >3 mg/L had cholesterol >150 mg/dL. Data are presented as mean ± standard error. *unadjusted $p < 0.05$; +$p < 0.05$ in contrasts controlling for covariates. BL: baseline; Chol: cholesterol; CRP: C-reactive protein; FC: functional connectivity; L-DOPA: levodopa; NEFA: non-esterified fatty acids; vmPFC: ventromedial prefrontal cortex; VS: ventral striatum.

(1–2 weeks) of anti-cytokine or dopaminergic therapies (NCT04723147; NCT03004443), secondary analyses will further establish whether lipid signatures were enriched in these patients and/or associated with the responsiveness of common outcomes related to motivation and FC in reward circuitry.

This study provided evidence of common inflammatory and metabolic contributions to an immunometabolic phenotype of depression and identified potential clinical markers, CRP and cholesterol, that may be used to identify patients for targeted therapies. While interesting relationships between CRP and anhedonia response to infliximab were uncovered, more specific laboratory assessments of inflammation, particularly related to TNF signaling, may have greater predictive validity [30]. As with our prior work on infliximab responses based on depression severity [29,33,34], future studies will explore relationships between anhedonia response, cytokines and their soluble receptors, and immunometabolic peripheral blood gene expression signatures. Furthermore, small samples sizes for interactions in these studies, especially for the combined effects of CRP and cholesterol (Fig. 4), will require future validation in larger studies and should be interpreted with caution.

Several additional limitations should be noted. First, Study 1 was a small pilot trial to collect preliminary information on the antidepressant effects of infliximab in TRD patients and did not collect neuroimaging data. As anhedonia was not a planned outcome, the study also did not use a full scale to probe hedonic capacity such as SHAPS. The subscale of the IDS-SR (which probes interest in people and activities in addition to pleasure) has been previously associated with higher inflammation and lower VS-vmPFC FC in MDD patients in our prior work [2,20,22] and was used as an exploratory measure of anhedonia. Additionally, Study 2 was designed as an acute fMRI challenge study to determine whether L-DOPA could impact reward circuit FC in MDD patients with high CRP and thus change in anhedonia symptoms over time with the IDS-SR subscale was not possible. However, combined data from the two studies allowed us to assess whether lipid biomarkers were associated with both brain and behavioral responses to therapies intended to reverse the effects of inflammation on dopamine-modulated reward circuits and relevant behaviors. As discussed above, similar findings across studies further support both shared pathophysiology involving metabolic and inflammatory processes and common mechanisms of the anhedonia or FCresponses. Another potential issue is the small sample sizes of both studies. However, it should be noted that these were carefully selected, medically stable populations that, despite being less generalizable to all depressed samples, allowed controlled experimental environments for testing mechanism. Despite the double-blind randomized design, baseline cholesterols and triglycerides were higher in patients assigned to placebo. These differences should not impact results as all analysis focused on relationships between the lipid-related biomarkers and change in anhedonia scores within and across treatment groups rather than between group comparisons, and all analyses controlled for demographic and clinical covariates. It should be noted that BMI was included as covariate to examine the contribution of unmeasured confounders that exert potential influence on the brain and behavioral outcomes independent of the metabolic and inflammatory variables of interest. While elevations in CRP and lipids may be driven in part by adiposity, BMI was not a significant predictor of the anhedonia response to infliximab or the FC response to L-DOPA ($p > 0.99$ and > 0.57, respectively, controlling for other covariates). Nevertheless, BMI is an excellent means to enrich for patients with evidence of immune and metabolic disturbance and can be used as a proxy when biomarkers are not available.

Taken together, findings showed that both peripheral inflammatory and lipid-related biomarkers are predictive of response to therapies that inhibit inflammation or reverse its effects on neurotransmitters like dopamine in patients with depression. This exploratory work highlights a potential role for dyslipidemia in the pathophysiology immunometabolic depression and contributes to our knowledge of biomarkers that may be used to identify patients that might benefit from appropriately targeted therapies.

CRediT authorship contribution statement

Aditya Singh: Writing – review & editing, Writing – original draft, Formal analysis. **Mandakh Bekhbat:** Writing – review & editing, Formal analysis, Data curation. **David R. Goldsmith:** Writing – review & editing, Methodology, Conceptualization. **Ngoc-Anh Le:** Writing – review & editing, Validation, Supervision, Methodology. **Evanthia C. Wommack:** Writing – review & editing, Supervision, Methodology, Data curation. **Zhihao Li:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ebrahim Haroon:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Jennifer C. Felger:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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All authors declare no conflicts of interest and have nothing to disclose.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

"Jennifer Felger and Ebrahim Haroon are on the Editorial Board for C-PNEC, but as indicated, will not be involved in the editorial review or the decision to publish this article."

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2025.100284.

References

[1] D.R. Goldsmith, M.H. Rapaport, B.J. Miller, A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression, Mol Psychiatry 21 (2016) 1696–1709.
[2] J.C. Felger, E. Haroon, T.A. Patel, D.R. Goldsmith, E.C. Wommack, B.J. Woolwine, N.A. Le, R. Feinberg, M.G. Tansey, A.H. Miller, What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry 25 (2020) 1301–1311.
[3] L. Sforzini, M. Marizzoni, C. Bottanelli, V. Kunšteková, V. Zonca, S. Saleri, M. Kose, G. Lombardo, N. Mariani, M.A. Nettis, N. Nikkheslat, C. Worrell, Z. Zajkowska, L. Pointon, P.J. Cowen, J. Cavanagh, N.A. Harrison, M.A. Riva, V. Mondelli, E. T. Bullmore, A. Cattaneo, C.M. Pariante, Transcriptomic profiles in major depressive disorder: the role of immunometabolic and cell-cycle-related pathways in depression with different levels of inflammation, Mol Psychiatry (2024).
[4] L. Capuron, J. Lasselin, N. Castanon, Role of adiposity-driven inflammation in depressive morbidity, Neuropsychopharmacology 42 (2017) 115–128.
[5] E. Esteve, W. Ricart, J.M. Fernández-Real, Dyslipidemia and inflammation: an evolutionary conserved mechanism, Clin Nutr 24 (2005) 16–31.
[6] C. Popa, M.G. Netea, P.L. van Riel, J.W. van der Meer, A.F. Stalenhoef, The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk, J. Lipid Res. 48 (2007) 751–762.
[7] S.M.A. Mehdi, A.P. Costa, C. Svob, L. Pan, W.J. Dartora, A. Talati, M.J. Gameroff, P. J. Wickramaratne, M.M. Weissman, L.B.J. McIntire, Depression and cognition are associated with lipid dysregulation in both a multigenerational study of depression and the National Health and Nutrition Examination Survey, Transl. Psychiatry 14 (2024) 142.
[8] Y. Milaneschi, F. Lamers, M. Berk, B.W.J.H. Penninx, Depression heterogeneity and its biological underpinnings: toward immunometabolic depression, Biol. Psychiatr. 88 (2020) 369–380.
[9] N. Vogelzangs, A.T. Beekman, A.K. van Reedt Dortland, R.A. Schoevers, E.J. Giltay, P. de Jonge, B.W. Penninx, Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users, Neuropsychopharmacology 39 (2014) 1624–1634.
[10] E. Haroon, A.W. Daguanno, B.J. Woolwine, D.R. Goldsmith, W.M. Baer, E. C. Wommack, J.C. Felger, A.H. Miller, Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder, Psychoneuroendocrinology 95 (2018) 43–49.
[11] S.R. Vreijling, C.R. Chin Fatt, L.M. Williams, A.F. Schatzberg, T. Usherwood, C. B. Nemeroff, A.J. Rush, R. Uher, K.J. Aitchison, O. Köhler-Forsberg, M. Rietschel, M.H. Trivedi, M.K. Jha, B. Penninx, A.T.F. Beekman, R. Jansen, F. Lamers, Features of immunometabolic depression as predictors of antidepressant treatment outcomes: pooled analysis of four clinical trials, Br. J. Psychiatry 224 (2024) 89–97.
[12] M.K. Jha, A. Minhajuddin, B.S. Gadad, T. Greer, B. Grannemann, A. Soyombo, T. L. Mayes, A.J. Rush, M.H. Trivedi, Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial, Psychoneuroendocrinology 78 (2017) 105–113.
[13] A.R. van der Heijden, T. Houben, Lipids in major depressive disorder: new kids on the block or old friends revisited? Front Psychiatry 14 (2023) 1213011.
[14] M.J. Lucido, M. Bekhbat, D.R. Goldsmith, M.T. Treadway, E. Haroon, J.C. Felger, A.H. Miller, Aiding and abetting anhedonia: impact of inflammation on the brain and pharmacological implications, Pharmacol. Rev. 73 (2021) 1084–1117.
[15] J.C. Felger, M.T. Treadway, Inflammation effects on motivation and motor activity: role of dopamine, Neuropsychopharmacology 42 (2017) 216–241.
[16] E.G. Vichaya, R. Dantzer, Inflammation-induced motivational changes: perspective gained by evaluating positive and negative valence systems, Curr Opin Behav Sci 22 (2018) 90–95.
[17] D.R. Goldsmith, M. Bekhbat, N.D. Mehta, J.C. Felger, Inflammation-related functional and structural dysconnectivity as a pathway to psychopathology, Biol Psychiatry 93 (2023) 405–418.
[18] K. Burrows, J.L. Stewart, R. Kuplicki, L. Figueroa-Hall, P.A. Spechler, H. Zheng, S. M. Guinjoan, I. Tulsa, J.B. Savitz, T. Kent Teague, M.P. Paulus, Elevated peripheral inflammation is associated with attenuated striatal reward anticipation in major depressive disorder, Brain Behav. Immun. 93 (2021) 214–225.
[19] S. Costi, L.S. Morris, A. Collins, N.F. Fernandez, M. Patel, H. Xie, S. Kim-Schulze, E. R. Stern, K.A. Collins, F. Cathomas, M.K. Parides, A.E. Whitton, D.A. Pizzagalli, S. J. Russo, J.W. Murrough, Peripheral immune cell reactivity and neural response to reward in patients with depression and anhedonia, Transl. Psychiatry 11 (2021) 565.
[20] J.C. Felger, Z. Li, E. Haroon, B.J. Woolwine, M.Y. Jung, X. Hu, A.H. Miller, Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression, Mol Psychiatry 21 (2016) 1358–1365.
[21] M. Rengasamy, L. Brundin, A. Griffo, B. Panny, C. Capan, C. Forton, R.B. Price, Cytokine and reward circuitry relationships in treatment-resistant depression, Biol Psychiatry Glob Open Sci 2 (2022) 45–53.
[22] L. Yin, X. Xu, G. Chen, N.D. Mehta, E. Haroon, A.H. Miller, Y. Luo, Z. Li, J.C. Felger, Inflammation and decreased functional connectivity in a widely-distributed network in depression: centralized effects in the ventral medial prefrontal cortex, Brain Behav. Immun. 80 (2019) 657–666.
[23] A.R. Aruldass, M.G. Kitzbichler, S.E. Morgan, S. Lim, M.-E. Lynall, L. Turner, P. Vertes, J. Cavanagh, P. Cowen, C.M. Pariante, N.A. Harrison, E.T. Bullmore, Dysconnectivity of a brain functional network was associated with blood inflammatory markers in depression, Brain Behav. Immun. 98 (2021) 299–309.
[24] K.A. van Galen, A. Schrantee, K.W. ter Horst, S.E. la Fleur, J. Booij, R.T. Constable, G.J. Schwartz, R.J. DiLeone, M.J. Serlie, Brain responses to nutrients are severely impaired and not reversed by weight loss in humans with obesity: a randomized crossover study, Nat. Metab. 5 (2023) 1059–1072.
[25] R. Baynham, S.J.E. Lucas, S.R.C. Weaver, J. Veldhuijzen van Zanten, C. Rendeiro, Fat consumption attenuates cortical oxygenation during mental stress in young healthy adults, Nutrients 15 (2023).
[26] K.A. Page, O. Chan, J. Arora, R. Belfort-Deaguiar, J. Dzuira, B. Roehmholdt, G. W. Cline, S. Naik, R. Sinha, R.T. Constable, R.S. Sherwin, Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways, JAMA 309 (2013) 63–70.
[27] L. Kang, W. Wang, Z. Nie, Q. Gong, L. Yao, D. Xiang, N. Zhang, N. Tu, H. Feng, X. Zong, H. Bai, G. Wang, F. Wang, L. Bu, Z. Liu, Dysregulated cerebral blood flow, rather than gray matter Volume, exhibits stronger correlations with blood inflammatory and lipid markers in depression, Neuroimage Clin 41 (2024) 103581.
[28] J. Wei, Z. Zhang, X. Yang, L. Zhao, M. Wang, Y. Dou, Y. Yan, R. Ni, M. Gong, Z. Dong, X. Ma, Abnormal functional connectivity within the prefrontal cortex is associated with multiple plasma lipid species in major depressive disorder, J. Affect. Disord. 350 (2024) 713–720.
[29] C.L. Raison, R.E. Rutherford, B.J. Woolwine, C. Shuo, P. Schettler, D.F. Drake, E. Haroon, A.H. Miller, A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers, JAMA Psychiatr. 70 (2013) 31–41.
[30] Y. Lee, R.B. Mansur, E. Brietzke, N.E. Carmona, M. Subramaniapillai, Z. Pan, M. Shekotikhina, J.D. Rosenblat, T. Suppes, V.E. Cosgrove, N.E. Kramer, R. S. McIntyre, Efficacy of adjunctive infliximab vs. placebo in the treatment of anhedonia in bipolar I/II depression, Brain Behav. Immun. 88 (2020) 631–639.
[31] R.S. McIntyre, M. Subramaniapillai, Y. Lee, Z. Pan, N.E. Carmona, M. Shekotikhina, J.D. Rosenblat, E. Brietzke, J.K. Soczynska, V.E. Cosgrove, S. Miller, E.G. Fischer, N.E. Kramer, K. Dunlap, T. Suppes, R.B. Mansur, Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: a randomized clinical trial, JAMA Psychiatr. 76 (2019) 783–790.
[32] G. Salvadore, A. Nash, C. Bleys, B. Hsu, Z. Saad, A. Gause, J. Moyer, L. Xi, H. Manji, L. Van Nueten, W. Drevets, A double-blind, placebo-controlled, multicenter study of sirukumab as adjunctive treatment to a monoaminergic antidepressant in adults with major depressive disorder, in ACNP 57th annual meeting: poster session II, hollywood, FL, Neuropsychopharmacology 43 (2018) 228–382.
[33] M. Bekhbat, K. Chu, N.A. Le, B.J. Woolwine, E. Haroon, A.H. Miller, J.C. Felger, Glucose and lipid-related biomarkers and the antidepressant response to infliximab in patients with treatment-resistant depression, Psychoneuroendocrinology 98 (2018) 222–229.

[34] D. Mehta, C.L. Raison, B.J. Woolwine, E. Haroon, E.B. Binder, A.H. Miller, J. C. Felger, Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression, Brain Behav. Immun. 31 (2013) 205–215.
[35] J.C. Felger, J. Mun, H.L. Kimmel, J.A. Nye, D.F. Drake, C.R. Hernandez, A. A. Freeman, D.B. Rye, M.M. Goodman, L.L. Howell, Chronic interferon-α decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates, Neuropsychopharmacology 38 (2013) 2179–2187.
[36] L. Capuron, G. Pagnoni, D.F. Drake, B.J. Woolwine, J.R. Spivey, R.J. Crowe, J. R. Votaw, M.M. Goodman, A.H. Miller, Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration, Arch Gen Psychiatry 69 (2012) 1044–1053.
[37] J.C. Felger, C.R. Hernandez, A.H. Miller, Levodopa reverses cytokine-induced reductions in striatal dopamine release, Int. J. Neuropsychopharmacol. 18 (2015) 1–5.
[38] M. Bekhbat, Z. Li, N.D. Mehta, M.T. Treadway, M.J. Lucido, B.J. Woolwine, E. Haroon, A.H. Miller, J.C. Felger, Functional connectivity in reward circuitry and symptoms of anhedonia as therapeutic targets in depression with high inflammation: evidence from a dopamine challenge study, Mol Psychiatry 27 (2022) 4113–4121.
[39] C.A. Agostinis-Sobrinho, C. Moreira, S. Abreu, L. Lopes, L.B. Sardinha, J. Oliveira-Santos, A. Oliveira, J. Mota, R. Santos, Muscular fitness and metabolic and inflammatory biomarkers in adolescents: results from LabMed physical activity study, Scand. J. Med. Sci. Sports 27 (2017) 1873–1880.
[40] N.D. Mehta, J.S. Stevens, Z. Li, C.F. Gillespie, N. Fani, V. Michopoulos, J.C. Felger, Inflammation, reward circuitry and symptoms of anhedonia and PTSD in trauma-exposed women, Soc Cogn Affect Neurosci 15 (2020) 1046–1055.
[41] D.R. Goldsmith, M. Bekhbat, N.A. Le, X. Chen, B.J. Woolwine, Z. Li, E. Haroon, J. C. Felger, Protein and gene markers of metabolic dysfunction and inflammation together associate with functional connectivity in reward and motor circuits in depression, Brain Behav. Immun. 88 (2020) 193–202.
[42] P.M. Ridker, Clinical application of C-reactive protein for cardiovascular disease detection and prevention, Circulation 107 (2003) 363–369.
[43] N.A. Le, W. Innis-Whitehouse, X. Li, R. Bakker-Arkema, D. Black, W.V. Brown, Lipid and apolipoprotein levels and distribution in patients with hypertriglyceridemia: effect of triglyceride reductions with atorvastatin, Metabolism 49 (2000) 167–177.
[44] A.J. Rush, C.M. Gullion, M.R. Basco, R.B. Jarrett, M.H. Trivedi, The inventory of depressive Symptomatology (IDS): psychometric properties, Psychol. Med. 26 (1996) 477–486.
[45] R.M. Birn, E.K. Molloy, R. Patriat, T. Parker, T.B. Meier, G.R. Kirk, V.A. Nair, M. E. Meyerand, V. Prabhakaran, The effect of scan length on the reliability of resting-state fMRI connectivity estimates, Neuroimage 83 (2013) 550–558.
[46] H.J. Jo, Z.S. Saad, W.K. Simmons, L.A. Milbury, R.W. Cox, Mapping sources of correlation in resting state FMRI, with artifact detection and removal, Neuroimage 52 (2010) 571–582.
[47] Martino A. Di, A. Scheres, D.S. Margulies, A.M. Kelly, L.Q. Uddin, Z. Shehzad, B. Biswal, J.R. Walters, F.X. Castellanos, M.P. Milham, Functional connectivity of human striatum: a resting state FMRI study, Cereb Cortex 18 (2008) 2735–2747.
[48] E.K. Diekhof, L. Kaps, P. Falkai, O. Gruber, The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude - an activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing, Neuropsychologia 50 (2012) 1252–1266.
[49] C.D. Robinson, S. Tomek, R. Schumacker, Tests of Moderation Effects: Difference in Simple Slopes versus the Interaction Term. *Multiple Linear Regression*, vol. 39, 2013, pp. 16–24.
[50] S.M. Grundy, N.J. Stone, A.L. Bailey, C. Beam, K.K. Birtcher, R.S. Blumenthal, L. T. Braun, S. de Ferranti, J. Faiella-Tommasino, D.E. Forman, R. Goldberg, P. A. Heidenreich, M.A. Hlatky, D.W. Jones, D. Lloyd-Jones, N. Lopez-Pajares, C. E. Ndumele, C.E. Orringer, C.A. Peralta, J.J. Saseen, S.C. Smith Jr., L. Sperling, S. S. Virani, J. Yeboah, 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American college of cardiology/American Heart association task force on clinical practice guidelines, J. Am. Coll. Cardiol. 73 (2019) 3168–3209.