Full Length Article

Innate immunity impacts social-cognitive functioning in people with multiple sclerosis and healthy individuals: Implications for IL-1ra and urinary immune markers

Jason A. Turner [a,*], Christine Padgett [a], Skye McDonald [b], Kiran D.K. Ahuja [c], Heather M. Francis [d], Chai K. Lim [e,1], Cynthia A. Honan [a,1]

[a] School of Psychological Sciences, College of Health and Medicine, University of Tasmania, Hobart and Launceston, Australia
[b] School of Psychology, University of New South Wales, Sydney, Australia
[c] School of Health Sciences, University of Tasmania, Launceston, Australia
[d] Department of Psychology, Macquarie University, Sydney, Australia
[e] Department of Biomedical Sciences, Macquarie University, Sydney, Australia

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ABSTRACT

Social-cognitive difficulties can negatively impact interpersonal communication, shared social experience, and meaningful relationships. This pilot investigation examined the relationship between social-cognitive functioning and inflammatory markers in people with multiple sclerosis (MS) and demographically-matched healthy individuals. Additionally, we compared the immune marker profile in serum and urine-matched samples. Social cognitive functioning was objectively assessed using The Awareness of Social Inference Test – Short (TASIT-S) and subjectively assessed using self-reports of abilities in emotion recognition, emotional empathy, and cognitive theory of mind. In people with MS and healthy individuals, there were moderate-to-large negative relationships between pro-inflammatory biomarkers (serum IL-1β, IL-17, TNF-α, IP-10, MIP-1α, and urine IP-10, MIP-1β) of the innate immune system and social-cognitive functioning. In MS, a higher serum concentration of the anti-inflammatory marker IL-1ra was associated with better social-cognitive functioning (i.e., self-reported emotional empathy and TASIT-S sarcasm detection performance). However, there were mixed findings for anti-inflammatory serum markers IL-4 and IL-10. Overall, our findings indicate a relationship between pro-inflammatory cytokines and social-cognitive abilities. Future studies may provide greater insight into biologically-derived inflammatory processes, sickness behaviour, and their connection with social cognition.

1. Introduction

Inflammation has broad-ranging effects across the body and can disrupt brain functioning. Biological markers of the innate immune system and sickness behaviour have been recently implicated in poor social cognition, including reduced mentalising of another's affective state or psychological perspective, reduced social interaction, and increased social disconnectedness (Bollen et al., 2017; Hennessy et al., 2014; Moieni and Eisenberger, 2018). Multiple sclerosis (MS) is an immune-mediated neuroinflammatory and neurodegenerative disease (Dendrou et al., 2015) for which poor social processing and difficulties in social

functioning are a common outcome (Batista et al., 2017; Chalah and Ayache, 2017). However, despite the involvement of dysregulated inflammatory processes in MS (Kothur et al., 2016; Lim et al., 2017), whether these biomarkers play a role in poor social functioning is not understood.

Social cognition concerns the ability to perceive, interpret, and process interpersonal cues and socially relevant stimuli that enable a person to understand another person's intentions, thoughts, and feelings (McDonald et al., 2013, 2018). Difficulties in social-cognitive functioning are reported in around 30–40% of people with MS (pwMS) (Genova et al., 2016) and may include reduced facial emotion recognition (Henry et al.,

2011; Lenne et al., 2014) and Theory of Mind (ToM; the ability to accurately predict and interpret another's mental state that may differ from one's own beliefs, emotions, and desires) (Cotter et al., 2016; Pöttgen et al., 2013) abilities. Poor social-cognitive functioning negatively impacts communication, shared experience, and the ability to form meaningful relationships, which may contribute to social isolation and higher caregiver burden (Adams et al., 2019; Caplan et al., 2015). However, the identification of possible prognostic markers of social-cognitive difficulties may assist in identifying pwMS who may benefit from more extensive neuropsychological testing.

In pwMS, dysregulated cytokine production can result in aberrant concentrations of pro-inflammatory markers interleukin 1-beta (IL-1β), IL-17, tumour necrosis factor-alpha (TNF-α), and interferon gamma (IFN-γ); as well as anti-inflammatory markers IL-1 receptor antagonist (IL-1ra), IL-4, and IL-10 (Dendrou et al., 2015; Opdenakker and Van Damme, 2011; Sorenson et al., 2017; Turner et al., 2014). Prior research examining cytokine profiles indicate IL-1ra, IL-4, IL-10, TNF-α, and IFN-γ to be pleiotropic, having dualistic properties (Turner et al., 2014). For example, while IL-1ra concentrations can increase with inflammation, it also acts as an inflammatory regulator on IL-1α and IL-1β receptors. Thus, the terms pro- and anti-inflammatory are not absolute.

Research has shown that inflammatory processes and sickness behaviour can negatively affect social experience. Three prior double-blind placebo-controlled randomised crossover design studies using the International Affective Picture System (Bradley and Lang, 2007) and the Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001) found endotoxin-induced inflammation reduced the ability to recall emotional faces and the ability to mentalise the affective and psychological states in others (Bollen et al., 2017; Grigoleit et al., 2011; Moieni et al., 2015). However, in another double-blind placebo-controlled crossover design fMRI study using the RMET, no such effects on social-cognitive performance were found (Kullmann et al., 2014). A key distinction between these studies was the differing dose to trigger the inflammatory response. Changes in behavioural and physiological functioning from endotoxic processes can be dose-dependent (Grigoleit et al., 2011). For example, Kullmann et al. (2014) used 0.4 ng/kg of body weight to induce low-grade inflammation, while Moieni et al. (2015) used 0.8 ng/kg of body weight for a more robust inflammatory response. Thus, it remains possible that inflammatory markers that typically modulate responses to illnesses selectively affect social-cognitive processes.

The innate immune mediators, particularly interferon-gamma-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), and granulocyte colony-stimulating factor (G-CSF), have been implicated in MS (Carrieri et al., 1998; Cheng and Chen, 2014; Opdenakker and Van Damme, 2011; Rust et al., 2016). Dysregulation of innate immunity (such as that which would occur during an MS relapse) can result in increased concentrations of these circulating inflammatory mediators in the brain, cerebrospinal fluid, and blood (Broux et al., 2012; Cheng and Chen, 2014). For instance, IP-10 and G-CSF can markedly increase during disease activity in relapsing-remitting MS, which may exacerbate inflammatory processes, demyelination, and lesion development (Balashov et al., 1999; Rust et al., 2016; Scarpini et al., 2002). Dysregulated innate immune responses have been reported to affect cognitive functioning in other neurological disorders such as schizophrenia, Alzheimer's disease, and autism (Novellino et al., 2020); however, their relationship with social-cognitive abilities in MS has not yet been examined.

The present study was a pilot investigation to delineate the possible relationship between the various *serum*- and *urine*-based inflammatory markers known to be implicated in MS and social-cognitive functioning. We first hypothesised that, in pwMS, there would be a negative association between pro-inflammatory markers (i.e., IL-1β, IL-17, IFN-γ, TNF-α, IP-10, MIP-1β and MCP-1) and social-cognitive abilities. Second, we hypothesised that, in pwMS, there would be a positive association between anti-inflammatory markers (i.e., IL-1ra, IL-4 and IL-10) and social-

cognitive abilities. We compared these relationships to those found in healthy individuals without MS and examined if urine markers were associated with respective serum markers.

2. Materials and methods

2.1. Participants

Participants comprised 20 pwMS (17 relapsing-remitting, 1 secondary-progressive, 2 primary-progressive) and 20 healthy control (HC) individuals without MS, demographically-matched for sex, age, and education (Table 1). PwMS were diagnosed according to the McDonald criteria (Novellino et al., 2020; Thompson et al., 2018). MS phenotypes were not analysed separately as this study was interested in the level of inflammation found rather than understanding the disease types' unique pathological features. Participants with MS completed the Disease Steps Scale (Hohol et al., 1999), which indicated 'mild' to 'moderate' levels of disability in the present sample ($Mdn = 1.50$, $IQR = 1.00–2.75$). Exclusion criteria included any psychotic, bipolar, or related disorder; a history of brain injury or other neurological illness such as stroke or epilepsy; a history of alcohol or drug abuse; inability to speak and read English fluently; uncorrected visual difficulties affecting task completion; and pregnancy. Smoking was not an exclusion criterion in this study; we had three participants, two MS and one healthy participant, who indicated they were smokers (between 10 and 15 per day). Additional exclusion criteria included use of steroid medications within the past two months or MS disease relapse within the past 14 days for the MS participants as assessed by the Relapse Status Checklist (Brown et al., 2006) to reduce the potential confounding effect of disease-related inflammatory dysregulation that occurs during an MS relapse. All aspects of this study were approved by the Tasmania Health and Medical Research Ethics Committee (H00156630) and adhered to the World Medical Association's *Declaration of Helsinki*.

2.2. Data and sample collection

Following recruitment (by invitation letter and referral), participants completed a questionnaire containing demographic and disease-related questions, and standardised questionnaires to assess self-reported social-cognitive functioning and mood within seven days before attending a face-to-face testing session. The self-report social cognitive questionnaires included two subscales of The Social and Emotional Questionnaire (SEQ) (Bramham et al., 2009) – *Emotion Recognition* and *Emotional Empathy*, and the *Perspective Taking* subscale of the Interpersonal Reactivity Index (IRI) (Davis, 1980). All objective assessment occurred in the morning (start time between 9 and 10am) and in a temperature-controlled room (24°C) to control for time of day and temperature effects on performance and biological markers. At the testing session, participants were firstly interviewed to ascertain their disease history and characteristics before completing a battery of neuropsychological tests that included tests of general cognitive functioning (to be reported elsewhere) and a social-cognitive test, The Awareness of Social Inference Test - Short (TASIT-S) (Honan et al., 2016). TASIT-S was administered approximately 50 min into the testing session. Following testing, 30 mL of venous blood was extracted from the participant by a qualified phlebotomist. Mid-stream urine was also collected either during or immediately after testing. The venous blood was processed to extract the serum and then stored at approximately −80 °C until transferred for analysis. Prior to biochemical analysis, blinding measures such as unsorting and re-labelling were undertaken (Fig. 1).

2.3. Social cognitive and neuropsychological tests

TASIT-S (Honan et al., 2016) is an objectively assessed social cognition task comprised of three parts. Part 1 is a dynamic Emotional Evaluation Test (EET) containing 10 short video vignettes of professional

Table 1

Descriptive and inferential statistics for demographic information, TASIT-S, SEQ subscales, IRI Perspective Taking, and HADS in MS and HC individuals.

Variable	MS $n = 20$	HC $n = 20$	t or χ^2	df	p	95% CI $_{Difference}$		V or d
						LL	UL	
Male	4 (40%)	6 (60%)						
Female	16 (53.3%)	14 (46.7%)	.53	1	.465			.12[c]
Age, years (SD)	47.25 (11.04)	44.35 (11.43)	.81	38	.420	−4.30	10.10	.25
Education, years (SD)	12.45 (1.76)	13.25 (1.99)	1.34	38	.187	−2.01	.41	.42
TASIT-S, mean (SD)								
Part 1 Emotion Evaluation Test	6.70 (1.34)	7.45 (1.05)	1.97	38	.056	−1.52	0.02	**.62**
Part 2 Sincerity	13.00 (2.29)	12.85 (3.18)	.17	38	.865	−1.63	1.93	.05
Part 2 Sarcasm[b]	16.15 (3.69)	18.30 (1.81)	2.34	27.64	.027[a]	−4.03	0.27	**.74**
Part 3 Lies	11.40 (2.06)	11.65 (2.60)	.34	38	.738	−1.75	1.25	.11
Part 3 Sarcasm	15.85 (2.25)	17.10 (2.13)	1.80	38	.079	−2.65	0.15	**.57**
SEQ, mean (SD)								
Emotion Recognition	18.85 (3.39)	19.85 (3.15)	.97	38	.340	−3.10	1.10	.31
Emotional Empathy	19.00 (2.90)	18.70 (2.30)	.36	38	.719	−1.38	1.98	.12
IRI, mean (SD)								
Perspective Taking	18.35 (7.10)	15.60 (7.42)	1.20	38	.239	−1.90	7.40	.38
HADS, mean (SD)								
Anxiety	7.40 (4.43)	5.50 (3.30)	1.54	38	.420	−0.60	4.40	.49
Depression	5.50 (3.00)	3.20 (3.44)	2.25	38	.030[a]	0.23	4.37	**.71**

Note: Descriptive and inferential statistics for between-group comparisons on demographics, TASIT-S, SEQ subscales Emotion Recognition and Emotional Empathy, IRI Perspective Taking subscale, and the HADS. Frequencies are reported for sex. Means and standard deviations for all other variables are reported. CI, Confidence Interval; *d*, Cohen's *d* effect size; df, degrees of freedom; HADS, Hospital Anxiety and Depression Scale; IRI, Interpersonal Reactivity Index; LL, Lower Level; SEQ, Social and Emotional Questionnaire; TASIT-S, The Awareness of Social Inference Test-Short; UL, Upper Level; and *V*, Cramer's *V* effect size.

[a] Denotes significant between-group differences (*p* < .05). Cohen's *d* effect size > .5 are in bold.

[b] Denotes a significant Levene's Test for Equality of Variances; thus, equal variances not assumed was interpreted.

[c] Denotes Cramer's *V* effect size.

actors depicting five basic facial emotions: *happy*, *sad*, *anger*, *fear*, *disgust*, and no specific emotion – *neutral*. Part 2 Social Inference *Minimal* is a task that examines the comprehension of conversational meanings from paralinguistic cues (tone of voice, facial expression, and gesture). It comprises nine video vignettes depicting four *sincere* and five *sarcastic* (tapping into ToM) social exchanges. Each vignette requires the participant to answer questions that assess the participants' understanding of an actor's *belief* (what they are doing), *meaning* (what they are trying to say), *intention* (what they are thinking), and *feeling* (how they are feeling). Part 3 Social Inference *Enriched* is another social-cognitive task similar to Part 2, but with additional contextual information to aid interpretation. It is comprised of nine video vignettes depicting four blatant *lies* and five *sarcastic* social exchanges.

Self-reported social-cognitive abilities were assessed using two 5-item subscales of the SEQ (Bramham et al., 2009) – Emotion Recognition and Emotional Empathy. In the SEQ, statements are rated on a 5-point scale from *1 = strongly disagree* to *5 = strongly agree*. Self-reported cognitive ToM was assessed using the 7-item Perspective Taking subscale from the IRI (Davis, 1980). In the IRI, statements are rated on a 5-point scale from *A = does not describe me well* to *E = describes me well*. Higher scores on the SEQ and IRI are indicative of higher social-cognitive abilities.

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was administered to profile self-reported anxiety and depression levels over the preceding week. The HADS comprises 14-items where various statements are rated on a 4-point scale where *0 = not at all* to *3 = most of the time*. Scores are summed for anxiety and depression subscales with higher scores indicative of higher symptomatology.

2.4. Profiling of immunological markers

Cytokines, chemokines, and growth and colony-stimulating factors were concurrently quantified according to the manufacturer's protocols using commercial Human Cytokine 27-plex magnetic bead-based immunoassay kits (Bio-Rad, CA, USA). In accordance with current practice, median fluorescence intensities (FI) were used to analyse immune profile data. Due to its increased sensitivity, this technique has higher statistical power to detect variance compared to the use of

absolute concentration values (Breen et al., 2015). The urine markers are expressed as FI value/creatinine (Allen et al., 2004). Notably, serum concentrations of IFN-γ, GM-CSF and VEGF, and urine concentrations of IL-1β, MIP-1α, and IL-4 were minimally or undetectable and thus were not analysed and reported.

2.5. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26 (IBM Corporation, 2019). The normality of the variables was checked using histograms, visual inspection of the residual/Q-Q plots, and Shapiro-Wilk tests. Homogeneity of variance was examined utilising Levene's test with equal variances not assumed, interpreted as required. Before analyses, the data were inspected case-by-case for outliers. Subsequently, one MS (urine IP-10) and two HC (1 urine IL-1ra; 1 urine TNF-α, G-CSF, and GM-CSF) cases were removed. Independent samples *t*-tests assessed between-group differences on the social-cognitive measures. To normalise the biomarker data, logarithmic and square root transformations were applied; however, the variables could not be normalised, thus Spearman's ρ, and Mann-Whitney *U* analyses (with Hodges-Lehman 95% confidence intervals of the difference) were used. Due to a priori hypotheses about the direction of between-group effects and correlations, *p*-values < .05 were deemed to be statistically significant. Effect sizes that were at least moderate in size per the guidelines of Cohen (2013) were reported. This included correlations >0.30 and Cohen's *d* > 0.50.

Figures are provided for statistically significant biomarker comparisons and correlations, while tables containing complete descriptive data and inferential statistics for the variables are included in the supplemental information (S1 to S4).

3. Results

3.1. Demographic and between-group differences on TASIT-S, SEQ, IRI, and HADS

Descriptive and inferential statistics for the questionnaire and social-cognitive measures are shown in Table 1. There were no significant
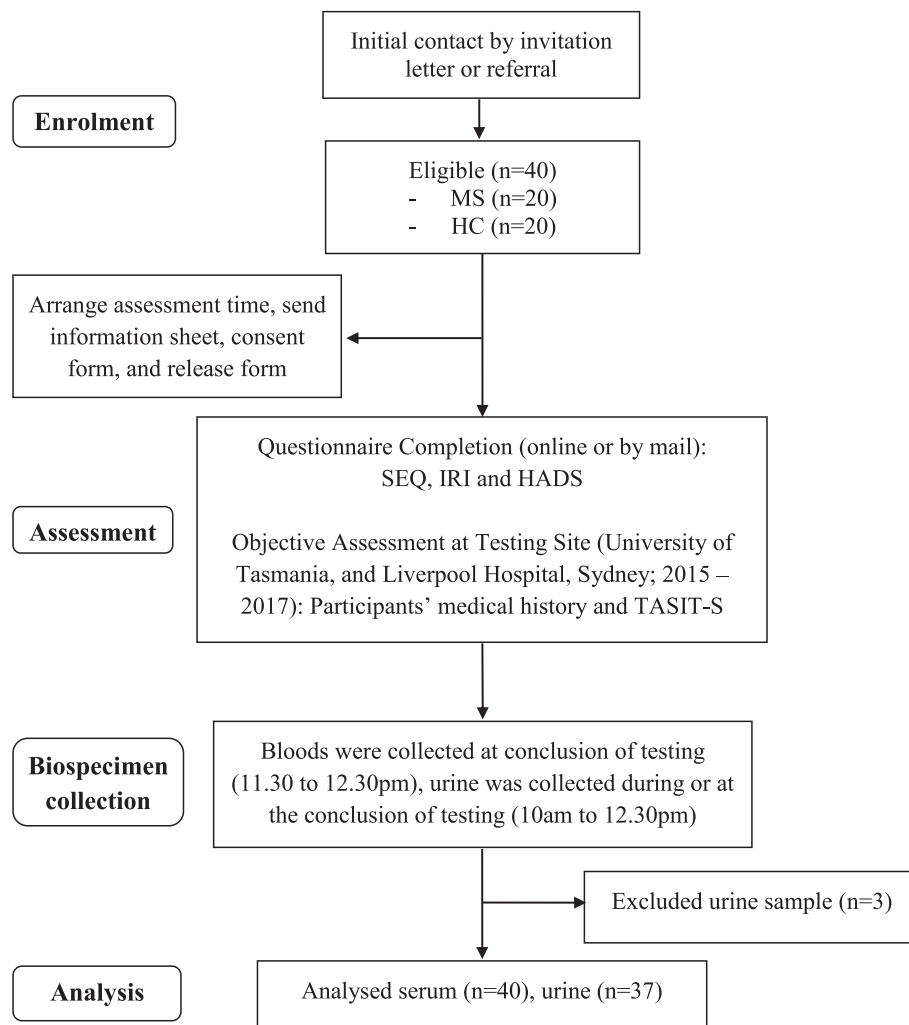
Fig. 1. Flow diagram of the study. MS, multiple sclerosis; HC, healthy control; SEQ, Social and Emotional Questionnaire; IRI, Interpersonal Reactivity Index; HADS, Hospital Anxiety and Depression Scale; TASIT-S, The Awareness of Social Inference Test-Short. Self-reported questionnaires (i.e., SEQ, IRI and HADS) were completed < 7 days before the objective assessment at testing site.

between-group differences in sex, age, and education. On TASIT-S, pwMS had poorer Part 1 EET scores and Part 2 Sarcasm scores (moderate-to-large effects). Although significance was not met for Part 3 Sarcasm, a moderate effect for poorer scores in pwMS was present. On the HADS, pwMS self-reported higher depression scores (moderate-to-large effect) and higher anxiety scores (a moderate effect).

3.2. Between-group differences on pro- and anti-inflammatory biomarkers

PwMS had significantly higher serum concentrations of pro-inflammatory IP-10 ($U = 117.00$, $p = .024$, $d = 0.76$, Fig. 2A) and anti-inflammatory IL-1ra ($U = 90.00$, $p = .002$, $d = 1.07$, Fig. 2B) than HC (large effects). PwMS also had significantly lower urine concentrations of pro-inflammatory IFN-γ ($U = 293.00$, $p = .011$, $d = 0.78$), TNF-α ($U = 306.00$, $p = .001$, $d = 1.23$, Fig. 2C), GM-CSF ($U = 294.00$, $p = .003$, $d = 1.06$), PDGF-bb ($U = 317.00$, $p = .001$, $d = 1.16$, Fig. 2D), RANTES ($U = 282.50$, $p = .024$, $d = 0.75$, Fig. 2E), and anti-inflammatory IL-10 ($U = 297.00$, $p = .008$, $d = 0.91$, Fig. 2F) than HC (large effects) (for all comparisons, see Supplementary Tables S1 and S2). Intra-correlational analyses between serum and urine biomarkers are shown in Table 2.

3.3. Pro-inflammatory biomarkers correlated with social-cognitive functioning

3.3.1. Objective social-cognitive measures

For TASIT-S Part 1 EET, no significant correlations were found with pro-inflammatory markers from serum or urine in pwMS or HCs. For TASIT-S Part 2 and 3 Sarcasm, urine IP-10 showed large negative correlations in pwMS, but not in HCs (Fig. 3A–B). Conversely, urine MIP-1β and PDGF-bb showed moderate-to-large negative correlations in HCs, but not in pwMS (Fig. 3C–F), which also applied for urine VEGF and TASIT-S Part 3 Sarcasm (Fig. 3G). Further, serum IL-1β and G-CSF showed large negative correlations with TASIT-S Part 3 Lies in HCs, but not in pwMS (Fig. 3H–I), while serum MCP-1 showed a moderate-to-large positive correlation with TASIT-S Part 2 Sincerity in HCs (Fig. 3J).

For TASIT-S in pwMS, positive correlations that were at least moderate in size, but not statistically significant, were found between both serum IP-10 (MS ρ = 0.42, $p = .066$; HCs ρ = −0.30, $p = .205$) and urine IL-17 (MS ρ = 0.36, $p = .120$; HCs ρ = 0.07, $p = .789$) and Part 1 EET. However, negative correlations were found between serum TNF-α (MS ρ = −0.30, $p = .204$; HCs ρ = −0.07, $p = .773$) and Part 2 Sarcasm, and
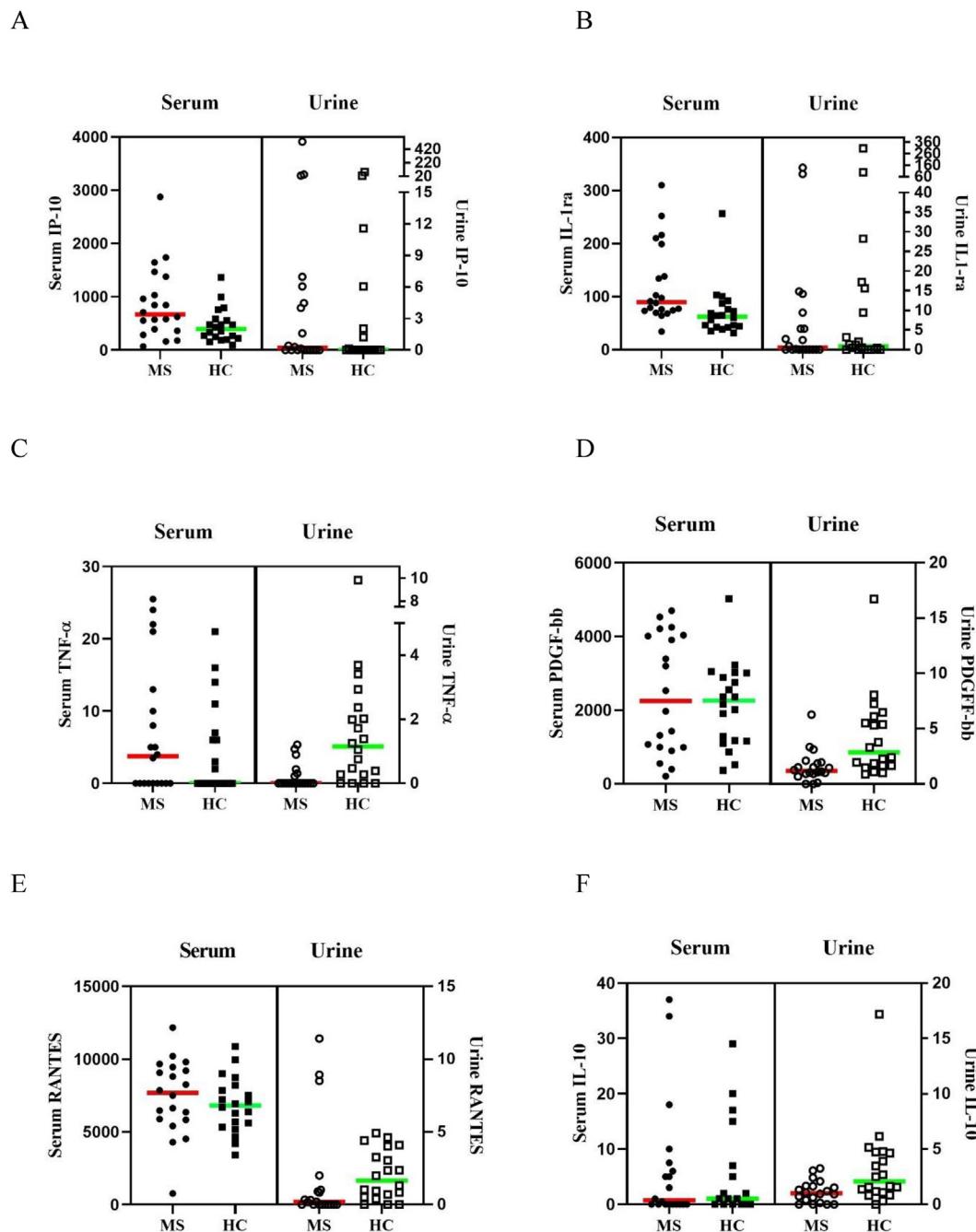
Fig. 2. Significant between-group differences for pro-inflammatory IP-10 (A) and anti-inflammatory IL-1ra (B) markers from serum (with non-significant urine comparisons), and significant between-group differences for pro-inflammatory TNF-α (C), PDGF-bb (D), RANTES (E) and anti-inflammatory IL-10 (F) markers from urine (with non-significant serum comparisons) in people with multiple sclerosis and matched healthy control participants. Interferon-gamma and Granulocyte-macrophage colony-stimulating factor is not shown due to having minimal or undetectable levels from serum. IL-1ra, Interleukin 1 receptor antagonist; IL-10, Interleukin 10; IP-10, Interferon-gamma inducible protein 10; PDGF-bb, Platelet-derived growth factor 2 b subunits; RANTES, Regulated on activation normal T-cell expressed and secreted; and TNFα, Tumour necrosis factor-alpha. Concentrations are shown in fluorescence intensity values for serum and fluorescence intensity/creatinine values for urine.

between urine MIP-1β (MS ρ = −0.34, p = .139; HCs ρ = −0.03, p = .887) and Part 3 Lies.

In HCs, positive correlations that were at least moderate in size, but not statistically significant, were found between TASIT-S Part 1 EET and serum RANTES (MS ρ = 0.03, p = .897; HCs ρ = 0.34, p = .148). While negative correlations were found between Part 2 Sincerity and both serum G-CSF (MS ρ = −0.08, p = .727; HCs ρ = −0.41, p = .070) and MIP-1α (MS ρ = 0.04, p = .880; HCs ρ = −0.35, p = .134); Part 2 Sarcasm

and serum G-CSF (MS ρ = −0.13, p = .596; HCs ρ = −0.34, p = .145) and urine markers IFN-γ (MS ρ = 0.26, p = .231; HCs ρ = −0.38, p = .065), TNF-α (MS ρ = −0.12, p = .614; HCs ρ = −0.37, p = .121), MCP-1 (MS ρ = −0.06, p = .814; HCs ρ = −0.42, p = .069), and VEGF (MS ρ = 0.13, p = .573; HCs ρ = −0.38, p = .095); Part 3 Lies and both serum TNF-α (MS ρ = 0.10, p = .689; HCs ρ = −0.38, p = .101) and IP-10 (MS ρ = 0.17, p = .474; HCs ρ = −0.32, p = .165); and Part 3 Sarcasm and urine G-CSF (MS ρ = 0.02, p = .951; HCs ρ = −0.36, p = .133).

$\rho = 0.32, p = .163$), and VEGF (MS $\rho = 0.13, p = .599$; HCs $\rho = 0.33, p = .162$).

Table 2
Spearman's ρ correlations between serum and urine markers stratified by MS and HC individuals.

Biomarker dyads *Serum* correlated with *Urine* samples	Overall ρ Correlation n = 40	MS ρ Correlation n = 20	HC ρ Correlation n = 20
Pro-inflammatory biomarkers			
IL-17	−.24	−.08	−.39
TNFα	.11[a]	.06	.41[a]
G-CSF	−.11[a]	−.06	−.10[a]
IP-10	.01[a]	−.14[a]	.16
MCP-1(MCAF)	.05	.28	−.12
MIP-1β	.41*	.47*	.32
PDGF-bb	−.11	−.08	−.03
RANTES	.01	.04	.01
Anti-inflammatory biomarkers			
IL-1ra	.24[a]	−.09	.18[a]
IL-10	−.03	−.01	−.16
Head-to-head serum marker comparison			
IL-1ra vs IL-17	−.16	−.54*	.07
IL-1ra vs IL-1β	.11	−.21	.18

Note. Spearman's ρ correlation for serum versus urine derived biomarkers overall and stratified by multiple sclerosis and healthy matched control participants. Abbreviations: G-CSF, granulocyte colony-stimulating factor; IL-1β, interleukin 1 beta; IL-1ra, interleukin 1 receptor antagonist; IL-4, interleukin 4; IL-10, interleukin 10; IL-17, interleukin 17; IP-10, interferon inducible protein-10; MCP-1(MCAF), monocyte chemotactic protein-1 and activating factor; MIP-1β, macrophage inflammatory protein-1 beta; PDGF-bb, platelet-derived growth factor-two b subunits; RANTES, regulated upon activation normal T-cell expressed and secreted; TNFα, tumour necrosis factor-alpha. Intra-correlations are not shown for pro-inflammatory markers IL-1β, IFNγ, GM-CSF, MIP-1α, VEGF and anti-inflammatory IL-4 due to minimal or undetectable concentration levels.
*Denotes significant correlation $p < .05$.
[a] Denotes the removal of 1 outlier case before analyses.

3.3.2. Subjective social-cognitive measures

For the SEQ subscales, only serum TNF-α showed large negative correlations with Emotion Recognition and Emotional Empathy in pwMS, but not in HCs (Fig. 4A & B). There was also a large positive correlation found between urine G-CSF and Emotional Empathy in pwMS that was not present in HCs (Fig. 4C). For the IRI subscale, only urine IFN-γ showed a moderate-to-large positive correlation with Perspective Taking in HCs, but not in pwMS (Fig. 4D). Further, serum IP-10 showed a moderate-to-large negative correlation with Perspective Taking in pwMS, which was not present in HCs (Fig. 4E). Conversely, urine IP-10 showed a large negative correlation with Perspective Taking in HCs, but not in pwMS (Fig. 4F).

For the SEQ subscales in pwMS, positive correlations that were at least moderate in size, but not statistically significant, were found between Emotion Recognition and urine G-CSF (MS $\rho = 0.43, p = .056$; HCs $\rho = 0.13, p = .590$); and between Emotional Empathy and urine VEGF (MS $\rho = 0.30, p = .204$; HCs $\rho = -0.15, p = .521$). However, negative correlations were found between Emotion Recognition and urine GM-CSF (MS $\rho = -0.36, p = .115$; HCs $\rho = -0.17, p = .494$); and between Emotional Empathy and serum IP-10 (MS $\rho = -0.34, p = .138$; HCs $\rho = -0.15, p = .541$) and MIP-1α (MS $\rho = -0.37, p = .113$; HCs $\rho = -0.07, p = .785$) and urine GM-CSF (MS $\rho = -0.35, p = .131$; HCs $\rho = -0.14, p = .561$) and IP-10 (MS $\rho = -0.31, p = .199$; HCs $\rho = -0.04, p = .857$). For the IRI subscale in pwMS, only serum IL-1β showed a moderate negative correlation with Perspective Taking (MS $\rho = -0.31, p = .188$; HCs $\rho = 0.01, p = .966$). Whereas in HCs, moderate positive correlations were found between IRI Perspective Taking and urine MIP-1β (MS $\rho = 0.13, p = .572$; HCs $\rho = 0.30, p = .198$), PDGF-bb (MS $\rho = -0.12, p = .604$; HCs

3.4. Anti-inflammatory biomarkers correlated with social-cognitive functioning

3.4.1. Objective social-cognitive measures

On TASIT-S in pwMS, there was a large positive correlation between Part 3 Sarcasm and serum IL-1ra (Fig. 5A) and a moderate-to-large negative correlation between Part 3 Lies and serum IL-4 (Fig. 5B). In HCs, there were no significant correlations between TASIT-S and anti-inflammatory markers from serum and urine.

For TASIT-S in pwMS, a positive correlation that was moderate in size, but not statistically significant, was found between Part 2 Sarcasm and serum IL-1ra (MS $\rho = 0.36, p = .116$; HCs $\rho = 0.07, p = .780$), however a moderate negative correlation was found between Part 2 Sincerity and serum IL-4 (MS $\rho = -0.36, p = .122$; HCs $\rho = -0.22, p = .361$). In HCs, moderate negative correlations were found between TASIT-S Part 2 Sincerity and IL-1ra from serum (MS $\rho = 0.04, p = .879$; HCs $\rho = -0.36, p = .115$) and urine (MS $\rho = -0.06, p = .803$; HCs $\rho = -0.32, p = .183$), Part 2 Sarcasm and serum IL-4 (MS $\rho = -0.04, p = .858$; HCs $\rho = -0.32, p = .165$), and IL-10 (MS $\rho = 0.21, p = .365$; HCs $\rho = -0.32, p = .175$), urine IL-1ra (MS $\rho = 0.15, p = .516$; HCs $\rho = -0.31, p = .196$) and IL-10 (MS $\rho = 0.16, p = .500$; HCs $\rho = -0.43, p = .058$), and Part 3 Lies and serum IL-10 (MS $\rho = -0.27 p = .256$; HCs $\rho = -0.40, p = .084$).

3.4.2. Subjective social-cognitive measures

No significant correlations were found between the anti-inflammatory markers and subjective social-cognitive measures. For the SEQ subscales in pwMS, positive correlations that were at least moderate in size, but not statistically significant, were found between Emotion Recognition and serum IL-10 (MS $\rho = 0.44, p = .054$; HCs $\rho = -0.25, p = .285$) and between Emotional Empathy and serum IL-4 (MS $\rho = 0.32, p = .175$; HCs $\rho = -0.23, p = .341$). However, there was a moderate negative correlation between Emotion Recognition and urine IL-10 (MS $\rho = -0.30, p = .196$; HCs $\rho = 0.21, p = .372$). In HCs, a moderate positive correlation was found between Emotional Empathy and serum IL-1ra (MS $\rho = 0.28, p = .233$; HCs $\rho = 0.38, p = .103$). For the IRI subscale, there was a moderate positive correlation between Perspective Taking and urine IL-10 (MS $\rho = -0.05, p = .821$; HCs $\rho = 0.31, p = .177$), and moderate negative correlations with both serum IL-1ra (MS $\rho = 0.23, p = .339$; HCs $\rho = -0.32, p = .174$) and IL-4 (MS $\rho = 0.14, p = .564$; HCs $\rho = -0.37, p = .114$).

Further alternative exploratory analyses were conducted to examine whether sex, age, smoking, depression, and anxiety could explain any additional variance in the above relationships. The strength of all relationships remained similar with these variables added as covariates, with the maximum change in correlation size being $\Delta r = 0.05$ (or 25% of variance). A chi-square test of independence showed that there were no significant association between group and time of year tested, χ^2 (3, $N = 40$) = 3.47, $p = .325$.

4. Discussion

This study investigated the relationship between various inflammatory markers and social-cognitive functioning in pwMS and demographically-matched healthy individuals. Our results highlight a novel role that the innate immune system may be linked to a disruption in social-cognitive functioning. Specifically, higher levels of serum IL-1β, IL-17, TNF-α, IP-10, MIP-1α, and urine IP-10, and MIP-1β were associated with poorer social-cognitive abilities relating to the detection of blatant lies and sarcasm in conversation, and poorer self-reported emotion recognition, emotional empathy, and perspective taking abilities. These
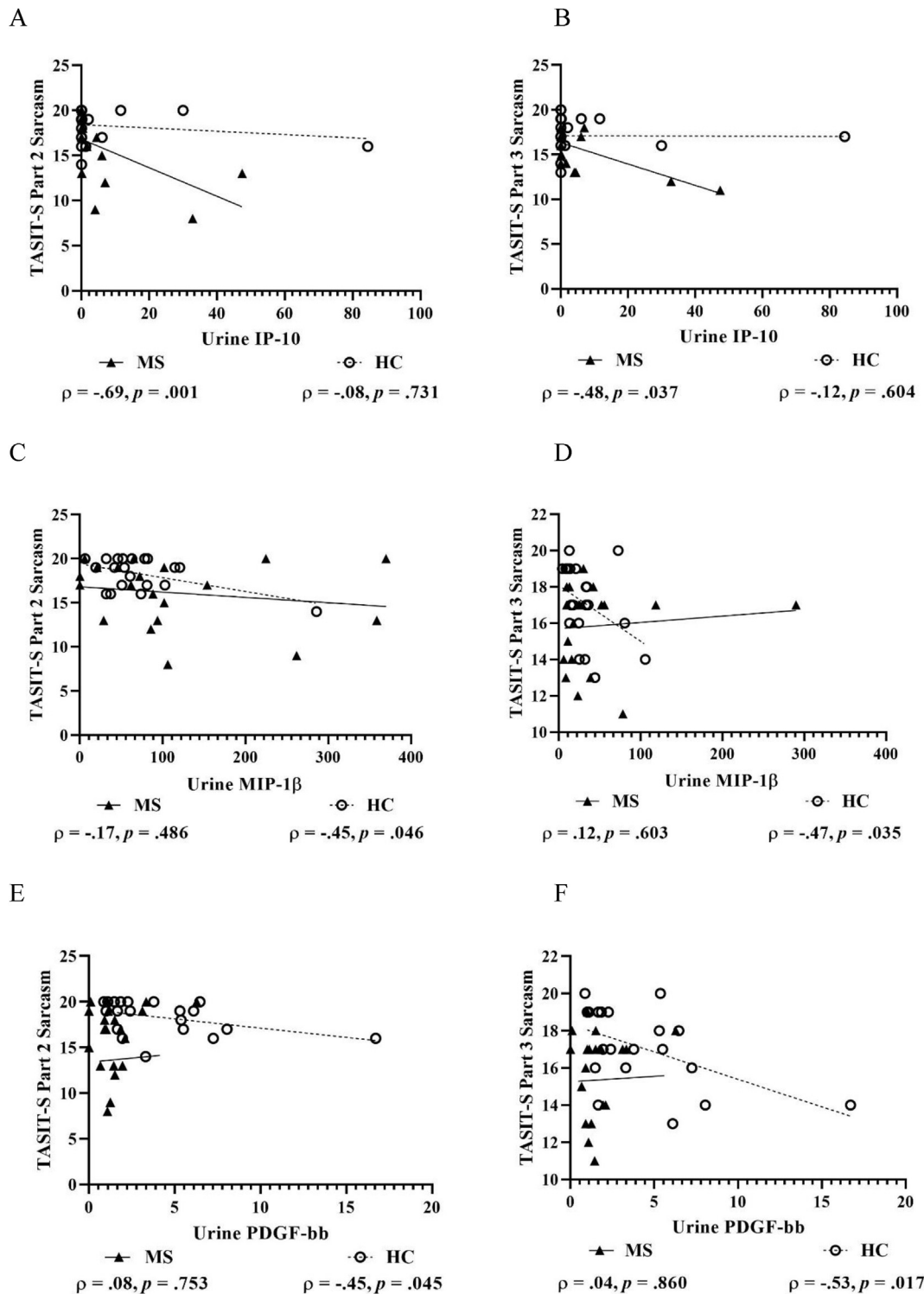
Fig. 3. Scatterplots with selected correlations between pro-inflammatory markers and objectively assessed social-cognitive measures in people with multiple sclerosis (MS) and matched healthy control (HC) participants. Figures show pro-inflammatory markers from urine IP-10 and TASIT-S Part 2 Sarcasm (A) and Part 3 Sarcasm (B), MIP-1β and TASIT-S Part 2 Sarcasm (C) and Part 3 Sarcasm (D), PDGF-bb and TASIT-S Part 2 Sarcasm (E) and Part 3 Sarcasm (F), VEGF and TASIT-S Part 3 Sarcasm (G) markers, and pro-inflammatory markers from serum IL-1β and TASIT-S Part 3 Lies (H), G-CSF and TASIT-S Part 3 Lies (I), and MCP-1 and TASIT-S Part 2 Sincerity (J). G-CSF, Granulocyte colony-stimulating factor; IFNγ, Interferon-gamma; IL-1β, Interleukin 1 beta; IP-10, Interferon-gamma inducible protein 10; IRI, Interpersonal Reactivity Index; IL-17, Interleukin 17; MCP-1, Monocyte chemoattractant protein-1; MCP-1, Macrophage inflammatory protein-1β; PDGF-bb, Platelet-derived growth factor-2 b subunits; TASIT-S, The Awareness of Social Inference Test-Short; TNFα, Tumour necrosis factor-alpha; and VEGF, Vascular endothelial growth factor. Concentrations are shown in fluorescence intensity values for serum and fluorescence intensity/creatinine values for urine.
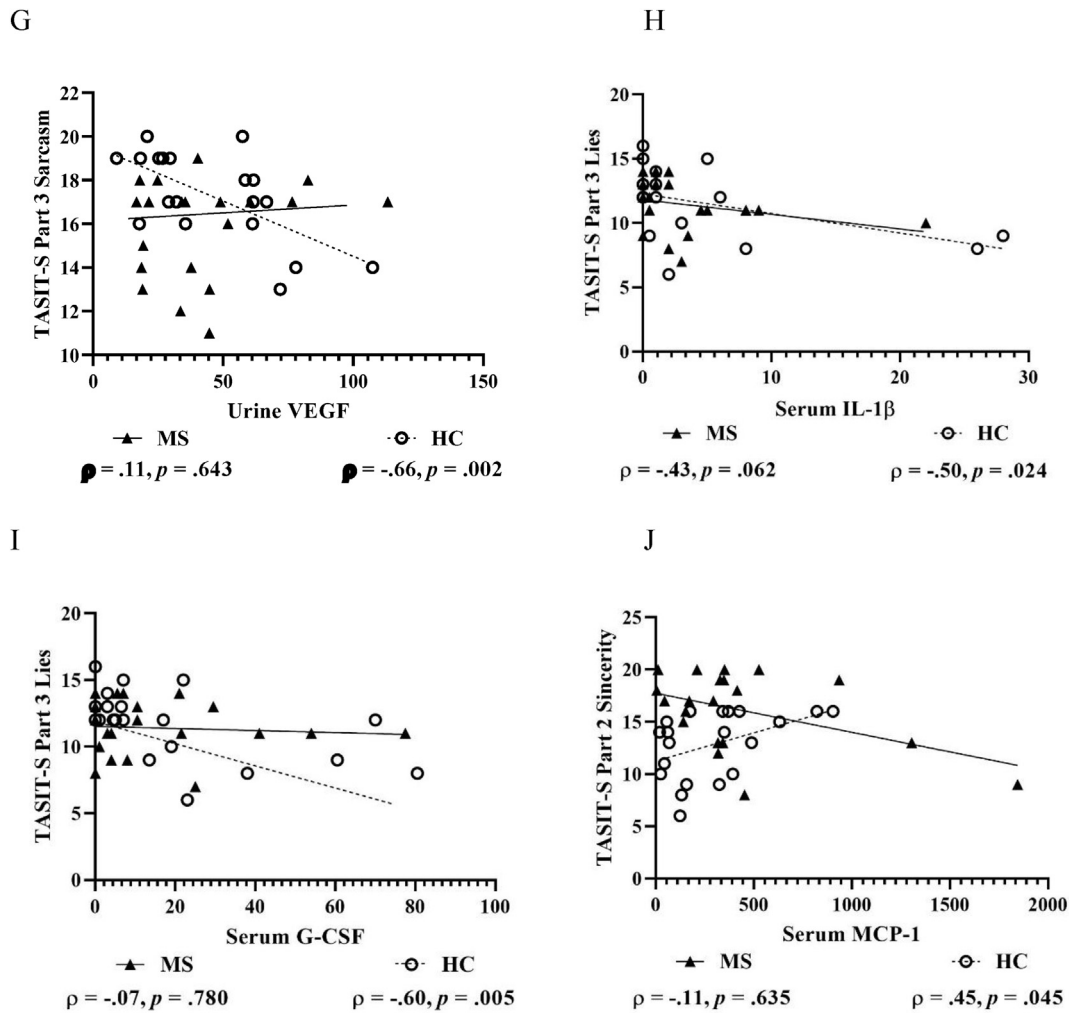
G

H

I

J

Fig. 3. (continued).

immune markers are known as pro-inflammatory mediators in the context of immune dysregulation in MS or sickness behaviour in healthy individuals.

Surprisingly, two cytokines most associated with MS, IFN-γ and IL-17 in the serum, were not higher in pwMS than HCs, suggesting its pathological dysregulation may be limited to the brain and not the peripheral regions of the body (Stromnes et al., 2008; van Langelaar et al., 2018). However, we found a negative correlation between serum IL-1ra and IL-17, indicating inhibition of IL-17 production via the IL-1-IL-17 signalling axis by IL-1ra (Table 2) (Nakae et al., 2003). This possible explanation for the attenuated IL-17 is supported by findings of prior alternative research that serum concentration of IL-17 and IFN-γ, cytokines associated with cell-mediated innate immunity (helper T cells of the Th1 and Th17 axes), can be similar in people with relapsing-remitting MS (the type of MS characterising the majority of the current sample) and healthy individuals (Arellano et al., 2017; Ghaffari et al., 2017). Our result reflects a broader implication and link with immune regulators such as the aryl hydrocarbon receptor and interactions with the kynurenine pathway in modulating MS progression, relevant to our MS cohort (Bessede et al., 2014; Yan et al., 2010). It would be of interest to examine how the kynurenine pathway fits into our current hypothesis considering its role in both mood and immune regulation in MS (Tan et al., 2021).

A novel aspect of this study was collecting paired serum and urine samples, which allowed us to investigate unique immune fingerprints in compartmentalised biological systems. Interestingly, we found that healthy individuals excreted a greater concentration of inflammatory

markers in urine than pwMS, whereas the corresponding serum levels were in opposing trend (Fig. 2A–F). Potentially, this discrepancy may either reflect differential urinary filtration processes (An and Gao, 2015), biomarker-specific fluctuation (Schenk et al., 2019), epitopic remnant accumulation that is theorised in autoimmune disease (Opdenakker et al., 2020), or is an artefact of poor urine quality from bladder dysfunction and reduced fluid intake (Katsavos and Anagnostouli, 2013). However, we controlled for creatinine levels to minimise potential confounder variables such as fluid consumption and age. Another possible explanation is based on the generalised assumption that increased serum metabolite concentration will result in increased urine metabolite excretion (Ritscher et al., 2020). However, while this may hold true for healthy individuals, in the context of MS or an alternative disease state, the possible incapacity to excrete these inflammatory mediators as efficiently as healthy individuals, may have resulted in these findings. Despite blood-based immune profiling being an established and widely used technique, the addition of a urinary immune profile may provide a feasible and non-invasive alternative technique to fully extrapolate the effects of inflammation in pwMS (Prasad et al., 2016). This approach of using urine samples may provide a new avenue for enabling longitudinal sampling in pwMS with greater disability levels.

In both pwMS and healthy individuals, we found higher concentration of numerous pro-inflammatory biomarkers to be associated with lower social-cognitive functioning (Figs. 3 and 4). Social-cognitive processing recruits a unique neural network called the "social brain", which includes the amygdala, insular cortex, superior temporal sulcus, anterior
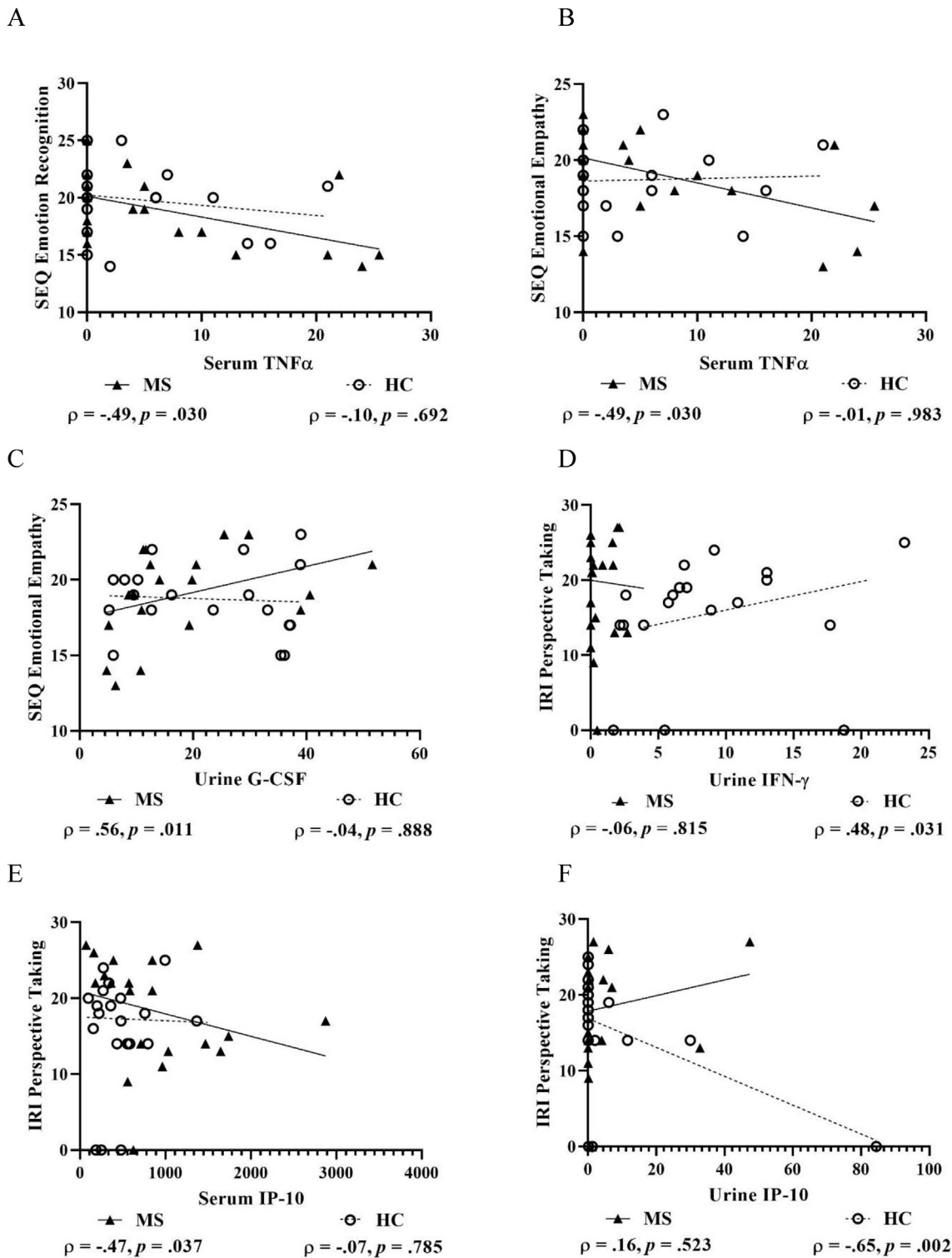
Fig. 4. Scatterplots with selected correlations between pro-inflammatory markers and subjectively assessed social-cognitive measures in people with multiple sclerosis and matched healthy control participants. Figures show pro-inflammatory serum TNF-α and both SEQ Emotion Recognition (A) and SEQ Emotional Empathy (B), urine G-CSF and SEQ Emotional Empathy (C) urine IFNγ and IRI Perspective Taking (D), serum IP-10 and IRI Perspective Taking (E), and urine IP-10 and IRI Perspective Taking (F). G-CSF, Granulocyte colony-stimulating factor; IFN-γ, Interferon-gamma; IP-10, Interferon-gamma inducible protein 10; IRI, Interpersonal Reactivity Index; SEQ, Social and Emotional Questionnaire; and TNFα, Tumour necrosis factor-alpha. An alternative analysis was performed on Figure F (urine IP-10 & IRI Perspective Taking), removing the HC outlier, which showed minimal change in the strength, direction and significance of the correlation ($\rho = -0.60$, $p = .007$); thus, this case was retained. Concentrations are shown in fluorescence intensity values for serum and fluorescence intensity/creatinine values for urine.
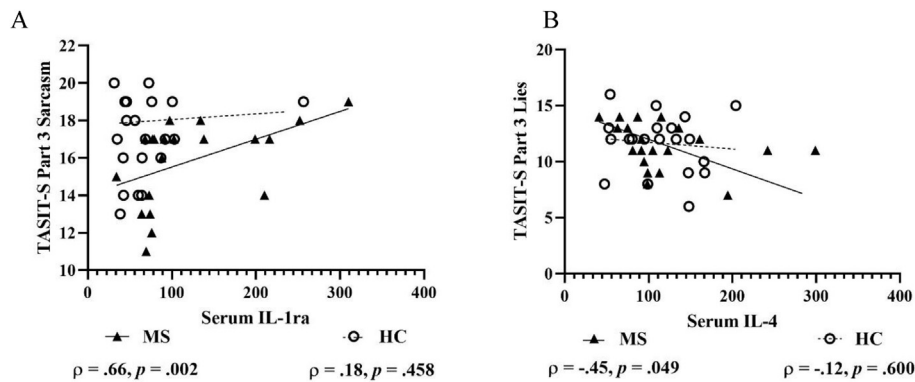
Fig. 5. Scatterplots with selected correlations between anti-inflammatory markers and objectively assessed social-cognitive measures in people with multiple sclerosis and matched healthy control participants. Figures show anti-inflammatory serum IL-1ra and TASIT-S Part 3 Sarcasm (A) and serum IL-4 and TASIT-S Part 3 Lies (B). IL-1ra, Interleukin 1 receptor antagonist; IL-4, Interleukin 4; and TASIT-S, The Awareness of Social Inference Test-Short. Concentrations are shown in fluorescence intensity values for serum.

and posterior cingulate, temporoparietal junction, and ventromedial and orbitofrontal cortices (Wang et al., 2017). Our findings indicate that the social brain may be particularly vulnerable to pro-inflammatory processes related to innate immunity. Our results support current findings that inflammatory processes, or sickness behaviour, can negatively shape social perception (Grigoleit et al., 2011; Moieni et al., 2015), and negatively affect social-cognitive abilities (Bollen et al., 2017; Eisenberger et al., 2010; Hennessy et al., 2014). Thus, in pwMS, social cognition may be particularly affected, given that dysregulated inflammatory processes are a characteristic of MS.

As expected, in pwMS, we found elevated serum concentration of anti-inflammatory IL-1ra relates to better social-cognitive abilities, specifically improved sarcasm detection and better self-reported emotion recognition and emotional empathy (Fig. 5A and S4). These findings were in agreement with recent evidence in clinical and pre-clinical MS models, which suggest a multi-faceted role of the IL-1 system in MS pathophysiology, whereby IL-1ra is the only known endogenous neuroprotective antagonistic cytokine to downregulate the pro-inflammatory action of IL-1α/β (Musella et al., 2020). Furthermore, in MS, the results of prior pharmacological research reports that disease modifying therapies, such as glatiramer acetate, natalizumab, laquinimod, and interferon beta, can restore the inflammatory imbalance by increasing circulating concentration of IL-1ra; thus, reducing relapse rates and moderating the development of new brain lesions (Group, 1993; Jacobs et al., 1996; Nicoletti et al., 1996; Ruiz et al., 2019). Extending to other anti-inflammatory markers, IL-4 and IL-10, our findings were mixed (Table S3). Similar to our findings in IL-1ra, in pwMS, elevated serum concentrations of IL-4 and IL-10 were related to better self-reported social cognitive abilities. However, serum IL-4 and IL-10 were associated with poorer social-cognitive performance on objective assessment (TASIT-S; Honan et al., 2016). This contradictory finding may reflect the lack of concordance that is often seen between subjective and objective cognitive assessments (Honan et al., 2015). Nevertheless, it remains clinically valuable to evaluate one's perception of functioning as this too can be predictive of functional outcomes (Honan et al., 2015). Together, our findings indicate that IL-1ra may be an important therapeutic target for improved social-cognitive functioning.

There are limitations associated with this pilot study. The small sample size means that we have not sufficiently captured other MS types and do not have the statistical power to examine the differences that might exist among different disease profiles. However, given our pilot results show promise, we would expect that a larger exploratory study with a broader cohort of participants will be able to more thoroughly examine the relationship between inflammatory biomarkers and social-cognitive functioning, and how this may be mediated or moderated by particular disease characteristics. Given that we examined pwMS who were not in a relapse phase, our findings are limited to inflammatory processes during remission phases. Future research may benefit from exploring pwMS during relapse phases and further extending to other MS subtypes. Comparing urinary-based immune markers to those in

cerebrospinal fluid may also help identify surrogate biomarkers for interventionist strategies to regulate inflammation in individuals experiencing social-cognitive difficulties. For example, current pharmaceutical interventions may benefit from research into complementary medicines such as probiotics, vitamin D, and resveratrol that may reduce inflammation (Morshedi et al., 2019).

5. Conclusion

Overall, our findings highlight the important implications that inflammatory processes, sickness behaviour, and the innate immune system, have on everyday social-cognitive functioning. In pwMS, better social-cognitive performance was associated with higher serum concentration of IL-1ra. Thus, it may be possible to improve social-cognitive abilities by limiting inflammatory processes, and IL-1ra may be a potential therapeutic target for future clinical trials. In both pwMS and healthy individuals, poorer social-cognitive functioning was related to pro-inflammatory biomarkers with an innate immunity signature (i.e., IL-1β, IL-17, TNF-α, IP-10, and MIP-1α, and higher urine concentration of IP-10, and MIP-1β). However, the findings were mixed for IL-4 and IL-10, such that they were negatively associated with objective social-cognitive performance, and positively related to better self-reports of social-cognitive abilities. Further cross-sectional and longitudinal research examining relationships between inflammatory markers and social-cognitive functioning according to various disease-related factors (MS subtypes) and biological sample type (serum, urine, and cerebrospinal fluid) is warranted.

Declaration of competing interest

There are no known conflicts of interest reported.

Acknowledgement

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100254.

Contributions

CAH, CKL, SM conceptualised and designed the study. JAT, CAH, CKL wrote the manuscript. CAH, HMF, KDKA, CKL were involved in data

acquisition. JAT, CKL, CAH, and CP analysed and/or interpreted the data. All authors contributed to the review and approved the final version of the manuscript.

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