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The role of inflammatory markers and cortisol in the association between early social cognition abilities and later internalising or externalising problems: Evidence from a UK birth cohort

Dongying Ji*, Marta Francesconi, Eirini Flouri, Efstathios Papachristou

Department of Psychology and Human Development, UCL Institute of Education, 25 Woburn Square, London WC1H 0AA, UK

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ABSTRACT

Objective: Deficits in social cognition are associated with internalising (emotional and peer problems) and externalising (conduct problems and hyperactivity/inattention) symptoms in youth. It has been suggested that stress may be one of the mechanisms underlying these associations. However, no empirical studies have investigated if physiological stress can explain the prospective associations between social cognition deficits and internalising and externalising symptoms in the general youth population. This study addressed this question and focused on two indicators of physiological stress, dysregulated diurnal cortisol patterns and systemic inflammation.

Method: Participants were 714 individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC), a UK population-based birth cohort. Bayesian structural equation modelling was used to investigate a) the associations of social cognition abilities at ages 8, 11, and 14 years with internalising and externalising problems at age 17 years and b) the potential mediating effects of cortisol parameters at age 15 years and inflammatory markers [interleukin 6 (IL-6) and C-reactive protein (CRP)] at ages 9 and 16 years.

Results: We found that social cognition difficulties were associated with later internalising and externalising problems. Flattened diurnal cortisol slope was associated with hyperactivity/inattention problems two years later. Lower morning cortisol partially mediated the direct association between social communication deficits at 8 years and hyperactivity/inattention and conduct problems at 17 years, even after adjustments for inflammation and confounders (for hyperactivity/inattention: indirect effect $= 0.07, 95\% \text{ CI} [0.00, 0.18], p = .042$; for conduct problems: indirect effect $= 0.04, 95\% \text{ CI} [0.00, 0.11], p = .040$). We did not find a significant association between systemic inflammation and social cognition difficulties, internalising problems, or externalising problems.

Conclusion: Our findings suggest that part of the effect of social communication difficulties in childhood on externalising problems in adolescence was mediated by lower morning cortisol. Hence, our study indicates that the hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis may be one of the physiological mechanisms linking some social cognition deficits to externalising problems.

1. Introduction

Social cognition refers to the abilities involved in recognising, interpreting, and responding to social cues (Frith and Frith, 2008). Social cognition difficulties, such as poor emotion perception and understanding, have been canvassed as important risk factors for a variety of internalising and externalising problems (Trentacosta and Fine, 2010). One of the potential intervening factors in the pathway linking social skills deficits with negative psychological outcomes is psychosocial stress (Segrin, 2017; Segrin et al., 2007). According to the social skills deficit vulnerability model (Segrin, 2000; Segrin et al., 2016), children with social cognition difficulties are more likely to experience both chronic and acute stressors in their lives, such as peer victimisation, social rejection, and physical conflicts. They are also less able to secure the social support necessary for dealing with such stressors (Knox and Douglas, 2009; Shakoor et al., 2012). Stress, in turn, is a robust predictor of adverse mental health outcomes (Cohen, 2000; Esch et al., 2002; Gershon et al., 2013). At the biological level stress is known to activate a

* Corresponding author.
E-mail addresses: dongying.ji@ucl.ac.uk (D. Ji), m.francesconi@ucl.ac.uk (M. Francesconi), e.flouri@ucl.ac.uk (E. Flouri), efstathios.papachristou@ucl.ac.uk (E. Papachristou).

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hormonal response system, the hypothalamic-pituitary-adrenal (HPA) axis, and to impact on the body's ability to regulate the immune system (i.e., the body's inflammatory response) (Miller and Blackwell, 2006; Rohleder, 2014; Ruttle et al., 2011; Slavich and Irwin, 2014). Drawing on this evidence, we theorised that HPA axis dysregulation and inflammation might be the biological pathways linking childhood social cognition deficits with internalising and externalising problems in adolescence.

The HPA axis and immune system work together to help the body to cope with stress and injuries. However, repetitive or prolonged exposure to stressors can lead to a dysregulation of these systems. When facing threatening situations, the HPA axis is activated, upregulating the secretion of cortisol to prepare the individual for a “fight-or-flight” response. Cortisol exerts a strong anti-inflammatory effect which allows the body to react to the acute threat without being hampered by sickness behaviours, such as lethargy and reduced social exploration (Slavich and Irwin, 2014). Yet under chronic stress, prolonged activation of the HPA axis to stressors can lead to a dysregulation of these systems. When facing social cognition difficulties in childhood can predict internalising or externalising problems in adolescence.

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Several empirical studies have found that dysregulated HPA axis activity and/or immune processes are involved in the development of various mental disorders (Liukkonen et al., 2011; Miller and Blackwell, 2006). For example, about half of the patients with depression or anxiety disorders display basal hypercortisolism, glucocorticoid resistance and elevated levels of inflammatory markers (Checkley, 1996; Feder et al., 2004; Mannie et al., 2007; Vreeburg et al., 2010; Osimo et al., 2019; Pariente and Miller, 2001). Longitudinal studies have also shown that increased cortisol levels at night (Hsiao et al., 2013) and higher levels of inflammatory markers in childhood (Flouri et al., 2020) are associated with worsening depressive symptoms over time. Dysregulated cortisol profiles are also shown in youth with externalising problems, with hypocortisolism - including low morning cortisol levels, a flatter diurnal rhythm, and low hair cortisol concentration (Figueiredo et al., 2020; Pauli-Pott et al., 2019) - rather than hypercortisolism tending to be the typical profile. Importantly, there is also evidence that increased levels of inflammatory markers are related to hyperactivity/inattention and conduct disorder both concurrently and longitudinally, supporting the possibility that low levels of basal cortisol cause the inadequate regulation of inflammation (Chang et al., 2020; O'dgers et al., 2007; O'Shea et al., 2014; Pajer et al., 2001). However, most studies on their links with mental health in youth have measured either cortisol or inflammation, but not both jointly. The few exceptions we are aware of were cross-sectional case-control studies conducted in clinical samples (Chang et al., 2020; Kaestner et al., 2005; Lammers et al., 2013). The synergistic longitudinal effects of HPA-axis dysregulation and inflammation on the development of mental health problems in the general adolescent population remain unclear.

This study therefore sought to examine for the first time whether HPA axis dysregulation, inflammation, or both, can mediate the association between social cognition difficulties and internalising and externalising problems in adolescence. Our purpose was twofold; a) to investigate if social cognition difficulties in childhood can predict internalising or externalising problems in late adolescence; (2) to assess if inflammatory markers or cortisol can, at least partially, explain the longitudinal association between social cognition difficulties in childhood and internalising and externalising problems in late adolescence.

2. Method

2.1. Participants

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing transgenerational longitudinal cohort study (Boyd et al., 2013) that enrolled 14,541 pregnant women with expected delivery dates between 1 April 1991 and 31 December 1992 (https://www.bristol.ac.uk/alspac/researchers/our-data/ for details of all the data that is available through a fully searchable data dictionary and variable search tool). Children were invited to attend annual assessment clinics, including face-to-face interviews and psychological and physical tests from age seven years onwards (Fraser et al., 2013). Additional children were recruited using the original enrolment definition from the participating children’s age seven years onwards, increasing the number to 15,454 pregnancies, resulting in 15,589 foetuses to date. Of these, 14,901 were alive at one year of age. Ethical approval for all measures was gained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (NHS Haydock REC: 10/H1010/70). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). All participants provided written informed consent and there was no financial compensation (details at http://www.bristol.ac.uk/alspac/).

At age 15 years, 5,501 of the ALSPAC cohort children were recruited for a clinical assessment. Of those, 3,020 were invited at random to participate in the cortisol data collection and 1,845 agreed. For 968 participants who provided at least one valid saliva sample, we applied the following exclusion criteria: (1) second born in case of a twin birth; (2) gestation at birth <= 32 weeks; (3) birth weight <= 1500 g; (4) exposure to steroid medication when cortisol was measured; (5) infection when inflammation was measured; and (6) IQ < 70 (two standard deviations below the mean). IQ was assessed using the Wechsler abbreviated scale of intelligence at age 15 (Wechsler et al., 1992). Of 864 participants who survived the exclusion process, 714 had data on internalising and externalising problems at 17 years old, and therefore comprised the analytic sample (Fig. 1).

2.2. Measures

2.2.1. Cortisol, age 15 years

As described by O'Donnell et al. (2013) and Carnegie et al. (2014), each participant was given a cortisol sampling pack during their clinic visit. Each pack contained detailed sampling instructions, 12 saliva collection devices (Sarstedt, Germany), a sample collection sheet and a prepaid envelope in which to return the samples to the laboratory. For each participant, four measurements were taken daily over three consecutive school days: at wake-up, 30 min post-wake-up, mid-afternoon, and before bedtime. Participants were shown how to collect saliva and were instructed to avoid eating or brushing their teeth before the collection of each sample, to record collection times, and to place samples in their freezers until they returned the samples to the laboratory. Samples were mailed back and stored at -20°C until they were assayed. Cortisol samples, expressed as nmol/L, were assayed using a commercially available enzyme immunoassay (Salimetrics, UK). Inter-assay and intra-assay coefficients of variation were 7.9% and 8.9% respectively (O'Donnell et al., 2013). Cortisol data were treated as missing if the values were undetectable, greater than 82 nmol/L, or greater than 4 standard deviations above the sample mean for that time point. We derived four cortisol measures 1) diurnal cortisol slope, calculated using the difference between mean morning and bedtime cortisol levels divided by time in hours; 2) cortisol awakening response (CAR), calculated by subtracting the wake-up cortisol from the post-waking cortisol; 3) total morning cortisol
output, estimated as the sum of the two morning samples; 4) total daily cortisol output, derived from the area under the curve with respect to ground (AUCg) of four time points based on the trapezoid formula (Pruessner et al., 2003). To enhance measurement accuracy of CAR, the data of individuals whose first sample was taken after 10.00 a.m., or the second sample was provided less than 20 or more than 60 min after the first, were treated as missing for that day. Following previous practice (Carnegie et al., 2014), we also replaced absent or negative CAR values as missing in case this was the result of sampling error or non-adherence (Kudielka et al., 2003). Each cortisol measure was calculated as the mean of the available samples over the study period. To correct for skewed distributions, the values of cortisol measures were log-transformed in all analyses.

2.2.2. Inflammation, ages 9 and 16 years

Inflammation was measured with IL-6 at age 9 years and CRP at ages 9 and 16 years. Blood samples were collected from non-fasting participants at age 9 years and fasting participants at age 16 years, when they fasted overnight or at least for 6 h before attending the clinic. Blood samples were immediately spun, frozen and stored at -80 °C. There was no evidence of freeze–thaw cycles during storage. IL-6 (pg/mL) was measured by enzyme-linked immunosorbent assay (RandD Systems, Abingdon, UK) and high-sensitivity CRP (mg/L) was measured by automated particle-enhanced immunoturbidimetric assay (Roche, UK, Welwyn Garden City, UK). All inter-assay coefficients of variation for IL-6 and CRP were less than 5%. Both CRP and IL-6 were log-transformed to correct their skewness for the analyses.

2.2.3. Social cognition, ages 8, 11 and 14 years

Social communication ability was assessed using the parent-rated Social Communication Disorders Checklist (SCDC) at ages 8, 11, and 14 years. There are 12 items in the SCDC measuring social reciprocity and verbal/nonverbal characteristics in the past 6 months, each ranging from 0 (“not true”) to 2 (“very or often true”). Higher scores indicate more difficulties in social communication. SCDC has been demonstrated to have high internal consistency, test–retest reliability, and heritability in both sexes (Skuse et al., 2005). For participants with less than 50 % missing data on the SCDC, total scores were calculated using prorating [if more than six items had missing data then total score was set to missing; otherwise, total score was scaled by a factor of 12 / (12 - the number of missing items) and rounded to the nearest integer]. To account for the positive skewness of total scores, SCDC scores were also dichotomised using a cut-off of ≥ 9, which has been found to yield sound screening accuracy for autistic traits in the ALSPAC sample (Barona et al., 2016).

Fig. 1. Analytic sample selection process.
2.2.5. Covariates

We controlled for a number of characteristics which are known to be associated with children’s internalising and externalising problems, social cognition, inflammation and HPA axis activity. These included sex (Dolsen et al., 2019; Goel et al., 2011; Hermens et al., 2005; Thompson and Voyer, 2014), ethnicity (Bax et al., 2019; Craig et al., 2017; DeSantis et al., 2007; Richman, 2018), being overweight (Luppino et al., 2010; Percinel et al., 2018; Visser et al., 2001; Yu et al., 2020), socioeconomic status (Marsman et al., 2012; Richman, 2018; Russell et al., 2016), stressful life events (Elzinga et al., 2008; Klewer et al., 2009; Nettle et al., 2017; Vrijen et al., 2018), vigorous physical activity (Pengpid and Peltzer, 2020; Anderson and Wideman, 2017), and unhealthy behaviours (Chang et al., 2005; Eiden et al., 2020; Homman et al., 2019; Ruttle et al., 2015). Sex and ethnicity were recorded at birth and coded as dichotomous (male vs female and White vs non-White, respectively). Being overweight was determined using the International Obesity Task Force (IOTF; Cole et al., 2000) age- and sex-specific cut-offs for body mass index (BMI; males: 23.29 kg/m²; females: 23.94 kg/m² at age 15 years). Socioeconomic status was derived from a principal components analysis of maternal education (below O-level, O-level only, A-level only, university degree or more), social class at 32 weeks of pregnancy (I, II, III - non-manual, III - manual, IV, V), and the mean score of financial difficulties at 8, 21 and 33 months (a sum score of dichotomous items about being unable to afford the cost of food, clothes, heating, housing and things for the baby, ranging 0 to 20 for each time-point). Higher composite score indicates lower socioeconomic status here. Stressful life events were assessed as the sum of events at child’s age 8 months, 21 months, 33 months, 47 months, 61 months, 73 months and 134 months. At each time-point, a stressful events checklist with 43 dichotomous items was completed by the mother (Barnett et al., 1983; Flouri et al., 2020). The frequency of doing vigorous activities, such as running, playing football and swimming, was measured with a 3-point scale of 1 = “less than once a week”, 2 = “1–3 times a week” and 3 = “more than three times a week” at age 15 years. Regarding unhealthy behaviours, we included two binary variables at age 15: ‘daily smoker’ (Yes vs No), for those who reported that they usually smoke at least one cigarette per day, and ‘alcohol user’ (Yes vs No), for those who reported drinking on more than two days a week over the last six months. In addition, we controlled for characteristics known to be associated with cortisol levels, including the mean wake-up time during the period of cortisol data collection (Dahlgren et al., 2009; Stalder et al., 2009) and contraceptive and psychotropic medication use at age 15 years (Yes vs No; O’Donnell et al., 2013). The exact age (in months) of children when social cognition was assessed was also controlled for in all analyses. Because at the time of measurement of cortisol none of the individuals in the sample were pre-pubertal (taken as a Tanner stage < 2), pubertal stage was not considered as a covariate.

2.3. Analytic strategy

Analyses were performed in Stata 16 (StataCorp, 2019) and Mplus 8.1 (Muthén and Muthén, 1998–2017). First, demographic characteristics, social cognition abilities, inflammatory markers and internalising and externalising problems were compared between the analytic and non-analytic samples (the remaining ALSPAC members who were excluded from the analyses; Fig. 1), to describe the sample and assess potential sample bias. Next, for the analytic sample, Pearson’s correlation coefficients between social cognition abilities, cortisol measures, inflammatory markers, and internalising and externalising problems were calculated.

1 As BMI at 15 years (when cortisol was measured) is significantly correlated with BMI at 9 years (when inflammation was measured) (Pearson’s r = 0.81, p < .001), and BMI at 15 years old had more valid data (missingness 0.4%) than BMI at 9 years old (missingness 3.4%), we chose BMI at 15 years old here.
If cortisol and inflammation were correlated with both social cognition abilities and internalising or externalising problems, Bayesian structural equation modelling (BSEM) was performed to test their mediating effects on the association between social cognition and internalising or externalising problems. We used a Bayesian estimator with non-informative priors (default normal distribution with a mean hyperparameter of zero and a variance of 10\(^{-15}\); Muthén and Muthen, 1998–2017). We chose a Bayesian estimator for the mediation analyses as it does not assume normal distribution of estimates (Muthén, 2010). This is particularly relevant for indirect effects which are commonly skewed (Yuan and MacKinnon, 2009). In addition, BSEM has been shown to produce more accurate estimates than frequentist approaches using maximum likelihood estimation with bootstrapping (Kuss et al., 2005; Wang and Preacher, 2015), especially in small sample sizes (Ozchowski, 2014; Ulitzsch et al., 2021). For the Bayesian mediation model, a Markov Chain Monte Carlo (MCMC) algorithm was used for the estimation of direct and indirect effects (Yuan and MacKinnon, 2009). Model convergence was assessed by the potential scale reduction (PSR) factor and the convergence criterion was set at 1.001. To meet the PSR convergence criterion in this study the number of iterations was set to 6,000 for unadjusted models, and 10,000 for the fully adjusted models. Model fit was assessed by the posterior predictive p-value (PPP), calculated based on chi-square difference tests in structural equation models (Muthén and Asparouhov, 2012). PPP values above 0.05 represent an acceptable model fit, and values close to 0.50 indicate a good fit (Muthén and Asparouhov, 2012). BSEM uses 95% credible interval (CI) to indicate the range of posterior probability distribution which the true parameter has a 95% chance of falling in. Full information maximum likelihood (FIML) was used to account for missing data in social cognition scores, inflammation or cortisol measures, and covariates. For each mediation model, unadjusted models were initially fitted, followed by models with adjustments for covariates (sex, exact age when social communication was assessed, ethnicity, overweight, socioeconomic status, wake-up time, vigorous physical activity, smoking, alcohol use, medication use, stressful life events, and cortisol or inflammation - when not included in the model as mediators).

3. Results

3.1. Descriptive statistics

The analytic sample included 714 ALSPAC members with valid data on hyperactivity/inattention and conduct problems at age 17 years, and with very little missingness on emotional problems (one case) and peer problems (three cases). Of the 714 study participants, 56.44% (n = 403) were female, 97.03% (n = 653) were white, 18.71% (n = 133) were overweight at 15 years, 15.78% (n = 110) were taking steroid medication when cortisol was measured, 6.59% (n = 41) were daily smokers and 3.98% (n = 36) were overweight at 15 years, 15.78% (n = 105) were taking steroid medication when cortisol was measured

### Table 1

| Continuous variables | Analytic sample (N = 714) | Non-analytic sample (N = 14931) | \(\chi^2\) (df) | P-value a |
|----------------------|--------------------------|-------------------------------|-----------------|-----------|
| Social cognition     |                          |                               |                 |           |
| SCDC at 8 years      | 0.06 (0.23)              | 0.09 (0.27)                   | 2.22            | 0.026     |
| SCDC at 11 years     | 0.03 (0.17)              | 0.07 (0.26)                   | 4.20            | 0.000     |
| SCDC at 14 years     | 0.05 (0.21)              | 0.07 (0.26)                   | 2.64            | 0.008     |
| DANVA at 8 years     | 1.84 (0.37)              | 1.82 (0.38)                   | 0.81            | 0.421     |
| Triangle test at 14  | 57.81 (7.10)             | 56.62 (7.61)                  | 3.90            | 0.000     |
| Conduct problems     | 0.86 (1.19)              | 1.05 (1.38)                   | 3.48            | 0.001     |
| Emotion problems     | 1.28 (1.63)              | 1.53 (1.88)                   | 3.38            | 0.001     |
| Peer problems        | 1.06 (1.39)              | 1.12 (1.52)                   | 1.11            | 0.267     |

### Table 2

| Categorical variables | Analytic sample (N = 714) | Non-analytic sample (N = 14931) | \(\chi^2\) (df) | P-value a |
|-----------------------|--------------------------|-------------------------------|-----------------|-----------|
| Sex (male)            | 311 (43.56%)             | 7380 (51.52%)                 | 17.25           | 0.000     |
| Ethnicity (white)     | 653 (97.03%)             | 10,871 (94.66%)               | 6.42            | 0.011     |
| Overweight            | 133 (18.71%)             | 971 (20.67%)                  | 1.47            | 0.225     |
| Medication use        | 110 (15.78)              | 762 (16.46%)                  | 0.20            | 0.651     |
| Daily smoker          | 41 (6.59%)               | 378 (8.40%)                   | 2.38            | 0.123     |
| Alcohol greater than 2 days/week | 24 (3.98%) | 216 (5.41%)                  | 2.16            | 0.141     |

Note. a P-values comparing two samples from Pearson’s Chi-squared tests for categorical variables and from t-tests for continuous variables. S.D.: standard deviations. IL-6: interleukin 6. CRP: C-reactive protein. SCDC: Social and Communication Disorders Checklist (Skuse et al., 2005). DANVA: Diagnostic Analysis of Non-Verbal Accuracy (Nowicki & Duke, 1994). b Exact month age at which social communication difficulties were first assessed in ALSPAC. c Inflammatory markers are log-transformed. Bold: p < .05.

at 14 years suggesting that these capture substantively distinct cognitive domains. Social communication difficulties at 8, 11, and 14 years were significantly associated with more hyperactivity/inattention (all p < .01) and conduct problems at 17 years (all p < .01). There were also significant positive associations between social communication difficulties at 11 and 14 years and emotional problems (both p < .01) at age 17, while social communication difficulties at 14 were additionally positively related to peer problems (p < .01). Emotion recognition abilities were not associated with internalising or externalising problems. The four cortisol measures were positively associated with each other (all p < .01). Of the four cortisol measures, total morning cortisol and CAR were positively associated with CRP at age 9 (both p < .01), but...
not with IL-6 at age 9 or CRP at age 16. Regarding the associations between cortisol measures and the outcomes, diurnal cortisol slope was negatively associated with hyperactivity/inattention at 17 years (all \( p < .01 \)) while total morning cortisol was also negatively correlated with conduct problems at 17 years (\( p < .01 \)). There was no significant association between any of the cortisol measures and the outcomes, diurnal cortisol slope and inflammatory markers emerged either.

Finally, regarding the relationship between social cognition and cortisol, only social communication at 8 was correlated with total morning cortisol (\( \rho = -0.21, \text{SD} = 0.10, 95 \% \text{CI} = [-0.36, -0.05] \), \( p = 0.008 \)). The covariates in the adjusted models include inflammation (IL-6) at 9 years and all other covariates, presented in the Supplementary document (Table S1, S2) revealed the same findings.

### 3.3. Mediation models

Of all associations of the inflammatory markers and cortisol measures with the outcomes and exposures, only total morning cortisol was associated with at least one of the social cognition measures (social communication deficits at 8 years) and two of the outcomes (hyperactivity/inattention and conduct problems at 17 years). Therefore, our mediation analysis tested whether total morning cortisol can mediate the link between (1) social communication at 8 and hyperactivity/inattention at 17; (2) social communication at 8 and conduct problems at 17.

Table 3 summarises the results of the mediation models before and after adjustments for confounding. Both unadjusted and fully adjusted models for hyperactivity/inattention (unadjusted model: \( \text{PPP} = 0.54 \); adjusted model: \( \text{PPP} = 0.43 \)) and conduct problems (unadjusted model: \( \text{PPP} = 0.54 \); adjusted model: \( \text{PPP} = 0.43 \)) showed satisfactory model fit. For hyperactivity/inattention, a significant direct path from social communication difficulties at 8 years was found (unadjusted model: \( b = 0.21, \text{SD} = 0.08, 95 \% \text{CI} = [-0.36, -0.05], p = 0.008 \)).

### Table 3

| Social cognition | Main Variables | Unadjusted models | Adjusted models |
|------------------|----------------|-------------------|-----------------|
|                  | 1              | 2 \( \rho \)       | 95% CI  \( P \)-value | 1              | 2 \( \rho \)       | 95% CI  \( P \)-value |
| Social cognition | 2              | 0.37**            |                  | 3              | 0.20**           |                  |
| 3. SCDC at 14    | 4.06**         |                  |                  | 4. DCS at 15   | -0.01            | -0.03            |
| 5. Trangles at 14| 0.09**         | 0.07             | 0.04            | 6. TMC at 15   | -0.11**          | -0.06            | -0.07            |
| Cortisol measures | 7. CAR at 15    | -0.07            | 0.04            | -0.02          | 0.10*            | -0.02            | 0.45**           |
|                   | 8. CAR at 15    | -0.07            | 0.04            | -0.02          | 0.10*            | -0.02            | 0.45**           |
|                   | 9. AUQ at 15    | 0.00             | -0.01           | 0.05           | 0.04             | 0.02             | 0.67**           |
|                   |                 |                  |                 | 7. TMC at 15   | -0.11**          | -0.06            | -0.07            |
|                   |                 |                  |                 | -0.07          | 0.04             | -0.02            | 0.45**           |
|                   |                 |                  |                 | -0.02          | 0.10*            | -0.02            | 0.45**           |
|                   |                 |                  |                 | -0.02          | 0.10*            | -0.02            | 0.45**           |
|                   |                 |                  |                 | -0.04          | -0.02            | -0.04            | -0.00            |
|                   |                 |                  |                 | -0.02          | -0.04            | -0.00            | 0.12*            |
|                   |                 |                  |                 | -0.02          | -0.04            | -0.00            | 0.12*            |
|                   |                 |                  |                 | -0.02          | -0.04            | -0.00            | 0.12*            |
|                   |                 |                  |                 | -0.02          | -0.04            | -0.00            | 0.12*            |

Note: \( \rho < .05 \); **\( \rho < .01 \).
Social communication difficulties also significantly predicted lower levels of total morning cortisol at 15 years (unadjusted model: \( b = -0.21, 95\% \text{ CI } [-0.36, -0.05], p = .008 \)), indicating that childhood social communication difficulties were related to hypoactivity of the HPA axis in adolescence. Lower total morning cortisol further predicted later hyperactivity/inattention at 17 years (unadjusted model: \( b = -0.48, 95\% \text{ CI } [-0.81, -0.16], p = .004 \)). The links between social communication difficulties and hyperactivity/inattention (adjusted model: \( b = 1.80, 95\% \text{ CI } [1.13, 2.47], p < .001 \)), social communication difficulties and morning cortisol (adjusted model: \( b = -0.18, 95\% \text{ CI } [-0.33, -0.02], p = .024 \)), and morning cortisol and hyperactivity/inattention (adjusted model (\( b = -0.41, 95\% \text{ CI } [-0.76, 0.07], p = .016 \)) survival adjustment for covariates. A significant indirect path from social communication difficulties to hyperactivity/inattention was found via total morning cortisol (indirect effect = 0.10, 95% CI [0.02, 0.22], \( p = .014 \)) and the path remained significant after adjustment for inflammation and other covariates (indirect effect = 0.07, 95% CI [0.00, 0.18], \( p = .042 \)). Similarly, there was evidence for a direct association between social communication difficulties at 8 and conduct problems at 17 years (unadjusted model: \( b = 1.06, 95\% \text{ CI } [0.66, 1.44], p < .001 \)), and for a significant indirect effect through lower total morning cortisol at 15 years (unadjusted model: indirect effect = 0.04, 95% CI [0.00, 0.11], \( p = .046 \)). The direct effect (adjusted model: \( b = 0.90, 95\% \text{ CI } [0.51, 1.30], p < .001 \)) and indirect effect (adjusted model: indirect effect = 0.04, 95% CI [0.00, 0.11], \( p = .040 \)) also survived adjustments for all covariates including inflammation.

4. Discussion

In the present study, we investigated the role of inflammation and diurnal cortisol in the longitudinal association between social cognition in childhood and early adolescence and internalising and externalising problems in late adolescence using data from a UK population-based cohort study. Consistent with existing evidence (Lancelot and Nowicki, 1997; Sullivan et al., 2017; Zadeh et al., 2007) and theory (Segrin, 2000; Cole, 1991; Dodge, 1993), we found social communication difficulties to be longitudinally related to internalising and externalising problems. Cortisol measures, including flattened diurnal slope and low morning cortisol levels, were associated with externalising, but not internalising problems. Further, we found that children with social communication difficulties at 8 years were more likely to have lower morning cortisol levels at 15 years and we observed a significant indirect effect of social communication difficulties at 8 on externalising problems at 17 via low morning cortisol. Although the effects were small in magnitude, they were robust to adjustments for confounding. These findings expand the literature by suggesting that hypoactivity of the HPA axis can, at least partially, explain the longitudinal relation between childhood social communication difficulties and externalising problems in late adolescence. We did not find evidence for an
association between the remaining social cognition components and inflammation or diurnal cortisol measures.

To our knowledge, this study is the first to reveal a mediating role of HPA axis hypoactivity in the association between difficulties in social cognition in childhood and externalising problems in adolescence. Dysregulation of the HPA axis has been implicated as one physiological pathway that mediates the effects of chronic stress or serious stressors on physical and mental health (McEwen, 2004; Raison and Miller, 2003). It is well documented for instance that exposure to serious adversity in the early years is conducive of blunted HPA axis activity (Anda et al., 2006; Trickett et al., 2010). Our study suggests that childhood social communication deficits may be a source of stress. The results of our mediation models further supported the stress strand of theories on the importance of social cognition in mental health (e.g., the social skills deficit vulnerability model and the social competence theory; Bornstein et al., 2010; Cole, 1991) by demonstrating that adolescents with downregulated HPA axis, partly due to early difficulties in social cognition, had more externalising problems. It must be emphasised however that in our study the long-term effect of impaired social cognition on externalising problems was not fully explained by HPA axis hypoactivity in adolescence. Future research should explore other types of stress measures (e.g., HPA axis response to acute stressors and perceived stress level) but also other social processes, especially those relating more strongly to externalising problems, such as social information processing (Andrade et al., 2012; Dodge, 1993; Milich and Pettit, 2008). A more comprehensive understanding of how social cognition difficulties can bring about mental problems via a pathophysiological pathway is important, both theoretically and practically.

Surprisingly, we found that social communication at 8 years, but not at 11 or 14 years, was associated with cortisol measures in adolescence. There might be two possible explanations for this. First, social communication difficulties in the primary school years might be considered a significant early stressor. As discussed earlier, stress experienced early in life is related to a low, flat diurnal cortisol rhythm (Anda et al., 2006; Trickett et al., 2010). In our study, social communication difficulties in childhood were related to hypoactivity of the HPA axis in adolescence, in turn linked to externalising problems later. Second, only very few children showed social communication difficulties at 11 (2.82%) and 14 years (4.69%), which may cause Type 2 error and not provide adequate statistical power to detect small effects.

Another important finding that merits discussion is that emotion recognition difficulties were not related to morning cortisol levels. This finding expanded the body of knowledge on the longitudinal link between different domains of social cognition and basal HPA axis activity. This non-significant correlation is in line with findings from research on cortisol response to laboratory induced stressors. For example, Smeets et al. (2009) found no association between stress-induced cortisol elevations and emotion recognition ability. The result also echoes the findings of a recent meta-analysis of studies on social cognition domains and basal cortisol levels which suggested that emotion regulation, but not emotion recognition, is related to higher cortisol levels (Ji et al., 2020). It is possible that emotion recognition is more automatic and less effortful than other cognitive processes involved in general social communication ability, such as social reciprocity and attribution of non-verbal cues. As such it would be less likely to induce dysregulation of the HPA axis (Happe and Frith, 2014). In addition, compared to children with poor general social communication ability, children with difficulties in emotion recognition may be high-functioning socially if they have intact higher-level social cognition abilities (e.g., emotion regulation and social reciprocity). Thus, they may experience fewer social stressors and therefore may be less likely to show dysregulated HPA axis activity. However, this could not be tested in this study. Further investigation is needed to disentangle the relationship between the various social cognition abilities and stress.

The finding of the longitudinal association between lower morning cortisol and externalising problems is consistent with the existing literature on hyperactivity/inattention and conduct problems (Angeli et al., 2018; Ibrahim et al., 2016; Salis et al., 2016). For example, systematic reviews suggested that youth with attention-deficit/hyperactivity disorder or conduct disorder have lower basal cortisol levels (Chang et al., 2021; Figueiredo et al., 2020). Importantly, Salis et al. (2016) found that a flattened cortisol rhythm could predict a greater increase of conduct and aggressive behaviours over three years in young school-age children. Our finding adds to this evidence by indicating that hypercortisolism may be related to externalising problems in adolescence. One explanation for this link may be that children with underregulated HPA axis tend to seek more stimulation to raise their arousal levels, thereby engaging in more disruptive or aggressive behaviours (Krueger et al., 1989). Regarding internalising problems, contrary to previous evidence of hypercortisolism in depression (Paslasik et al., 2011), we did not find an association with cortisol. This non-significant finding may be related to the measure of internalising problems in this study, a broad screening instrument. Hence, using narrow measures for each component of the internalising symptom construct may be useful in future research.

Regarding inflammation, measured using IL-6 and CRP levels in our study, we did not find a significant correlation with any of the social cognition measures or the internalising and externalising problems considered. However, this result needs to be interpreted with caution. First, the longitudinal associations of inflammation and psychological functioning in the general population, especially among the young, are normally much weaker, hence, more difficult to be detected in a sample such as ours. For example, significant associations between inflammation and psychosocial outcomes have largely been reported in clinical populations (Chang et al., 2020; Leffa et al., 2018) and large community samples (e.g., n = 4,583 in Flouri et al., 2019; n = 13,775 in Niles et al., 2018). However, in our analytic sample, only around 500 participants had valid data on inflammation, which might not provide enough statistical power to detect a small effect. Second, we only tested two inflammatory markers that are available in ALSPAC. It is possible that other inflammatory markers may show a stronger association with social cognition and mental wellbeing, for example interferon-γ and tumour necrosis factor-α (Costello et al., 2019). In addition, levels of IL-6 and CRP at age 9 years were measured from non-fasting samples, which may increase measurement error caused by diurnal variation in the levels of cytokines. Future studies should use a larger sample size and fasting blood samples, and consider more pro and anti-inflammatory markers for a more accurate and comprehensive understanding of the role of the immune response in the link between social abilities and mental wellbeing.

Our study has a number of strengths. First, although there had been several studies in clinical samples linking HPA axis function to inflammatory markers (Miller et al., 2014; O’Donovan et al., 2010), ours is the first and largest population-based longitudinal study to explore the roles of both inflammation and cortisol as mediators of the link between social cognition and mental health in youth. This means that our findings are more likely to be generalised to the broader population. Second, it controlled for a wealth of confounders, including demographic characteristics, measures of lifestyle and psychosocial and biological risk. Third, it used Bayesian methods for the mediation models which provide more robust estimates compared to more traditional statistical methods testing for indirect effects as they do not rely on assumptions of normality for the indirect effects (Muthén, 2010).

This study also has limitations, and the results should be interpreted with these caveats in mind. First, the assessment of HPA axis function was limited to basal salivary cortisol. Other hormones released by the HPA axis, such as corticotropin-releasing hormone and adrenocorticotropic hormone, and HPA-related genetic polymorphisms, were not directly assessed. Cortisol levels may be similar in individuals with different levels of glucocorticoid sensitivity, cortisol-evoked genomic activity, and the expression of glucocorticoid receptors (GR), which are
also related to physical and mental health problems (Saxbe, 2008). Nevertheless, as the final product of the HPA axis, cortisol is sensitive to all the upstream hormones, and it has a direct impact on GR expression. Second, this study was also limited by the data available in ALSPAC. Inflammation and cortisol were not measured at exactly the same time, so we were not able to examine the concurrent effects of inflammation and cortisol. In addition, as cortisol was not measured in childhood, we could not adjust for early HPA axis function to determine temporal precedence of HPA axis deregulation and social communication difficulties. Relatedly, if our variables of interest were available at more time-points, we would be able to fit more sophisticated longitudinal models, such as cross-lagged mediation models which allow the inference of tentative causal relationships. Future research should seek to address this. Third, social communication difficulties and internalising and externalising symptoms were reported by mothers, which may raise concerns about potential reporting bias. However, many scholars consider caregiver-reported internalising and externalising symptoms on the SDQ to have high validity (Stokes et al., 2014), even in late childhood. Nevertheless, future studies may consider using multiple informant evaluation on the SDQ, as parent and self reports on it yield different factor loadings and only modest agreement (Goodman, 2001; van Roy et al., 2008). Fourth, although this study included a large and socioeconomically diverse sample, it did not vary widely across other demographic characteristics, such as ethnicity. This, alongside the fact that we included only those participants with valid cortisol data in ALSPAC, who tended to come from advantaged families (Table 1), suggests that selection bias can also be factor. Therefore, the external validity of the study might be somewhat compromised. Finally, while we were able to adjust for a range of confounders in our analysis, there are other factors that we were unable to account for because they are not available in ALSPAC, such as perceived stress.

From a practical perspective, the findings of this study revealed that hypocortisolism in the general adolescent population may be a biomarker for childhood social communication difficulties, which in turn are robustly linked to externalising problems. Interventions that help children with social communication difficulties cope with stress may prevent future externalising problems. In addition to interventions for stress management, policies and actions are needed to identify social cognition problems at an early age. These could involve direct training for young people, but also education programmes for parents, teachers, and community social workers to build positive social environments and promote young people’s social skills.

5. Conclusion

We found that lower morning cortisol partially mediates the associations between social communication difficulties at 8 years and hyperactivity/inattention and conduct problems at 17 years after adjustment for confounding. In contrast, inflammation did not appear to mediate this association. Emotion recognition was not associated with later inflammation, cortisol levels, or internalising and externalising problems. The findings suggest that hypocortisolism may partly explain the association between some social cognition deficits and externalising problems in the general youth population.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbi.2022.07.002.

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