Journal Pre-proofs

Full-length Article

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

Dongying Ji, Marta Francesconi, Flouri, Efstathios Papachristou

PII: S0889-1591(22)00176-3
DOI: https://doi.org/10.1016/j.bbi.2022.07.002
Reference: YBRBI 4889

To appear in: *Brain, Behavior, and Immunity*

Received Date: 2 February 2022
Revised Date: 29 May 2022
Accepted Date: 3 July 2022

Please cite this article as: Ji, D., Francesconi, M., Flouri, Papachristou, E., The role of inflammatory markers and cortisol in the association between early social cognition abilities and later internalising or externalising problems: Evidence from a U.K. birth cohort, *Brain, Behavior, and Immunity* (2022), doi: https://doi.org/10.1016/j.bbi.2022.07.002

Title:

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

Authors (Surname, First name):

Ji, Dongying (Corresponding author)

Department of Psychology and Human Development, UCL Institute of Education, 25 Woburn Square, London WC1H 0AA, UK dongying.ji@ucl.ac.uk

Francesconi, Marta

Department of Psychology and Human Development, UCL Institute of Education, 25 Woburn Square, London WC1H 0AA, UK m.francesconi@ucl.ac.uk

Flouri, Eirini

Department of Psychology and Human Development, UCL Institute of Education, 25 Woburn Square, London WC1H 0AA, UK e.flouri@ucl.ac.uk

Papachristou, Efstathios

Department of Psychology and Human Development, UCL Institute of Education, 25 Woburn Square, London WC1H 0AA, UK efstathios.papachristou@ucl.ac.uk

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% CI

[0.00, 0.18], p = .042; for conduct problems: indirect effect = 0.04, 95% 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.

Keywords: Adolescence; ALSPAC; cortisol; hyperactivity; externalising problems; inflammation; social cognition.

Introduction

Social cognition refers to the abilities involved in recognising, interpreting, and responding to social cues (Frith & 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 & 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 & 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 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' inflammatory response) (Miller & Blackwell, 2006; Rohleder, 2014; Ruttle et al., 2011; Slavich & 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 an 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 & Irwin, 2014). Yet under chronic stress, prolonged activation of the HPA axis and excessive secretion of cortisol can impair the immune system's sensitivity to cortisol signals, resulting in elevated levels of inflammatory markers (Danese et al., 2008; Miller et al., 2002; Miller et al., 2008; Walther et al., 2017). Thus, the impact of chronic stress on the activity of the HPA axis may change over time, reflecting a transition from hyperactivity to hypoactivity (i.e., low basal cortisol levels), ending in inadequate regulation of inflammation (Agorastos et al., 2019; Fries et al., 2005; Susman, 2006). The timing of the exposure also seems to matter. For example, a longitudinal study found that, compared to non-abused females, females with experience of childhood sexual abuse showed higher morning cortisol in adolescence, which became lower in adulthood (Trickett et al., 2010). Therefore, depending on the duration of the stress response, the synergistic effects of cortisol and inflammation can differ.

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 & 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; Pariante & 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; Odgers 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; Lamers 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 symptoms. 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.

Method

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 (http://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 (Figure 1).

Measures

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 larger 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-awakening 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.

Inflammation, ages 9 and 16 years

Inflammation was measured with IL-6 at age 9 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 (R&D Systems) 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 were less than 5%. Both CRP and IL-6 were log-transformed to correct their skewness for the analyses.

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 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 diagnostic accuracy for autism in the ALSPAC sample (Barona et al., 2015; Kothari et al., 2015; Skuse et al., 2009).

Emotion recognition from facial expressions was assessed with the Diagnostic Analysis of Non-Verbal Accuracy (DANVA) test during an annual assessment clinic held when the children were approximately 8 years (Nowicki & Duke, 1994). The faces subtest of the DANVA consists of 24 colour photos of both boys and girls at school age, with each face showing one of four emotions: fear, happiness, sadness, or anger. Each photo was presented for 2 seconds, and the child was asked to choose which emotion was displayed. Pictures were

classified as high (easy to identify) or low (harder to identify) intensity. The measure is scored by simply adding up the number of errors/misattributions for each emotion. The number of errors made for each emotion with high- and low-intensity stimuli can also be used. DANVA scores were also positively skewed, therefore, cut-offs for each of the variables (based on the upper 20th percentile) were derived in collaboration with the author who developed the DANVA test (Stephen Nowicki) for ALSPAC and were based upon the distribution of results in the entire sample. These specific cut-offs have been previously used in studies using ALSPAC (Barona et al., 2015; Kothari et al., 2015; Thompson et al., 2011). For all emotions, participants who made at least 7 errors were coded as 1 (versus 0 "total errors < 7"), indicating deficits in emotion recognition from facial expressions. The DANVA has been shown to have good internal consistency, test–retest reliability, and convergent and construct validity in children aged 6 to 10 years (Nowicki & Duke, 1994).

Emotion recognition from movements was assessed using the computer-based Emotional Triangles test at 14 years. Participants were asked to attribute an emotion to a nonhuman animate entity which consisted of a black outline triangle and a circle. The movements of the triangle were designed to represent a particular emotion: happy, sad, angry, and scared. For example, "angry" was depicted by the triangle repeatedly 'jabbing' at the circle (For more details on the task, see Boraston et al., 2007). For each of the four emotion trials, there were two positive questions, where the mental state of the triangle matched the mental state described in the question (e.g., "is the triangle happy?" for a happy animation), and two negative questions, where the mental state of the triangle did not match the mental state described in the question (e.g., "is the triangle sad?" for a happy animation). Hence, there were four questions that were scored for each emotion and 16 in total. Each question was scored from 0 ("the triangle did not possess the mental state") to 5 ("the triangle

definitely possessed the mental state"). The total score was calculated by adding the scores of all the positive questions and subtracting the score of the negative items. High scores represent better ability in identifying particular emotions. To avoid negative scores, we added 40 to the total score, giving the score a range from 0-80, following previous studies using this test (Holland et al., 2020; Warrier & Baron-Cohen, 2018). Reliability and validity of the Emotional Triangles test has been well-established (Boraston et al., 2007). The Cronbach's alpha in our analytic sample is 0.69.

Internalising and externalising problems, age 17 years

Internalising and externalising problems were assessed using the mother-rated Strengths and Difficulties Questionnaire (SDQ) at ages 17 years (Goodman et al., 2010). SDQ consists of 20 "difficulties" items related to behaviours in the past 6 months, which form four scales: emotional problems, conduct problems, hyperactivity/inattention, and peer problems. The internalising problems scale comprises the 10 items from the emotional and peer problems subscales, and the externalising problems scale comprises the 10 items from the hyperactivity/inattention and conduct problems subscales. Scores on the internalising and externalising problems scales range from 0 to 20 with higher scores indicating more serious problems. The SDQ is widely used to screen for mental health problems in children and adolescents and has shown good validity and reliability in different population samples (Goodman & Scott, 1999; Goodman, 2001; Shojaei et al., 2009). SDQ scores above the 90th centile can predict a substantially raised probability of independently diagnosed psychiatric disorders (Goodman, 2001).

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 & 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; Kliewer et al., 2009; Nettle et al., 2017; Vrijsen et al., 2018), vigorous physical activity (Pengpid & Peltzer, 2020; Anderson & 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 a 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/m^2; females: 23.94 kg/m^2 at age 15 years[1]). 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

[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.

events at child's age 8 months, 21 months, 33 months, 47 months, 61 months, 73 months 110 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.

Analytic strategy

Analyses were performed in *Stata 16* (StataCorp, 2019) and *Mplus 8.1* (Muthén & 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; Figure 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.

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/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^{10}; Muthén & Muthén, 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 & 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 & Preacher, 2015), especially in small sample sizes (Ozechowski, 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 & 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 & Asparouhov, 2012). PPP values above 0.05 represent an acceptable model fit, and values close to 0.50 indicate a good fit (Muthén & 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 the adjustments of 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).

Results

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% were white (n = 653), 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 = 24) were consuming alcohol on more than two days a week at age 15. Comparison of the descriptive information between the analytic and the non-analytic samples demonstrated some sample selection bias (Table 1). On average, children in the analytic sample had a less deprived socioeconomic background, experienced more stressful events, were more likely to be female, scored lower in the internalising and externalising problems considered and had lower average levels of inflammation. They also showed better emotion recognition from movements and social communication abilities.

Correlation analyses

Pairwise associations between social cognition measures, cortisol measures, inflammatory markers, and externalising and internalising problems were tested using Pearson's correlations. The results are summarised in Table 2. Social communication difficulties (SCDC at 8, 11 and 14 years) were not correlated with emotion recognition ability from facial expression (DANVA) at 8 years or motions (Triangles) 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 with 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 and total morning cortisol were negatively associated with hyperactivity/inattention at age 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 internalising problems. No significant associations of internalising and externalising problems with inflammation emerged either. Finally, regarding the relationship between social cognition and cortisol, only social communication at 8 was correlated with total morning cortisol ($p < .01$).

Mediation models

Of all associations between 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 included testing 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: PPP = 0.54; adjusted model: PPP = 0.43) and conduct problems (unadjusted model: PPP = 0.54; adjusted model: 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 = 2.03, 95% CI [1.38, 2.69], $p < .001$). Social communication difficulties also significantly predicted lower levels of total morning cortisol at 15 years (unadjusted model: b = -0.21, 95% 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% CI [-0.81, -0.16], $p = .004$). The links between social communication difficulties and hyperactivity/inattention (adjusted model: b = 1.80, 95% CI [1.13, 2.47], $p < .001$), social communication difficulties and morning cortisol (adjusted model: b = -0.18, 95% CI [-0.33, -0.02], $p = .024$), and morning cortisol and hyperactivity/inattention (adjusted model (b = -0.41, 95% CI [-0.76, 0.07], $p = .016$) survived 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% 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% 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. Figure 2 illustrates the results of the two adjusted mediation models and presents the standardised coefficients (β) for the direct and indirect effects.

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 & 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 with 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 & 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 & Dodge, 1984; Mize & 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 (Happé & 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 add to this evidence by indicating that hypocortisolism 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 (Kruesi et al., 1989). Regarding internalising problems, contrary to previous evidence of hypercortisolism in depression (Paslakis 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 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 adolescence (Vugteveen et al., 2021; van Roy et al., 2008; van Widenfelt et al., 2003). 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.

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.

Acknowledgments

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, including interviewers, computer and laboratory technicians, clerical workers, research scientists, statisticians, volunteers, managers, receptionists, and nurses. The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf). This research was specifically funded by the UK Economic and Social Research Council (Grant ref.: ES/P001742/1; PI Eirini Flouri). This publication is the work of the authors and Dr. Efstathios Papachristou, Dr. Marta Francesconi, Dr Eirini Flouri, and Miss Dongying Ji will serve as guarantors for the contents of this paper. The authors report no biomedical financial interests or potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Tables and figure captions

Table 1

Sample characteristics in the analytic sample and non-analytic sample

	Analytic sample (N=714)	Non-analytic sample (N=14931)	F(df)	P-value
Categorical variables	N (%)	N (%)		
Sex (male)	311 (43.56%)	7380 (51.52%)	17.27 (1, 15037)	**0.000**
Ethnicity (white)	653 (97.03%)	10871 (94.66%)	1.17 (1, 12155)	0.279
Overweight	133 (18.71%)	971 (20.67%)	1.47 (1, 5406)	0.225
Medication use	110 (15.78)	762 (16.46)	0.20 (1, 5324)	0.651
Daily smoker	41 (6.59%)	378 (8.40%)	2.38 (1, 5119)	0.122
Alcohol > 2 days/week	24 (3.98%)	216 (5.41%)	2.16 (1, 4594)	0.142
Continuous variables	Mean (S.D.)	Mean (S.D.)		
Age (months)[a]	91.63 (1.35)	91.91 (1.72)	16.59 (1, 8169)	**0.000**
Socioeconomic status	-0.32 (1.20)	0.02 (1.27)	40.80 (1, 9087)	**0.000**
Vigorous physical activity	2.33 (0.61)	2.31 (0.66)	0.75 (1, 4805)	0.388
Stressful life events	37.42 (17.35)	25.32 (17.98)	7.89 (1, 8039)	**0.005**
Inflammation [b]				
IL-6 at 9 years	-0.29 (0.87)	-0.19 (0.81)	6.98 (1, 4983)	**0.008**
CRP at 9 years	-1.47 (1.11)	-1.33 (1.16)	6.81 (1, 5036)	**0.009**
CRP at 16 years	-0.84 (0.98)	-0.71 (1.05)	6.89 (1, 3454)	**0.009**
Social cognition				
SCDC at 8 years	0.06 (0.23)	0.09 (0.27)	4.97 (1, 8102)	**0.026**
SCDC at 11 years	0.03 (0.17)	0.07 (0.26)	17.66 (1, 7714)	**0.000**
SCDC at 14 years	0.05 (0.21)	0.07 (0.26)	6.95 (1, 7000)	**0.008**

DANVA at 8 years	1.84 (0.37)	1.82 (0.38)	0.65 (1, 6811)	0.421
Triangle test at 14 years	57.81 (7.10)	56.62 (7.61)	15.21 (1, 6026)	**0.000**
Internalising and externalising problems at 17 years				
Hyperactivity	2.31 (2.01)	2.58 (2.13)	10.55 (1, 5658)	**0.001**
Conduct problems	0.86 (1.19)	1.05 (1.38)	12.11 (1, 5658)	**0.001**
Emotion problems	1.28 (1.63)	1.53 (1.88)	11.41 (1, 5648)	**0.001**
Peer problems	1.06 (1.39)	1.12 (1.52)	1.23 (1, 5650)	0.267

Note. 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). [a] Exact month age at which social communication difficulties were first assessed in ALSPAC. [b] Inflammatory markers are log-transformed. Bold: $p < .05$.

Table 2

Bivariate correlations between the main variables of the study

Main Var.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Social cognition															
1. SCDC at 8															
2. SCDC at 11	0.37**														
3. SCDC at 14	0.20**	0.40**													
4. DANVA at 8	-0.01	-0.03	-0.03												
5. Trangles at 14	0.09*	0.07	0.04	0.11**											
Cortisol measures[a]															
6. DCS at 15	-0.01	-0.06	-0.03	-0.02	-0.02										
7. TMC at 15	-0.11**	-0.06	-0.07	0.05	-0.05	0.84**									
8. CAR at 15	-0.07	0.04	-0.02	0.10*	-0.02	0.45**	0.54**								
9. AUCg at15	0.00	-0.01	-0.05	0.04	0.02	0.67**	0.82**	0.61**							
Inflammatory markers[a]															
10. IL-6 at 9	-0.02	-0.03	-0.04	0.02	0.00	0.00	0.06	0.09	0.09						
11. CRP at 9	0.01	-0.02	0.03	0.04	0.01	0.06	0.14**	0.11*	0.09	0.47**					
12. CRP at 16	0.08	0.01	0.06	0.02	0.06	-0.04	-0.02	-0.04	-0.00	0.12*	0.39**				
Internalising and externalising problems[b]															
13. Hyperactivity	0.24**	0.21**	0.23**	-0.08	-0.02	-0.12**	-0.13**	-0.01	-0.06	-0.02	-0.00	-0.02			
14. Conduct problems	0.21**	0.19**	0.24**	-0.07	0.01	-0.06	-0.10**	-0.00	-0.04	-0.00	-0.00	0.05	0.45**		
15. Emotion problems	0.06	0.14**	0.11**	-0.00	-0.03	-0.02	-0.01	0.03	0.02	-0.05	-0.03	-0.00	0.27**	0.25**	
16. Peer problems	0.06	0.07	0.12**	-0.08*	0.00	-0.03	-0.05	-0.08	-0.06	0.02	-0.01	0.00	0.16**	0.14**	0.30**

Note. SCDC: Social and Communication Disorders Checklist (Skuse et al., 2005). DANVA: Diagnostic Analysis of Non-Verbal Accuracy (Nowicki & Duke, 1994). DCS: diurnal

cortisol slope. TMC: total morning cortisol. CAR: cortisol awakening response. AUCg: area under curve with respect to ground. IL-6: interleukin 6. CRP: C-reactive protein. [a] Cortisol measures and inflammatory markers are log-transformed. [b] Internalising and externalising problems were measured at 17 years old. *$p < .05$; **$p < .01$.

Table 3

Unstandardised regression coefficients of unadjusted and adjusted mediation models testing the association between social communication difficulties with hyperactivity/inattention and conduct problems via total morning cortisol (N=714).

	Unadjusted models				Adjusted models			
	b	**SD_P**	**95% CI**	**P-value**	**b**	**SD_P**	**95% CI**	**P-value**
SCD → TMC → HI								
Direct effects								
SCD → TMC	-0.21	0.08	[-0.36, -0.05]	**0.008**	-0.18	0.08	[-0.33, -0.02]	**0.024**
SCD → HI	2.03	0.34	[1.38, 2.69]	**0.000**	1.80	0.34	[1.13, 2.47]	**0.000**
TMC→ HI	-0.48	0.17	[-0.81, -0.16]	**0.004**	-0.41	0.18	[-0.76, -0.07]	**0.016**
Indirect effect	0.10	0.05	[0.02, 0.22]	**0.014**	0.07	0.05	[0.00, 0.18]	**0.042**
Total effect	2.13	0.34	[1.48, 2.79]	**0.000**	1.87	0.34	[1.20, 2.53]	**0.000**
SCD → TMC → CP								
Direct effects								
SCD → TMC	-0.21	0.08	[-0.37, -0.06]	**0.008**	-0.18	0.08	[-0.34, -0.03]	**0.020**
SCD → CP	1.06	0.20	[0.66, 1.44]	**0.000**	0.90	0.20	[0.51, 1.30]	**0.000**
TMC→ CP	-0.21	0.10	[-0.40, -0.01]	**0.040**	-0.24	0.11	[-0.44, -0.04]	**0.020**
Indirect effect	0.04	0.03	[0.00, 0.11]	**0.046**	0.04	0.03	[0.00, 0.11]	**0.040**
Total effect	1.10	0.20	[0.70, 1.49]	**0.000**	0.95	0.20	[0.55, 1.35]	**0.000**

Note: b: unstandardised coefficient. SD_P: standard deviations of the posterior distribution. 95% CI: 95% credible interval. SCD: social communication difficulties. TMC: total morning cortisol. HI: hyperactivity/inattention. CP: conduct problems. Bold: $p < .05$. The covariates in the adjusted models include inflammation (IL-6) at 9 years old, sex, exact age when social communication was assessed, ethnicity, overweight, socioeconomic status, wake-up time,

vigorous physical activity, smoking, alcohol use, medication use and stressful life events. Mediation models adjusting for inflammation (CRP) at 9 or 16 years and all other covariates, presented in the Supplementary document (Table S1, S2) revealed the same findings.

Figure 1.

Analytic sample selection process

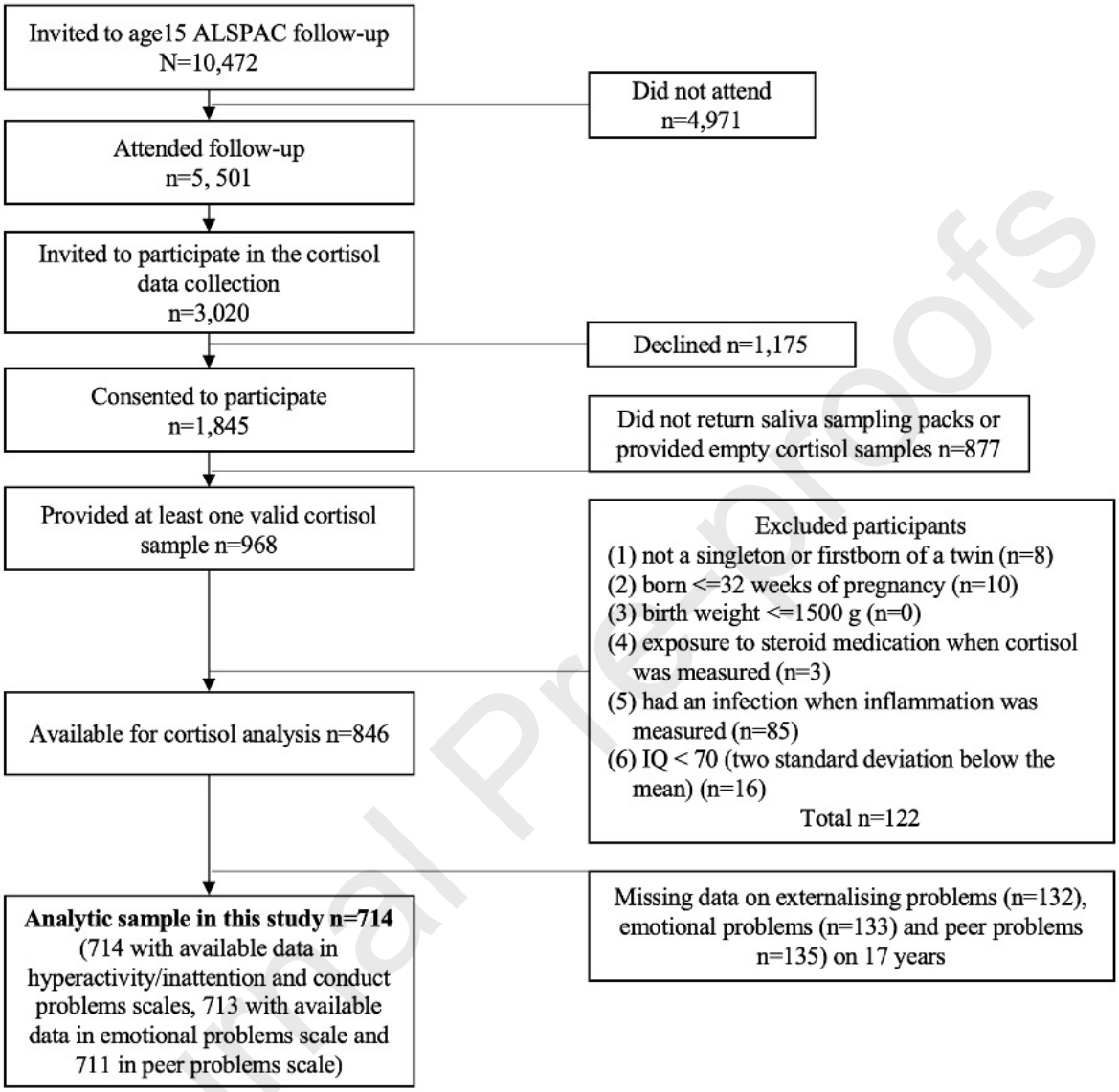
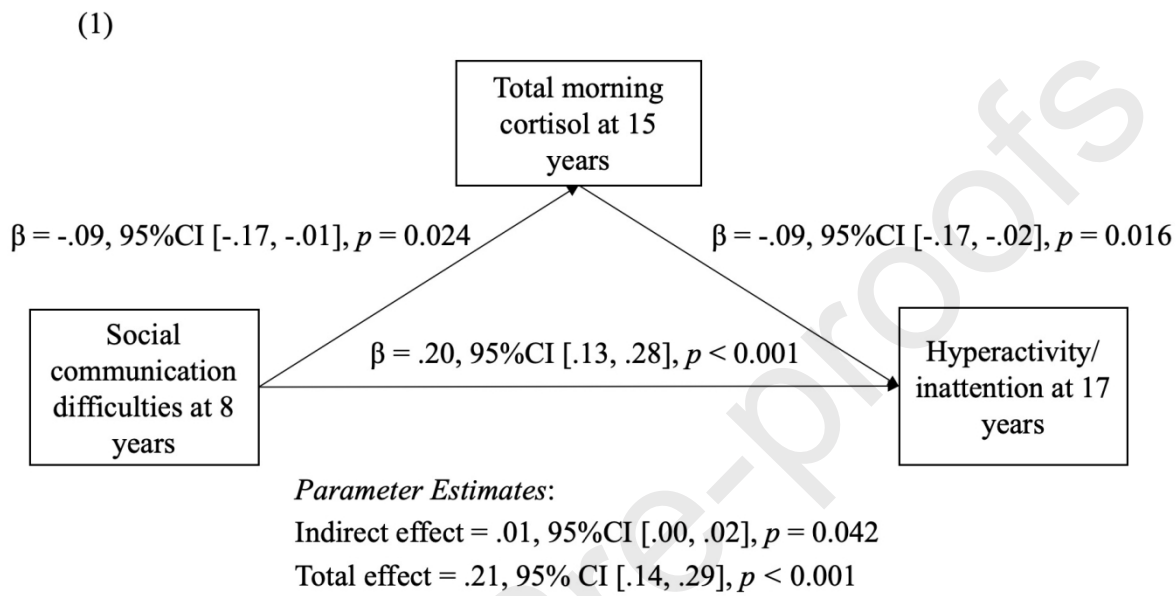
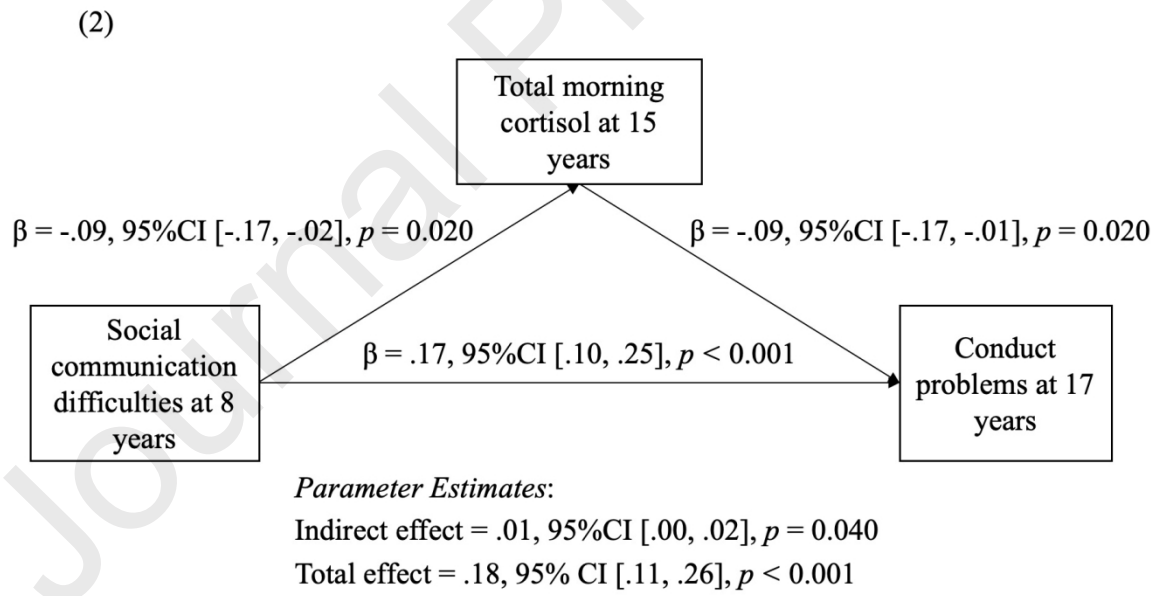


Figure 2.

Summary of fully adjusted mediation models with standardised coefficients for hyperactivity/inattention and conduct problems via total morning cortisol (N=714)





References

Agorastos, A., Pervanidou, P., Chrousos, G. P., & Baker, D. G. (2019). Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. *Frontiers in psychiatry*, *10*, 118. https://doi.org/10.3389/fpsyt.2019.00118

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C. H., Perry, B. D., ... & Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. *European archives of psychiatry and clinical neuroscience*, *256*(3), 174-186. https://doi.org/10.1007/s00406-005-0624-4

Anderson, T., & Wideman, L. (2017). Exercise and the cortisol awakening response: a systematic review. *Sports medicine-open*, *3*(1), 37. https://doi.org/10.1186/s40798-017-0102-3

Andrade, B. F., Waschbusch, D. A., Doucet, A., King, S., MacKinnon, M., McGrath, P. J., ... & Corkum, P. (2012). Social information processing of positive and negative hypothetical events in children with ADHD and conduct problems and controls. *Journal of Attention Disorders*, *16*(6), 491-504. https://doi.org/10.1177%2F1087054711401346

Angeli, E., Korpa, T., Johnson, E. O., Apostolakou, F., Papassotiriou, I., Chrousos, G. P., & Pervanidou, P. (2018). Salivary cortisol and alpha-amylase diurnal profiles and stress reactivity in children with Attention Deficit Hyperactivity Disorder. *Psychoneuroendocrinology*, *90*, 174-181. https://doi.org/10.1016/j.psyneuen.2018.02.026

Barnett, B. E., Hanna, B., & Parker, G. (1983). Life event scales for obstetric groups. *Journal of psychosomatic research*, *27*(4), 313-320. https://doi.org/10.1016/0022-3999(83)90054-5

Barona, M., Kothari, R., Skuse, D., & Micali, N. (2015). Social communication and emotion difficulties and second to fourth digit ratio in a large community-based sample. *Molecular autism*, *6*(1), 1-11. https://doi.org/10.1186/s13229-015-0063-7

Bax, A. C., Bard, D. E., Cuffe, S. P., McKeown, R. E., & Wolraich, M. L. (2019). The association between race/ethnicity and socioeconomic factors and the diagnosis and treatment of children with attention-deficit hyperactivity disorder. *Journal of Developmental & Behavioral Pediatrics*, *40*(2), 81-91. doi: 10.1097/DBP.0000000000000626

Boraston, Z., Blakemore, S. J., Chilvers, R., & Skuse, D. (2007). Impaired sadness recognition is linked to social interaction deficit in autism. *Neuropsychologia*, *45*(7), 1501-1510. https://doi.org/10.1016/j.neuropsychologia.2006.11.010

Bornstein, M. H., Hahn, C. S., & Haynes, O. M. (2010). Social competence, externalizing, and internalizing behavioral adjustment from early childhood through early adolescence: Developmental cascades. *Development and psychopathology*, *22*(4), 717-735. https://doi.org/10.1017/s0954579410000416

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., ... & Davey Smith, G. (2013). Cohort profile: the 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology*, *42*(1), 111-127. https://dx.doi.org/10.1093%2Fije%2Fdys064

Carnegie, R., Araya, R., Ben-Shlomo, Y., Glover, V., O'Connor, T. G., O'Donnell, K. J., ... & Lewis, G. (2014). Cortisol awakening response and subsequent depression:

prospective longitudinal study. *The British Journal of Psychiatry*, *204*(2), 137-143. https://doi.org/10.1192/bjp.bp.113.126250

Chang, J. P. C., Su, K. P., Mondelli, V., & Pariante, C. M. (2021). Cortisol and inflammatory biomarker levels in youths with attention deficit hyperactivity disorder (ADHD): evidence from a systematic review with meta-analysis. *Translational psychiatry*, *11*(1), 1-10. https://doi.org/10.1038/s41398-021-01550-0

Chang, G., Sherritt, L., & Knight, J. R. (2005). Adolescent cigarette smoking and mental health symptoms. *Journal of Adolescent Health*, 36(6), 517-522. https://doi.org/10.1016/j.jadohealth.2004.05.008

Chang, J. P. C., Mondelli, V., Satyanarayanan, S. K., Chiang, Y. J., Chen, H. T., Su, K. P., & Pariante, C. M. (2020). Cortisol, inflammatory biomarkers and neurotrophins in children and adolescents with attention deficit hyperactivity disorder (ADHD) in Taiwan. *Brain, Behavior, and Immunity*, *88*, 105-113. https://doi.org/10.1016/j.bbi.2020.05.017

Checkley, S. (1996). The neuroendocrinology of depression and chronic stress. *British medical bulletin*, *52*(3), 597-617. https://doi.org/10.1093/oxfordjournals.bmb.a011570

Cohen, J. I. (2000). Stress and mental health: a biobehavioral perspective. *Issues in mental health nursing*, *21*(2), 185-202. https://doi.org/10.1080/016128400248185

Cole, D. A. (1991). Change in self-perceived competence as a function of peer and teacher evaluation. *Developmental Psychology*, *27*(4), 682. https://psycnet.apa.org/doi/10.1037/0012-1649.27.4.682

Cole, T. J., Bellizzi, M. C., Flegal, K. M., & Dietz, W. H. (2000). Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*, *320*(7244), 1240. https://doi.org/10.1136/bmj.320.7244.1240

Costello, H., Gould, R. L., Abrol, E., & Howard, R. (2019). Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. *BMJ open*, *9*(7), e027925. https://doi.org/10.1136/bmjopen-2018-027925

Craig, B. M., Zhang, J., & Lipp, O. V. (2017). Facial race and sex cues have a comparable influence on emotion recognition in Chinese and Australian participants. *Attention, Perception, & Psychophysics*, 79(7), 2212-2223. https://doi.org/10.3758/s13414-017-1364-z

Dahlgren, A., Kecklund, G., Theorell, T., & Åkerstedt, T. (2009). Day-to-day variation in saliva cortisol—relation with sleep, stress and self-rated health. *Biological Psychology*, *82*(2), 149-155. https://doi.org/10.1016/j.biopsycho.2009.07.001

Danese, A., Moffitt, T. E., Pariante, C. M., Ambler, A., Poulton, R., & Caspi, A. (2008). Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Archives of general psychiatry*, *65*(4), 409-415. doi:10.1001/archpsyc.65.4.409

DeSantis, A. S., Adam, E. K., Doane, L. D., Mineka, S., Zinbarg, R. E., & Craske, M. G. (2007). Racial/ethnic differences in cortisol diurnal rhythms in a community sample of adolescents. *Journal of Adolescent Health*, *41*(1), 3-13. https://doi.org/10.1016/j.jadohealth.2007.03.006

Dodge, K. A. (1993). Social-cognitive mechanisms in the development of conduct disorder and depression. *Annual review of psychology*, *44*(1), 559-584. https://www.annualreviews.org/doi/pdf/10.1146/annurev.ps.44.020193.003015?casa_token=R1uZUGRkjqUAAAAA:Trc0qlrfyy41S8davXH_qBcW9aOV0j9ZhMr3KKeoYVXjCf5Mu7-u710Ff2kN3LICfver7n1Vamwm

Dolsen, M. R., Crosswell, A. D., & Prather, A. A. (2019). Links between stress, sleep, and inflammation: are there sex differences? *Current psychiatry reports*, *21*(2), 1-6. https://doi.org/10.1007/s11920-019-0993-4

Eiden, R. D., Shisler, S., Granger, D. A., Schuetze, P., Colangelo, J., & Huestis, M. A. (2020). Prenatal Tobacco and Cannabis Exposure: Associations with Cortisol Reactivity in Early School Age Children. *International Journal of Behavioral Medicine*, 1-14. https://doi.org/10.1007/s12529-020-09875-8

Elzinga, B. M., Roelofs, K., Tollenaar, M. S., Bakvis, P., van Pelt, J., & Spinhoven, P. (2008). Diminished cortisol responses to psychosocial stress associated with lifetime adverse events: a study among healthy young subjects. *Psychoneuroendocrinology*, *33*(2), 227-237. https://doi.org/10.1016/j.psyneuen.2007.11.004

Esch, T., Stefano, G. B., Fricchione, G. L., & Benson, H. (2002). The role of stress in neurodegenerative diseases and mental disorders. *Neuroendocrinology Letters*, *23*(3), 199-208. PMID: 12080279. https://pubmed.ncbi.nlm.nih.gov/12080279/

Feder, A., Coplan, J. D., Goetz, R. R., Mathew, S. J., Pine, D. S., Dahl, R. E., ... & Weissman, M. M. (2004). Twenty-four-hour cortisol secretion patterns in prepubertal children with anxiety or depressive disorders. *Biological psychiatry*, *56*(3), 198-204. https://doi.org/10.1016/j.biopsych.2004.05.005

Figueiredo, P., Ramião, E., Azeredo, A., Moreira, D., Barroso, R., & Barbosa, F. (2020). Relation between basal cortisol and reactivity cortisol with externalizing problems: A systematic review. *Physiology & Behavior, 225,* 113088. https://doi.org/10.1016/j.physbeh.2020.113088

Flouri, E., Francesconi, M., Midouhas, E., & Lewis, G. (2020). Prenatal and childhood adverse life events, inflammation and depressive symptoms across adolescence. *Journal of affective disorders*, *260*, 577-582. https://doi.org/10.1016/j.jad.2019.09.024

Flouri, E., Francesconi, M., Papachristou, E., Midouhas, E., & Lewis, G. (2019). Stressful life events, inflammation and emotional and behavioural problems in children: A population-based study. *Brain, behavior, and immunity*, *80*, 66-72. https://doi.org/10.1016/j.bbi.2019.02.023

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology*, *30*(10), 1010-1016. https://doi.org/10.1016/j.psyneuen.2005.04.006

Francesconi, M., Minichino, A., Khandaker, G. M., Midouhas, E., Lewis, G., & Flouri, E. (2020). Internalising symptoms mediate the longitudinal association between childhood inflammation and psychotic-like experiences in adulthood. *Schizophrenia research*, *215*, 424-429. https://doi.org/10.1016/j.schres.2019.07.035

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Smith, G. D., Henderson, J., Macleod, J., Molloy, L., Ness, A., Ring, S., Nelson, S. M., Lawlor, D. A., (2013). Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology, 42*, 97-110 https://doi.org/10.1093/ije/dys066

Frith, C. D., & Frith, U. (2008). Implicit and explicit processes in social cognition. *Neuron*, *60(3),* 503-510. https://doi.org/10.1016/j.neuron.2008.10.032

Gershon, A., Sudheimer, K., Tirouvanziam, R., Williams, L. M., & O'Hara, R. (2013). The long-term impact of early adversity on late-life psychiatric disorders. *Current psychiatry reports*, *15*(4), 352. DOI: 10.1007/s11920-013-0352-9

Goel, N., Workman, J. L., Lee, T. T., Innala, L., & Viau, V. (2011). Sex differences in the HPA axis. *Comprehensive Physiology*, *4*(3), 1121-1155. https://doi.org/10.1002/cphy.c130054

Goodman, A., Lamping, D. L., & Ploubidis, G. B. (2010). When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the Strengths and Difficulties Questionnaire (SDQ): data from British parents, teachers and children. *Journal of abnormal child psychology*, *38*(8), 1179-1191. https://doi.org/10.1007/s10802-010-9434-x

Goodman, R. (2001). Psychometric properties of the strengths and difficulties questionnaire. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(11), 1337-1345. https://doi.org/10.1097/00004583-200111000-00015

Goodman, R., & Scott, S. (1999). Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: is small beautiful? *Journal of abnormal child psychology*, *27*(1), 17-24. https://doi.org/10.1023/A:1022658222914

Happé, F., & Frith, U. (2014). Annual research review: Towards a developmental neuroscience of atypical social cognition. *Journal of Child Psychology and Psychiatry*, *55*(6), 553-577. https://doi.org/10.1111/jcpp.12162

Hermens, D. F., Kohn, M. R., Clarke, S. D., Gordon, E., & Williams, L. M. (2005). Sex differences in adolescent ADHD: findings from concurrent EEG and EDA. *Clinical neurophysiology*, *116*(6), 1455-1463. https://doi.org/10.1016/j.clinph.2005.02.012

Holland, J. F., Khandaker, G. M., Dauvermann, M. R., Morris, D., Zammit, S., & Donohoe, G. (2020). Effects of early life adversity on immune function and cognitive performance: results from the ALSPAC cohort. *Social Psychiatry and Psychiatric Epidemiology*, *55*(6), 723-733. https://doi.org/10.1007/s00127-019-01813-8

Homman, L. E., Perra, O., Higgins, K., & O'Neill, F. (2019). The longitudinal relationship of alcohol problems and depressive symptoms and the impact of externalising symptoms: findings from the Belfast Youth Developmental Study. *Social psychiatry and psychiatric epidemiology*, *54*(10), 1231-1241. https://doi.org/10.1007/s00127-019-01696-9

Hsiao, F. H., Chang, K. J., Kuo, W. H., Huang, C. S., Liu, Y. F., Lai, Y. M., ... & Chan, C. L. (2013). A longitudinal study of cortisol responses, sleep problems, and psychological well-being as the predictors of changes in depressive symptoms among breast cancer survivors. *Psychoneuroendocrinology*, *38*(3), 356-366. https://doi.org/10.1016/j.psyneuen.2012.06.010

Ibrahim, O., El-Lithy, W., & Abd El-Moez, K. (2016). Cortisol and its effects on cognitive function in a sample of Egyptian school-aged children with attention-deficit hyperactivity disorder. *Egyptian Journal of Psychiatry*, *37*(1), 41. DOI: 10.4103/1110-1105.180270

Ji, D., Flouri, E., & Papachristou, E. (2020). Social cognition and cortisol in the general population: A systematic review and meta-analysis. *Stress and Health, 37*(3), 415-430. https://doi.org/10.1002/smi.3013

Kaestner, F., Hettich, M., Peters, M., Sibrowski, W., Hetzel, G., Ponath, G., ... & Rothermundt, M. (2005). Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis

activity. *Journal of affective disorders*, *87*(2-3), 305-311. https://doi.org/10.1016/j.jad.2005.03.012

Kliewer, W., Reid-Quiñones, K., Shields, B. J., & Foutz, L. (2009). Multiple risks, emotion regulation skill, and cortisol in low-income African American youth: A prospective study. *Journal of Black Psychology*, *35*(1), 24-43. https://doi.org/10.1177%2F0095798408323355

Knox, L., & Douglas, J. (2009). Long-term ability to interpret facial expression after traumatic brain injury and its relation to social integration. *Brain and Cognition*, 69(2), 442-449. https://doi.org/10.1016/j.bandc.2008.09.009

Kothari, R., Barona, M., Treasure, J. O., & Micali, N. (2015). Social cognition in children at familial high-risk of developing an eating disorder. *Frontiers in behavioral neuroscience*, *9*, 208. doi: 10.3389/fnbeh.2015.00208

Kruesi, M. J., Schmidt, M. E., Donnelly, M., Hibbs, E. D., & Hamburger, S. D. (1989). Urinary free cortisol output and disruptive behavior in children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *28*(3), 441-443. https://doi.org/10.1097/00004583-198905000-00024

Kudielka, B. M., Broderick, J. E., & Kirschbaum, C. (2003). Compliance with saliva sampling protocols: electronic monitoring reveals invalid cortisol daytime profiles in noncompliant subjects. *Psychosomatic medicine*, *65*(2), 313-319. https://doi.org/10.1097/01.psy.0000058374.50240.bf

Kuss, M., Jäkel, F., & Wichmann, F. A. (2005). Bayesian inference for psychometric functions. *Journal of Vision, 5*(5), 8-8. https://doi.org/10.1167/5.5.8

Lamers, F., Vogelzangs, N., Merikangas, K. R., De Jonge, P., Beekman, A. T. F., & Penninx, B. W. J. H. (2013). Evidence for a differential role of HPA-axis function,

inflammation and metabolic syndrome in melancholic versus atypical depression. *Molecular psychiatry*, *18*(6), 692-699. https://doi.org/10.1038/mp.2012.144

Lancelot, C., & Nowicki Jr, S. (1997). The association between receptive nonverbal processing abilities and internalizing/externalizing problems in girls and boys. *The Journal of Genetic Psychology, 158*(3), 297-302. https://doi.org/10.1080/00221329709596669

Leffa, D. T., Torres, I. L., & Rohde, L. A. (2018). A review on the role of inflammation in attention-deficit/hyperactivity disorder. *Neuroimmunomodulation*, *25*(5-6), 328-333. https://doi.org/10.1159/000489635

Liukkonen, T., Räsänen, P., Jokelainen, J., Leinonen, M., Järvelin, M. R., Meyer-Rochow, V. B., & Timonen, M. (2011). The association between anxiety and C-reactive protein (CRP) levels: results from the Northern Finland 1966 birth cohort study. *European Psychiatry*, *26*(6), 363-369. https://doi.org/10.1016/j.eurpsy.2011.02.001

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W., & Zitman, F. G. (2010). Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of general psychiatry*, *67*(3), 220-229. https://doi.org/10.1001/archgenpsychiatry.2010.2

Mannie, Z. N., Harmer, C. J., & Cowen, P. J. (2007). Increased waking salivary cortisol levels in young people at familial risk of depression. *American Journal of Psychiatry*, *164*(4), 617-621. https://doi.org/10.1176/ajp.2007.164.4.617

Marsman, R., Nederhof, E., Rosmalen, J. G., Oldehinkel, A. J., Ormel, J., & Buitelaar, J. K. (2012). Family environment is associated with HPA-axis activity in adolescents. The

TRAILS study. *Biological Psychology*, *89*(2), 460-466. https://doi.org/10.1016/j.biopsycho.2011.12.013

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences*, *1032*(1), 1-7. https://doi.org/10.1196/annals.1314.001

Milich, R., Dodge, K. A. (1984). Social information processing in child psychiatric populations. *Journal of Abnormal Child Psychology, 12*, 471-489. doi:10.1007/BF00910660

Miller, G. E., & Blackwell, E. (2006). Turning up the heat: Inflammation as a mechanism linking chronic stress, depression, and heart disease. *Current Directions in Psychological Science*, *15*(6), 269-272. https://doi.org/10.1111/j.1467-8721.2006.00450.x

Miller, G. E., Chen, E., Sze, J., Marin, T., Arevalo, J. M., Doll, R., ... & Cole, S. W. (2008). A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-κB signaling. *Biological psychiatry*, *64*(4), 266-272. https://doi.org/10.1016/j.biopsych.2008.03.017

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology, 21*, 531–541. http://dx.doi.org/10.1037/0278-6133.21.6.531

Miller, G. E., Murphy, M. L., Cashman, R., Ma, R., Ma, J., Arevalo, J. M., ... & Cole, S. W. (2014). Greater inflammatory activity and blunted glucocorticoid signaling in monocytes of chronically stressed caregivers. *Brain, behavior, and immunity*, *41*, 191-199. https://doi.org/10.1016/j.bbi.2014.05.016

Mize, J., & Pettit, G. S. (2008). Social information processing and the development of conduct problems in children and adolescents: Looking beneath the surface. In C. Sharp, P. Fonagy, & I. Goodyer (Eds.), *Social cognition and developmental psychopathology* (pp. 141–174). Oxford University Press. https://doi.org/10.1093/med/9780198569183.003.0006

Muthén, B. (2010). Bayesian analysis in Mplus: A brief introduction. Retrieved from https://www.statmodel.com/download/IntroBayesVersion%203.pdf

Muthén, B., & Asparouhov, T. (2012). Bayesian structural equation modeling: A more flexible representation of substantive theory. *Psychological Methods, 17*(3), 313–335. https://doi.org/10.1037/a0026802

Muthén, L. K., & Muthén, B. O. (1998-2017). *Mplus User's Guide*. *Eighth Edition*. Los Angeles, CA: Muthén & Muthén.

Nettle, D., Andrews, C., Reichert, S., Bedford, T., Kolenda, C., Parker, C., ... & Bateson, M. (2017). Early-life adversity accelerates cellular ageing and affects adult inflammation: experimental evidence from the European starling. *Scientific Reports*, *7*(1), 1-10. https://doi.org/10.1038/srep40794

Niles, A. N., Smirnova, M., Lin, J., & O'Donovan, A. (2018). Gender differences in longitudinal relationships between depression and anxiety symptoms and inflammation in the health and retirement study. *Psychoneuroendocrinology*, *95*, 149-157. https://doi.org/10.1016/j.psyneuen.2018.05.035

Nowicki, S., & Duke, M. P. (1994). Individual differences in the nonverbal communication of affect: The Diagnostic Analysis of Nonverbal Accuracy Scale. *Journal of Nonverbal behavior*, *18*(1), 9-35. https://psycnet.apa.org/doi/10.1007/BF02169077

O'Donnell, K. J., Glover, V., Jenkins, J., Browne, D., Ben-Shlomo, Y., Golding, J., & O'Connor, T. G. (2013). Prenatal maternal mood is associated with altered diurnal cortisol in adolescence. *Psychoneuroendocrinology,* 38(9), 1630-1638. https://dx.doi.org/10.1016%2Fj.psyneuen.2013.01.008

O'Donovan, A., Hughes, B. M., Slavich, G. M., Lynch, L., Cronin, M. T., O'Farrelly, C., & Malone, K. M. (2010). Clinical anxiety, cortisol and interleukin-6: Evidence for specificity in emotion–biology relationships. *Brain, behavior, and immunity*, *24*(7), 1074-1077. https://dx.doi.org/10.1016%2Fj.bbi.2010.03.003

O'Shea, T. M., Joseph, R. M., Kuban, K. C., Allred, E. N., Ware, J., Coster, T., ... & Leviton, A. (2014). Elevated blood levels of inflammation-related proteins are associated with an attention problem at age 24 mo in extremely preterm infants. *Pediatric research*, *75*(6), 781-787. https://dx.doi.org/10.1038%2Fpr.2014.41

Odgers, C. L., Caspi, A., Broadbent, J. M., Dickson, N., Hancox, R. J., Harrington, H., ... & Moffitt, T. E. (2007). Prediction of differential adult health burden by conduct problem subtypes in males. *Archives of general psychiatry*, *64*(4), 476-484. https://doi.org/10.1001/archpsyc.64.4.476

Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B., & Khandaker, G. M. (2019). Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychological medicine*, *49*(12), 1958-1970. https://doi.org/10.1017/S0033291719001454

Ozechowski, T. J. (2014). Empirical Bayes MCMC estimation for modeling treatment processes, mechanisms of change, and clinical outcomes in small samples. *Journal of Consulting and Clinical Psychology*, *82*(5), 854. https://doi.org/10.1037%2Fa0035889

Pajer, K., Gardner, W., Rubin, R. T., Perel, J., & Neal, S. (2001). Decreased cortisol levels in adolescent girls with conduct disorder. *Archives of General Psychiatry*, *58*(3), 297-302. https://doi.org/10.1001/archpsyc.58.3.297

Pariante, C. M., & Miller, A. H. (2001). Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biological psychiatry*, *49*(5), 391-404. https://doi.org/10.1016/s0006-3223(00)01088-x

Paslakis, G., Krumm, B., Gilles, M., Schweiger, U., Heuser, I., Richter, I., & Deuschle, M. (2011). Discrimination between patients with melancholic depression and healthy controls: comparison between 24-h cortisol profiles, the DST and the Dex/CRH test. *Psychoneuroendocrinology*, *36*(5), 691-698. https://doi.org/10.1016/j.psyneuen.2010.10.002

Pauli-Pott, U., Schloss, S., Skoluda, N., Nater, U. M., & Becker, K. (2019). Low hair cortisol concentration predicts the development of attention deficit hyperactivity disorder. *Psychoneuroendocrinology*, *110*, 104442. https://doi.org/10.1016/j.psyneuen.2019.104442

Pengpid, S., & Peltzer, K. (2020). Vigorous physical activity, perceived stress, sleep and mental health among university students from 23 low-and middle-income countries. *International journal of adolescent medicine and health*, *32*(2). https://doi.org/10.1515/ijamh-2017-0116

Percinel, I., Ozbaran, B., Kose, S., Simsek, D. G., & Darcan, S. (2018). Increased deficits in emotion recognition and regulation in children and adolescents with exogenous obesity. *The world journal of biological psychiatry*, 19(2), 112-118. https://doi.org/10.1080/15622975.2016.1265147

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, *28*(7), 916-931. https://doi.org/10.1016/S0306-4530(02)00108-7

Raison, C. L., & Miller, A. H. (2003). When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry*, *160*(9), 1554-1565. https://doi.org/10.1176/appi.ajp.160.9.1554

Richman, A. D. (2018). Concurrent social disadvantages and chronic inflammation: the intersection of race and ethnicity, gender, and socioeconomic status. *Journal of racial and ethnic health disparities, 5(4),* 787-797. https://doi.org/10.1007/s40615-017-0424-3

Rohleder, N. (2014). Stimulation of systemic low-grade inflammation by psychosocial stress. *Psychosomatic medicine*, *76*(3), 181-189. doi: 10.1097/PSY.0000000000000049

van Roy, B., Veenstra, M., & Clench-Aas, J. (2008). Construct validity of the five-factor Strengths and Difficulties Questionnaire (SDQ) in pre-, early, and late adolescence. *Journal of Child Psychology and Psychiatry*, *49*(12), 1304-1312. https://doi.org/10.1111/j.1469-7610.2008.01942.x

Russell, A. E., Ford, T., Williams, R., & Russell, G. (2016). The association between socioeconomic disadvantage and attention deficit/hyperactivity disorder (ADHD): a systematic review. *Child Psychiatry & Human Development*, *47*(3), 440-458. https://doi.org/10.1007/s10578-015-0578-3

Ruttle, P. L., Maslowsky, J., Armstrong, J. M., Burk, L. R., & Essex, M. J. (2015). Longitudinal associations between diurnal cortisol slope and alcohol use across adolescence: A seven-year prospective study. *Psychoneuroendocrinology*, *56*, 23-28. https://doi.org/10.1016/j.psyneuen.2015.02.019

Ruttle, P. L., Shirtcliff, E. A., Serbin, L. A., Fisher, D. B. D., Stack, D. M., & Schwartzman, A. E. (2011). Disentangling psychobiological mechanisms underlying internalizing and externalizing behaviors in youth: Longitudinal and concurrent associations with cortisol. *Hormones and behavior*, *59*(1), 123-132. https://doi.org/10.1016/j.yhbeh.2010.10.015

Salis, K. L., Bernard, K., Black, S. R., Dougherty, L. R., & Klein, D. (2016). Examining the concurrent and longitudinal relationship between diurnal cortisol rhythms and conduct problems during childhood. *Psychoneuroendocrinology*, *71*, 147-154. https://doi.org/10.1016/j.psyneuen.2016.05.021

Saxbe, D. E. (2008). A field (researcher's) guide to cortisol: tracking HPA axis functioning in everyday life. *Health psychology review*, *2*(2), 163-190. https://doi.org/10.1080/17437190802530812

Segrin, C. (2000). Social skills deficits associated with depression. *Clinical psychology review*, *20*(3), 379-403. https://doi.org/10.1016/s0272-7358(98)00104-4

Segrin, C. (2017). Indirect effects of social skills on health through stress and loneliness. *Health communication*, *34*(1), 118-124. https://doi.org/10.1080/10410236.2017.1384434

Segrin, C., Hanzal, A., Donnerstein, C., Taylor, M., & Domschke, T. J. (2007). Social skills, psychological well-being, and the mediating role of perceived stress. *Anxiety, stress, and coping*, *20*(3), 321-329. https://doi.org/10.1080/10615800701282252

Segrin, C., McNelis, M., & Swiatkowski, P. (2016). Social skills, social support, and psychological distress: A test of the social skills deficit vulnerability model. *Human Communication Research*, *42*(1), 122-137. https://doi.org/10.1111/hcre.12070

Shakoor, S., Jaffee, S. R., Bowes, L., Ouellet-Morin, I., Andreou, P., Happé, F. ... & Arseneault, L. (2012). A prospective longitudinal study of children's theory of mind and adolescent involvement in bullying. *Journal of child psychology and psychiatry*, *53*(3), 254-261. https://dx.doi.org/10.1111%2Fj.1469-7610.2011.02488.x

Shojaei, T., Wazana, A., Pitrou, I., & Kovess, V. (2009). The strengths and difficulties questionnaire: validation study in French school-aged children and cross-cultural comparisons. *Social psychiatry and psychiatric epidemiology*, *44*(9), 740-747. https://doi.org/10.1007/s00127-008-0489-8

Skuse, D. H., Mandy, W. P., & Scourfield, J. (2005). Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. *The British Journal of Psychiatry*, 187(6), 568-572. doi:10.1192/bjp.187.6.568.

Skuse, D. H., Mandy, W., Steer, C., Miller, L. L., Goodman, R., Lawrence, K., ... & Golding, J. (2009). Social communication competence and functional adaptation in a general population of children: preliminary evidence for sex-by-verbal IQ differential risk. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(2), 128-137. https://doi.org/10.1097/chi.0b013e31819176b8

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin*, *140*(3), 774. https://dx.doi.org/10.1037%2Fa0035302

Smeets, T., Dziobek, I., & Wolf, O. T. (2009). Social cognition under stress: differential effects of stress-induced cortisol elevations in healthy young men and

women. *Hormones and behavior*, *55*(4), 507-513. https://doi.org/10.1016/j.yhbeh.2009.01.011

Stalder, T., Hucklebridge, F., Evans, P., & Clow, A. (2009). Use of a single case study design to examine state variation in the cortisol awakening response: relationship with time of awakening. *Psychoneuroendocrinology*, *34*(4), 607-614. https://doi.org/10.1016/j.psyneuen.2008.10.023

StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

Stokes, M., Mellor, D., Yeow, J., & Hapidzal, N. F. (2014). Do parents, teachers and children use the SDQ in a similar fashion? *Quality & Quantity*, *48*(2), 983-1000. https://doi.org/10.1007/s11135-012-9819-8

Sullivan, S. A., Thompson, A., Kounali, D., Lewis, G., & Zammit, S. (2017). The longitudinal association between external locus of control, social cognition and adolescent psychopathology. *Social psychiatry and psychiatric epidemiology*, *52*(6), 643-655. https://doi.org/10.1007/s00127-017-1359-z

Susman, E. J. (2006). Psychobiology of persistent antisocial behavior: Stress, early vulnerabilities and the attenuation hypothesis. *Neuroscience & Biobehavioral Reviews*, *30*(3), 376-389. https://doi.org/10.1016/j.neubiorev.2005.08.002

Thompson, A. E., & Voyer, D. (2014). Sex differences in the ability to recognise non-verbal displays of emotion: A meta-analysis. *Cognition and Emotion*, *28*(7), 1164-1195. https://doi.org/10.1080/02699931.2013.875889

Thompson, A., Sullivan, S., Heron, J., Thomas, K., Zammit, S., Horwood, J., ... & Harrison, G. (2011). Childhood facial emotion recognition and psychosis-like symptoms in a nonclinical population at 12 years of age: results from the ALSPAC birth

cohort. *Cognitive neuropsychiatry*, *16*(2), 136-157. https://doi.org/10.1080/13546805.2010.510040

Trentacosta, C. J., & Fine, S. E. (2010). Emotion knowledge, social competence, and behavior problems in childhood and adolescence: A meta-analytic review. *Social Development, 19*(1), 1-29. https://dx.doi.org/10.1111%2Fj.1467-9507.2009.00543.x

Trickett, P. K., Noll, J. G., Susman, E. J., Shenk, C. E., & Putnam, F. W. (2010). Attenuation of cortisol across development for victims of sexual abuse. *Development and Psychopathology, 22*(1), 165–175. https://doi.org/10.1017/S0954579409990332

Ulitzsch, E., Lüdtke, O., & Robitzsch, A. (2021). Alleviating estimation problems in small sample structural equation modeling—A comparison of constrained maximum likelihood, Bayesian estimation, and fixed reliability approaches. *Psychological Methods.* Advance online publication. https://doi.org/10.1037/met0000435

Vugteveen, J., de Bildt, A., Theunissen, M., Reijneveld, S. A., & Timmerman, M. (2021). Validity aspects of the strengths and difficulties questionnaire (SDQ) adolescent self-report and parent-report versions among Dutch adolescents. *Assessment*, *28*(2), 601-616. https://doi.org/10.1177/1073191119858416

Visser, M., Bouter, L. M., McQuillan, G. M., Wener, M. H., & Harris, T. B. (2001). Low-grade systemic inflammation in overweight children. *Pediatrics*, *107*(1), e13-e13. DOI: 10.1542/peds.107.1.e13

Vreeburg, S. A., Zitman, F. G., van Pelt, J., DeRijk, R. H., Verhagen, J. C., van Dyck, R., ... & Penninx, B. W. (2010). Salivary cortisol levels in persons with and without different anxiety disorders. *Psychosomatic medicine*, *72*(4), 340-347. doi: 10.1097/PSY.0b013e3181d2f0c8

Vrijsen, J. N., Tendolkar, I., Onnink, M., Hoogman, M., Schene, A. H., Fernández, G., ... & Franke, B. (2018). ADHD symptoms in healthy adults are associated with stressful life events and negative memory bias. *ADHD Attention Deficit and Hyperactivity Disorders*, *10*(2), 151-160. https://doi.org/10.1007/s12402-017-0241-x

Walther, A., Penz, M., Ijacic, D., & Rice, T. R. (2017). Bipolar spectrum disorders in male youth: the interplay between symptom severity, inflammation, steroid secretion, and body composition. *Frontiers in psychiatry*, *8*, 207. https://doi.org/10.3389/fpsyt.2017.00207

Wang, L., & Preacher, K. J. (2015). Moderated mediation analysis using Bayesian methods. *Structural Equation Modeling: A Multidisciplinary Journal*, 22(2), 249-263. https://doi.org/10.1080/10705511.2014.935256

Warrier, V., & Baron-Cohen, S. (2018). Genetic contribution to 'theory of mind' in adolescence. *Scientific reports*, *8*(1), 1-9. https://doi.org/10.1038/s41598-018-21737-8

Wechsler, D., Golombok, S., & Rust, J. (1992). *WISC-III UK Wechsler intelligence scale for children: UK manual.* Sidcup, UK: The Psychological Corporation.

van Widenfelt, B. M., Goedhart, A. W., Treffers, P. D., & Goodman, R. (2003). Dutch version of the Strengths and Difficulties Questionnaire (SDQ). *European child & adolescent psychiatry*, *12*(6), 281-289. https://doi.org/10.1007/s00787-003-0341-3

Yu, T., Zhou, W., Wu, S., Liu, Q., & Li, X. (2020). Evidence for disruption of diurnal salivary cortisol rhythm in childhood obesity: relationships with anthropometry, puberty and physical activity. *BMC Pediatrics*, *20*(1), 1-10. https://doi.org/10.1186/s12887-020-02274-8

Yuan, Y., & MacKinnon, D. P. (2009). Bayesian mediation analysis. *Psychological methods, 14*(4), 301. https://doi.org/10.1037/a0016972

Zadeh, Z. Y., Im-Bolter, N., & Cohen, N. J. (2007). Social cognition and externalizing psychopathology: An investigation of the mediating role of language. *Journal of abnormal child psychology*, *35*(2), 141-152. https://doi.org/10.1007/s10802-006-9052-9

Highlights

- Social cognition difficulties were longitudinally linked to externalising problems.
- This link was partially mediated by low morning cortisol.
- The mediating role of morning cortisol persisted after controlling for confounders.
- Flat diurnal cortisol slope also indicated risk for future externalising problems.
- Inflammation was not related to social cognition or mental health problems.