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Social pain is associated with altered developmental trajectories of connectivity among the triple network model of psychopathology

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Abstract

Childhood and adolescence are sensitive periods for the refinement of increasingly complex executive and social functions. A particularly important skill is the ability to navigate and interpret interpersonal relationships, which is reflected in part by the maturation of distributed resting networks. However, the relationships between negative social perceptions in youth and long-term alterations in between-network connectivity are limited. To partially address this gap, we utilized longitudinal resting-state functional magnetic resonance imaging ($N = 93$) with social pain measures from the NIH Toolbox Emotion Battery to determine the links between negative social perceptions on the trajectory of connectivity between the salience, frontoparietal, and default mode networks in the triple network model of psychopathology. Higher scores of perceived hostility, but not perceived rejection, tended to increase functional connectivity between the salience and both frontoparietal and default mode networks over time. These results suggest that more direct forms of threat (hostility) may be more impactful than rejection (limited desired social interactions), highlighting the importance of a dimensional approach to understanding developmental trajectories. While these connectivity changes align with several aberrant connectivity signatures observed across mental health disorders, these phenotypes are not pathognomonic of psychopathology and may reflect adaptive mechanisms in the context of social adversity.

Keywords: fMRI; social distress; structural equation modelling; longitudinal development

Introduction

Prominent theories of neurodevelopment highlight systematic changes towards the well-defined functional organization of the mature brain, both during task-oriented behaviour and in the absence of specified goals (i.e. rest; Biswal et al. 1995, Fox et al. 2005, Seeley et al. 2007, Fair et al. 2008, 2009, Doucet et al. 2011, Yeo et al. 2011, Sato et al. 2014, Sherman et al. 2014, Solé-Padullés et al. 2016, Baum et al. 2017, 2020, Sotiras et al. 2017). The functional specialization of brain regions and the transition to a more distributed, network-level form of information processing are thought to reflect maturation of neural networks underlying increasingly complex social and affective processing, skill acquisition, and interpersonal relationships (Masten et al. 2009, Crone and Dahl 2012, Pfeifer and Peake 2012, Baum et al. 2017, 2020, Sotiras et al. 2017, Alkire et al. 2018). Despite substantial methodological variability in the acquisition (scanner and sequence parameters), processing (motion correction and global signal regression), and analysis (independent components analysis and seed-based connectivity) of neural data, several intrinsic connectivity networks (ICNs) have been consistently identified that evince functionally coordinated regions of functional activity (Seeley et al. 2007, Menon 2011, Yeo et al. 2011, Yan et al. 2013,

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Murphy and Fox 2017, Doucet et al. 2019, Qiao et al. 2019, Picci et al. 2023).

Aberrant functional connectivity phenotypes have been identified transdiagnostically in mental health disorders, namely in the default mode, salience, and frontoparietal (central executive) networks (Garrity et al. 2007, Menon 2011, McTeague et al. 2016, 2017, Jiang et al. 2017, Malhi et al. 2019, Sha et al. 2019, Bolton et al. 2020, Jones et al. 2023, Picci et al. 2023). These three networks exhibit complementary roles that facilitate a wide range of higher-order functions. Evidence suggests that the insula-anchored salience network is responsible for evaluating the relevance of stimuli, relating them to goals and output behaviours, and contributing to the relative engagement of the frontoparietal and default mode networks (Menon 2011, Goulden et al. 2014). Interestingly, there is some support for a causal model of network-level interactions, such that structural integrity of the white matter tracts connecting the salience and default mode networks directly impacts the default mode network's ability to disengage during tasks when the salience network is active (Bonnelle et al. 2012). Furthermore, directed causal modelling analyses have indicated that activity within the salience network directly leads to suppression of the default mode network in humans (Chiong et al. 2013), mirrored by optogenetic studies of salience network stimulation in animal models (Menon et al. 2023). Impairments in the salience network lead to disruptions in connectivity between the frontoparietal and default mode networks Deming et al. 2023), and the degree of neural alteration correlates with the degree of impairment (Chand et al. 2017). Alterations in salience network connectivity have also been linked with panic disorder, depression, and social anxiety disorder (Pannekoek et al. 2013, Pannekoek et al. 2014; Peterson et al. 2014). Changes to the interconnectedness and transition probabilities between these ICNs are thought to impact individuals' abilities to appropriately detect, integrate, and interpret endogenous and external cues in an efficient and accurate manner (Koster et al. 2011, Menon 2011, Sha et al. 2019, Jones et al. 2023). Importantly, given that 50% of psychopathologies begin prior to the age of 14 years, there is a growing emphasis on investigating the factors that contribute to aberrant developmental trajectories of connectivity profiles in children and adolescents (Kessler et al. 2005, Di Martino et al. 2014). To date, many factors, including traumatic experiences, subclinical symptoms of psychopathology, and socioeconomic status, have been shown to impact neurodevelopmental trajectories of ICNs (Bolling et al. 2011, Herringa et al. 2013, Sacchet et al. 2016, Weissman et al. 2022, Jones et al. 2023, Picci et al. 2023, Son et al. 2023).

In a developmental context, children and adolescents exhibit increased sensitivity to social rejection during adolescence, particularly from peers, with concomitant neurodevelopmental changes (Masten et al. 2009, 2012, Onoda et al. 2010, Bolling et al. 2011, Eisenberger 2012, Puetz et al. 2014). Importantly, previous work has demonstrated that increased reports of social isolation or loneliness are linked with greater psychiatric symptomatology, including increased risk of distress (e.g. depressive and anxious symptoms), suicidal ideation, as well as worsened mental and physical health outcomes (Beutel, 2017; Mann et al. 2022; SMITH and VICTOR, 2019). Adolescence is a sensitive period during which these social experiences can be particularly impactful. Coupled with the increasing motivational salience of social interactions and increased opportunities for social exploration (e.g. identity formation, finding romantic partners, and social media use) during adolescence, negative interpersonal experiences and loneliness may propagate to altered neural networks that are sensitive to social pain and isolation, potentially leading to further behavioural disruption. Of note, several brain regions have been proposed to be particularly sensitive to social pain, including the anterior insula, anterior cingulate cortex (ACC), prefrontal cortex, posterior cingulate cortex/precuneus, and temporoparietal junction (Eisenberger 2012, Mars et al. 2012, Perini et al. 2018). Furthermore, these association cortices are among the most variable across individuals and continue to develop throughout adolescence, opening a window of opportunity for significant refinement and optimization, as well as a vulnerable period for perturbation (Sydnor et al. 2023). Interestingly, many of these regions correspond to critical components of the default mode, salience, and frontoparietal networks, indicating that network-level dynamics in the triple network model of psychopathology may be sensitive to perceptions of social interactions and the pain associated with negative self-rumination and peer rejection (Menon 2011, Eisenberger 2012). Indeed, connectivity between the default mode and salience networks has been implicated in supporting negativity bias (Guha et al. 2021), the default mode network shows hyperconnectivity in response to negative social feedback (Rappaport and Barch 2020), and hyperconnectivity between the insula and medial prefrontal cortex has been reported in social anxiety disorder (Peterson et al. 2014). Furthermore, these networks include brain regions that are critical for effective emotion regulation, and alterations in these regions have been linked with transdiagnostic measures of psychopathology (Pan et al. 2018, Beauchaine and Cicchetti 2019). However, these neural alterations do not exclusively portend negative consequences, as challenging environments such as social adversity may lead to enhancement of stress-adapted skills (i.e. 'hidden talents'; Frankenhuis et al. 2020, Ellis et al. 2022) or faster maturational processes (i.e. stress acceleration hypothesis; Callaghan and Tottenham 2016). These skills may promote security and well-being in the environment for which these skills were developed, but could also have limited translatability when extended to other contexts. However, this is largely speculative, as the current literature is extremely sparse with respect to the impact of negative social perception measures on trajectories of brain functional connectivity using a longitudinal framework.

To that end, we use a latent growth curve modelling approach in a longitudinal sample of functional magnetic resonance imaging (fMRI) data acquired from children and adolescents to investigate the impact of negative social perception measures on developmental trajectories of functional connectivity among the default mode, salience, and frontoparietal networks, which have demonstrated significant alterations in a wide range of psychopathologies (Menon 2011, Mulders et al. 2015, Kaiser et al. 2015a, Abbott et al. 2016, Jiang et al. 2017, Gürsel et al. 2018, Shao et al. 2018). To quantify negative social perception (e.g. perceived hostility and perceived rejection), we used measures from the National Institutes of Health Toolbox Emotion Battery (NIHTB-EB) that gauge one's perception of interpersonal interactions and self-referential processing (Babakhanyan et al. 2018, Paolillo et al. 2020). We hypothesize that the functional connectivity between these ICNs will be significantly modulated as a function of both perceived hostility and rejection, and that the degree of negative social perception will scale with the rate of connectivity change between ICNs. To our knowledge, this is the first longitudinal examination of the impact of negative social perception subtypes on the developmental trajectory of ICNs.

Materials and methods

Participants

Data were collected from 93 typically developing youth (aged 9–15 years at enrollment; 47 females; Table 1) who were recruited from the local community as part of the National Science Foundation-supported Developmental Chronnecto-Genomics study at the University of Nebraska Medical Center in Omaha, Nebraska (Stephen et al. 2021). All participants were invited to return annually over a 3-year period for repeated neuroimaging. Inclusion criteria included English as a primary language and aged 9–15 years at enrolment. Exclusionary criteria included any medical illnesses that affect neurological function (e.g. 22q11.2 deletion syndrome), history of neurological or psychiatric disorder, history of substance use, head trauma, and any metallic material contraindicated for MRI. All participants completed assessments of IQ during year 1 (Table 1; Wechsler 1999), and parents of participants completed the Barratt Simplified Measure of Social Status as a measure of the family's social status, accounting for parental education level, occupation, and overall socioeconomic status. After a complete description of the study, all parents provided written informed consent, and children signed assent forms following the guidelines of the local institutional review board.

NIH emotional toolbox measures

All participants completed the negative social perception measures of the NIH Toolbox Emotion Domain at time point 1, including the five-item fixed-form of the Perceived Hostility Survey and the five-item fixed-form of the Perceived Rejection Survey (Babakhanyan et al. 2018, Paolillo et al. 2020). For each survey, each item was scored on a five-point Likert scale with options ranging from 'never' to 'always'. Normalized *T*-scores (mean: 50, standard deviation: 10) were used in subsequent analyses, with higher scores indicating either greater peer hostility or rejection and *T*-scores >60 considered to be 'potentially problematic'. Example items include the following: in the past month, please describe how often people in your life … 'blame me when things go wrong' and 'act in an angry way toward me' for perceived hostility, and 'act like they don't care about me' and 'make me feel like I don't fit in' for perceived rejection.

Table 1. Sample demographics and variables of interest.

Demographic information			
	n		%
Sex (male)	46		50
Race			
White	78		84
Black/AA	3		4
Mixed race	6		6
Not reported	6		6
	Mean	**SD**	**Range**
Age T1	11.98	1.59	9.03–14.94
Age T2	13.01	1.6	9.99–15.99
Age T3	13.93	1.63	10.98–16.98
Socioeconomic status (Barratt measure)	46.86	12.22	11–64.67
Full scale IQ	112.51	14.88	68–148
Hostility raw score T1	12.76	7.69	6–20
Rejection raw score T1	10.29	7.22	5–23
Hostility *T*-score T1	49.22	7.3	34.9–72.0
Rejection *T*-score T1	50.69	7.25	38.0–77.0
Salience-frontoparietal T1	0.05	0.28	−0.45–0.88
Salience-default mode T1	−0.21	0.31	−1.00–0.59
Frontoparietal-default mode T1	0.33	0.25	−0.33–0.93
Salience-frontoparietal T2	0.14	0.28	−0.63–0.67
Salience-default mode T2	−0.17	0.31	−0.80–0.35
Frontoparietal-default mode T2	0.37	0.27	−0.29–0.91
Salience-frontoparietal T3	0.15	0.23	−0.35–0.63
Salience-default mode T3	−0.09	0.3	−0.82–0.62
Frontoparietal-default mode T3	0.4	0.22	−0.02–0.99

T1 = time point 1, T2 = time point 2, T3 = time point 3.

Magnetic resonance image acquisition and processing

All participants completed a 5-min eyes-open resting state fMRI (rs-fMRI) scan with a Siemens 3T Skyra scanner (Stephen et al. 2021). Whole-brain blood oxygen level–dependent data were acquired using a 32-channel head coil, with the following parameters: field of view (FOV) = 268 mm, resolution = 3.3 × 3.3 × 3.0 mm, flip angle = 44°, TE = 29 ms, and TR = 460 ms with a multiband acceleration factor of 8. Participants were instructed to rest with their eyes open and were monitored throughout the scan. A high-resolution T1-weighted anatomical scan was also acquired for co-registration using an MPRAGE sequence with the following parameters: FOV = 256 mm, resolution = $1\ \text{mm}^3$ isotropic, flip angle = 8°, TE = 1.94 ms, TR = 2400 ms. The rs-fMRI data were preprocessed using the DPABI toolbox (Yan et al. 2016). Preprocessing procedures included removal of the first 10 volumes, motion correction to the first volume with rigid-body alignment, co-registration of functional data to their anatomical T1-weighted images, linear detrending, regression of motion parameters and their derivatives (24-parameter model; Friston et al. 1996), scrubbing parameters (Power et al. 2012), white matter and cerebrospinal fluid time series using a component-based noise reduction method with five principal components (Behzadi et al. 2007), normalization of functional images to Montreal Neurological Institute standardized space, spatial smoothing within the functional mask with a 6-mm full-width half-maximum Gaussian kernel, wavelet despiking (Patel et al. 2014), and bandpass filtering at 0.01–0.1 Hz (Cordes et al. 2001).

Extraction of functional connectivity measures

We used the Yeo-7 network atlas, a previously established functional brain atlas based on 1000 resting state fMRI scans, to partition the functional connectome into seven ICNs: visual, somato-motor, dorsal attention, ventral attention (i.e. salience network), frontolimbic, frontoparietal, and default mode (Yeo et al. 2011). For each of the three pairs of networks in the triple network model of psychopathology (i.e. salience network, frontoparietal network, and default mode network), the DPABI toolbox was used to determine between-network functional connectivity as the average Pearson correlation coefficient between the average time series of each pair of networks (Menon 2011, Yan et al. 2016). Thus, each participant had one correlation value representing connectivity between each pair of networks (i.e. salience-frontoparietal, salience-default mode, and frontoparietal-default mode) for each of their available resting state scans across the 3-year collection period. The resulting values were further motion corrected by regressing out the mean framewise displacement; the residual values were used for subsequent analysis.

Statistical analysis

We sought to identify individual differences in the trajectories of default mode network connectivity over three time points as a function of the NIH Emotion Toolbox's perceived hostility and rejection scores measured at the first time point. To that end, we used latent growth curve modelling, an implementation of structural equation modelling that is well suited for estimating intraindividual change over time and working with partially missing data (Curran et al. 2010). Furthermore, modelling with latent variables optimizes power, reduces type-1 error by reducing the number of statistical parameters that are estimated, and improves reliability by enhancing effect size and predictive validity (Poldrack et al. 2017, Cooper et al. 2019). All statistical analyses were completed using Mplus version 8.6 and the Statistical Package for Social Sciences (SPSS) version 25.

For each of the between-network relationships of interest, we used a three-step process to examine the relationships between perceived hostility and perceived rejection and the intercept and slope of change in between-network connectivity over time. Initially, we specified a baseline latent growth curve model to examine changes in between-network connectivity over the 3-year period without any control and predictor variables. The intercept was defined by between-network connectivity at each time point constrained to 1. The slope was constrained to 0, 1, and 2 for connectivity measures obtained during data collection years 1, 2, and 3, respectively. The second model added in covariates of age at time 1, and sex as control variables. The latent intercept and slope variables were regressed on age and sex to account for potential effects of systematic demographic differences, which may influence connectivity measures. The final models added the predictor variables of interest, including the perceived hostility and rejection measures collected at time 1. The latent intercept and slope variables were regressed on perceived hostility and rejection measures, and the aforementioned control variables. These final models allowed us to examine the extent to which perceived hostility and rejection in healthy youth were associated with baseline connectivity (i.e. at enrolment) and the rate of change in between-network connectivity over time (Fig. 1). Models were assessed for goodness of fit using classical measures, including the chi-squared test (where a nonsignificant result indicates a good fit), root mean square error of approximation ($\text{RMSEA} < 0.06$, or a measure of 'badness of fit', with larger values indicating worse fit), and the comparative fit index (CFI), which indicates relative improvement in model fit from a baseline model ($\text{CFI} > 0.95$; Hu and Bentler 1999, Schermelleh-Engel et al. 2003). Given that each of these indices assess different aspects of goodness of fit, we provide an array of model fit indices to more comprehensively evaluate the fit of the model. For each of the models that were run, any model convergence issues due to negative residual variance estimates were addressed by constraining the variables to have a residual variance of zero (Heywood cases; Dillon et al. 1987). Furthermore, model fit comparisons were conducted by calculating the change in chi-squared values with each step in our model to test whether adding additional variables to the model had a negative effect on model fit, with a significant test suggesting that a more parsimonious model is favourable (Supplementary Table 1).

Missing data estimation

Of the sample of 93 youth, 84 had complete data for year 1, 66 returned and had complete data for year 2, and 33 returned and had complete data for year 3. Thus, we completed latent growth curve model estimation without and with missing data estimation, using full information maximum likelihood (FIML; Enders 2001, Enders and Bandalos 2001). The pattern of results was similar from both models; thus, we used the models with FIML estimation to mitigate the likelihood of biased parameters and standard errors. A detailed report of attrition analyses, as well as primary analyses that include only those participants with all three time points (i.e. no FIML), is available in the Supplementary Results.

Results

Descriptive statistics

Sample demographics and descriptive statistics for measures of interest for the participants in this analysis are presented in Table 1. A full correlation table of the variables of interest is available in Supplementary Table 2. The majority of youth in the study reported at least some perceived hostility with a raw score range of 6–20 (maximum possible score = 25), and *T*-scores from 34.9 to 72. Youth in the study also reported at least some perceived rejection with a raw score range of 5–23 (maximum possible score = 25), and *T*-scores from 38 to 77.

Latent growth curve modelling results between the salience and frontoparietal networks

The baseline growth model using the longitudinal trajectory of salience-frontoparietal connectivity without predictors or control variables had excellent model fit [$\chi^2(1) = 0.033$, $P = .86$; $\text{RMSEA} = 0.000$, 90% confidence interval (CI): 0.000, 0.151; $\text{CFI} = 1.000$]. Using the motion-corrected residuals of salience-frontoparietal connectivity as the inputs for our model, the latent intercept mean indicated that across the whole sample, baseline salience-frontoparietal connectivity significantly differed from zero ($b = -0.109$, $\text{SE} = 0.030$, $P < .01$; $\beta = -0.509$). There was no significant longitudinal change in residual connectivity between the salience and frontoparietal networks in the baseline model ($b = 0.027$, $\text{SE} = 0.025$, $P = .29$; $\beta = 0.183$). The full model results are available in the Supplementary material. We then imposed the control variables of age at time 1 and sex on the estimated latent intercept and slope variables. This model also had excellent fit ($\chi^2(5) = 2.010$, $P = .85$; $\text{RMSEA} = 0.000$, 90% CI: 0.000, 0.080; $\text{CFI} = 1.000$). Participant sex was significantly with baseline salience-frontoparietal connectivity ($b = -0.107$, $\text{SE} = 0.056$, $P = .05$; $\beta = -0.490$), such that male participants had less anticorrelated salience-frontoparietal connectivity than female participants. Sex was not associated with baseline slope ($b = 0.031$, $\text{SE} = 0.047$, $P = .51$; $\beta = 0.993$). Age was not significantly associated with either the latent intercept ($b = 0.023$, $\text{SE} = 0.018$, $P = .21$; $\beta = 0.329$) or latent slope ($b = 0.000$, $\text{SE} = 0.015$, $P = .98$; $\beta = -0.043$) variables. We then included the perceived hostility and rejection *T*-scores into our latent growth curve model. This model had excellent fit ($\chi^2(11) = 8.002$, $P = .71$; $\text{RMSEA} = 0.000$, 90% CI: 0.000, 0.083; $\text{CFI} = 1.000$). Perceived hostility *T*-scores were associated with the latent slope variable (Fig. 2), such that participants who self-reported more perceived hostility tended to have increased frontoparietal-salience connectivity over time ($b = 0.008$, $\text{SE} = 0.004$, $P = .05$; $\beta = 0.700$). In contrast, perceived rejection was not significantly associated with the latent slope variable ($b = 0.005$, $\text{SE} = 0.004$, $P = .27$; $\beta = 0.410$). The latent intercept variable was not significantly associated with either perceived hostility ($b = -0.004$, $\text{SE} = 0.005$, $P = .46$; $\beta = -0.229$) or perceived rejection ($b = 0.000$, $\text{SE} = 0.005$, $P = .93$; $\beta = -0.026$).

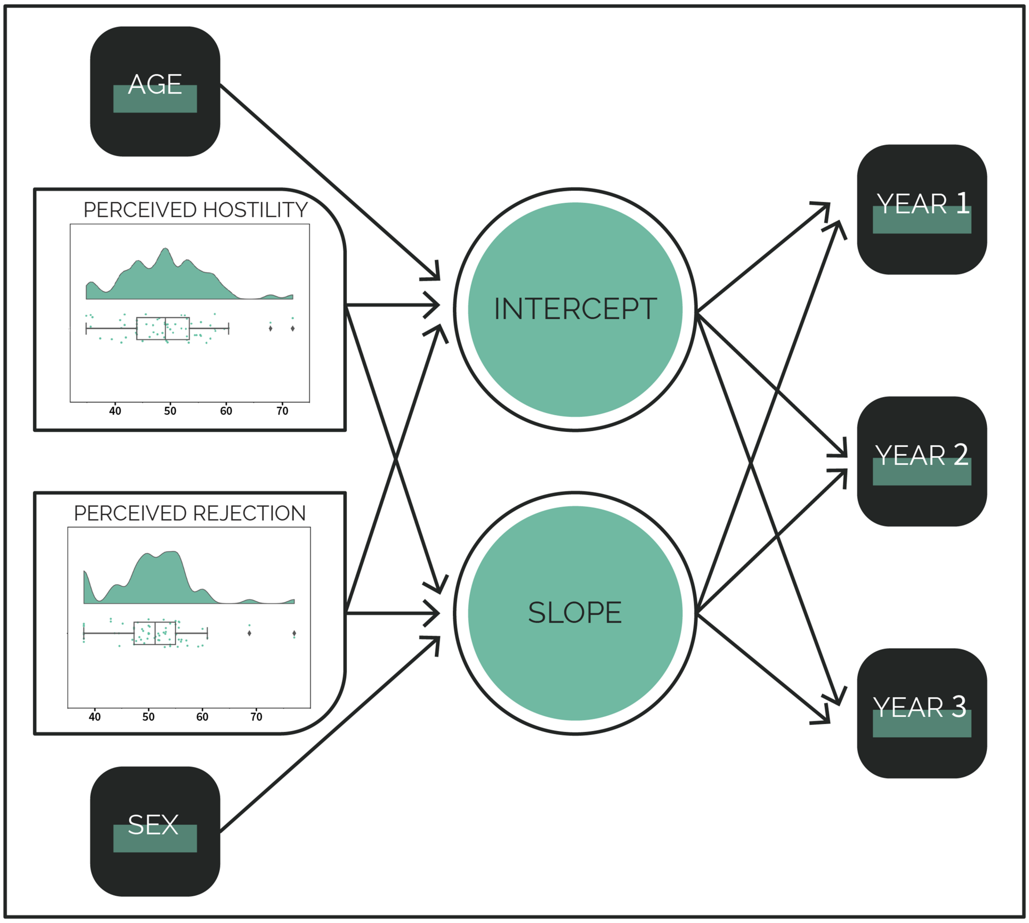

Figure 1. Data distribution for negative social perception measures and conceptual path diagram. Latent growth curve modelling was used to estimate the impact of perceived hostility and rejection on baseline connectivity and longitudinal changes in connectivity, while controlling for age and sex. *T*-score distributions for perceived hostility and perceived rejection are shown in the raincloud plots, with *T*-scores > 60 considered to be potentially problematic.

Latent growth curve modelling results between the salience and default mode networks

The baseline growth model using the longitudinal trajectory of frontoparietal-default mode connectivity without predictors or control variables had excellent model fit ($\chi^2(3) = 1.424$, $P = .70$; RMSEA = 0.000, 90% CI: 0.000, 0.198; CFI = 1.000). Using the motion-corrected residuals of salience-default mode network connectivity as the inputs for our model, the latent intercept mean indicated that across the whole sample, baseline frontoparietal-default mode connectivity significantly differed from zero ($b = -0.095$, SE = 0.031, $P < .01$; $\beta = -0.713$), while the slope did not ($b = 0.021$, SE = 0.028, $P = .45$). The full model results are available in the Supplementary. We then imposed control variables of age at time 1 and sex on the estimated latent intercept and slope variables. This model had excellent fit ($\chi^2(5) = 1.341$, $P = .93$; RMSEA = 0.000, 90% CI: 0.000, 0.041; CFI = 1.000). Age was not significantly associated with the latent intercept ($b = 0.028$, SE = 0.020, $P = .16$; $\beta = 0.316$) or the latent slope ($b = -0.002$, SE = 0.018, $P = .94$; $\beta = -0.121$) variables. Sex was not significantly associated with the latent intercept ($b = -0.078$, SE = 0.062, $P = .21$; $\beta = -0.280$) or the latent slope ($b = 0.039$, SE = 0.057, $P = .50$; $\beta = 0.976$) variables. We then included the perceived hostility and rejection *T*-scores into our latent growth curve model. This model had excellent fit ($\chi^2(11) = 6.037$, $P = .87$; RMSEA = 0.000, 90% CI 0.000, 0.056; CFI = 1.000). Perceived hostility *T*-scores were associated with the latent slope variable (Fig. 3), such that participants who self-reported more perceived hostility tended to have increased salience-default mode connectivity over time ($b = 0.009$, SE = 0.005, $P = .04$; $\beta = 0.910$). Perceived hostility was not associated with the latent intercept variable ($b = -0.008$, SE = 0.006, $P = .15$; $\beta = -0.388$). Perceived rejection scores were not significantly associated with either the latent intercept ($b = 0.003$, SE = 0.006, $P = .60$; $\beta = 0.142$) or slope ($b = 0.001$, SE = 0.005, $P = .80$; $\beta = 0.124$) variables.

Latent growth curve modelling results between the frontoparietal and default mode networks

In brief, there were no significant associations between the variables of interest (negative social perception measures) and the latent or control variables. The full results can be found in the Supplementary Results. Model comparisons for all three network pairs can be found in Supplementary Table 1.

Discussion

In the present study, we applied latent growth curve modelling to probe the potential impact of negative social perception measures on longitudinal trajectories of ICNs in a sample of children and adolescents (aged 9–15 at time point 1). Specifically, we fit latent growth curve models to functional connectivity measures collected annually at three time points, as well as measures

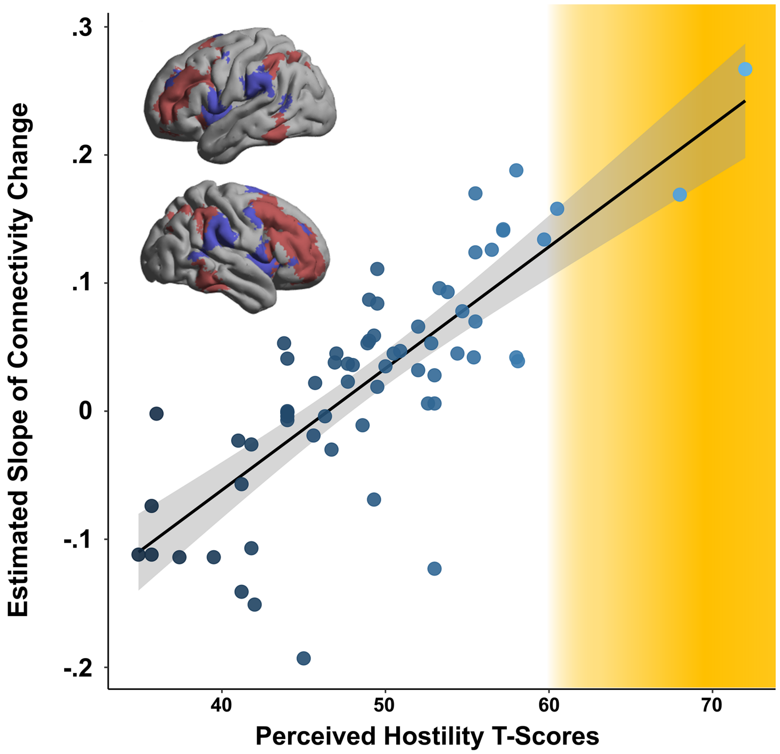

Figure 2. Relationship between the slope of connectivity change between the salience and frontoparietal networks and perceived hostility *T*-scores. The scatterplot shows individual *T*-scores of perceived hostility, as well as the estimated slope of connectivity change (following adjustment by regressing out the effect of sex and age in the latent growth curve model). The salience network is shown in blue (darker) and the frontoparietal network is shown in red (lighter colored areas). *T*-scores >60 are considered to be 'potentially problematic'.

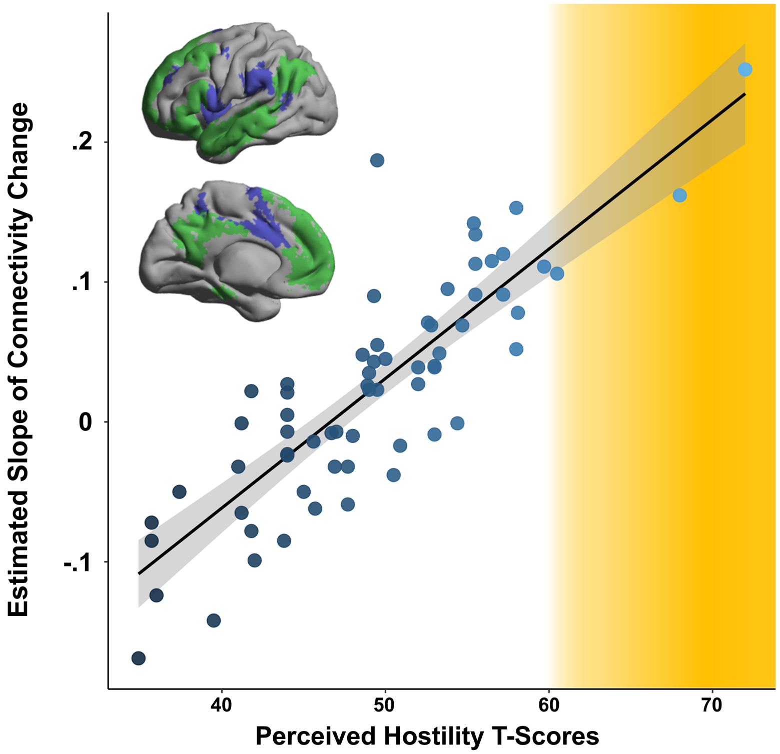

Figure 3. Relationship between the slope of connectivity change between the salience and default mode networks and perceived hostility *T*-scores. The scatterplot shows individual *T*-scores of perceived hostility, as well as the estimated slope of connectivity change, which were adjusted by regressing out the effect of sex and age in the latent growth curve model. The salience network is shown in blue (darker) and the default mode network is shown in green (lighter colored areas). *T*-scores >60 are considered to be 'potentially problematic'.

of negative social perception collected at the first time point. We provide compelling evidence that the longitudinal trajectories of network connectivity between ICNs of the triple network model of psychopathology are differentially associated with the severity and subtype of negative social perception in a network specific manner. In particular, changes in functional connectivity over time between the salience and frontoparietal networks, as well as the salience and default mode networks were positively correlated with levels of perceived social hostility, but not perceived social rejection. Taken together, these findings suggest that the salience network, which is critical for emotion regulation and largely overlaps with the social pain network, may be particularly vulnerable to the effects of perceived hostility. This is the first investigation that elucidates the longitudinal impact of negative social perception on network connectivity in youth and contributes to the growing literature examining the role of social processing in a critical developmental period where interpersonal interactions and their perceived valence can have increased motivational salience (Masten et al. 2009, 2012, Onoda et al. 2010, Bolling et al. 2011, Crone and Dahl 2012, Puetz et al. 2014).

Our main results indicate that perceived hostility, but not perceived rejection, impacts the longitudinal trajectory of connectivity between ICNs in healthy children and adolescents. Interestingly, although both perceived hostility and rejection loaded strongly onto the same factor in a recent factor analysis of a large sample ($N = 920$) of children and adolescents (Paolillo et al. 2020), our results demonstrate the specificity of subtypes (i.e. rejection vs. hostility) of negative social perception on the longitudinal trajectory of connectivity between ICNs. From the perspective of relational valuation, it is unsurprising that perceived hostility and rejection have differential effects on neurodevelopment. In favour of a dichotomous framework of rejection vs. acceptance, perceptions of interpersonal relationships may be viewed along a continuum (Leary 2006). For instance, the rejection measure evaluates the degree to which people 'don't pay attention to me' or 'don't listen when I ask for help' that may limit desired social interactions, while hostility refers to more active or direct forms of threat (e.g. 'how often people yell at me' and 'argue with me'), which may be a more direct catalyst of neural and behavioural alterations. These differences in experiences of social isolation vs. social threat are reminiscent of the dimensional model of adversity (in favour of a cumulative risk model), where distinct neurodevelopmental differences were observed in response to measures of threat and deprivation (McLaughlin et al. 2014, Sheridan and McLaughlin 2014). While cumulative risk models (i.e. combining multiple risk factors to generate an aggregate trauma score) have been highly informative, they may obscure potentially distinct mechanisms and processes that are differentially impacted by more granular measures of developmentally relevant factors. In other words, distinguishing between social pain measures allowed us to identify the unique relationship between perceived hostility and neurodevelopment, while a unitary model of social pain may have conflated the relative contributions of hostility and rejection. This is particularly important during adolescence, given that these social dimensions increase in motivational salience and can drive behavioural changes, leading to further alterations and exposure to various social environments. For instance, while adolescents experience heightened novelty seeking and autonomy (e.g. driver's licence and employment), negative social experiences may motivate individuals to isolate themselves or generate hostile attributions, exacerbating the initial impact of social pain. The majority of existing studies utilized in-scanner measures of perceived social pain extracted from the Cyberball task during fMRI acquisition, where participants believe they are being excluded from a social game of passing the ball among themselves and two confederates, who do not actually exist and are programmed into the task (Williams and Jarvis 2006, Masten et al. 2009, 2012, Onoda et al. 2010, Bolling et al. 2011, Puetz et al. 2014). Studies using this task have repeatedly demonstrated increased activity and connectivity in the social pain network, a matrix of brain regions [primarily the dorsal ACC (dACC) and anterior insula] that exhibit increases in activity in response to social pain, as measured by the Needs Threats Scale, which is frequently used to assess participants' level of distress related to social exclusion immediately following completion of the Cyberball task (Eisenberger et al. 2003, Eisenberger 2006, 2012, 2015, van Beest and Williams 2006, Gerber et al. 2017, Perini et al. 2018). Previous work has shown that these regions are sensitive to a variety of measures, including the availability of positive relationships, early life stress exposure, and self-esteem (Eisenberger et al. 2003, Onoda et al. 2010, Eisenberger 2012, 2015, Masten et al. 2012, Puetz et al. 2014).

The social pain network exhibits substantial overlap with the salience network (i.e. dACC and anterior insula), although the salience network does not include the subgenual ACC (sgACC), a component of the social pain network that plays a particularly important role in affective processing and is implicated in various mood disorders (Eisenberger and Lieberman 2004, Seeley et al. 2007, Eisenberger 2012, 2015, Perini et al. 2018, Seeley 2019). The sgACC exhibits grey matter volume reductions and increased activity in individuals with depression and was identified as a key locus of ketamine's antidepressive mechanism of action, perhaps due to its substantial connectivity with limbic structures (Drevets et al. 2008, Alexander et al. 2021). More broadly, the salience network is believed to monitor the pertinence of endogenous and exogenous stimuli and map goal-relevant information to switch between cognitive demand-heavy states (frontoparietal network) and more introspective states (default mode network; Dosenbach et al. 2007, Goulden et al. 2014, Eisenberger 2015, Perini et al. 2018). Connectivity alterations in regions of the salience network have been identified across a range of disorders, including obsessive compulsive disorder, major depressive disorder, and schizophrenia (Menon 2011, Mulders et al. 2015, Gürsel et al. 2018, Shao et al. 2018). In line with such findings, we identified alterations to the connectivity profile among the salience and frontoparietal networks, which may reflect the sensitivity of such networks to social pain. Furthermore, these relationships were present even though our sample only included three participants with perceived hostility and rejection T-scores >60, or 'potentially problematic', indicating that perceived hostility can impact connectivity profiles within a subclinical range of values (Paolillo et al. 2020). Finally, since the NIHTB-EB measures ask about negative social perceptions over the past month, our results indicate that the salience network is sensitive not only to immediate (i.e. Cyberball), but also to long-term feelings of negative social perceptions. Importantly, these neural alterations are not a diagnostic feature of psychopathology, rather a characterization of the heterogeneity observed in neurodevelopmental trajectories. Thus, to interpret these changes as universally detrimental would belie the underlying complexity of neural changes and accompanying behavioural alterations, as imposing a pure deficit model does not accommodate the multifinality of outcomes commonly observed in clinical settings. Taken together, changes to connectivity among the salience and frontoparietal networks associated with measures of perceived hostility may contribute to broader variation in the patterns of connectivity across this developmental window.

We also identified an increased rate of change in connectivity between the salience and default mode networks. One study identified increased connectivity between these networks following the Cyberball task, which normalized to pre-stress levels roughly 1 h after the stressor (Clemens et al. 2017). Our results indicate that these connectivity changes may persist in the presence of chronic social pain (i.e. NIHTB-EB estimates over the past month), although it remains unclear whether these changes are permanent or transient elevations that may diminish following reductions in social pain levels. While alterations in salience network connectivity have been linked with panic disorder, depression, and social anxiety disorder and may reflect inadequate functional segregation (Pannekoek et al. 2013, 2014; Peterson et al. 2014), increased connectivity between the salience and default mode networks could indicate an 'altered default mode' that is an adaptive response to social pain, whereby the brain at rest is more primed to detect salient events and react in stressful social environments (Clemens 2017). In line with the Socio-cognitive Integration of Abilities Model (SOCIAL), a theoretical framework of factors that may impact the acquisition and maintenance of social skills, neurodevelopmental trajectories in youth may be particularly vulnerable to environmental factors (i.e. social isolation) that may lead to alterations in social and executive function (Beauchamp and Anderson 2010). Thus, it is unsurprising that the default mode network is sensitive to negative social perceptions, given that these regions are consistently recruited during social cognition (Mars et al. 2012). Interestingly, we did not observe any longitudinal changes in connectivity between the frontoparietal and default mode networks in relation to social pain measures. Furthermore, connectivity between these networks was positive, which was somewhat surprising given the anticorrelations that are commonly reported in the literature. However, the majority of this work focuses on adults, and the developmental literature is more heterogeneous. For instance, evidence suggests that regions of the frontoparietal and default mode networks are positively correlated in childhood/adolescence using seed-based connectivity analyses, and then become anticorrelated in adulthood (Chai et al. 2014). Such subtle differences may be more readily identifiable in developmentally specific parcellations, such as the Dev-Atlas which is based entirely on resting-state fMRI data from over a thousand typically developing youth (Doucet et al. 2025).

Before concluding, it is important to note limitations of the study. Although we separate negative social perceptions into hostility and rejection subtypes, these are still relatively gross measures and future research may benefit from examining the frequency, severity, and context-dependent (i.e. peers vs. adults, social media) nature of social perceptions (Petro et al. 2025). A more granular approach to examining ICNs (e.g. more parcellations) may also provide a more nuanced perspective of longitudinal changes in the connectivity profiles among ICNs. While the current analyses focus on cortical networks associated with psychiatric symptoms, subcortical structures (e.g. amygdala and ventral striatum) are most likely sensitive to social pain and warrant further investigation. Such studies could identify altered interactions between subcortical and cortical regions linked to social pain. In addition, future research could utilize dynamic functional network connectivity modelling to examine microstates and transition probabilities within and between ICNs (Wang et al. 2020, Snyder et al. 2021). Furthermore, while 5–7 min of resting-state fMRI data are adequate for approximating connectivity measures, increasing the scan duration (and thus the reliability of connectivity estimates) may confer additional sensitivity to longitudinal changes in network connectivity. Thus, longer scan durations should be employed in future work. While FIML is equipped to generate minimally biased parameter estimates and standard errors with missing data, the significant attrition in this dataset is a major limitation of the study, as the substantial loss of participants over time and 35% retention at time point 3 may have introduced bias into the study. Specifically, test–retest reliability is critical in longitudinal studies as it indicates the stability of the measured construct and allows for inferences that changes observed over time are variations in the underlying construct, rather than random measurement error and sample bias. Examining the correlation coefficients year-to-year in the full sample indicated that the magnitude of the stability coefficients was acceptable for neural data between time points 1 and 2, while these estimates between time points 2 and 3 were much lower. We reran our analyses with a subset of participants with data from all three time points (i.e. without FIML), which improved our stability coefficients between time points 2 and 3, as well as comparable estimates from the statistical models with social pain measures. Specifically, while the beta coefficient for perceived hostility on latent slope in the models did not significantly differ from zero in these models, the beta coefficients did not statistically differ from those in the original model (with FIML) for the salience—frontoparietal or the salience—default mode network pairs. Given that the sample with data from all three time points was approximately a third of the original sample, we attribute this to a lack of statistical power. Overall, the substantial longitudinal attrition in the sample likely affected the generalizability of results from this study and these analyses should be replicated in future work. Furthermore, while our analyses modelled longitudinal changes in a linear fashion, these connectivity profiles may also exhibit nonlinear forms that should be examined using higher-order polynomial or latent basis modelling in future work. Including pubertal measures such as Tanner staging in the model would be advantageous and important in future work. Finally, it is important to note that our analyses focus on a normative community sample and that generalizing our findings to children and adolescents who have been diagnosed with mental health disorders should be done with caution.

In sum, this study is one of the first and largest longitudinal studies across development to examine the impact of social distress across the triple network model of psychopathology. Our results underscore the importance for a dimensional approach to examining social distress, with alterations to longitudinal trajectories of between-network connectivity in a network specific manner. These novel results offer evidence for the impact of perceptions of interpersonal interactions that may contribute to negative social perceptions in a subtype-specific manner that modulates connectivity between ICNs of the triple network model of psychopathology.

Supplementary data

Supplementary data is available at *SCAN* online.

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