Psychological Medicine

cambridge.org/psm

Longitudinal changes in within-salience network functional connectivity mediate the relationship between childhood abuse and neglect, and mental health during adolescence

Divyangana Rakesh[1], Nicholas B. Allen[2] and Sarah Whittle[1]

[1]Department of Psychiatry, Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Melbourne, VIC, Australia and [2]Department of Psychology, The University of Oregon, Eugene, OR, USA

Original Article

Cite this article: Rakesh D, Allen NB, Whittle S (2023). Longitudinal changes in within-salience network functional connectivity mediate the relationship between childhood abuse and neglect, and mental health during adolescence. *Psychological Medicine* **53**, 1552–1564. https://doi.org/10.1017/S0033291721003135

Received: 3 December 2020
Revised: 7 July 2021
Accepted: 15 July 2021
First published online: 25 August 2021

Key words:
Abuse; adolescence; childhood maltreatment; default mode network; depression; fMRI; longitudinal; neglect; resting-state functional connectivity; salience network; substance use

Authors for correspondence:
Divyangana Rakesh,
E-mail: divyangana.rakesh@gmail.com;
Sarah Whittle,
E-mail: swhittle@unimelb.edu.au

Abstract

Background. Understanding the neurobiological underpinnings of childhood maltreatment is vital given consistent links with poor mental health. Dimensional models of adversity purport that different types of adversity likely have distinct neurobiological consequences. Adolescence is a key developmental period, during which deviations from normative neurodevelopment may have particular relevance for mental health. However, longitudinal work examining links between different forms of maltreatment, neurodevelopment, and mental health is limited.

Methods. In the present study, we explored associations between abuse, neglect, and longitudinal development of within-network functional connectivity of the salience (SN), default mode (DMN), and executive control network in 142 community residing adolescents. Resting-state fMRI data were acquired at age 16 (T1; $M = 16.46$ years, S.D. = 0.52, 66F) and 19 (T2; mean follow-up period: 2.35 years). Mental health data were also collected at T1 and T2. Childhood maltreatment history was assessed prior to T1.

Results. Abuse and neglect were both found to be associated with increases in within-SN functional connectivity from age 16 to 19. Further, there were sex differences in the association between neglect and changes in within-DMN connectivity. Finally, increases in within-SN connectivity were found to mediate the association between abuse/neglect and lower problematic substance use and higher depressive symptoms at age 19.

Conclusions. Our findings suggest that childhood maltreatment is associated with altered neurodevelopmental trajectories, and that changes in salience processing may be linked with risk and resilience for the development of depression and substance use problems during adolescence, respectively. Further work is needed to understand the distinct neurodevelopmental and mental health outcomes of abuse and neglect.

Introduction

Childhood maltreatment is associated with increased mental health issues in adolescence and adulthood, including disorders with high disease burden, such as depression, anxiety, and substance use disorders (Green et al., 2010; Kessler et al., 2010). Due to the strong relationship between childhood maltreatment and poor mental health outcomes, a significant body of research has attempted to examine the underlying neurobiological mechanisms of this association – although a precise characterization of these has so far proven to be elusive (McLaughlin, Weissman, & Bitrán, 2019; Teicher, Samson, Anderson, & Ohashi, 2016). It has been hypothesized that childhood maltreatment has the capacity to impact neurodevelopmental processes during critical periods such as adolescence, and consequently contribute to negative developmental outcomes (Teicher et al., 2016). However, current research approaches, which either examine different types of maltreatment cumulatively, or examine single types of maltreatment in isolation, may have limitations that impede the ability to elucidate mechanisms (Lambert, King, Monahan, & McLaughlin, 2017; McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). Investigating key dimensions of maltreatment that may differentially impact neurodevelopment, and consequently psychopathology, is therefore vital.

The Dimensional Model of Adversity and Psychopathology (DMAP) suggests that different types of maltreatment can impact neurodevelopmental processes, as well as the development of cognitive and emotion function, differently (McLaughlin & Sheridan, 2016; McLaughlin et al., 2014, 2019; Sheridan & McLaughlin, 2014). The model conceptualizes two main dimensions of adversity: threat and deprivation. The dimension of threat encompasses threatening or harmful experiences, such as physical, sexual, or emotional abuse. In contrast, deprivation refers to the lack of expected nurturing environmental inputs, such as physical and emotional support, as well as cognitive and social stimulation (i.e. core features of neglect) (McLaughlin

CAMBRIDGE UNIVERSITY PRESS

& Sheridan, 2016; McLaughlin et al., 2014, 2019; Sheridan & McLaughlin, 2014). The model purports that a history of abuse (i.e. experiences of threat) may lead to adaptive mechanisms that facilitate rapid threat detection. As such, it has been suggested that abuse may be associated with alterations in neural systems associated with threat detection, and salience processing (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014). In contrast, neglect (i.e. the experience of deprivation), which is associated with reduced exposure to a diverse range of experiences that are essential for early learning and development, and deviation from species-expectant cognitive and social stimulation, is posited to have a profound influence on higher-order cognitive development. As such, neglect may uniquely be associated with neural systems involved in executive function and higher-order cognition (McLaughlin et al., 2019).

Indeed, a recent systematic review of the literature supports these hypotheses (McLaughlin et al., 2019). Specifically, the review found evidence that threat/abuse-related exposures are more consistently associated with alterations in regions of the salience network [SN; comprised of the insula and dorsal anterior cingulate cortex (dACC)]. The review also suggested that deprivation/neglect is more consistently associated with alterations in regions of the executive control network [ECN; comprised of frontoparietal regions such as the dorsolateral prefrontal cortex (PFC) and parietal cortex]. However, while aberrant neural interactions between different regions may be relevant to the pathophysiology of psychiatric disorders (DiMartino et al., 2014), most work supporting DMAP has been conducted on brain structure and function rather than *connectivity* (Dennison et al., 2019; Edmiston et al., 2011; Hanson et al., 2010, 2015b; Martin, 2015; McLaughlin et al., 2016, 2019; Tottenham et al., 2011).

Further, adolescence is associated with considerable functional brain maturation. Therefore, research on brain development during this period may provide insight into the effects of abuse and/or neglect on neurodevelopmental processes that are suggested to be particularly relevant for the development of psychopathology (McLaughlin et al., 2019). As such, there has been a call to investigate the impact of adversity on brain development during developmentally sensitive periods (Ho, Dennis, Thompson, & Gotlib, 2018; McLaughlin et al., 2019). Therefore, a fruitful next step in our understanding of the impact of childhood maltreatment on functional brain development is to examine resting-state functional connectivity (rsFC). Resting-state fMRI has proven to be a valuable tool for examining multiple functional domains at rest, while circumventing task-associated confounds (such as ceiling and floor effects), thus making it particularly suitable for developing populations and longitudinal designs (Fox & Greicius, 2010; Kelly, Biswal, Craddock, Castellanos, & Milham, 2012). Further, evidence shows superior reliability of rsFC as compared to task-based methods (Choe et al., 2015; Herting, Gautam, Chen, Mezher, & Vetter, 2018; Plichta et al., 2012), which is especially critical for longitudinal designs.

Using rsFC-based approaches, normative increases in 'within-network' integration through adolescence and young adulthood have been reported consistently (Dumontheil, 2016; Stevens, 2016; Truelove-hill et al., 2020). This increase in within-network connectivity has been posited to be one of the neural substrates for progressive increases in cognitive control, self-regulation, and social function (Dumontheil, 2016; Ernst, Torrisi, Balderston, Grillon, & Hale, 2015; Stevens, 2016; Stevens, Pearlson, & Calhoun, 2009). As such, the disruption of normative patterns of functional development (i.e. alterations to the pattern of increase in within-network connectivity) of core neural systems involved in emotion and cognitive function (such as the SN and ECN) by the experience of abuse and/or neglect may pave the way for adaptive or maladaptive mental health outcomes (Teicher et al., 2016).

It has been suggested that the experience of maltreatment during childhood accelerates neural development as an ontogenetic response to adversity (Callaghan & Tottenham, 2016). However, most work in this area has been cross-sectional, and longitudinal work – which has been sparse in the literature – is required to test this hypothesis (McLaughlin et al., 2019). Longitudinal work provides the opportunity to examine trajectories and therefore developmental deviations (DiMartino et al., 2014) associated with childhood maltreatment. Our recent work (with a sub-sample of participants in this study) found widespread maltreatment-associated rsFC changes from mid to late adolescence (Rakesh et al., 2021); however, we did not explore these effects on *a priori* networks of interest. To our knowledge, no longitudinal studies have looked at the differential impact of abuse and neglect on the development of connectivity of neural systems hypothesized to be associated with maltreatment history (i.e. SN and ECN), and their association with mental health symptoms.

The goal of the present study was to examine the relationship between the history of abuse and neglect and change in within-network connectivity of key functional systems purported to be impacted by a history of abuse or neglect (i.e. the SN and ECN) during adolescence. Given that studies have observed sex-specific effects of childhood maltreatment on functional connectivity (Burghy et al., 2012; Herringa et al., 2013), and the importance of examining sex differences in the neurobiological consequences of adversity has also recently been highlighted in the literature (Bath, 2020), we examined the moderating effect of sex on these associations in exploratory analyses. Next, in exploratory analyses, we investigated whether change in connectivity of these systems was associated with mental health symptoms. We examined symptoms of depression, anxiety, and substance use as they are all strongly associated with childhood maltreatment (Kessler et al., 2010), and also have high incidence rates during adolescence (Kessler et al., 2005). Finally, other work in youth has shown that both deprivation (Edmiston et al., 2011; Silvers et al., 2016; Sripada, Swain, Evans, Welsh, & Liberzon, 2014; Weissman, Conger, Robins, Hastings, & Guyer, 2018) and threat (Edmiston et al., 2011; Hanson et al., 2010; Hart et al., 2018; Saxbe et al., 2018) are associated with alterations in the structure, function, and connectivity of regions of the default mode network [DMN, comprised of the medial PFC (mPFC), posterior cingulate cortex (PCC), hippocampus, and precuneus (amongst other regions)]. However, current theories on adversity and brain development do not describe how exposure to threat or deprivation may differentially sculpt DMN circuitry (McLaughlin et al., 2019). As such, we conducted exploratory analyses to examine the differential effects of abuse and neglect on within-DMN connectivity.

Given that adversity is posited to accelerate neural development (Callaghan & Tottenham, 2016), and within-network integration increases throughout adolescence (Dumontheil, 2016; Stevens, 2016; Truelove-hill et al., 2020), we hypothesized that abuse would be associated with greater increases in within-network connectivity of the SN, while neglect would be associated with greater within-network connectivity of the ECN. Due to the paucity of studies in this space, we did not have specific hypotheses about sex differences in abuse and neglect-associated rsFC

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

development. Finally, while we expected abuse- and neglect-associated changes to be relevant for mental health, due to a dearth of literature on this topic, we did not have specific hypotheses about these associations.

Methods

Participants

Participants were from a large longitudinal study; the Orygen Adolescent Development Study (OADS). Please refer to Whittle et al. (2008) for a detailed description. Briefly, the OADS is a longitudinal study that aims to investigate risk and resilience factors for adolescent mental health. Informed consent was obtained for all participants and their parent or guardian at each study wave in accordance with the human research ethics committee of The University of Melbourne, Australia. Participants ($N = 142$) underwent resting-state functional MRI at mid- (T1; $n = 130$, mean age = 16.46 years, S.D. = 0.52, 66F) and late-adolescence [T2; $n = 102$ (including 12 participants that did not have scans at T1), mean age = 18.83 years, S.D. = 0.45, 54F, mean follow-up period = 2.35 years). Attrition from T1 to T2 was not associated with change in key demographic, childhood trauma questionnaire (CTQ), and psychopathology variables ($p > 0.05$). For further details, see online Supplementary Material. The 2006 Socio-Economic Indexes for Areas Index of Relative Socioeconomic Disadvantage was used to assess socioeconomic status (SES). Full-scale IQ was estimated using a short form of WISC-IV, based on three subtests (Vocabulary, Matric Reasoning, Symbol Search) (Wechler, 2003).

Measures of abuse and neglect

Childhood maltreatment history was assessed in early adolescence (at age 14) through the CTQ, a well-established 28-item self-report questionnaire that assesses maltreatment history and has been shown to have acceptable psychometric properties in community samples (Cronbach $\alpha = 0.90$) (Scher, Stein, Asmundson, Mccreary, & Forde, 2001). Participants responded about maltreatment that occurred prior to T1. Items can be summed to obtain a total maltreatment score as well scores on five subscales: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse (Bernstein et al., 1994). In order to examine the differential effects of abuse and neglect, we summed the scores for physical, emotional, and sexual abuse – hereafter referred to as abuse, and of emotional and physical neglect – hereafter referred to as neglect. Continuous abuse and neglect scores (used in analyses) were significantly correlated ($r = 0.63$, $p < 0.001$). See online Supplementary Fig. S1 for distributions and online Supplementary Fig. S2 for the prevalence of abuse and neglect in our sample. Of note, 36 (25%) and 31 participants (22%) met cut-offs for abuse and neglect, respectively (based on Walker et al., 1999).

Depression, anxiety, and substance use

At both T1 and T2, adolescents completed the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988), and the Centers for Disease Control and Prevention's Youth Risk Behavior Survey (YRBS). Participants were administered the CES-D and the BAI at the time of each scan to assess the presence of depressive and anxiety symptoms, respectively. Problematic substance use at the time of each scan was assessed using the YRBS and defined based on a method used previously (Rakesh et al., 2020b) (see online Supplementary Material for details).

MRI pre-processing

For MRI acquisition protocol, see online Supplementary Material. Images were preprocessed using fMRIPrep (version 1.3.2) (Esteban et al., 2019). Details of the pipeline can be found in online Supplementary Material. To minimize motion-associated confounds, we employed a rigorous approach; we included ICA aroma in our fMRIPrep pipeline, did not include participants with a mean framewise displacement (FD) > 0.5 mm (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), and included mean FD values as covariates of no interest in our models. Residual noise was removed by means of white matter and CSF signal regression (based on ICA aroma output) and bandpass filtering (0.01–0.1 Hz) (Pruim et al., 2015) using FSL. Previous work has shown that the inclusion of individual motion estimates as nuisance regressors in group-level analyses effectively accounts for motion-associated inter-individual variation in resting-state fMRI measures (Fair et al., 2013; Satterthwaite et al., 2012). However, given that functional connectivity is susceptible to motion (Satterthwaite et al., 2019), we have also provided results excluding participants with a mean FD > 0.2 mm. Using this more stringent thresholding, we lost a total of 26 (out of 232) scans across two time points ($n = 130$ participants).

Resting-state within-network functional connectivity

To perform focused analyses on the impact of abuse and neglect on network cohesion, data were extracted from the dorsal DMN (which contains the mPFC, PCC, and several other regions), anterior SN (which contains the dACC, insula, and several other regions), and bilateral ECN in the present study (Fig. 1; Table 1). Within-network connectivity was computed for the SN, DMN, and ECN using a commonly used parcellation scheme (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012; https://findlab.stanford.edu/functional_ROIs.html). For details, see online Supplementary Material.

Statistical methods

Linear mixed-effects models (LMMs) were used to examine the relationship between abuse/neglect and change in connectivity of the SN, DMN, and ECN with age. LMMs are particularly suited to longitudinal analyses as they permit the use of all available data (including participants with data at only one time point) (Gibbons, Hedeker, & DuToit, 2010). Subsequent cross-sectional analyses (for significant longitudinal findings) were conducted using ordinary least squares regression. We verified if unstandardized residuals were normally distributed in all analyses, and analyses were conducted using robust regression if residuals were found to not be normally distributed. We covaried for sex (where relevant), SES, IQ, and FD (as time-varying covariates) in all our models and controlled for multiple comparisons using the false discovery rate ($p < 0.05$) (Benjamini & Hochberg, 1995). In order to determine whether findings were specific to abuse/neglect, we also covaried for abuse in neglect models, and *vice versa*. Model equations and collinearity checks can be found in online Supplementary Material.

Next, we examined the relationship between abuse/neglect, within-network FC for those networks where a significant

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

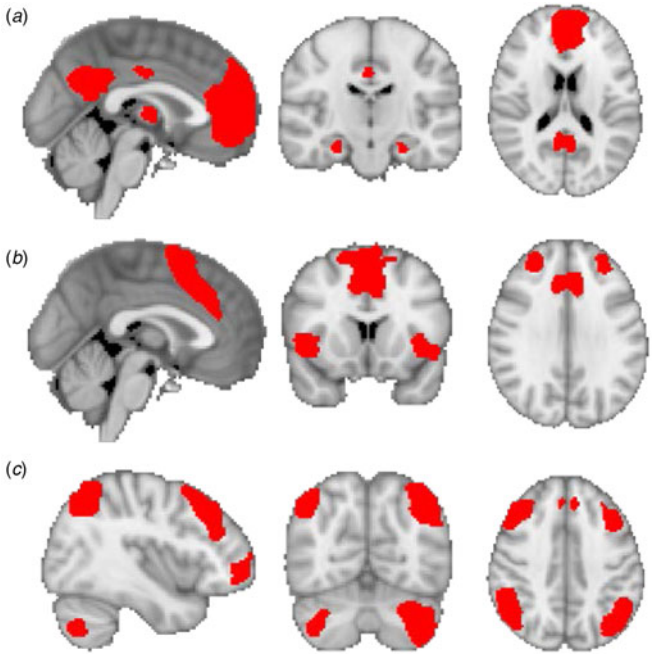

Fig. 1. Networks of interest: (*a*) dorsal default mode network (DMN); (*b*) anterior salience network (SN); (*c*) bilateral executive control network (ECN).

relationship was found longitudinally, and mental health at T2 using mediation models, with CTQ abuse/neglect scores as the predictor, change in within-network connectivity as the mediator (obtained using random slopes from LMM), and CES-D, BAI, and problematic substance use scores at T2 as the outcome variable. Moderated mediation models were then run to test the role of sex as a moderator. IQ, SES, sex (models where sex was not a moderator), and the respective T1 psychopathology score (CES-D, BAI, and problematic substance use) were included as covariates. Mediation analyses were conducted using the PROCESS Macro in SPSS (Hayes, 2018). Scatter plots and correlations between abuse, neglect, and outcome variables as well as covariates (SES and IQ) can be found in online Supplementary Material.

Results

Demographic information

Demographic information can be found in Table 2.

Relationships between abuse/neglect and change in within-network connectivity

We found a significant positive association between both abuse and neglect, and change in within-SN connectivity ($B = 0.01$, S.E. = 0.004, $p = 0.005$; Fig. 2*a*; $B = 0.01$, S.E. = 0.003, $p = .003$; Fig. 2*b*, respectively). Results were also significant when excluding participants with mean FD > 0.2 mm (abuse: $B = 0.01$, $t = 2.63$, $p = 0.01$; neglect: $B = 0.012$, $t = 3.03$, $p = 0.003$). These associations were not significant when controlling for abuse-associated change in the neglect model and *vice versa*. See online Supplementary Material for model output. We did not find significant associations between abuse or neglect and changes in within-DMN connectivity or within-ECN connectivity (online Supplementary Fig. S6). In addition, in order to aid with our interpretation of abuse- and neglect-associated changes in within-SN connectivity, we also investigated whether the same relationship existed for cumulative maltreatment. We found a significant association between total CTQ scores and change in within-SN connectivity from mid to late adolescence ($B = 0.006$, S.E. = 0.002, $p = 0.002$; Fig. 2*c*).

In order to elucidate at which ages the developmental trajectories diverged as a function of maltreatment, we examined cross-sectional relationships for within-SN connectivity at each time point. At T1 we found a significant negative relationship between abuse (Fig. 3*a*) but not neglect (Fig. 3*c*), and within-SN connectivity. At T2, we found a significant positive association between neglect (Fig. 3*d*), but not abuse (Fig. 3*b*), scores and within-SN connectivity.

Table 1. Regions in the DMN, ECN, and SN

Network	Regions	BA
Default mode network	mPFC, ACC, OFC	9, 10, 24, 32, 11
	Left angular gyrus	39
	Right SFG	9
	PCC, precuneus	23, 30
	Midcingulate cortex	23
	Right angular gyrus	39
	Thalamus	N/A
	Hippocampus	20, 36, 30
Executive control network	Left MFG, left SFG	8, 9
	Left IFG, OFG	45, 47, 10
	Left SPG, IPG, precuneus, angular gyrus	7, 40, 39
	Left ITG, MTG	20, 37
	Right crus I	N/A
	Left thalamus	N/A
	Right MFG, right SFG	46, 8, 9
	Right MFG	10, 46
	Right IPG, SMG, angular gyrus	7, 40, 39
	Right SFG	8
	Left crus I, crus II, lobule VI	N/A
	Right caudate	N/A
Salience network	Left MFG, left SFG	9, 46
	Left insula	48, 47
	ACC, mPFC, SMA	24, 32, 8, 6
	Right MFG	46, 9
	Right insula	48, 47
	Left lobule VI, crus I	N/A
	Right lobule VI, crus I	N/A

mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; SFG, superior frontal gyrus; PCC, posterior cingulate cortex; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; OFG, orbitofrontal gyrus; SPG, superior parietal gyrus; IPG, inferior parietal gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; SMG, supramarginal gyrus.

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

Table 2. Demographic information for time 1 and time 2

	T1 (age 16)	T2 (age 19)
N	130 (66F)	102 (54F)
Age	16.46 ± 0.52	18.83 ± 0.45
Age range	15.0–18.1	17.3–20.0
WISC IV	105.3 ± 10.49	106.68 ± 12.4
FD	0.14 ± 0.053	0.13 ± 0.05
SES[a]	63.5 ± 26.73	
Total CTQ[a]	33.41 ± 9.41	
Physical abuse[a]	5.66 ± 1.6	
Physical neglect[a]	6.1 ± 1.64	
Emotional abuse[a]	7.77 ± 3.85	
Emotional neglect[a]	8.62 ± 4.04	
Sexual abuse[a]	5.13 ± 0.73	
Abuse[a]	18.56 ± 5.15	
Neglect[a]	14.71 ± 5.09	
CES-D	9.54 ± 7.33	12.41 ± 110.01
BAI	8.18 ± 7.52	8.85 ± 9.79
Problematic substance use (N)	15	38

BAI, Beck Anxiety Inventory; CTQ, childhood trauma questionnaire; CES-D, Center for Epidemiological Studies Depression Scale; FD, framewise displacement; SES, socioeconomic status; WIS-C, Wechsler Intelligence Scale for Children IV (used to assess IQ).
Values correspond to mean ± standard deviation.
[a]Time-invariant variables were reported for all 142 participants in the study. Collected prior to T1.

Sex as a moderator of relationships between abuse/neglect and change in within-network connectivity

Given that sex has been shown to moderate the relationship between early adversity and brain development (Bath, 2020), we tested the role of sex as a moderator. We found that sex significantly moderated the relationship between neglect history and change in within-DMN connectivity ($B = -0.015$, S.E. = 0.006, $p = 0.014$; see online Supplementary Material for model output). Results were also significant when excluding participants with mean FD > 0.2 mm ($B = -0.015$, $t = -2.29$, $p = 0.02$). While males exhibited neglect-associated increases in within-DMN connectivity (Fig. 4*a*), no effect was found in females (Fig. 4*b*). This effect was found to be significant when controlling for abuse-associated change ($p = 0.004$). Cross-sectionally, sex was found to moderate the relationship between neglect and within-DMN connectivity at T2 but not T1 (Fig. 4*c*, *d* depicts the relationship in males and females at T2). For non-significant findings, see online Supplementary Material.

Relationships between change in connectivity and mental health

Although there were no total or direct effects of abuse/neglect on problematic substance use (i.e. no effects with or without controlling for FC), we found a significant role of change in within-SN connectivity (obtained using random slopes from LMM) as a mediator between abuse and problematic substance use at T2 (CI −0.0581 to −0.007; Fig. 5*a*) and neglect and problematic substance use at T2 (CI −0.0758 to −0.0032; Fig. 5*b*). These mediation effects were also significant when excluding participants with mean FD > 0.2 mm (abuse: CI −0.0711 to −0.0016; neglect: CI −0.0855 to −0.005). However, in analyses with the subsample excluding participants with mean FD < 0.2 mm, within-SN connectivity was also found to mediate the association between abuse/neglect and higher depressive symptoms at T2 (abuse: CI 0.004–0.254; neglect: CI 0.006–0.256; Fig. 5*c*, *d*). See online Supplementary Material for non-significant mediation findings.

Discussion

The aim of the present study was to examine the differential impact of abuse and neglect on the functional development of the SN, DMN, and ECN. We found a significant relationship between both abuse and neglect scores and the development of within-SN connectivity, such that higher abuse and neglect scores were associated with greater increases in within-network connectivity of the SN with age. We also found that only in males, neglect history was uniquely associated with the development of within-DMN connectivity (i.e. findings remained when accounting for abuse). Further, we found that increases in within-SN connectivity mediated the association between abuse and neglect, and reduced incidence of problematic use, and higher depressive symptoms in late adolescence.

We hypothesized that we would see abuse-, but not neglect-associated increases in within-SN connectivity. Our findings only partially supported this hypothesis, as we observed alterations in the development of SN connectivity as a function of both abuse and neglect. Increased abuse/neglect scores were found to be associated with greater increases in within-SN connectivity. The SN, which contains the bilateral anterior insula and dACC, has been suggested to be critically involved in the evaluation of internal and external states in order to guide behavior (Seeley et al., 2007; Uddin, 2015). Indeed, altered SN function and connectivity have previously been reported in individuals with a history of childhood maltreatment (McLaughlin et al., 2019; Van der Werff et al., 2013).

The pattern of greater functional segregation and therefore specialization during adolescence seen in the resting-state fMRI neurodevelopment literature (Dumontheil, 2016; Truelove-hill et al., 2020) has been posited to be one of the neural substrates for increased functioning observed during the same period (Stevens, 2016; Stevens et al., 2009). Our finding of abuse- and neglect-associated increase within-SN connectivity could therefore reflect more advanced salience processing and consequently greater sensitivity to threat. Further, accelerated neurodevelopment has been suggested to be an ontogenetic response to early adversity (Callaghan & Tottenham, 2016), and it has been suggested that the experience of adversity leads to reprioritization of developmental strategy in favor of quicker maturation of stress-associated systems. As such, given that development has shown to be associated with increased functional integration within individual systems (Truelove-hill et al., 2020), our finding of increased within-network connectivity of the SN from mid to late adolescence (as a function of both abuse and neglect) could be consistent with the stress-acceleration hypothesis, particularly because within SN connectivity (which was negatively associated with abuse at time 1) it was found to 'speed up' between time 1 and time 2, leading to a positive relationship at time 2 (with neglect).

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

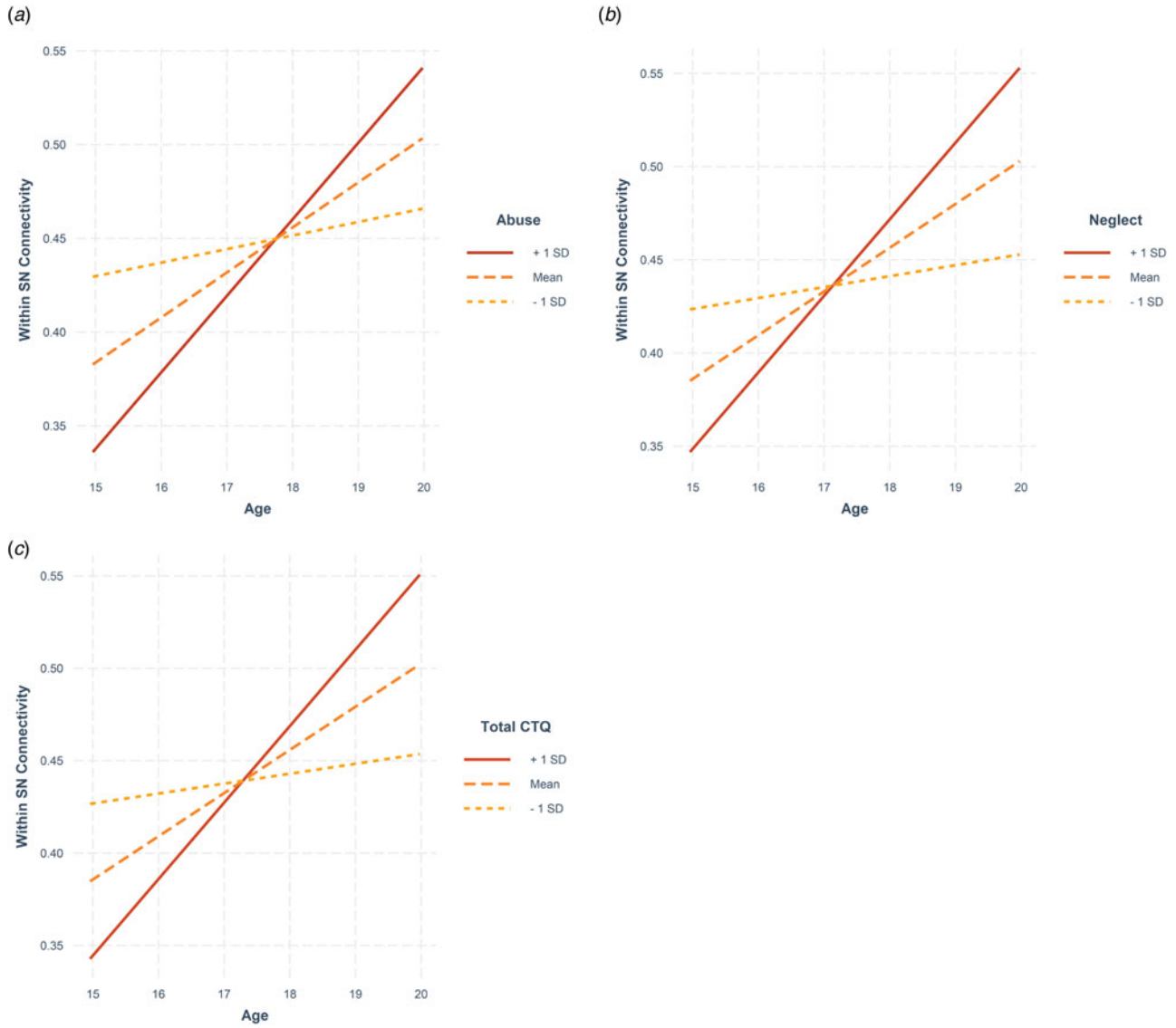

Fig. 2. Developmental trajectories are represented for within-SN connectivity, for adolescents with relatively high and low abuse (*a*), neglect (*b*), and total CTQ (*c*) scores. The slopes represent the average trajectories for groups based on + 1s.d., mean, and −1s.d. of abuse, neglect, and total CTQ scores. CTQ, childhood trauma questionnaire.

That both abuse and neglect were associated with the development of within-SN connectivity may not be surprising because of the high correlation between them, thereby making it more difficult to observe differential associations; however, the variance explained by the model that included both abuse and neglect as predictors was higher than that of the standalone models, giving us confidence that both types of maltreatment are contributing to the relationship. Our finding of abuse and neglect both being associated with changes in the same network does not contradict the DMAP model, as it is possible that abuse and neglect impact SN connectivity through different underlying mechanisms. For example, given that the SN is considered important for evaluative responses to threat and safety (Marstaller, Fynes-Clinton, Burianová, & Reutens, 2021; Menon & Uddin, 2010; Seeley et al., 2007; Uddin, 2015), and that threat/abuse is purported to impact emotional and fear learning, abuse could be acting on SN connectivity through activation of the HPA axis and downstream hormonal and metabolic changes (McLaughlin et al., 2014). On the other hand, neglect (or deprivation) may be acting on SN connectivity through a distinct mechanism via aberrant synaptic proliferation and pruning processes due to a deviation from the species-expectant experience of cognitive, social, and other forms of stimulation (McLaughlin, Sheridan, & Nelson, 2017). Indeed, the anterior insula (a core region of the SN) plays a crucial role in integrating sensory information from multiple modalities in order to support cognitive awareness and identify salient information. Accordingly, from a theoretical standpoint, an alteration in said inputs (e.g. less parental warmth/contact) could potentially reshape SN circuitry (Liu et al., 2017). For example, several studies have reported functional and structural re-organization of the SN in response to different types of sensory deprivation (e.g. Bavelier et al., 2008; Ding et al., 2016).

Nevertheless, there might be other reasons for our findings. For instance, an even clearer distinction between the neurobiological consequences of abuse and neglect may only be seen in cohorts where individuals have one experienced only or the other form

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

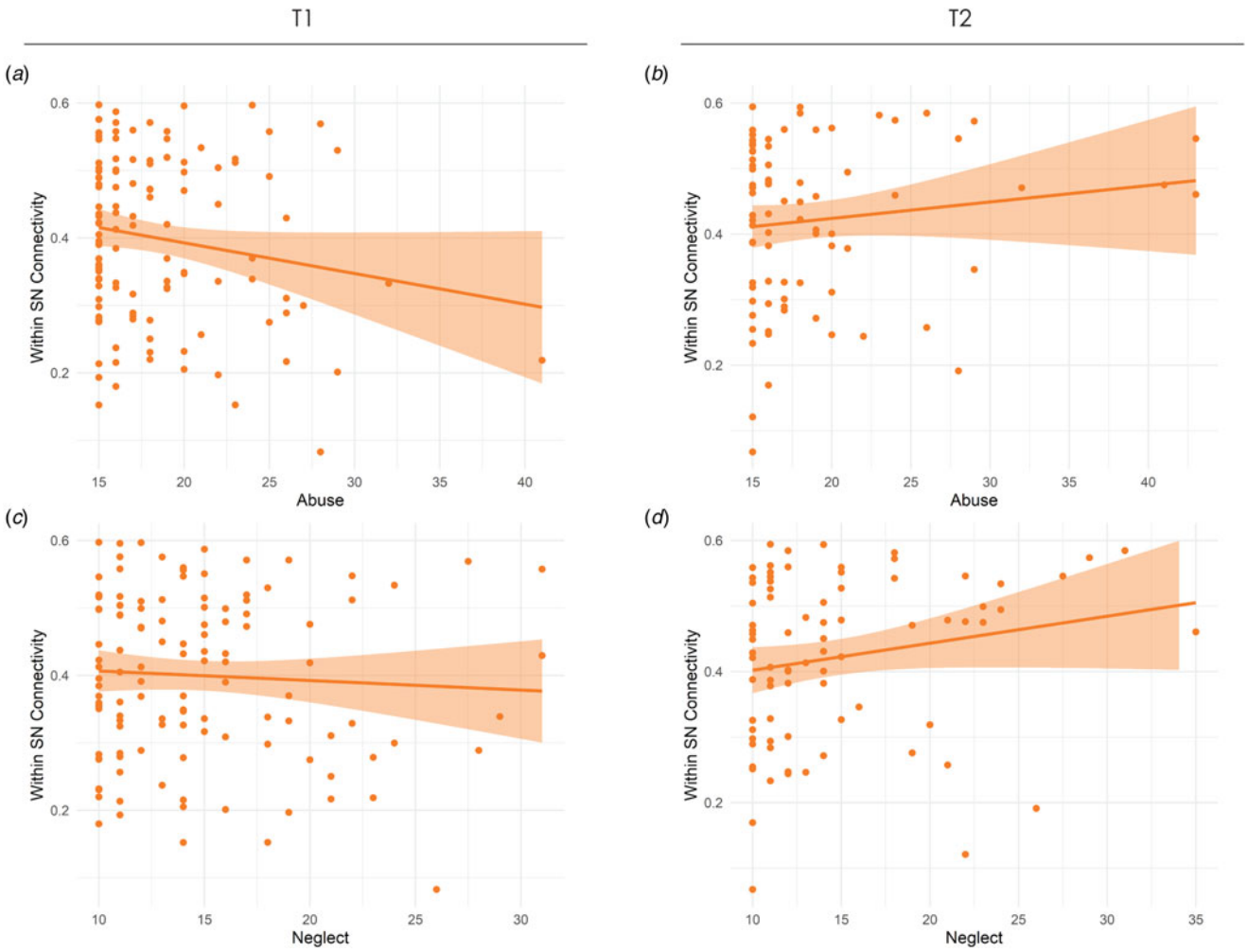

Fig. 3. Cross-sectional relationships are represented for within-SN connectivity with abuse and neglect at time 1 (*a*, *b*) and time 2 (*c*, *d*). The slopes represent the average trajectories for the whole sample. T1: abuse and within SN connectivity: $R^2 = 0.096$, $F_{(5,124)} = 2.622$, $B = -0.005$, $p = 0.048$; neglect and within-SN connectivity $R^2 = 0.084$, $F_{(5,124)} = 2.261$, $B = -0.004$, $p = 0.132$. T2: neglect and within-SN connectivity: $R^2 = 0.113$, $F_{(5,96)} = 2.445$, $B = 0.006$, $p = 0.033$; abuse and within-SN connectivity: $R^2 = 0.089$, $F_{(5,96)} = 1.867$, $B = 0.005$, $p = 0.163$. Findings with participants excluded based on FD > 0.2 mm: T1: abuse and within-SN: $R^2 = 0.079$, $F_{(5,107)} = 2.93$, $B = -0.004$, $t = -1.507$, $p = 0.135$; neglect and within-SN: $R^2 = 0.078$, $F_{(5,107)} = 2.89$, $B = -0.004$, $t = -1.446$, $p = 0.151$. T2: abuse and within-SN: $R^2 = 0.029$, $F_{(5,87)} = 1.56$, $B = 0.005$, $t = 1.459$, $p = 0.148$; neglect and within-SN: $R^2 = 0.061$, $F_{(5,87)} = 2.2$, $B = 0.007$, $t = 2.276$, $p = 0.025$.

of maltreatment. Further, we also found a similar relationship between change in within-SN rsFC and total maltreatment scores. This may suggest that a 'cumulative risk' framework may be beneficial, particularly in community samples where only very few individuals have experienced only abuse or neglect. In addition, cross-sectional analyses showing results being driven by T1 connectivity for abuse and T2 connectivity for neglect further suggest differential effects of abuse and neglect. These findings may indicate that neglect could have more long-lasting effects on within-SN connectivity (i.e. effects were present for a longer duration). In any case, larger longitudinal samples with exposure to multiple forms, and severity, of threat and deprivation are required to investigate this further (McLaughlin et al., 2019).

In the present study, we found sex to moderate the relationship between neglect and the development of within-DMN connectivity. Specifically, higher neglect scores were associated with increased within-DMN integration with age in males. This finding was consistent with the DMAP model's prediction of differential effects of abuse and neglect, as we found that the effect was specific to neglect and remained after covarying for abuse. Further, this finding is partially consistent with hypotheses regarding temporal patterns of development. Given that normative development has shown to be associated with increased age-associated within-DMN functional integration (Truelove-hill et al., 2020), our findings could be interpreted to reflect neglect-associated acceleration of development in males. This finding is somewhat inconsistent with other work that found deprivation (i.e. childhood poverty and neighborhood disadvantage) to be associated with *reduced* connectivity within the DMN (Rakesh, Seguin, Zalesky, Cropley, & Whittle, 2021; Sripada et al., 2014), which could be due to the difference in age of the sample (~24 *v.* ~16–18), the study design (cross-sectional *v.* longitudinal), and/or the utilization of different measures of deprivation (poverty *v.* neglect). Moreover, studies have also shown reduced DMN *structural* connectivity as a function of neglect/deprivation (Kumar et al., 2014). We speculate that it is possible that reduced structural connectivity as a function of neglect could lead to regions 'working harder' to communicate, thereby causing an increase in functional connectivity. While these previous findings are not consistent with our finding being only in males, sex

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

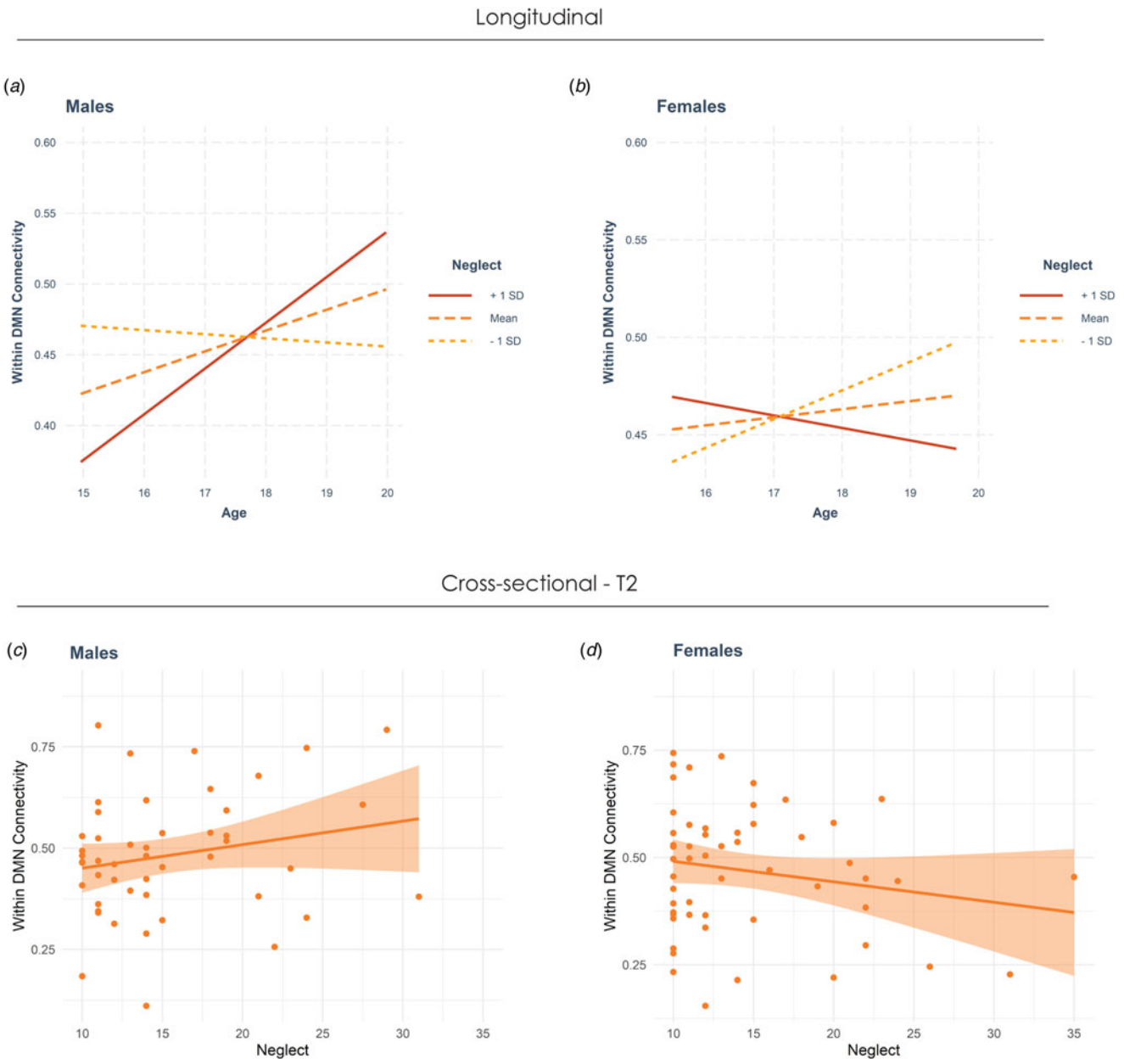

Fig. 4. Sex differences in neglect-associated changes in within-DMN connectivity in males (*a*) and females (*b*). The slopes represent the average trajectories for groups based on + 1s.d., mean, and −1s.d. of abuse and neglect scores. Of note, sex was binary variable with females coded as 1 and males as 0. Males and change in within-DMN connectivity: $B = 0.004$, s.e. = 0.002, $p = 0.04$; females and change in within-DMN connectivity: $B = -0.002$, s.e. = 0.002, 0 = 0.163. Cross-sectional relationships are represented for neglect and within-DMN connectivity for males and females at time 2 (*c*, *d*). Sex was found to moderate the relationship between neglect and within-DMN connectivity at T2 [$R^2 = 0.072$, $F_{(5,96)} = 1.233$, $B = -0.01$, $p = 0.042$]. Findings with participants excluded based on FD > 0.2 mm: neglect and within DMN: $R^2 = 0.0001$, $F_{(5,86)} = 1.01$, $B = -0.008$, $t = -1.493$, $p = 0.139$.

differences were not investigated in these prior studies, and so a positive association between neglect and within DMN connectivity in males could be masked if sex differences are not investigated. Although it is unknown why findings were specific to males, it is of note that sex differences in the neurobiological consequences of maltreatment have been highlighted in the literature (Bath, 2020; Helpman et al., 2017). Previous work has also reported early life stress-associated differences in rsFC to be moderated by sex (Burghy et al., 2012; Herringa et al., 2013). Several studies have also reported male-specific alterations in brain structure as a function of maltreatment (De Bellis & Keshavan, 2003; De Bellis et al., 2015; Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010; Karl et al., 2006; Samplin, Ikuta, Malhotra, Szeszko, & DeRosse, 2013; Whittle et al., 2016); however, work on sex differences in FC has been less common (McLaughlin et al., 2019). Of note, however, in a recent analysis of the sample reported here, we reported male-specific maltreatment-associated alterations in limbic circuitry (Rakesh et al., 2021). These results provide evidence to support the differential impact of early life adversity on males and females, and highlight the importance of examining sex differences in future work (Bath, 2020).

Importantly, we found that change in within-SN connectivity mediated the relationship between childhood maltreatment (both abuse and neglect) and lower problematic substance use at T2.

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

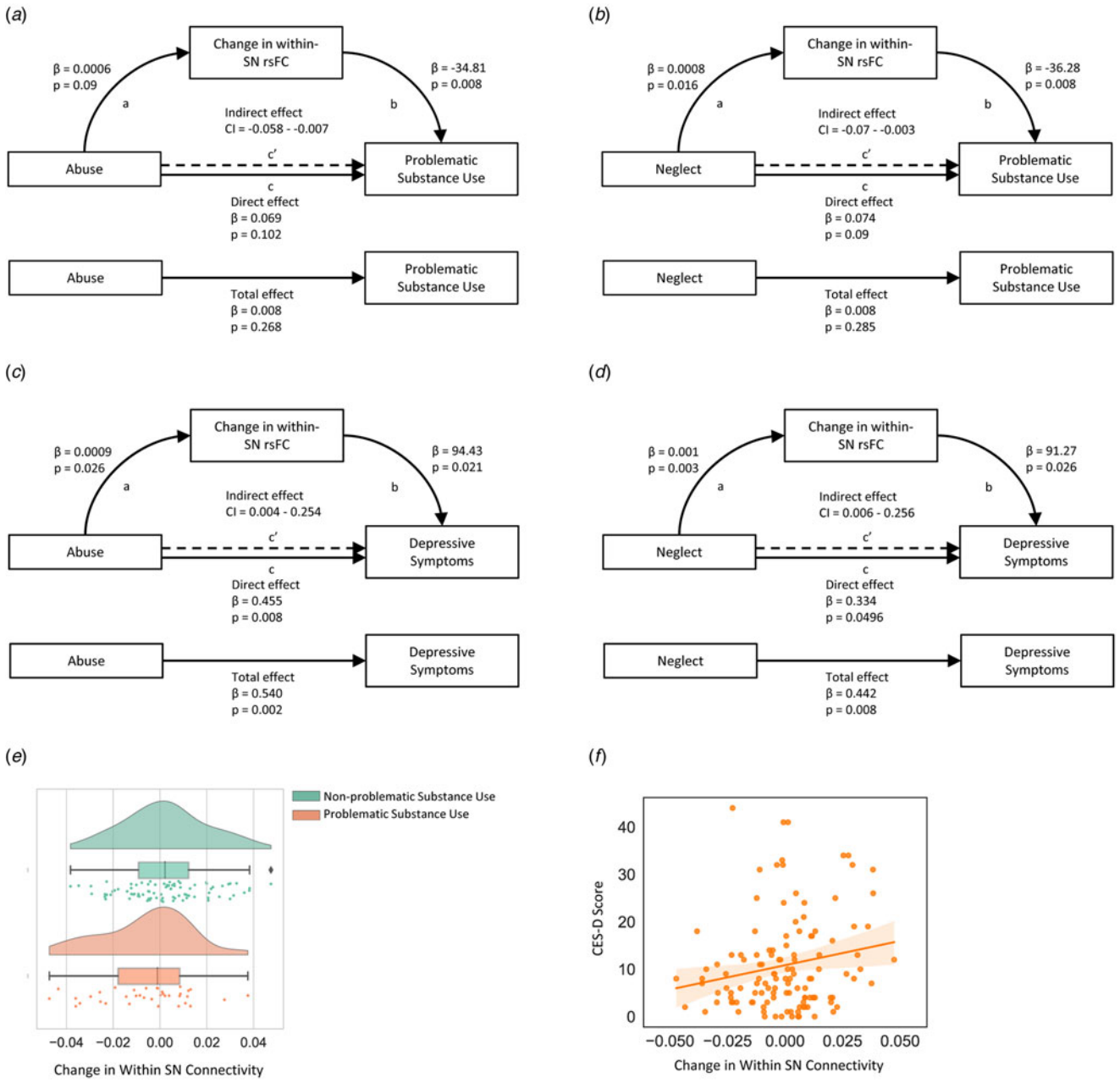

Fig. 5. Mediation model for (*a*) abuse (reported during early adolescence) predicting problematic substance use at late adolescence, (*b*) neglect (reported during early adolescence) predicting problematic substance use at late adolescence, through change in within-SN connectivity from mid- to late-adolescence. Mediation model for (*c*) abuse (reported during early adolescence) predicting depressive symptoms at late adolescence, (*d*) neglect (reported during early adolescence) predicting depressive symptoms at late adolescence, through change in within-SN connectivity from mid- to late-adolescence. Statistical values reported in (*c*) and (*d*) are from the sample excluding participants with FD > 0.2 mm. (*e*) Raincloud plot for the slope of change in within-SN connectivity for problematic substance use and non-problematic substance use groups (path b). (*f*) Association between the slope of change in within-SN connectivity and CES-D scores (path b).

The direction of this effect was unexpected and inconsistent with our hypotheses; however, the SN, and in particular the insula, has been heavily implicated in substance use and addiction (Droutman, Read, & Bechara, 2015). Indeed, studies have consistently shown substance-use/dependence-associated reductions in insula volume and reduced activation during affective and decision-making tasks (Gilman & Hommer, 2008; Kim et al., 2011; Rakesh, Allen, & Whittle, 2020a; Stewart et al., 2014) in adults and adolescents. Recent work from our group has also shown insula hypoconnectivity to be associated with substance use disorder in adolescents (Rakesh et al., 2020b). Although the direction of our findings may seem somewhat counter-intuitive, they could be interpreted to reflect a resilience or protective mechanism. Specifically, the SN is also considered to be a hub for the integration of affective information (such as reward). Previous work has reported trauma-associated increased connectivity within the SN, and higher within-SN connectivity to be associated with reduced reward sensitivity in youth (Marusak, Etkin, & Thomason, 2015) – these results could potentially explain our finding of abuse and neglect-associated increases in within-SN connectivity contributing to lower problematic substance use [associated with higher reward sensitivity

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

(Kim-Spoon et al., 2016)] during late adolescence. Thus, increased integration within the salience system as a function of abuse and neglect could reflect an adaptive or compensatory mechanism in maltreated individuals, and may act as a neuroprotective factor against the development of problematic substance use during adolescence.

Furthermore, in the subsample with stricter thresholding for motion, we also found increases in within-SN rsFC to mediate the association between abuse/neglect and higher depressive symptoms. Regions of the SN have been consistently implicated in both substance use and depression in youth (Droutman et al., 2015; Lee et al., 2019; Rakesh et al., 2020a). We speculate that maltreatment-associated increases in within-SN connectivity may dampen reward sensitivity, and decrease the likelihood of adolescents engaging in risky but rewarding behaviors such as substance use, and at the same time increase the risk for depression, which is associated with low reward function (Forbes & Dahl, 2012). We did not find such a relationship with anxiety, which may highlight that this relationship is specific to reward-associated behavioral/psychopathological outcomes (i.e. depression and substance use). However, given that this finding was not found in the whole sample, we make these interpretations very cautiously. Given no differences between the full sample and subsample (with stricter motion thresholding) in key demographic and maltreatment variables, the reason for the difference in findings is challenging to comment on; however, we speculate that it could be because of the differences in average head motion.

While this study has strengths, including the longitudinal design, some limitations must be considered. First, as noted above, our sample was from the community and did not have a large number of people who have experienced significant abuse or neglect, which may have made it difficult to tease apart their distinct neurobiological consequences. Second, childhood maltreatment was self-reported retrospectively, and thus could have been impacted by recall bias; however, subjective self-reported maltreatment has recently been shown to be reliable in predicting psychopathology (Danese & Widom, 2020). Third, sex differences could be a result of differences in pubertal trajectories, which have previously been linked to neurodevelopment (Chahal et al., 2018). Future longitudinal work should account for pubertal stage and development in analyses. Fourth, reconciling findings with past work was challenging, as our review of the literature and our Discussion was limited by the fact that researchers have only recently begun to make consistent efforts to investigate the effects of abuse and neglect on brain development separately, particularly for rsFC. Fifth, our study only examined specific resting-state networks of interest (i.e. the SN, ECN, and DMN); however, several other regions and individual connections not examined here could potentially be impacted differentially by abuse and neglect. For example, abuse has been suggested to specifically impact the development of affective circuits (e.g. amygdala-mPFC) (Cisler, 2017; Cisler et al., 2013; Thomason et al., 2014), and deprivation likely preferentially sculpts reward circuitry (e.g. fronto-striatal circuitry) (Goff et al., 2013; Hanson, Hariri, & Williamson, 2015a; Mehta et al., 2010), which is considered significant for both depression and substance use (Baskin-Sommers & Foti, 2015). The differential impact of abuse and neglect on the development of these connections remains an open question for future work. Sixth, mediation without entirely temporally separated variables has limitations (Maxwell & Cole, 2007; Maxwell, Cole, & Mitchell, 2011) and there was overlap between when outcome variables were well collected and when the second imaging scan was conducted. Future work should explore mechanistic links between abuse, neglect, and psychopathology using extended longitudinal designs and completely temporally separated variables. , (Maxwell & Cole, 2007; Maxwell et al., 2011) Seventh, it is also plausible that there could have been ongoing maltreatment between when maltreatment was measured (age 14) and when the scans were taken (age 16 and age 19). This could have confounded some of the relationships that were measured. Future work should also examine relationships between maltreatment experienced at different points in development and change in connectivity. Finally, the present study did not have enough power to examine the impact of the age at which maltreatment was experienced. Future longitudinal work should investigate this in more detail.

In sum, the present study extends the current literature by demonstrating links between childhood maltreatment, and connectivity of the salience and DMNs. It also sheds light on potential neurobiological mechanisms for problematic substance use and risk for depression. Our findings show that childhood maltreatment has long-term effects on neurodevelopment, particularly on systems underlying salience processing and emotion regulation. Notably, our findings are largely consistent with DMAP, but suggest that abuse and neglect impact similar as well as distinct neural circuitry. These findings have implications for our understanding of the underlying neurobiological mechanisms of how childhood maltreatment may affect the risk for mental health problems. The present study highlights the importance of understanding early markers of risk and resilience in order to guide prevention efforts.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721003135

Financial support. This study was funded by the Colonial Foundation, the National Health and Medical Research Council (NHMRC; Australia; Program Grant 350241), and the Australian Research Council (ARC; Discovery Grants DP0878136 and DP109 2637). DR was supported by a Melbourne Research Scholarship (MRS; University of Melbourne). SW was supported by an NHMRC Career Development Fellowship (ID: 1125504).

Conflict of interest. The authors report no biomedical financial interests or potential conflicts of interest.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Baskin-Sommers, A. R., & Foti, D. (2015). Abnormal reward functioning across substance use disorders and major depressive disorder: Considering reward as a transdiagnostic mechanism. *International Journal of Psychophysiology*, *98* (2), 227–239. https://doi.org/10.1016/j.ijpsycho.2015.01.011.

Bath, K. G. (2020). Synthesizing views to understand sex differences in response to early life adversity. *Trends in Neurosciences*, *43*(5), 300–310. https://doi.org/10.1016/j.tins.2020.02.004.

Bavelier, D., Newman, A. J., Mukherjee, M., Hauser, P., Kemeny, S., Braun, A., & Boutla, M. (2008). Encoding, rehearsal, and recall in signers and speakers: Shared network but differential engagement. *Cerebral Cortex*, *18*(10), 2263–2274. https://doi.org/10.1093/cercor/bhm248.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897. https://doi.org/10.1037/0022-006X.56.6.893.

Benjamini, Y., & Hochberg, Y. (1995). Benjamini-1995.pdf. *Journal of the Royal Statistical Society B*, *57*, 289–300. https://doi.org/10.2307/2346101.

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., … Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry*, *151* (8), 1132–1136. https://doi.org/10.1176/ajp.151.8.1132.

Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. A., … Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nature Neuroscience*, *15* (12), 1736–1741. https://doi.org/https://dx.doi.org/10.1038/nn.3257.

Callaghan, B. L., & Tottenham, N. (2016). The stress acceleration hypothesis: Effects of early-life adversity on emotion circuits and behavior. *Current Opinion in Behavioral Sciences*, *7*, 76–81. https://doi.org/10.1016/j.cobeha.2015.11.018.

Chahal, R., Vilgis, V., Grimm, K. J., Hipwell, A. E., Forbes, E. E., Keenan, K., & Guyer, A. E. (2018). Girls' pubertal development is associated with white matter microstructure in late adolescence. *NeuroImage*, *181*, 659–669. https://doi.org/10.1016/j.neuroimage.2018.07.050.

Choe, A. S., Jones, C. K., Joel, S. E., Muschelli, J., Belegu, V., Caffo, B. S., … Pekar, J. J. (2015). Reproducibility and temporal structure in weekly resting-state fMRI over a period of 3.5 years. *PLoS ONE*, *10*(10), e0140134. https://doi.org/10.1371/journal.pone.0140134.

Cisler, J. (2017). Childhood trauma and functional connectivity between amygdala and medial prefrontal cortex: A dynamic functional connectivity and large-scale network perspective. *Frontiers in Systems Neuroscience*, *11*, 29. https://doi.org/10.3389/fnsys.2017.00029.

Cisler, J. M., James, G. A., Tripathi, S., Mletzko, T., Heim, C., Hu, X. P., … Kilts, C. D. (2013). Differential functional connectivity within an emotion regulation neural network among individuals resilient and susceptible to the depressogenic effects of early life stress. *Psychological Medicine*, *43*(3), 507–518. https://doi.org/10.1017/S0033291712001390.

Danese, A., & Widom, C. S. (2020). Objective and subjective experiences of child maltreatment and their relationships with psychopathology. *Nature Human Behaviour*, *4*(8), 811–818.

De Bellis, M. D., Hooper, S. R., Chen, S. D., Provenzale, J. M., Boyd, B. D., Glessner, C. E., … Woolley, D. P. (2015). Posterior structural brain volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. *Development and Psychopathology*, *27*(4 Pt 2), 1555–1576. https://doi.org/10.1017/S0954579415000942.

De Bellis, M. D., & Keshavan, M. S. (2003). Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. *Neuroscience and Biobehavioral Reviews*, *27*(1–2), 103–117. https://doi.org/10.1016/S0149-7634(03)00013-7.

Dennison, M. J., Rosen, M. L., Sambrook, K. A., Jenness, J. L., Sheridan, M. A., & McLaughlin, K. A. (2019). Differential associations of distinct forms of childhood adversity with neurobehavioral measures of reward processing: A developmental pathway to depression. *Child Development*, *90*(1), e96–e113. https://doi.org/10.1111/cdev.13011.

DiMartino, A., Fair, D. A., Kelly, C., Satterthwaite, T. D., Castellanos, F. X., Thomason, M. E., … Milham, M. P. (2014). Unraveling the miswired connectome: A developmental perspective. *Neuron*, *83*(6), 1335–1353. https://doi.org/10.1016/j.neuron.2014.08.050.

Ding, H., Ming, D., Wan, B., Li, Q., Qin, W., & Yu, C. (2016). Enhanced spontaneous functional connectivity of the superior temporal gyrus in early deafness. *Scientific Reports*, *6*(1), 1–11. https://doi.org/10.1038/srep23239.

Droutman, V., Read, S. J., & Bechara, A. (2015). Revisiting the role of the insula in addiction. *Trends in Cognitive Sciences*, *19*(7), 414–420. https://doi.org/10.1016/j.tics.2015.05.005.

Dumontheil, I. (2016). Adolescent brain development. *Current Opinion in Behavioral Sciences*, *10*, 39–44. https://doi.org/10.1016/j.cobeha.2016.04.012.

Edmiston, E. E., Wang, F., Mazure, C. M., Guiney, J., Sinha, R., Mayes, L. C., & Blumberg, H. P. (2011). Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Archives of Pediatrics and Adolescent Medicine*, *165*(12), 1069–1077. https://doi.org/10.1001/archpediatrics.2011.565.

Ernst, M., Torrisi, S., Balderston, N., Grillon, C., & Hale, E. A. (2015). fMRI functional connectivity applied to adolescent neurodevelopment. *Annual Review of Clinical Psychology*, *11*(1), 361–377. https://doi.org/10.1146/annurev-clinpsy-032814-112753.

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., … Gorgolewski, K. J. (2019). fMRIPrep: A robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111–116. https://doi.org/10.1038/s41592-018-0235-4.

Fair, D. A., Nigg, J. T., Iyer, S., Bathula, D., Mills, K. L., Dosenbach, N. U. F. F., … Milham, M. P. (2013). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*(Feb), 1–31. https://doi.org/10.3389/fnsys.2012.00080.

Forbes, E. E., & Dahl, R. E. (2012). Research review: Altered reward function in adolescent depression: What, when and how? *Journal of Child Psychology and Psychiatry*, *53*(1), 3–15. https://doi.org/http://dx.doi.org/10.1111/j.1469-7610.2011.02477.x.

Fox, M. D., & Greicius, M. (2010). Clinical applications of resting state functional connectivity. *Frontiers in Systems Neuroscience*, *4*, 19. https://doi.org/10.3389/fnsys.2010.00019.

Frodl, T., Reinhold, E., Koutsouleris, N., Reiser, M., & Meisenzahl, E. M. (2010). Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. *Journal of Psychiatric Research*, *44*(13), 799–807. https://doi.org/10.1016/j.jpsychires.2010.01.006.

Gibbons, R. D., Hedeker, D., & DuToit, S. (2010). Advances in analysis of longitudinal data. *Annual Review of Clinical Psychology*, *6*(1), 79–107. https://doi.org/10.1146/annurev.clinpsy.032408.153550.

Gilman, J. M., & Hommer, D. W. (2008). Modulation of brain response to emotional images by alcohol cues in alcohol-dependent patients. *Addiction Biology*, *13*(3–4), 423–434. https://doi.org/10.1111/j.1369-1600.2008.00111.x.

Goff, B., Gee, D. G., Telzer, E. H., Humphreys, K. L., Gabard-Durnam, L., Flannery, J., & Tottenham, N. (2013). Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience*, *249*, 129–138. https://doi.org/10.1016/j.neuroscience.2012.12.010.

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. *Archives of General Psychiatry*, *67*(2), 113–123. https://doi.org/10.1001/archgenpsychiatry.2009.186.

Hanson, J. L., Chung, M. K., Avants, B. B., Shirtcliff, E. A., Gee, J. C., Davidson, R. J., & Pollak, S. D. (2010). Early stress is associated with alterations in the orbitofrontal cortex: A tensor-based morphometry investigation of brain structure and behavioral risk. *Journal of Neuroscience*, *30*(22), 7466–7472. https://doi.org/10.1523/JNEUROSCI.0859-10.2010.

Hanson, J. L., Hariri, A. R., & Williamson, D. E. (2015a). Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. *Biological Psychiatry*, *78*(9), 598–605. https://doi.org/10.1016/j.biopsych.2015.05.010.

Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., … Davidson, R. J. (2015b). Behavioral problems after early life stress: Contributions of the hippocampus and amygdala. *Biological Psychiatry*, *77*(4), 314–323. https://doi.org/10.1016/j.biopsych.2014.04.020.

Hart, H., Lim, L., Mehta, M. A., Simmons, A., Mirza, K. A. H., & Rubia, K. (2018). Altered fear processing in adolescents with a history of severe childhood maltreatment: An fMRI study. *Psychological Medicine*, *48*(7), 1092–1101. https://doi.org/10.1017/S0033291716003585.

Hayes, A. F. (2018). *Introduction to mediation, moderation, and conditional process analysis: A regession approach*. https://www.guilford.com/books/Introduction-to-Mediation-Moderation-and-Conditional-Process-Analysis/Andrew-Hayes/9781462534654.

Helpman, L., Zhu, X., Suarez-Jimenez, B., Lazarov, A., Monk, C., & Neria, Y. (2017). Sex differences in trauma-related psychopathology: A critical review of neuroimaging literature (2014–2017). *Current Psychiatry Reports*, *19*, 1–13. https://doi.org/10.1007/s11920-017-0854-y.

Herringa, R. J., Birn, R. M., Ruttle, P. L., Burghy, C. A., Stodola, D. E., Davidson, R. J., & Essex, M. J. (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press

adolescence. *Proceedings of the National Academy of Sciences of the USA*, *110*(47), 19119–19124. https://doi.org/10.1073/pnas.1310766110.

Herting, M. M., Gautam, P., Chen, Z., Mezher, A., & Vetter, N. C. (2018). Test-retest reliability of longitudinal task-based fMRI: Implications for developmental studies. *Developmental Cognitive Neuroscience*, *33*, 17–26. https://doi.org/10.1016/j.dcn.2017.07.001.

Ho, T. C., Dennis, E. L., Thompson, P. M., & Gotlib, I. H. (2018). Network-based approaches to examining stress in the adolescent brain. *Neurobiology of Stress*, *8*, 147–157. https://doi.org/10.1016/j.ynstr.2018.05.002.

Karl, A., Schaefer, M., Malta, L. S., Dörfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience and Biobehavioral Reviews*, *30*(7), 1004–1031. https://doi.org/10.1016/j.neubiorev.2006.03.004.

Kelly, C., Biswal, B. B., Craddock, R. C., Castellanos, F. X., & Milham, M. P. (2012). Characterizing variation in the functional connectome: Promise and pitfalls. *Trends in Cognitive Sciences*, *16*(3), 181–188. https://doi.org/10.1016/j.tics.2012.02.001.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey. *Archives of General Psychiatry*, *62*, 593–602. https://doi.org/10.1001/archpsyc.62.6.593.

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO world mental health surveys. *British Journal of Psychiatry*, *197*(5), 378–385. https://doi.org/10.1192/bjp.bp.110.080499.

Kim-Spoon, J., Deater-Deckard, K., Holmes, C., Lee, J., Chiu, P., & King-Casas, B. (2016). Behavioral and neural inhibitory control moderates the effects of reward sensitivity on adolescent substance use. *Neuropsychologia*, 318–326. https://doi.org/10.1016/j.neuropsychologia.2016.08.028.

Kim, Y.-T., Song, H.-J., Seo, J.-H., Lee, J.-J., Lee, J., Kwon, D.-H., … Chang, Y. (2011). The differences in neural network activity between methamphetamine abusers and healthy subjects performing an emotion-matching task: Functional MRI study. *NMR in Biomedicine*, *24*(10), 1392–1400. https://doi.org/10.1002/nbm.1702.

Kumar, A., Behen, M. E., Singsoonsud, P., Veenstra, A. L., Wolfe-Christensen, C., Helder, E., & Chugani, H. T. (2014). Microstructural abnormalities in language and limbic pathways in orphanage-reared children. *Journal of Child Neurology*, *29*(3), 318–325. https://doi.org/10.1177/0883073812474098.

Lambert, H. K., King, K. M., Monahan, K. C., & McLaughlin, K. A. (2017). Differential associations of threat and deprivation with emotion regulation and cognitive control in adolescence. *Development and Psychopathology*, *29*(3), 929–940. https://doi.org/10.1017/S0954579416000584.

Lee, J., Pavuluri, M. N., Kim, J. H., Suh, S., Kim, I., & Lee, M. S. (2019). Resting-state functional connectivity in medication-naïve adolescents with major depressive disorder. *Psychiatry Research – Neuroimaging*, *288*, 37–43. https://doi.org/10.1016/j.pscychresns.2019.04.008.

Liu, L., Yuan, C., Ding, H., Xu, Y., Long, M., Li, Y., … Yu, C. (2017). Visual deprivation selectively reshapes the intrinsic functional architecture of the anterior insula subregions. *Scientific Reports*, *7*(1), 1–11. https://doi.org/10.1038/srep45675.

Marstaller, L., Fynes-Clinton, S., Burianová, H., & Reutens, D. C. (2021). Salience and default-mode network connectivity during threat and safety processing in older adults. *Human Brain Mapping*, *42*(1), 14–23. https://doi.org/10.1002/hbm.25199.

Martin, S. (2015). Comment on 'Behavioral problems after early life stress: Contributions of the hippocampus and amygdala'. *Journal of the American Psychoanalytic Association*, *63*(6), 1244–1246. https://doi.org/http://dx.doi.org/10.1177/0003065115620405.

Marusak, H. A., Etkin, A., & Thomason, M. E. (2015). Disrupted insula-based neural circuit organization and conflict interference in trauma-exposed youth. *NeuroImage: Clinical*, *8*, 516–525. https://doi.org/10.1016/j.nicl.2015.04.007.

Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods*, *12*(1), 23–44. https://doi.org/10.1037/1082-989X.12.1.23.

Maxwell, S. E., Cole, D. A., & Mitchell, M. A. (2011). Bias in cross-sectional analyses of longitudinal mediation: Partial and complete mediation under an autoregressive model. *Multivariate Behavioral Research*, *46*(5), 816–841. https://doi.org/10.1080/00273171.2011.606716.

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond cumulative risk: A dimensional approach to childhood adversity. *Current Directions in Psychological Science*, *25*(4), 239–245. https://doi.org/10.1177/0963721416655883.

McLaughlin, K. A., Sheridan, M. A., Gold, A. L., Duys, A., Lambert, H. K., Peverill, M., … Pine, D. S. (2016). Maltreatment exposure, brain structure, and fear conditioning in children and adolescents. *Neuropsychopharmacology*, *41*(8), 1956–1964. https://doi.org/10.1038/npp.2015.365.

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews*, *47*, 578–591. https://doi.org/10.1016/j.neubiorev.2014.10.012.

McLaughlin, K. A., Sheridan, M. A., & Nelson, C. A. (2017). Neglect as a violation of species-expectant experience: Neurodevelopmental consequences. *Biological Psychiatry*, *82*(7), 462–471. https://doi.org/10.1016/j.biopsych.2017.02.1096.

McLaughlin, K. A., Weissman, D., & Bitrán, D. (2019). Childhood adversity and neural development: A systematic review. *Annual Review of Developmental Psychology*, *1*(1), 277–312. https://doi.org/10.1146/annurev-devpsych-121318-084950.

Mehta, M. A., Gore-Langton, E., Golembo, N., Colvert, E., Williams, S. C. R., & Sonuga-Barke, E. (2010). Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *Journal of Cognitive Neuroscience*, *22*(10), 2316–2325. https://doi.org/10.1162/jocn.2009.21394.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure & Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0.

Plichta, M. M., Schwarz, A. J., Grimm, O., Morgen, K., Mier, D., Haddad, L., … Meyer-Lindenberg, A. (2012). Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. *NeuroImage*, *60*(3), 1746–1758. https://doi.org/10.1016/j.neuroimage.2012.01.129.

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018.

Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage*, *112*, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064.

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306.

Rakesh, D., Allen, N. B., & Whittle, S. (2020a). Balancing act: Neural correlates of affect dysregulation in youth depression and substance use – A systematic review of functional neuroimaging studies. *Developmental Cognitive Neuroscience*, *42*, 100775. https://doi.org/10.1016/j.dcn.2020.100775.

Rakesh, D., Kelly, C., Vijayakumar, N., Zalesky, A., Allen, N. B., & Whittle, S. (2021). Unraveling the consequences of childhood maltreatment: Deviations from typical functional neurodevelopment mediate the relationship between maltreatment history and depressive symptoms. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(3), 329–342. https://doi.org/10.1016/j.bpsc.2020.09.016.

Rakesh, D., Lv, J., Zalesky, A., Allen, N. B., Lubman, D. I., Yücel, M., … Whittle, S. (2020b). Altered resting functional connectivity patterns associated with problematic substance use and substance use disorders during adolescence. *Journal of Affective Disorders*, *279*, 599–608. https://doi.org/10.1016/j.jad.2020.10.051.

Rakesh, D., Seguin, C., Zalesky, A., Cropley, V., & Whittle, S. (2021). Associations between neighborhood disadvantage, resting-state functional connectivity, and behavior in the Adolescent Brain Cognitive Development (ABCD) Study®: Moderating role of positive family and school environments. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2021.03.008.

Samplin, E., Ikuta, T., Malhotra, A. K., Szeszko, P. R., & DeRosse, P. (2013). Sex differences in resilience to childhood maltreatment: Effects of trauma history on hippocampal volume, general cognition and subclinical psychosis

in healthy adults. *Journal of Psychiatric Research*, *47*(9), 1174–1179. https://doi.org/10.1016/j.jpsychires.2013.05.008.

Satterthwaite, T. D., Ciric, R., Roalf, D. R., Davatzikos, C., Bassett, D. S., & Wolf, D. H. (2019). Motion artifact in studies of functional connectivity: Characteristics and mitigation strategies. *Human Brain Mapping*, *40*(7), 2033–2051. https://doi.org/10.1002/hbm.23665.

Satterthwaite, T. D., Wolf, D. H., Loughead, J., Ruparel, K., Elliott, M. A., Hakonarson, H., … Gur, R. E. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. *NeuroImage*, *60*(1), 623–632. https://doi.org/10.1016/j.neuroimage.2011.12.063.

Saxbe, D., Khoddam, H., Del Piero, L., Stoycos, S. A., Gimbel, S. I., Margolin, G., & Kaplan, J. T. (2018). Community violence exposure in early adolescence: Longitudinal associations with hippocampal and amygdala volume and resting state connectivity. *Developmental Science*, *21*(6), 1–11. https://doi.org/http://dx.doi.org/10.1111/desc.12686.

Scher, C. D., Stein, M. B., Asmundson, G. J. G., Mccreary, D. R., & Forde, D. R. (2001). The childhood trauma questionnaire in a community sample: Psychometric properties and normative data. *Journal of Traumatic Stress*, *14*(4), 843–857. https://doi.org/10.1023/A:1013058625719.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007.

Sheridan, M. A., & McLaughlin, K. A. (2014). Dimensions of early experience and neural development: Deprivation and threat. *Trends in Cognitive Sciences*, *18*(11), 580–585. https://doi.org/10.1016/j.tics.2014.09.001.

Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, *22*(1), 158–165. https://doi.org/10.1093/cercor/bhr099.

Silvers, J. A., Lumian, D. S., Gabard-Durnam, L., Gee, D. G., Goff, B., Fareri, D. S., … Tottenham, N. (2016). Previous institutionalization is followed by broader amygdala–hippocampal–PFC network connectivity during aversive learning in human development. *The Journal of Neuroscience*, *36*(24), 6420–6430. https://doi.org/10.1523/JNEUROSCI.0038-16.2016.

Sripada, R. K., Swain, J. E., Evans, G. W., Welsh, R. C., & Liberzon, I. (2014). Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. *Neuropsychopharmacology*, *39*(9), 2244–2251. https://doi.org/10.1038/npp.2014.75.

Stevens, M. C. (2016). The contributions of resting state and task-based functional connectivity studies to our understanding of adolescent brain network maturation. *Neuroscience and Biobehavioral Reviews*, *70*, 13–32. https://doi.org/10.1016/j.neubiorev.2016.07.027.

Stevens, M. C., Pearlson, G. D., & Calhoun, V. D. (2009). Changes in the interaction of resting-state neural networks from adolescence to adulthood. *Human Brain Mapping*, *30*(8), 2356–2366. https://doi.org/10.1002/hbm.20673.

Stewart, J. L., May, A. C., Poppa, T., Davenport, P. W., Tapert, S. F., & Paulus, M. P. (2014). You are the danger: Attenuated insula response in methamphetamine users during aversive interoceptive decision-making. *Drug and Alcohol Dependence*, *142*, 110–119. https://doi.org/10.1016/j.drugalcdep.2014.06.003.

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews Neuroscience*, *17*(10), 652–666. https://doi.org/10.1038/nrn.2016.111.

Thomason, M. E., Marusak, H. A., Tocco, M. A., Vila, A. M., McGarragle, O., & Rosenberg, D. R. (2014). Altered amygdala connectivity in urban youth exposed to trauma. *Social Cognitive and Affective Neuroscience*, *10*(11), 1460–1468. https://doi.org/10.1093/scan/nsv030.

Tottenham, N., Hare, T. A., Millner, A., Gilhooly, T., Zevin, J. D., & Casey, B. J. (2011). Elevated amygdala response to faces following early deprivation. *Developmental Science*, *14*(2), 190–204. https://doi.org/10.1111/j.1467-7687.2010.00971.x.

Truelove-hill, M., Erus, G., Bashyam, V., Varol, E., Sako, C., Gur, R. C., … Davatzikos, C. (2020). A multidimensional neural maturation index reveals reproducible developmental patterns in children and adolescents. *Journal of Neuroscience*, 40(6), 1265–1275.

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience*, *16*(1), 55–61. https://doi.org/10.1038/nrn3857.

Van der Werff, S. J. A., Pannekoek, J. N., Veer, I. M., van Tol, M. J., Aleman, A., Veltman, D. J., … van der Wee, N. J. A. (2013). Resilience to childhood maltreatment is associated with increased resting-state functional connectivity of the salience network with the lingual gyrus. *Child Abuse and Neglect*, *37*(11), 1021–1029. https://doi.org/10.1016/j.chiabu.2013.07.008.

Walker, E. A., Gelfand, A., Katon, W. J., Koss, M. P., Von Korff, M., Bernstein, D., & Russo, J. (1999). Adult health status of women with histories of childhood abuse and neglect. *American Journal of Medicine*, *107*(4), 332–339. https://doi.org/10.1016/S0002-9343(99)00235-1.

Wechler, D. (2003). *Wechsler intelligence scale for children* (4th ed.). San Antonio, TX: Harcourt Assessment.

Weissman, D. G., Conger, R. D., Robins, R. W., Hastings, P. D., & Guyer, A. E. (2018). Income change alters default mode network connectivity for adolescents in poverty. *Developmental Cognitive Neuroscience*, *30*, 93–99. https://doi.org/10.1016/j.dcn.2018.01.008.

Whittle, S., Vijayakumar, N., Dennison, M., Schwartz, O., Simmons, J. G., Sheeber, L., & Allen, N. B. (2016). Observed measures of negative parenting predict brain development during adolescence. *PLoS ONE*, *11*(1), 1–15. https://doi.org/10.1371/journal.pone.0147774.

Whittle, S., Yap, M. B. H., Yucel, M., Fornito, A., Simmons, J. G., Barrett, A., … Allen, N. B. (2008). Prefrontal and amygdala volumes are related to adolescents' affective behaviors during parent-adolescent interactions. *Proceedings of the National Academy of Sciences*, *105*(9), 3652–3657. https://doi.org/10.1073/pnas.0709815105.

https://doi.org/10.1017/S0033291721003135 Published online by Cambridge University Press