Development and Psychopathology (2024), **36**, 1698–1708
doi:10.1017/S0954579423001013

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Regular Article

Transdiagnostic indicators predict developmental changes in cognitive control resting-state networks

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Abstract

Over the past decade, transdiagnostic indicators in relation to neurobiological processes have provided extensive insight into youth's risk for psychopathology. During development, exposure to childhood trauma and dysregulation (i.e., so-called AAA symptomology: anxiety, aggression, and attention problems) puts individuals at a disproportionate risk for developing psychopathology and altered network-level neural functioning. Evidence for the latter has emerged from resting-state fMRI studies linking mental health symptoms and aberrations in functional networks (e.g., cognitive control (CCN), default mode networks (DMN)) in youth, although few of these investigations have used longitudinal designs. Herein, we leveraged a three-year longitudinal study to identify whether traumatic exposures and concomitant dysregulation trigger changes in the developmental trajectories of resting-state functional networks involved in cognitive control ($N = 190$; 91 females; time 1 $M_{age} = 11.81$). Findings from latent growth curve analyses revealed that greater trauma exposure predicted increasing connectivity between the CCN and DMN across time. Greater levels of dysregulation predicted reductions in within-network connectivity in the CCN. These findings presented in typically developing youth corroborate connectivity patterns reported in clinical populations, suggesting there is predictive utility in using transdiagnostic indicators to forecast alterations in resting-state networks implicated in psychopathology.

Keywords: fMRI; brain development; trauma; developmental psychopathology

(Received 17 January 2023; revised 26 July 2023; accepted 26 July 2023; First Published online 24 August 2023)

Introduction

In recent years, transdiagnostic processes have been highlighted as providing potent links between childhood traumatic experiences and subsequent psychopathology (McLaughlin et al., 2020). There is consistent evidence that childhood traumatic exposures put individuals at an elevated risk of developing anxiety, depression, substance use disorders, and post-traumatic stress disorders (Buckingham & Daniolos, 2013; Gur et al., 2019; Mills et al., 2013). Moreover, an overlapping literature has shown that such traumatic experiences affect resting-state functional connectivity within key neural networks associated with transdiagnostic markers (e.g., cognitive control, emotion dysregulation, irritability; Barch, 2017; Beauchaine & Cicchetti, 2019; Demir-Lira et al., 2016; Klein et al., 2021; McTeague et al., 2016) known to predict poor outcomes (Lu et al., 2017; Luo et al., 2022; Stone et al., 2018). By and large, this work has had limitations in sample size, use of cross-sectional designs, and retrospective adult reporting. The current study addressed these limitations by employing a longitudinal design in youth to interrogate whether traumatic experiences and concomitant transdiagnostic processes (i.e., dysregulation) alter developmental trajectories of key resting-state functional networks (e.g., cognitive/executive control network (CCN), default mode network (DMN)).

Much of the literature linking trauma and aberrant functional connectivity has focused on resting-state activity. These studies have yielded crucial insights into trauma-related sequalae in neurodevelopment broadly and functional organization of neural networks specifically. Of particular relevance to the current investigation are altered patterns of within- and between-network connectivity in the CCN (i.e., the executive control network, or the fronto-parietal network). The CCN consists of functional connections between hubs in the frontal and posterior parietal cortices and is critical to adaptive engagement in goal-directed behaviors (Seeley et al., 2007; Yeo et al., 2011). Importantly, disruptions in cognitive control and the underlying neural circuitry have previously been implicated in an array of mental health disorders (Sheffield & Barch, 2016; Solomon et al., 2017; Sutcubasi et al., 2020; Williams, 2016), as well as following childhood trauma (Silveira et al., 2020; Wu et al., 2021), underscoring its potential as a transdiagnostic indicator. In individuals with childhood trauma exposure, patterns of CCN functional connectivity are largely

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Cite this article: Picci, G., Petro, N. M., Son, J. J., Agcaoglu, O., Eastman, J. A., Wang, Y.-P., Stephen, J. M., Calhoun, V. D., Taylor, B. K., & Wilson, T. W. (2024). Transdiagnostic indicators predict developmental changes in cognitive control resting-state networks. *Development and Psychopathology* **36**: 1698–1708, https://doi.org/10.1017/S0954579423001013

mixed, with reports of some (Rakesh et al., 2021) or no longitudinal changes in within- or between-network connectivity as a function of trauma exposure (Chahal et al., 2022; Rakesh et al., 2021). Other longitudinal work has highlighted that connectivity patterns of key hubs in the CCN (e.g., intraparietal sulcus) as portending subsequent executive dysfunction and substance misuse in youth following trauma exposure, suggesting predictive ability of CCN hubs in long-term outcomes of major risk factors for psychopathology (Silveira et al., 2020). Cross-sectionally and longitudinally, children with trauma exposure exhibiting lower CCN connectivity seem to be at elevated risk of inflammatory reactivity, suggesting that trauma may induce neurobiological alterations to the stress system, including stress-sensitive regions within the CCN (Miller et al., 2021; Nusslock et al., 2019).

In addition to childhood trauma exposure, dysregulation has been highlighted as a robust predictor of a multitude of psychopathological diagnoses and comorbidities, making it a relevant transdiagnostic risk factor (Althoff & Ametti, 2021). Dysregulation is typically defined as impairments in regulating affect, behavior, and cognition (ABCs), with some evidence for an inverted-U developmental trajectory, with peak symptoms in early adolescence (Deutz et al., 2018). As a behavioral phenotype, it does not fit neatly within classic diagnostic classification systems, as it shares features of both internalizing and externalizing symptomology. The Child Behavior Checklist Dysregulation Profile (CBCL-DP) consists of three symptom subscales, including anxiety/depression, attention problems, and aggression, and is among the most commonly used instruments measuring dysregulation in youth. Specifically, prior studies have shown that as early as preschool age, higher dysregulation symptoms are related to persistent impairments in emotional functioning (e.g., self-regulation; Kim et al., 2012). Longitudinal studies have documented that elevated dysregulation in children is highly predictive of internalizing, externalizing, personality, and substance use disorders, as well as suicidality in adolescence and adulthood, up to 20 years later (Althoff et al., 2010; Halperin et al., 2011; Holtmann et al., 2011; Meyer et al., 2009), suggesting that CBCL-DP carries meaningful transdiagnostic qualities. Thus, interest has grown across the research community in evaluating dysregulation symptoms as a developmental precursor and marker of general psychopathology (Bellani et al., 2012). Despite its clinical relevance, few studies have examined associations between dysregulation symptoms and functional connectivity patterns in the developing brain (McGough et al., 2013), particularly in networks subserving the specific behaviors implicated in dysregulation (e.g., self-control, cognitive control). Although limited, extant findings suggest that otherwise healthy youth with elevated emotional and behavioral dysregulation exhibit altered intrinsic connections among networks thought to serve flexible cognitive control (e.g., ventromedial prefrontal cortex (PFC), insula, anterior cingulate; Hwang et al., 2010). During development, greater dysregulation has been shown to relate to weaker resting-state functional connectivity between a number of regions pertinent to cognitive control, including amygdala to medial PFC (Park et al., 2018), as well as between dorsolateral and ventromedial PFC, (Lopez et al., 2018), and between insular and amygdala regions (Bebko et al., 2015). These findings suggest that there are likely alterations in resting-state connectivity within the CCN that relate to dysregulation, but the extent to which dysregulation is associated with longitudinal aberrations in connectivity within the CCN and other key networks is unknown. Thus, we sought to fill this gap in the literature by examining whether dysregulation symptomology predicts changes in resting-state functional connectivity in these networks.

Existing studies using a developmental lens have made important longitudinal links between psychopathology outcomes in youth and within and between CCN connectivity (Chahal et al., 2022; Rakesh et al., 2021). Despite these contributions, there have yet to be studies examining whether childhood trauma exposure and dysregulation modulate the developmental trajectories of within and between CCN connectivity during development. Moreover, despite associations between trauma and dysregulation, studies modeling these constructs together are limited. In other words, existing work has focused on neurodevelopmental trajectories predicting outcomes, and not how initial levels of potent risk factors forecast changes in CCN connectivity. The current study addressed the latter in an otherwise healthy sample of youth with variability in traumatic exposures and dysregulation behavior using a latent growth modeling approach. In so doing, the present study allowed for rigorous investigation of deviations from typical neurodevelopment associated with two interrelated transdiagnostic indicators of future mental health concerns.

Methods

Participants

A sample of 212 typically developing children and adolescents (106 males) were recruited to participate in the Developmental Chronnecto-Genomics study (Stephen et al., 2021). Of those, a total of 7 participants were excluded due to poor quality T1 structural MRI data, and 15 had unusable or incomplete resting-state fMRI data. Thus, data from a sample of 190 typically-developing children and adolescents with usable eyes-open resting-state fMRI were examined (8–15 years old; $\text{mean}_{\text{age}} = 11.81$ years, SD = 1.73; 91 females). The study was multisite, with 95 participants recruited at the University of Nebraska Medical Center (UNMC) and 95 participants from the Mind Research Network (MRN) for the initial study assessment. Participants were invited back to participate annually for three years (time between visits: $\text{mean}_{\text{time1to2}} = 1.12$ years, SD = 0.20, $\text{mean}_{\text{time2to3}} = 1.09$ years, SD = 0.24). Of the initial sample, 120 and 50 participants completed a usable resting-state fMRI scan for years 2 and 3, respectively. Inclusion criteria included English as a primary language, ages 9–15 at the time of their first visit, and participant and parent willingness to assent/consent. Exclusion criteria were as follows: inability to assent/consent, history of developmental delays and/or psychiatric disorders, history of neurological disorders, history of concussion or head injury, pregnancy, prenatal exposure to drugs, use of medications known to affect brain function, and magnetic resonance imaging (MRI) contraindications.

Ethical considerations

All parents and youth provided written consent and assent, respectively, prior to participating in the study. The appropriate institutional review boards for both study sites approved all study procedures.

Structural and functional MRI data acquisition

Participants underwent a structural T1-weighted magnetic resonance imaging (MRI) scan during each visit (i.e., 3 scans total). Children recruited at UNMC were scanned using a Siemens

https://doi.org/10.1017/S0954579423001013 Published online by Cambridge University Press

3T Skyra scanner and those at MRN were scanned using a Siemens 3T TIM Trio. A 32-channel head coil was used at both sites and all sequences were optimized to minimize inter-site differences. Structural MR images at both sites were acquired with an MPRAGE sequence with the following parameters: TR = 2400 milliseconds; TE = 1.94 milliseconds; flip angle = 8°; FoV = 256 mm; slice thickness = 1 mm (no gap); base resolution = 256; 192 slices; voxel size = 1 mm^3. Eyes-open resting-state multiband fMRI data were also collected during each visit using a standard echo planar BOLD sequence with the following parameters: 650 volumes, TR = 0.46s, TE = 29 ms, FA = 44°, with a slice thickness of 3 mm (no gap); site 1: 48 sequential axial slices with a FOV of 268 × 268 mm (82 × 82 matrix), and site 2: 56 sequential axial slices with a FoV of 246 × 246 mm (82 × 82 matrix).

Functional network connectivity processing

Complete details of the resting-state functional connectivity (rsFC) preprocessing and analysis are reported in Supplementary Materials and recent publications (Agcaoglu et al., 2019, 2020; Taylor et al., 2022). Briefly, scans were corrected for head motion and differences in slice timing, followed by despiking to reduce outliers. Data were warped into Montreal Neurological Institute space, and then rewarped to a study-specific template due to the age range of the participants (Agcaoglu et al., 2019, 2020). Group independent component analysis (ICA; (Calhoun & Adali, 2012) of the preprocessed functional data yielded 150 spatially-independent components, 51 of which were identified as components comprising seven different resting-state networks (RSNs). rsFC was measured as the average Pearson correlation between different RSN time courses. The present study focused on the connectivity within the cognitive control network (CCN) and its connections with default mode network (DMN), sensorimotor (SM), visual (VIS), and auditory (AUD) networks. The CCN was comprised of connectivity among 11 subnetworks across frontal, insular, and parietal regions, as well as several key temporal areas (for complete details of regions, see Supplementary Table S1).

Child behavior checklist

During all three visits, a caregiver completed the Child Behavior Checklist (CBCL, (Achenbach et al., 2001)) to assess their child's dysregulation behaviors over the past 6 months. The dysregulation profile is a summed score of the attention, aggression, and anxious/depressed subscales (Holtmann et al., 2011). Scores from the first visit were used in the primary models and scores from all three visits were used in the alternative models. Raw scores were used in our models, as sex and age were both controlled for in our models.

Trauma history profile

Participants completed the self-report Trauma History Profile (THP), which was derived from the UCLA Post-Traumatic Stress Disorder (PTSD) Reaction Index for DSM IV (Steinberg et al., 2004) and assessed a variety of trauma types and events. Participants endorsed whether they experienced 12 different types of trauma in their lifetime (No = 0, Yes = 1). Example items include: "*was hit, punched, kicked very hard (not play fighting)*", "*in a bad accident, like a serious car accident or fall*", "*had a painful or scary medical treatment*". A summed score of each participants' trauma exposure was used (Figure S1). Information regarding the percentage of participants reporting on each trauma subtype can be found in the Supplemental Material (Figure S2).

Data analytic plan

We first computed descriptive statistics on demographics and all variables of interest. Variables entered into subsequent models were examined for violations of normality (i.e., skewness and kurtosis) and were transformed accordingly. We used ANOVAs and chi-square tests to determine whether participants who discontinued participation during time 2 and 3 were demographically (i.e., age, sex, race, and ethnicity) different from those who completed all 3 timepoints. Next, we fit a series of latent growth curve models (LGCM) to evaluate changes in intrinsic connectivity within and between the CCN across time, and whether these changes were associated with dysregulation symptoms and trauma exposure at time 1. Each set of networks was modeled separately, with 5 final models (i.e., CCN-CCN, CCN-AUD, CCN-SM, CCN-DMN, CCN-VIS). We first fit the base LGCM for change in connectivity across the 3-year period, without control variables. The intercept was defined by intrinsic network connectivity at each time point, constrained to 1. The slope was defined by intrinsic network connectivity to 0, 1, and 2 for timepoints 1, 2, and 3. The next set of models added in sex (0=males, 1=females), age at time 1, and data collection site (0 = UNMC site; 1 = MRN site) as control variables. Latent intercept and slope variables were regressed on all control variables to account for demographic and site differences on the network connectivity measures. The third and final set of models added in the dysregulation and trauma exposure scores from time 1. Total raw scores for both scales were regressed on age, sex, and site to account for potential demographic developmental effects and differences between sites. The latent intercept and slope variables were regressed on the dysregulation and trauma exposure scores and previously added control variables. The dysregulation, trauma scales, and control variables were permitted to freely correlate. All parameters were freely estimated. The final models enabled us to discern whether symptoms and trauma exposure (at time 1) were predictive of the baseline (i.e., intercept) and rate of change (i.e., slope) in intrinsic network connectivity across time.

We also fit an alternative set of models testing the opposite effects whereby time 1 connectivity predicted change in dysregulation across the three timepoints. This was done to test whether alterative, plausible models offer a more robust account of brain-symptomology correspondence during this particular developmental window. Note that trauma exposure was assessed in all participants at time 1; only those participants who endorsed a traumatic exposure at time 2 and/or 3 were administered the THP at subsequent time points. Thus, the THP was not amenable to growth curve analyses in the current sample. To ensure that these models were as comparable as possible to the models examining time 1 symptomology predicting changes in connectivity, we included the same set of covariates.

We examined the goodness of fit for each model using standard criteria (Hu & Bentler, 1999), including root mean square error of approximation (RMSEA) < .06, and comparative fit index (CFI) > .95. We also examined the χ^2 test of model fit, where a nonsignificant result indicates good model fit. In addition, model fit comparisons were inspected, including absolute fit indices such as Akaike's Information Criterion and Bayesian Information Criterion (Akaike, 1974; Rissanen, 1983). To determine model fit improvement, we primarily relied on χ^2 difference tests for the

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Table 1. Sample demographics and study variables of interest

	Final Sample $N = 190$	
Variable	*n*	%
Sex (F: M)	91: 99	48: 52
Race (W: A: B/AA: AI/A: M: N)	161: 1: 4: 5: 11: 8	84: .5: 2: 2.5: 6: 5
Ethnicity (L: NL)	46: 144	24: 76
	n	Mean (SD); range
Age (years)	190	11.81 (1.73); 8–15
Dysregulation symptoms T1	185	7.84 (6.39); 0–28
Dysregulation symptoms T2	162	6.48(6.47); 0–38
Dysregulation symptoms T3	122	6.65(6.40); 0–28
Trauma exposure count	185	2.20 (1.89); 0–10
CCN – CCN connectivity T1	190	.10 (.08); −.05–.43
CCN – CCN connectivity T2	120	.11 (.09); −.02–.39
CCN – CCN connectivity T3	50	.10 (.09); −.03–.42
CCN – AUD connectivity T1	190	.10 (.10); −.06–.57
CCN – AUD connectivity T2	120	.13 (.11); −.06–.45
CCN – AUD connectivity T3	50	.13 (.11); −.02–.59
CCN – SM connectivity T1	190	.14 (.09); −.03–.47
CCN – SM connectivity T2	120	.16 (.10); .01–.44
CCN – SM connectivity T3	50	.16 (.11); .01–.51
CCN – DMN connectivity T1	190	.08 (.08); −.09–.41
CCN – DMN connectivity T2	120	.08 (.08); −.11–.37
CCN – DMN connectivity T3	50	.09 (.09); −.08–.30
CCN – VIS connectivity T1	190	.07 (.09); −.12–.40
CCN – VIS connectivity T2	120	.08 (.10); −.07–.42
CCN – VIS connectivity T3	50	.07 (.09); −.07–.43

AI/A = American Indian/Alaskan; A = Asian; AUD = auditory network; B/AA = Black, African American; CCN = cognitive control network; DMN = default mode network; F = female; M = male; M = mixed race; N = not reported; NL = Not Latino/a; SM = sensorimotor network; T1 = time 1, T2 = time 2, T3 = time 3; VIS = visual network; W = White. Dysregulation symptoms are reported as raw values from the CBCL.

nested models (i.e., baseline, covariates, final model) for each network. All models were tested in Mplus (v8.6).

Missing data

Of the 190 children recruited at time 1, not all participants had a resting state, structural scan, or CBCL dysregulation scores (for the alternative models) at times 2 and 3 (reported in Table 1). We conducted each LGCM with and without missing data estimation using full-information maximum likelihood (FIML) and the same conclusions were reached. In order to reduce potential bias from data missing at random, we report results using FIML estimation.

Results

Demographic & descriptive statistics

Demographic and descriptive statistics of the final sample are reported in Table 1. Participants who did and did not continue study participation across the 3 time points did not differ by age ($F_{(2,187)} = 0.68, p = .50$), sex ($\chi_{2(2,N=190)} = 1.45, p = .48$), ethnicity ($\chi_{2(8,N=182)} = 11.58, p = .17$), or race ($\chi_{2(2,N=190)} = 0.11, p = .95$). In addition, participants were demographically well-matched across the 2 study sites with respect to age ($t_{(188)} = 0.001, p = .99$), sex ($\chi_{2(1,N=190)} = 0.53, p = .47$), and race ($\chi_{2(4,N=182)} = 6.79$, $p = .15$). There were, however, a significantly greater proportion of Latino/a participants at the MRN study site compared to the UNMC site ($\chi_{2(1,N=190)} = 19.39, p < .001$). There were no site differences in study retention ($\chi_{2(2,N=190)} = 2.82, p = .24$).

Correlations among study variables of interest are reported in Table S2. An example LGCM is illustrated in Figure 1 and model fit results and comparisons for each step of the analysis are reported in Table S3. With the exception of the CCN-SM and CCN-AUD models (discussed below), the final models for the CCN-CCN, CCN-DMN, and CCN-VIS rsFC trajectories had good to excellent fit. In the next section, we report the LGCM model results from each of the RSNs CCN-CCN, CCN-AUD, CCN-SM, CCN-DMN, CCN-VIS.

For the alternative LGCM estimating dysregulation symptoms across time, the baseline model had poor model fit ($\chi^2_{(1)} = 4.00$, $p = .045$; RMSEA = .10, 90% CI [.02,.26]; CFI = .99). Thus, we did not proceed with modeling or interpreting the time 1 rsFC predicting intercept and slope of dysregulation.

LGCM model results for cognitive control network connectivity

Results describing the base models and models with only the control variables are reported in the Supplement. The final models included age, site, sex, dysregulation symptoms scores, and trauma exposure as predictors of the intercept and slope of change in CCN rsFC. Based upon χ^2 difference tests, there were significant decrements in model fit for the CCN-SM (χ^2diff = 18.93, $p < .001$) and CCN-AUD (χ^2diff= 11.56, $p = .01$) when covariates were entered into the model (i.e., age, sex, site), making the parameter estimates uninterpretable. The remaining 3 models had good to excellent fit. An illustrative set of results for the CCN-CCN model are illustrated in Figure 2. Tables S4–S6 contain a complete report of model results. In what follows, we report model results for the CCN-CCN, CCN-DMN, and CCN-VIS networks.

CCN-CCN network connectivity results

In terms of the effects of interest, dysregulation symptoms were significantly associated with baseline rsFC within the CCN network ($b = 0.004$, $p < .001$), such that youths with greater dysregulation symptoms tended to have greater baseline CCN-CCN rsFC. In addition, elevated dysregulation symptoms at time 1 related to decreasing CCN-CCN rsFC across time ($b = -0.002$, $p = .03$) (Fig. 3a). Trauma exposure did not relate to baseline CCN-CCN rsFC ($b = -0.002$, $p = .57$). In addition, trauma exposure at time 1 did not relate to changes in CCN-CCN rsFC across time ($b = 0.003$, $p = .40$).

The base model showed that youths tended to have positive within-network CCN rsFC at time 1 (mean = 0.01, $p < .001$), though there was no systematic change in rsFC over time (mean = 0.01, $p = .39$; details in supplement). Age at time 1 was not associated with baseline rsFC ($b = -0.005$, $p = .11$) or changes in rsFC across time ($b = 0.006$, $p = .07$). Age did not correspond with dysregulation symptoms ($b = -0.298$, $p = .27$) or trauma exposure ($b = -0.075$, $p = .35$). Sex was related to baseline CCN-CCN rsFC ($b = 0.024$, $p = .03$), such that females tended to have greater rsFC between regions of the CCN network compared to males. There were no sex differences in change across time in rsFC among

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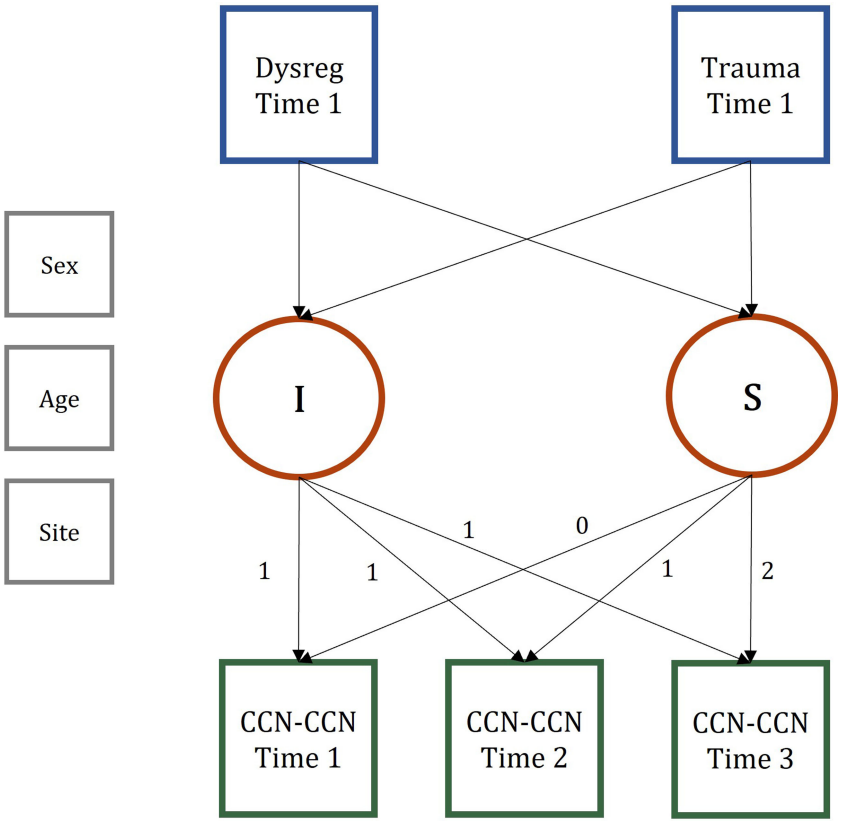

Figure 1. Example latent growth curve model of cognitive control connectivity. I = Intercept, S = Slope. Dysreg = dysregulation was measured via the CBCL at time 1. Trauma = trauma exposure was collected via the UCLA Trauma History Profile at Time 1. CCN-CCN = within cognitive control network functional network connectivity. Sex, age at time 1, and study site were included as covariates for the intercept and slope, as well as each of the symptomology predictors.

CCN network regions ($b = -0.011$, $p = .32$). Moreover, males and females did not differ in their number of dysregulation symptoms ($b = -0.345$, $p = .71$) or trauma exposures ($b = 0.014$, $p = .96$). Study site was not associated with baseline rsFC within the CCN network ($b = -0.013$, $p = .22$), nor was it associated with change in rsFC within the CCN network ($b = 0.002$, $p = .87$). Study site was also not related to dysregulation symptoms ($b = -0.209$, $p = .82$) or trauma exposure ($b = -0.098$, $p = .72$).

CCN-DMN network connectivity results

Dysregulation symptoms were significantly associated with baseline CCN-DMN rsFC ($b = 0.003$, $p = .004$), where youths with a greater number of dysregulation symptoms had greater baseline CCN-DMN rsFC. Time 1 dysregulation symptoms did not predict the rate of change in CCN-DMN rsFC across time ($b = -0.002$, $p = .06$). Although trauma exposure did not relate to baseline CCN-DMN rsFC ($b = -0.003$, $p = .27$), more trauma exposures reported at time 1 predicted increases in CCN-DMN rsFC across time ($b = 0.007$, $p = .036$) (Fig. 3b).

In the base model, youths generally exhibited a pattern of positive between-network rsFC in CCN-DMN at time 1 (mean = 0.08, $p < .001$), though there were no changes in the rate of change in CCN-DMN rsFC over time (mean = 0.01, $p = .34$). Age at time 1 was not related to baseline levels of CCN-DMN rsFC ($b = -0.001$, $p = .81$) nor change in rsFC across time ($b = 0.00$, $p = .95$). Age did not correspond with dysregulation symptoms ($b = -0.292$, $p = .28$) or trauma exposure ($b = -0.077$, $p = .34$). Sex was not related to baseline CCN-DMN rsFC ($b = 0.017$, $p = .12$) or the rate of change in CCN-DMN rsFC ($b = -0.010$, $p = .38$). Moreover, males and females did not differ in their number of dysregulation symptoms ($b = -0.342$, $p = .72$) or trauma exposures ($b = 0.019$, $p = .94$). Study site was associated with baseline CCN-DMN rsFC ($b = -0.021$, $p = .05$), whereby the MRN site had greater baseline rsFC compared to the UNMC site. Though, study site was not systematically related to changes in CCN-DMN rsFC across time ($b = 0.014$, $p = .21$). Study site was also not related to dysregulation symptoms ($b = -0.342$, $p = .72$) or trauma exposure ($b = -0.100$, $p = .72$).

CCN-VIS network connectivity results

Dysregulation symptoms were significantly associated with baseline levels of CCN-VIS rsFC ($b = 0.003$, $p = .005$), where youths with greater dysregulation symptoms had greater baseline CCN-VIS rsFC. Dysregulation symptoms at time 1 did not correspond with the slope of change in CCN-VIS rsFC over time ($b = -0.001$, $p = .08$). Similarly, trauma exposure did not relate to baseline CCN-VIS rsFC ($b = -0.001$, $p = .78$) nor the rate of change in CCN-VIS rsFC ($b = -0.001$, $p = .75$).

The base model showed that youths tended to show a pattern of positive between-network CCN-VIS rsFC at time 1 (mean = 0.07, $p < .001$), though there were no significant changes in rsFC over time (mean = 0.004, $p = .46$). Age at time 1 related to baseline CCN-VIS rsFC ($b = -0.010$, $p = .005$), such that older participants showed lower levels of CCN-VIS rsFC. Age at time 1 was not associated with fluctuations in CCN-VIS rsFC across time ($b = 0.006$, $p = .09$). In addition, age did not relate to dysregulation symptoms ($b = -0.292$, $p = .28$) or trauma exposure ($b = -0.075$, $p = .35$). Sex was related to baseline CCN-VIS rsFC ($b = 0.027$, $p = .03$), such that females tended to have greater rsFC than males. There were also sex differences in the rate of change in CCN-VIS rsFC across time, with females exhibiting more sharply decreasing connectivity relative to males ($b = -0.030$, $p = .007$). There were no sex differences in dysregulation symptoms ($b = -0.295$, $p = .75$) or trauma exposure ($b = 0.013$, $p = .96$). Study site was not

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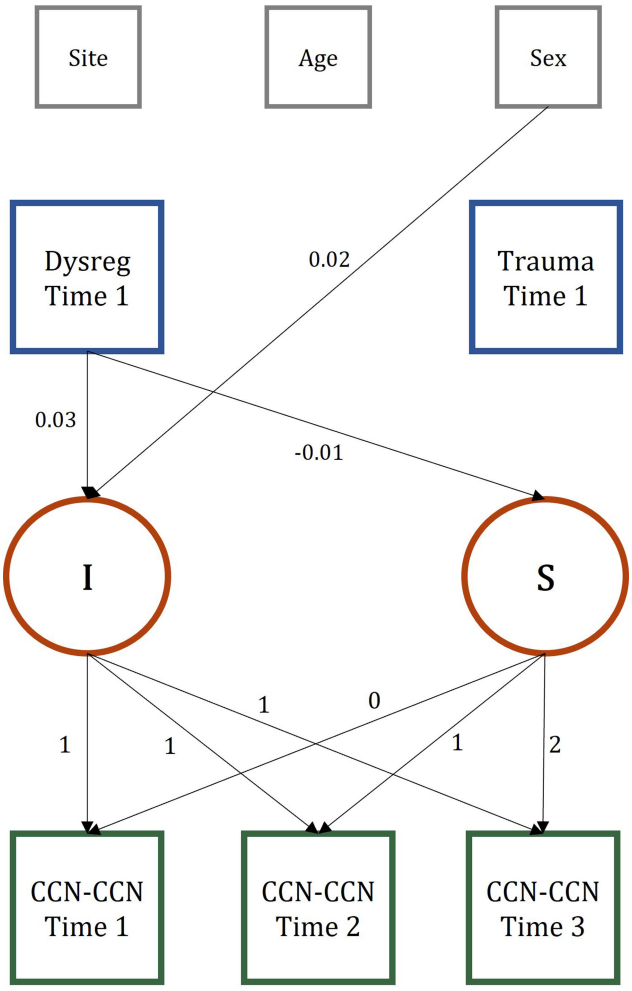

Figure 2. Latent growth curve model results for connectivity between cognitive control regions. Final model results in which sex, age at time 1, study site, CBCL dysregulation symptoms, and trauma exposure all predict the latent intercept and slope of change in cognitive control network connectivity. Solid lines indicate statistically significant estimates at $p < .05$. All estimates are unstandardized. I = intercept, S = slope. Dysreg = dysregulation measured via the CBCL; trauma = trauma measured via the UCLA THP at time 1. CCN = cognitive control network connectivity. Sex, age at time 1, and study site were included as covariates for the intercept and slope, as well as each of the symptomology predictors. For sex, males = 0 and females = 1.

associated with baseline CCN-VIS rsFC ($b = -0.012$, $p = .31$), nor was it related to the rate of change in CCN-VIS rsFC ($b = -0.003$, $p = .80$). Study site was also not related to dysregulation symptoms ($b = -0.194$, $p = .84$) or trauma exposure ($b = -0.098$, $p = .72$).

Discussion

The present study examined the extent to which key transdiagnostic precursors to psychopathology - trauma exposure and dysregulation symptoms - predict longitudinal fluctuations in rsFC of the cognitive control network (CCN). We report two key findings regarding changes in rsFC across time. First, youths with higher dysregulation generally showed greater within-network CCN rsFC at time 1; those with higher levels of dysregulation tended to have decreasing within CCN rsFC across adolescence. Second, greater levels of trauma exposure at time 1 predicted increasing CCN-DMN connectivity over time. No other resting-state networks demonstrated changes related to these transdiagnostic indicators. In addition, although not a core aim of the study, we did not uncover age-related changes in network connectivity across time, as others have previously reported in intra- and inter-network connectivity patterns of the DMN and CCN (e.g., Sherman et al., 2014). An alternative set of models testing whether rsFC at baseline predicted variability in dysregulation yielded poor model fits. It is plausible that changes in dysregulation over the developmental window examined here tended to be non-linear, which is consistent with work documenting trajectories of the CBCL dysregulation profile in typically developing youth (Deutz et al., 2018).

Consistent with prior cross-sectional and longitudinal designs (Bebko et al., 2015; Lopez et al., 2018; Park et al., 2018), our findings show that in an otherwise healthy sample, greater dysregulation is linked to decreasing rsFC among regions of the CCN. It should be noted that the present study is, to the authors' knowledge, the only systematic investigation of associations between the CBCL dysregulated profile and changes in CCN connectivity. Other studies include nodes commonly attributed to the CCN (e.g., insula, dorsomedial/lateral prefrontal cortices), but not necessarily the traditional fronto-parietal connections that comprise the CCN. In typically developing youth, lower within CCN connectivity has been reported previously, as the CCN is expected to be an incohesive connector during development, meaning it is likely to exhibit higher between-network connectivity and lower within-network connectivity (Gu et al., 2015). However, these patterns shift during adolescence into adulthood, as brain networks become more segregated and modular, within-network rsFC is expected to increase due to functional specialization (Grayson & Fair, 2017). With these predictions in mind, findings reported here contribute two insights: (1) greater initial within CCN rsFC in youth with more dysregulation may be a marker of atypical trajectories to come and (2) longitudinal trajectories in those with higher dysregulation seem to indicate aberrant decreases in CCN rsFC, as the normative trajectory is characterized by increases in CCN connectivity with development.

These findings offer unique insights into the dynamics of the broader CCN while providing convergent evidence of greater dysregulated behavior being linked to weaker rsFC across key regions in the CCN reported in pairwise approaches (Park et al., 2018). Results suggest that youth with elevated dysregulation may exhibit a functional de-coupling of regions within the CCN during a developmental window in which there should be enhanced coupling. This functional de-coupling may challenge youth's ability to effectively self-regulate behavior in concert with the mood instability and attentional problems that are present in most accounts of dysregulation, all of which are generally predictive of subsequent psychopathology (Holtmann et al., 2011). Notably, the current set of findings are among the first to show dysregulation predicting longitudinal changes in CCN connectivity in youth, as prior work leveraging longitudinal designs have not examined change in these networks per se (Lopez et al., 2018). Reduced within-network CCN rsFC has been highlighted as a potential transdiagnostic vulnerability, as it seems to be shared across a number of psychiatric disorders, including anxiety (Geiger et al., 2016), and depression (Stange et al., 2017), as well as subclinical levels of depression in adults (Hwang et al., 2015) and emergent depression in youth (Pan et al., 2020). Thus, the current study contributes to a burgeoning literature that has largely been conducted in adults, by demonstrating that a transdiagnostic behavioral profile (i.e., dysregulation) that is present during development also corresponds with the emergence of selective

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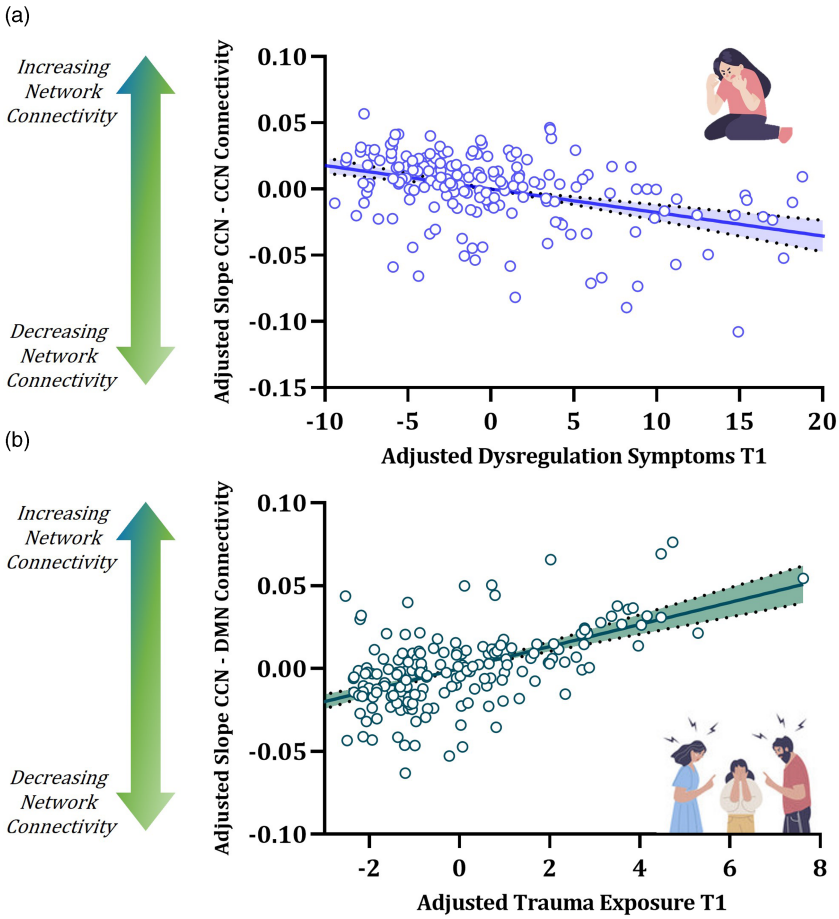

Figure 3. Associations between dysregulation symptomology and trauma at T1 and functional connectivity slope of change. Scatterplots displaying associations between trauma exposure or CBCL symptomology at time 1 (i.e., dysregulation symptoms) and the estimated slope of change in functional network connectivity at rest. Slope values were adjusted by regressing out effects of other variables in the latent growth curve model (e.g., 3a slope was adjusted for age, sex, site, and trauma exposure). Symptoms and trauma exposure were also adjusted for covariates in the model (i.e., age, sex, and site). CCN = cognitive control network, DMN = default mode network; T1 = time 1.

rsFC reductions in the CCN and is a potent predictor of future psychopathology and a shared neurobiological feature of multiple psychiatric conditions (Kaiser et al., 2015; McTeague et al., 2016) (Kaiser et al., 2015; McTeague et al., 2016). It may be that youth with greater dysregulation are at heightened risk of developing rsFC patterns that typify generalized psychopathology; in concert, dysregulation may represent a malleable set of behaviors that if targeted early in development, could be amenable to preventative interventions to more adaptively engage the CCN.

Another key finding was that greater trauma exposure predicted increasing functional connectivity between CCN-DMN across time. Existing literature linking trauma exposure with CCN-DMN connectivity is largely mixed (Ross & Cisler, 2020) and sparse in developmental samples (Sheynin et al., 2020). However, findings of greater connectivity between the CCN-DMN have been shown in pediatric samples with PTSD compared to controls (Patriat et al., 2016; Viard et al., 2019), suggesting that the pattern of increasing connectivity between these networks may be indicative of emergent neurodevelopmental abnormalities seen in psychiatric samples who are at a similar developmental stage. DMN and CCN are thought to have competing activation patterns, with regions of the DMN engaged during more internally-oriented states, and the CCN engaged during goal-directed tasks (Fox et al., 2009). Further, studies have shown that connectivity between the DMN and CCN tends to be negatively correlated (i.e., anticorrelated) in healthy adults during rest (Chai et al., 2012; Fox et al., 2009). Thus, elevated levels of DMN-CCN connectivity at rest likely signify a disruption in the normative patterns of connectivity, and our finding of trauma-predicted increases in connectivity between DMN-CCN across time may indicate that trauma represents a significant risk factor for alterations in neurodevelopment. It is an open question whether such trauma-related increases in connectivity among the DMN and CCN are an indicator that CCN regions are less segregated from the DMN, which would stand in contrast to the expected increasing segregation of large-scale resting-state networks that occurs during adolescence (Grayson & Fair, 2017; Sherman et al., 2014). As others have shown in prior work, reduced segregation between task-positive networks and the DMN may be a transdiagnostic mechanism by which core behavioral deficits emerge in psychiatric disorders (Owens et al., 2020).

Though this study did not specifically aim to test sex differences, we uncovered several noteworthy patterns. First, the current sample did not have higher levels of dysregulation in females than males, as others have reported (Mbekou et al., 2014; but see Boomsma et al., 2006). This may be due to sampling differences, as prior studies have focused on treatment-seeking samples whereas the present sample is community-based. Moreover, prior longitudinal work has shown that there may not be initial sex differences in dysregulation levels, but that elevated levels in males and females confer risk for different psychopathology diagnostic outcomes; females are at elevated risk of mood disorders, while males are at elevated risk of substance use disorders and conduct-related disorders (Althoff et al., 2010). Second, findings revealed that females had higher baseline within-CCN and CCN-VIS connectivity compared to males. In addition, females had steeper decreases in CCN-VIS connectivity across time relative to males. There is a scarcity of findings indicating that males and females have divergent resting-state connectivity

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patterns and brain function in general, with sex accounting for approximately 1% of variance in brain function and structure across modalities, including resting state (Eliot et al., 2021). Thus, given that the current sample is within the pubertal window, which is known to onset earlier in females than males, we speculate that the results may reflect differences in pubertal status, which has previously been linked to development of resting-state networks (Gracia-Tabuenca et al., 2021). In other words, the sex differences reported here are likely due to puberty, not sex in and of itself. This interpretation should be explicitly followed up in future analyses designed to evaluate pubertal status and/or hormones in youth (e.g., Ladouceur et al., 2023; Penhale et al., 2022).

The current study has many strengths, but there are several limitations that should be acknowledged. First, the quantification of trauma is based upon a cumulative exposure approach (Evans et al., 2013), which lacks specificity in terms of identifying subtypes or dimensions of trauma that may lead to unique and dissociable alterations to neurodevelopment. For instance, recent theoretical frameworks have highlighted threat and deprivation experiences as specific early adversity subtypes that predict alterations to neural circuits in importantly different ways (Machlin et al., 2019; McLaughlin & Sheridan, 2016). Future work building upon the current study would benefit from incorporating a more dimensional, rather than a cumulative risk approach to delineating changes in functional connectivity patterns of key resting-state networks following specific trauma exposure types. Relatedly, other transdiagnostic measures that have recently been highlighted as potent predictors of subsequent psychopathology (e.g., dimensional psychopathology or a *p-factor*; Parkes et al., 2021) would be a promising avenue to pursue. Moreover, examining the extent to which neural connectivity patterns mediate associations between earlier transdiagnostic indicators and longer-term psychopathology outcomes would be a crucial next step in this line of inquiry (Rakesh et al., 2021). Finally, it is worth noting that the current study focused on deviations from normative developmental trajectories in an otherwise healthy sample, which likely limits generalizability to samples with clinical levels of psychopathology. That said, there is utility in examining subclinical and/or transdiagnostic processes underlying neurobiological responses to trauma experiences (Picci et al., 2022a; Picci et al., 2022b; Taylor et al., 2021), as these efforts may promote eventual discoveries of preclinical biomarkers for psychopathology that may emerge during development.

Taken together, the present study offers novel evidence for two putative predictors of psychopathology forecasting alterations to large-scale neural networks. Findings here suggest that dysregulated behavior and trauma exposure uniquely predict changes in within-network connectivity in the CCN and between-network connectivity between the CCN-DMN, respectively. These findings corroborate prior literature showing comparable connectivity patterns in cross-sectional designs and in samples with clinical levels of psychopathology. This work represents one of the few longitudinal investigations revealing long-term developmental associations between transdiagnostic indicators and emergent, altered connectivity patterns seen in clinical populations in an otherwise healthy sample.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579423001013.

Funding statement. This work was supported by the National Science Foundation (#1539067 to TWW, YPW, JMS, and VDC and #2112455 to VDC), the National Institutes of Health (R01-MH121101, R01-MH116782, and P20-GM144641 to TWW; R01-EB020407 and R01-MH118695 to VDC), and At Ease, USA. Funding agencies had no part in the study design or the writing of this report.

Competing interests. None.

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