

Resting-state network topology characterizing callous-unemotional traits in adolescence

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Abstract

Background: Callous-unemotional (CU) traits, a youth antisocial phenotype, are hypothesized to associate with aberrant connectivity (dis-integration) across the salience (SAL), default mode (DMN), and frontoparietal (FPN) networks. However, CU traits have a heterogeneous presentation and previous research has not modeled individual heterogeneity in resting-state connectivity amongst adolescents with CU traits. The present study models individual-specific network maps and examines topological features of individual and subgroup maps in relation to CU traits.

Methods: Participants aged 13-17 completed resting-state functional connectivity and the inventory of callous-unemotional traits as part of the Nathan Klein Rockland study. A sparse network approach (GIMME) was used to derive individual-level and subgroup maps of all participants. We then examined heterogeneous network features associated with CU traits.

Results: Higher rates of CU traits increased probability of inclusion in one subgroup, which had the highest mean level of CU traits. Analysis of network features reveals less density within the FPN and greater density between DMN-FPN associated with CU traits.

Discussion: Findings indicate heterogeneous person-specific connections and some subgroup connections amongst adolescents associate with CU traits. Higher CU traits associate with lower density in the FPN, which has been associated with attention and inhibition, and higher density between the DMN-FPN, which have been linked with cognitive control, social working memory, and empathy. Our findings suggest less efficiency in FPN function which, when considered mechanistically, could result in difficulty suppressing DMN when task positive networks are engaged. This is an area for further exploration but could explain cognitive and socio-affective impairments in CU traits.

Keywords: callous-unemotional traits, adolescence, network topology, fMRI

1. Introduction

Callous unemotional (CU) traits describe an antisocial phenotype in youth (Frick & White, 2008) that represent the affective component of adult psychopathy (Barry et al., 2000; Frick et al., 2014). Adolescents with these traits incur a societal cost that is 10 times greater than typically developing youth (Cohen & Piquero, 2009; Foster et al., 2005). Because current treatments for antisocial phenotypes have limited efficacy (for meta-analysis: van der Stouwe et al., 2014), there is an ongoing need to develop a better understanding of these phenotypes. Identifying biomarkers related to callousness could inform development of new interventions and aid faster assessment of treatment response by monitoring treatment outcomes prior to changes being manifested behaviorally (Mayeux, 2004; Perez et al., 2014). However, this has been difficult because CU traits are heterogeneous (i.e., there are multiple variants underlying individual differences; e.g., Fanti et al., 2013; Fanti et al., 2018; Hadjicharalambous & Fanti, 2018; Catherine L. Sebastian et al., 2012). Prior investigations of neural mechanisms underlying CU traits use methods that do not account for individual heterogeneity. Given that adult psychopathy is viewed as a neurodevelopmental disorder with origins in youth (Frick & Viding, 2009) and children with CU traits share symptoms with adult psychopathy (Barry et al., 2000; Frick et al., 2014), it is critical to characterize neural networks, and previously uncaptured heterogeneity, underlying CU traits prior to adulthood. Thus, the present study examines CU traits amongst a community sample of adolescents using a novel method for characterizing neural networks that leverages individual heterogeneity.

Multiple lines of research document candidate brain abnormalities associated with CU traits and its adult counterpart, psychopathy (Barry et al., 2000). Task-based fMRI studies in adolescents suggest aberrant activity in the limbic, temporal, and frontal cortex regions in nodes

associated with the salience (SAL), default mode (DMN), and frontoparietal (FPN; also called central executive) networks (Finger et al., 2008; Herpers et al., 2014; Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2013; Pujol et al., 2012; Catherine L Sebastian et al., 2012; Veroude et al., 2016; Viding et al., 2012; White et al., 2012). Further support of the importance of these regions is found in studies measuring grey matter volume demonstrating abnormalities in similar regions (Caldwell et al., 2019; Cardinale et al., 2019; Cohn et al., 2016; Raschle et al., 2018; Rogers & De Brito, 2016; Sebastian et al., 2016; Wallace et al., 2014). These findings in youth are mirrored in adult studies on neural mechanisms underlying psychopathy (e.g., Sethi et al., 2018) supporting both the theory on psychopathy as a neurodevelopment disorder (Frick & Viding, 2009) as well as the importance of examining the SAL, DMN, and FPN.

As opposed to regional differences in volume or activation during a task, a recent theory by Hamilton et al. (2015) suggests that psychopathic traits involve an impaired integration within and between the SAL, DMN, and FPN. This dis-integration has been used to explain the prevalent theories on neural mechanisms underlying emotion (Blair, 2010; Kiehl, 2006) and attention (Larson et al., 2013; Neumann & Hare, 2008) impairments in adult psychopathy. Given the neurodevelopmental disorder view of psychopathy (Frick & Viding, 2009), dis-integration of these networks could also be applied to investigating impairments CU traits shares with psychopathy such as emotion (Blair, 2008), socio-affective functioning (Blair et al., 2005; Hawes & Dadds, 2012), and attention (Dadds et al., 2011). Initial support for this perspective includes both within and between network associations. For example, where we would expect stronger connectivity within network, CU traits associate with reduced connectivity within the SAL (Yoder et al., 2016) and DMN (Cohn et al., 2015; Umbach & Tottenham, 2020), as well as aberrant connectivity in the FPN (Cohn et al., 2015). Additionally, for between networks, where

we would expect an anticorrelation between task positive and task negative networks in typically developing brains (Uddin et al., 2009), higher CU traits associate with a lower anticorrelation between the DMN and FPN (Pu et al., 2017). Although previous task-based findings provided insights into the brain regions activated by specific tasks, these results suggest etiology of CU trait impairments may reflect a trait like pattern of disintegration within and between these networks. This compelling body of work makes it clear that understanding the neural mechanism underlying CU traits could lead to novel intervention.

Several barriers remain before the neural mechanisms of CU can be used to drive new interventions. First, while these studies reveal similar differences in each network, the individual studies do not converge on regions or demonstrate the same network across all studies. This is possibly due to the heterogeneity of CU traits (e.g., Fanti et al., 2013; Fanti et al., 2018; Hadjicharalambous & Fanti, 2018; Catherine L. Sebastian et al., 2012) that is not modeled in the above adolescent studies. Ignoring the heterogeneity of CU traits can produce spurious connections that fail to describe the individuals in the sample, whereas modeling this heterogeneity can more accurately characterize network patterns in the brain (Gates & Molenaar, 2012). Given it has been demonstrated with psychopathic traits in adults (e.g., Baskin-Sommers et al., 2011; Dotterer et al., 2020; Efferson & Glenn, 2018; Espinoza et al., 2018; Korponay et al., 2017), it is critical we examine the heterogeneity of neural mechanisms underlying CU traits in adolescents.

Second, these studies often use methods that average across the entire times series to examine the strength of contemporaneous connections only. Ignoring lagged connections in resting state connectivity fails to model important neural connections – reflecting neuronal processes – critical for characterizing neural networks (Mitra et al., 2014). Modeling this as well

as other important network function and architecture involves modeling the way networks are arranged, or their topology (De Vico Fallani et al., 2014). Network topology captures important features including relations between regions that have shown to be important for understanding health and mental health disorders (Rezaeinia et al., 2020; Stiso & Bassett, 2018) making it appropriate to leverage for understanding CU traits.

Third, most of this research is conducted on clinical or forensic samples when the spectrum of CU traits plausibly exists at some level (although lower) amongst community samples. The idea that psychiatric symptoms are on a spectrum and a disorder of neural circuits is consistent with the research domain criteria (RDoC) framework and a move away from symptom categories (Insel, 2014). Samples selected for extreme problem behaviors raise potential issues such as ceiling effects while also making it difficult to parse CU traits association with brain features from multiple other comorbid symptoms such as conduct problems. One exception is a study on a community sample children by Umbach and Tottenham (2020) that demonstrates the dimensionality of CU traits as well as its unique association with the brain independent of conduct problems. However, this study models the mean time series to examine the strength of contemporaneous connectivity, which may not identify important network features that are crucial for understanding brain associations with CU traits. Examining a community sample of adolescents using a topological approach that models individual variability can improve our understanding of CU traits by reducing uncertainty and endogeneity around associated brain correlates.

To address these methodological limitations, we use a novel network approach that includes traditional group level analyses while accounting for person-specific individual heterogeneity without averaging over the entire time series – group iterative multiple model

estimation (GIMME; Beltz & Gates, 2017; Gates & Molenaar, 2012). GIMME uses data driven methods to, first, model statistically meaningful subgroup-level connections and, second, adds statistically meaningful connections at the individual-level that are unique to each participant (both are blind to CU traits). These connections include both contemporaneous and lagged connections. The results include the identification of subgroup patterns that model heterogeneity by providing person-specific estimates. GIMME outperforms other network modeling approaches, such as bayes nets and Granger causality, in simulation studies when modeling data heterogeneity (Gates & Molenaar, 2012). Studies examining psychopathology using GIMME have found variation in network patterns within the same diagnosis (Beltz, 2018; Price et al., 2017), including adult psychopathy (Dotterer et al., 2020), demonstrating reliable biological heterogeneity within diagnoses.

We can then examine topological features of person-specific networks in relation to CU traits, which capture more nuanced information beyond mean strength such as connection density, directionality, and centrality of node importance. Network density is the number of connections in a sparse network that indicate to what extent information travels between nodes within or between networks (De Vico Fallani et al., 2014). Node centrality is the number of connections into and/or out of a node which is used as a measure of node importance within a network or for communicating with other networks (De Vico Fallani et al., 2014; Kaiser, 2011). These network features have been shown to predict cognitive functioning by way of capturing information processing streams in the brain (Cohen & D'Esposito, 2016).

The present study aims to characterize network features of CU traits in a community sample of early-to-mid adolescents (ages 13-17) using person specific network connectivity within and between the SAL, DMN, and FPN. We used GIMME (Beltz & Gates, 2017; Gates &

Molenaar, 2012) to generate person specific connectivity maps and to identify any subgroups of similar connectivity patterns. First, we examine CU traits association with identified subgroups. Then we examine associations of CU traits with individual-level network features of network density and node centrality across all participants. As suggested by previous research, we expect to see less connection density within the SAL, DMN, and FPN. For between network associations, given that adults demonstrate greater density (Dotterer et al., 2020) and adolescents demonstrate greater connectivity strength (Pu et al., 2017), we hypothesize greater density of between DMN-FPN connections in the present sample. We have no a priori hypotheses about subgroup homogeneity in network patterns, network centrality, or associations with CU trait subscales, but examine these to further characterize network features of these symptoms.

2. Methods

2.1. Sample

Adolescent participants (ages 13-17) were from the Nathan Kline Institute's Rockland study, a study with a community sample on ages between 6-85 conducted in Rockland, New York (for study procedures see: Nooner et al., 2012). Data were collected from participants which involved a series of questionnaires and an fMRI session (both task and resting state). To our knowledge the resting state data and its relationship to CU traits in an adolescent sample have not been published.

2.2. Measures

Inventory of Callous-Unemotional Traits (ICU). The ICU is a 24-item assessment of CU traits (Frick, 2004). The ICU has a confirmed factor structure and demonstrates convergent and divergent validity after removing two items for poor psychometrics (Kimonis et al., 2008). We used the same factor structure that excluded two items for poor psychometrics, which had

adequate reliability in the present sample ($\alpha = 0.72$). The ICU consists of three subscales: callousness, unemotional, and uncaring. Participants rate items on a four-point Likert scale from 0 (“not true at all”) to 3 (“definitely true”) on items such as “I do not show my emotions to others”. Higher scores indicate greater level of CU traits.

Covariates and Demographics. The youth self-report (YSR) is a measure for behavior problems in youth ages 11-18 (Achenbach & Rescorla, 2001). The externalizing ($\alpha = 0.87$) subscale was used to control for conduct issues in the present analysis. Items from the externalizing subscale are rated on a three-point scale (0 not true – 2 very true) indicating how much they agree with the statement for the previous 6-months. Higher scores indicate higher externalizing symptoms. Validity and reliability of the YSR externalizing measure are within acceptable standards (Achenbach & Rescorla, 2001). Raw scores were used as recommended for research purposes by Achenbach and Rescorla (2001). We conducted analyses both controlled for and did not control for externalizing behavior to detect where CU traits accounted for unique variance.

Both pubertal development and sex were measured by the genital and breast development subscales of the Tanner assessment ($\alpha = 0.77$), in which parents rated pictures representing development of secondary sex characteristics on a scale of 1 (pre-pubertal) to 5 (full maturity) (Petersen et al., 1988). Higher scores indicate greater developmental maturity. Given there is significant variation in the timing of puberty when measured by age (about five years, Parent et al., 2003) and that hormonal changes during puberty have a direct effect on the adolescent brain, which in turn impact mental state and behavior (Cameron, 2004; Dahl, 2004; Sisk & Foster, 2004), we choose to control for pubertal stage instead of using age. Similarly, sex effects are

known to associate with CU traits and demonstrate differences in brain structure amongst adolescents with CU traits, we included sex as a covariate (Raschle et al., 2018).

Imaging Acquisition. Resting state images were analyzed from the Rockland dataset (www.nitrc.org/projects/fcon_1000/). We republish those parameters here for convenience.

Images were collected with a Siemens TimTrio 3T scanner using a blood oxygen level dependent (BOLD) contrast with an interleaved multiband echo planar imaging (EPI) sequence. Participants were instructed to keep their eyes closed without falling asleep and to not think of anything while they let their mind wander. Each participant received an fMRI scan during resting state (260 EPI volumes; repetition time (TR) 1400ms; echo time (TE) 30ms; flip angle 65°; 64 slices, Field of view (FOV) = 224mm, voxel size 2mm isotropic, duration = 10 minutes) and a magnetization prepared rapid gradient echo (MPRAGE) anatomical image (TR= 1900ms, flip angle 9°, 176 slices, FOV= 250mm, voxel size= 1mm isotropic). T1 stabilization scan removal was not necessary given that the Siemens sequence collects images after saturation is achieved.

Resting-state fMRI preprocessing. Preprocessing was conducted using Statistical Parametric Mapping (SPM version 12; Penny et al., 2011) using the standard preprocessing pipeline via the CONN toolbox (version 18b; Whitfield-Gabrieli & Nieto-Castanon, 2012). Using the Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect), motion outliers were flagged for correction if > 0.5mm and regressed out using binary motion covariates. No timing correction was used due to the short TR and multiband sequence used for acquisition. Physiologic CSF and white matter noise was regressed out of the BOLD signal using anatomic component-based noise correction method (aCompCor) (Whitfield-Gabrieli & Nieto-Castanon, 2012). Co-registered MPRAGE and EPI images were normalized to an MNI template. Smoothing of images were conducted using a 6mm Gaussian kernel. Finally, to preserve

meaningful resting state associations, the data was bandpass filtered to between .008 and .09Hz (Satterthwaite et al., 2013).

Region of Interest Selection. Neural investigations on CU traits supported focus on the DMN, SAL, and FPN in the current analysis (Pu et al., 2017; Umbach & Tottenham, 2020; Yoder et al., 2016). Consistent with examining psychopathology generally (Menon, 2011), targeting these networks is in line with contemporary theory on psychopathic traits (Hamilton et al., 2015). Eight a priori core ROIs for each network were defined anatomically using the Harvard-Oxford atlas involving the medial prefrontal and posterior cingulate cortex (mPFC and PCC) for the DMN; anterior cingulate cortex (ACC) and bilateral insula for the SAL; as well as the bilateral lateral prefrontal cortices and bilateral posterior parietal cortices (LPFC and PPC) for the FPN (MNI coordinates: Supplementary Table 1). These ROIs represent the core regions of these networks and have been used to examine the associations within and between the DMN, SAL, and FPN (Menon, 2015; Menon & Uddin, 2010; Uddin et al., 2009).

GIMME. Network maps from each participants timeseries were constructed using R (Version 4.04; R Core Team, 2021) along with the ‘GIMME’ (Lane et al., 2021) and ‘lavaan’ packages (Rosseel, 2012). This method uses a data-driven sparse modeling approach that iteratively adds network connections and using LaGrange multipliers (Sörbom, 1989) to assess model fit and retain statistically meaningful connections (defined as connections that improve model fit for 75% of the sample). Sparse modeling used here minimizes spurious contemporaneous connections generated by saturated models (Gates et al., 2010). GIMME models contemporaneous (occurring at the same functional volume) or lagged (occurring at the previous volume) connections that apply to the entire sample, subgroups (data-derived subsample), or individual level (individual-specific connections). The result is a unified

structural equation model (uSEM; Gates et al., 2011) for each participant that includes both contemporaneous and first order lagged connections. Non-significant connections are pruned during model fitting if their influence changed with the addition of new connections (Gates & Molenaar, 2012). Model-building ends when the network fits the data well, which were assessed using excellent fit criteria by Brown (2015) requiring two out of four alternative fit indices are met: root mean squared error of approximation (RMSEA) ≤ 0.05 , standardized root mean residual (SRMR) ≤ 0.05 , comparative fit index (CFI) ≥ 0.95 , or non-normed fit index (NNFI) ≥ 0.95 .

During model generation, GIMME identifies shared connectivity patterns while accounting for individual heterogeneity using a community detection algorithm (walktrap) (Gates & Molenaar, 2012), which simulations have proven to be a reliable method of detecting subgroups of network patterns (Gates et al., 2017; Pons & Latapy, 2005). Because each subgroup is defined by similarities in features, each is best described by their shared network features (e.g., Goetschius et al., 2020). Using both individual and subgroup level network features increase reliability of estimates for both individual and subgroups in comparison to other network approaches (Gates et al., 2017; Gates & Molenaar, 2012; Smith et al., 2011).

2.3. Statistical Analysis

All inferential statistical analyses were conducted with the statistical language R (Version 4.04; R Core Team, 2021). We extracted network features from the GIMME networks and conducted inferential statistic on these features using maximum likelihood estimation. Prior to path analyses, variables demonstrated linear relationships and data met assumptions for normality of residuals, auto correlation, and multicollinearity; and t tests revealed participants that were excluded were not significantly different from those included on demographics or variables of interest.

Network features. We extracted network features for all individual networks including density, node centrality within (SAL, DMN, and FPN) and between (DMN-SAL, DMN-FPN, and SAL-FPN) networks of interest. To account for individual differences, we extracted proportions and calculated positive and negative features separately. *Network density* involved the number of connections between nodes (regardless of contemporaneous or lagged connections) for within and between networks separately. *Node centrality* involved calculating the number of connections a node has relative to the number of potential connections within a network or between networks ($\text{connections} / \text{nodes} - 1$). Higher number of connections toward or away from a node or between nodes suggests greater information flow regarding that node or set of nodes.

Associations between network features and callous-unemotional traits. We first examined the probability of being included in identified subgroups given the presence of CU traits using a multinomial logistic regression. For individuals, we used path analysis to examine CU trait's association with network features (network density and node centrality), which estimates all parameters simultaneously in one model and reduces multiple comparisons. Total CU traits were the independent variable of interest while controlling for sex and tanner stage. CU traits can be independent of conduct disorder (e.g., Baskin-Sommers, Waller, et al., 2015; Hyde et al., 2015), and, because the present analysis seeks to understand CU traits association with network features, we controlled for conduct problems. To ensure we are not capturing a suppression effect (e.g., Hyde et al., 2016; Lozier et al., 2014), we also ran all models without controlling for conduct problems. All results of were identical whether we controlled for conduct problems or not, suggesting there are no suppression or impact to model coefficients; thus, we only report on models that include conduct problems. To correct for multiple comparisons we

used a false discovery rate correction (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001) for each analysis using ‘p.adjust’ in base R (R Core Team, 2021).

We then conducted exploratory and confirmatory analyses. First, to determine if any subgroups were more characteristic of CU traits, we used an ANOVA to examine if there were mean differences in CU traits across subgroups and conducted Tukey’s post hoc test for individual differences. Second, for individual-specific features, we ran exploratory analyses with CU trait subscales of callousness, uncaring, and unemotionality to determine if associations found with total scores were driven by these subscales. We did not control for multiple comparisons for exploratory or confirmatory analyses.

3. Results

3.1. Descriptives

To ensure integrity of the data, we excluded participants with a WAIS-II IQ score < 80 ($\alpha = .96$; Wechsler, 2011), movement in global signal intensity or translation and rotational movement parameters $> 3\text{mm}$, or $> 20\%$ invalid scans. Out of a total of 122 participants between the ages of 13-17, 10 participants were removed for $\text{IQ} < 80$, 24 participants for motion, and four participants for invalid scans. Leaving a total of 84 participants for analysis. The analyzed sample were predominantly White (White= 63%, Black = 24%, Asian = 9%, Indian = 1%, other= 3%) balanced between sex (female = 45%) and a mean age of 14.59 ± 1.48 . Mean ICU total score (Boys= 23.11 ± 7.56 ; Girls= 22.27 ± 10.31 ; Total= 22.71 ± 8.93) were within one standard deviation of other studies with community samples (Byrd et al., 2013; Essau et al., 2006).

3.2. GIMME

Resting state networks met a priori criteria of good fit on two out of four fit indices according to average fit (SRMR = 0.024, CFI = 0.953, see Supplementary Table 2) and identified

significant heterogeneity indicated by low modularity (modularity = 0.024). Connections for all participants were detected between the lateral prefrontal cortex and posterior parietal cortex in the FPN and bilateral insulae in the SAL. Four subgroups were identified that comprised 65% participants (n=54). The remaining 35% of participants (n=30) did not match any subgroup (for subgroup depiction: Supplementary Figures 1 and 2). All person specific maps contained individual level connections (23.85 ± 4) and had positive connections (16.49 ± 2.04). Whereas 83.3% had negative connections (7.36 ± 2.19). All models contained both contemporaneous and lagged connections (contemporaneous = 7.75 ± 2.00 , lagged = 16.18 ± 2.17). Subgroup maps indicated connections were heterogeneous within three of the subgroups and homogeneous in the fourth subgroup only. Specifically, the first subgroup (n=19, modularity = 0.191) was characterized by 18 shared connections and 33 connections that varied between individuals; second subgroup (n=10, modularity = 0.190) was characterized by 19 shared connections and 36 connections that varied between individuals; and the third subgroup (n=19, modularity = 0.225) was heterogeneous with 8 shared connections and 57 connections that varied between individuals, whereas the fourth subgroup (n=6, modularity = 0.213) was homogeneous with 24 shared connections and no individual connections (individual heterogeneity depicted in Supplementary Figure 3). The first subgroup had the highest overall average network density (Supplementary Table 3). A depiction of network features can be found in Supplementary Figure 2.

3.3. Subgroup Association with Callous-Unemotional Traits

Increases in CU traits associated with increases in odds of being in the heterogeneous second subgroup ($\beta = 0.17$, $p_{(FDR\ corrected)} = 0.048$, odds ratio = 1.19; see Table 1 and Figure 1

Panel B.), which performed better than a null model ($\Delta\text{Chi}= 25.14$, $p= 0.012$). Associations were not significant with other subgroups and conduct problems had no significant associations.

Analysis confirming subgroup differences on callous-unemotional traits. Subgroups were significantly different on mean level of CU traits and, specifically, the second subgroup had the highest mean level of CU traits ($F(3.50)=6.51$, $p= 0.001$; Figure 1 Panel C.).

Exploratory analysis on dimensional ICU subscale. Uncaring subscale was positively associated with an increase in odds that participants would fall into subgroup two ($\beta = 0.195$, $p = 0.048$, odds ratio = 1.21, see Supplementary Table 5 and Supplementary Figure 4).

3.4. Individual-Specific Features Associated with Callous-Unemotional Traits

Individual-specific resting-state network density and callous-unemotional traits. CU traits associated with both within and between network density. Increases in CU traits associated with decreases in number of positive connections within the FPN ($\beta = -0.001$, $p_{(FDR\ corrected)} = 0.042$, Figure 2 Panel B and Table 2). For between network density, higher levels of CU traits associated with greater number of positive connections between the DMN-FPN ($\beta = 0.002$, $p_{(FDR\ corrected)} = 0.023$, Figure 2 Panel C and Table 3).

Individual-specific node centrality and callous-unemotional traits. For within network, CU traits associated with increased positive node centrality in the left insula within the SAL ($\beta = 0.010$, $p_{(FDR\ corrected)} = 0.009$) and decreases in both positive and negative centrality of the right lateral prefrontal cortex in the FPN ($\beta = -0.005$, $p_{(FDR\ corrected)} = 0.019$, $\beta = -0.010$, $p_{(FDR\ corrected)} = 0.006$ [respectively], see Supplementary Tables 6-8). For between networks, CU traits associated with central between DMN-FPN connections positively for PCC- left LPFC and negatively for PCC – right PCC ($\beta = 0.002$, $p_{(FDR\ corrected)} < 0.001$; $\beta = 0.004$, $p_{(FDR\ corrected)} = 0.019$ [respectively]). Central DMN-SAL network connections showed a positive association

between CU traits and positive centrality and a negative association with negative centrality between the PCC-ACC ($\beta = 0.003$, $p_{(FDR\ corrected)} = 0.014$; $\beta = -0.002$, $p_{(FDR\ corrected)} = 0.024$ [respectively]; Supplementary Tables 9-14, depiction of node centrality Figure 2 Panel A.).

Exploratory analyses on individual-specific network features. Facets underlying callous unemotional traits (i.e., callousness, unemotional, and uncaring) had no association with network density features (Supplementary Tables 15-16); but there were associations with centrality network features. The callousness subscale of the ICU associated with decreases in positive network centrality of the right lateral prefrontal cortex within the FPN ($\beta = -0.015$, $p = 0.012$) and negatively for positive connections between the posterior cingulate cortex and left lateral prefrontal cortex for between DMN-FPN connectivity ($\beta = -0.005$, $p = 0.009$; see Supplementary Figures 17-19). The uncaring subscale negatively associated with positive network centrality of the left insula within the SAL ($\beta = 0.013$, $p = 0.033$) and negatively with negative network centrality of the right lateral prefrontal cortex within the FPN ($\beta = -0.013$, $p = 0.044$). No other significant findings were revealed for ICU subscales (supplementary tables 20-25).

Covariate results on individual-specific network features. Covariates also had results of note. Externalizing symptoms positively associated with increases in positive connections between the SAL and FPN ($\beta = 0.003$, $p_{(FDR\ corrected)} = 0.038$) and negatively associated with both positive and negative network centrality of the anterior cingulate cortex within the salience network ($\beta = -0.012$, $p_{(FDR\ corrected)} = 0.049$, $\beta = -0.028$, $p_{(FDR\ corrected)} = 0.034$ [respectively]). Pubertal stage positively associated with negative centrality between DMN-SAL at the mPFC-left insula ($\beta = 0.011$, $p_{(FDR\ corrected)} = 0.024$) and negative SAL-FPN centrality at the insula(L)-

LPFC(R) ($\beta = 0.009$, p (*FDR corrected*) = 0.003). Interestingly sex had no significant associations after controlling for multiple comparisons.

4. Discussion

Results from a community sample of adolescents reveals significant heterogeneity in resting state network connections and supports the notion that CU traits associate with network disintegration. Data-driven results revealed a subset of adolescents with few shared and many individual heterogeneous connections that had higher CU traits, which was independent of conduct problems. This suggests CU traits may lead to more individual-specific alterations in neural circuitry. Individual-specific features indicated less density within the FPN and greater density between the DMN and FPN associated with higher CU traits. Within the FPN this is likely due to fewer connections with the right lateral prefrontal cortex; between DMN-FPN this is likely due to more positive connections between the posterior cingulate cortex-bilateral lateral prefrontal cortices. The present findings connect both adolescent and adult literature on similar features – suggesting 1) psychopathy may be a neurodevelopmental disorder with ontogeny of affective features in youth CU traits and 2) that this can be studied by examining disintegration between the SAL, DMN, and FPN. We extend the current line of research methodologically by examining topological features that modeled both heterogeneity and lagged connections of adolescent brains to reveal the information processing between networks, specifically between DMN-FPN with within the FPN, may be of particular importance.

4.1. Network Connection Heterogeneity

The heterogeneity revealed in the present analysis even within identified subgroups emphasizes the issues of relying on the prevalent averaging approaches that hide important individual specific features. For example, the lagged connections modeled by GIMME would

have been missed with common network approaches that average across entire timeseries. Because lagged connections are critical features of resting state networks (Beltz & Molenaar, 2015; Mitra et al., 2014) and simulation studies demonstrate GIMME is both accurate and robust (Gates & Molenaar, 2012), the network connections identified here are plausibly more specific to adolescents for which we can make more precise inferences on CU traits relation to these network features.

4.2. Subgroup Two associates with Greater Callous-Unemotional Traits

The finding that a subgroup had higher representation of CU traits is novel and, if replicated, could provide a base for investigating the heterogeneity of individual connections represented in the group. Exploratory analyses revealed the uncaring CU trait subscale also increased probability in the same subgroup. Although this finding would not have withstood multiple comparison correction, it may be worth further examination to understand whether uncaring drives the association with subgroup two. This subgroup may be replicated and used in future studies to examine shared and heterogeneous connections amongst adolescents with CU traits.

4.3. Individual-Specific Network Features Underlie Callous-Unemotional Traits

Individual-specific findings are consistent with theory of dis-integration between networks; and the consistency with the adult literature partially supports the idea that psychopathy is a neurodevelopmental disorder with ontogeny in youth. First, we found that as CU traits increase, the density of connections within the FPN decreases and that the right lateral prefrontal cortex is a central node. This is consistent with adult literature demonstrating interpersonal features of psychopathy negatively associate with node connectivity within the FPN (Philippi et al., 2015), which may indicate a developmental feature of the brain underlying

adult psychopathy. Future work examining FPN connections longitudinally could determine this. The FPN is implicated in various aspects of attention alerting, orienting, and cognitive control (e.g., Corbetta, 1998; Scolari et al., 2015; Shulman et al., 2010). Multiple lines of research converge on higher order cognitive processes being impaired in psychopathy (e.g., Baskin-Sommers, Brazil, et al., 2015; Delfin et al., 2018; Maes & Brazil, 2013) and CU traits (e.g., Gluckman et al., 2016; Javakhishvili & Vazsonyi, 2021; Racer et al., 2011). In the context of the literature, the present finding of reduced information flow within the FPN may be related to attention impairments observed in the behavioral literature and it a plausible mechanism for future investigation.

For between network features, our present findings are consistent with both adult findings by Dotterer et al. (2020) and adolescent findings Pu et al. (2017) indicating psychopathic and CU traits associated with greater between DMN-FPN connection density and less anticorrelation (respectively). We extend this work to reveal greater connection density found in adults is present in adolescents with CU traits as well – suggesting a disintegration between networks that may have developmental underpinnings prior to adult psychopathy.

Less connectivity between the DMN-FPN is implicated healthy cognitive functioning, such as social working memory (Xin & Lei, 2015) and cognitive control (Marek et al., 2015; Sheffield et al., 2015), as well as socio-affective processes, such as the interpersonal component of emotional intelligence (Takeuchi et al., 2013) and empathy (Xin & Lei, 2015). Greater connectivity is implicated in aberrant cognitive function (Menon, 2011) and associated with conditions with cognitive and socio-affective impairments such as psychopathy (Dotterer et al., 2020) and schizophrenia (Anticevic et al., 2013; Palaniyappan et al., 2013). Because the FPN suppresses the DMN to improve externally focused task performance (e.g., DeSerisy et al.,

2021), these findings suggest cognitive and socio-affective impairments associated with CU traits may be due to failure to suppress the DMN during task directed behavior. Thus, it is plausible that increased information flow between DMN-FPN may interfere with cognitive processes involved in social affective and higher order cognitive functioning. Future studies could examine whether increased DMN-FPN connectivity underlies those with CU traits difficulties in socio-affective tasks or prosocial behavior; and examining the development of between DMN-FPN connections over time may reveal the ontogeny underlying the development of psychopathy.

We did not find aberrant connectivity within the SAL or DMN as hypothesized. However, this was also found in an adult study of psychopathy examining individual network topology (Dotterer et al., 2020). Given that previous studies in adolescents have been inconsistent by not finding aberrant connectivity in the SAL (Umbach & Tottenham, 2020) or DMN (Pu et al., 2017) whereas others have, it is plausible that this may be due differences in modeling approach where using averages across the entire time series are known to create spurious results (Molenaar, 2004). It may also be that the nodes we selected a priori based on previous studies did not include subsystems outside the core regions and, thus, did not demonstrate the disintegration that previous studies have. While it may be argued that adding nodes outside the core nodes for each network may present spurious results that are extraneous to core functions of a network – future studies examining whether the inclusion of subsystems of networks in addition to the core regions may reveal important differences when trying to target specific underlying processes or interactions with subsystems.

4.4. Limitations

While the present study presents many strengths there are some limitations to consider. First, this is a small sample size and, thus, may have failed to identify some connections due to a limited power. Also, the results with this community sample may not generalize to forensic samples. However, it is important to note that there is considerable support that CU traits is dimensionally present in the community and demonstrate a range of the same neurocognitive correlates as clinical/forensic samples (Viding & McCrory, 2012). Future studies could build on this research by examining larger samples that include community and forensic samples or oversampling for higher CU traits in community samples.

5. Conclusion

The present study demonstrates heterogeneous functional connections in the brains of a community sample of adolescents. The present approach improves upon traditional methods by modeling both contemporaneous, lagged, and directional connections to derive topological features while accounting for individual heterogeneity – improving inference of network features with CU traits. CU traits was more represented in one data-driven identified subgroup that was heterogeneous. Individual-specific features demonstrated lower in density within the FPN and higher density between the DMN and FPN associated with higher CU traits. These findings held whether or not we included conduct problems and withstood multiple comparisons correction. Overall, the present findings suggest less efficiency within the FPN and between DMN-FPN, which are associated with attention, cognitive control, and socio-affective functioning. In the context of the literature on impairments amongst youth with CU traits, these results may explain common impairments amongst these youth. The consistency of these findings with adult literature may suggest neurodevelopmental disorder for adult psychopathy worth further investigation. Disintegration observed in the FPN and between DMN-FPN information

processing streams provides support for disintegration between these core networks when examining CU and psychopathic traits. Overall, we demonstrate the importance of modeling individual heterogeneity of network patterns to improve inferences to understand CU traits in adolescents. Modeling individual heterogeneity that investigates topological features of large-scale networks can reveal important neural underpinnings of youth with CU traits that can be used to improve development of individualized treatment approaches for these youth.

Table 1. Probability of inclusion in GIMME identified subgroups for callous unemotional traits.

	Subgroup 2				Subgroup 3				Subgroup 4			
	β	S.E.	OR	FDR p	β	S.E.	OR	FDR p	β	S.E.	OR	FDR p
Callous-Unemotional Traits	0.171*	0.066	1.187	0.048	-0.001	0.053	0.991	0.966	-0.047	0.083	0.954	0.920
Conduct Issues	-0.105	0.094	0.900	0.438	-0.215	0.086	0.801	0.064	0.009	0.092	1.009	0.920
Tanner Stage	0.057	0.507	1.059	0.909	0.200	0.367	1.222	0.966	0.074	0.496	1.077	0.921
Male	0.461	1.024	1.584	0.816	-0.031	0.751	0.969	0.966	-0.885	1.043	0.412	0.920

Note: reference category is subgroup 1

*= FDR corrected $p < 0.05$

Table 2. Within network density across participants

Network connections	β	S.E.	Z	p	FDR p
DMN positive ($R^2 = 0.151$)					
CU traits	-0.001	0.001	-1.217	0.224	0.447
Tanner	0.006	0.006	0.963	0.335	0.447
Conduct Issues	-0.002	0.001	-2.258	0.024	0.096
Sex	-0.005	0.011	-0.408	0.683	0.683
SAL positive ($R^2 = 0.098$)					
CU traits	0.000	0.001	-0.124	0.901	0.921
Tanner	0.005	0.006	0.855	0.393	0.785
Conduct Issues	-0.002	0.001	-2.098	0.036	0.144
Sex	0.001	0.012	0.099	0.921	0.921
SAL negative ($R^2 = 0.095$)					
CU traits	0.000	0.000	-0.846	0.397	0.795
Tanner	0.000	0.003	0.122	0.903	0.903
Conduct Issues	-0.001	0.001	-1.750	0.08	0.321
Sex	0.002	0.007	0.295	0.768	0.903
FPN positive ($R^2 = 0.223$)					
CU traits	-0.001*	0.000	-2.557	0.011	0.042
Tanner	0.008	0.004	2.132	0.033	0.066
Conduct Issues	-0.001	0.001	-1.689	0.091	0.122
Sex	-0.003	0.007	-0.418	0.676	0.676
FPN negative ($R^2 = 0.136$)					
CU traits	0.000	0.000	-1.319	0.187	0.374
Tanner	-0.001	0.002	-0.672	0.501	0.502
Conduct Issues	-0.001	0.000	-1.556	0.12	0.374
Sex	0.004	0.004	0.862	0.389	0.502

Note: there were no negative DMN connections analysis was not conducted on his outcome.

*= FDR $p < 0.05$

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Table 3. Between network density

Network connections	β	S.E.	Z	p	FDR p
DMN-FPN positive ($R^2 = 0.185$)					
CU traits	0.002*	0.001	2.753	0.006	0.024
Tanner	0.004	0.005	0.776	0.437	0.443
Conduct Issues	-0.001	0.001	-1.143	0.253	0.443
Sex	-0.007	0.010	-0.767	0.443	0.443
DMN-FPN negative ($R^2 = 0.137$)					
CU traits	0.002	0.001	2.242	0.025	0.100
Tanner	0.006	0.006	0.918	0.359	0.718
Conduct Issues	0.000	0.001	-0.353	0.724	0.877
Sex	0.002	0.012	0.155	0.877	0.877
DMN-SAL positive ($R^2 = 0.187$)					
CU traits	0.001	0.001	1.847	0.065	0.129
Tanner	-0.006	0.005	-1.264	0.206	0.275
Conduct Issues	0.002	0.001	2.059	0.039	0.129
Sex	0.009	0.009	0.948	0.343	0.343
DMN-SAL negative ($R^2 = 0.202$)					
CU traits	0.001	0.001	0.957	0.339	0.339
Tanner	-0.006	0.005	-1.136	0.256	0.339
Conduct Issues	0.002	0.001	2.473	0.013	0.054
Sex	0.018	0.010	1.759	0.079	0.157
SAL-FPN positive ($R^2 = 0.176$)					
CU traits	-0.001	0.001	-1.393	0.163	0.327
Tanner	-0.005	0.006	-0.759	0.448	0.448
Conduct Issues	0.003*	0.001	2.593	0.01	0.038
Sex	-0.012	0.012	-0.96	0.337	0.448
SAL-FPN negative ($R^2 = 0.153$)					
CU traits	-0.001	0.001	-1.484	0.138	0.184
Tanner	-0.01	0.006	-1.674	0.094	0.184
Conduct Issues	0.002	0.001	1.691	0.091	0.184
Sex	-0.009	0.012	-0.723	0.47	0.470

*= FDR $p < 0.05$

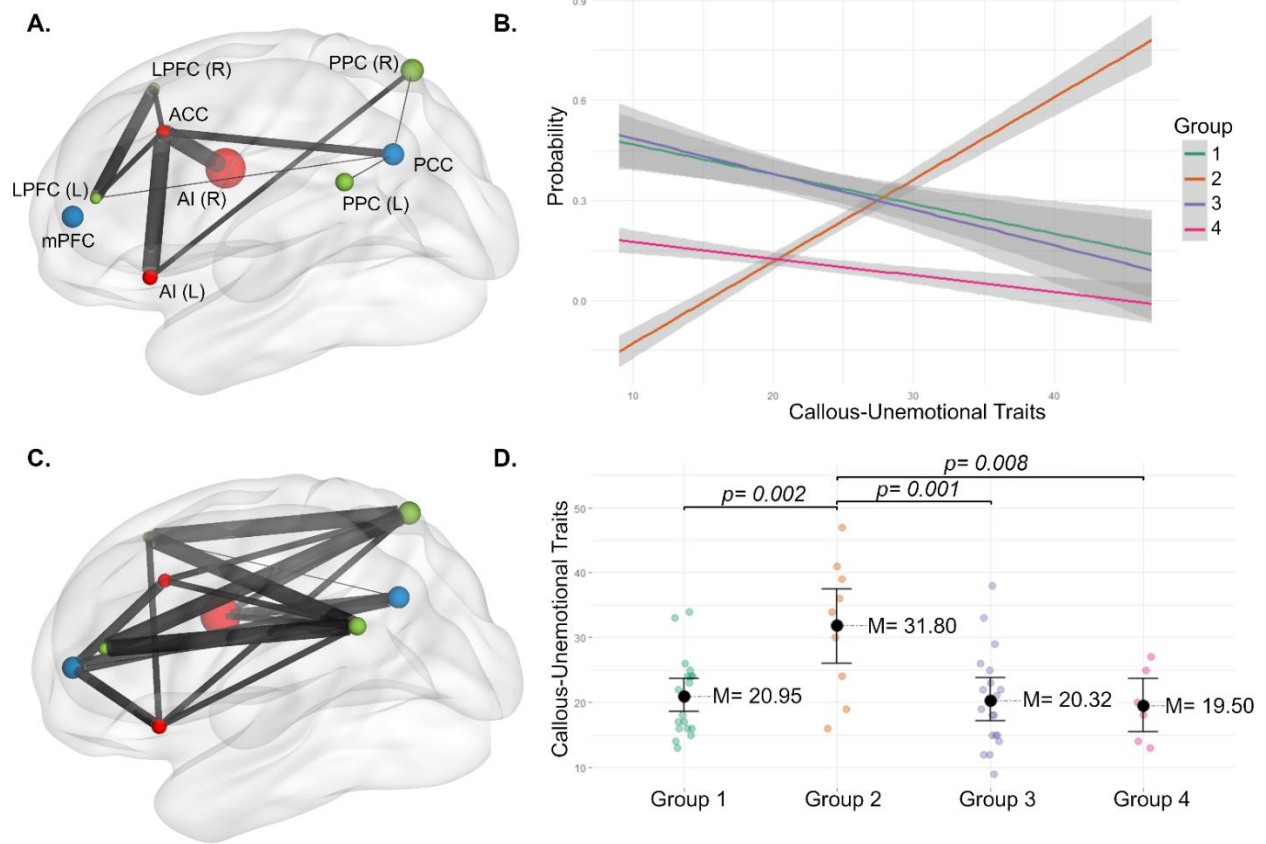


Figure 1. Group-level associations of subgroup two with callous-unemotional traits. A. Depiction of the shared connections for subgroup two. Size of spherical nodes indicate within network centrality (bigger node spheres = more centrality) and size of edges indicate connection density (thicker connection = more density); B. Depicting probability of subgroup inclusion in the presence of total callous-unemotional traits; C. Depicting the heterogeneity of all unshared connections in subgroup 2; D. Mean differences in CU traits by GIMME identified network subgroup. Note: only significant pairwise tests are shown. Node colors: blue = default mode network, red = salience network, green = frontoparietal network.

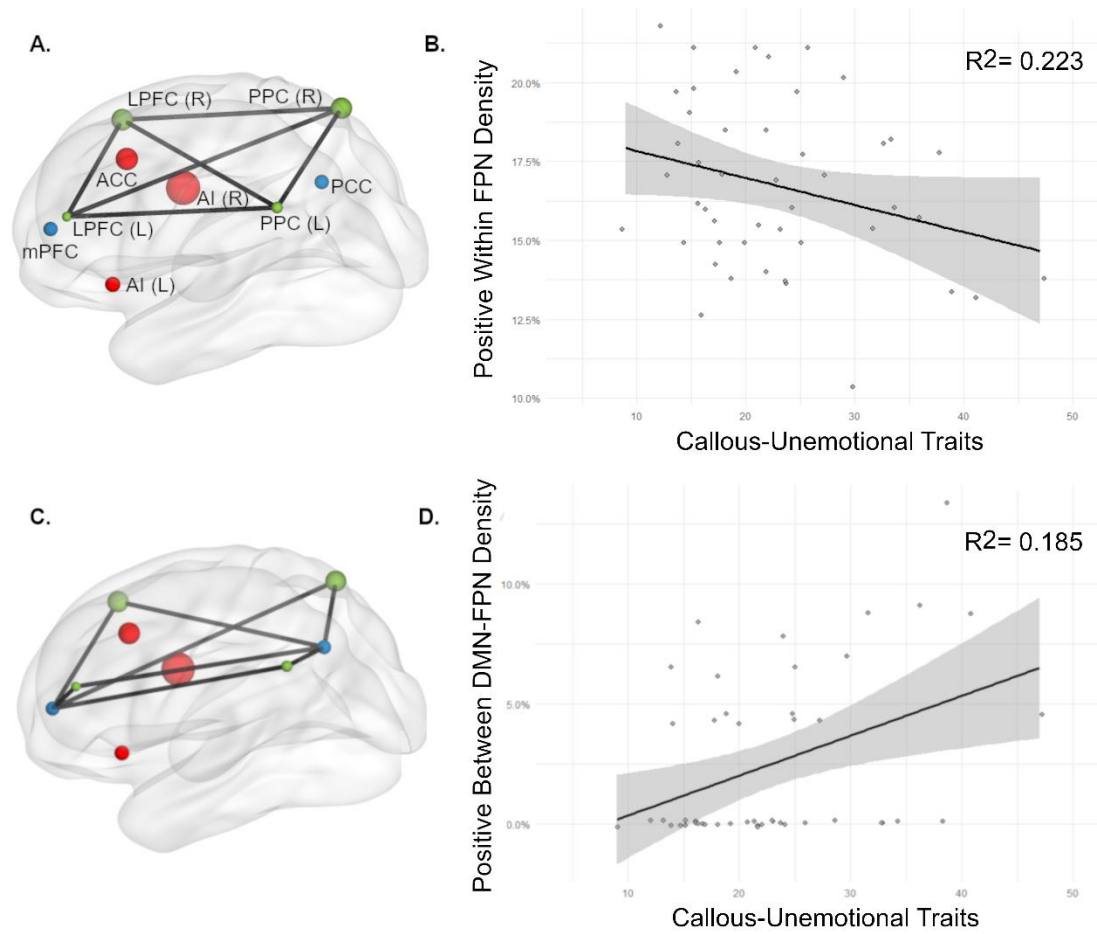


Figure 2. Individual-level associations across all participants with callous-unemotional traits. A. Depiction of all potential connections in the frontoparietal network (FPN); B. Association between positive connections within the FPN; C. Depiction of all possible connections between default mode-frontoparietal networks (DMN-FPN); D. Association between CU traits and positive connections between DMN-FPN. Node: blue = DMN, red = salience network (SAL), green = FPN.

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