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## Network Functional Connectivity Underlying Dissociable Cognitive and Affective Components of Empathy in Adolescence

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### Abstract

Empathy, the capacity to understand and share others' emotions, can occur through cognitive and affective components. These components are different conceptually, behaviorally, and in the brain. Neuroimaging task-based research in adolescents and adults document that cognitive empathy associates with the default mode and frontoparietal networks, whereas regions of the salience network underlie affective empathy. However, cognitive empathy is slower to mature than affective empathy and the extant literature reveals considerable developmental differences between adolescent and adult brains within and between these three networks. We extend previous work by examining empathy's association with functional connectivity within and between these networks in adolescents. Participants (n=84, aged 13–17; 46.4% female) underwent resting state fMRI and completed self-report measures (Interpersonal Reactivity Index) for empathy as part of a larger Nathan-Kline Institute study. Regression analyses revealed adolescents reporting higher cognitive empathy had higher within DMN connectivity. Post hoc analysis revealed cognitive empathy's association within DMN connectivity is independent of affective empathy or empathy in general; and this association is driven by positive pairwise connections between the bilateral angular gyri and medial prefrontal cortex. These results suggest introspective cognitive processes related to the DMN are specifically important for cognitive empathy in adolescence.

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Credit statement

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## Keywords

Adolescence; cognitive empathy; affective empathy; functional connectivity

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## 1. Introduction

Empathy, broadly defined as the ability to understand others' emotions, is critical for effective social functioning and underlies prosocial or altruistic behavior (Decety et al., 2016; Eisenberg & Miller, 1987). Adolescence is a period of rapid neural changes coinciding with increased complexity in social relationships and environments, making it a critical time for social cognitive development (see for review: Blakemore, 2012b). Most major mental health disorders have their onset during adolescence (e.g. major depression, bipolar, schizophrenia; Paus et al., 2008), though adolescents with healthy levels of empathy have fewer transdiagnostic mental health symptoms and behavioral problems compared to controls (i.e. internal and externalizing symptoms; Gambin & Sharp, 2016, 2018). Empathy is supported by cognitive and affective processes that have distinct conceptual and neural contributions (Decety & Cowell, 2015; Smith, 2006; Walter, 2012). Therefore, it is important to examine empathy and its underlying neural networks in adolescents.

Cognitive empathy (i.e. Perspective-taking) involves adopting the view point of another and attributing their thoughts and feelings (Decety, 2011; Decety & Cowell, 2015). Task-based imaging studies with adolescents demonstrate activation in regions underlying the default mode network (DMN; i.e. medial prefrontal cortex and posterior cingulate cortex) and the frontoparietal network (FPN; i.e. the inferior parietal lobule and dorsolateral prefrontal cortices) when asked to take the perspective of others (perspective-taking) while viewing videos describing emotional events (Kral et al., 2017), facial emotions (D'Argembeau et al., 2007), or cartoon vignettes (Gallagher et al., 2000). The DMN is involved in processes of internally focused self-referential thought and understanding others' states (Buckner et al., 2008; Buckner & Carroll, 2007; Uddin et al., 2009). The FPN engages during externally-focused tasks, such as focusing on relevant social stimuli and guiding social behavior (Dixon et al., 2018) that are important for perspective-taking (Eslinger, 1998; Grattan & Eslinger, 1989). These two networks correlate negatively indicating the dichotomy between tasks requiring introspective and extrospective focus, including cognitive empathy (Uddin et al., 2009). Previous research indicates that the functional coupling between externally and internally focused cognitive processes is enabled by a third brain network, i.e., the salience network, through its role in signaling switching between the DMN and FPN (Menon & Uddin, 2010).

Affective empathy involves sharing another's emotional experience which can involve the additional component empathic concern, or empathic feelings of concern for their emotional wellbeing (Decety, 2011; Decety & Cowell, 2015). Regions of the salience network (SAL; e.g. anterior insula, anterior cingulate and rostral prefrontal cortex) are activated when targeting neural mechanisms of affective empathy during a task of viewing images of others' pain in both adults (Singer et al., 2004; Van Overwalle, 2009) and adolescents (Decety & Michalska, 2010; Decety et al., 2008). Sensory, affective, and cognitive information are

integrated by regions making up the SAL (for review see: Menon, 2015), which has been shown to support empathic feelings (Craig & Craig, 2009; Singer et al., 2009). The rostral prefrontal cortex is involved in attention to sensory input and the thought processes around it are necessary for emotional mentalizing (Gilbert et al., 2006); the anterior cingulate cortex integrates affective information for social decision-making (for review see: Lavin et al., 2013); and the anterior insula is involved in emotional awareness and responses involved in empathic processes (Menon & Uddin, 2010). Together the anterior cingulate cortex and insula are involved in vicarious experiences that support affective sharing with another (Fan et al., 2011; Lamm et al., 2011; Lockwood, 2016).

Communication patterns within and between the DMN, SAL, and FPN undergo significant changes during adolescence (Menon, 2013); thus, characterizing the functional connectivity within and between these networks in adolescents is important for understanding complex neural and psychological processes (Ernst et al., 2015). The studies described above investigate brain activation during empathy tasks. Differences in functional connectivity related to empathic processes have been examined in adults and to a lesser extent in adolescents and focus exclusively on one component of empathy (Blakemore, 2012a). The current study aims to complement the extant literature by determining the task-independent functional relationships within and between previously identified intrinsic brain networks that underlie *both cognitive and affective empathy in adolescents* (DMN, FPN, and SAL). This approach allows us to model the different components of cognitive and affective empathy by capturing the unique relationships within and between these brain networks during a developmental stage pivotal for socio-emotional and brain maturation (Ernst et al., 2015).

Guided by the previous task-based research, we hypothesized that affective empathy would positively associate with connectivity within the SAL and cognitive empathy would positively associate with connectivity within the DMN and FPN. We had no specific hypothesis for between network connectivity, therefore we explored potential between network connectivity differences for cognitive and affective empathy. Finally, because some conceptualize empathy as a singular construct (Stietz et al., 2019), it is important to examine uniqueness of cognitive versus affective empathy in brain associations. Thus, we aim to parse out which empathy component has the strongest association with their respective network, as well as what pairwise connections underlie significant network associations with their respective empathy component.

## 2. Methods

### 2.1 Participants

The sample was composed of right-handed, early to mid-adolescent boys and girls (i.e. ages 13–17; Elliott & Feldman, 1990) drawn from Nathan Kline Institute’s Rockland data set (Nooner et al., 2012) obtained through the 1000 Functional Connectomes Project ([www.nitrc.org/projects/fcon\\_1000/](http://www.nitrc.org/projects/fcon_1000/)). Data were collected from the community in Rockland, New York, with a data collection protocol consisting of behavioral measures and MRI scanning collected in one day. For the present study, participants were included if they had an IQ  $\geq 80$  assessed by the WAIS-II ( $\alpha = .96$ ; Wechsler, 2011) to ensure they were

cognitively able to understand self-report measures. The study's ethical considerations, including approval and informed consent, is outlined in Nooner et al. (2012). We conducted an a-priori two-tailed power analysis specifying one independent with three covariates, a moderate effect ( $f = .15$ ), and alpha of .05 that indicated a sample of 80 would be sufficient at 80% power to detect true effects in these regressions. Out of 122 potential participants, 10 were removed for  $IQ < 80$  and 28 were removed for motion-related data quality issues (Supplemental Figure 1). The final sample consisted of 84 right-handed male and female participants (46.4% female) aged 13–17 ( $14.64 \pm 1.36$ ).

## 2.2 Assessments

**Interpersonal Reactivity Index (IRI).**—Empathy was measured using the affective empathy (empathic concern) and cognitive empathy (perspective-taking) subscales of the interpersonal reactivity index (Davis, 1980, 1983), which is a common practice with this scale (Konrath, 2013). Two additional subscales (fantasy and personal distress) were not used because they likely measure constructs beyond empathy such as imagination and emotional control (Baron-Cohen & Wheelwright, 2004). The perspective-taking and empathic concern subscales are more relevant for the present analysis, which are also the subscales used in a prior examination of neural underpinnings of empathy in adolescents (Kral et al., 2017).

The affective empathy subscale ( $\alpha = .74$ ) consists of seven items measuring the tendency to experience other's feelings and have concern for them (e.g. "When I see someone being taken advantage of, I feel kind of protective towards them"). The cognitive empathy subscale ( $\alpha = .79$ ) consists of seven items measuring the tendency to adopt the psychological point of view of others (e.g. "I try to look at everybody's side of a disagreement before I make a decision"). These subscales have been identified by factor analyses and replicated in other samples across age groups and nation of origin; have evidence of convergent and concurrent validity; and are the most widely used measures for cognitive and affective empathy (Konrath, 2013). Importantly, the factor structure of the IRI has been confirmed in 13-year-old youth and older (e.g., Hawk et al., 2013). Items in this measure were rated on a five-point scale ranging from "does not describe me" (0) to "describes me well" (4), with higher scores indicating higher levels of dispositional empathy.

**Covariates and Demographics.**—Demographic variables for race and sex were recorded via self-report. The sample was predominantly White (White= 63%, Black = 24%, Asian = 9%, Indian = 1%, other= 3%), therefore the race variable was grouped into white and non-white categories for analyses. Pubertal development was measured by the genital and breast development subscales of the Tanner assessment ( $\alpha = .77$ ; Petersen et al., 1988). This scale has parents rate pictures representing development of secondary sex characteristics of their child on a scale of 1 (pre-pubertal) to 5 (full maturity) as a measure of pubertal development maturity. Race, sex, and Tanner stage were used as control variables to account for additional variation in the regressions.

## 2.3 Imaging Analyses

**Imaging Acquisition and Preprocessing.**—Images were collected using a Siemens TimTrio 3T scanner using a blood oxygen level dependent (BOLD) contrast using an interleaved multiband echo planar imaging (EPI) sequence. Participants were instructed to keep their eyes closed and just let their mind wander without thinking of anything in particular but not to fall asleep. For each participant, a resting state fMRI scan (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) were acquired. The Siemens sequence does not collect images until magnet saturation is achieved so no scan removal for T1 stabilization was necessary.

Preprocessing and quality checking of functional and structural MRI data were conducted using the default pipeline implemented in the CONN Toolbox (version 18b; Whitfield-Gabrieli & Nieto-Castanon, 2012) using Statistical Parametric Mapping (SPM version 12; Penny et al., 2011). This included scan realignment, coregistration to MPRAGE, and spatial normalization and smoothing using a 6mm gaussian kernel. Because of the fast TR and multiband sequence used at data collection, no slice timing correction was used. Anatomical images were segmented into grey matter, white matter, and cerebrospinal fluid maps. Time-series were inspected for motion using the Artifact Detection Tools (ART; [http://www.nitrc.org/projects/artifact\\_detect](http://www.nitrc.org/projects/artifact_detect)). Timepoints with > 0.5mm volume-to-volume movement and were modeled out using a binary nuisance regressor. Participants with > 3mm volume-to-volume motion in any direction on any single volume and/or participants with > 20% outlier volumes were excluded from the analysis. Nuisance factors (white matter signal, CSF signal, three translation and three rotation motion parameters) were regressed out of each voxel time series. CONN uses an anatomic component-based noise correction method (aCompCor) (Whitfield-Gabrieli & Nieto-Castanon, 2012) that regresses out noise from the CSF and white matter unrelated to neural activity that is effective in mitigating the effects of motion (Behzadi et al., 2007). As opposed to global signal regression, aCompCor ensures observed anti-correlations are not induced artificially (Chai et al., 2012). Functional and structural images were normalized to Montreal Neurological Institute space (MNI152). Finally, data was band-pass filtered to preserve frequencies between .008 and .09Hz to preserve the most meaningful resting state correlations (Amft et al., 2015).

**Region of Interest Selection.**—A priori regions of interest (ROI) were selected based on previous neural investigations of empathy (Decety & Michalska, 2010; Decety et al., 2008; Fan et al., 2011; Kral et al., 2017; Lamm et al., 2011). Regions making up the DMN (medial prefrontal cortex, posterior cingulate cortex, and angular gyri), the FPN (bilateral lateral prefrontal and posterior parietal cortices), and SAL (bilateral anterior insulae, anterior cingulate, and bilateral rostral prefrontal cortices) are used as seed regions. These regions are anatomically defined using the default network ROIs in the Harvard-Oxford Atlas available in the CONN toolbox (MNI coordinates in Table 1).

**Participant-Level Analysis.**—Participant-level analyses were conducted using the CONN toolbox (version 18b; Whitfield-Gabrieli & Nieto-Castanon, 2012). BOLD time-series of each ROI was extracted from the 4D preprocessed resting state scan. Then within- and between-network time series extraction was conducted by averaging all pairwise connections within- and between each network for an averaged within- and between-network connectivity value for each participant. Participant-level pairwise connections were converted to a Z-value using Fisher’s r-to-z transformation to prepare for group-level comparisons.

**Group-Level Analysis.**—Group level analyses were done in the R statistical language (Version 3.6.3; R Core Team, 2020) using the extracted averaged within- and between-network pairwise connections. First, we examined variable relationships using scatterplots, which suggested linear relationships. Pearson correlations were conducted to examine these linear relationships between self-reports of empathy and both within- and between-network connectivity parameters. To avoid missing important exploratory associations, we did not adjust for multiple comparisons for the correlations (Feise, 2002; Rothman, 1990); therefore, an uncorrected two-tailed p-value of  $< .05$  defined statistical significance for correlations. The correlation results informed which models to focus on in the F-tests and regressions. Correlations values  $> 0.2$  or  $< -0.2$  were considered for subsequent analysis.

Then, linear regression models were fitted to examine the relationship between self-report measures of empathy, along with nuisance covariates (sex, race, Tanner stage), with extracted within- and between-network patterns. For the regression analyses, we controlled for multiple comparisons using false discovery rate (FDR) error control for each regression. Regression models were assessed for fit using  $R^2$  for linearity of the model (effect size), as well as standardized residuals and sum of squared errors to examine the precision of modeling associations between variables (de Souza & Junqueira, 2005). The variance explained in the outcome for each predictor in the model was estimated using squared semi-partial correlations. To reduce bias from influential outliers, results are reported after removing outliers based on Cook’s D using a cutoff threshold of  $D(i) > 4/n$  and all outliers were removed from corresponding figures (Cook & Weisberg, 1982). All results did not change when outliers were removed.

To determine what component of empathy had the strongest association with identified networks, we used a type III F-test to quantitate whether cognitive, affective or the interaction of both empathy components associated with their respective functional connectivity parameter identified in the regression, after accounting for each other. Then we examined pairwise connections to assess which neural connections drove significant network level associations with cognitive or affective empathy followed by a contrast of cognitive  $>$  affective empathy. We tested this using post-hoc t-tests that were calculated in the CONN toolbox in order to examine which seeds (1) drove the significant associations for each regression fitted and (2) determine seed level differences using a contrast between cognitive and affective empathy. These t-tests compared ROI mean within and between network connectivity against zero or no functional connectivity. We controlled for multiple comparisons for each t-test using FDR error control. These tests were conducted to pinpoint

the key network level and pairwise seed level relationships underlying empathy in adolescents

### 3. Results

The distributions of the IRI in the present sample were in the moderate range of scores for cognitive ( $12.81 \pm 4.9$ , range= 4–24) and affective ( $17.65 \pm 4.7$ , range= 8–28) with higher scores indicating greater dispositional empathy. Mean IRI scores of other larger adolescent studies are within a standard deviation of the present study IRI scores (e.g., Hawk et al., 2013; Overgaauw et al., 2017)

#### Network associations with empathy.

Pearson correlations (Figure 1) revealed that both cognitive and affective empathy positively associated with DMN connectivity (cognitive [ $r = 0.27$ ,  $p = 0.012$ ]; affective [ $r = 0.24$ ,  $p = 0.026$ ]) and negatively with DMN – SAL between-network connectivity (cognitive [ $r = -0.25$ ,  $p = 0.022$ ]; affective [ $r = -0.25$ ,  $p = 0.023$ ]). The robustness of these bivariate associations were then tested in regression using specified covariates.

Regression analyses indicated that cognitive empathy (Table 2, Figure 2) positively associated with DMN within-network connectivity, accounting for 9% of the variance ( $b = 0.008$ , corrected  $p = 0.049$  [uncorrected .019], semi-partial<sup>2</sup> = 0.0925) and the overall model accounted for 13% of the variance ( $R^2 = .131$ ,  $F(4,75) = 2.832$ ,  $p = 0.030$ , 4 outliers removed) after controlling for sex, race, and tanner stage. Although there was a bivariate relationship between affective empathy and DMN within-network connectivity, the inclusion of covariates in regression model reduced that relationship to non-significance (Table 2;  $b = 0.006$ , corrected  $p = 0.102$  [uncorrected .061], semi-partial<sup>2</sup> = 0.0552). And DMN – SAL between-network connectivity regressions found no significant results for neither cognitive ( $b = 0.006$ , corrected  $p = 0.120$  [uncorrected  $p = 0.028$ ], semi-partial<sup>2</sup> = 0.0675) nor affective empathy ( $b = 0.007$ , corrected  $p = 0.102$  [uncorrected  $p = 0.012$ ], semi-partial<sup>2</sup> = 0.0615), after controlling for multiple comparisons. Correlations that did not account for sex, age, and developmental differences in the sample may have detected spurious associations; therefore, the regressions, because of inclusion of covariates, support more realistic associations.

#### Differentiating empathy components with network associations and regions.

Next, we conducted F-tests and pairwise t-tests to parse out network and ROI level associations that most strongly associate with cognitive and affective empathy and drive network level associations (Table 3). For DMN within-network connectivity, F-tests revealed that cognitive empathy significantly associated with DMN within-network connectivity over and above both affective empathy and the interaction between affective and cognitive (cognitive:  $F = 4.22$ ,  $p = 0.043$ ; affective:  $F = 3.43$ ,  $p = 0.071$ ; interaction:  $F = 2.50$ ,  $p = 0.117$ ). A pairwise t-test revealed that greater connectivity between the medial prefrontal cortex and bilateral angular gyri underlies cognitive empathy, while greater connectivity between the medial prefrontal cortex and left angular gyrus underlies affective empathy. However, a contrast of cognitive > affective empathy for DMN within-network connectivity revealed no discernable seed level pairwise differences (Supplemental Table 1).

For DMN – SAL between-network connectivity, the F-test was unable to identify one component of empathy holding significance over other components (cognitive:  $F=2.16$ ,  $p=0.145$ ; affective:  $F=3.22$ ,  $p=0.076$ ; interaction:  $F=1.57$ ,  $p=0.214$ ). However, the t-test suggested that a negative association between the left angular gyrus with the left rostral prefrontal cortex underlies cognitive empathy. A contrast of cognitive > affective empathy for SAL – DMN between-network connectivity revealed no discernable seed-level pairwise connections after FDR correction (Supplemental Table 1).

#### 4. Discussion

The present study found that adolescents who reported having higher cognitive empathy also had higher functional connectivity within the DMN. In addition, cognitive empathy has a distinct pattern of functional connectivity compared to affective empathy or the interaction between cognitive and affective empathy. Previous research has identified neural regions underlying cognitive and affective empathy using tasks (Blakemore, 2008; Kral et al., 2017; Sebastian et al., 2012). Although uncorrected bivariate associations showed between DMN-SAL connectivity with cognitive and affective empathy as well a DMN connectivity with affective empathy, only the association between cognitive empathy and DMN survived after with the inclusion of covariates and correction for multiple comparisons. Including covariates in regression allowed us to model more realistic accounts of these associations by accounting for sex, age, and developmental differences in the sample. The current findings complement and extend this previous work by characterizing the task-independent, trait-like functional relationships within the DMN that underlie cognitive empathy.

Cognitive empathy positively associated with within-network DMN connectivity, as expected, which held after controlling for nuisance covariates, removing four influential outliers, and controlling for multiple comparisons. Subsequent F-tests supported that cognitive empathy uniquely associated with DMN within-network connectivity. Multiple lines of task-based research on empathy including adults (Fan et al., 2011; Lamm et al., 2011) and adolescents (Decety & Michalska, 2010; Decety et al., 2008; Kral et al., 2017) converge on DMN involvement in cognitive empathy. The present analysis extends previous findings by revealing trait-like strength of connectivity within the DMN associates with cognitive empathy in adolescents.

It is important to note that the DMN is involved in many processes other than empathy; however, its association with cognitive empathy underscores the involvement of internally focused cognitive processes in adolescents. For example, cognitive empathy processes, such as thinking about others emotional and mental states and reasoning with social behavior, associate with the function of the DMN (Buckner et al., 2008; Buckner & Carroll, 2007; Uddin et al., 2009). The present adolescent results support the Uddin et al. (2009) conclusion that introspective processes of the DMN are important during social cognition. Given that these neural regions are still in development in adolescents (Blakemore, 2012a; Singer, 2006), it is surprising the DMN and cognitive empathy association would be the strongest finding. This may be the result of the developmental importance of the DMN and cognitive empathy during this age period. In the context of previous research, the present



results suggest introspective cognitive processes may facilitate the understanding of others and are important for cognitive empathy in adolescents.

Pairwise ROI post-hoc analysis of cognitive and DMN connectivity revealed a positive association between the medial prefrontal cortex and bilateral angular gyri that drove DMN within-network connectivity. The medial prefrontal cortex is involved in forming social judgements and attributing thoughts and feelings of others (for review see: Bzdok et al., 2013), whereas the angular gyrus is involved in mental representations and internal mentalization (for review see: Seghier, 2013). The connectivity between these regions further suggests that internal reasoning with external social stimuli may support understanding others emotions via perspective-taking (i.e. cognitive empathy; Molnar-Szakacs & Uddin, 2013). Together, the post hoc analyses suggest some overlap in neural recruitment by both components of empathy at the seed-level; however, at the network level, cognitive empathy associated with the DMN over affective empathy and the interaction between the two empathy components. This finding is well-supported in the literature and differentiates cognitive from affective empathy in adolescents.

Between network associations did not hold after controlling for multiple comparisons; however, exploratory post hoc analyses suggest that cognitive empathy negatively associated a pairwise connection between the left angular gyrus of the DMN and rostral prefrontal cortex of the SAL (Table 3). A cautious interpretation may be that this association signals the deactivation of the DMN when switching to extrospective cognitive processes associated with cognitive empathy. The angular gyrus associates with mental representations and internal mentalization in the DMN (for review see: Seghier, 2013); and the rostral prefrontal cortex associates with stimulus attending in the SAL (Gilbert et al., 2006) that switches between introspective and extrospective cognitive processes (Menon & Uddin, 2010). Given that this association was found with cognitive empathy, introspective processes and attending to social stimuli during perspective taking (cognitive empathy) may signal the SAL to switch to extrospective processes associated with cognitive empathy in adolescents. This may be the brain mechanism by which cognitive empathy has an influential relationship on affective processes and empathy overall suggested by Kral et al. (2017).

We found little evidence for race and sex influencing empathy's association with adolescent brains. Sex differences in empathy is a contentious topic, with many suggesting females self-report higher empathy than males (Baron-Cohen & Wheelwright, 2004; Cohen & Strayer, 1996; Davis, 1983). But, investigations of brain differences during empathic tasks have found no evidence for empathic differences between sexes (Decety & Michalska, 2010; Kral et al., 2017; Michalska et al., 2013), leading these authors to suggest that self-report measures may capture social conditioning related to gender and may not reflect true empathic ability between sexes. In general, the present results largely support the position that sex does not affect brain associations with empathy in adolescents.

### **Limitations.**

The present findings must be interpreted with the following limitations. First, this was a cross-sectional analysis, which made it impossible to discern causality between empathy and functional connectivity. Similarly, our sample could not separate heterogeneous periods of

adolescence. Thus, future work with a longitudinal design, combined with matched age at each time point, would provide the strongest test of development of cognitive and affective empathy and underlying functional connectivity in adolescents. Second, the empathy measure used defined affective empathy as empathic concern, which is different from other measures' definitions. For example, the basic empathy scale defines affective empathy as emotional congruence (Jolliffe & Farrington, 2006), which is more in line with emotional sharing than having concern for another's emotional state. This may have had an impact on results associated with affective empathy. Third, the NKI Rockland dataset did not assess for alexithymia, which has been known to account for variance in empathy (e.g., Valdespino et al., 2017). Future studies could include Alexithymia as a covariate to account for this variance. Fourth, we defined our ROIs using a predefined atlas. This method may not accurately reflect the neural regions for the present sample, which can impact results. However, these atlases are defined across larger sample sizes that evidence generalizability and mitigate researcher error in region definition. Finally, although fMRI is powerful, examining BOLD signals does not capture the hundreds of neurons in each region that may have important stories to tell about neural function. Each region detected in the present analysis is involved in multiple processes, making it difficult to pinpoint exactly which process our results indicate. Although this was further investigated by examining which neural regions were underlying the associations found, using tasks can help further parse which exact processes recruited regions are engaged in.

### **Implications and conclusions.**

The pattern of findings revealed here has important implications for promoting empathy in adolescents – specifically via internal referencing associated with cognitive empathy. In conclusion, higher DMN within-network connectivity appears to be important for cognitive empathy in adolescents. Although replications and further examination is needed, the present analysis demonstrated only the association between cognitive empathy and DMN connectivity survived after controlling for multiple comparisons and including covariates in the model. This suggests that introspective cognitive processes are important for cognitive empathy in adolescents and supports previous task-based findings on the association between the DMN and cognitive empathy in adolescents (Kral et al., 2017). However, the current findings extend this previous work by identifying the strength of functional relationships within the DMN and how this functional specificity in the DMN supports empathy. Future research could build on the finding that SAL - DMN between-network connectivity negatively associates with cognitive empathy by examining the association between the angular gyri and rostral prefrontal cortex in relation to cognitive empathy. This line of investigation shows promise in understanding of attending and cognitive processes that influence switching between social cognitive processes in adolescents. Overall, this study supports work suggesting that the association between the DMN and cognitive empathy is important for adolescent empathy.

### **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**Highlights**

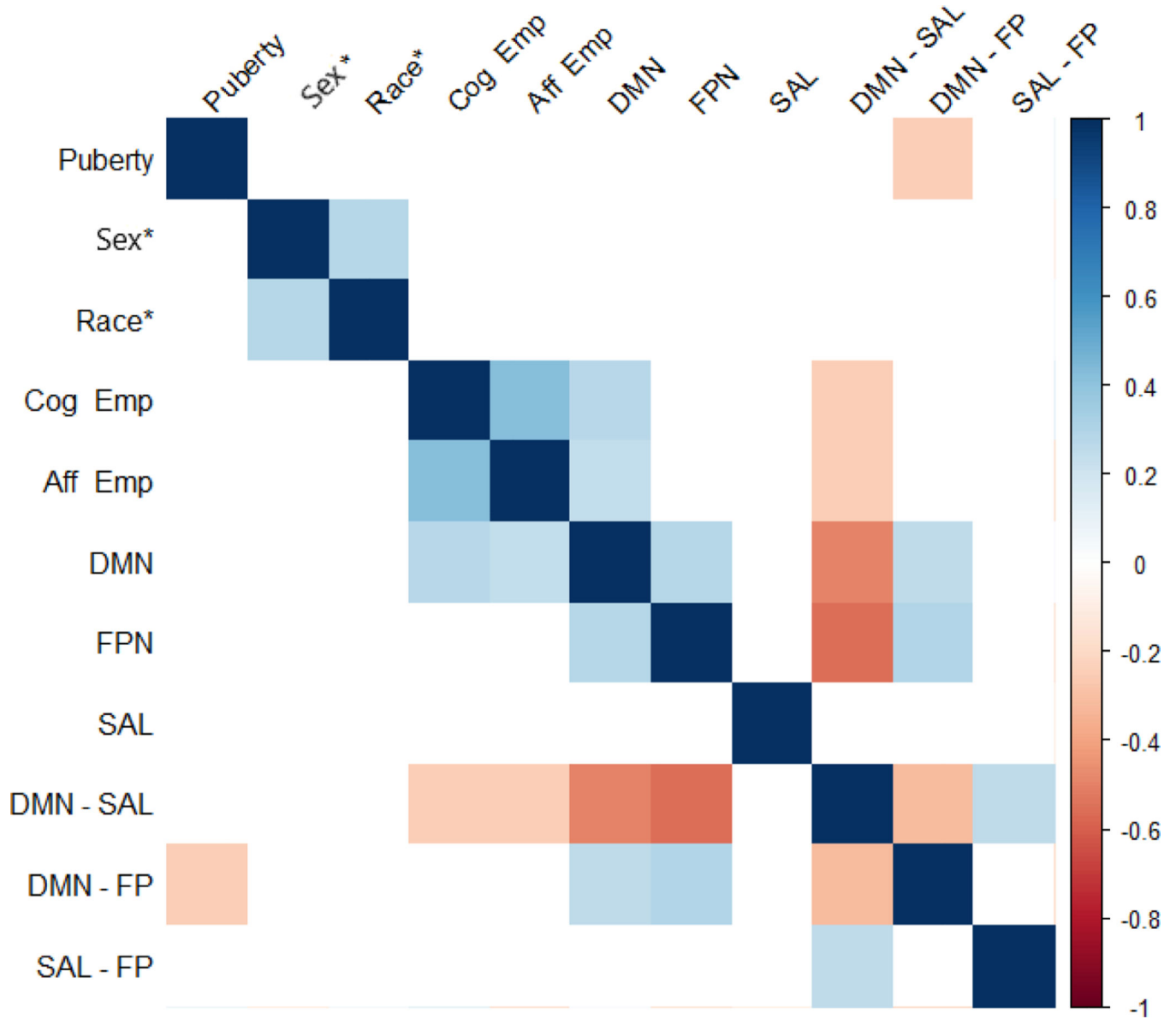
Greater cognitive empathy associates with stronger default mode network connectivity

Angular gyri and medial prefrontal pairwise connections underlie cognitive empathy

Cognitive empathy and default mode positively relate independent of affective empathy

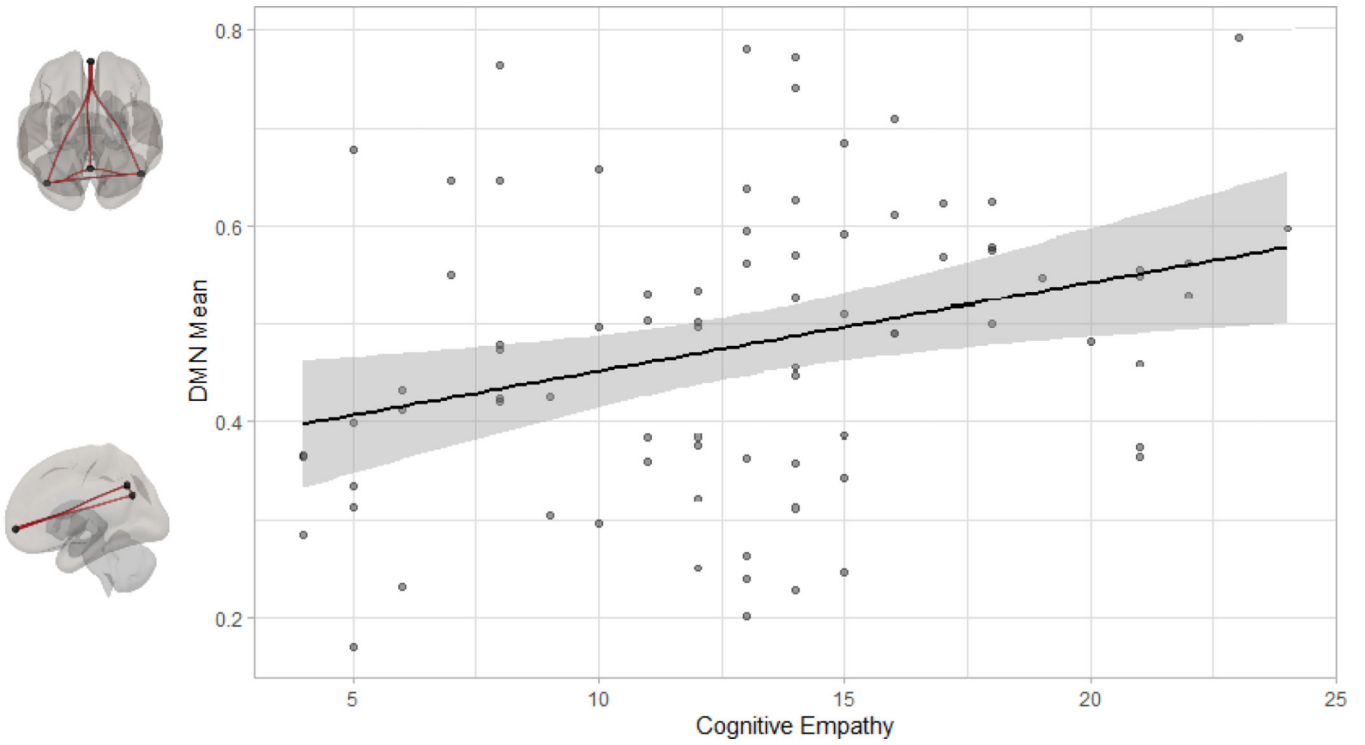
Affective empathy did not significantly associate with salience network connectivity

Our findings may suggest introspective cognition is important for cognitive empathy



**Fig. 1.** Correlation matrix of functional connectivity parameters and empathy scores. All colors shown have a p-value < .05 and all white squares have a p-value > .05. \* = Spearman correlation.





**Fig. 2.** Significant OLS line showing a positive association between cognitive empathy and DMN within-network connectivity after controlling for covariates.

**Table 1.**

## MNI Coordinates for ROIs

| <b>Network</b>                | <b>MNI coordinates of seed regions (x, y, z)</b> |
|-------------------------------|--|
| <b>Region in network</b>      |  |
| <b>Default Mode Network</b>   |  |
| Medial Prefrontal Cortex      | 1, 55, -3  |
| Angular Gyrus (L)             | -39, -77, 33                                     |
| Angular Gyrus (R)             | 47, -67, 29                                      |
| Posterior Cingulate Cortex    | 1, -61, 38                                       |
| <b>Salience Network</b>       |  |
| Anterior Cingulate Cortex     | 0, 22, 35  |
| Anterior Insula (L)           | -44, 13, 1                                       |
| Anterior Insula (R)           | 47, 14, 0  |
| Rostral Prefrontal Cortex (L) | -32, 45, 27                                      |
| Rostral Prefrontal Cortex (R) | 32, 46, 27                                       |
| <b>Frontoparietal Network</b> |  |
| Lateral Prefrontal Cortex (L) | -43, 33, 28                                      |
| Lateral Prefrontal Cortex (R) | 41, 38, 30                                       |
| Posterior Parietal Cortex (L) | -46, -58, 49                                     |
| Posterior Parietal Cortex (R) | 52, -52, 45                                      |

Note: (L) = left, (R) = right

**Table 2.**

Results of Regression Analysis

| Variable   | b     | se b | 95% CI        | t      | semi-partial <sup>2</sup> | P (FDR corrected) |
|--|-------|------|---------------|--------|---------------------------|-------------------|
| <b>Cognitive empathy on default mode network connectivity<sup>a</sup></b>                  |       |      |               |        |                           |                   |
| Cognitive Empathy  | .008  | .003 | .001, .014    | 2.385  | 9.25%                     | .049 *            |
| Tanner   | .000  | .018 | -.036, .036   | .001   | .371%                     | .999              |
| Race (White)   | -.022 | .034 | -.091, .046   | -.0648 | .389%                     | .648              |
| Sex (Male)   | -.055 | .034 | -.112, .012   | -1.636 | 3.10%                     | .176              |
| <b>Affective empathy on default mode network connectivity<sup>b</sup></b>                  |       |      |               |        |                           |                   |
| Affective Empathy  | .007  | .003 | .0003, .014   | 1.899  | 5.52%                     | .102              |
| Tanner   | .013  | .018 | -.022, .050   | .745   | .002%                     | .458              |
| Race (White)   | -.043 | .035 | -.115, .027   | -1.221 | 1.50%                     | .282              |
| Sex (Male)   | -.081 | .034 | -.148, -.014  | -2.415 | 6.70%                     | .045 *            |
| <b>Cognitive empathy on between default mode/salience network connectivity<sup>c</sup></b> |       |      |               |        |                           |                   |
| Cognitive Empathy  | -.011 | .003 | -.012, -.0006 | -2.240 | 6.75%                     | .140              |
| Tanner   | .017  | .016 | -.017, .044   | .851   | .437%                     | .397              |
| Race (White)   | -.042 | .028 | -.097, .013   | -1.523 | 2.81%                     | .219              |
| Sex (Male)   | .033  | .027 | -.020, .086   | 1.226  | 1.76%                     | .280              |
| <b>Affective empathy on between default mode/salience network connectivity<sup>d</sup></b> |       |      |               |        |                           |                   |
| Affective Empathy  | -.007 | .003 | -.012, -.002  | -2.553 | 6.14%                     | .063              |
| Tanner   | -.002 | .015 | -.032, .028   | -.127  | .673%                     | .898              |
| Race (White)   | -.009 | .027 | -.065, .045   | -.358  | .273%                     | .898              |
| Sex (Male)   | .020  | .026 | -.032, .072   | .774   | 2.14%                     | .898              |

<sup>a</sup>: R<sup>2</sup> = .1312, adj. R<sup>2</sup> = .0843, F = 2.832, p = .0301\*, df = 4, 75; n = 80 (4 outliers removed)

<sup>b</sup>: R<sup>2</sup> = .1374, adj. R<sup>2</sup> = .0914, F = 2.987, p = .0240\*, df = 4, 75; n = 80 (4 outliers removed)

<sup>c</sup>: R<sup>2</sup> = .1177, adj. R<sup>2</sup> = .0706, F = 2.501, p = .0494\*, df = 4, 75; n = 80 (4 outliers removed)

$R^2 = .1087$ , adj.  $R^2 = .0611$ ,  $F = 2.286$ ,  $p = .0679$ ,  $df = 4, 75$ ;  $n = 80$  (4 outliers removed)

\* FDR corrected  $p < .05$

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Table 3.

Pairwise ROI connectivity associated with empathy

| Contrast  | Connectivity     | t     | P <sub>(FDR corrected)</sub> |
|---|------------------|-------|------------------------------|
| The main effect of <i>default mode</i> within-network connectivity as a result of <i>cognitive</i> empathy (4 outliers removed)               | MPFC – AG(L)     | 3.74  | .0011*                       |
|   | MPFC – AG(R)     | 2.51  | .0212*                       |
| The main effect of <i>default mode</i> within-network connectivity as a result of <i>affective</i> empathy (4 outliers removed)               | MPFC – AG(L)     | 2.93  | .0135*                       |
|   | PCC – AG(R)      | 2.03  | .138                         |
| The main effect of <i>default mode and salience</i> between-network connectivity as a result of <i>cognitive</i> empathy (4 outliers removed) | AG(L) – RPPFC(L) | -3.46 | .0108*                       |

Note: Outliers from regressions were removed; controls in regressions also included in this analysis

MPFC = medial prefrontal cortex, AG = angular gyrus, RPPFC = rostral prefrontal cortex, ACC = anterior cingulate cortex, PPC = posterior parietal cortex (L) = left (R) = Right

\* = FDR corrected  $p < .05$