SOCIAL COGNITIVE AND AFFECTIVE NEURAL SUBSTRATES OF ADOLESCENT TRANSDIAGNOSTIC SYMPTOMS

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Dedication

This dissertation is dedicated to my wife Nina Leung and all others who have sacrificed during the years it took me to reach this point. I further dedicate to all the adolescents who completed a study protocol so that we can learn from your experiences.

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Nina, you have done incredible things to support me and sacrificed a great deal as I completed doctoral education and this dissertation. From picking up and moving so I could start a PhD program to organizing time around my work schedule as well as all the highs and lows in between. Words cannot do justice for the appreciation I have for all your effort and your support through the entire process.

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Drew E. Winters

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The social cognitive ability to identify another's internal state and social affective ability to share another's emotional experience, known as empathy, are integral to healthy social functioning. During tasks, neural systems active when adolescents empathize include cognitive (medial prefrontal cortex and posterior cingulate cortex with the dorsolateral prefrontal cortex) and affective (anterior insula and anterior cingulate cortex) regions that are consistent with the adult task-based literature implicating the default mode, salience, and frontoparietal networks. However, task-based studies are limited to examining neural regions probed by the task; thus, do not capture broader patterns of information processing associated with complex processes, such as empathy. Methods of functional connectivity capture broader patterns of information processing at the level of network connectivity. Although it has clear advantages in identifying neural vulnerabilities to disorder, functional connectivity has yet to be used in adolescent investigations of empathy. Via parent- and self-report, deficits in either cognitive or affective processes central to empathy associate with the most widely agreed on classifications of behavioral disorders in adolescents – transdiagnostic symptoms of internalizing and externalizing. However, this evidence relies exclusively on self-report measures and research has yet to examine the neural connectivity underlying transdiagnostic symptoms in relation to cognitive and affective empathy. What has yet to be known is (1) how the social cognitive and affective processes of empathy are functionally connected across a heterogeneous sample of adolescents and (2) the association of cognitive, affective, and imbalanced

empathy with transdiagnostic symptoms. Addressing these gaps in knowledge is an important incremental step for specifying vulnerabilities not fully captured via subjective report alone. This information can be used to improve prevention and intervention strategies. The present study will examine the functional connectivity of neural networks underlying empathy in early to mid-adolescents and their association with transdiagnostic symptoms.

Kathy Lay, PhD., Chair

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List of Abbreviations

Specific to Study Description

SES	Socioeconomic status
DMN	Default mode network
SAL	Salience network
FPN	Frontoparietal network

Specific to Imaging Methods Description

BOLD	Blood oxygen level dependent
EPI	Echo planar imaging
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
MNI	Montreal Neurological Institute (referring to a brain coordinate atlas)
MPRAGE	Magnetization prepared rapid gradient echo
SCA	Seed-based correlation analysis
TR	Repetition time
TE	Echo time

Chapter One: Introduction

Empathy is a *social cognitive* and *social affective* process that is essential to healthy function in a social environment (Decety, Bartal, Uzefovsky, & Knafo-Noam, 2016). Cognitive empathy (aka. perspective taking, mentalizing, or theory of mind) involves the process of taking on the perspective of another and inferring another's thoughts, intentions, and affective states (Decety, 2011; Decety & Cowell, 2015). Affective empathy (aka. empathic concern or affective theory of mind) incorporates an emotional sharing that is similar (isomorphic) with another and elicits concern for their emotional wellbeing (Decety, 2011; Decety & Cowell, 2015). These two components involve interacting yet distinct brain networks (Fan, Duncan, de Greck, & Northoff, 2011). Adolescent task-based imaging studies suggest social cognitive processes involve the medial prefrontal and posterior cingulate cortices constituting the default mode network (DMN) along with the dorsolateral prefrontal cortex and inferior parietal lobule that constitute the frontoparietal network (FPN); and social affective processes involve the anterior insula and anterior cingulate cortex that constitute the salience network (SAL) (Decety & Michalska, 2010; Decety, Michalska, & Akitsuki, 2008; Kral et al., 2017). These regions and networks are consistent with adult studies identifying empathy neural networks via meta-analyses of task-based imaging studies (Fan et al., 2011; Lamm, Decety, & Singer, 2011).

What is less known is how the functional connectivity within and between networks underlie cognitive and affective empathy in adolescents. Adolescence is a particularly important period for neural development in regions underlying cognitive and affective empathy. This is crucial during adolescence because of the increased complexity of social contexts and importance of peer relationships (Crone & Dahl, 2012) and that empathy development of an adolescent predicts social competence as an adult (Allemand, Steiger, & Fend, 2015). Regions underlying both cognitive and affective empathy change during this age period but regions underlying cognitive empathy go through more drastic changes during adolescence (Choudhury, Blakemore, & Charman, 2006; T. Singer, 2006). These neural differences make adolescent empathy different from adults which can be observed behaviorally via a perspective taking task (Tamnes et al., 2018). Functional connectivity within and between neural networks undergo a significant change during adolescence; thus, examining functional connectivity is an important source of information to describe complex processes and brain organization in adolescents (Ernst, Torrisi, Balderston, Grillon, & Hale, 2015). Current evidence examining empathy in adolescents rely exclusively on task-based probing that limit the neural investigations to those associated with the task (Cox et al., 2011; Ernst et al., 2015; Pu et al., 2017; Regenbogen & Habel, 2015). However, complex processes such as empathy have broader patterns of information processing than a task can probe (Blakemore, 2008; Kral et al., 2017; Sebastian et al., 2012). Thus, the above studies can be built upon by examining the functional connectivity of neural networks underlying cognitive and affective empathy in adolescents. Examining neural connectivity of cognitive and affective empathy in adolescents is crucial for understanding social and interpersonal functioning.

Impaired social and interpersonal function is central to psychiatric conditions (Bornstein, Hahn, & Haynes, 2010; Decety & Moriguchi, 2007). In adults, functional differences and imbalances dominated by either cognitive or affective processes via self-report and neurally (reflected in associations between SAL and FPN) indicate a psychopathological vulnerability that characterize social impairments in psychiatric conditions (Cox et al., 2011; Decety & Moriguchi, 2007). For example, psychopathy is characterized by self-reports of a deficit in affective empathy with intact cognitive empathy (Blair, 2013; Dadds et al., 2009), and an underlying network connectivity of diminished anticorrelations between the DMN and FPN networks (Cohn et al., 2015; Pu et al., 2017). Borderline personality disorder is characterized by behavioral measures of abnormally high affective empathy with abnormally low cognitive empathy (Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010), and a pattern of SAL connectivity that includes diminished anticorrelation with the DMN and abnormally strong correlations with the FPN (Krause-Utz et al., 2014). A final example, autism is characterized by an impairment of cognitive empathy but unaffected affective empathy (Dziobek et al., 2008), and an underlying network connectivity of anticorrelations within the DMN and reduced anticorrelations between the DMN and SAL networks in adolescents (Neufeld et al., 2018). The development of neural networks associated with cognitive and affective empathy associates with the onset of most major mental health disorders that occur during adolescence (e.g. anxiety, mood, and psychotic disorders) (Blakemore & Mills, 2014; Decety, 2010; Nock, Kazdin, Hiripi, & Kessler, 2007). Investigating empathy impairments and an imbalance between empathy components in adolescents is crucial to understand the development of mental health symptoms.

In discussing their association with mental health symptoms, cognitive and affective empathy deficits are present across several DSM-V disorders as well as *internalizing* and *externalizing* symptoms. Internalizing and externalizing symptoms comprise the most widely agreed upon classifications of behavior disorders that cross diagnostic categories (Achenbach, Ivanova, Rescorla, Turner, & Althoff, 2016).

Internalizing symptoms define depressive and anxious symptoms whereas *externalizing* symptoms describe aggression, impulse control, and conduct problems (Achenbach et al., 2016; Achenbach & Rescorla, 2001). Studies focusing on a single behavior or symptom domain ignore heterogeneity of mental health symptoms and the associated social impairments that traverse diagnostic categories. Therefore, the studies above examining empathy in relation to diagnostic categories can be improved upon by examining internalizing and externalizing symptoms. Establishing biologically informed targets for intervention requires the investigation of neurobiology beyond diagnostic categories. The NIMH Research Domain Criteria (RDoC) effort has motivated research to seek circuit level abnormalities in brain networks to symptoms present across diagnostic categories. A common way to evaluate this is using transdiagnostic symptoms of psychopathology and their causes. Functional connectivity analysis is a particularly valuable source of information for detecting neural vulnerabilities that cause transdiagnostic symptoms of psychopathology, such as cognitive and affective empathy on both internalizing and externalizing symptoms.

Internalizing and externalizing symptoms have differential associations with cognitive and affective empathy in adolescents via self-report. For example Gambin, Gambin, and Sharp (2015) found latent classes of internalizing and externalizing symptoms in adolescents that were characterized by aberrant cognitive empathy functioning (i.e. hypermentalizing and undermentalizing). Gambin and Sharp (2016) found both cognitive and affective empathy negatively associated with externalizing symptoms and affective empathy positively associated with internalizing symptoms. Gambin and Sharp (2018) found, in association with contextual guilt, affective empathy positively associated with depressive symptoms while cognitive empathy was unrelated. Together these findings suggest that cognitive and affective empathy associate with internalizing and externalizing symptoms differently and require separate investigations.

However, the neural connectivity underlying cognitive and affective empathy in relation to adolescent internalizing and externalizing symptoms has rarely been researched. As reported above, task-based imaging studies suggest activations of anterior insula and anterior cingulate of the SAL, medial prefrontal and posterior cingulate cortex of the DMN and lateral prefrontal cortices of the FPN while observing pain being inflicted on others (Decety & Michalska, 2010; Decety et al., 2008) and during a empathic accuracy task (Kral et al., 2017). For transdiagnostic symptoms, Xia et al. (2018) used a large sample to investigate adolescent brains and found, compared to typically developing controls, those with internalizing symptoms had greater connectivity within and between the SAL, DMN, and FPN; whereas those with externalizing symptoms, in comparison to controls, had less within network connectivity of the DMN and greater between network connectivity of the SAL, DMN, and FPN. Given the lines of research connecting 1) cognitive and affective empathy with transdiagnostic symptoms, 2) cognitive and affective empathy with SAL, DMN, and FPN, and 3) transdiagnostic symptoms with underlying neural connectivity of the SAL, DMN, and FPN, it is plausible that functional connectivity underlies the relationship between empathy and transdiagnostic symptoms. The next logical step is to model these relationships to test underlying neural mechanisms driving these associations. Important insights can be derived from neural models investigating how the direct relationship between functional connectivity and transdiagnostic symptoms are mediated by both components of empathy.

The DMN, SAL, and FPN networks have distinct relationships characterizing psychopathological vulnerability of transdiagnostic symptoms (see for review: Menon, 2011). In typically developing brains, DMN seed regions anticorrelate with the SAL and FPN networks; but SAL positively associate with the FPN (Menon & Uddin, 2010; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009; Zhou et al., 2017). These relationships are important to cognitive function because they indicate healthy, dynamic interactions across brain networks (Menon & Uddin, 2010; Padmanabhan, Lynch, Schaer, & Menon, 2017). Specifically, the SAL acts as a switch between self-referential processes of the DMN and external cognitive processes of the FPN (Menon, 2015; Menon & Uddin, 2010). The DMN anticorrelates with both networks because it deactivates during stimulus-driven cognition; and the FPN activates when the SAL switches to external processing, thus accounting for a positive association (Buckner, Andrews□Hanna, & Schacter, 2008; Uddin et al., 2009). Differences in these correlations suggest more neural segregation and less dynamic interaction between networks that can explain psychopathology (Menon, 2011). Brains deviating from these expected between-network associations demonstrate impairments in cognitive performance and empathy (Pu et al., 2017; Putcha, Ross, Cronin-Golomb, Janes, & Stern, 2015; Xin & Lei, 2015). The shared connections between cognitive/affective empathy and internalizing/externalizing symptoms substantiate the importance of focusing on specific hypotheses regarding the functional connectivity of the DMN, SAL, and FPN networks.

Current neural evidence of cognitive and affective empathy and their association with internalizing and externalizing symptoms in adolescents focus on either construct separately or rely on task-based probing that, due to restricted assessment of neural regions probed by the task, does not fully capture empathy or underlying psychological vulnerabilities (Cox et al., 2011; Ernst et al., 2015; Pu et al., 2017; Regenbogen & Habel, 2015). Trait-like psychopathological vulnerabilities can be detected and characterized by examining within- and between- network connectivity that task-based studies miss by probing state-like condition changes in brain activation (Menon, 2011). Examinations of adolescent empathy and psychiatric vulnerabilities are enhanced by using methods that capture broader patterns of information processing across multiple neural regions — such as functional connectivity (Ernst et al., 2015). Using resting-state fMRI data, i.e. in the absence of a task, functional connectivity estimates a value of brain connectivity and derives a spatial map of neural relationships between multiple regions composing networks. These connectivity maps can improve examinations of complex processes and detection of adolescent psychiatric vulnerabilities (Ernst et al., 2015; Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015; Magnan et al., 2013; Menon, 2011).

This study will examine the functional connectivity of brain regions previously associated with cognitive and affective empathy in relation to transdiagnostic symptoms of internalizing and externalizing. The primary contribution of the proposed research is developing knowledge that characterizes neural mechanisms underlying (1) cognitive and affective empathy, and (2) their relation to transdiagnostic symptoms in adolescents by examining shared underlying neural networks using functional connectivity. Functional connectivity is uniquely capable of capturing neural complexity underlying complex processes (i.e. empathy and transdiagnostic symptoms) beyond what can be reported subjectively or via task (Killgore & Yurgelun-Todd, 2007; Yamada & Decety, 2009), while characterizing this populations vulnerabilities that can improve prediction of behavior and prevention strategies (Ernst et al., 2015; Gabrieli et al., 2015; Magnan et al., 2013).

Investigating the functional connectivity associated with empathy is an essential incremental step toward larger goals of improving prevention and intervention strategies. Brief interventions can modify empathy across diverse (see for review: Massey, Newmark, & Wakschlag, 2017) and difficult to treat populations (Caldwell, Skeem, Salekin, & Van Rybroek, 2006; Marlow et al., 2012; Palusci, Crum, Bliss, & Bavolek, 2008), indicating the potential for a viable treatment target across diagnostic and demographic categories. Given that current evidence-based interventions for transdiagnostic symptoms that involve empathy deficits commonly have a reoccurrence of behavioral issues (Henggeler, Clingempeel, Brondino, & Pickrel, 2002; Myers, Stewart, & Brown, 1998), research on previously unresearched and modifiable targets is needed. This study will examine the previously uninvestigated network connectivity underlying empathy in adolescents and identify the association of cognitive, affective, and imbalanced empathy with internalizing and externalizing symptoms. On a basic level, this is an important contribution to knowledge building on vulnerabilities to transdiagnostic symptoms; and, on an applied level, is valuable for future investigations tailoring interventions to this specific population (i.e. important implications for social work practice).

Aims

Detecting vulnerabilities before they manifest behaviorally or can reported subjectively across broad neural processes is important to the present research question. Because of its unique position to capture these sources of information, functional connectivity methods is used to examine cognitive, affective, and imbalanced empathy in adolescent brains. The proposed research will further previous research examining social cognitive and affective processes of empathy in adolescence and its relation to early transdiagnostic symptoms by extending previous work to:

Aim 1: Examine the association between the brain's functional connectivity and self-reported cognitive and affective empathy in adolescents. Based on previous research, I hypothesize that empathic concern will associate with SAL within-network connectivity and DMN – SAL between-network connectivity; and perspective taking will associate with DMN within-network connectivity and DMN – FPN between-network connectivity. This approach allows us to examine the different neural networks underlying cognitive and affective empathy in adolescents.

Aim 2: Examine the association between the empathy imbalance score and functional connectivity in the brain. Based on previous research, I hypothesize that imbalanced empathy will associate with SAL – FPN between-network connectivity. This analysis is compared with results from this previous aim, which will allow us to determine if and how an imbalance in empathy reveals unique associations with internalizing and externalizing symptoms.

Aim 3: Examine the mediating effect of cognitive, affective, and imbalanced empathy on the association of network functional connectivity with various transdiagnostic symptoms [i.e. internalizing and externalizing]. Based on previous research, I hypothesize that cognitive empathy will mediate the relationship between DMN within-network connectivity and internalizing symptoms; whereas within SAL within-network connectivity on externalizing symptoms is mediated by affective empathy. Additionally, FPN – SAL between-connectivity on externalizing symptoms is mediated by imbalanced empathy. This design will allow us to determine if and how functional connectivity of neural networks associate with established relationships between cognitive, affective, and imbalanced empathy with internalizing and externalizing symptoms.

Methodology

General Approach. Adolescent task-based (Decety & Michalska, 2010; Decety et al., 2008; Kral et al., 2017; Zaki & Ochsner, 2012) and adult meta-analyses of task-based studies (Decety, 2010; Fan et al., 2011; Lamm et al., 2011) demonstrate similarities in neural regions implicated in empathy, thus are used to define regions of interest (ROI) for the present study. These ROIs are used in a seed-based correlation analysis (SCA) to examine the functional connectivity of neural networks associated with empathy. SCA describes the strength of functional connectivity between seed regions (regions of interest), representing a spatial map and time-series. By examining the brains of participants at rest (the absence of cognitive demands), SCA observes the relationship between the extracted time-series (a blood oxygen level dependent contrast of brain activation over time) of voxels (three-dimensional unit in the brain) representing the regions of interest constituting within network and between network connectivity. This method espouses the Hebbian principle that when regions have a stronger association in a time-series they are functionally connected; or, in other words, when regions fire together they are wired together. This study will use an SCA approach to examine the relationship between self-report measures with the strength of functional connectivity to derive inferences about neural networks underlying empathy and its neural differences as a risk for transdiagnostic symptoms.

Advantages. The primary advantage of SCA is it addresses specific questions relevant to the topic of interest by using literature supported seed regions to investigate changes in connectivity pattern across subjects. This is advantageous for the present investigation because it builds on prior knowledge to target the most relevant regions for investigating the broader patterns of information processing associated with empathy in adolescence. As a hypothesis driven approach, SCA builds on support from previous research to contextualize results meaningfully. This has a clear advantage over model free data-driven approaches for the interpretation. Seed-based correlation analysis is a powerful method that reveals large-scale spatial organization of the brain, and how this is affected in different disorders (Ernst et al., 2015).

Limitations. Two important limitations of this approach are that it is limited to the chosen seed regions and is sensitive to the spatial definition of the seed. An incorrect definition of the seed region can impact the results of the analysis. Using objective methods can reduce the potential impact of this limitation, such as defining the regions of interest using predefined templates or data driven methods. Seed region limitation may miss out on connections outside the regions selected. However, this is usually seen as a strength as it reduces extraneous multiple comparisons, is theory informed, and allows for testing a specific hypothesis that builds on existing literature (S. M. Smith & Beckmann, 2017).

Data Sample

To investigate the above aims, I will use the Nathan Kline Institute's Rockland data set (Nooner et al., 2012). This dataset includes a diverse set of participants from age 6–85 with representative gender and minority groups. The data collection took place in Rockland County New York over a period of four years. Each participant was financially compensated for their participation in the study. Initially, data collection occurred over two visits involving a screening with an assessment battery at day 1 and an imaging session at day 2 but then switched to data collection and imaging all in one day.

From the identified data set, participant selection for the present study was restricted to boys and girls who were administered the necessary measures (described below in assessments), in their early- to mid-adolescents (i.e. ages 13–17; Elliott & Feldman, 1990), with an IQ ≥ 80 assessed by the WAIS-II (α = .96; Wechsler, 2011) to ensure they are cognitively able to understand self-report measures (n=112). These inclusion criteria were implemented to provide a heterogeneous sample across demographic and diagnostic categories. Participants not meeting these criteria were excluded from this analysis. Given that age related patterns of substance use peak in late-adolescence (i.e. 19-mid 20's; Dennis & Scott, 2007), the early- to mid-adolescent age range (13-17) was selected because participants are old enough to fully express a transdiagnostic symptom phenotype but young enough to have lower instances substance use behavior that may bias the brain measurement.

Assessments

All assessment measures were collected in the first session during the assessment battery outlined in the procedure described in the section above (see data sample). Self-report measures are used in the present study. The acquisition of imaging data is described in the following section (see imaging analysis).

Dependent Variables. Dependent variables will measure internalizing and externalizing symptoms. Considering the variety of comorbidities across mental health symptoms, a multidimensional behavior assessment using both parent and child ratings are appropriate. Assessing internalizing and externalizing has an advantage over symptom clusters based on a single domain or diagnosis by integrating pertinent aspects of adolescent functioning indicative of risk across diagnostic domains. Because there is evidence that internalizing is better assessed via self-report whereas externalizing is better assessed via parent report (Lauth et al., 2010), the scales in these domains that mirror each other across reporting types are compared.

Internalizing/Externalizing. The Child Behavior Checklist (CBCL; α=.89-.94; parent report) and Youth Self-Report (YSR; α=.87-.90; child report) assess child's emotional and behavioral functioning (Achenbach, 1991). Items (e.g. "my child argues a lot", "my child destroys other people's things") are rated on a three-point scale from "not true" (0) to "very true" (2) with higher scores indicating greater symptoms. For both measures, the raw total scores are used as recommended by Achenbach and Rescorla (2001).

The child-report Child Depression Inventory Two (CDI-II; α=.68-91; Kovacs, 2004) is a 28-item measure that assesses various mood and behavioral dimensions of depression in youth (e.g. "my family is better off without me"). Items are rated on a four-point scale with higher scores indicating stronger internalizing symptoms. The total raw score is used to assess internalizing symptoms.

Independent Variables. Independent variables will measure social cognitive and affective processes of empathy. Cognitive and affective processes are assessed, as is commonly done in studies of empathy (Konrath, 2013), using the cognitive (perspective taking; α= .75) and affective (empathic concern; α = .72) subscales of the Interpersonal Reactivity Index (Davis, 1980, 1983). Items on this measure are rated on a five-point scale from “behavior does not describe me” (0) to “behavior describes me” (4) with higher scores indicating higher trait empathy. An imbalance score was calculated using criteria outlined by Cox et al. (2011) that subtracts affective empathy from cognitive empathy to create a relative empathy index score where positive scores indicate a dominance of cognitive empathy and negative scores indicate a dominance of affective empathy. A difference score was chosen over a ratio score given that cognitive and affective empathy are associated and ratio measures have highly questionable reliability, particularly when measures are non-independent (Arndt, Cohen, Alliger, Swayze II, & Andreasen, 1991). Although a valid concern is that a total empathy score would influence the imbalance score, preliminary analysis indicate they are uncorrelated ($r = .061$, $p = .377$).

Covariates. Demographic and individual factors that associate with both empathy and transdiagnostic symptoms were included as covariates. These control variables will include race measured by self-report; and both pubertal development and gender measured by the genital and breast development subscales of the Tanner assessment ($\alpha = .77$; Petersen, Crockett, Richards, & Boxer, 1988).

Imaging Analysis

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^o; 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^{o}, 176 slices, FOV= 250mm, voxel size= 1mm isotropic) were acquired.

Preprocessing of MRI data was conducted using Statistical Parametric Mapping (SPM version 12; Penny, Friston, Ashburner, Kiebel, & Nichols, 2011) with the CONN toolbox (version 18b; Whitfield-Gabrieli & Nieto-Castanon, 2012). Because of the sequence of the Siemens TimTrio, scans were not collected until there was magnet saturation, so no scans needed removed. The MPRAGE structural image were registered to the mean unwrapped EPI. Normalization parameters were obtained by segmenting the co-registered T1 image to the T1 and functional EPI images to normalize to an MNI template. Functional images were spatially smoothed with an isotropic 5mm full-width half maximum Gaussian kernel. The time-series were inspected for motion using the Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect). Timepoints identified as outliers were defined as those > 0.5mm in movement were modeled out using nuisance regressions. Participants with > 3mm motion in any direction were excluded from the analysis. Because of the fast TR and multiband sequence used at data collection, no slice timing correction was used. To reduce spurious correlations, multiple regression was used to detect variances that could be explained by nuisance factors (white matter, CSF, and six motion parameter), which were removed from each voxels time-series. In order to decrease physiologic and other sources of noise form the BOLD signal, CONN uses an anatomic component-based noise correction method (aCompCor) (Whitfield-Gabrieli & Nieto-Castanon, 2012). This method regresses out noise form the CSF and white matter unrelated to neural activity that is effective in mitigating the effects of motion (Behzadi, Restom, Liau, & Liu, 2007). As opposed to global signal regression, aCompCor ensures observed anti-correlations are not induced artificially (Chai, Castañón, Öngür, & Whitfield-Gabrieli, 2012). Finally, data were then 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). For cognitive empathy, regions making up the DMN (medial prefrontal cortex, posterior cingulate cortex, and angular gyri and the FPN (bilateral lateral prefrontal and posterior parietal cortices) were used as seed regions. For Affective empathy, regions making up the SAL (bilateral insulae, anterior cingulate cortex, and bilateral rostral prefrontal cortices) were used as seed regions. These regions were anatomically defined using the Harvard-Oxford Atlas available in the CONN toolbox. Defining regions using an existing atlas can reduce definition error and increase generalizability by capitalizing on larger sample sizes and methodological rigor used to define this atlas.

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 were extracted from the 4D preprocessed resting state scan by averaging the pairwise connections within each identified network for an averaged within network connectivity value for each participant. Next, between-network time series extraction will involve an average of all pairwise connections between each network's ROI for an averaged between connectivity value of each network for each participant. Then participant-level correlation maps 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 carried out using the r statistical language (R Core Team, 2018) using the extracted averaged within and between pairwise connections in the previous step. A generalized linear regression model was used that examines the relationship between self-report measures of empathy with extracted network connectivity. The analysis for aim 1 will examine the association of self-report cognitive and affective empathy, along with nuisance covariates (i.e. gender, SES, Tanner), with extracted within- and between- network patterns. Post-hoc analyses were conducted to examine the specific seeds driving the significant connections observed using a t test against no difference for each significant within and between network connection found in the initial analysis. For aim 2, the association between an empathy imbalance score, along with nuisance covariates, with extracted within- and between- network patterns were calculated. For aim 3, a mediation model was tested for cognitive, affective, and imbalanced empathy as mediators for the association between functional connectivity and transdiagnostic symptoms.

Potential issues. Inspection of the data may reveal that regions of interest do not align with the Harvard-Oxford Atlas. This could impact the results and confound meaningful interpretation. If quality inspection of the data suggests this, the use of an independent component analysis, a data driven approach, to define the chosen regions of interest with this specific sample may be necessary. However, this is highly unlikely given the registration of all subject's brains with a standardized space that should align with the atlas. If this is an issue, it can be addressed prior to analysis.

Another issue that may arise is a proportion of participants having motion artifacts (movement > 3mm) making some images unusable. Many studies expect 10-15% of participants will have unreconcilable motion artifacts and must be excluded from the analysis. If this were the case this study would still have a significant proportion of participants (n= 111-117) that have enough power to detect differences in functional connectivity. It is unlikely that enough of the participants were excluded from the study to impact the ability to detect differences in functional connectivity between participants.

Statistical Analysis

Because of the exploratory nature of the present study and a high potential for missing important findings by implementing a p-value correction in such a study (Feise, 2002; Rothman, 1990; Streiner & Norman, 2011), A two-tailed uncorrected p-value will define statistical significance. Practical significance was assessed by examining the effect size for each analysis that can aid in decisions of relevance of analysis outcomes. All statistical analyses were conducted using r statistical programing language (R Core Team, 2018). As is commonly practice in fMRI analyses, missing entire measures used in the present study were handled by listwise deletion (Mulugeta, Eckert, Vaden, Johnson, & Lawson, 2017).

Aim 1: Examine the association between functional connectivity in the brain and self-reported cognitive and affective empathy. Using the extracted within- and between network averaged time-series, linear regression was used to examine the relationship of self-reported cognitive and affective empathy with within- and between network resting-state functional connectivity. To examine each process individually, cognitive (perspective taking) and affective (empathic concern) scales were entered in separate models as covariates of interest, along with relevant covariates, to examine their association with seed-based connectivity across the entire sample. To reduce the number of models tested, correlations were run first to determine which associations are appropriate for testing in a regression model. I anticipate stronger within network associations in the DMN will relate to cognitive empathy and SAL to associate with affective empathy.

Aim 2: Examine the association between the empathy imbalance score and functional connectivity in the brain. Using linear regression, the association with an empathy imbalance with within- and between network associations were examined. The empathy imbalance score was entered in as a covariate of interest, along with relevant nuisance covariates. I anticipate that greater imbalances with a dominance in either dimension will associate with weaker associations within the DMN (dominance in affective) and SAL (dominance in cognitive) networks. For between networks, I anticipate an empathy imbalance will associate with connectivity between the SAL and FPN networks. Finally, this analysis was compared with cognitive and affective subscales in separate analysis to determine whether the empathy imbalance provides information about neural connectivity beyond the two domains individually.

Aim 3: Examine the mediating effect of cognitive, affective, and imbalanced empathy on the association of network functional connectivity with various transdiagnostic symptoms [i.e. internalizing, externalizing]**.** Mediation models were used to examine the mediation effects functional connectivity has on the associations between cognitive and affective empathy with primary transdiagnostic symptoms (i.e. internalizing and externalizing). To avoid issues of multicollinearity, separate analyses were fitted for cognitive, affective, and imbalance scores predicting transdiagnostic symptoms. Prior to fitting each mediation model, correlations were used to identify the most relevant predictors prior to testing the mediation models. First, functional connectivity parameters were entered as independent variables on transdiagnostic symptoms with the mediator as cognitive and affective empathy determined to be significant from the correlation analyses. It is anticipated that cognitive empathy will mediate the relationship between functional connectivity (specifically within the DMN and between the DMN and SAL connectivity) and internalizing symptoms; whereas within SAL connectivity on externalizing symptoms were mediated by affective empathy. Next, the functional connectivity parameters were entered in as an independent variable on transdiagnostic symptoms with the mediator as imbalance empathy score determined to be significant from the correlation analyses. Here it is anticipated that between FPN and SAL connectivity on externalizing symptoms will be mediated by imbalanced empathy.

Power Considerations. For all regressions, assuming a medium effect size ($f = .15$), a two-tailed p-value of .05 with power at 80% with four predictor variables results in requiring 79 participants to accurately detect linear relationships. Given literature support that increases in empathy will likely have an additive effect (positive or negative) on outcome variables related to transdiagnostic symptoms, applying a linear model is appropriate. For mediation analysis, using the 'powerMediation' package in r (Qiu & Qiu, 2018), assuming we have medium effects with a beta value for the mediation of .3, error of 1, a mediator correlation of .3 , and alpha of .05 at 80% power, we would need 95 participants to reach adequate power. Thus, the sample size for the current study is adequate for all aims.

Considering Factors that Threaten Validity. The data collection protocol kept a consistent environment during data collection that occurred at one period, thus, limiting threats to validity at the data collection stage. The measures used are assessing trait as opposed state characteristics so the fact that measurements were in the lab likely had minimal effects on validity in comparison to behavioral observations. For neuroimaging acquisition, there are several external factors that may affect the results at the time of imaging acquisition (e.g. caffeine intake, present physical state, time of day). A review of the notes taken on each participant during neuroimaging acquisition were reviewed for issues that may impact the images for that participant. If there are any issues of concern, I will make a note and consult with committee members before coming to a consensus on what course of action to take. Finally, the measures selected, although they have a history of validity and reliability, may not be internally consistent with the present sample. However, the use of both parent and child reported measures will likely mitigate this issue.

For external factors, relevant control variables are selected to account for additional variability related to the relationship of interest. However, the present study is limited to measures used in the parent study that may not tap into additional external factors important for the present topic. Variables that may account for variability not included in the present study include family functioning or attachment type, but the included covariate of trauma symptoms can act as an adequate proxy for these variables. The results of this study may suggest the need for future data collection that include unaccounted external factors. Finally, for region of interest definition, the spatial definition of the regions of interest, if incorrect, could affect the validity of results. In order to address this, a predefined template that used a large sample and rigorous methods could be used to reduce error on the account of the researcher. If this method does not adequately define the regions of interest, a data driven approach may be used to define these regions specific to this data set.

Human Subjects Review. The present study is a secondary analysis. Therefore, many of the considerations of working with human subjects during data collection were already addressed at time of the data collection. Such considerations include recruitment and data collection. For participant recruitment, enrollment was monitored and adjusted to ensure that the relative proportions of age, gender, and ethnicity remained stable through the project. The location of Rockland county in New York is representative of the national distribution of these demographic categories and these efforts ensured a representative sample. All identifying information has been removed from the data prior to receiving it from the database.

To protect participants during neuroimaging data collection, participants were asked to remove medication patches, checks for comfort related to claustrophobia were done and study was stopped if they were uncomfortable, participants were not exposed to high enough magnetic fields that could promote neurostimulation, all female participants were tested for pregnancy prior to imaging session and were excluded if test was positive, and all objects that may interact with the magnetic field (i.e. jewelry, metal earrings) were removed from the scanning room. Appropriate participants were screened via a phone screening and initial assessment that was reviewed by the research team prior to the scanning session. Finally, participants were provided ear plugs during the imaging session to ease discomfort with machine noise during the session.

Logical Connections Between Studies

This study comprises two studies. The first is examining self-reported empathy with functional connectivity in adolescents. The second study examines the neural connectivity underlying cognitive, affective, imbalanced empathy as a mediator in the relationship between empathy and transdiagnostic symptoms. These two studies examine key variables underlying social functioning at a crucial period of development. The first study lays foundational information for how the components of empathy are functionally connected in adolescents. The second study builds on this knowledge base to examine how the functional connectivity associated with the components of empathy in the brains of adolescents' associate with transdiagnostic symptoms. Together these two studies provide base level knowledge for understanding mechanisms underlying healthy and aberrant social emotional functioning in adolescents that have significant implications at a basic and practical level.

Relevance for Social Work

The present investigation is relevant and important for social work inquiry. First, empathy is the fundamental psychological construct underlying the function of society and the individuals within that society. Disruptions in the cognitive and affective dimensions impact wellbeing via social behavior and mental health. Because of the relevance for promoting health for individuals and society, investigating empathy in adolescents is an appropriate topic.

Using neuroimaging to investigating empathy in adolescents is important for this line of research and relevant for Social Work. The preamble to the mission of social work states "the primary mission of social work is to promote wellbeing … with a particular focus on those who are most vulnerable" (National Association of Social Workers, 2008). Behavioral theories alone have not been adequate for identifying vulnerabilities to threats of wellbeing such as mental health illness or specifying targets for promoting wellbeing (Michie et al., 2013; Whitfield-Gabrieli et al., 2016). Interventions based in behavioral theories alone take a considerable time to observe any change behaviorally making it difficult to determine the best course of action until the full treatment has been provided (Whitfield-Gabrieli et al., 2016). On the other hand, neuroimaging is a method that has been demonstrated to detect vulnerabilities for mental health symptoms before they can be observed behaviorally (Keller et al., 2015; R. et al., 2019; Vaidya & Gordon, 2013). And, neuroimaging results have defined specific targets for interventions that can also be examined before outcomes can be behaviorally observed, thus aiding detection of viable interventions earlier (Gabrieli et al., 2015; Magnan et al., 2013; Whitfield-Gabrieli et al., 2016). Studying behavioral changes alone is not sufficient for deeply understanding developmental processes of cognitive brain functions of complex processes (Morita, Asada, & Naito, 2016). Given that these methods aid the primary mission of Social Work, using neuroimaging to answer questions in this area is appropriate.

Finally, harnessing technology for social good is a grand challenge of social work (Fong, Lubben, & Barth, 2017). Neuroimaging is a technology that is uniquely positioned to promote social good. From the points made above about its potential to detect what makes people more vulnerable and defining specific targets to promote wellbeing, using this data in Social Work research has the potential to promote wellbeing for the populations we serve. Given the potential to uniquely serve the primary mission of social work, these methods are relevant for Social Work research.

Chapter Two: Study One

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

Empathy, broadly defined as the ability to understand others' emotions, is a critical skill for effective functioning in the social environment, and is central to prosocial and altruistic behavior (Decety et al., 2016; Eisenberg & Miller, 1987). Adolescence is a period of rapid neural changes that coincides with increasing complexity in social relationships and environments, which makes this a particularly important time for social emotional development in empathy (see for review: Blakemore, 2012b). Research indicates that the onset of most major mental health disorders (e.g. major depression, bipolar, schizophrenia) occurs during adolescence (Paus, Keshavan, & Giedd, 2008) and that adolescents with higher levels of empathy have less behavioral problems or mental health symptoms (internalizing and externalizing symptoms) that span categorical mental health disorders (Gambin et al., 2015; Gambin & Sharp, 2016, 2018).

Empathy is supported by cognitive and affective processes that have distinct conceptual and neural contributions (Decety & Cowell, 2015; A. Smith, 2006; Walter, 2012). Cognitive empathy (or perspective taking) involves adopting the view point of another via processing contextual information to infer their thoughts, feelings, and affective states (Decety, 2011; Decety & Cowell, 2015). Task-based studies demonstrate activation in areas such as the medial prefrontal cortex and posterior cingulate cortex constituting the default mode network (DMN) , and the inferior parietal lobule and dorsolateral prefrontal cortices that constitute the frontoparietal network (FPN) during images of pain (Decety & Michalska, 2010; Decety et al., 2008), videos describing emotional events (Kral et al., 2017), and cartoon vignettes (Gallagher et al., 2000). The DMN is involved in internally focused thought and simulations based on previous experiences (Buckner, Andrews-Hanna, & Schacter, 2008; Buckner & Carroll, 2007) that is thought to underly the understanding of another's perspective facilitating cognitive empathy processes (Uddin et al., 2009). The FPN is involved in externally focused tasks such as processing social information and social reasoning (Dixon et al., 2018) that supports focus on and switch between relevant social stimuli in support of empathy (Eslinger, 1998; Grattan & Eslinger, 1989).

Affective empathy (or empathic concern) involves an emotional sharing that is similar (isomorphic) with another and elicits concern for their emotional wellbeing (Decety, 2011; Decety & Cowell, 2015). Neural investigations of empathic concern that use stimuli for pain demonstrate activation of neural regions that are active during first-hand experience in adults (Tania Singer et al., 2004) and youth aged 7 – 12 years old (Decety et al., 2008). Task-based studies demonstrate activation in the anterior insula, anterior cingulate and rostral prefrontal cortex that constitute the salience network (SAL) during images of pain (Decety & Michalska, 2010; Decety et al., 2008) and videos describing emotional events (Kral et al., 2017). Regions underlying the SAL work together to integrate sensory, affective, and cognitive information that facilitate affective empathy (for review see: Menon, 2015). The rostral prefrontal cortex is consistently involved in emotional mentalizing (Gilbert et al., 2006), the anterior cingulate cortex is 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 as well as empathic processes (Menon & Uddin, 2010). Together the anterior cingulate cortex and insula are involved in vicarious experiences (Fan et al., 2011; Lamm et al., 2011; Lockwood, 2016) that support affective sharing with another.

The cognitive and affective components of empathy associate with activation in distinct neural networks and different behavioral outcomes. Neural networks involved in perspective taking undergo substantial changes during adolescence that mature much later than those underlying empathic concern. For example, the medial prefrontal cortex does not fully develop until 25 years of age (Blakemore, 2012a; T. Singer, 2006). Age related differences between adolescents and adults are observed in the medial and dorsolateral prefrontal cortices during task-based activations (Decety & Michalska, 2010). Behavioral data suggests that adolescents do not perform as well and show less frequent perspective taking than adults (Choudhury et al., 2006; Dumontheil, Apperly, & Blakemore, 2010; Symeonidou, Dumontheil, Chow, & Breheny, 2016). Behaviorally, although both cognitive and affective empathy negatively associate with aggression in typically developing adolescents, affective empathy deficits associate with more reactive aggression; whereas cognitive empathy deficits associate with more proactive aggression (Pouw, Rieffe, Oosterveld, Huskens, & Stockmann, 2013). Prosocial behavior is driven by empathy (Decety et al., 2016) and a longitudinal investigation demonstrates affective empathy has a consistent and direct association, whereas cognitive empathy an indirect relationship with prosocial behavior (Van der Graaff, Carlo, Crocetti, Koot, & Branje, 2018). Moreover, imbalances between cognitive and affective empathy, where one component is more dominant over the other, associates with different mental health symptoms that underly aberrant social behaviors and is reflected in connectivity between SAL and FPN networks (Cox et al., 2011).

Given the neurodevelopmental differences and distinguishable behavioral outcomes, it is important to characterize the neural mechanisms underlying the different components of empathy in adolescents. Although the studies described above investigate neural activation during empathy tasks in adolescents, none have used methods to investigate broader patterns of information involved in the cognitive and affective components or the imbalance of empathy. One exception is the study by Blakemore (2012a) which examined resting state functional connectivity between adolescents and adults; however, this study focused exclusively on social cognitive functioning. The majority of research to date in adolescents has focused on isolating brain activation in either perspective taking or empathic concern using task-based paradigms investigating one of these processes. Although useful, task-based studies of neural activation probes the neural regions associated with a task capturing a state-dependent measure that may miss out on broader trait-like network level connection patterns associated with complex processes, such as empathy (Ernst et al., 2015). Functional connectivity captures the brains intrinsic functional architecture that can identify broad neural underpinnings of complex processes and their ontogeny during adolescents (Ernst et al., 2015). Significant adolescent neural changes mostly involve functional connections within and between networks (Ernst et al., 2015); thus, examining functional connections can capture neural functioning underlying complex processes in adolescents.

In the present study, we expand on prior task-based research on empathy in adolescence to determine the neural connections underlying empathy across identified networks. We investigated what neural connections within and between the DMN, FPN, and SAL networks associate with cognitive, affective, and imbalanced empathy. We hypothesized that empathic concern would associate with SAL connectivity and between SAL and DMN connectivity; perspective taking would associate with DMN connectivity and between DMN and FPN connectivity; and imbalanced empathy would associate with connectivity between the SAL and FPN networks.

Methods

Participants. The sample was composed of right-handed early to mid-adolescents (i.e. ages 13–17; Elliott & Feldman, 1990) boys and girls drawn from Nathan Kline Institute's Rockland data set (Nooner et al., 2012) that was obtained through the 1000 functional connectomes project (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 all in one day. Participants were included if they had an IQ ≥ 80 assessed by the WAIS-II (α = .96; Wechsler, 2011) to ensure they are cognitively able to understand self-report measures. The study ethical considerations including approval and informed consent is outlined in Nooner et al. (2012).

Assessments

Self-report assessment of empathy. Empathy was measured using the affective empathy (empathic concern) and cognitive empathy (perspective taking) subscales of the interpersonal reactivity index (Davis, 1980, 1983). The affective empathy subscale (α=.74) consisted 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 (α=.79) consisted 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 confirmed on other samples across age groups and nation of origin; has evidence of convergent and concurrent validity; and is the most widely used measure for cognitive and affective empathy (Konrath, 2013). Items in this measure were rated on a five-point scale rating behavior that “does not describe me” (0) to “describes me well” (4) with higher scores indicating higher levels of dispositional empathy.

An imbalance score was calculated using criteria outlined by Cox et al. (2011) that subtracts affective empathy from cognitive empathy to create a relative empathy index score. In this difference empathy score, positive scores indicate a dominance of cognitive empathy and negative scores indicate a dominance of affective empathy. A difference score was chosen over a ratio score given that cognitive and affective empathy are associated and ratio measures have highly questionable reliability, particularly when measures are non-independent (Arndt et al., 1991). Although a valid concern is that a total empathy score would influence the imbalance score, preliminary analysis indicate they are uncorrelated ($r = .054$, $p = .625$).

Covariates and Demographics. Demographic variables for race and gender were recorded via self-report and included as control variables. Because the sample was predominantly white (61.9%) the sample was grouped into white and non-white categories for the 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. These three variables were used as control variables to account for additional variation in the regressions.

For demographic information, socioeconomic status was assessed by the Hollingshead four-factor index of social status (Hollingshead, 1975). This measure examines the four domains of education, occupation, gender, and marital status by scoring each domain and a higher total score indicates a higher socioeconomic status

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^o; 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^o, 176 slices, FOV= 250mm, voxel size= 1mm isotropic) were acquired. The siemens sequence does not collect images until magnate saturation is achieved so no scan removal for T1 stabilization was necessary.

Preprocessing of MRI data were conducted using Statistical Parametric Mapping (SPM version 12; Penny et al., 2011) with the CONN toolbox (version 18b; Whitfield-Gabrieli & Nieto-Castanon, 2012). The MPRAGE structural image was registered to the mean unwrapped EPI. Normalization parameters were obtained by segmenting the co-registered T1 image to the T1 and functional EPI images to normalize to an MNI template.

Functional images were spatially smoothed with an isotropic 6mm full-width half maximum Gaussian kernel. The time-series was inspected for motion using the Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect). Timepoints identified as outliers were defined as those > 0.5mm in movement that were modeled out using nuisance regressions. Participants with > 3mm motion in any direction and participants with > 20% invalid scans were excluded from the analysis. Because of the fast TR and multiband sequence used at data collection, no slice timing correction was used. To reduce spurious correlations, multiple regression was used to detect variances that could be explained by nuisance factors (white matter, CSF, and six motion parameter), which were removed from each voxels time-series. In order to decrease physiologic and other sources of noise form the BOLD signal, CONN uses an anatomic component-based noise correction method (aCompCor) (Whitfield-Gabrieli & Nieto-Castanon, 2012). This method regresses out noise form 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). Finally, data was 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). For cognitive empathy, regions making up the DMN (medial prefrontal cortex, posterior cingulate cortex, and angular gyri) and the FPN (bilateral lateral prefrontal and posterior parietal cortices) are used as seed regions. For Affective empathy, regions making up the SAL (bilateral anterior insulae, anterior cingulate, and bilateral rostral prefrontal cortices) are used as seed regions. These regions are anatomically defined using the Harvard-Oxford Atlas available in the CONN toolbox (MNI coordinates on 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 by averaging all pairwise connections within each network for an averaged within network connectivity value for each participant. Next, between-network time series extraction will involve an average of all pairwise connections between each network's ROI for an averaged between connectivity value of each network for each participant. Then participant-level correlation maps 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 software (R Core Team, 2018) using the extracted averaged within and between pairwise connections in the previous step. In order to avoid missing important findings in this exploratory study with a small sample (Feise, 2002; Rothman, 1990), we did not adjust for multiple comparisons, therefore an uncorrected two-tailed p-value of $< .05$ defined statistical significance. First Pearson correlations were conducted to examine linear relationships between self-reports of empathy and both within and between network connectivity parameters for further analyses. Correlations $> .2$ with an uncorrected $p < .05$ were considered for further investigation for regressions.

Then linear regression models were fitted to examine the relationship between self-report measures of empathy, along with nuisance covariates (gender, race, Tanner stage), with extracted within- and between- network patterns. An a-priori two-tailed power analysis specifying one independent with three covariates, a moderate effect ($f = .15$) and alpha of .05 suggested a sample of 80 would be sufficient at 80% power to detect significant associations in these regressions. 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). Results and figures are reported after removing influential outliers as a result of regressions based on cook's D where using a threshold cutoff of $D(i) > 4/n$ (Cook & Weisberg, 1982). All results stayed the same without outliers removed, except in one case identified in the results. Then post-hoc t-tests were used to examine the seeds driving the significant associations form the regressions were run in the Conn toolbox. These t-tests compared the means of ROIs within and between network connection against zero or no BOLD signal connectivity.

Results

Out of 155 potential participants, 43 did not fill out key measures and 28 more were removed for motion issues or high level of invalid scans (Figure 1). The final sample consisted of 84 right-handed male and female participants (46.4% female) aged 13-17 (14.64±1.36) with an average SES of 48.58±9.32 (range = 21 - 66). Average within and between network connectivity across all participants indicates heterogeneity in connectivity parameters (Table 1).

Correlations of mean network connectivity with empathy. Pearson correlations (Figure 2) revealed that both cognitive and affective empathy positively associate with DMN connectivity (cognitive[$r=.27$, $p=.012$]; affective[$r=.24$, $p=.026$]) and negatively with between DMN and SAL network connectivity (cognitive[r= -.25, p=.022]; affective[r= -.25, p=.023]). The empathy imbalance score has a positive association with SAL – FPN between-network connectivity suggesting an imbalance dominance of cognitive empathy associates with a stronger connection between these two networks (r= .23, p= .031).

Regressions of mean network connectivity with empathy. For within DMN connectivity results, *cognitive empathy* (Table 2, Figure 3) significantly associated with within network DMN connectivity (b=.008, p= .019) and the overall model accounted for 13% of the variance (R^2=.131, F(4,75) = 2.832, p=.0848, 4 outliers removed). However, *affective empathy* (Table 2) did not significantly associate with DMN connectivity (b=.006, p= .061; different from the significant association [b=.008, p=.034] prior to removing the influential outliers); although, gender was statistically significant (b=-.081, p= .018) and the overall model accounted for 14% of the variance (R^2=.137, F(4,75) = 2.987, p=.0240, 4 outliers removed).

For DMN – SAL between-network connectivity, results of regressing *cognitive empathy* (Table 2, Figure 3) indicated it significantly associated (b=.006, p=.028) and the model accounted for 12% of the variance (R^2=.117, F(4,75) = 2.501, p=.0494, 4 outliers removed). *Affective* empathy (Table 2, Figure 3) also significantly associated with between DMN and SAL connectivity (b=.007, p=.012) and the overall model accounted for 11% of the variance (R^2=.108, F(4,75) = 2.286, p=.0679, 4 outliers removed).

For FPN – SAL between-network connectivity (Table 2, Figure 3), regressing empathy imbalance significantly associated with within network DMN connectivity (b=.006, p=.017) and the overall model accounted for 16% of the variance (R^2=.155, F(4,70) = 3.211, p=.0494, 9 outliers removed). This finding suggests that an imbalance dominance in cognitive empathy associates with greater FPN – SAL between-network connectivity.

Post-hoc ROI t-tests of empathy. Results of the ROI analyses paralleled the regression results, such that higher cognitive empathy associated positively with DMN connectivity, both cognitive and affective negatively associate with DMN – SAL between-network connectivity, and imbalanced empathy positively associates with FPN – SAL between-network connectivity (Table 3, Figure 4). These tests revealed what pairwise connections drove the significant network level associations. For within DMN connectivity, greater medial prefrontal cortex connectivity with the angular gyri underlie cognitive empathy. For DMN – SAL between-network connectivity, less connectivity between the left angular gyrus with the left rostral prefrontal cortex underlies cognitive empathy; and less connectivity between the left angular gyrus with both the right anterior insula and left rostral prefrontal cortex underlies affective empathy. Finally, greater FP – SAL between-network connectivity is driven by the anterior cingulate and posterior parietal cortex, which underlies an empathy imbalance where greater value indicates an imbalance dominance in cognitive empathy.

Discussion

This study provides the first evidence that cognitive, affective, and imbalanced empathy in adolescents associate with differences in functional connectivity within and between the DMN, SAL, and FPN networks. Previous work also implicates neural regions underlying cognitive and affective empathy; however, these studies used tasks that probe neural regions associated with the task and miss out on trait-like patterns across networks underling these processes (Blakemore, 2008; Kral et al., 2017; Sebastian et al., 2012). This study expands upon prior work by examining the intrinsic connectivity of adolescent brains to examine broader connections that are not captured in task-based studies.

For within-network, cognitive empathy positively associates with DMN connectivity as expected, which held after controlling for nuisance covariates. This may be due to reasoning with or simulation of others mental and affective states via self-referential and perspective-taking processes associated with this network (Buckner, Andrews-Hanna, et al., 2008; Buckner & Carroll, 2007). Post hoc analyses revealed the medial prefrontal cortex connectivity with the bilateral angular gyrus drove this within network association. 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 suggest internally reasoning with external social stimuli, which may drive cognitively simulating emotions of others via perspective taking (Istvan Molnar-Szakacs & Lucina Q. Uddin, 2013). The DMN and its underlying regions are involved in may processes not just those specific to empathy. The significance of its association is that referencing oneself (emotions, behavior, mental state) and reasoning about stimuli received from the external environment and the states of people in it is integral to taking on the perspectives of others. Although the neural regions associated with perspective taking are still developing in adolescents, this finding is consistent with literature showing adolescents can engage in perspective taking (Lanciano & Curci, 2019; Tamnes et al., 2018).

For between network connectivity, the finding that a negative association of DMN – SAL between-network connectivity for both cognitive and affective empathy is particularly interesting. One interpretation of these findings is that higher levels of empathy in either domain associates with greater functional coupling between the DMN and SAL. Lower anticorrelations between the DMN and SAL associate with mental health disorders such as bipolar disorder (Gong et al., 2019), obsessive compulsive disorder (Chen et al., 2018), and schizophrenia (Hare et al., 2018). Stronger anticorrelations associate with maturity in brain development (Uddin, Supekar, Ryali, & Menon, 2011). It may be that higher empathy in either domain associates with brain maturity or greater mental health.

After controlling for nuisance covariates, neural regions underlying cognitive empathy were driven by correlations between left rostral prefrontal cortex and left angular gyrus. Because of stimulus attending and the processes around it associated with the rostral prefrontal cortex (Gilbert et al., 2006) and mental representations and internal mentalization associated with the angular gyrus (for review see: Seghier, 2013), this relationship suggests reasoning with environmental stimuli. Similarly, neural regions underlying affective empathy were driven by the same anticorrelations but also included the anterior insula. The insula adds awareness of body states and emotions (Menon & Uddin, 2010; Suzuki, 2012) suggesting a reasoning with stimuli related to the environment and current emotional state. These may be the point at which the salience network switches to externally focused processes in the frontoparietal network, but we are unable to determine this from the present analysis. The similar seed region connectivity underlying these processes between the networks suggest similar processes driving both components of empathy. It may be that cognitive empathy has an influential relationship on affective empathy found in task-based studies on adolescents as suggested by Kral et al. (2017), which may explain the shared ROIs driving the significant relationships.

The empathy imbalance measure provided information beyond cognitive or affective empathy alone. Specifically, an empathy imbalance toward a dominance in cognitive empathy positively associated with stronger connectivity between the FPN and SAL networks. The SAL is known as a switch between the internally focused cognitive processes of the DMN to external systems in the FPN (Menon & Uddin, 2010); thus this finding suggest less efficiency switching to externally focused cognitive processes with an imbalance dominance in affective empathy and more efficiency with an imbalance dominance in cognitive empathy. One interpretation of this result is that an imbalance in cognitive empathy associates with a stronger proclivity toward externally focused social cognitive processes. The null findings between an empathy imbalance with DMN connectivity or between DMN and SAL connectivity partially supports this interpretation. It is important to note that, in adults, an imbalance dominance in cognitive empathy associates with anger (Cox et al., 2011) and abnormally strong connection SAL – FPN between-network connectivity underlies borderline personality disorder (Krause-Utz et al., 2014).

Post hoc analysis suggests the positive relationship between the anterior cingulate cortex and right posterior parietal cortex drive this association. The anterior cingulate integrates affective information for social decision making (for review see: Lavin et al., 2013) and the right posterior parietal cortex is involved in social decision-making processes (Gilaie-Dotan et al., 2014). It may be that adolescents with an imbalance in cognitive empathy form more social judgements and switch to external processes far more often to seek external social information for social decision making. Although more examination is needed, this association may underlie impairments related to adult imbalances in adolescents.

Across all analyses, tanner developmental stage, race, or gender did not significantly associate with functional connectivity. One exception was the results between affective empathy and within network DMN connectivity where being a female (as opposed to a male) was significant after holding affective empathy, tanner stage, and race constant. This finding contrasts with literature on DMN connectivity in youth suggesting DMN connectivity is stronger in boys than in girls (Ernst et al., 2019). Gender differences in empathy is highly debated with many suggesting females self-report higher empathy than males (Baron-Cohen & Wheelwright, 2004; D. Cohen & Strayer, 1996; Davis, 1983). However, when examining neural activations, these differences are not existent, which has led some to assert self-reports alone are biased by social conditioning of gender and may not reflect true empathic ability between genders (Decety & Michalska, 2010; Michalska, Kinzler, & Decety, 2013). Although self-reports for empathy are used, the present results support that latter position the there are no neural differences in empathy between gender.

Limitations. This study used resting state functional connectivity analyses of the DMN, FPN, and SAL networks with early to middle adolescent self-reported perspective taking and empathic concern. This was a cross sectional, which made it impossible to discern causality between empathy and functional connectivity. Similarly, we did not have enough of a sample to separate heterogeneous periods of adolescents. 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.

In the present study, empathy was defined as perspective taking and 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 cognitive empathy.

There are also concerns about detecting the true effects. The analysis using imbalanced empathy did not reach a priori determined sample size to reach adequate power. It maybe that the current findings reflected reality, but it is worth noting that there may be effects that we could not detect due to a loss of power. Additionally, we did not control for multiple comparisons which increases chances of spurious effects. To mitigate these, we examined the effect size to assess the plausibility of the effect.

Additionally, 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. And, each region detected in the present analysis is involved in multiple processes making it difficult to pinpoint exactly what process our results are involved in. Although this was further investigated by examining what neural regions underly the associations found, using tasks can help further parse what processes regions that are recruited are engaged in.

Implications and conclusions. In the context of supporting empathy in adolescence, the pattern of connectivity uncovered in the present study identifies mechanisms important for further examination. Specifically, the positive association found between cognitive empathy and the DMN suggests the importance of self-referential processing and thinking about others states in perspective taking. Self-referential processing also plays an important role in the association between affective empathy and functional coupling of DMN – SAL between-network connectivity. Targeting self-referential processes underlying cognitive empathy is an important consideration for future investigations seeking to balance a cognitive dominance imbalance in empathy. This is consistent with task-based studies suggesting perspective taking plays a key role in empathy development during this age and may be a key target for increasing empathy (Kral et al., 2017). Interventions such as mindfulness (for review: Cheang, Gillions, & Sparkes, 2019; Donald et al., 2019) or CBT (Garber, Frankel, & Herrington, 2016; Thwaites et al., 2017) have been shown to improve empathy that could be tailored toward targeting cognitive empathy in adolescents. Because this is a heterogenous sample, these connectivity patterns may generalize to adolescent populations that are at high risk for development of mental illness. Future investigations along this line of research may lead to improvements in school-based programs aimed at cultivating empathy. More research is needed to assess how neural connectivity may be different and modified in different clinical populations or transdiagnostic symptom clusters during this important developmental period. The present study is an important incremental step toward larger goals of supporting empathy in adolescents.

Chapter Three: Study Two

Functional connectivity associations with transdiagnostic symptom related to cognitive and affective empathy

Empathy is the ability to understand and share in another's affective state that allows humans to skillfully navigate a social world (Decety, 2007; Decety et al., 2016). This ability is supported by cognitive and affective components. Cognitive empathy (perspective taking or mentalizing) is adopting another's point of view to see their situation from their perspective and infer their thoughts, feelings, and intentions (Decety, 2011; Decety & Cowell, 2015). Affective empathy (empathic concern) is an affective resonance that involves sharing another's affective state that elicits a concern for their emotional wellbeing (Decety, 2011; Decety & Cowell, 2015). Disruptions in social functioning occur when one component is dominant over the other in an imbalance (Cox et al., 2011). The function of these two empathy components are particularly important during adolescence when there are increases in complexity of social context and focus on peer relations; thus making effective social functioning crucial (Kral et al., 2017).

Adolescence is a critical period for the onset of most major mental health disorders (e.g. major depression, bipolar, schizophrenia; Paus et al., 2008), and research shows differences in empathy components underlie distinct psychiatric conditions in adolescence. For example, major depression associates with extremely high or extremely low cognitive empathy (Tully, Ames, Garcia, & Donohue, 2016), participants with bipolar disorder score lower on perspective taking and abnormally higher on affective empathy (Shamay-Tsoory, Harari, Szepsenwol, & Levkovitz, 2009), and participants with schizophrenia score significantly lower on both cognitive and affective empathy (Bonfils, Lysaker, Minor, &

Salyers, 2017). These findings suggest distinct differences in cognitive and affective empathy characterize social impairments in different psychiatric conditions.

These studies focus on symptom-based diagnostic criteria even though there is considerable co-morbidity and heterogeneity within each category. Instead, the delineation of symptoms that cross these diagnostic categories has been motivated by the NIMH Research Domain Criteria (RDoC) effort, which seeks to link circuit level abnormalities in brain systems with symptoms that present across clinical diagnoses (Insel, 2014). Internalizing and externalizing symptoms comprise the most widely agreed upon classifications of behavior disorders that cross diagnostic categories (Achenbach et al., 2016), and have shown to associate differently with cognitive and affective empathy via self-report. For example, Gambin et al. (2015) found aberrant cognitive empathy (hyper- and under-mentalization) were defining group characteristics predicting externalizing symptoms in inpatient adolescents. Gambin and Sharp (2016) demonstrated both affective and cognitive empathy negatively associated with conduct problems and affective empathy positively associated with internalizing symptoms observed by parents in an inpatient adolescent sample. And, Gambin and Sharp (2018) demonstrated a positive association between affective empathy and depressive symptoms that was partially mediated by guilt and shame. This line of research has improved our understanding of the association between social functioning and transdiagnostic symptoms. In line with the RDoC effort, the next logical step in this line of research is to examine neural mechanisms underlying empathy and transdiagnostic symptoms to identify biologically informed targets for intervention and prevention efforts.

Neural mechanisms underlying cognitive and affective empathy are distinct and share similar neural network activations with transdiagnostic symptoms. Task-based studies in adolescents (Decety & Michalska, 2010; Decety et al., 2008; Gallagher et al., 2000; Kral et al., 2017) and adults (Fan et al., 2011; Lamm et al., 2011) demonstrate that cognitive empathy associates with neural regions in the default mode (DMN; medial prefrontal and posterior cingulate cortex) and frontoparietal networks (FPN; lateral prefrontal cortices and posterior parietal cortex) whereas affective empathy associates with neural regions in the salience network (SAL; anterior insula, anterior cingulate, and rostral prefrontal cortices). Similarly, imbalanced empathy associates with activity between the SAL and FPN networks (Cox et al., 2011). Transdiagnostic internalizing and externalizing symptoms also associate with these same networks. For example, externalizing symptoms were found to have the strongest positive association within the SAL and FPN networks and between the DMN with both and SAL and FPN networks; whereas internalizing symptoms has the strongest positive association with the FPN and greater connectivity between the DMN with both the SAL and FPN networks (Xia et al., 2018). Although previous research reveals connections between cognitive and affective empathy, the brain, and transdiagnostic symptoms, research has yet to examine the mediating relationship cognitive and affective empathy has on the relationship between network connectivity and internalizing and externalizing symptoms in adolescents.

The above studies primarily rely on task-based neural probing and self-report measures, which can be built on by examining neural connectivity in relation to empathy and transdiagnostic symptoms. Task-based imaging probes neural regions associated with the task that is a state dependent measure and may miss out on the broader neural connections within and between networks of complex processes – such as empathy or transdiagnostic symptoms (Ernst et al., 2015). Significant changes occur in connectivity of the brain during adolescence; thus, examining neural connections across networks via functional connectivity captures broader patterns of information processing that improves detection of mechanisms underlying complex processes and symptoms (Ernst et al., 2015). Testing the mediating effect of cognitive and affective empathy on the association between functional connectivity of the brain and transdiagnostic symptoms can capture the neural mechanisms underlying symptom vulnerabilities and complex processes in adolescents (Ernst et al., 2015; Lindquist, 2012). Using these methods provides a particularly important source of information to examine mechanisms and mediating factors of social cognitive and affective functioning underlying transdiagnostic symptoms. This information is crucial for identifying targets for intervention.

The present study expands on three lines of prior research linking (1) self-reported cognitive and affective empathy with transdiagnostic symptoms, (2) neural activations with empathy, and (3) functional connectivity with transdiagnostic symptoms in adolescents by testing these relationships in one model. Contemporary perspectives suggest that the brain drives behavior (Nielsen et al., 2018), and previous investigations have used empathy as an independent variable on transdiagnostic symptoms. Therefore, we ordered our investigation as functional connectivity as the independent variable associating with transdiagnostic symptoms with empathy mediating this relationship. We hypothesized (1) cognitive empathy will mediate the relationship between DMN within-network connectivity and internalizing symptoms, (2) affective empathy will mediate the relationship between SAL within-network connectivity and externalizing symptoms, and

(3) imbalanced empathy will mediate the relationship between FPN - SAL between-network connectivity and externalizing symptoms.

Methods

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) that was obtained through the 1000 functional connectomes project (www.nitrc.org/projects/fcon_1000/). Data were collected from the community of Rockland, New York with a data collection protocol consisting of behavioral measures and MRI scanning collected all in one day. Participants were included if they had an IQ ≥ 80 assessed by the WAIS-II ($\alpha = .96$; Wechsler, 2011) to ensure they are cognitively able to understand self-report measures. The study ethical considerations including approval and informed consent is outlined in Nooner et al. (2012).

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). The affective empathy subscale (α=.74) consisted 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 (α=.79) consisted 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 confirmed on other samples across age groups and nation of origin; has evidence of convergent and concurrent validity; and is the most widely used measure for cognitive and affective empathy (Konrath, 2013). Items in this measure were rated on a five-point scale rating behavior that “does not describe me” (0) to “describes me well” (4) with higher scores indicating higher levels of dispositional empathy.

An imbalance score was calculated using criteria outlined by Cox et al. (2011) that subtracts affective empathy from cognitive empathy to create a relative empathy index score. In this difference empathy score, positive scores indicate a dominance of cognitive empathy and negative scores indicate a dominance of affective empathy. A difference score was chosen over a ratio score given that cognitive and affective empathy are associated and ratio measures have highly questionable reliability, particularly when measures are non-independent (Arndt et al., 1991). Although a valid concern is that a total empathy score would influence the imbalance score, preliminary analysis indicate they are uncorrelated ($r = .054$, $p = .625$).

Child Depression Inventory 2 (Kovacs, 2004) is a self-report screening tool (α=.84) that measures components of internalizing symptoms composing two scales (Emotional [α=.72], Functional [α=.68]). The emotional subscale constitutes components such as mood and self-esteem whereas the functional subscale is defined by interpersonal functioning. This measure consists of 28 statements and child selects the response (between 0 [does not] – 2 [describes me very well]) that describes their feelings in the past two weeks. This scale has been validated for use in youth aged 8-18 (Logan et al., 2013).

Youth Self-Report (Achenbach & Rescorla, 2001) is a self-report questionnaire for youth ages 11-18 where youth rate their problem behavior. Youth rate 112 items on a three-point scale (0 not true – 2 very true) indicating how much they agree with the statement. The measure yields several empirically derived syndrome scales (DSM-oriented scales). In accordance with previous work, the current study the subscale scores of internalizing (α=.876), externalizing (α=.872), anxious/depressed (α=.833), withdrawn/depressed (α=.752), rule breaking behavior (α=.570), aggression (α=.795), and attention issues (α=.772) were used as continuous measures for internalizing and externalizing symptoms. Raw scores were used as recommended for research purposes by Achenbach and Rescorla (2001).

Child Behavior Checklist (Achenbach & Rescorla, 2001) is a Parent-report questionnaire where parents rate their adolescent's problem behavior that mirrors the Youth Self-Report. Parents rate 112 items on a three-point scale (0 not true – 2 very true) indicating how much they agree with the statement. The measure yields several empirically derived syndrome scales (DSM-oriented scales). In accordance with previous work, the current study the subscale scores of internalizing (α=.894), externalizing (α=.897), anxious/depressed (α=.857), withdrawn/depressed (α=.837), rule breaking behavior (α=.736), aggression (α=.892), and attention issues (α=.865) were used as continuous measures for internalizing and externalizing symptoms. Raw scores were used as recommended for research purposes by Achenbach and Rescorla (2001).

Covariates and Demographics. Demographic variables for race and gender were recorded via self-report and included as nuisance covariates. Because the sample was predominantly white (61.9%) the sample was grouped into white and non-white categories for the analyses. Pubertal development was measured by the genital and breast development subscales of the Tanner assessment (α = .77; Petersen et al., 1988). This scale has parents rate pictures representing development of secondary sex characteristics on a scale of 1 (pre-pubertal) to 5 (full maturity) as a measure of pubertal development maturity.

For demographic information, socioeconomic status was assessed by the Hollingshead four-factor index of social status (Hollingshead, 1975). This measure examines the four domains of education, occupation, gender, and marital status by scoring each domain and a higher total score indicates a higher socioeconomic status.

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^{o}; 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^{o}, 176 slices, FOV= 250mm, voxel size= 1mm isotropic) were acquired. The siemens sequence does not collect images until magnate saturation is achieved so no scan removal for T1 stabilization was necessary.

Preprocessing of MRI data were conducted using Statistical Parametric Mapping (SPM version 12; Penny et al., 2011) with the CONN toolbox (version 18b; Whitfield-Gabrieli & Nieto-Castanon, 2012). The MPRAGE structural image was registered to the mean unwrapped EPI. Normalization parameters were obtained by segmenting the co-registered T1 image to the T1 and functional EPI images to normalize to an MNI template.

Functional images were spatially smoothed with an isotropic 6mm full-width half maximum Gaussian kernel. The time-series was inspected for motion using the Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect). Timepoints identified as outliers were defined as those > 0.5mm in movement that were modeled out using nuisance regressions. Participants with > 3mm motion in any direction and participants with > 20% invalid scans were excluded from the analysis. Because of the fast TR and multiband sequence used at data collection, no slice timing correction was used. To reduce spurious correlations, multiple regression was used to detect variances that could be explained by nuisance factors (white matter, CSF, and six motion parameter), which were removed from each voxels time-series. In order to decrease physiologic and other sources of noise form the BOLD signal, CONN uses an anatomic component-based noise correction method (aCompCor) (Whitfield-Gabrieli & Nieto-Castanon, 2012). This method regresses out noise form 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). Finally, data was 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). For cognitive empathy, regions making up the DMN (medial prefrontal cortex, posterior cingulate cortex, and angular gyri) and the FPN (bilateral lateral prefrontal and posterior parietal cortices) are used as seed regions. For Affective empathy, regions making up the SAL (bilateral anterior insulae, anterior cingulate, and bilateral rostral prefrontal cortices) are used as seed regions. These regions are anatomically defined using the Harvard-Oxford Atlas available in the CONN toolbox (MNI coordinates on Table 4).

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 by averaging all pairwise connections within each network for an averaged within network connectivity value for each participant. Next, between-network time series extraction will involve an average of all pairwise connections between each network's ROI for an averaged between connectivity value of each network for each participant. Then participant-level correlation maps 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 software (R Core Team, 2018) using the extracted averaged within and between pairwise connections in the previous step. In order to avoid missing important findings in this exploratory study with a small sample (Feise, 2002; Rothman, 1990), we did not adjust for multiple comparisons and an uncorrected two-tailed p-value of $< .05$ defined statistical significance. First Pearson correlations were conducted to examine linear relationships between self-reports of empathy, internalizing and externalizing symptoms, and both within and between network connectivity parameters for further analyses. To identify which relationships to test in a mediation model, criteria for identifying relationships to test required a Pearson's $r > .2$ and a $p < .05$ between independent, mediator, and outcome.

Then mediation models were fitted to examine the mediating relationship extracted within- and between- network connectivity has between self-reported empathy and internalizing and externalizing symptoms. Mediation analysis tested the indirect effect while controlling for nuisance covariates (gender, race, Tanner stage) using 10,000 bootstrap resamples for calculating bias-corrected confidence intervals using the 'psych' package in r (Revelle & Revelle, 2015). These models were evaluated using r^2 of the model for the effect size using criteria established by Fairchild, Mackinnon, Taborga, and Taylor (2009) (small = r^2=.14; medium = r^2=.39; large = r^2=.49). Prior to analysis assumptions for mediation of linearity, skewness, kurtosis, and heteroscedasticity were tested using the Global Validation of Linear Models Assumptions ('gvlma') package in r (Slate, 2019). Variables that violated these assumptions were transformed by using a log transformation and the resulting coefficient exponentiated for interpretation (exp(b) - 1 * 100). Because of the cross-sectional data, reveres models were tested to identify viable over non-viable models. An a priori power analysis using the 'powerMediation' package in r (Qiu & Qiu, 2018) specifying an independent, mediating, and dependent variables with three covariates, a b2 of .3, standard deviation and error of 1 and correlation between predictor and mediator of .3 requires a sample size of 95 to reach 80% power.

Results

Out of 155 potential participants, 43 did not fill out key measures and 28 were removed for motion issues or high level of invalid scans (Figure 5). Final sample consisted of 84 right-handed male and female participants (46.4% female) aged 13-17 (14.64±1.36) with an average SES of 48.58±9.32 (range = 21 - 66).

Prior to analysis, assumption testing indicated all mediation models did not meet assumptions for the analysis because of variables being skewed. Inspection of the distributions of the data revealed slightly skewed distributions for all outcome variables (Skewness: YSR internalizing = 1, YSR externalizing = 1.66, CBCL internalizing = 1.24, CBCL externalizing = 2.34, CDI emotional = 1, CDI functional = 1.06). A natural log transform was applied to the data and assumptions retested and all assumptions were met after transforming the outcome variable for each analysis. Assumptions for each model where then checked again using the transformed outcome variables and all assumptions were met. Thus, the transformed outcome variables were used in all analyses. Because of this transformation, we exponentiated the coefficient (exp(b) - 1 * 100) to aid interpretation as percentage change (Gelman, Gelman, & Hill, 2007). All reverse mediation models were not significant, and the originally theorized models are reported on and reflected in tables.

Correlations of mean network connectivity with empathy and symptoms. Pearson correlations (Figure 6-8) revealed significant correlations of the child depression inventory's emotional subscale with the DMN and both (1) cognitive empathy as well as (2) the functional subscale with the DMN and cognitive empathy. The youth self-report subscale of (3) anxious depression significantly associated with SAL – FPN between network connectivity and the imbalanced empathy score. No significant relationships were found with the CBCL parent report measures and functional connectivity measures (Figure 6). The three identified models were tested in mediation analysis.

Default mode network connectivity changes in emotional internalizing symptoms associated with cognitive and cognitive empathy. Mediation analysis indicates that all paths between DMN connectivity, cognitive empathy, and emotional internalizing symptoms were significant (Table 5, Figure 9). Specifically, DMN connectivity positively associates with cognitive empathy and both DMN connectivity and cognitive empathy negatively associate with emotional internalizing symptoms. The indirect effects (ab) are significant suggesting there is a mediation because a change in the mediator influences the dependent variable when holding the independent variable constant. The overall model was statistically ($p < .05$) and practically significant ($r^2 = .24 > .14$ small effect size) suggesting the model is appropriate for estimating this data.

Default mode network connectivity changes in functional internalizing symptoms associated with cognitive empathy. This model had issues with heteroscedasticity that was addressed by calculating cook's d to detect and remove three outliers. Mediation analysis indicates all paths are significant except the path between DMN connectivity and cognitive empathy in this model (Table 5). Subsequently, the mediation effect is also not significant as indicated by the bootstrapped confidence interval. This indicates that changes in the mediator when holding the independent variable constant does not change the outcome variable.

Imbalanced empathy changes in anxious depression internalizing symptoms associated with between network connectivity of the salience and frontoparietal networks. Mediation analysis indicates all paths are significant for the model examining between FPN and SAL network connectivity on anxious depression with imbalanced empathy mediating (Table 5). However, the indirect effects, indicated by the bootstrapped confidence interval, are not significant. This suggests that imbalanced empathy does not mediate the relationship between the independent and dependent variables.

Discussion

This study demonstrated the associations between the effect of functional connectivity of the DMN on internalizing symptoms being mediated by cognitive empathy. This study builds on previous and separate lines of research demonstrating the association between (1) empathy and (2) functional connectivity with transdiagnostic symptoms. No associations were found between functional connectivity and externalizing symptoms with empathy as a mediator. In addition, current developmental stage, race, or gender did not influence these relationships indicated by $p > .05$. This study presents a framework for examining the effects of functional connectivity of the brain on transdiagnostic internalizing symptoms in relation to cognitive empathy in adolescents.

The literature converges on DMN involvement in self-referential cognition (Buckner, Andrews□Hanna, et al., 2008; Istvan Molnar-Szakacs & Lucina Q. Uddin, 2013; Uddin et al., 2009) that is important for cognitive empathy (Betti & Aglioti, 2016; Kim et al., 2017b; Silva et al., 2018). Impairments in the DMN underlie internalizing symptoms (Sheline et al., 2009) and the present findings further support this literature in a sample of adolescents. We extend these results to parse out specific dimensions of internalizing symptoms as a function of empathy and adolescent DMN connectivity. The DMN changes significantly during adolescent development with within DMN connectivity indicating developmental maturity (Blakemore, 2008; T. Singer, 2006). The connectivity within the DMN may be of particular importance for mental health during this age period and beyond (Broulidakis et al., 2016; Sato et al., 2016). The DMN is associated with may processes that are not specific to empathy or internalizing symptoms. Its association with both internalizing and cognitive empathy suggests the recruitment of specific processes involving reasoning with one's own state, the states or others, and social behavior. One interpretation of this finding is that lower connectivity within the DMN associates with lower cognitive empathy and both present as a risk for internalizing symptoms in adolescents.

The null models suggest that cognitive empathy in relationship to DMN within-network connectivity and internalizing symptoms may be specific to emotional internalizing symptoms. Functional internalizing and anxious depression did not have significant mediations. Additionally, an empathy imbalance score did not mediate the relationship between SAL – FPN between-network connectivity and anxious depression indicating that an imbalance in empathy does not account for this association. Anecdotally, those who report feeling socially isolated even in environments with friends and loved ones are likely to develop internalizing symptoms (Hawkley & Capitanio, 2015). It may be the case that a lower capacity in cognitive empathy may prevent the identification of a cognitive connection with others and lead to feeling socially isolated independent of environmental factors. Increasing empathy may be an important component for addressing or preventing internalizing symptoms in adolescents

Contrary to hypothesized, neither empathy nor functional connectivity associated with externalizing symptoms. This finding stands in contrast to research by Gambin and Sharp (2016, 2018) demonstrating empathy's association with externalizing symptoms and Xia et al. (2018) demonstrating distinct patterns of functional connectivity underlying externalizing symptoms. Additionally, the present study found a negative association between affective empathy and internalizing symptoms where as Gambin and Sharp (2016) found a positive association. The differences in findings may be due to the previous studies had greater power with larger sample sizes. Additionally, the Gambin articles sampled inpatient adolescents and used an empathy measure that defines empathy differently than the measure use in the present study. The present study had a smaller sample size, used a an older empathy measure derived from older definitions, and used a community sample, which may all account for differences between findings. The contrasts in findings suggest that there are differences between empathy and internalizing and externalizing symptoms from inpatient and community populations that are important for tailoring risk and treatment approaches.

Across all analyses, controls of tanner developmental stage, race, or gender had no statistically significant contribution to any pathway in the mediation analysis. These findings stand in contrast to research suggesting pubertal development associates with differences in empathic responses and underlying neural circuitry (Masten, Eisenberger, Pfeifer, Colich, & Dapretto, 2013) and gender differences exist when self-reporting empathy (Baron-Cohen & Wheelwright, 2004; D. Cohen & Strayer, 1996; Davis, 1983). For the former, the measures of empathy included an empathic task that probed regions specific to social pain that may account for differences from the present study. The association of gender with empathy is a highly debated topic where others demonstrate there are no differences in empathy between genders when using objective measures such as neuroimaging (Decety & Michalska, 2010; Michalska et al., 2013). The present results suggest that brain connectivity may have a different association regarding empathy than tasks and that gender differences do not exist.

Limitations. The present study must be interpreted under the following limitations. First, this is a cross-sectional design, thus causal paths could not be determined. Additionally, because there were no temporal associations between variables a true mediation model could not be tested but rather the mediator acted more as a covariate between variables. Further testing is necessary to determine the best target for intervention.

Second, analyses did not reach adequate power. It is completely plausible that the current findings reflect reality and it's also worth noting the current analysis may not have detected all effects. We did not control for multiple comparisons which increases chances of spurious effects. To mitigate these, we examined the effect size to assess the plausibility of the effect.

ROIs were defined using a predefined atlas. This method may not accurately reflect the neural regions for the present sample that may 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. And, each region detected in the present analysis is involved in multiple processes making it difficult to pinpoint exactly what process our results are involved in. Although this was further investigated by examining what neural regions underly the associations found, using tasks can help further parse what processes regions that are recruited are engaged in. Despite these limitations, the present study provides evidence of the importance of DMN within-network connectivity covariation with cognitive empathy in relationship to emotional internalizing symptoms.

Implications and Conclusions. The present significant models have important implications for future lines of research that may inform approaches addressing internalizing symptoms in adolescence. Specifically, future studies focusing on cognitive empathy and DMN connectivity appear to be particularly important for internalizing symptomology that is prominent in diagnostic categories such as depression, bipolar, and schizophrenia (Bonfils et al., 2017; Shamay-Tsoory et al., 2009; Tully et al., 2016). Self-referential processing that is an important component of cognitive empathy and internalizing symptoms associated with the DMN (Kim et al., 2017b). It will be important to focus investigations on perspective taking processes associated with the DMN to discern what processes are involved in internalizing symptoms that can be targeted. It may be that an inability to mirror others via self-understanding and self-referential processing may underlie emotional internalizing symptoms. Future studies can target these processes for an experimental manipulation of cognitive empathy and examining connectivity in the DMN. This is important for future intervention testing that may improve current interventions and wellbeing programs aimed at cultivating empathy (e.g. social emotional learning, compassion-based training; Reddy et al., 2013; Weissberg, Durlak, Domitrovich, & Gullotta, 2015). The use of imaging in the present analysis aids identification of specific targets and processes involved in cognitive empathy to reason for future approaches to internalizing symptoms. These are additional data points that could not be measured via self-report alone. More research is needed to examine temporal associations and causality amongst these relationships so that we may accurately identify the proper targets for future intervention testing.

Chapter Four: Conclusions

The findings from the present two studies provide important information on adolescent brain mechanisms underlying cognitive and affective empathy as well as their association with transdiagnostic mental health symptoms (i.e. internalizing and externalizing). Together these studies provide the foundation for understanding social and emotional development in adolescents. Each study is a unique contribution that complements each other as foundational work on identifying neural targets that promote health social and interpersonal functioning in adolescents.

Study 1 Conclusions

The first study successfully addressed the first aim by examining the neural connectivity underlying cognitive and affective empathy within and between the default mode (DMN), frontoparietal (FPN), and salience (SAL) networks. For cognitive empathy, this study concluded it 1) positively associated with within DMN connectivity and 2) negatively associated with SAL-DMN between-network connectivity. Higher levels of cognitive empathy associates with greater connectivity within the DMN. It is likely that higher levels of cognitive empathy implies greater communication within the DMN that underlies self-referential cognitions (Buckner, Andrews□Hanna, et al., 2008; Istvan Molnar-Szakacs & Lucina Q. Uddin, 2013; Uddin et al., 2009). This finding supports the adult literature demonstrating cognitive empathy's association with DMN within-network connectivity and that individuals with lower empathy demonstrate decreased DMN within-network connectivity (Kim et al., 2017a; Silva et al., 2018).

The significant negative finding for SAL – DMN between-network connectivity suggest higher levels of cognitive empathy associates with more functional coupling between these networks as healthier brain functioning shows anticorrelations between these networks (Uddin et al., 2009). It is plausible that differentiation between these networks underlies ones empathic capacity. Post hoc analyses shown that this finding was driven by the left angular gyrus and rostral prefrontal cortex. However, this analysis could not tell us the direction of these relationships. One could posit that connectivity of the DMN drove the differentiation between network connectivity given its association with cognitive empathy, but this requires further testing. Task-based findings from Kral et al. (2017) suggest increasing cognitive empathy may be the important target for cultivating empathy in adolescents, which provides context and support for the present study's findings. This would be important for future research to understand what to target when fostering empathy in adolescents.

Contrary to expectations, affective empathy did not associate with functional connectivity within the SAL as hypothesized. This null finding stands in opposition to task-based literature in adolescents. This may be that affective empathy does not associate with SAL connectivity in adolescents. It is also worth noting this null result may be due to differences in task independent BOLD signals from tasks or due to a lack of power for the analysis that could not capture the true effect.

The present study did find that affective empathy negatively associated with DMN – SAL between-network connectivity. This finding was also found with cognitive empathy suggesting a healthy differentiation between the DMN and SAL associate with both components of empathy. Post hoc analyses demonstrate more anticorrelations between two ROIs in the SAL with one DMN ROI. Thus, suggesting SAL connectivity in relation to affective empathy may drive this relationship. However, the present analysis does not measure directionality between ROIs and was underpowered so it may not have been able to detect this. Future studies with larger sample sizes and using effective connectivity may elucidate this. The similarity of findings between cognitive and affective may be specific to adolescents because of differences in neural maturity or that both components of empathy involve similar processes that are important for differentiation between these networks. Further investigating the directions in these associations is important for elucidating targets and approaches to promote affective empathy in adolescents.

The second aim was successfully addressed and suggested that imbalanced empathy provided information unique from cognitive or affective empathy alone. Specifically, this study concluded that a positive imbalance in empathy (when one is more dominant in cognitive empathy and deficient in affective empathy) associates with greater SAL – FPN between-network connectivity; and an imbalance dominance in affective empathy negatively associates with SAL – FPN between-network connectivity. Post hoc analyses revealed this was driven by a positive association between and anterior cingulate and posterior parietal cortex. The SAL network acts as a switch from internally focused cognitive processes housed in the DMN to externally focused social processes housed in the FPN. The greater connectivity between the FPN and SAL networks may reflect increased frequency of switching to external social processing. In adults this imbalance associated with increased aggression (Cox et al., 2011) and abnormally strong connection between SAL and FPN underlies borderline personality disorder (Krause-Utz et al., 2014). It may be that an abnormally high correlation between these networks underlies more frequent switching to external social processing that drives aberrant emotional responses in adolescents when self-reflection is not present. More research is warranted to determine if this pattern, specifically a need for more self-referential social cognition via the DMN, is an appropriate target for cultivating empathy in adolescents.

Study 1 Implications

Implications of the first study results indicate targets for consideration for future studies looking to cultivate empathy in adolescents. Present findings suggest examining DMN within-network connectivity and SAL – DMN between network connectivity are particularly important patterns of functional connectivity associating with empathy in adolescents. These findings are an initial incremental step toward a line of research that may lead toward changing the way social workers and other direct practice practitioners' approach social emotional development in adolescents.

For example, the finding that cognitive empathy associates with DMN connectivity could plausibly indicate targeting self-reflective processes this network is involved in (See for review: Istvan Molnar-Szakacs & Lucina Q Uddin, 2013). Referencing oneself in the moment and self-reflection is important for perspective taking (De Waal, 2008) and uses autobiographical memories and awareness of self in the DMN (Istvan Molnar-Szakacs & Lucina Q. Uddin, 2013). This suggest that intentionally practicing self-reflective processes underlying cognitive empathy is worth investigating in relationship to DMN within-network connectivity. For example, mindfulness exercises focused on present awareness of oneself has shown improvement in self-reflection (Harrington, Loffredo, & Perz, 2014) and DMN connectivity (Brewer et al., 2011). Although future research is necessary to test this, it may be the case that this process improves SAL – DMN between-network functional coupling as well as address a dominance imbalance in cognitive empathy. The present findings provide a direction for future research that may incorporate feasible practices such as self-reflection in direct practice applications for social work practitioners to improve social and emotional functioning in adolescents.

Study 2 Conclusions

The second study successfully addressed the third aim by examining the associations between functional connectivity of neural networks (DMN, SAL, and FPN) and transdiagnostic symptoms in relation to cognitive, affective, and imbalanced empathy. This study concluded that within DMN connectivity associated with emotional internalizing symptoms that was mediated by cognitive empathy. This finding suggests that cognitive empathy may be an important target for addressing internalizing symptoms in adolescents.

Several analyses did not have significant mediations. There were associations between functional connectivity and various internalizing symptoms with empathy but no mediating effect. It is plausible that these null results reflected reality, but it is also important to note these analyses did not have adequate power to detect the true effect. Future studies examining these associations will need larger sample sizes to detect all effects.

It is important to note that there were no associations with externalizing symptoms as anticipated. This finding stands in contrast to research by Gambin and Sharp (2016, 2018) demonstrating empathy's association with externalizing symptoms and Xia et al. (2018) demonstrating distinct patterns of functional connectivity underlying externalizing symptoms. These studies had larger samples and had a power advantage to detect the true effect. Also, the functional connectivity study by Xia et al. (2018) used different self-report measures and did a factor analysis on those participants to detect which items more accurately reflects symptoms. These two factors may account for the differences from these previous studies.

Overall, this study concludes that cognitive empathy mediates the relationship between DMN connectivity with internalizing symptoms, specifically emotional internalizing symptoms, in adolescents. This is an important initial step toward identifying targets for prevention and intervention efforts in adolescence.

Study 2 Implications

The second study identifies an important covariation for further investigation to inform causal targets that address internalizing symptoms in adolescents. Specifically, cognitive empathy and DMN within-network connectivity in relation to emotional internalizing symptoms. There were no associations found for other components of internalizing symptoms suggesting cognitive empathy has implications for emotional internalizing symptoms alone. Although further investigation is needed to assess the best target for intervention, the cross-sectional analysis suggests cognitive empathy accounts for the relationship and may be a viable target. Specifically, examining self-referencing and taking on others perspectives that associate with cognitive empathy and the DMN may be viable targets for investigation. This extends previous research beyond linking cognitive empathy with internalizing symptoms by inferring the specific neural targets and processes underlying cognitive empathy in relation to internalizing symptoms. The present study has important implications for a line of research that may improve how social workers address social emotional development in adolescence and treatment of mental health symptoms.

Overall Implications

Overall findings suggest that DMN connectivity is demonstrated to be integral for cognitive empathy and important for addressing internalizing symptoms in adolescents. Previously it was understood that activity in regions of the DMN were activated during cognitive empathy tasks (Kral et al., 2017) and that DMN connectivity has some association with internalizing symptoms (Xia et al., 2018) but connecting these findings in one analysis paves the way for understanding what kinds of processes are associated with cognitive empathy in relation to internalizing symptomology. This has implications to inform future research pertaining to cultivating empathy and addressing mental health in adolescents at policy and direct practice levels.

Policy. Developing empathy through social emotional learning programs has been extensively written about as a crucial part of a child's development within the current school system (J. Cohen, 1999; Weissberg et al., 2015; Yeager, 2017). However, this is not often implemented successfully in public school systems (Greenberg, Domitrovich, Weissberg, & Durlak, 2017; Weissberg & Cascarino, 2013) where it could reach more students. Having knowledge of underlying neural mechanisms provides evidence of important considerations for adolescent development that can inform policy targeting adolescent needs. For example, this evidence could help refine existing programs to target specific mechanisms of self-reflective processing such as social emotional learning and compassion-based training methods (J. Cohen, 1999; Weissberg et al., 2015; Yeager, 2017). This line of research can impact policy regarding programs implemented in schools that build not only a child's knowledge, but how to relate with the world and to one another. For example, research evidencing the impact of refining these interventions toward specific targets identified in this research may push forward policy funneling financial resources to schools in need.

Social Work. Social work and other direct practice practitioners can use information regarding neural processes underlying empathy when working with adolescents to focus prevention and intervention efforts for cultivating empathy and addressing internalizing symptomology. Current evidence-based interventions for internalizing symptoms in the CBT tradition, behavioral activation, focus on doing behaviors that are healthy despite the affective inertia to not do them, which have shown high efficacy for treating depression (Cuijpers, Van Straten, & Warmerdam, 2007). However, behavioral activation does not attend to cultivating cognitive empathy; although it could be incorporated as a relapse prevention effort in direct practice to improve long term outcomes. More work needs to be done to examine how these neural findings can be practically applied in direct practice. However, the present results are promising and have significant implications for changes to the way social workers and other direct practice practitioners cultivate empathy and address internalizing symptoms in adolescents.

Future Research

This study identifies areas important for future research. First, it is important to employ longitudinal methods for determining temporal associations between the identified relationships. This will aid identifying viable treatment targets for further testing. Additionally, employing effective connectivity methods for examining the causal relationships between mechanisms underlying empathy will further specify targets for intervention and support intervention development. The two areas of research above will support future longitudinal studies where empathy can be modified by targeting these mechanisms to determine causal associations and viable prevention and treatment methods.

Summary

The present two studies provide important information on mechanisms underlying empathy in adolescents as well as how they both associate with mental health. The contributions of these studies to the literature on adolescent empathy are that they elucidate 1) functionally connected mechanisms underlying cognitive and affective empathy and 2) how these mechanisms associate with transdiagnostic mental health symptoms. Together these findings suggest the importance of DMN connectivity and cognitive empathy in adolescent development. Further examination of cognitive empathy in the context of default mode network processes is warranted. Future studies in this line of research may identify specific targets for promoting cognitive empathy in adolescents and promote better mental health.

These findings support knowledge about neural mechanisms underlying empathy in adolescents and are applicable to further research on promoting empathy and social emotional development. These are important considerations for addressing internalizing symptoms in adolescents. With further research, practical implications of the present results may be implemented at the policy and direct practice level. Future studies could improve on the present study by implementing longitudinal and effective connectivity methods for inferring causality in mediating relationships. Additionally, recruiting larger sample sizes to detect all effects and targeting recruitment of different age periods in adolescence (early, mid, late adolescence) to examine meaningful differences in the heterogeneity of this age period. The present dissertation is a small incremental step by identifying functionally connected mechanisms that may be used to reach larger goals of cultivating empathy and addressing internalizing symptoms in adolescents.

Appendix A. Figures & Tables

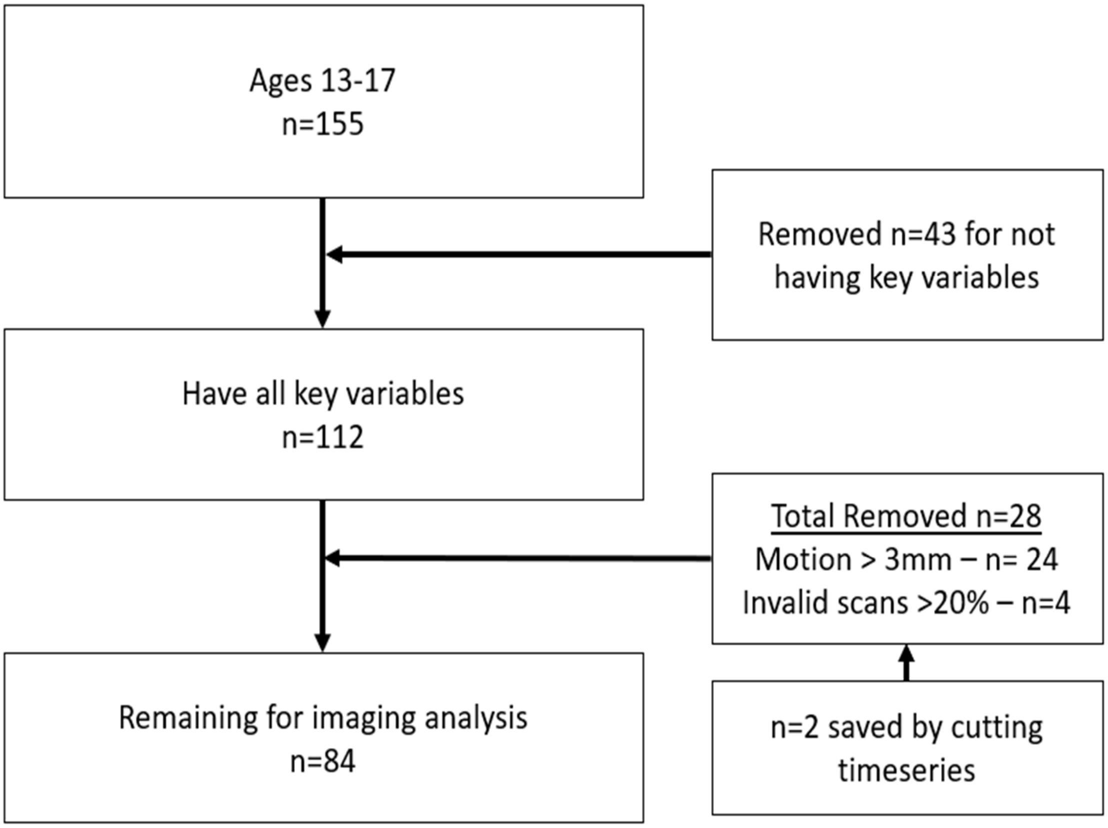

Figure 1. Participant selection and exclusion process. This figure depicts the selection and exclusion decisions made for study inclusion.

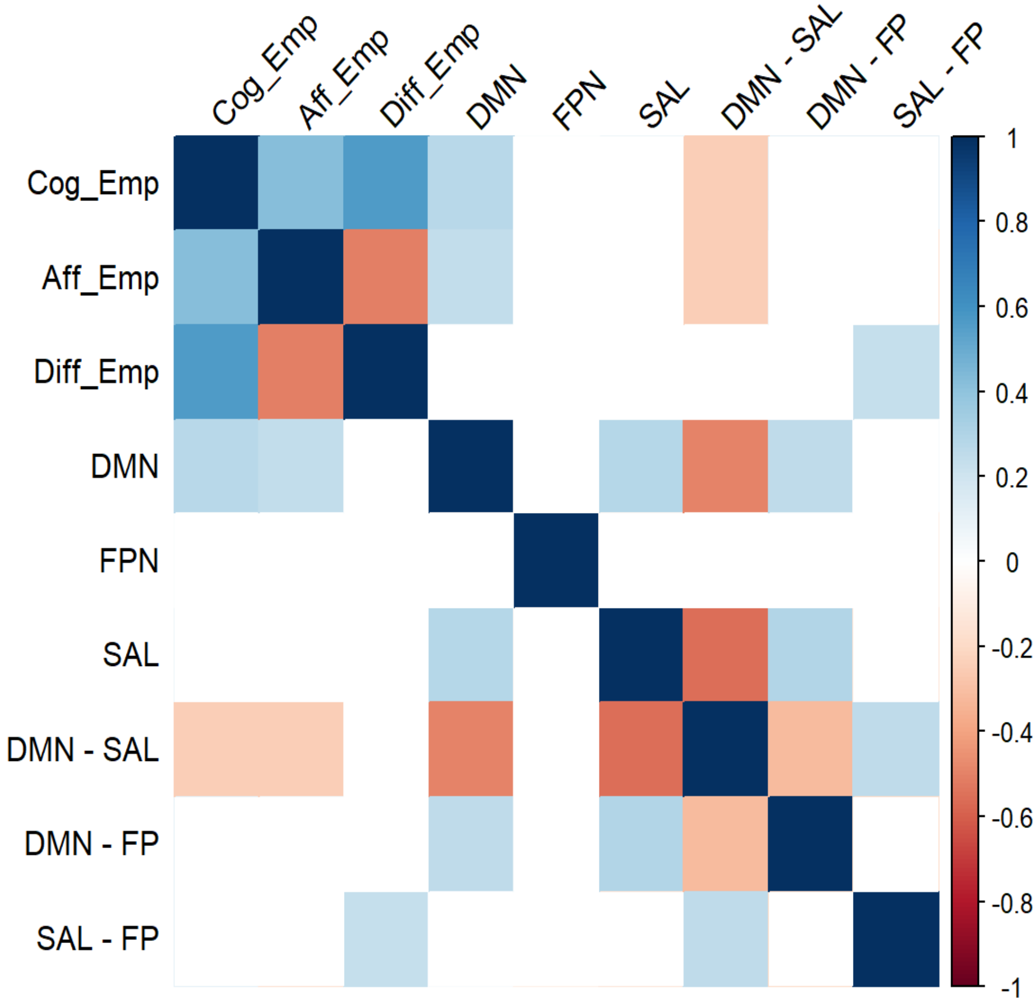

Figure 2. Correlation matrix of functional connectivity parameters and empathy scores. All colors shown have a p-value < .05 and all white squares have a p-value > .05

Table 1. Average network connectivity values (z score) and MNI Coordinates

Network Region in network	M ± SD	Range	MNI coordinates of seed regions (x, y, z)
Default Mode Network	.478 ± .164	.155 – .824	
MPFC			1, 55, -3
Angular Gyrus (L)			-39, -77, 33
Angular Gyrus (R)			47, -67, 29
Posterior Cingulate Cortex			1, -61, 38
Salience Network	.632 ± .178	.111 – 1.03	
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
Frontoparietal Network	.501 ± .178	.130 – .990	
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
Default Mode / Salience Networks	-.161 ± .139	-.604 – .101	
Default Mode / Frontoparietal	.090 ± .108	-.129 – .382	
Salience / Frontoparietal Networks	-.009 ± .132	-.320 – .369	

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

Table 2. Results of regression analyses

Variable	b	se b	95% CI	t	P-value
Cognitive empathy on default mode network connectivity [a]					
Cognitive Empathy	.008	.003	.001,.014	2.385	.019*
Tanner	.000	.018	-.036, .036	.001	.999
Race (White)	-.022	.034	-.091, .046	-0.648	.519
Gender (Male)	-.055	.034	-.112, .012	-1.636	.106
Affective empathy on default mode network connectivity [b]					
Affective Empathy	.007	.003	.0003,.014	1.899	.061
Tanner	.013	.018	-.022, .050	.745	.458
Race (White)	-.043	.035	-.115, .027	-1.221	.225
Gender (Male)	-.081	.034	-.148, -.014	-2.415	.018*
Cognitive empathy on between default mode/salience network connectivity [c]					
Cognitive Empathy	-.011	.003	-.012, -.0006	-2.240	.028*
Tanner	.017	.016	-.017, .044	.851	.397
Race (White)	-.042	.028	-.097, .013	-1.523	.131
Gender (Male)	.033	.027	-.020, .086	1.226	.224
Affective empathy on between default mode/salience network connectivity [d]					
Affective Empathy	-.007	.003	-.012, -.002	-2.553	.012*
Tanner	-.002	.015	-.032, .028	-.127	.898
Race (White)	-.009	.027	-.065, .045	-.358	.721
Gender (Male)	.020	.026	-.032, .072	.774	.441
Empathy imbalance on between frontoparietal/salience network connectivity [e]					
Empathy imbalance	.007	.003	.002, .012	3.146	.002*
Tanner	.014	.014	-.013, .042	1.001	.320
Race (White)	-.002	.025	-.052, .047	-.109	.913
Gender (Male)	.015	.023	-.031, .060	.646	.520

[a]: R^2 =. 1312, adj. R^2 = .0843, F = 2.832, p=.0848, df = 4, 75; n = 80 (4 outliers removed)
[b]: R^2 = .1374, adj. R^2 = .0914., F = 2.987, p=.0914, df = 4, 75; n = 80 (4 outliers removed)
[c]: R2 = .1177, adj. R2 = .0706, F = 2.501, p=.0494*, df = 4, 75; n = 80 (4 outliers removed)
[d]: R2 = .1087, adj. R2 = .0611, F = 2.286, p = .0679, df = 4, 75; n = 80 (4 outliers removed)
[e]: R2 = .155, adj. R2 = .1068, F = 3.211, p= .0176*, df = 4, 70; n = 75 (9 outliers removed)
*p < .05

Table 3. Individual ROI connectivity associated with empathy when controlling for confounding factors

Contrast	Connectivity	t	$P_{(uncorrected)}$
The main effect of ***default mode*** within-network connectivity as a result of ***cognitive*** empathy (4 outliers removed)	MPFC – AG(L)	3.74	.0004
	MPFC – AG(R)	2.51	.0154
The main effect of ***default mode and salience*** between-network connectivity as a result of ***cognitive*** empathy (4 outliers removed)	AG(L) – RPFC(L)	-3.46	.0009
The main effect of ***default mode and salience*** between-network connectivity as a result of ***affective*** empathy (4 outliers removed)	AG(L) – Insula(R)	-2.25	.0275
	AG(L) – RPFC(L)	-2.44	.0172
The main effect of ***salience and frontoparietal*** between-network connectivity as a result of ***empathy imbalance*** (9 outliers removed)	ACC – PPC(R)	2.23	.0287

Note: Outliers from regressions were removed
MPFC = medial prefrontal cortex, AG = angular gyrus, RPFC = rostral prefrontal cortex, ACC = anterior cingulate cortex, PPC = posterior parietal cortex
(L) = left (R) = Right

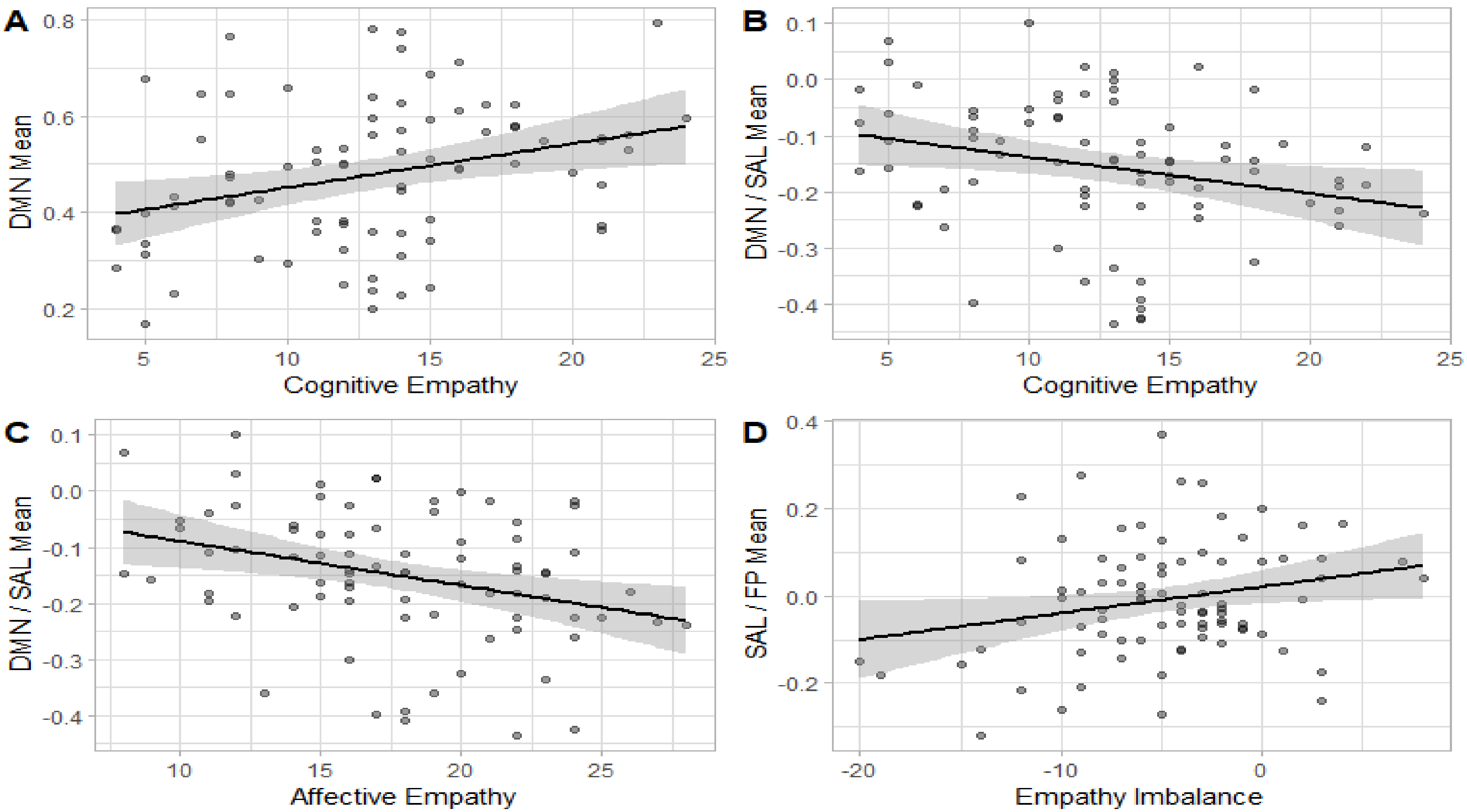

Figure 3. Scatterplots of Significant relationships of empathy with brain functional connectivity: A) cognitive empathy positively associating with DMN within-network connectivity B) Cognitive empathy negatively associating with DMN – SAL between-network connectivity C) affective empathy negatively associating with DMN – SAL between-network connectivity D) empathy imbalance positively associating with SAL – FP between-network connectivity (positive value = cognitive empathy dominance)

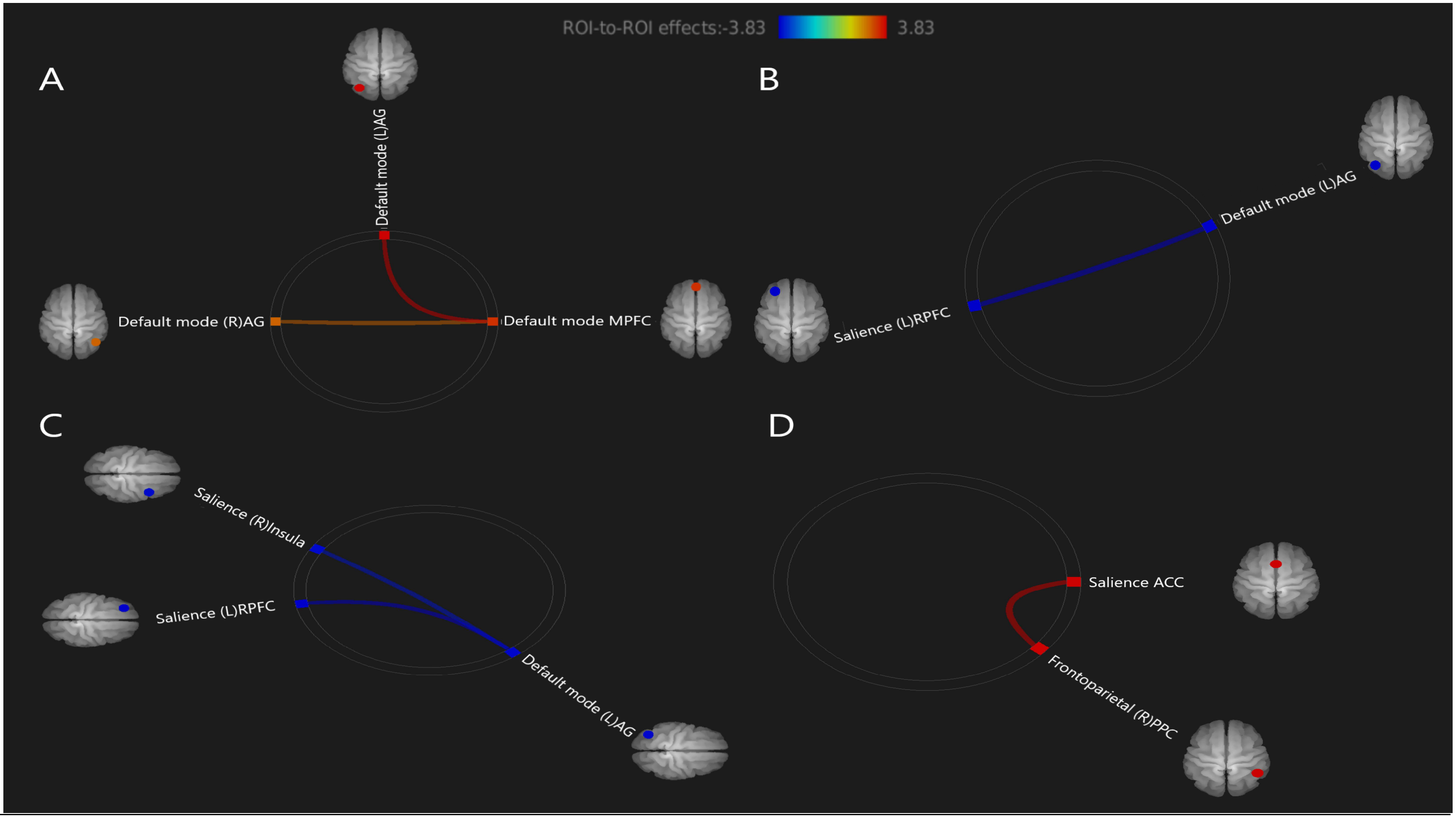

Figure 4. Post hoc ROI to ROI analysis*:* A) cognitive empathy positively associating with DMN within-network connectivity B) Cognitive empathy negatively associating with DMN – SAL between-network connectivity C) affective empathy negatively associating with DMN – SAL between-network connectivity D) empathy imbalance positively associating with SAL – FP between-network connectivity. Note: (L) = Left; (R) = Right; ACC = anterior cingulate cortex; AG = angular gyrus; MPFC = medial prefrontal cortex; RPFC = rostral prefrontal cortex

Appendix B. Figures & Tables

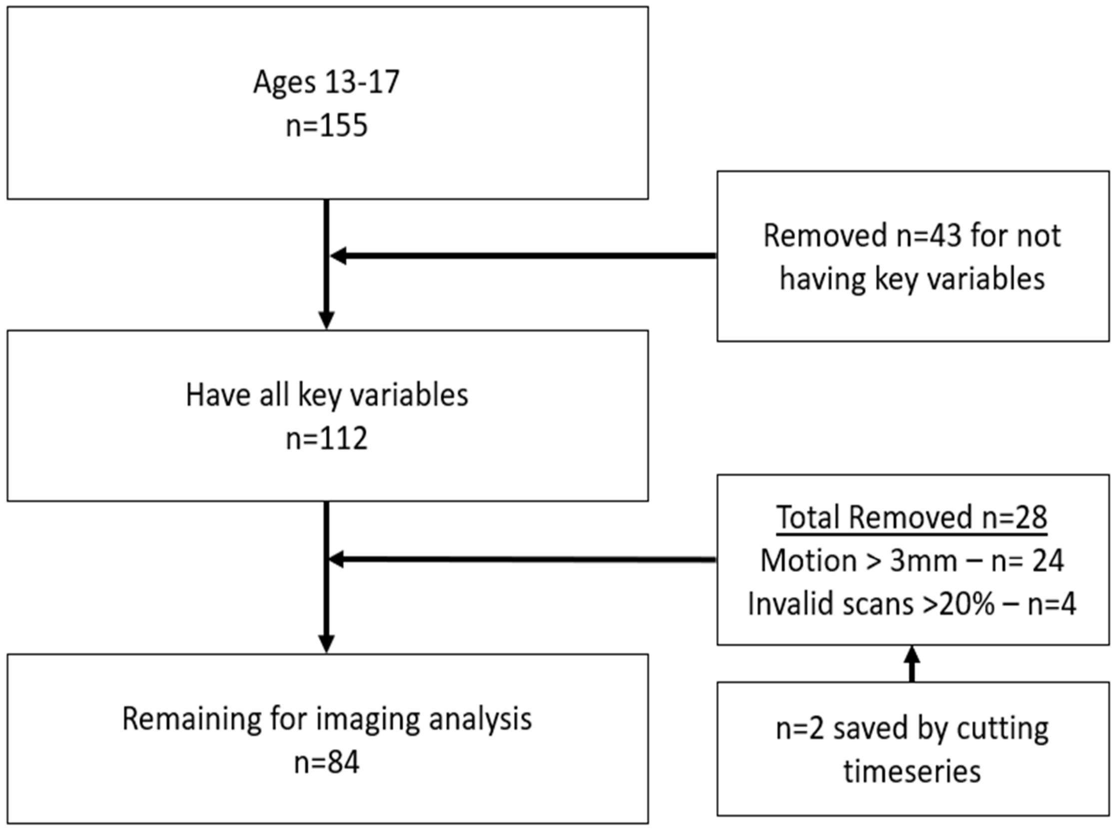

Figure 5. Participant selection and exclusion process. This figure depicts the selection and exclusion decisions made for study inclusion.

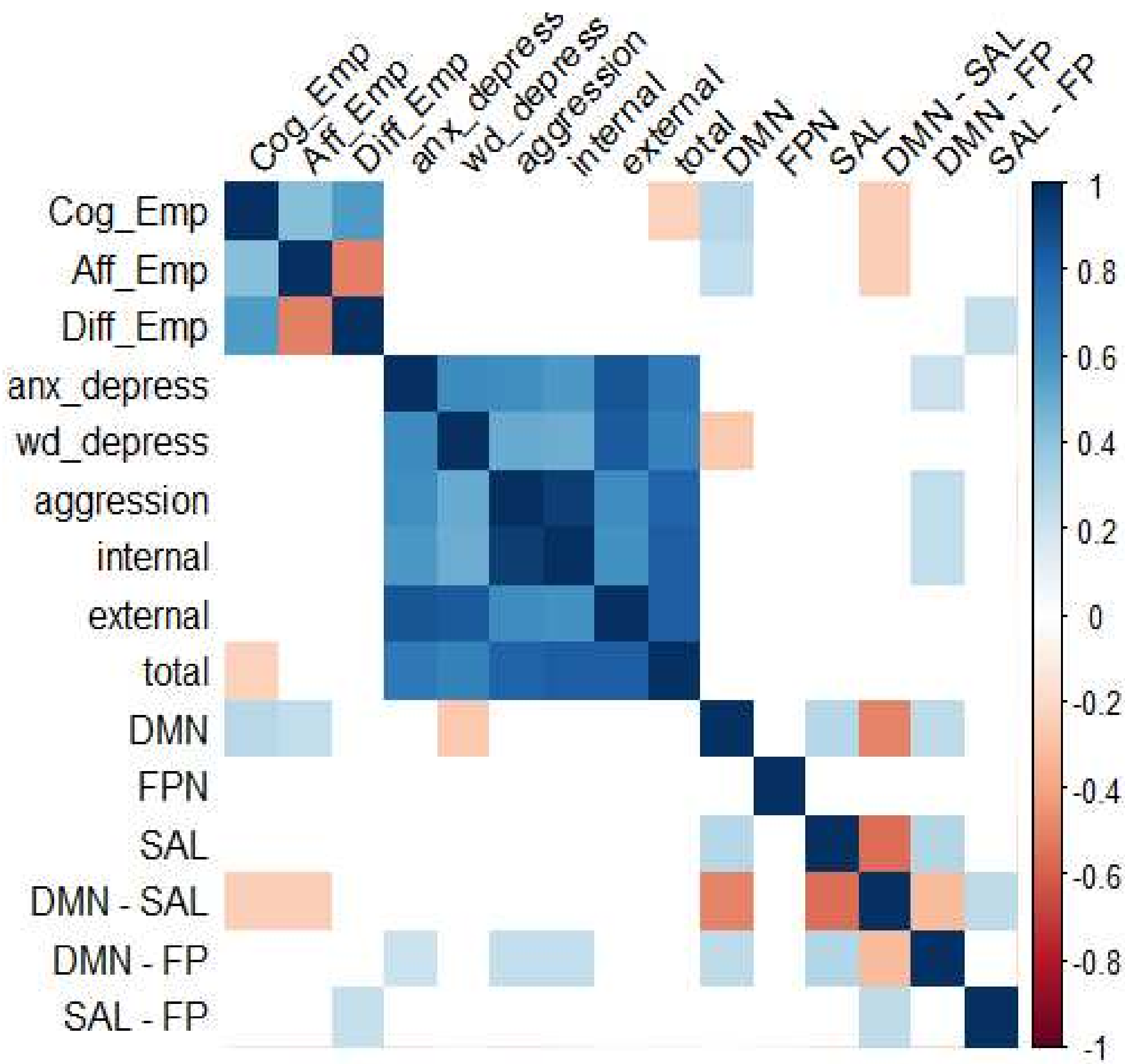

Figure 6. Correlations of child behavior checklist with empathy and brain connectivity parameters.

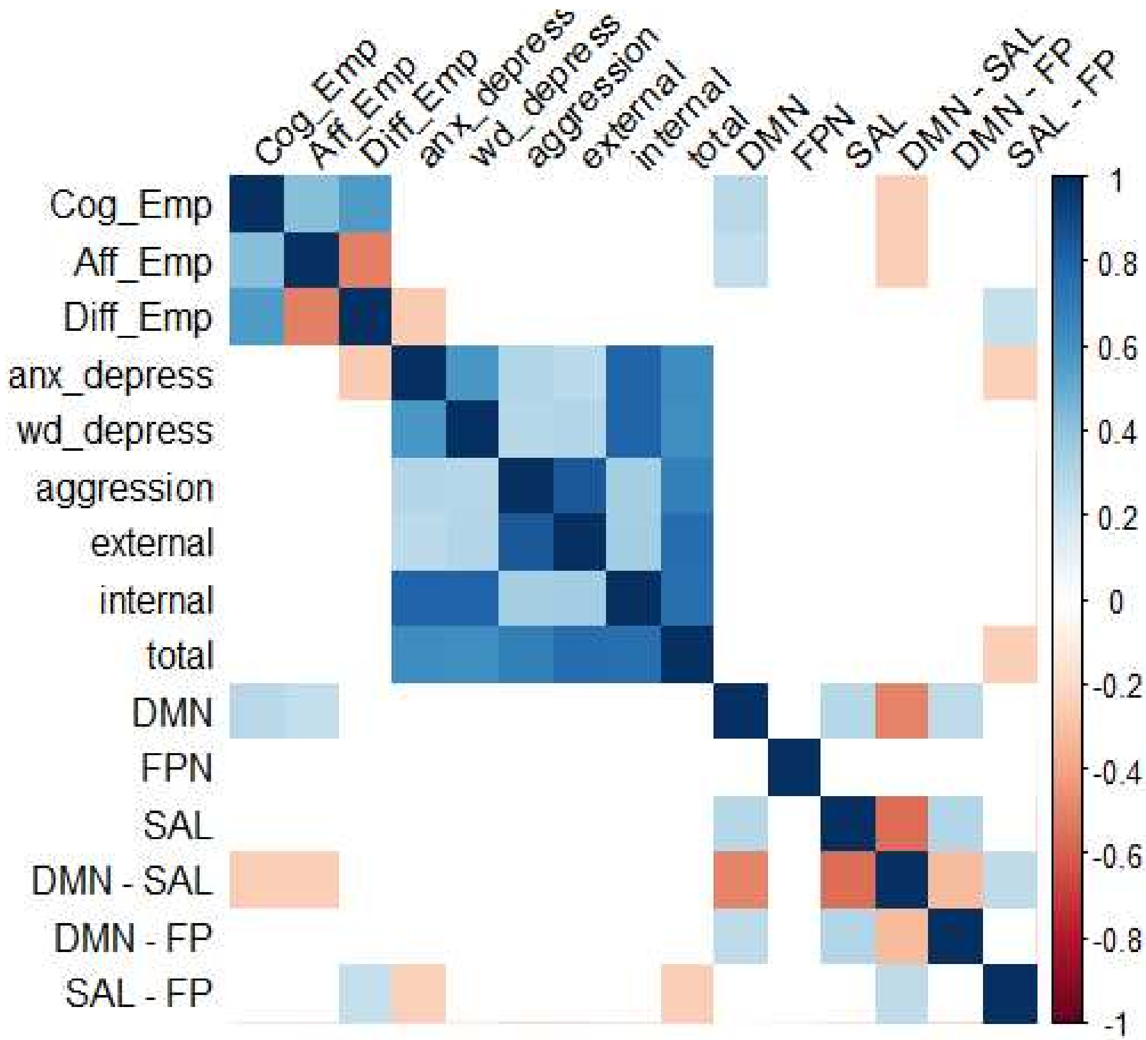

Figure 7. Correlations of Youth Report Survey with empathy and brain connectivity parameters.

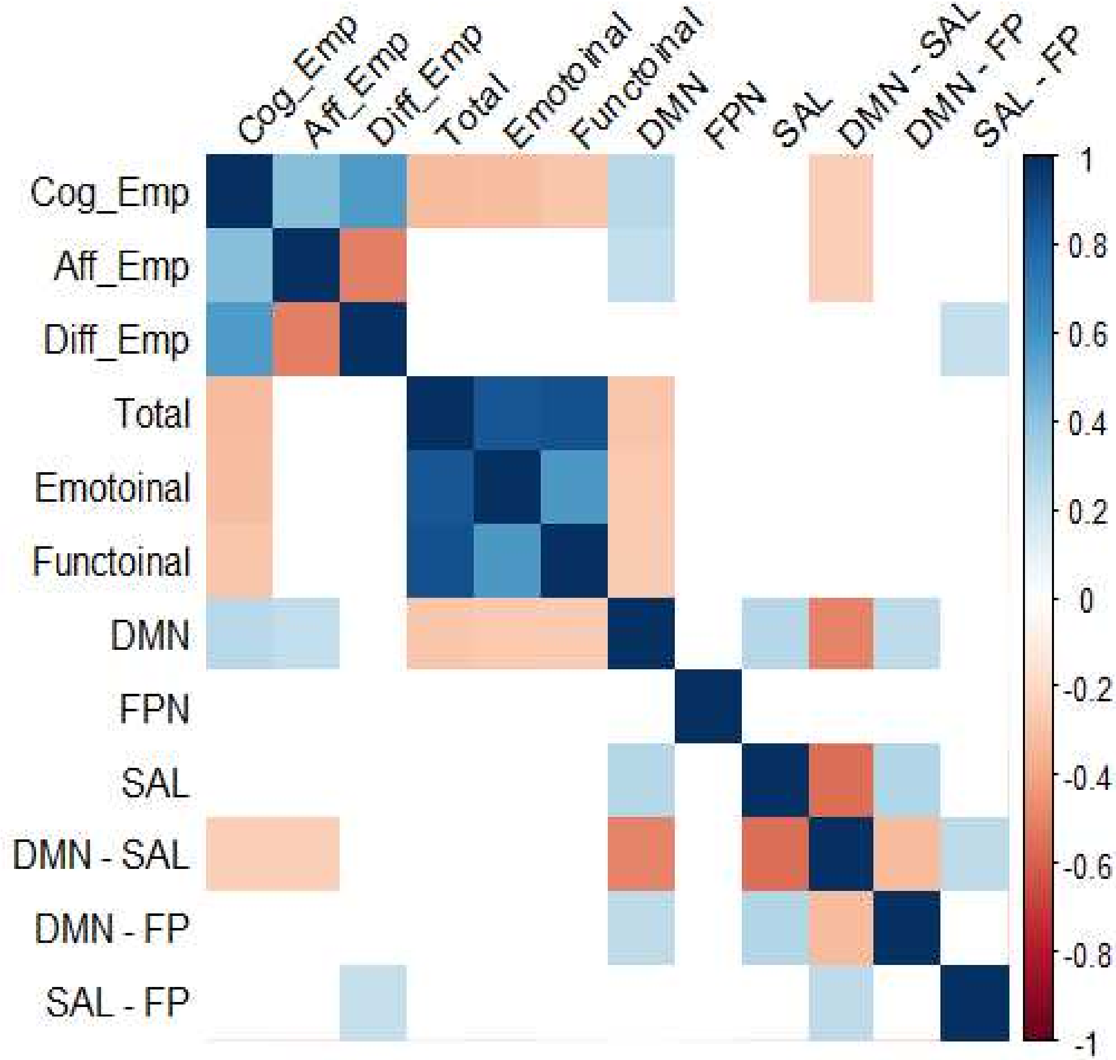

Figure 8. Correlations of Child Depression Inventory with empathy and brain connectivity parameters.

Table 4. MNI coordinates for Network ROIs

Network	Region	MNI coordinates (x, y, z)
Default Mode Network	MPFC	1, 55, -3
	Angular Gyrus (L)	-39, -77, 33
	Angular Gyrus (R)	47, -67, 29
	Posterior Cingulate Cortex	1, -61, 38
Salience Network	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
Frontoparietal Network	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 5. Results of Mediation analyses

Model	**c (exp)[1]**	**a[1]**	**b (exp)**	**c' (exp)[1]**	**R^2**	**ab Indirect effect (95% CI)**
			DMN (IV) → Cognitive empathy (M) → emotional (DV)			
F=4.92(5,78)*	-1.65(-80.79)*	7.43*	-0.05(-4.87)*	-1.27(-71.91)*	.24	-.39 (-.83, -.06)*
			DMN (IV) → Cognitive empathy (M) → functional (DV)			
F=4.69(5,75)*	-1.64(-80.60)*	6.57	-0.04 (-3.92)*	-1.35(-74.07)*	.24	-.029 (-.70, .00)
			SAL – FPN (IV) → Imbalanced empathy (M) → anxious depressed (DV)			
F=5.1(5,78)*	-1.43(-76.06)*	8.62*	-0.04 (-3.92)*	-1.10(-66.71)*	.25	-.033 (-.92, .04)

Notes: c = total effect of age group on speeded task performance; a = effect of IV on M; b= relationship between M and DV; c' =direct effect of IV on DV; CI =95% bootstrap confidence interval for the indirect effect (10,000 stratified resamples);
All tests corrected for gender, race, and tanner stage;
DMN = default mode network; SAL = salience network, FPN = frontoparietal network;
all (exp) numbers are interpreted as percent change in outcome for each path;
[1] paths from functional connectivity parameters are interpreted as one change in SD predicts unit change in Y
*p,0.05.

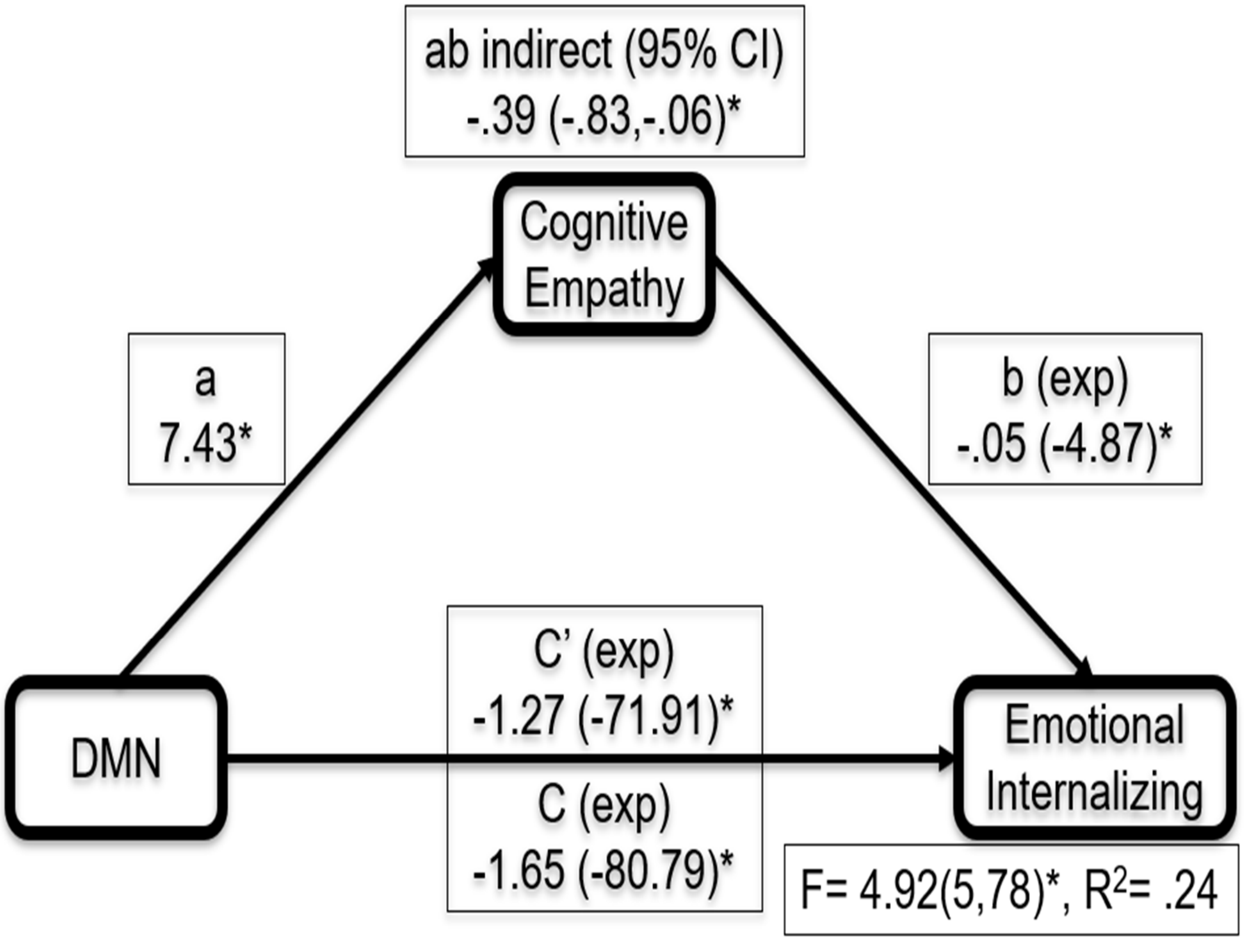

Figure 9. Mediation model and coefficients for default mode (DMN) within-network connectivity associating with emotional internalizing symptoms in relation to cognitive empathy. This model depicts a significant mediation model where DMN connectivity covaries with cognitive empathy in association with emotional internalizing symptoms.
* = p < .05

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Weissberg, R. P., & Cascarino, J. (2013). Academic learning+ social-emotional learning= national priority. *Phi Delta Kappan, 95*(2), 8-13.

Weissberg, R. P., Durlak, J. A., Domitrovich, C. E., & Gullotta, T. P. (2015). Social and emotional learning: Past, present, and future.

Whitfield-Gabrieli, S., Ghosh, S., Nieto-Castanon, A., Saygin, Z., Doehrmann, O., Chai, X., . . . Gabrieli, J. (2016). Brain connectomics predict response to treatment in social anxiety disorder. *Molecular Psychiatry, 21*(5), 680.

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect, 2*(3), 125-141. doi:10.1089/brain.2012.0073

Xia, C. H., Ma, Z., Ciric, R., Gu, S., Betzel, R. F., Kaczkurkin, A. N., . . . Satterthwaite, T. D. (2018). Linked dimensions of psychopathology and connectivity in functional brain networks. *Nature communications, 9*(1), 3003-3003. doi:10.1038/s41467-018-05317-y

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Yamada, M., & Decety, J. (2009). Unconscious affective processing and empathy: An investigation of subliminal priming on the detection of painful facial expressions. *Pain, 143*(1), 71-75.

Yeager, D. S. (2017). Social and emotional learning programs for adolescents. *The Future of Children*, 73-94.

Zaki, J., & Ochsner, K. N. (2012). The neuroscience of empathy: Progress, pitfalls and promise. *Nature Neuroscience, 15*(5), 675-680.

Zhou, Y., Chen, J., Friston, K. J., Zeidman, P., Li, S., & Razi, A. (2017). The Hierarchical Organization of the Default, Dorsal Attention and Salience Networks in Adolescents and Young Adults. *Cerebral Cortex, 28*(2), 726-737. doi:10.1093/cercor/bhx307

Curriculum Vitae
Drew E. Winters

Professional Preparation

August 2016 - April 2020	Ph.D. Indiana University, Indianapolis, IN. Major: Social Work Minor: Psychology – Statistics and Cognitive Neuropsychology Dissertation Title: *Social Cognitive and Affective Neural Substrates of Adolescent Transdiagnostic Symptoms*. Chair: Kathy Lay, PhD. Melissa Cyders, PhD., HSPP Jessica Damoiseaux, PhD. Sadaaki Fukui, PhD. Barbara Pierce, PhD., LCSW
May 2013 - May 2016	M.S.W., Indiana University, Indianapolis, IN. Major: Social Work, Concentration: Advanced Generalist
August 2011 - May 2013	B.S., Purdue University, Fort Wayne, IN. Major: Human Services, Minor: Psychology, Concentration: Addictions

Advanced Training

2020	Statistician using R statistical language 14 class and 56-hour course. *DataCamp.com online learning for statistics and computer language*
2019	Statistical methods: Maximum likelihood & advanced regression *ICPSR Summer Quantitative Methods of Social Research, Ann Harbor, MI*
2019	Data analyst using R statistical language: 16 class and 64-hour course *DataCamp.com online learning for statistics and computer language*
2019	Neuroimaging: The Conn Toolbox for functional connectivity analysis *Martino's Center for Biomedical Imaging, Boston, MS*
2018	Statistical methods: Structural equation modeling & longitudinal analysis *ICPSR Summer Quantitative Methods of Social Research, Ann Harbor, MI*
2018	Neuroimaging: Resting state functional connectivity analysis *Martino's Center for Biomedical Imaging, Boston, MS*
2016 - 2019	Statistical software: R (2016-2019), Mplus (2018), Stata (2018)
2017	Independent study: Neuroimaging task research designs Dr. Hummer
2016	Independent study: Structural equation modeling

Honors and Awards

2020	Data Scientist using R certification, *DataCamp*
2020	Statistician using R certification, *DataCamp*
2019	Data Analyst using R certification, *DataCamp*
2018	Certification: Empirical Implications of Theoretical Models *Structural Equation Modeling with latent models*
2018	Developmental, Child, and Family Psychology Scholarship *ICPSR Quantitative Methods of Social Research* Ann Harbor, MI
2017 - 2019	Indiana University Travel Fellowship
2016	Graduate Professional Student Government Fellowship
2014	Maranda Pang Endowment
2013	Phi Kappa Phi: Academic Honor Society
2013	Tau Upsilon Alpha: Human Services Academic Honor Society
2012	Hellen I. Rodney Nern Scholarship
2011 - 2013	Dean's List. Purdue University, Fort Wayne, IN

Academic Positions

Research Positions

2019 - Present	**Research Assistant,** Dr. Barbara Pierce: Department of Pediatrics in Adolescent Health, Indiana University Health, Indianapolis, IN
2016 - 2019	**Research Assistant,** Dr. Jim Hall: Department of Pediatrics in Adolescent Health, Indiana University Health, Indianapolis, IN
2013 - 2015	**Research Assistant,** Dr. Melissa Cyders: Risk-taking, Impulsivity and Social Cognition (RISK) lab, Department of Psychology, Indiana University Purdue University, Indianapolis, IN

Teaching

Semester/Year	Course Taught	Format	Enrollment
Indiana University School of Social Work – Teaching Assistant			
Fall 2016	S623 Practice Research Integrative Seminar	Seminar	19
Spring 2017	S623 Practice Research Integrative Seminar	Online	20
Summer 2017	S623 Practice Research Integrative Seminar	Online	20
University of Michigan – Inter-university Consortium for Political and Social Research			
Summer 2019	Regression Analysis II: Linear models	Seminar	80
Summer 2020	Regression Analysis II: Linear models	Online	80
Indiana University School of Social Work – Adjunct Professor			

Summer 2018	S517 Assessment in Mental Health and Addictions	Seminar	15
Fall 2018	S718 Intermediate Statistics – Lab	Seminar	6
Spring 2019	S728 Advanced Statistics – Lab	Seminar	6
Fall 2019	S718 Intermediate Statistics – Lab	Seminar	8
Spring 2020	S728 Advanced Statistics – Lab	Seminar	8

Invited Presentations

1/2020	Winters, D.E., Secondary data analysis. S728 multivariate statistics, Dr. Sadaaki Fukui. Indiana University School of Social Work, Indianapolis, IN.
6/2017	Winters, D.E. *Mindfulness and Acceptance and Commitment Therapy in Clinical Practice.* Advanced clinical practice, Dr. Vincent Starnino, instructor. Indiana University School of Social Work, Indianapolis, IN.
8/2016	Winters, D.E. *Mindfulness in Addictions Treatment*. Presentation to staff and clients at the Life Recovery Center, Indianapolis, IN.
4/2016	Winters, D.E. *Mindfulness in Clinician Self-Care and Clinical Practice.* Presented to the staff and honor society recipients of Chi Eta Sigma for marriage and family therapist. Purdue University, Fort Wayne, IN.

Publications and Research

Published Journal Articles

Winters, D.E., Wu, W., Fukui, S. (2020). Longitudinal effects of cognitive and affective empathy on adolescent substance use. *Substance Use & Misuse*, 1-7. DOI: 10.1080/10826084.2020.1717537

Winters, D.E., Fukui, S., Leibenluft, E., Hulvershorn L.A., (2018). Improvements in Irritability with Open-Label Methylphenidate in Youth with Comorbid Attention Deficit/Hyperactivity Disorder and Disruptive Mood Dysregulation Disorder. *Journal of Child and Adolescent Psychopharmacology,* 28(5): 298-305.

Beerbower, E., **Winters, D.E**., Kondrat, D. (2018). Bio-psycho-social-spiritual needs of adolescents and young adults with life-threatening illnesses: Implications for social work practice. *Social Work in Health Care*, 1-17. DOI: 10.1080/00981389.2018.1430091

Winters, D.E., Beerbower, E. (2017). Mindfulness and Meditation as an Adjunctive Treatment for Adolescents Involved in the Juvenile Justice System: Is Repairing the Brain and Nervous System Possible? *Social Work in Health Care*, 1-21. Doi:10.1080/00981389.2017.1316341

Articles Under Review

Winters, D.E., Pierce, B. J., Imburgia, T. (Under Review) Effects of concrete service spending on stability for youth receiving child welfare services. (Title-IV-E waiver)

Winters, D.E., Brandon-Friedman, R. (Under Review). Systematic review of socio-cognitive and socio-affective function as an early risk for development of substance use disorder in adolescents.

Winters, D.E., Starnino, V. (Under Review). Healing or hurting? Clinician perception and application of mindfulness with at-risk adolescents.

Articles in Preparation

Winters, D.E., Neural connectivity of cognitive and affective empathy in adolescents.

Winters, D.E., Neural connectivity covariation with cognitive and affective empathy in relation to transdiagnostic symptoms in adolescents.

Winters, D.E., Contextual social cognitive and affective neural development in adolescence as risk and resilience for addiction: The empathic attunement model.

Winters, D.E., Imburgia, T., Pierce, B. J., Ten-year trends in home stability of families receiving social services and provider concrete service spending. (Title-IV-E waiver)

Winters, D.E., Imburgia, T., Pierce, B. J., Impact of concrete service spending on number of out of home placements for youth. (Title-IV-E waiver)

Published Book Chapters

Armstrong, E., **Winters, D.E.**, Jaggers, J. (2018). Mental Health in Prison Populations. Serving the Stigmatized: Working within the Incarcerated Environment. W.T. Church and D.W. Springer, Oxford University Press.

Technical Reports on the Title-IV-E Waiver for State of Indiana

Winters, D.E., Imburgia, T., Pierce, B. J. (2017, 2018, 2019). Concrete Services Spending and outcomes for youth.

Research Presentations at Conferences

1/2020	**Winters, D.E.,** *Longitudinal effects of cognitive and affective empathy on adolescent substance use.* Society for Social Work Research, Washington, DC
1/2020	**Winters, D.E.,** *Effects of concrete service spending on stability for youth receiving child welfare services.* Society for Social Work Research, Washington, DC
10/2019	**Winters, D.E.,** Imburgia, T., Pierce B.J., *Social Cognitive/Affective Functioning in Youth at High-Risk for Substance Use Disorder*. Council on Social Work Education Annual Program Meeting. Denver, CO
5/2019	**Winters, D.E.** *Social Connection and Substance Use Disorder Risk: Social Cognitive and Affective Neural Network Differences*. Indiana University 2019 Social Work PhD Symposium. Indianapolis, IN
5/2019	**Winters, D.E.,** Imburgia, T., Pierce B.J., *Trends in Home Stability of Families Receiving Social Services and Providers*

	Concrete Service Spending. Indiana University 2019 Social Work PhD Symposium. Indianapolis, IN
4/2018	**Winters, D.E.**, Fukui S., Konrath S., Hummer T., Hulvershorn L.A. Poster Presentation. *A Translational Framework of Empathic Processes in Early Adolescent Risk for Substance Use Disorders: A Research Agenda*. Indiana University 2018 Social Work PhD Symposium. Indianapolis, IN
10/2017	**Winters, D.E**. Paper Presentation. *Clinician Perception and Application of Mindfulness with At-Risk Youth: A Mixed Methods Frame Analysis*. Council on Social Work Education Annual Program Meeting. Dallas, TX
7/2017	**Winters D.E**. Poster Presentation. *Neurobiological Correlates in Persistent Adolescent Offenders: A Systematic Review.* National Organization of Forensic Social Workers. Boston, MS
5/2017	**Winters, D.E**. Poster Presentation. *Helping or Hurting? Clinician Perception and Application of Mindfulness with At-Risk Youth: A Frame Analysis.* Indiana University 2017 Social Work PhD Symposium. Indianapolis, IN
7/2014	Bates, S.M., Myslinski, J.S., **Winters, D.E**., Cyders, M.A., Oberlin, B.G. Poster Presentation. *Behavioral quantification of Preference for High Intensity Stimuli Correlates with Self-Reported Sensation Seeking*. Indiana University 2014 Research Day, Indianapolis, IN

Service and Leadership

Ad Hoc Reviewer for Refereed Journals

2018	*Journal of Juvenile Justice*	Invited reviewer
2017	*Journal of Child and Family Studies*	Invited reviewer
2016 - Present	*Mindfulness*	Invited reviewer

Volunteer Professional Leadership

2011 - 2018	Board of Directors, National Association of Alcohol and other Drugs of Abuse Counselors, Indiana Chapter, Indianapolis, IN

Volunteer Service

2011 - 2018	Student committee, Indiana Association of Addiction Professionals, Indianapolis, IN
2015 - 2016	Volunteer, Lincoln Park Community Shelter. Chicago, IL
2016 - 2019	Volunteer, Illinois Vipassana Center. Rockford, IL

University Service: Indiana University

Fall 2018	Professional group on statistical analysis using R
2016 - 2018	Interdisciplinary writing group based on Gopen’s teachings

Clinical Experience

2016 - Present	**Therapist,** Family Works Inc., Indianapolis, IN Conduct individual and family psychotherapy with adults,

adolescents, and children involved in the child welfare system who are experiencing a wide range of emotional, behavioral, and psychosomatic issues.

2015 - 2016 **Therapist,** Rogers Behavioral Health, Skokie, IL
Conducted individual and family psychotherapy with adults and adolescents in a specialized intensive anxiety treatment clinic offering intensive outpatient and partial hospitalization services. Focus on treating anxiety and related anxiety conditions, depression, and trauma. Conducted psychological assessments for admission. Facilitated group in cognitive therapy and acceptance and commitment therapy. Extensively trained and supervised in Cognitive Therapy, Acceptance and Commitment Therapy (ACT), Exposure Response Prevention (ERP), Prolonged Exposure (PE) and Behavioral Activation (BA) under Dr. Karen Cassiday, ACT.

2013 - 2015 **Care Coordinator/Life Skills Instructor,** Aspire Indiana, Indianapolis, IN
Provided in-home therapeutic services and case management for adults, adolescents and children experiencing a wide range of emotional, behavioral, and psychosomatic issues. Provided therapeutic interventions to reach treatment goals, develop parenting skills, repairing family relationships and support, life skills development and crisis intervention. Provide referrals, attend and testify at court hearings, as well as coordinate with all providers attached to the family.

2011 - 2013 **Case Worker II,** Park Center Inc., Fort Wayne, IN
Provided in-home therapeutic services and case management for adults, adolescents and children experiencing a wide range of emotional, behavioral, and psychosomatic issues. Provided therapeutic interventions to reach treatment goals, develop parenting skills, repairing family relationships and support, life skills development and crisis intervention. Provide referrals, attend and testify at court hearings, as well as coordinate with all providers attached to the family.

Professional Memberships

2013 - Present National Association of Social Workers (NASW)
2017 - Present Society for Social Work and Research (SSWR)
2016 - Present Counsel on Social Work Education (CSWE)

Licensure

Indiana Licensed Social Worker (LSW)