Developmental differences in the effect of trait anxiety on neural network structure: A DTI study in adolescents and adults

Short title: Age-by-anxiety interactions in network structure

Nele A.J. De Witte^{1,2}, Sofie Cromheeke¹, Sven C. Mueller¹

Affiliation:

¹ Department of Experimental Clinical and Health Psychology; Ghent University;
Ghent; Belgium

² Expertise unit Psychology, Technology & Society; Department of Applied
Psychology; Thomas More University of Applied Sciences; Belgium

Contact information:

Nele De Witte

Expertise unit Psychology, Technology & Society;

Molenstraat 8

2018 Antwerp, Belgium

Mail: nele.dw@thomasmore.be

Abstract

In adults, anxiety affects the connectivity of four core brain networks, specifically fronto-parietal network (FPN), default mode network (DMN), ventral attention network, and cingulo-opercular network. Comparative research across developmental periods is scarce despite critical developmental changes in cognitive-affective processing and neural reorganization. This structural DTI study investigated age-by-anxiety interactions in structural connectivity within these networks and their amygdala connections in 44 healthy adolescents and 32 healthy adults. A significant interaction emerged in the FPN and DMN, with adults showing increased structural connectivity in relation to trait anxiety. This provides evidence for developmentally-specific influences of trait anxiety on cognitive-affective network structure.

Keywords: white matter, network structure, anxiety, PFC, development

Introduction

Anxiety disorders often find their onset during adolescent development (Paus, Keshavan, & Giedd, 2008), have become the leading cause of mental illness in this age cohort (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015), and significantly increase the risk for adult anxiety and depression (Pine, Cohen, Gurley, Brook, & Ma, 1998). While evidence demonstrates the impact of adolescent anxiety on affective processing and grey matter volume in core structures such as the amygdala (Mueller et al., 2013; Williams et al., 2015), research on the association between anxiety and functional and structural network connectivity between brain regions in this age group is scarce (Guyer et al., 2008; Monk et al., 2008; Roy et al., 2013). This is surprising given that knowledge on the early impact of anxiety on neural network structure may inform on the neural (and possibly linked behavioral) vulnerabilities associated with anxiety. This, in turn, may have implications for adequate treatment options.

In adults, anxiety is hypothesized to impact the functional connectivity of four core brain networks essential for cognitive-affective processing including 1) bottom-up (ventral attention network; VAN) and 2) top-down attention processes (fronto-parietal network; FPN), 3) salience detection (cingulo-opercular network; CON), and 4) default mode (default mode network; DMN) (Liao et al., 2010; Sylvester et al., 2012). Structurally, trait anxiety and depression in adulthood are associated with reduced white matter connectivity between the amygdala and all four of these networks, which could have important consequences for cognitive-affective functioning (De Witte & Mueller, 2016). Although many problems related to anxiety arise in adolescence, constituting risk for normative development, the current evidence for anxiety-related changes in structural connectivity is less clear in children and adolescents (e.g., Guyer et al., 2008; Monk et al., 2008).

The brain undergoes tremendous changes in white matter across development (Paus et al., 1999). However, studies reporting on the directionality of age-dependent changes in white matter microstructure are scarce and to date inconsistent. On the one hand, Dennis et al. (2013) reported decreases in structural connectivity to and from the prefrontal cortex from adolescence to adulthood. On the other hand, Lebel and Beaulieu (2011) and Lebel et al. (2012) observed increases with age in white matter pathway strength (fractional anisotropy, FA) in fronto-parietal fibers (present in FPN, VAN, and DMN) and fronto-limbic fibers. Functionally, the FPN, CON, and DMN evolve from being highly dependent on local level interactions in childhood to a more distributed organization in adulthood (the VAN was not investigated by these authors; Fair et al., 2009). Disruption of the normative developmental trajectory of such networks might confer increased risk for psychopathology such as anxiety and alter neural communication across the brain.

Relying mostly on adult samples, Sylvester et al. (2012) theorize that anxiety is associated with increased activity in the CON and VAN, resulting in increased sensitivity to conflict and bottom-up stimuli, and decreased activity of the FPN and DMN, which is related to deficits in cognitive control. In youths, anxiety-related deficits in functional connectivity have already been reported between the VAN and the amygdala, albeit also with mixed findings (Guyer et al., 2008; Monk et al., 2008; Roy et al., 2013). While Monk et al. (2008) documented lower negative connectivity between ventrolateral prefrontal cortex (vIPFC) and amygdala in children with generalized anxiety disorder, Guyer et al. (2008) observed increased positive connectivity between vIPFC and amygdala in youths with social anxiety disorder. Finally, discrepancies also exist developmentally. Dennis, Gotlib, Thompson, and Thomason (2011) showed increased anxiety-related functional connectivity between

the parahippocampal gyrus (PHG) and posterior cingulate and other DMN hubs in adults, but increased DMN – caudate functional connectivity in relation to trait anxiety in youth.

Even in non-clinical samples, trait anxiety can already impact the development of white matter connectivity in important neural pathways. Subclinical symptoms of anxiety and depression in healthy youth are associated with the rate of microstructural development within important white matter pathways involved in emotion regulation and mood and anxiety disorders (Albaugh et al., 2016). Healthy youth between 5 and 18 years of age with elevated symptoms of anxiety and depression showed lower rates of age-related increases in FA in the bilateral anterior thalamic radiation, bilateral inferior longitudinal fasciculi, the left superior longitudinal fasciculi, and right cingulum. However, similar to the functional literature, inconsistencies between different studies are apparent (for review see Ayling, Aghajani, Fouche, & van der Wee, 2012).

Discrepancies in the previous structural literature could be due to the methods and indices used to index tract integrity. Trait anxiety in adults is related to lower volume (Baur, Hanggi, & Jancke, 2012) but increased FA (Modi et al., 2013) in the uncinate fasciculus, an important fronto-temporal white matter tract that connects the amygdala with regions of the CON, VAN, and DMN. This suggests that tract volume and FA can have different directions of effect and might therefore tap into different underlying processes of structural connectivity. Other possible sources of divergence between studies can be found in the definition of the region(s) of interest and differences in the age or clinical status of the participants.

Taken together, there is a lack of research on developmental differences in the effect of trait anxiety on structural connectivity. Additionally, large inconsistencies exist between the results of different studies, and existing structural research mostly focused on a specific region or network of interest. Therefore, the present study aimed to investigate age differences in the effect of trait anxiety on white matter microstructure in four networks essential for cognitive-affective functioning. To this end probabilistic tracking was implemented in these neural networks (VAN, FPN, CON, and DMN) as well as between the networks and the amygdala. Since the use of different methods to map structural connectivity could have contributed to the inconsistencies in previous literature, the current study will use three different indices of white matter integrity. Although previous research shows age-related differences in functional DMN connectivity in relation to trait anxiety (Dennis et al., 2011) as well as an impact of trait anxiety on white matter development in youth (Albaugh et al., 2016), structural connectivity research is still very limited in adolescents and large inconsistencies remain in previous research on the effect of anxiety on neural connectivity. Therefore, it is not possible to make strong theory-driven hypotheses about age-differences in the effect of trait anxiety on network connectivity in these four core brain networks.

Materials and methods

Sample

The final study sample consisted of 32 healthy adults (ages 25 to 34, $M = 27.52$, $SD = 2.32$) and 44 healthy adolescents (ages 13 to 17, $M = 14.54$, $SD = 1.26$). Initially, 42 adults and 51 youth were recruited but two adults and three adolescents

were excluded because they presented symptoms in the clinical range of the externalizing or total scale of the Adult Self Report (ASR) (Achenbach & Rescorla, 2003) or Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) and eight adults and four adolescents suffered from missing or invalid diffusion data¹. Participants were not screened for past psychiatric diagnoses. Adults were recruited via a participant website and adolescents were recruited through local high schools. Demographic information for the final study sample is presented in Table 1. For estimated IQ, the subscales 'vocabulary' and 'block design' of the Wechsler Intelligence Scale for Children (WISC) (Kort et al., 2005; Wechsler, 1991) and Wechsler Adults Intelligence Scale (WAIS) (Wechsler, 2012) were used. Depression symptoms were assessed with the Dutch version of the Beck Depression Inventory (BDI) (Beck, Steer, Ball, & Ranieri, 1996; Van der Does, 2002) in adults and the Childhood Depression Inventory (CDI) (Kovacs, 1992; Timbremont & Braet, 2002) in adolescents. The Spielberger State-Trait Anxiety Inventory, adult version (STAI) (Spielberger, Gorsuch, & Lushene, 1970) and child-version (STAI-C) (Bakker, van Wieringen, van der Ploeg, & Spielberger, 2004; Spielberger, 1973) were used to measure trait anxiety. Both STAI and STAI-C contain 20 items that assess general feelings of anxiety and proved to be reliable in the current sample ($\alpha = .90$ and $\alpha = .85$ respectively). The STAI scores are normally distributed in both the adolescents ($W = .94$, $p = .10$) and adults ($W = .97$, $p = .43$). To ensure comparability between the adult and child measures in both STAI(-C) and CDI/BDI, the results were transformed into a z-score (cf. Cromheeke & Mueller, 2016). All participants as well as their

¹ The DTI data collection took place within the context of a developmental fMRI study on emotional working memory, the data of which are reported elsewhere (Mueller, Cromheeke, Siugzdaite, & Nicolas Boehler, 2017)

parents (if participants were underage) filled out informed consent forms (adults) and assent forms (youths). The experiments were done in accord with the Helsinki Declaration of 1975 and ethical approval was obtained from the ethical committee of Ghent University Hospital.

MRI acquisition

Data was collected on a 3T Siemens Trio MR scanner at Ghent University Hospital. Diffusion MRI was recorded with an echo planar imaging (EPI) sequence (repetition time (TR) = 7300 ms, echo time (TE) = 83 ms, field of view (FOV) = 256 mm, slice thickness = 2 mm, 60 slices, echo spacing = 0.69 ms, bandwidth = 1698 Hz/Px, phase partial Fourier = 6/8, and a b-value of 850 s/mm²). The dMRI protocol consisted of 64 directions and 1 B0 acquisition applied in both anterior to posterior phase encoding. A structural image was also collected using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR = 2250 ms, TE = 4.18 ms, flip angle 9°, FOV = 256 mm).

Analysis of diffusion MRI

The key brain regions of the FPN, CON, VAN, and DMN, which were reported in the theoretical article by Sylvester et al. (2012) will be used as seeds and targets in the subsequent analyses (Table 2). Since these authors did not provide coordinates for these regions, the current study used the coordinates that were collected for these regions in a previous large study by the first author (De Witte & Mueller, 2016). The ROIs needed to be sufficiently large to account for differences due to brain maturation since specialization of function in the brain is more diffuse earlier in life (e.g. adolescence) and becomes more focal with age (Casey, Tottenham, Liston, & Durston, 2005). Consequently, ten mm spheres were created around the peak

coordinates (using `fslmaths`) to produce ROIs of approximately the same size. These masks were subsequently transformed from standard space to native space for probabilistic fibertracking (using FSL `flirt` and `fnirt`) (Andersson, Jenkinson, & Smith, 2007; Jenkinson, Bannister, Brady, & Smith, 2002). Since it is difficult to construct accurate standard masks for subcortical structures, individual amygdala masks were created for each subject with FSL FIRST model-based segmentation (Patenaude, Smith, Kennedy, & Jenkinson, 2011).

Diffusion data was reoriented, visually inspected for large errors, and saved in `nifti` format before analysis with the commonly used FSL pipeline for DTI analysis (e.g., Eden et al., 2015; Korgaonkar, Fornito, Williams, & Grieve, 2014; Peeva et al., 2013) on the UGent High Performance cluster. As a first step, the diffusion images were corrected for eddy currents. Subsequently, we performed brain extraction (FSL BET; Smith, 2002) on structural and diffusion images and created a binary brain mask for the diffusion data. Whole-brain FA was calculated with FSL DTIFIT. The FSL-tool `BedpostX` was used to calculate the two dominant fiber distributions per voxel from the preprocessed data (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Jbabdi, Sotiropoulos, Savio, Grana, & Behrens, 2012). Subsequently, FSL `ProbtrackX` was used to calculate the connections between the different regions of interest in diffusion space (Behrens et al., 2007). Five thousand samples were sent from each voxel in the seed region, using a curvature threshold of 0.2 and step length of 0.5 mm, and a midline exclusion mask was implemented since we did not have any hypotheses on interhemispheric connectivity.

FSL reports the number of streamlines connecting seed and target regions (`waytotal`). The `waytotal` of both directions of a tract was summed and averaged over the two hemispheres (for all networks except the VAN, which is mainly right

lateralized; Sylvester et al., 2012) to calculate connection probability. Two other complementary indices of white matter connectivity were calculated: FA and tract volume. To this end, the calculated path was averaged over both directions to optimize tract reliability (Clewett, Bachman, & Mather, 2014) and a relative threshold of 15% of the maximum value was applied to account for individual differences as well as be stringent enough to optimize tract quality (De Witte & Mueller, 2016). Tract FA and tract size were calculated based on these tracts and averaged over the two hemispheres (except for the tracts of the VAN).

Hence three measures of structural connectivity were calculated: *connection probability* (white matter connection strength: the number of streamlines connecting seed and target regions), *tract FA* (representing white matter directionality), and *tract volume* (in voxels) (Peeva et al., 2013). While previous research mostly focuses on only one index of white matter connectivity (typically FA), these indices provide complementary information and connection probability and tract volume have also shown interesting results (Budisavljevic et al., 2016; Khalsa, Mayhew, Chechlac, Bagary, & Bagshaw, 2013; Peeva et al., 2013). Therefore, since differences in measures could contribute to discrepancies in previous research and the debate on the effectiveness of the different indices of structural white matter connectivity is still ongoing, all three measures were included.

Statistical analysis

The three outcome variables (*tract FA*, *tract volume*, and *connection probability*) were exported from the high performance cluster using unix-based scripts. These variables and the demographic information were subsequently imported in SPSS (version 20, IBM, Chicago, IL, USA) for statistical analysis. Linear

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regression was implemented to assess whether the effect of trait anxiety on structural white matter connectivity differs between adolescents and adults. The predictor of interest was the *trait anxiety by age group* interaction term. To examine the microstructure of the white matter tracts connecting the *a priori* regions of interest, the predictors were: trait anxiety, age group (i.e. categorical variable representing whether the participant was an adult or adolescent), depression, gender, estimated IQ, whole-brain FA, and amygdala volume (in the amygdala-network connections). Data were screened for influential cases to prevent the results from being driven by a small subsample of participants. For each regression, influential cases were defined as having a Cook's distance higher than $4/n$ (Bollen & Jackman, 1990) and excluded from further analysis. This did not result in major changes in sample characteristics².

Given the amount of tests performed, we controlled for multiple comparisons (i.e., multiple ROIs) by adjusting the significant p-values for the group by anxiety interaction variable using the step-down Finner procedure ($p < .05$ adjusted) (Finner, 1990, 1993). In addition, Cohen's f^2 was used as a measure of effect size and post-hoc power was calculated for each significant regression model. Significant effects were explored by use of bivariate correlations in each age group and the Fisher r-to-z test to compare whether the correlations were statistically significantly different from one another.

² Tables describing the characteristics of the resulting samples are available upon request.

Results

Connection probability

The model predicted connection probability within the FPN ($R^2 = .40$, adjusted $R^2 = .33$, $p < .001$, power = 1.00; Table 3) with a large effect size (Cohen's $f^2 = .67$). The interaction between trait *anxiety* and *age group* significantly predicted connection probability of dlPFC – inferior parietal lobe tract. While FPN connection probability was not correlated with anxiety in healthy youth ($r(41) = -.10$, $p = .53$), there was a strong positive association between anxiety and connection probability in adulthood ($r(26) = .74$, $p < .001$). These correlation coefficients were significantly different from one another ($z = -3.98$, $p < .001$) (Figure 1).

The model also significantly predicted connection probability of the tract between the precuneus and the subgenual anterior cingulate cortex (sgACC) within the DMN ($R^2 = .34$, adjusted $R^2 = .25$, $p = .001$, power = .99; Table 3) with a large effect size (Cohen's $f^2 = .52$). The interaction between trait *anxiety* and *age group* significantly predicted connection probability. While connection probability in the precuneus – sgACC tract was not correlated with anxiety in healthy youth ($r(43) = -.08$, $p = .62$), there was a positive, but non-significant, association between anxiety and connection probability in adulthood ($r(23) = .35$, $p = .11$). The difference in correlation coefficients did not reach significance ($z = -1.63$, $p = .10$) (Figure 1).

Tract fractional anisotropy (FA)

The trait anxiety by age group interaction did not predict tract FA in any of the networks.

Tract volume

The trait *anxiety by age group* interaction did not predict tract volume in any of the networks.

Discussion

This study examined the extent to which the association between trait anxiety and the structural integrity of four essential networks implicated in cognitive-affective functioning is affected by developmental status. Two main findings became apparent. Trait anxiety-related developmental differences between healthy adolescents and adults emerged in (1) connection probability of the dlPFC and IPL in the FPN and (2) connection probability of the sgACC and precuneus of the DMN. However, developmental status did not influence the effect of anxiety on CON and VAN and while connection probability showed these age-related differences, no effects were found in FA or tract volume.

The FPN is involved in top-down attention control and attentional sets and goals (Corbetta & Shulman, 2002). This network showed a different pattern of anxiety-related white matter connectivity in adolescents as compared to adults. While trait anxiety was not associated with FPN connection probability in adolescence, there was a strong positive correlation between trait anxiety and connection probability in adulthood. This could indicate that anxiety in adults, as compared to adolescents, is related to more efficient top-down control processes since both activation of, and functional connectivity between, the dlPFC and the inferior parietal lobe of the FPN are related to inhibitory processes (Cromheeke & Mueller, 2014;

Stevens, Kiehl, Pearlson, & Calhoun, 2007). The lack of structural associations between anxiety and FPN connectivity in youth could be related to protracted PFC maturation during adolescence (Gogtay et al., 2004). These two FPN regions were found to play a central role in cognition-emotion interactions in a recent meta-analysis (Cromheeke & Mueller, 2014). Consequently, increased structural FPN connectivity could be associated with changes in cognitive control and emotion-cognition interactions. However, the functions of the FPN and the execution of cognitive control and emotion regulation is further supported by the DMN (Sylvester et al., 2012), a second network that showed developmental differences in the effect of anxiety.

In line with the resting state functional connectivity study of Dennis et al., the DMN also showed anxiety by age group interactions in structural connectivity (Dennis et al., 2011). However, while that study observed differences in the functional connectivity of the PHG in relation to anxiety in different age groups, the current study observed an anxiety by age group interaction in the structural connection probability in the precuneus – sgACC tract. Adults appeared to have increased anxiety-related connectivity between these regions, but a follow-up test on this effect was not statistically significant. Functional resting state hyper-connectivity of the precuneus and sgACC has been reported in adults with social anxiety disorder as compared to healthy controls (Arnold Anteraper et al., 2014). Interestingly, and similarly to the FPN regions mentioned above, the precuneus and sgACC also play a key role in cognition-emotion integration (Cromheeke & Mueller, 2014). The precuneus is activated during cognitive control and emotion regulation but activation of these regions during the exertion of cognitive control is higher in adults as compared to adolescents (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Veroude, Jolles, Croiset, & Krabbendam, 2013). Of note, the interpretations of the

effects in the DMN should be considered tentative because the follow-up test showed that the correlations between anxiety and connectivity were not significantly different in adults and adolescents.

Taken together, the present findings suggest that increased trait anxiety in healthy adults is associated with increased FPN and DMN connectivity that might improve attention and emotion control processes (cf. Diamond, Campbell, Park, Halonen, & Zoladz, 2007). High anxious adolescents do not show this association and might therefore lack the necessary cognitive control capacity to cope with anxiety. This could underlie the increased vulnerability for anxiety disorders in adolescence (Paus et al., 2008). On the other hand, stronger intrinsic FPN connectivity has also been shown in individuals high in social inhibition (a core feature of social anxiety (Blackford et al., 2014)) and increased functional connectivity between the dlPFC and more posterior parts of the brain (including precuneus) has also been associated with elevated worry in adults (Forster, Nunez Elizalde, Castle, & Bishop, 2015). Future research should investigate the functional consequences of these structural alterations to distinguish between the effects of cognitive control and anxious worry.

Finally, no age by anxiety interactions reached significance in the structural connectivity of the CON and VAN. However, care has to be taken when interpreting null findings since this might be due to the definition or exact location of the key regions. There was a main effect of age that also requires discussion. The effect of age on structural connectivity measures is in line with increasing connectivity throughout development, which allows for more effective communication between different regions (Fair et al., 2009). However, our findings show that this is not a uniform process and that external factors, such as anxiety can interact with brain

development. Interestingly, the anxiety by age interactions were only present in one of the three indicators of white matter microstructure (i.e., connection probability). Previous research has suggested that connection probability, FA and tract volume measure different aspects of white matter connectivity (Peeva et al., 2013), however, previous research suggests that connection probability and tract volume might suffer from some limitations (Jones, Knosche, & Turner, 2013). Future research should elucidate how connection probability, tract volume, and FA are related to one another.

This study has some limitations. The adult and adolescent groups were not matched for depression. However, this variable was used as a covariate in the linear regression and can therefore not explain the effects. Nonetheless, future research should replicate these findings in better-matched samples. Secondly, the coordinates of the ROIs that were used in the current study were based on previous adult research. Although there might be differences in the peak point of activation of a certain region in adolescents and adults, spheres were sufficiently large to account for such interindividual differences. Finally, this cross-sectional study investigated the effects of trait anxiety in a healthy population and used a categorical approach to examine developmental differences (which does not permit the detection of quadratic patterns with trait anxiety). Future research using longitudinal designs in a sample of both healthy and clinically anxious youth could shed more light on the interaction between anxiety and brain development and elucidate the roles of brain maturation and disease progression. Price et al. already performed a longitudinal study in youth that showed that anxiety-related alterations in attention processes can predict 2-year depression scores (Price et al., 2016).

In conclusion, the current study highlights developmental differences in how trait anxiety is related to structural connectivity in two important networks involved in cognitive and affective processing. While adolescents did not show altered connectivity in the FPN and DMN in relation to anxiety, these networks (representing top-down attentional processes and emotion regulation) seem to show increased structural connectivity in relation to trait anxiety in adults. However, future research should verify whether the white matter deficits observed in this study indeed translate into cognitive-affective processes served by the networks.

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Conflicts of interest

The authors have no conflict of interest to report.

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Tables

Table 1. Sample characteristics

	Adults (<i>n</i> = 32)		Adolescents (<i>n</i> = 44)		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Age	27.52	2.32	14.54	1.26	$t(74) = 31.31, p < .001^{***}$
Gender (ratio f/m)	17/15		24/20		$\chi^2(1, N = 76) = .02, p = .90$
STAI trait raw ¹	32.56	7.26	32.11	6.85	$t(74) = -0.28, p = .78$
WISC/WAIS sum ²	23.35	3.95	21.66	3.59	$t(73) = 1.93, p = .06$
CDI/BDI raw ¹	3.65	4.13	8.45	6.28	$t(73) = 3.73, p < .001^{***}$
Whole-brain FA	.25	.01	.25	.01	$t(74) = 2.22, p = .03^*$
Amygdala volume	1461.41	264.62	1325.57	198.30	$t(74) = 2.56, p = .01^*$

Notes. * $p < .05$, ** $p < .01$, *** $p < .001$; ¹In the regression analyses the Z-transformed scores of these variables were used; ²In the Dutch version of these tests estimated IQs are not possible hence the sum scores are presented

Table 2. Overview of key regions of the neural networks compromised in anxiety and their peak MNI coordinates. Reproduced from De Witte and Mueller (2016)

Network	Region	Right hemisphere	Left hemisphere
Fronto-parietal network (FPN)	dIPFC ^a	46,28,31	-44,27,33
	Inferior parietal lobe ^a	54,-44,43	-53,-50,39
Cingulo-opercular network (CON)	Anterior insula ^b	41,3,6	-41,3,6
	dACC ^b	0,21,36	0,21,36
	Anterior PFC ^b	32,45,30	-35,45,30
Ventral attention network (VAN)	vlPFC ^c	42,19,-1	
	TPJ ^d	57,-40,22	
Default mode network (DMN)	sgACC ^e	-2,33,0	-2,33,0
	parahippocampal gyrus ^f	25,-26,-14	-22,-26,-16
	lateral parietal cortex ^b	49,-63,30	-46,-66,30
	Precuneus ^b	0,-52,27	0,-52,27

Notes. If the coordinates were reported in Talairach space they were converted to MNI space using FreeSurfer (Fischl, 2012). ^a Dosenbach et al. (2007) as reported in Power et al. (2011), ^b Raichle (2011), ^c Kollndorfer et al. (2013), ^d Kim (2014), ^e Drevets et al. (1997), ^f Greicius, Krasnow, Reiss, & Menon (2003)

Table 3. Connection probability significantly predicted by the age group by trait anxiety interaction. The predictor of interest is presented in bold ($p < .05$, corrected).

	Dorsolateral prefrontal cortex – inferior parietal lobe¹			Precuneus – subgenual anterior cingulate cortex²		
Variable	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
Constant	9341.25	52836.70		105030.49	103580.76	
Age group	21219.05	4345.85	1.58***	26123.65	10445.19	.96*
X Anxiety						
Trait anxiety	-23105.60	6511.178	-1.225***	-35026.74	13555.43	-1.01*
Age group	14923.22	3998.54	.41***	39577.45	8840.46	.60***
Depression	-177.252	2624.55	-.01	14400.17	5791.67	.35*
n						
Gender	-5843.44	3776.50	-.16	11097.55	6879.53	.18
Estimated IQ	-355.46	504.67	-.08	-418.98	959.34	-.05
Wholebrain FA	15474.24	213560.46	.01	-454450.75	412450.18	-.13

Note. * $p < .05$, ** $p < .01$, *** $p < .001$; ¹ $R^2 = .40$, $F = 5.65^{***}$, $n = 67$; ² $R^2 = .34$, $F = 4.17^{***}$, $n = 66$

Figures

Figure 1. Visual representation of the significant tracts from an adolescent participant and scatter plots representing the association between trait anxiety and connectivity in the two age groups in the subgenual anterior cingulate cortex (ACC) – precuneus tract of the DMN (left) and the dorsolateral prefrontal cortex (PFC) – inferior parietal lobe tract of the FPN (right).