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Rostral anterior cingulate cortex volume correlates with depressed mood in normal healthy children

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Abstract

BACKGROUND—The rostral anterior cingulate cortex (rACC) has been implicated as a structural neural correlate of familial major depressive disorder, raising the possibility that the structure of this region may act as a biologic marker of depression vulnerability. The aim of the current study was to determine whether children and adolescents with depressive symptoms have lower rACC volume relative to those without symptoms and examine how a positive family history of depression affects this relationship.

METHODS—112 normal healthy children (59 boys, 53 girls), age 7–17, without a current diagnosis or history of depression or other psychiatric illness, were recruited from the community. Mood symptoms were collected using the Pediatric Behavior Scale, a parent- and teacher-reported questionnaire. Volumetric measures of the rACC were generated using structural MRI. The relationship of depressive symptoms and rACC volume was examined.

RESULTS—1) The rACC volume was significantly lower in boys with subclinical depressive symptoms compared to boys with no depressive symptoms, particularly on the left side (14.6% reduction; $F = 8.90$, $p = .005$). 2) In comparing the correlation of depressive symptoms and rACC volume in boys with a positive family history of depression to those with no family history there was a more robust negative correlation in subjects with a positive family history. 3) In girls there was not a significant association of depressive symptoms and rACC volume.

CONCLUSIONS—These findings lend further support to the notion that rACC structure may act as a biologic marker of vulnerability or trait-marker of depression.

Keywords

Depression; FreeSurfer; children; anterior cingulate; subgenual

INTRODUCTION

Depression is a mood disorder often characterized by sadness and apathy, affecting as many as 1 in 6 people at some point in their life. The World Health Organization ranks depression as the fourth leading contributor to the global burden of disease and projects it to be the second

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in 2020 (1). To address the rising impact of depression, a major focus of future research must be aimed at prevention. Two promising avenues of research to achieve this goal are aimed at detecting young people at risk, including the identification of 1) behavioral precursors to depression (2–4) and 2) biological markers of depression susceptibility (5). The current study attempts to meld these two lines of research by investigating the relationship of depressive symptoms and a candidate biological marker of depression, the structure of the rostral anterior cingulate cortex (rACC), in a healthy sample of children and adolescents.

The rACC is located on the medial surface of the brain, ventral (subgenual) and anterior (pregenual) to the genu of the corpus callosum (see Figure 1). This cortical territory has a well-established role in mood and emotional processing (6; 7) as well as being a key site of convergence for several neural pathways, neurotransmitters, and neuromodulator systems implicated in depression. Functional imaging studies have demonstrated rACC activity during transient sadness in healthy adults (8;9) and abnormal activity associated with depression (10–16). Similarly, structural magnetic resonance imaging (MRI) studies have demonstrated decreased gray matter volume in the left subgenual region of the ACC in depressed individuals, including a previous study from our lab (11;17–19). Evidence of structural change in the rACC in association with major depression in adults has also come from post-mortem studies revealing a reduction in glial cells, altered neuronal density, or a reduction in the size of neuronal soma (20–22). These structural differences in the subgenual ACC detected using MRI and histology report the most robust differences in groups with a positive family history of depression (19;22). Interestingly, many of the structural findings reported above have been localized to the left subgenual ACC (11;17–19;22), while the functional studies typically reveal bilateral rACC findings that correlate positively with depressive symptoms (23).

While much evidence has implicated the rACC in adult depression, much less is known about the role of the rACC in pediatric depression. Reduced blood flow in the rostral portion of the ACC has been correlated to the degree of depressed mood in children (24;25). Also, decreased glutamate (a neurotransmitter implicated in depression) has been reported in the ACC in depressed children relative to a comparison group (26–28). Structural MRI findings in children with bipolar depression have revealed that the entire left ACC is much smaller relative to a healthy comparison group (29;30). A meta-analysis of 30 structural brain imaging studies has also concluded that the left ventral part of the rACC is a candidate neuroanatomical risk factor for bipolar depression (31). It isn't known whether unipolar depression in children is associated with reduced rACC volume.

Identification of the subgenual subregion of the rACC as a structural correlate to major depression in adults has introduced a tantalizing question; that is, is this structural deficit present prior to the onset of major depression? If so, is it possible that the structure of this region could be considered a marker of biologic susceptibility or an endophenotype of depression? Further, if the structural deficit exists in the rACC prior to the onset of disease, are there behavioral manifestations of subclinical depressive symptoms, a well-documented risk factor of depression (2–4)? There is evidence to suggest that unipolar depression may exist along a continuum in the population as a dimensional rather than categorical construct (32; 33). It is reasonable, then, to surmise that a parallel continuum may exist in the structural correlates of depression, particularly in those individuals with an inherited susceptibility to depression. However, structural MRI has not yet been used to investigate whether volumetric reductions of the rACC correspond to increased depressive symptoms in non-clinically depressed adults or children.

This study was designed to evaluate the relationship between measures of mood and volume of the rACC in a sample of children and adolescents without a current diagnosis or history of depression or any other psychiatric illness. We hypothesize that subjects exhibiting depressive

symptoms will have lower rACC volume and these measures will inversely correlate (higher levels of depressive symptoms will correspond to decreased rACC volume). Based on previous studies demonstrating a lateralized relationship of depression and left subgenual volume in adults, we predict a stronger relationship of depressive symptoms and left rACC volume relative to the right. Finally we hypothesize that the strength of correlation will be more robust in a sample limited to individuals with a positive family history of depression, lending support to the hypothesis that the morphology of the rACC acts as a biologic marker of vulnerability or trait-marker of depression.

METHODS AND MATERIALS

Participants

112 healthy children and adolescents (59 boys, 53 girls), age 7–17, were recruited from the community using local advertisements. Subjects were recruited as a normal comparison group for another study of brain structure and function in children with clefting disorders (34). Subjects were excluded if medical or neurological disease was present that required significant medical intervention. Additional exclusion criteria included: an IQ below 85, a history of depression or any other psychiatric or learning disorder (based on parent report). No clinical interview or formal evaluation was performed to rule out the possibility of clinical depression or other unreported psychopathology. The protocol was approved by the University of Iowa Human Subjects Institutional Review Board and written informed consent was obtained for all subjects prior to participation.

Demographics

Demographic data included gender, age, parental socioeconomic status (SES), IQ, and family history of depression. SES was determined using a modified Hollingshead scale of 1 to 5, with a lower number corresponding to higher social class (35). IQ was estimated using the full scale Wechsler Intelligence Scale for Children, 4th ed. (36). Family history of depression was obtained using a standardized questionnaire given to the subject's parent. The parent is instructed to list all relatives that have received a formal diagnosis of depression and indicate the relationship of the individual to the child. The number of relatives, their relation to the subject, and the nature of their depression (e.g. treatment, duration) were all recorded. Only the nuclear family was considered in classifying whether a subject has a positive family history of depression.

Behavioral Measure

The *Pediatric Behavior Scale, short version* (PBS) is a 30 question screening tool for emotional and behavioral problems derived from the Child Behavior checklist (37) and Pediatric Behavior Scale (38). The PBS assesses function in four areas: opposition-aggression, hyperactivity-inattention, depression-anxiety, and physical health. For each subject a parent and a teacher are asked to rate problems on a 4 point Likert scale (0 – 3), with a lower score indicating fewer problems. For the current study only depressive symptoms from the depression-anxiety category were included in the analysis, leaving the following questions: 1) sad, unhappy, or depressed, 2) feels lonely, unwanted, or unloved; complains that no one loves him/her, 3) feels worthless or inferior, and 4) blames self for problems, feels guilty.

The response rate for PBS scores from the parent and teacher were 98 and 86 percent, respectively. In order to reduce the number of comparisons for statistical analysis, the parent and teacher scores were collapsed into a single score by selecting the higher of the two scores when they differed. This method of data reduction was selected instead of a summation or average of the two scores because some subjects did not have both parent and teacher measures. The collapsed scores correlated significantly with individual parent- and teacher-reported

scores [$r = .797$, $p = .000$; $r = .751$, $p = .000$; respectively] using Pearson correlation. Interrater reliability (internal consistency coefficients) of the PBS depression-anxiety scale was estimated at .91 using the longer version of the PBS, which included the questions assessed in the current study (38).

MRI Acquisition

MRI scans were obtained using a 1.5 Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, WI). Three-dimensional (3D) T1 weighted images, using a spoiled grass sequence (SPGR), were acquired in the coronal plane with the following parameters: 1.5 mm coronal slices, 40 degree flip angle, 24 msec TR, 5 ms TE, 2 NEX, 26 cm FOV and a 256×192 matrix. The PD and T2 weighted images were acquired with the following parameters: 3.0 mm coronal slices, 36 msec TE (for PD) or 96 msec TE (for T2), 3000 msec TR, 1 NEX, 26 cm FOV, 256×192 matrix and an echo train length=1.

Image Processing

MRI data were processed using BRAINS2 (Brain Research: Analysis of Images, Networks, and Systems), our locally developed software, described elsewhere (39). T1-weighted images were spatially normalized and resampled to 1.015625 mm³ voxels and the anterior-posterior axis of the brain was realigned parallel to the anterior commissure–posterior commissure line and the interhemispheric fissure was aligned on the other two axes. T2 and PD weighted images were aligned to the spatially normalized T1 weighted image (40). The data sets were then segmented using the multi-spectral data and a discriminant analysis method based on automated training class selection (41) to produce a brain mask, which was used as the basis for our intracranial volume (ICV) measurement.

The brain was then parcellated into functional regions using FreeSurfer, an automated program capable of producing volumetric measures of the cerebral cortex (42). This produced volumetric measures for overall cortical gray matter and the rACC region. The FreeSurfer rACC boundaries are as follows: rostral: rostral extent of cingulate sulcus; caudal: caudal-most tip of the genu of the corpus callosum; medial: medial surface of the cortex; lateral: superior frontal gyrus superiorly and medial division of the orbitofrontal gyrus inferiorly (42). This region most closely approximates Brodmann area (BA) 33 and rostral BA 24 but does not include BA 25 (RJ Killiany, personal communication, November 11, 2006), though borders were not defined using cytoarchitecture. The rACC volume has an intraclass correlation of .811 and .835 for the left and right side respectively when comparing manual and automated methods of measurement, a measure near the average intraclass correlation for all parcellated cortical regions (0.835) (42). In an effort to increase the accuracy of rACC volumetric data, each FreeSurfer parcellation was visually inspected and those scans with unacceptable rACC parcellation were excluded from all analyses. 9 of 124 volumetric measures of the rACC were excluded.

Subject groups

All analyses were split by sex due to evidence of structural and functional differences between the male and female brain present in adults and children, including studies from our lab (43–46). Subgroups within the sample were also constructed based on differences in the predicted risk of depression. This included splitting the subjects into two groups based on depressive symptoms- those without any symptoms (PBS score = 0) and those with symptoms (PBS score > 0). Subjects were also categorized according to family history of depression; those with a positive family history of depression in the nuclear family (parents and/or sibling) formed one group, whereas those without any reported depression in the nuclear family formed another.

Table 1 displays descriptive data for demographic, behavioral, and structural measures for each group.

Statistical Analysis

All analyses were performed by using SPSS 13.0 for Windows. Volume of the rACC was compared in subjects without any depressive symptoms (PBS score = 0) to those with symptoms (PBS score > 0) using MANCOVA (General Linear Models Multivariate Analysis of Variance). Age, total cortical volume, and SES (but not IQ) were found to make a significant contribution to the model and thus included as covariates in this and additional analyses. Next, a followup analysis for significant MANCOVA findings involved calculating Spearman partial correlation coefficients to investigate the relationship between PBS measures and rACC volume after controlling for differences in age, total gray matter volume of the cortex, and SES. Spearman partial was selected instead of Pearson partial due to a non-normal distribution of depressive symptoms (positively skewed). These correlation tests were also performed separately in subgroups based on family history of depression.

We performed two additional analyses aimed at assessing the specificity of our correlation findings and ruling out alternative explanations. 1) To address the possibility that a significant correlation may be due to overall differences in cortical volume and not related specifically to the regions of interest, a Spearman partial correlation assessed the relationship of depression score and total cortical gray matter volume, controlling for age, ICV, and SES. 2) Next, we performed the same correlation analysis as described for the depression score –rACC volume, but replaced the depression score with the physical health PBS measure. We predicted that the physical health scale would not correlate with rACC volume.

RESULTS

Table 2 provides a comparison of rACC volume in subjects without any depressive symptoms (PBS score = 0) relative to a group with depressive symptoms (PBS score > 0). Boys with depressive symptoms had significantly smaller rACC volume bilaterally, a difference that was particularly robust on the left side (14.6% reduction). There were no significant differences in rACC volume in girls.

A second MANCOVA analysis using a different categorization scheme was tested post hoc in order to address the possibility that splitting subjects with and without depressive symptoms may have contributed to the lack of significant findings in girls. The alternate categorization scheme compared subjects whose depressive symptom score was a standard deviation above and below the mean. The pattern of results was identical with no significant findings in girls.

The Spearman partial correlation analyses between PBS depressive symptom measures and rACC volume, controlling for age, total cortical volume, and SES are illustrated in Table 3. There was an inverse correlation between depressive symptoms and rACC volume in boys, indicating that less neural tissue in the rACC is associated with higher levels of depressive symptoms. This relationship was not statistically significant in a group of boys without a nuclear family history of depression and strengthened by limiting the analysis to boys with a positive nuclear family history of depression. For the sake of being comprehensive, the same correlation analysis was performed in girls and revealed no significant relationship of depressive symptoms and rACC volume for any of the tests.

Tests aimed to assess specificity of the correlation analysis revealed a non-significant relationship of total gray matter volume of the cerebral cortex and depressive symptoms in boys after controlling for differences in age, ICV, and SES [$r = -.02$, $p = .87$]. This supports the notion that the relationship between PBS depressive scores and rACC are regionally

specific and not generalized to an overall decrease in cortical volume. Also, a non-significant relationship of rACC volume and physical health scores (a control behavioral score) was noted (see Table 3).

DISCUSSION

Structural MRI has been valuable in the study of major depression in that a specific region of the brain, the left subgenual ACC, has been found to be morphologically abnormal. The current study extends this line of study beyond adults with major depressive disorder to examine the relationship of rACC volume (which includes the subgenual region defined by Drevets et al, 1997) in relation to depressive symptoms in children and adolescents. There are two principle findings of this study: 1) boys with depressive symptoms have significantly lower rACC volume than boys without any depressive symptoms, 2) there is a significant correlative relationship of depressive symptom severity and rACC volume in boys, a finding that is particularly robust in subjects with a nuclear family history of depression. These findings support the notion that the rACC region of the brain is an important neural substrate of mood, complimenting functional imaging and lesion studies that have implicated this region in the pathologic features of depression. Structural deficits in this region may be a cause or an effect of depressive symptoms.

The demonstration of a more robust correlative relationship of depressive symptoms and rACC volume in boys with a positive nuclear family history of depression leaves open the possibility that rACC volume may serve as an endophenotype of depression. An endophenotype is a marker of disease susceptibility that isn't apparent to the unaided eye and represents an intermediate along the pathway from gene to disease (47). This possibility is contingent on the possibility that higher depression scores in boys with a positive family history of depression selectively identifies those individuals who have inherited a susceptibility factor for depression that is associated with a volumetric decrease in the rACC. The notion of decreased volume of the rACC acting as a trait marker for depression susceptibility is supported by three lines of evidence. 1) A volume reduction is present in the perigenual cingulate cortex in healthy adults at higher risk for developing depression due to a specific genetic variant (short allele of serotonin transporter polymorphism) (48). 2) A volume reduction of the left subgenual ACC persists even after depressive symptoms remit (11). 3) A reduction of left subgenual ACC volume was noted in a twin study of depression, and there was no difference in the disparity of within-pair subgenual ACC volume when comparing twin pairs discordant versus concordant for depression (49). However, for each of the studies mentioned here, the correlation of sub-clinical depressive symptoms and volumetric measures was not assessed.

An important caveat in this 'trait marker' interpretation is the possibility that the structure of the rACC is malleable to environmental stressors, which may also increase one's risk of developing depression. Stronger correlation of depressive symptoms and rACC volume in boys with a positive family history of depression may be mediated by stress-induced morphologic changes that accompany the experience of having a care-giver or loved one suffer from depression. In line with this hypothesis, a study of ACC volume in adults has shown an inverse correlation with number of stressful or traumatic adverse childhood events (50). There is also a mechanism in place to explain how environmental stressors may alter ACC anatomy; stress induces the release of glucocorticoids, which have been shown to mediate structural alterations of the medial prefrontal cortex (51–53). It is possible that these structural changes reflect a shift in the activity of neural systems that acts to favor increased vigilance and heightened reactivity to negative emotional stimuli. In an adverse environment such a shift may be adaptive and increase survival but have the unfortunate consequence of increasing one's risk for depression. Individuals with a family history of depression may be especially susceptible, as glucocorticoid dysregulation has been noted in familial depression (54;55).

The possibility that rACC volume is determined by both genetic and experiential factors underscores the difficulty in delineating these influences in human studies. However, both genes and environment must influence behavior through the common currency of altering the properties of neurons and neuron systems. These functional alterations may be reflected in regional morphological changes in brain structure and thus accessible to structural studies.

In the current study the positive findings in boys contrast with a lack of any significant association between depressive symptoms and rACC volume in girls. This discrepancy may be due to lower PBS scores in girls. This sex difference in depressive symptomatology is unexpected and may be unique to the current sample considering the higher incidence of depression in females relative to males that emerges after puberty (56). It is possible that girls internalize depressive symptoms to a greater extent than boys, thus being less accessible to a third-person rater. Another possible explanation is that higher scores on the PBS depression scale may be prodromal to psychiatric disorders in addition to depression that are characterized by less robust or even reversed female to male incidence ratios. For instance, ACC morphology may be altered in children and adults with schizophrenia (18;57) and bipolar disorder (58;59) but see Sanchez et al (60) for an exception).

An important distinction between the current study and previous findings of a brain-behavior relationship in major depression is that the current sample of subjects is presumed to be normal and healthy. In light of this, the current study may be interpreted as the identification of a structural neural correlate to a temperamental trait. There is a strong interest in elucidating the neural underpinnings of temperament based on its well documented association with psychopathology (61–63). Tremendous advances in neuroimaging have helped set the stage for such an endeavor and early work toward this objective has begun (64–67). We believe these studies along with the current study provide an avenue for early progress in defining the structural neural correlates of temperament; selecting characteristics that are highly associated with psychopathologies with known neural correlates. Advances in this enterprise will ultimately facilitate an integration of neuroscience and the social sciences, an important step in developing a more comprehensive understanding of the brain.

Our excitement for the current study is tempered by the following limitations: 1) A brain-behavior relationship is only as powerful as the behavioral measure is accurate. For the current study we used a crude assessment of mood, measured objectively by parents and teachers. We did not assess self-reported depressive ratings, which may have been helpful in accurately assessing symptoms. 2) There was no clinical interview performed to formally rule out clinically significant depression or other psychopathology. 3) The automated cortical parcellation method used for the current study has several advantages over manual methods of tracing, which have been the mainstay of structural imaging for years. Automated methods are less labor intensive and allow for larger studies with increased anatomical data. Similarly, human errors related to drifting anatomical boundaries over the course of a study are eliminated. Automated parcellation, however, is an evolving technology and is not without its own set of limitations. The gold standard in defining cortical regions is to use cytoarchitectural differences to establish boundaries, which are inaccessible using current MRI technology. Automated methods are twice removed from this gold standard in that tracing guidelines are established using manual tracing methods on MRI, which are themselves only an approximation of cytoarchitectural boundaries using local landmarks. While this is far from optimal, the likelihood of errors in volumetric measures is assumed to be equal for all subjects in the current study and should not have had a major impact on the results.

In summary, the association of behavioral measures of mood and rACC volume in a group of healthy boys is compelling in light of parallel findings in major depression. An important feature of this approach is that it lends itself to a longitudinal followup to determine if

depressive symptoms and rACC volume offers predictive information regarding the onset of major depression. By extending this brain-behavior relationship beyond the pathological condition of major depression there is promise that advances in structural MRI and automated methods to generate volumetric measures may someday be used clinically to more accurately and objectively assess depression risk prior to the onset of pathological symptoms. Such a tool would be especially powerful when used in conjunction with genetic screening, behavioral measures, and, of course, a clinician's judgment. Individuals found to be at high-risk may then opt to take preventative steps in an effort to avoid the escalation of depressive symptoms.

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Figure 1.

This figure shows a medial view of the cerebral cortex. The rACC is in purple and outlined in yellow. The corpus callosum (in gray) was generated manually and included to illustrate a relevant landmark.

Table 1

Descriptive data: demographic, behavioral, and structural.

Variable	Boys		All Boys (n=59)		(-) DSx (n=31)		(+) DSx (n=28)		(-) Nuclear FHx (n=39)		(+) Nuclear FHx (n=17)	
	Measure											
Age	Range		7.75-17.92		7.92-17.00		7.75-17.92		7.75-16.92		8.08-17.92	
	Mean (s.d.)		12.08 (2.75)		12.02 (2.72)		12.14 (2.83)		11.89 2.53		12.72 (3.36)	
IQ	Mean (s.d.)		113 (16)		112 (12)		115 (19)		112 (16)		114 (13)	
SES	Mean (s.d.)		2.27 (.59)		2.25 (.44)		2.30 (.73)		2.34 (.61)		2.29 (.46)	
PBS DSx	Range		0-7		0		1-7		0-7		0-6	
	Mean (s.d.)		1.08 (1.60)		0		2.28 (1.62)		1.05 (1.57)		1.11 (1.76)	
L rACC Vol	Mean (s.d.)		1.92 (.44)		2.11 (.47)		1.70 (.29)		1.94 (.43)		1.93 (.49)	
R rACC Vol	Mean (s.d.)		1.61 (.36)		1.73 (.35)		1.47 (.33)		1.58 (.38)		1.68 (.31)	
All Girls (n=53)												
Age	Range		7.08-17.58		7.08-17.50		8.00-17.58		7.08-17.58		7.17-14.83	
	Mean (s.d.)		12.37 (2.86)		11.74 (2.99)		13.12 (2.57)		12.63 (3.18)		11.72 (1.95)	
IQ	Mean (s.d.)		109 (12)		109 (10)		110 (14)		111 (12)		107 (11)	
SES	Mean (s.d.)		2.28 (.45)		2.28 (.46)		2.27 (.45)		2.20 (.41)		2.46 (.51)	
PBS DSx	Range		0-4		0		1-4		0-4		0-3	
	Mean (s.d.)		.81 (1.09)		0		1.79 (.93)		.90 (1.18)		.86 (1.06)	
L rACC Vol	Mean (s.d.)		1.80 (.37)		1.79 (.44)		1.80 (.27)		1.83 (.36)		1.76 (.33)	
R rACC Vol	Mean (s.d.)		1.51 (.37)		1.49 (.37)		1.53 (.37)		1.48 (.38)		1.56 (.35)	

DSx = Depressive Symptoms, FHx = Family history of depression, L = left, PBS = Pediatric Behavior Scale, R = right, rACC Vol = rostral anterior cingulate cortex volume, s.d. = standard deviation, SES = Parental socioeconomic class

Volumetric measures shown in cubic centimeters.

Table 2
Rostral anterior cingulate volume in subjects with depressive symptoms versus those without

	Adjusted Mean (Std. Error)		F value (p)
	(+) Depressive Sx	(-) Depressive Sx	
Boys ¹	N=22	N=26	
L rACC	1.75 (.07)	2.05 (.06)	8.90 (.005)**
R rACC	1.49 (.06)	1.66 (.05)	3.98 (.05)*
Girls ²	N=21	N=27	
L rACC	1.80 (.07)	1.82 (.06)	.03 (.84)
R rACC	1.57 (.07)	1.52 (.06)	.29 (.59)

¹Wilks' lambda = .78, p = .006, F = 5.86, Hypothesis df = 2, Error df = 42

Covariates appearing in the model are evaluated at the following values: Age = 12.00, Total Cortex Volume = 506.77, SES = 2.29.

²Wilks' lambda = .99, p = .85, F = .15, Hypothesis df = 2, Error df = 42

Covariates appearing in the model are evaluated at the following values: Age = 12.27, Total Cortex Volume = 472.03, SES = 2.25.

L=left, R=right, rACC=rostral anterior cingulate cortex, Sx=Symptoms

* Significant at the level of .05 (2-tailed)

** Significant at the level of .01 (2-tailed)

Table 3
Correlation[†] of PBS scores and volume of rACC in boys

Group ROI	PBS Measures	
	Depressive Symptoms	Physical Health (control)
All		
L rACC	-.34 (.01) [*]	-.14 (.32)
R rACC	-.33 (.02) [*]	-.16 (.25)
(-) Nucler FHx		
L rACC	-.31 (.07)	-.25 (.16)
R rACC	-.13 (.46)	-.29 (.11)
(+) Nuclear FHx		
L rACC	-.57 (.04) [*]	-.008 (.97)
R rACC	-.66 (.009) ^{**}	-.21 (.46)

[†] Spearman partial correlations control for total cortical volume, age and SES.

^{*} Significant at the level of .05 (2-tailed)

^{**} Significant at the level of .01 (2-tailed)

L = left, R = right, rACC = rostral anterior cingulate cortex, ROI = region of interest