Rostral Anterior Cingulate Cortex Volume Correlates with Depressed Mood in Normal Healthy Children

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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: One hundred twelve normal healthy children (59 boys, 53 girls), age 7 to 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 magnetic resonance imaging (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 with boys with no depressive symptoms, particularly on the left side (14.6% reduction; $F = 8.90$, $p = .005$). 2) There was a negative correlation of rACC volume and depressive symptoms in boys, a finding that was more robust in subjects with a positive family history of depression. 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.

Key Words: Anterior cingulate, children, depression, FreeSurfer, subgenual

Depression is a mood disorder often characterized by sadness and apathy, affecting as many as one in six 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 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 (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 anterior cingulate cortex (ACC) in depressed individuals, including a previous study from our laboratory (11,17–19). Evidence of structural change in the rACC in association with major depression in adults has also come from postmortem 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 is not 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: 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

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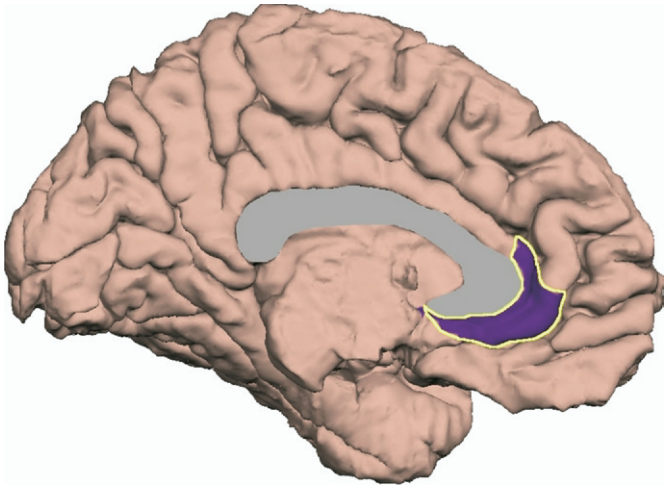

Figure 1. This figure shows a medial view of the cerebral cortex. The rACC is in purple and outlined in yellow. The corpus callosum (in gray) was generated manually and included to illustrate a relevant landmark. rACC, rostral anterior cingulate cortex.

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 nonclinically 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

One hundred twelve healthy children and adolescents (59 boys, 53 girls), age 7 to 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 intelligence quotient (IQ) below 85 or 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. Socioeconomic status was determined using a modified Hollingshead scale of 1 to 5, with a lower number corresponding to higher social class (35). Intelligence quotient was estimated using the full-scale Wechsler Intelligence Scale for Children (36). Family history of depression was obtained using a standardized questionnaire given to the subject's parent. The parent was instructed to list all relatives that had 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 had 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%, respectively. 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

Magnetic resonance imaging scans were obtained using a 1.5 Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, Wisconsin). Three-dimensional (3-D) T1-weighted images, using a spoiled gradient recalled acquisition in a steady state (GRASS) sequence (SPGR), were acquired in the coronal plane with the following parameters: 1.5 mm coronal slices, 40° flip angle, 24 msec repetition time (TR), 5 msec echo time (TE), 2 number of excitations (NEX), 26 cm field of view (FOV), and a 256 × 192 matrix. The proton density (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.