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Corpus callosum abnormalities associated with greater externalizing behaviors in subjects at high risk for alcohol dependence

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Abstract

Subjects at high risk for alcoholism have a greater propensity for externalizing behaviors and brain volume reductions of possible neurodevelopmental origin. Morphometric deficits in the corpus callosum (CC), which might reflect this neurodevelopmental abnormality, have been reported in other externalizing disorders such as attention deficit hyperactivity disorder, but not in subjects at high risk for alcoholism. The objective of the current study was to evaluate the CC morphometry in subjects at high risk for alcoholism. Magnetic resonance images of the CC in high-risk subjects ($n=20$) were compared with those of low-risk subjects matched to the high-risk subjects for age, sex, and handedness ($n=20$). Mid-sagittal areas of the CC, genu, body, isthmus and splenium were measured based on Witelson's method with good inter- and intra-rater reliability. Externalizing behaviors were assessed using the Semi-Structured Assessment for Genetics of Alcoholism-II. Total CC, genu and isthmus areas were significantly smaller in high-risk than low-risk subjects after controlling for age and intracranial area. The total externalizing symptoms score had a significant negative correlation with genu and isthmus areas. Smaller CC areas and their negative association with externalizing behaviors may represent yet another marker of susceptibility to alcoholism in high-risk subjects.

Keywords: Corpus callosum; High-risk subjects; Alcoholism

1. Introduction

Offspring of alcoholics with high familial loading for alcoholism and/or early onset of alcohol dependence are known to be at greater risk for developing early and severe alcohol-related problems (Haber et al., 2005). There is accruing literature that subjects at high risk for alcoholism differ significantly from others without such susceptibility on various endophenotypic markers, which predate the onset of drinking. These include a marked propensity for externalizing behaviors in childhood, often persisting into adulthood, neuroelectric and morphometric abnormalities of the brain suggestive of neurodevelopmental delay (Hill, 2004), and central nervous system hyperexcitability (Begleiter and Porjesz, 1999). At least some of these measures of susceptibility appear more pronounced for early onset alcoholism than for the late onset form (Benegal et al., 1995).

It has been suggested (Hill and Shen, 2002) that the greater externalizing symptoms found in high-risk (HR)

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subjects in comparison with low-risk (LR) subjects implicate a heritable state of central nervous system hyperexcitability in the former, which is critically involved in a genetic predisposition toward alcoholism and the development of dependence (Begleiter and Porjesz, 1999). The proposition is that behavioral phenomena such as psychopathy, antisocial and impulsive traits, änd substance and alcohol abuse should be viewed as variable expressions of a *generalized disinhibitory complex* (Gorenstein and Newman, 1980).

A recent study from our group (Benegal et al., 2007) showed that alcohol-naïve HR adolescent/young adult offspring of early onset alcoholic fathers from multiplex alcoholism families had reduced volume in the frontal cortex, cingulate gyrus, hippocampus, amygdala, thalamus and cerebellum in comparison with age- and sex-matched LR subjects without family histories of alcoholism. The volume differences strongly predicted the presence of an excess of externalizing behaviors in these subjects. The differences in comparative trajectories of growth of the amygdala between HR and LR subjects suggested a process of neurodevelopmental delay. A previous study (Hill et al., 2001) had reported reduced right amygdala volume in a group of alcohol-naïve HR adolescent/young adult offspring of early onset alcoholic fathers from multiplex alcoholism families.

Delayed neurodevelopment has a high likelihood to affect other brain structures with late maturation like the corpus callosum (CC) (Keshavan et al., 2002). Interestingly, children and adults with disruptive behavior disorders and attention deficit hyperactivity disorder (ADHD) (also hypothesized to be a neurodevelopmental disorder) have consistently been found to have abnormalities in CC morphology (Seidman et al., 2005) and disturbed transcallosally mediated motor inhibition (Buchmann et al., 2003). It has been suggested that behavioral phenomena such as antisocial and impulsive traits, and substance abuse should be viewed as variable expressions of a generalized disinhibitory complex (Begleiter and Porjesz, 1999). To our knowledge, the morphology of the CC in alcohol-naïve HR subjects, especially in relationship to externalizing symptoms, has yet to be examined.

On the other hand, the toxic effect of alcohol exposure on the CC has been consistently reported, with thinning of the CC in chronic alcoholics in postmortem and magnetic resonance imaging (MRI) studies (Pfefferbaum et al., 1996). Recently, a longitudinal MRI study on the effects of alcoholism on brain structure reported reduction of white matter structures, including the CC (Rohlfing et al., 2006). Also, prenatal alcohol exposure is a major cause of impaired development or complete absence of the CC, and approximately 7% of children with fetal alcohol syndrome lack a CC (Swayze et al., 1997).

In this study, we examined the externalizing symptoms and mid-sagittal areas of the CC and its sub-regions in alcohol-naïve HR subjects and age-, sex- and handedness-matched LR subjects. We hypothesized that HR subjects would have 1) smaller CC areas 2) greater externalizing symptoms. Also, we predicted the externalizing symptoms would correlate inversely with CC areas.

2. Methods

2.1. Subjects

Twenty alcohol-naïve HR males were ascertained from among offspring of treatment-seeking alcohol-dependent male patients (who belonged to multiplex alcoholism families) from the Deaddiction Center of the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. 'High risk' was defined as offspring of early onset alcohol-dependent individuals (who had developed dependence before 25 years of age) with two or more first-degree relatives with alcohol dependence. A convenient sampling method was used to select subjects to cover the developmental life span between 9 to 23 years of age, with not more than three subjects of the same age. Twenty LR male subjects were recruited from among offspring of volunteers and hospital employees, selected for the absence of DSM-IV Axis I psychopathology (American Psychiatric Association, 1994). Age (mean ± S.D.) of HR subjects (15.8 ± 4.6 years) did not differ from that of LR subjects (15.8 ± 4.6 years) ($P > 0.9$).

The Semi-Structured Assessment for Genetics of Alcoholism-II (SSAGA-II) — Adult version (Bucholz et al., 1994) was used to rule out any lifetime psychiatric disorder (other than alcohol dependence) in fathers of HR subjects and to rule out any lifetime psychiatric diagnosis (including alcohol dependence) in both parents of LR subjects as well as in mothers of HR subjects. The family history of psychiatric disorders in first-degree relatives (of both HR and LR subjects) was gathered using the Family Interview for Genetic Studies from three or more adult informants (both parents and at least one other adult family member) in the family. These adult informants provided details about the study subjects as well as about all other first-degree relatives in the family. The fathers of HR subjects had developed dependence by 19.95 (2.54) years of age and had on

average of three other affected first-degree relatives with alcohol dependence (minimum 3, maximum 8). None of the HR subjects had family history of psychiatric disorder (other than alcohol dependence) in their first-degree relatives. None of the LR subjects had family history of psychiatric disorders (including alcohol dependence) in their first-degree relatives.

The subjects (HR and LR) were interviewed on a single occasion, separate from their parents, and full confidentiality was assured. The interview included questions about use of alcohol, tobacco, other illicit substances of abuse and any other psychotropic medications. Subjects who reported regular drinking (more than once a month) were excluded from the study. All subjects in the HR and LR groups were alcohol-naïve. Two subjects in the HR group and one in the LR group reported that they had used alcohol but were included in the study, as they did not drink at a rate of more than once a month. There was no difference in tobacco use between the two groups (4 subjects in the HR group and 3 subjects in the LR group reported any tobacco use [$\chi 2 = 0.2$, $df = 1$, $P > 0.9$]). None of the subjects (HR and LR) had ever used any other illicit substances or psychotropic medications.

The mothers (of both HR and LR subjects) were specifically queried regarding their use of alcohol, tobacco or use of any other illicit drug at any time in the past and specifically during pregnancy. None of the mothers of any of the subjects (HR and LR) satisfied criteria for lifetime diagnoses of alcohol dependence or other substance dependence, and none of them reported using alcohol or any illicit substances during pregnancy.

2.2. Clinical assessment of the study subjects

Both HR and LR subjects were right handed as assessed by Annett Handedness Questionnaire (Annett, 1967). They were then assessed using the SSAGA-II (child, adolescent or adult versions as indicated) for externalizing symptoms (attention deficit, hyperactivity, conduct and oppositional defiant symptoms) and to rule out any other syndromal psychiatric diagnoses (psychoses, anxiety disorder, affective disorder). The SSAGA items pertaining to inattention, hyperactivity, impulsivity and conduct symptoms were added to calculate the total externalizing symptoms score.

In the HR group, 17 subjects satisfied a syndromal diagnosis of ADHD according to DSM-IV. None of the subject in the LR group satisfied a syndromal diagnosis of ADHD. None of the subjects in the HR or the LR group satisfied a syndromal diagnosis of oppositional defiant disorder (DSM-IV) or conduct disorder. There were no significant differences between the groups with regard to the internalizing disorders assessed on the SSAGA.

None of the subjects (HR and LR) had any neurological disorder, mental retardation, history of significant head injury or any contraindication to MRI. After complete description of the study to the subjects, written informed consent was obtained from the parents of minor subjects and from all adult subjects. The departmental review meeting for research ethics approved the study.

2.3. Morphometric analysis

MRI was performed with 1.5 Tesla scanner (Magnetom 'Vision', Siemens, Erhlangen, Germany). A T1-weighted three-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence was performed (TR = 9.7 ms, TE = 4 ms, nutation angle = 12°, field of view = 250 mm, slice thickness = 1 mm, NEX = 1, matrix = 256 × 256) yielding 160 sagittal slices.

The CC measurements are done in the mid-sagittal section using the principles of Witelson's method (Witelson, 1989) (Fig. 1). From the set of T1-weighted three-dimensional MP-RAGE sagittal images, the mid-sagittal section was chosen manually. The following were the criteria for the inclusion of mid-sagittal slices (Fig. 2A): 1) A distinct outline of the CC, 2) an easily identified cerebral aqueduct, 3) clear visibility of cortical gyral crests both anteriorly and posteriorly to the CC and 4) Absence of visible intrusion into gray and white matter (Woodruff et al., 1993). All the selected images were inspected and approved by the neuroradiologist (PNJ). Since the slice thickness was 1 mm and a uniform image

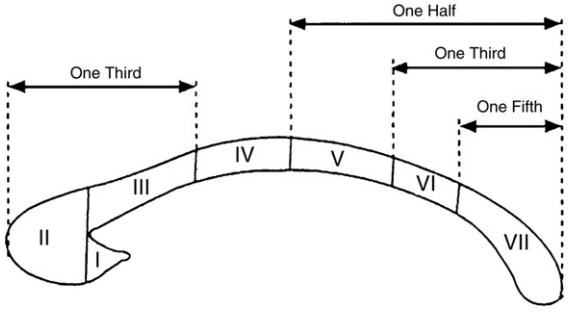

Fig. 1. Subdivisions of the corpus callosum as per Witelson's method (Witelson, 1989). I — Rostrum; II — Genu; III — Rostral body; IV — Anterior mid body; V — Posterior mid body; VI — Isthmus; VII — Splenium. In this study, rostral body, anterior mid body and posterior mid body (i.e., III, IV, V) were added together to form the body of the corpus callosum as per Keshavan et al. (2002).

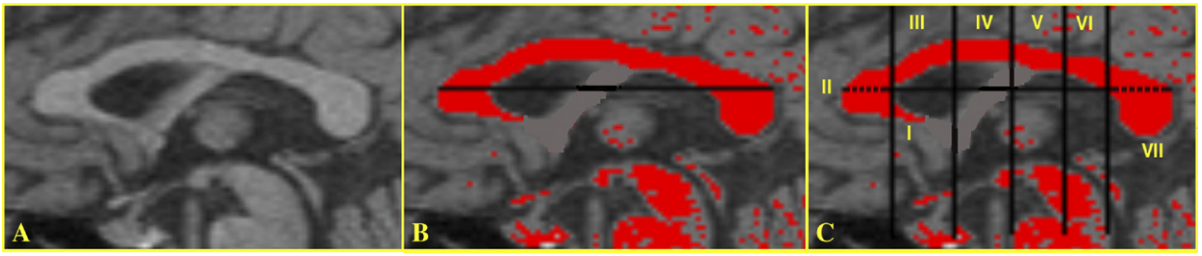

Fig. 2. Semi-automated morphometric analysis of the corpus callosum. 2A — Mid-sagittal MR image of the corpus callosum with clearly visible cerebral aqueduct. 2B — Corpus callosum segmentation with the black line connecting the most anterior CC pixel with the most posterior CC pixel through the point of maximum curvature of the inner border of the genu. 2C — Corpus callosum divided into various subdivisions semi-automatically by the software. The subdivisions divided by dotted black line on the anterior aspect of the corpus callosum (left side) were added to measure the genu and that on the posterior aspect of the corpus callosum (right side) were added to measure the splenium.

acquisition protocol was used, mid-sagittal images of all the subjects satisfied the inclusion criteria.

The mid-sagittal section of the CC was measured using Scion Image (Scion Corporation, http://www.scioncorp.com) which is the Windows© version of the NIH Image software that has been used reliably to measure CC areas in children, adolescents, and adults (Keshavan et al., 2002). This software provides valid and reliable measurements of specific structures using a semi-automated segmentation approach (Keshavan et al., 1995). This semi-automated segmentation method to measure volume of brain structures had been shown to correlate highly with the point-counting stereological approach (Keshavan et al., 1995). CC was divided into rostrum, genu, body, isthmus and splenium on a valid neuroanatomical basis as per Witelson's method (Witelson, 1989; Keshavan et al., 2002; Venkatasubramanian et al., 2003) (Fig. 1).

The steps for measuring the CC using the Scion Image software were as follows (Venkatasubramanian et al., 2003): The CC in the mid-sagittal section was segmented automatically, ware with the CC being highlighted in red, and the total CC area was measured (Fig. 2B). A straight line was drawn to connect the most anterior CC pixel with the most posterior CC pixel through the point of maximum curvature of the inner border of the genu (Fig. 2B). Using the scion image software, four perpendicular lines were automatically drawn on the CC. Finally, the fifth perpendicular line was drawn by the software at the point where the straight line cuts the inner body of the genu of the CC.

These five perpendicular lines divided the CC into rostrum, genu, rostral body, anterior mid-body, posterior mid-body, isthmus and splenium as per Witelson's validated neuroanatomical basis (Witelson, 1989). Since the pixels within the CC on which these lines were drawn form the borders of the CC sub-divisions (and hence they are in common to two neighboring subdivisions), they were not counted for the area of the subdivisions. Hence the sum of the areas of various CC sub-divisions was less than the total CC area that was measured directly from the undivided CC (Table 1).

The exact positions of these line placements with respect to the proportions of the CC area that they divide are shown in Fig. 1. Fig. 2C shows the correspondence of these subdivisions (i.e., I–VII) after segmentation to the proportions depicted in Fig. 1. In this study, as per Keshavan et al. (2002), the rostral body, the anterior mid-body and the posterior mid-body (i.e., subdivisions III, IV, V in Fig. 2C) were added together to form the body of the CC.

To assess inter-rater reliability, two raters (VVR and USR), after being trained initially by an experienced neuroradiologist (PNJ), rated 15 coded images independently. The intra-class correlation coefficients (ICC) for

Table 1
Mean±S.D. of CC areas (mm^2) of high-risk subjects ($n=20$) in comparison with low-risk subjects for alcohol dependence ($n=20$)

No	Brain area [a]	HR subjects	LR subjects	F [b]	P
1	Corpus callosum	586.9±87.1	643.9±95.3	4.3	0.045
2	Rostrum	23.4±11.4	18.1±9.7	2.7	0.108
3	Genu	120.4±21.3	138.7±33.8	4.4	0.042
4	Body	195.1±25.8	209.2±34.4	2.3	0.141
5	Isthmus	48.1±8.8	57.7±10.0	11.9	0.001
6	Splenium	162.0±33.8	166.0±28.6	0.14	0.709

Intracranial area (Mean±S.D.): High-risk subjects — 16152.6±1123.0 mm^2; Low-risk subjects — 16198.0±1324.8 mm^2.

[a] Since the pixels within the CC on which the lines were drawn form the borders of the CC subdivisions (and hence they are in common to two neighboring subdivisions), they were not counted for the area of the subdivisions. Hence the sum of the areas of various CC subdivisions was less than the total CC area that was measured directly from the undivided CC (see text for further details).

[b] Analysis of covariance using intracranial area and age as covariates.

the various brain measurements were as follows: intracranial area = 0.93; CC = 0.94; rostrum = 0.95; genu = 0.93; CC body = 0.95; isthmus = 0.91; splenium = 0.95. To assess the intra-rater reliability (VVR), 10 coded images were re-analyzed at the end. The ICC values for intra-rater reliability were as follows: intracranial area = 0.96; CC = 0.93; rostrum = 0.98; genu = 0.81; CC body = 0.91; isthmus = 0.86; splenium = 0.96.

The statistical analyses were performed using the Statistical Package for Social Sciences (version 10.0.1) [SPSS Inc.,]. The two-tailed statistical significance level was set at P;;0.05. The socio-demographic and clinical data were compared using independent samples t-test. The association between the ADHD diagnosis and subject status was examined using Chi-Square test. The morphometric data were compared using Analysis of Covariance (ANCOVA) with age and intracranial area as covariates. The relationship between CC areas and the total externalizing symptoms score was examined using Pearson's correlation test.

2.4. Methodological strengths

Strengths of the methodology included the following: examination of alcohol non-dependent HR and LR subjects; age-, sex- and handedness-matched LR subjects; 1-mm MRI slice for morphometry; neuroanatomically valid method for analyzing CC; analysis on coded mid-sagittal images and good inter- and intra-reliability for CC analysis. The mothers of all the subjects (HR and LR) were alcohol-naïve. This excluded the potential confounding effects of alcohol toxicity on the CC during perinatal development.

3. Results

The total externalizing symptoms (mean±S.D.) was significantly higher in the HR (17.7±6.1) than the LR (1.8±1.4) group (t=11.5; df=38; P<0.001). In the HR group, significantly higher number (17 out of 20) of subjects satisfied a syndromal diagnosis of ADHD according to DSM-IV, whereas none of the subjects in the LR group satisfied a syndromal diagnosis of ADHD (χ^2=29.6, P<0.001).

Table 2
Mean±S.D. of CC areas (mm^2) of high-risk subjects (n=10) in comparison with low-risk subjects for alcohol dependence (n=9) in the younger group (age ≤ 15 years)

No	Brain area	HR subjects	LR subjects	F[a]	P
1	Corpus callosum	562.3±92.4	639.8±68.9	4.7	0.045
2	Genu	114.0±24.0	143.9±35.2	5.0	0.040
3	Isthmus	45.1±9.0	54.9±8.1	5.9	0.028

Intracranial area (mean±S.D.) in the younger group: High-risk subjects — 15787.9±1234.5 mm^2; Low-risk subjects — 15861.4±1195.7 mm^2.
[a] Analysis of covariance using intracranial area and age as covariates.

Table 3
Mean±S.D. of CC areas (mm^2) of high-risk subjects (n=10) in comparison with low-risk subjects for alcohol dependence (n=11) in older group (age>15 years)

No	Brain area	HR subjects	LR subjects	F[a]	P
1	Corpus callosum	611.5±78.2	647.2±115.9	0.8	0.387
2	Genu	126.8±16.9	134.6±33.7	0.5	0.486
3	Isthmus	51.1±8.0	60.0±10.6	5.8	0.027

Intracranial area (mean±S.D.) in older group: High-risk subjects — 16517.4±917.9 mm^2; Low-risk subjects — 16473.4±1416.1 mm^2.
[a] Analysis of covariance using intracranial area as covariate.

The mean±S.D. values of respective areas (mm^2) of total CC, rostrum, genu, body, isthmus and splenium in high- and low-risk subjects are given in Table 1. CC, genu and isthmus areas were significantly smaller in HR subjects than in LR subjects after controlling for the intracranial area and age. The areas of rostrum, body and splenium did not differ significantly between the two groups (P>0.1).

To examine the for the effects of age, if any, we divided the entire sample into two groups, namely the younger subjects (age ≤ 15 years) and the older subjects (age> 15 years) (the mean age of the entire sample was 15.8 years). The younger group had 19 subjects (10 HR and 9 LR) and the older group had 21 subjects (10 HR and 11 LR). The total CC, genu and isthmus areas, which proved to be significantly different between HR and LR subjects (Table 1) were compared separately in the younger and older groups with the intracranial area as a covariate. In the younger group, the total CC, genu and isthmus areas were found to be significantly smaller in the HR than in the LR subjects (Table 2). However, in the older group, only the isthmus area was found to be smaller in HR than LR subjects (Table 3).

Total externalizing symptom scores had a significant negative correlation with the areas of the genu (r=−0.33, P=0.04) and isthmus (r=−0.43, P=0.006) but not with the other CC areas. There was no significant correlation between CC measures and father's alcoholism features (e.g., age at onset of drinking in the father, rapidity of tolerance or quantity of alcohol consumed).

4. Discussion

To our knowledge, this is the first report of CC abnormalities (smaller total CC, genu and isthmus) and

their relationship to externalizing symptoms in young, alcohol-naïve subjects at high risk for alcoholism. The genu of the CC contains fibers interconnecting the frontal cortices (Witelson, 1989). Previously, a functional MRI study documented decreased activation in the prefrontal cortices in subjects at high risk for alcoholism (Schweinsburg et al., 2004). Moreover, frontal lobe abnormalities have been implicated in the development of addictive disorders (Goldstein and Volkow, 2002). Hence, a smaller genu area in the HR subjects, as observed in this study, assumes significance when seen together with the reductions in the frontal cortex observed in these same individuals (Benegal et al., 2007).

The current observations are similar to the reduced areas of the total CC, genu and isthmus reported in children and adults with ADHD (Seidman et al., 2005). In this study, the total externalizing symptoms score had a significant negative correlation with the genu and the isthmus of the CC. Also, HR subjects had significantly more ADHD than LR subjects. ADHD symptoms are hypothesized to be a manifestation of CNS hyperexcitability, secondary to deficient myelination of fast conducting transcallosal fibers (Buchmann et al., 2003). The CC plays a vital role in inter-hemispheric information processing (Schulte et al., 2005). Also, CC total area has been shown to have a significant relationship with this processing (Schulte et al., 2004). Moreover, a study of regional glucose metabolism of the CC implicated the involvement of isthmus and midbody fibers in transcallosal inhibition (Karbe et al., 1998). It is possible that a deficient transcallosal inhibition due to a dysfunctional CC might result in CNS hyperexcitability, leading to externalizing symptoms in HR subjects. Our observation of CC abnormalities and their inverse relationship with externalizing symptoms may well represent a substrate for the heritable state of CNS hyperexcitability critically implicated in vulnerability to alcoholism.

Brain structures like the CC, whose maturation spans into adolescence and adulthood, are highly likely to demonstrate neurodevelopmental abnormalities (Keshavan et al., 2002). Such etio-pathogenesis has been implicated in many neuropsychiatric disorders including alcoholism (Hill, 2004). Previous studies have invoked the phenomenon of neurodevelopmental lag (Hill, 2004) to account for the demonstrated delay in reaching age-appropriate P300 amplitude in HR subjects. P300 abnormalities have been previously linked to callosal size and inter-hemispheric transmission efficacy (Hoffman and Polich, 1999). In line with these observations, in this study, younger HR subjects showed significantly smaller total CC, genu and isthmus areas than the corresponding younger LR subjects, whereas older HR subjects showed differences only in the isthmus (which was significantly smaller than in the corresponding older LR subjects). Hence, the CC abnormalities might support neurodevelopmental deviance in HR subjects.

The validity of the study findings is strengthened by various methodological advantages described in Section 2. One of the study's potential limitations is that the rater (GA) who assessed the externalizing symptoms was not blind to subject status. Also, the study did not examine female subjects. Though this might limit generalizability of study findings, only male subjects were chosen to avoid the potential sex effect on CC structure (Witelson, 1989; Westerhausen et al., 2003).

In summary, smaller CC areas and their negative association with externalizing behaviors may represent yet another marker of susceptibility to alcoholism in HR subjects. Further studies are needed to replicate and extend this novel finding.

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