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Preliminary communication

Corpus callosal morphology in early onset adolescent depression

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ABSTRACT

Background: Abnormalities in the corpus callosum and related white matter projections have been implicated in major depressive disorder (MDD). Although MDD is as common in adolescence as in adulthood, few studies have examined youth near illness onset in order to determine the possible influence of atypical development on the pathophysiology of this disorder.
Materials and methods: The area of the corpus callosum and its sub-regions were measured in 16 subjects affected by MDD (16.24 ± 2.03 years) and 16 age- and sex-matched healthy controls (16.52 ± 2.20 years) using magnetic resonance imagine (MRI).
Results: Mann–Whitney *U*-tests revealed a difference in corpus callosal areas ($u=75.00$, $p=0.047$). Corpus callosal area was smaller in MDD participants ($5.92 \pm 0.50\ cm^2$) as compared to age and sex matched controls ($6.44 \pm 0.75\ cm^2$). This difference was isolated to the genu ($U=62.00$, $p=0.012$; $2.53 \pm 0.34\ cm^2$ for controls and $2.24 \pm 0.20\ cm^2$ for MDD participants), with no other sub-region demonstrating a significant difference. There was no difference in intracranial area between groups. No structure correlated with clinical or demographic variables.
Limitations: Confirmation and extension of our findings requires a larger sample size and usage of diffusion tensor imaging.
Conclusions: While preliminary, our findings provide new evidence of abnormalities in the genu of the corpus callosum in early onset depression.

1. Introduction

Major depressive disorder (MDD) is a severe, common and devastating illness with alarming rates of morbidity and mortality. The lifetime prevalence of MDD in adolescence is approximately 15–20%, consistent with adult rates of MDD. Evidence also suggests that child and adolescent MDD is continuous with adult MDD (Lewinsohn et al., 1986). During childhood and adolescence, the maturation of the corpus callosum corresponds to the maturation of cognitive processes (Cowell et al., 1992; Giedd et al., 1996; Rajapakse et al., 1996). It is not known whether these developing neural pathways subtending attention and concentration, are disrupted in youth with MDD.

Previously, subjects with early-onset dysthymia or depressive personality disorder demonstrated smaller genu size compared to controls (Lyoo et al., 2002). In adults with MDD and healthy controls, no differences in callosal sub-regions (Lacerda et al., 2005) or signal intensity (Brambilla et al., 2004) were noted. However, MDD patients with a family history of MDD display a larger middle genu area than controls (Lacerda et al., 2005). In elderly MDD subjects, a thinner genu and splenium was observed relative to controls (Ballmaier et al., 2008). The thinning in the genu was restricted to early onset elderly patients. Using diffusion tensor imaging (DTI), lower fractional anisotropy (FA, a measure of tract integrity) was observed in the genu of elderly MDD patients who failed to achieve remission with escitalopram (Alexopoulos et al., 2008). However, Yuan et al. (2010) found that remitted elderly MDD patients also demonstrated lower FA in the genu. In adults with bipolar depression, lower FA of the genu was observed (Benedetti et al., 2011). In the only related study of adolescents, lower fractional anisotropy (FA) was observed in the tract connecting the subgenual area to the amygdala in adolescents with MDD as compared to controls (Cullen et al., 2010). The cortex under the genu is thought to pay a critical role in MDD (Drevets et al., 2008). Currently, the developmental and etiologic timeline of MDD remains unexamined. The identification of novel neurophysiological biomarkers for MDD will assist in the treatment design and improve outcomes of adolescents at risk for familial and spontaneous depression. This study aims to advance the understanding of the neurophysiological changes that are present at the time of depressive symptom onset.

Here, we examined the corpus callosum and its sub-regions using MRI in adolescents with MDD and age- and sex-matched

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healthy controls. Studies of younger patients with MDD near illness onset are critical in our efforts to delineate the pertinent neurobiological substrates of the disorder and to minimize confounds like course of illness and treatment intervention. Based on previous studies (Alexopoulos et al., 2008; Ballmaier et al., 2008; Benedetti et al., 2011; Lyoo et al., 2002; Yuan et al., 2010), we hypothesize that adolescents with MDD will have a smaller genu than healthy controls. To date, no study has examined regional corpus callosum morphology in adolescent MDD.

2. Methods

2.1. Participants

Sixteen subjects with MDD aged 13 to 21 years (6 males and 10 females) and 16 healthy controls matched pairwise for age and sex were recruited. The age of onset of the first clinical presentation in the patients with MDD was 14.33 ± 0.66 years (mean $\pm$ SD). Duration of illness in the MDD subjects was 2.08 ± 1.73 years. All case-control pairs were matched within 32 months of each other (7.31 ± 8.69 months).

Patients were recruited after being referred to the Izaak Walton Killam (IWK) Health Center's department of Psychiatry (Halifax, Nova Scotia). Controls were recruited through advertisement. Both patients and controls were paid a small honorarium for their participation in the study. The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present Lifetime version (K-SADS-PL)(Kaufman et al., 1997) was used to establish diagnosis. Exclusion criteria for participation in this study were a history of neurological illness, serious medical condition, claustrophobia, age greater than 21 years, or the presence of a ferrous implant or pacemaker. Depression symptom severity was assessed using the Childhood Depression Rating Scale (Poznanski et al., 1979). All depressed subjects had a CDRS score above 42, indicative of significant dysfunction. The Beck Depression Inventory (BDI) was also used to assess depressive symptoms. Two subjects had a comorbid diagnosis of substance abuse. One MDD participant had recently (<1 week) started medication (sertraline). The remainder of the MDD subjects was treatment naïve ($n=15$). Controls did not have any psychiatric illness. Written informed consent was obtained prior to initiating the study in compliance with the IWK Research Ethics Board.

2.2. Imaging acquisition and analysis

The MRI studies were conducted with a 1.5 T Siemens Magnetom Vision magnetic resonance system (Germany). A sagittal scout series was acquired to test image quality. A three-dimensional fast low angle shot (FLASH) sequence was used to acquire data from 124 1.5 mm thick contiguous coronal slices through the entire brain (echo time=5 ms, repetition time=25 ms, acquisition matrix=256×256 pixels, field of view=24 cm and flip angle=40°). Positioning was done in a standardized manner in order to ensure consistency of acquisitions.

Measurements were made by trained and reliable raters (F.P.M.), blind to subject identification and clinical data. Boundaries of the corpus callosum were adapted from previously published developmental psychiatric neuroimaging studies of the corpus callosum (Giedd et al., 1999; Rosenberg et al., 1997). To measure the corpus callosum and its sub-regions (genu, anterior and posterior bodies, isthmus and splenium), the mid-sagittal slice with the clearest visualization of corpus callosum, cerebellum and aqueduct was selected. Intracranial area (ICA) was also measured on the same mid-sagittal slice. Interrater reliabilities (intraclass r) were high for corpus callosum measures (0.85–0.99) and ICA (0.99). For a detailed description of methods please see Rosenberg et al. (1997).

Table 1
Summary of demographic and corpus callosum regions (BDI: Beck Depression Inventory, CDRS: Children's Depression Rating Scale, ICA: Intracranial area).

Measure	Healthy control participants	Major depressive disorder participants	Statistic	*p*-value
Age	16.52 ± 2.20 years	16.24 ± 2.03 years	123.00	0.867
Sex	6 male, 10 female	6 male, 10 female	–	–
CDRS	–	70.87 ± 12.71	–	–
BDI	–	22.53 ± 12.89	–	–
Age of Onset	–	14.33 ± 0.66 years	–	–
Corpus callosum	6.44 ± 0.75 cm^2	5.92 ± 0.50 cm^2	75.00	0.047
Genu	2.53 ± 0.34 cm^2	2.24 ± 0.20 cm^2	62.00	0.012
Anterior body	0.65 ± 0.11 cm^2	0.60 ± 0.10 cm^2	99.50	0.287
Posterior body	0.58 ± 0.10 cm^2	0.56 ± 0.10 cm^2	98.50	0.270
Isthmus	0.47 ± 0.08 cm^2	0.42 ± 0.09 cm^2	82.50	0.086
Splenium	1.75 ± 0.25 cm^2	1.65 ± 0.17 cm^2	91.50	0.171
ICA	138.75 ± 7.80 cm^2	133.48 ± 10.59 cm^2	91.00	0.171

2.3. Statistics

Given the small sample size non-parametric statistics were used. To compare groups for corpus callosal and sub-region areas, a Mann–Whitney *U* test was used. To examine the relationship between clinical and demographic variables, Spearman correlations were used (Table 1).

3. Results

Mann–Whitney *U* tests revealed a difference in corpus callosal areas ($u=75.00$, $p=0.047$). Corpus callosal area was smaller in MDD participants (5.92 ± 0.50 cm^2) as compared to age and sex matched controls (6.44 ± 0.75 cm^2). This was isolated to the genu ($U=62.00$, $p=0.012$; 2.53 ± 0.34 cm^2 for controls and 2.24 ± 0.20 cm^2 for MDD participants; see Fig. 1), with no other sub-region demonstrating a significant difference. There was no difference in intracranial area between groups. No structure correlated with clinical or demographic variables.

4. Discussion

The principal finding of this study is a smaller corpus callosum (8.07%) and genu (11.46%) area in early onset adolescent depression as compared to age- and sex-matched healthy controls. This differs from a previous study using similar methodology in adults with MDD (Lacerda et al., 2005). However, it is consonant with work in geriatric MDD (Alexopoulos et al., 2008; Ballmaier et al., 2008; Yuan et al., 2010), early-onset dysthymia or depressive personality disorder (Lyoo et al., 2002) and bipolar depression (Benedetti et al., 2011).

During development, the maturation of the corpus callosum parallels the maturation of cognitive processes (Cowell et al., 1992; Giedd et al., 1996; Rajapakse et al., 1996) and the development of the association cortex (Rakic et al., 1986). One physiological mechanism that is used to achieve this maturation is myelination (Paus et al., 1999). Small unmyelinated and myelinated axons are most dense in the genu of the corpus callosum and it is the last part of the corpus callosum to mature (Aboitiz et al., 1992). Within the genu region of adolescents with early-onset MDD, there may be a failure in myelination to develop on a similar trajectory to controls. Myelination-specific gene