Anatomical MRI study of corpus callosum in unipolar depression

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Abstract

Previous studies have suggested abnormal cerebral lateralization in major depressive disorder (MDD). Few controlled MRI studies have investigated the corpus callosum (CC), the largest commissura connecting the two cerebral hemispheres, in MDD. This study investigated anatomical abnormalities in the CC and its subdivisions in MDD patients. Twenty-two unmedicated MDD patients and 39 healthy subjects underwent brain magnetic resonance imaging (MRI). Measurements of the CC and its sub-regions were performed with a semi-automated software (NIH Image, version 1.62).

ANCOVA with age, gender, and intra-cranial volume (ICV) as covariates showed no significant differences in CC measurements between patients and controls (df = 1,56; $p > 0.05$). However, patients with familial MDD had a significantly larger middle genu area ($F_{1,45} = 4.252$; $p = 0.045$) compared to healthy controls, and significantly larger middle genu ($F_{1,13} = 5.366$; $p = 0.037$), anterior splenium ($F_{1,13} = 6.27$; $p = 0.026$), and middle splenium areas ($F_{1,13} = 4.706$; $p = 0.049$) compared to patients with non-familial MDD.

Although preliminary, our findings suggest that anatomical abnormalities in CC may be restricted to patients with familial MDD, with possible enlargement of CC in this particular sub-group. The possible role of callosal abnormalities in the pathogenesis of mood disorders should be further examined.
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1. Introduction

Over the past decade, we have witnessed important advances in the elucidation of brain mechanisms in- volved in pathophysiology of major depressive disorder (MDD). Neuroimaging studies have increasingly played an important role in these advances. Several studies have demonstrated both anatomical and functional brain abnormalities in this disorder (Guze and Gitlin, 1994; Soares and Mann, 1997a,b; Soares et al., 1996). Such investigations have culminated with the formulation

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of a biological model of depression, which postulates that abnormalities in frontal-limbic-subcortical circuits would play an important role in its pathophysiology (Cummings, 1993a; Davidson et al., 2002; Drevets and Ongur, 1998; Soares and Mann, 1997a,b; Mayberg, 2002; Strakowski et al., 2002).

The corpus callosum (commissura maxima) is the largest structure connecting corresponding regions of the cerebral cortex in the two cerebral hemispheres, integrating motor, sensory, and cognitive functions of the brain. More than half of the axons composing the corpus callosum (CC) are myelinated, what confers this structure its remarkable appearance in midsagittal T1-weighted MRI images (Egaas et al., 1995; Sperry, 1984). Supported by consistent findings from the classic commissurotomy ('split-brain') studies, the CC became a focus of interest for psychiatric research in the 1970s. Behavioral deficits observed in those patients permitted researchers to speculate about a potential role of this structure in pathophysiology of psychiatric disorders. In a classic study, Rosenthal and Bigelow (1972) found CC as the only brain structure significantly different in a group of schizophrenic patients compared to healthy controls, indicating a possible inter-hemispheric dysfunction in schizophrenia. A sizable literature suggests a possible involvement of the CC in the pathophysiology of different neuropsychiatric diseases such as attention-deficit hyperactivity disorder (Hynd et al., 1991), multiple sclerosis (Pozzilli et al., 1991), Down syndrome (Wang et al., 1992), Williams syndrome (Wang et al., 1992), schizophrenia (Mohr et al., 2000), autism (Egaas et al., 1995), and bipolar disorder (Brambilla et al., 2003; Coffman et al., 1990).

Accumulated data from neuropsychological, EEG, and neuroimaging studies, as well as studies implicating left-sided brain lesions in depression, have provided support for the hypothesis of abnormal cerebral lateralization in unipolar depression (Knott et al., 2001; Saxena et al., 2001; Vataja et al., 2001). Those findings suggest a possible involvement of abnormalities in inter-hemispheric information transfer in patients suffering from MDD. Hence, the corpus callosum, as the most important structure inter-connecting the cerebral hemispheres, could play a significant role in the pathophysiology of MDD.

Neuroimaging (Drevets et al., 1997; Drevets and Ongur, 1998; Nolan et al., 2002) and *postmortem* (Ongur et al., 1998; Rajkowska et al., 1999) studies have demonstrated that neuroanatomical abnormalities in sub-regions of the prefrontal cortex are most prominent in MDD patients who have a family history of mood disorders among first-degree relatives. Nonetheless, in regard to anatomical abnormalities in sub-genual prefrontal cortex, such abnormalities have not been found consistently in all studies (Brambilla et al., 2002; Bremner et al., 2002). Few controlled MRI studies have investigated the size or

shape of the CC in MDD, although there are different reports that relate depressive syndromes to callosal abnormalities or agenesis (David et al., 1993). Wu et al. (1993), found the anterior and posterior quarters of the CC significantly larger in MDD patients, whereas two subsequent studies (Husain et al., 1991; Parashos et al., 1998) did not find significant differences in CC size in MDD patients compared to controls.

Based upon regional differences in its fiber composition and topographic mapping of cortical areas to specific regions, the CC has previously been divided into nine sub-regions (Fig. 1) (Keshavan et al., 2002). The main objective of the present study was to examine possible abnormalities in area, length, and shape of the CC and its sub-divisions in a group of unmedicated depressive patients in comparison to healthy controls. Additionally, we investigated the relationship between callosal measures and clinical variables. Based on previous neuroimaging and neuropsychological studies that found prefrontal and temporal abnormalities in MDD (Biver et al., 1994; Freedman, 1994; George et al., 1993; Goodwin, 1997; Klemm et al., 1996; Liotti and Mayberg, 2001; Soares and Mann, 1997a,b), we hypothesized that patients would have abnormalities in anterior genu (callosal sub-region comprised primarily by fibers inter-connecting prefrontal cortex) and anterior and middle splenium (inter-connecting temporal cortex).

2. Methods

2.1. Subjects

Twenty-two MDD patients (mean age ± SD = 41.4 ± 11.1 years, ranging from 18 to 59 years), as determined by the Structured Clinical Interview for DSM IV (SCID-IV) (Spitzer et al., 1994), were enrolled in this study. All subjects were outpatients and were drug-free for at least 14 days preceding the scan. Symptom severity was rated with the Hamilton Depression Rating Scale (HDRS) 17 and 25 items (Hamiltom, 1960). Exclusion criteria were the presence of any comorbid psychiatric disorder, current medical problems, lifetime history of alcohol or substance dependence, as well as alcohol or substance abuse within the six months prior to the scanning.

Thirty-nine healthy subjects (mean age ± SD = 35.8 ± 10.5 years, ranging from 21 to 59 years), as determined by the SCID-IV non-patient version (SCID-NP) were recruited. We excluded subjects with any lifetime or current DSM-IV axis I diagnosis, current medical problems, history of psychiatric disorders among first-degree relatives, and history of neurological disease.

All subjects provided written informed consent, after being explained all relevant information related to study participation. This protocol was approved by the University of Pittsburgh IRB.