DTI studies of corpus callosum in bipolar disorder

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Abstract

Although the pathogenesis of bipolar disorder is still not completely understood, there is evidence from imaging studies that abnormalities in inter-hemispheric communication may play a major role in the pathophysiology of bipolar disorder. In the present review, we discuss the most consistent findings from diffusion imaging studies exploring corpus callosum integrity in bipolar disorder.

Introduction

Bipolar disorder is a severe illness characterized by recurrent episodes of mood swings along with periods of relatively normal mood. Although the underlying causes and pathogenesis of bipolar disorder still need to be fully elucidated, there is evidence that the CC (corpus callosum) may play a significant role in the pathophysiology of illness development and progress. Indeed, structural MRI (magnetic resonance imaging) studies found abnormalities in volume, signal intensity and microstructure in patients suffering from bipolar disorder [1–3], suggesting altered inter-hemispheric connectivity of bilateral homologous connections [4–7]. The CC represents the major white matter commissure connecting the two cerebral hemispheres. It matures through adolescence and early adulthood with a posterior–anterior axonal maturation [8,9], with degradation of microstructural tissue integrity in aging [10]. The CC is involved in integrating sensory-motor functions, attention, language and memory in humans [11,12], which are frequently altered in bipolar patients [13,14]. It can be partitioned into five different sections: rostrum, genu, body, isthmus and splenium [15] and is composed of over 200 million axons that mostly interconnect homologous brain regions of the opposing hemispheres [16]. Unilateral axonal connections are organized similarly in both hemispheres, from anterior to posterior, i.e. prefrontal, premotor, supplementary motor, sensory, parietal, temporal and occipital connections [17]. In general, unmyelinated axons are located in the prefrontal regions, whereas myelinated axons tend to be in the motor and sensory regions [11]. However, little is known about the functional role of each specific CC sub-region, although deficits in dichotic listening or somatosensory tasks are produced by disconnection of the genu and the body after a total or partial callosotomy, whereas visual information transfer is interrupted after the resection of splenium [17–19].

In the present review, we discuss the most consistent findings from diffusion imaging studies exploring CC integrity in bipolar disorder.

DTI (diffusion tensor imaging) studies in bipolar disorder

DTI is a non-invasive imaging technique used to measure the motion of water molecules in brain tissue and can provide information about the microstructural coherence of white matter. When the molecules are constrained, such as in the white matter, water diffusivity depends on tissue integrity and fibre orientation [20]. Thus water diffusion within the neural tissue is primarily impeded by myelin sheath, axonal density and thickness, and cellular structures. The degree of water molecule diffusion (mobility) can be quantified by the ADC (apparent diffusion coefficient), and the fibre tract directionality can be evaluated indirectly by FA (fractional anisotropy) [21]. Usually, high FA values (the highest being 1) in white matter suggest highly organized and normally myelinated axons, i.e. tightly packed in a highly organized extracellular matrix, which is largely made up of glial cells and dendrites that provide natural barriers to water movement within tissue. Low FA values reflect probable damage to axonal membrane, de-/dys-myelination or reduced amount of intra-axonal structures, such as microtubules of the cytoskeleton [22]. Therefore, when the integrity of white matter is disrupted, such as for axonal loss, localized oedema, astroglisis and demyelination, ADC and FA can be considered as biomarkers of white matter microstructure organization, being in most of the cases increased and decreased respectively.

The findings of DTI study in bipolar disorder are summarized in Table 1. Specifically, decreased FA or increased ADC values in the genu, body and splenium of CC of adult bipolar disorder patients have been shown using both ROI...
Table 1 | Diffusion imaging studies investigating CC integrity in patients with bipolar disorder and normal controls

BP, bipolar disorder; HC, healthy controls; MD, mean diffusivity; ROI, region of interest.

<table>
<thead>
<tr>
<th>Study</th>
<th>Healthy controls</th>
<th>Bipolar patients</th>
<th>Methods</th>
<th>Findings in the bipolar cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frazier et al. [26]</td>
<td>8 9.2 ± 2.4</td>
<td>10 BP 9.2 ± 3.0</td>
<td>ROI and voxel-based analysis</td>
<td>↓FA in BP in right anterior CC body compared with both ‘at-risk’ and HC</td>
</tr>
<tr>
<td>Yurgelun-Todd et al. [2]</td>
<td>10 32.4 ± 9.1</td>
<td>11 32.9 ± 10.5</td>
<td>ROI</td>
<td>↑FA in the genu, with preserved ADC</td>
</tr>
<tr>
<td>Bruno et al. [24]</td>
<td>28 Matched</td>
<td>36 38.7 (range 21–63)</td>
<td>Voxel-based analysis</td>
<td>↑MD in part of the CC</td>
</tr>
<tr>
<td>Wang et al. [25]</td>
<td>40 29.2 ± 9.2</td>
<td>33 32.0 ± 10.1</td>
<td>ROI and voxel-based analysis</td>
<td>↓FA in anterior and middle CC with ROI analyses</td>
</tr>
<tr>
<td>Barnea-Goraly et al. [28]</td>
<td>18 14.5 ± 2.7</td>
<td>21 16.1 ± 2.7</td>
<td>Voxel-based analysis</td>
<td>↑FA values in CC</td>
</tr>
<tr>
<td>Pavuluri et al. [27]</td>
<td>15 13.7 ± 2.7</td>
<td>13 14.8 ± 2.5</td>
<td>ROI</td>
<td>↑ADC and ↓fibre coherence index in the splenium of CC</td>
</tr>
<tr>
<td>Sussmann et al. [23]</td>
<td>38 37.2 ± 11.9</td>
<td>42 39.6 ± 10.1</td>
<td>ROI and voxel-based analysis</td>
<td>↓FA in the CC</td>
</tr>
</tbody>
</table>

(from region of interest) and voxel-based analyses in groups of medicated patients [23]; also mean diffusivity is shown to increase in the anterior part [24] and throughout the CC [25]. Interestingly, Yurgelun-Todd et al. [2] found increased FA in the genu (but not in the splenium) in a cohort of drug-free patients compared with matched healthy controls, suggesting specific impaired callosal-frontal connections, but the small sample size (11 patients and ten healthy subjects) limits the significance of these findings. The integrity of the CC in juvenile bipolar population has also been explored, revealing lower FA values in the genu and body [26], and higher ADC and reduced fibre coherence in the splenium [27] and throughout the CC [28]. This suggests that maldevelopment of the CC and potential impaired communication between hemispheres may affect brain maturation in paediatric bipolar disorder. However, these studies are limited by the small sample size and methodological differences.

From these findings, there is evidence that abnormal interhemispheric connectivity may represent a marker for bipolar disorder, potentially leading to cognitive and emotional deficits. This impairment may be due to damage of axonal membrane or permeability, intra-axonal microtubular integrity or axonal dysmyelination. It remains to be elucidated whether the quality of transcallosal communication is also affected. Moreover, diffusion imaging studies in bipolar disorder are limited by the small sample size and methodological differences.

However, it is still not clear whether these findings precede or accompany the onset of the illness. Future functional imaging studies combining with structural, diffusion MRI and other neuroimaging modalities would be helpful in exploring the inter-hemispheric communication by recruiting large populations of juvenile bipolar disorder patients.

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References


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