Topographic Anatomy of the Fornix as a Guide for the Transcallosal-Interforniceal Approach With a Special Emphasis on Sex Differences

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Abstract

The topographic anatomy and morphometry of the fornix is important for standardizing the transcallosal-interforniceal approach and avoiding memory disturbances. The detailed morphometry of the fornix was investigated with a special emphasis on sex differences using midsagittal magnetic resonance imaging of 80 males and 102 females. Various parameters of the fornix, including the length of the upper and lower fornices, the curvature of the upper and lower fornices, and the insertion point of the fornix to corpus callosum, were investigated. The thickness of the fornix at the attachment point to the anterior commissure, the maximum distance to the upper and lower surfaces of the fornix, and the curvature of the upper and lower fornices showed sex differences (p < 0.5). The upper insertion point of the fornix to the corpus callosum was more frontal in females, but the functional relevance of these differences need further investigation.

Key words: anatomy, fornix, magnetic resonance imaging, sex difference

Introduction

Various different surgical approaches to the anterior third ventricle region are available including the subfrontal approach through the lamina terminalis, the transcortical-transventricular approach through the interventricular foramen, and the transcallosal-interforniceal approach between the columns of the fornix. Although the transcortical-transventricular approach is usually preferred, the transcallosal-interforniceal approach is a straightforward midline approach with good exposure of the anterior portion of the third ventricle, particularly for lesions arising from the ventricle floor.²,¹⁸,³¹ Understanding of transcallosal-interforniceal approach region is important to preserve the anatomy and neuropsychological function by causing minimal interruption of neuronal pathways and important neuroanatomic structures such as the corpus callosum, anterior commissure, septum pellucidum, motor cortex, and pyramidal tract.²,²⁷

The fornix is the major fiber tract connecting the hippocampal formation with the subcortical brain regions and provides an indirect connection between the hippocampal formation and the prefrontal cortex. The human fornix contains approximately 1.2 million fibers.¹) Few studies have been made of fornix anatomy and none investigating sex differences except one study in schizophrenics.⁸,¹⁰,¹⁵,²⁶,²⁸) This study used magnetic resonance (MR) imaging for morphometry of the fornix to investigate sex differences as a guide in standardizing the transcallosal-interforniceal approach.

Materials and Methods

This study included a random sample of 182 right-handed patients (80 males and 102 females, aged 20–79 years, mean age 34.5 years) without apparent neuropathology. MR imaging was performed with a GE Vectra (General Electric, Milwaukee, Wis., U.S.A.) operating at 0.5 Tesla. Midsagittal T₁-weighted brain imaging (repetition time 500x msec, echo time 20 msec, number of excitations 1–2, slice thickness 5 mm) was used for the evaluation. Images were scanned and all measurements were performed with the computer image.

The anatomy of the fornix can be summarized briefly as follows. Axons of hippocampal pyramidal cells converge into bundles, called the fimbria of the hippocampus. Traced backwards on the floor of the
inferior horn of the ventricle, the fimbria ascend anterior and inferior to the splenium of the corpus callosum to form the crura of the fornices. The crura are attached to the anterior surface of the splenium. The two crura then pass forward and medially under the body of the corpus callosum, closely following the inferior surface. As the crura converge through the midline, they give off decussating fibers that form the hippocampal commissure (psalterium, lyre of David). Anteriorly, the two crura come together in the median plane and constitute the body of the fornix. At the anterior pole of the thalamus, the fornical fibers again diverge into the two anterior columns of the fornices. These form the superior, anterior, and medial walls of the interventricular foramen. About half of the fibers of each column of fornix pass behind the anterior commissure toward the anterior thalamus and mammillary body. In some patients, the columns, body, crura, and commissure of the fornices are separated from the body of the corpus callosum by the cavum vergae, a space filled with cerebrospinal fluid. The fornix does not only carry hippocampal efferents, but also prominent inputs from the medial septal complex and posterior hypothalamus. A topographical overlap of the fornix projection with areas receiving forelimb, snout, neck, and auditory-visual teleceptor input has been shown, suggesting that the fornix-mediated information may modulate cerebellar circuits involved in postural adjustment, general orientation, and exploratory motor behavior. Some recent studies propose the involvement of the fornix in schizophrenia, as a key fiber tract connecting the hippocampus and thalamus that are both implicated in schizophrenia. Therefore, damage of the fornix may result in memory disturbances.

A rectangle bounding the corpus callosum was drawn, with one side parallel to the line connecting the anterior and posterior commissures in accordance with the previous study and the bounding rectangle was divided into 10 equal parts (Fig. 1). The different insertion types were classified by determining the adherence of the upper fornical surface to the corpus callosum. The adherence point of the upper fornical surface to the corpus callosum was accepted as the insertion type.

The length of the upper fornix (ULFO) was measured as the length of the line extending from the anterior side of the fornix which adheres to the septum pellucidum and extends from the anterior commissure to the point where the fornix touches the lower surface of the corpus callosum (Fig. 2). The length of the lower fornix (LLFO) was measured as the length of the free posterior border extending from the anterior commissure to the point where the fornix touches the lower surface of the corpus callosum. The mean fornix length (MLFO) was calculated as the mean length of the upper and lower fornices. These measurements were previously defined.

Fornix-to-brain ratios (FBRs) were calculated as the ratio of the widest aspect of the fornix at the level of the anterior commissure to the distance between the anterior and posterior commissures. Curvatures of the fornix were measured in accordance with the previous study. For the curvature of the upper fornix, a straight line between the upper insertion point of the fornix to the anterior commissure and the upper insertion point of the fornix to the corpus callosum was drawn.
Table 1  Measurements of the anatomical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Probability</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>SE</td>
</tr>
<tr>
<td>ULFO (mm)</td>
<td>29.46 ± 5.34</td>
<td>18.72–39.39</td>
<td>0.56</td>
</tr>
<tr>
<td>LLFO (mm)</td>
<td>30.08 ± 4.83</td>
<td>20.47–38.84</td>
<td>0.51</td>
</tr>
<tr>
<td>MLFO (mm)</td>
<td>29.77 ± 5.02</td>
<td>19.59–38.41</td>
<td>0.53</td>
</tr>
<tr>
<td>FBR</td>
<td>0.16 ± 0.04</td>
<td>0.08–0.27</td>
<td>0.01</td>
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<tr>
<td>Curvature of the</td>
<td>0.23 ± 0.06</td>
<td>0.12–0.40</td>
<td>0.01</td>
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<tr>
<td>upper fornix</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Curvature of the</td>
<td>0.22 ± 0.05</td>
<td>0.12–0.40</td>
<td>0.01</td>
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<tr>
<td>lower fornix</td>
<td></td>
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<tr>
<td>Thickness of the</td>
<td>3.99 ± 1.12</td>
<td>2.12–6.76</td>
<td>0.12</td>
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<tr>
<td>fornix at the</td>
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<tr>
<td>attachment point</td>
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<td>to the corpus</td>
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<tr>
<td>callosum (mm)</td>
<td></td>
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<tr>
<td>Thickness of the</td>
<td>3.25 ± 0.89</td>
<td>1.43–5.43</td>
<td>0.09</td>
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<tr>
<td>fornix at the</td>
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<td>attachment point</td>
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<td>to the anterior</td>
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<tr>
<td>commissure (mm)</td>
<td></td>
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<tr>
<td>ULAFO (mm)</td>
<td>6.77 ± 2.27</td>
<td>1.84–12.49</td>
<td>0.24</td>
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<tr>
<td>LLAFO (mm)</td>
<td>6.80 ± 1.97</td>
<td>2.62–12.09</td>
<td>0.24</td>
</tr>
</tbody>
</table>

FBR: fornix-to-brain ratio, LLAFO: maximum distance to the lower surface of the fornix, LLFO: length of the lower fornix, MLFO: mean fornix length, SD: standard deviation, SE: standard error, ULAFO: maximum distance to the upper surface of the fornix, ULFO: length of the upper fornix.

**Table 1 Measurements of the anatomical characteristics**

**Results**

The measurements of the anatomical characteristics are summarized in Table 1. The curvature of the upper and lower fornices, thickness of the fornix at the attachment point to the anterior commissure, ULAFO, and LLAFO showed statistically significant differences between the sexes (p < 0.5).

Examples of various insertion points are illustrated in Fig. 3. The UFCC was in segment 6/10 in 4.54% and 1.06%, in segment 7/10 in 23.86% and 26.59%, in segment 8/10 in 26.14% and 42.56%, in segment 9/10 in 43.18% and 28.73%, and in segment 10/10 in 2.28% and 1.06% in males and females. These results show that the insertion point is more frontal in females compared to males.
Discussion

The transcallosal-interforniceal approach is performed by opening the interhemispheric fissure and dissecting the corpus callosum along a median-longitudinal line. The septum pellucidum is cut along its insertion line to the corpus callosum and the two leaves of the septum pellucidum are separated. The interforniceal approach carries the risk of damaging the fornices following removal of third ventricle lesions leading to long-term memory loss, which makes the topographic anatomy and morphometry of the fornix important. The curvatures of the fornix and the length of the fornix do not have a major impact on the interforniceal and transchoroidal approaches. If the fornix is short, there is a limitation of widening the space between the fornices that leads to restricted access to the third ventricle between the columns. This may alter the choice of the approach to third ventricle lesions, and subfrontal or transcortical-transfornical approaches are preferred. Also, the UFCC is the most anterior point of possible damage and it is extremely important to detect patients with anterior insertions to avoid fornix damage. Opening the corpus callosum behind the insertion point also might damage the hippocampal commissure and lead to memory disturbances.

Only a few studies of fornix anatomy have been made. Left/right asymmetry of the anterior columns of the fornix was found in a patient, with the left fornical column located caudal to the right. One patient had some fibers of the genu of the corpus callosum entrapped by a fornix fiber bundle and another patient had the unilateral anterior commissure running posterior to the column of the fornix, but both were clinically insignificant. No functional relevance has been described to such differences in location, and today it is only possible to speculate on the functional significance of fornix asymmetry. Differences in cell densities between the left and right hippocampi have been described recently in only epileptic male patients, and fornix asymmetry could correspond to hippocampal asymmetry, since the fornix connects the hippocampal formation to the mammillary body. Significant differences in volume were observed between the right and left sides of the hippocampus, amygdala, fornix, and mammillary bodies in healthy individuals, whereas there was no volume difference between the hemispheres. Asymmetry in the size of the fornix was present in patients with seizures caused by unilateral hippocampal sclerosis and MR imaging showed volume loss of the fornix ipsilateral to the side with hippocampal sclerosis. Lesion studies have not shown relevant left/right differences and histological studies are needed for further clarification of asymmetry in the hippocampal formation and fornices.

The fornix is an important white matter relay pathway connecting the temporal and frontal lobes, so is likely to be affected in schizophrenic patients. MR imaging found no marked changes in fornix volume in schizophrenic patients, but the fornix volume correlated significantly with the volumes of other limbic system structures in schizophrenic patients, but not in controls. On the other hand, the mean cross-sectional fornix area in patients with schizophrenia was significantly larger than in normal subjects. In another study, the fiber number or structure of the fornix was abnormal in schizophrenic patients and men had a lower fiber density in the fornix than in women. Traumatic brain injury also affects the fornix, as FBR is significantly reduced in patients with traumatic brain injury, indicating the vulnerability of the fornix.

ULFO, LLFO, and MLFO were previously measured without sex classification as 35.15, 37.61, and 36.38 mm, respectively. In this study, ULFO, LLFO, and MLFO were 30.16, 31.32, and 30.74 mm in the entire population. ULAFO and LLAFO were reported to be 6.56 ± 0.24 and 7.58 ± 0.25 mm, respectively. In this study, ULAFO was 6.77 ± 2.27 and 6.22 ± 1.94 mm, and LLAFO was 6.80 ± 1.97 and 6.17 ± 1.67 mm in females and males, respectively. The difference between the results of the studies is probably due to the different populations.

The upper insertion point of the fornix (the calloso-forniceal junction) is the most anterior point of possible damage to the fornix during surgical interventions resulting in loss of short-term memory. This point may also be important during callosotomy to treat some forms of generalized epilepsy and to access intraventricular pathology. Our study and previous studies divided the length of the corpus callosum into 10 equal segments or four segments to identify the insertions of the fornix. Comparison of the results is presented in Tables 2 and 3. These results show some inconsistency in the frontal half of the corpus callosum.

No sex differences have been reported in the gross anatomy of the fornix, although sex-dependent left/right asymmetries of some brain structures have been reported. Schizophrenic men had a lower fiber density of the fornix compared to schizophrenic women. In this study, we found that the thickness of the fornix at the attachment point to the anterior commissure, ULAFO, LLAFO, and the curvature of the upper and lower fornices showed

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sex differences. We also found the upper insertion point was more frontal in females compared to males.

Microsurgical approaches to the anterior third ventricle region should be performed with minimal disruption to the anatomy, neuropsychological function, and neuronal pathways. Normative data of this region can be used in planning and standardization of the transcallosal-interforniceal approach, allowing greater safety during the operation and avoiding damage to the fornices. This study provides detailed morphometry of the fornix based on a large series of individuals to guide surgical interventions in the anterior third ventricle region, and showed sex differences in some parameters of the fornix.

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Commentary

The authors performed a morphometric study of the fornix using magnetic resonance imaging. Special attention was paid to sex variation. Significant differences were found in the thickness of the fornix, the maximum distance to the upper and lower surfaces of the fornix, and the curvature of the upper and lower fornix. A curious finding was that females tended to present a more frontal point of attachment to the corpus callosum. As the authors declare, the functional importance of these differences needs additional investigation.

The surgical relevance of these measurements should not be overemphasized. The region of the third ventricle posterior to the foramen of Monro may be approached through two different routes: tranchoroidal and interfornicial. They have the advantage of giving access to the central portion of the third ventricle behind the foramen of Monro by displacing rather than transecting the fibers of fornix. When opening the choroidal fissure, it is safer to open through the tenia fornici than through the tenia choroidea, because fewer veins and arteries pass through the tenia fornici. In the interfornicial technique, the body of the fornix is dissected, allowing access to expose the structures in the third ventricle. Both techniques carry the risk of damaging the fornix. In spite of this, unilateral damage to the fornix produces no deficit. There is some evidence that the lesions in the crus and hippocampal commissure have a more deleterious effect on memory than injuries in the body and columns.

Thus, it is important to avoid injury to the hip-
pocampal commissure. This important structure interconnects the medial edge of the crura of the fornix and it is usually located below the splenium. It does not necessarily correspond to the point of insertion of the fornix to the corpus callosum.

Indeed, two anatomical measurements are relevant to the surgical planning: the distance between the foramen of Monro and the most anterior point of the hippocampal commissure, which would correspond to the surgical working space and the distance between the insertion point of the fornix to the corpus callosum and the hippocampal commissure, which could provide useful information when analyzing the preoperative MRI studies. Nonetheless, these parameters only can be determined by performing anatomical studies and may not be contemplated in a purely radiological assessment.

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The authors of this paper used MR imaging to study some morphological features of the fornix, and especially to investigate sex differences. One hundred and eighty-two right-handed patients (80 males, 102 females) were included. All of them underwent midsagittal T1-weighted MR brain imaging. The different insertion types of the fornix to the lower surface of the corpus callosum and its different curvatures from the corpus callosum to the anterior commissure were measured and classified. These measurements mainly showed that the insertion point of the fornix to the lower surface of the corpus callosum is more anterior in females than in males.

Although sex-dependent left/right asymmetries of several brain structures, including white matter bundles such as corpus callosum and anterior commissure, have been previously reported, this well-designed study is the first one to report a sex-related difference in the gross anatomy of the fornix. The functional relevance of such a difference remains unknown, but could partly be explained by the strong limbic involvement of the fornix.

Besides its possible neuropsychological implications, this study is important, in so far as a perfect knowledge of the anatomy and morphometry of the fornix is required to perform transcallosal-interforniceal approaches to the third ventricle region, and also to perform anterior callosotomies. In this regard, this study provides details, which may increase the safety of such surgical procedures.

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