The Fornix and Limbic System

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The limbic system is predominantly involved in memory and emotional output. Its 2 principle components are the hippocampus (involved in memory as part of the Papez circuit) and the amygdala (involved in emotional responses, memories and drives). The principle clinical manifestations of limbic disease are epilepsy, confusional states, and cognitive impairment. The connections of the limbic system are widespread and are now becoming visible on diffusion tensor imaging. Many different diseases may affect the limbic system. An appreciation of its functional anatomy along with its white matter tract connections improves assessment of infiltrative disease in particular. Small lesions in the Papez circuit may have devastating neuropsychological consequences. An active search strategy based on the knowledge presented in this paper will increase the likelihood of making an accurate diagnosis for patients affected by these conditions.

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Introduction
Anatomy

The limbic system is involved in emotion, drives, and memory. Although the list of structures typically included in the limbic system varies between authors, the 2 major systems are centered around the hippocampus and the amygdala.1

The hippocampal system is predominantly involved in the formation of new memories via a circuit of connections with many other parts of the brain. This circuit, referred to as the Papez circuit, consists of the following structures: the fornix, the hippocampus, the mamillary bodies and the cingulum.2 Sensory information from the various parietal, temporal, and occipital association cortices converge on the cingulate gyrus, which, via the cingulum, passes information in a “C”-shaped loop around the corpus callosum down into the temporal lobes. The destination is the entorhinal cortex—the principle input to the hippocampus. The output of the hippocampus starts as the alveus, a thin band of white matter between the hippocampus and the overlying ependymal margin of the temporal horn of the lateral ventricle. This gradually thickens posteriorly initially into the fimbriae and then into the crus of the fornix on each side. The crura unite in the midline just anterior to the splenium of the corpus callosum and pass anteriorly in the inferior free edge of the septum pellucidum. At the level of the foramen of Monro, they turn inferiorly and posteriorly to form the columns of the fornix, which divide around the anterior commissure, ending in the septal nuclei (precommissural fibers) and predominantly the mammillary bodies (postcommissural fibers). The mammillothalamic tract passes posterosuperiorly from the mammillary bodies to the anterior nucleus of the thalamus. From here, the loop is completed via projections back to the cingulum or cingulate cortex (Fig. 1).

This loop of structures needs to be intact for new memories to be “laid down.” Disruption of the whole system, per se, is more important than damage to individual components. Many of the individual components of this system can be identified on routine neuroimaging such as computed tomography (CT) or magnetic resonance imaging (MRI) (Figs. 2-4) but the application of diffusion tensor imaging (DTI) and subsequent tractography allows exquisite identification of orientation of white matter tracts and their integrity (Fig. 5).

The amygdala is predominantly involved in emotional responses to sensory stimuli. Connections of the amygdale run in a bidirectional fashion, with both inputs and outputs traveling along the same pathways.3 Many cortical areas project to the amygdala—particularly the insula, orbitofrontal, anterior cingulate cortex, and temporal lobes, but the most prominent input is from the olfactory cortex, along with
Figure 1  Anatomy of the limbic system or the Papez circuit: (A) coronal T1-inversion recovery image showing fimbriae (red arrows) and crura (blue arrows) of the fornix; (B) sagittal magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo (MPRAGE) image showing the body of the fornix (blue arrow) and mammillary body (purple arrow); (C) sagittal MPRAGE image showing retrocommissural posterior column of the fornix (blue arrow) and anterior commissure (green arrow); (D) coronal T1-inversion recovery image showing the hippocampus (yellow arrow), dentate gyrus (orange arrow), and parahippocampal gyrus (blue arrow); (E) axial MPRAGE image showing anterior commissure (green arrows), posterior columns of the fornix (blue arrow, left), and mammillothalamic tract (black arrows); and (F) sagittal MPRAGE image showing cingulated gyrus (blue arrows). (Image courtesy of Dr Adam G. Thomas.)

Figure 2  Methods of imaging the limbic system: (A) plain radiograph showing increased density projected over the left orbit; (B) coronal reformat of a CT scan showing a calcified left medial temporal lobe mass; and (C) coronal T1 MPRAGE image obtained after contrast administration showing a nonenhancing left medial temporal lobe ganglioglioma. PH = posterior hippocampus; AH = anterior hippocampus.
inputs from the basal septal nuclei and the hypothalamus. There is reciprocal output to all of these areas and also directly to the adjacent hippocampus or entorhinal cortex via the following structures or pathways (Fig. 6):

1. The stria terminalis: another C-shaped loop following the tail of the caudate nucleus around the temporal lobe and running in the caudothalamic notch in the body of the lateral ventricle. The fibers terminate in the hypothalamus and septal nuclei.

2. The ventral amygdalofugal pathway: fibers from the amygdala pass medially, beneath the lentiform nucleus, to a wide variety of structures, including the hypothalamus, basal septal nuclei and orbital and anterior cingulate cortices. There are strong connections to the ventral striatum—particularly the nucleus accumbens, along with connections to the dorsomedial nucleus of the thalamus.

The function of the hippocampus and amygdala are intimately related, particularly regarding memory. While the hippocampus can be thought of as dealing with the factual content of memory, the amygdala assigns emotional content to memories and can act to enhance the likelihood of memory formation via increasing the weight of its importance.

The outputs of both of these systems are integrated to effect behavioral change via the coordinating medial forebrain bundle, aided by the visceral effects generated by the hypothalamus.

**Imaging the Limbic System**

The role of conventional radiography or CT in evaluation of the limbic system is minimal, predominantly in the identification of calcification (Fig. 2) and in the acute setting (eg, looking for hemorrhage or mass effect on CT).
Conventional MRI
High-resolution MRI (particularly gradient or spin-echo T1 volumes) allows reconstruction of these complex structures without loss of spatial resolution in any plane.

Three-dimensional T1 assess both cortical formation, gray-white matter detail (particularly important in epilepsy assessment), but it is also useful for superposition of functional or tractographic data. Coronal imaging of the temporal lobe is

Figure 5  Diffusion tensor imaging (DTI) of the fornix: (A) color-coded fractional anisotropy (FA) map showing the left crus (colored red) passing medially and anterior columns (colored blue) passing superoinferiorly; (B) the bodies of the fornix pass anteroposteriorly and are colored green (arrows); (C) posterior columns of the fornix (colored blue, yellow arrows) pass behind the anterior commissure (colored red, passing right to left, white arrows); and (D) color-coded tractography of the fimbriae, crura, and bodies of the fornices—the anterior columns are not displayed. (A, B, and C courtesy of Dr Adam G. Thomas.)

Figure 6 Connections of the amygdala: (A) coronal MPRAGE image showing the ventral amygdalofugal pathway passing superomedially (red arrow) beneath the lentiform nucleus (yellow arrow) toward the hypothalamus, (B) sagittal oblique T1 volume showing the course of the stria terminalis passing from the amygdala (yellow star) and following the tail of the caudate nucleus in a loop and also ending in the hypothalamus, (C) the stria terminalis (green arrow) runs in the groove between the thalamus (red arrow) and the tail of the caudate nucleus (blue arrow) in the floor of the body of the lateral ventricle, and (D) slightly asymmetrically positioned color FA map showing the stria terminalis (arrows) bilaterally. (Image courtesy of Dr Adam G. Thomas.)
important in both epilepsy assessment and in evaluation of cognitive impairment. The coronal plane is actually obliquely orientated to be directly perpendicular to the body or head of the hippocampus to ensure accurate evaluation (Fig. 3). Sequences commonly employed in this plane are thin-section coronal T2 and fluid attenuation inversion recovery (FLAIR) imaging (particularly useful in mesial temporal sclerosis) and T1-inversion recovery (excellent gray-white matter separation). Calcification or hemorrhage is frequently a source of seizure generation, hence, a susceptibility-weighted sequence (gradient echo T2* or susceptibility weighted imaging) is also important. The superior signal-to-noise ratio obtained at 3 T can enhance diagnostic detection, particularly in the case of epileptogenic lesions.

**Diffusion and Advanced MRI Techniques**

Diffusion-weighted imaging (DWI) is now clinically routine and has a role to play in many pathologies that affect the limbic system (described later). DTI allows visualization of the white matter connections of the limbic system and their integrity in cases of disease. Perfusion MRI and MR spectroscopy are valuable in the evaluation of tumors and tumorlike conditions. Functional MRI is particularly useful in presurgical planning, particularly for language localization in patients who are about to undergo temporal lobe surgery.

**Clinical Presentation**

Owing to the widespread connections of the limbic system, pathology that affects it may present in varied, and often nonspecific, ways. However, given the functions outlined previously, there are 3 particular circumstances in which limbic system pathology should be suspected. The clinical presentations may overlap considerably in any of the conditions discussed.

**Epilepsy**

Temporal lobe epilepsy is the most common focal epilepsy in adults and the hippocampus may be involved in either secondary to seizure activity or as a seizure-generating focus itself. The most common hippocampal pathology associated with seizures is mesial temporal sclerosis. Although a causative relationship has not been established, increased rates of childhood febrile convulsions are seen in retrospective studies of patients with hippocampal sclerosis. The imaging findings are characteristic with reduced volume and T2 and FLAIR hyperintense signal (easily detected because of overlying cerebrospinal fluid suppression) of the affected hippocampus, best appreciated in the coronal plane. The condition may be encountered in childhood (Fig. 7) or adulthood (Fig. 8). Diffusion and perfusion changes encountered depend on whether the study is acquired in the ictal (hyperperfusion, diffusion restriction) or interictal period (hypoperfusion, increased diffusivity). The output tract of the hippocampus, the fornix, and even the mammillary body may be affected, with ipsilateral atrophy encountered in cases of severe hippocampal volume loss. This can be easily assessed using DTI.

![Figure 7](image_url) **Figure 7** Pediatric mesial temporal sclerosis: (A) sagittal MPRAGE image in a 3-year-old patient with epilepsy showing microcephaly; (B) axial FLAIR image showing a right middle cranial fossa arachnoid cyst; and (C) coronal FLAIR image showing loss of volume and hyperintensity of the right hippocampal body (arrow) but relative preservation on the patient’s left (arrow).
Any mass lesion in the temporal lobe may present with epilepsy. These range from benign vascular lesions to aggressive high-grade astroglial series tumors. Cavernomatous malformations (cavernomas) may be highly epileptogenic in any area of cortex but particularly within the temporal lobe (Fig. 9). Benign or low-grade lesions that particularly affect the temporal lobes include gangliogliomas and developmental neuroectodermal tumors (Fig. 2).

**Figure 8** Adult mesial temporal sclerosis—patient with complex partial seizures. (A and B) Coronal FLAIR images showing loss of volume and hyperintensity of the left hippocampus (arrows). (C) Axial color FA map showing reduced FA, which is better appreciated on coronal reconstructions (D and E—arrows). There is associated hypoperfusion (F, arrow).

**Figure 9** Hippocampal cavernoma: (A) heterogenous left medial temporal lobe lesion (arrow) with regions of T1 hyperintensity and (B) gradient echo T2*-weighted image showing hypointense signal (arrow) and blooming artifact consistent with a cavernoma.
Figure 10  Grade III hippocampal astroglial series tumor: (A) axial T1 image showing low signal mass (arrow); (B) the lesion shows patchy enhancement after contrast (arrow); (C) it is T2 hyperintense; and (D) there is evidence of infiltration of temporal white matter on the color FA map with reduced visualization of the occiptotemporal fasciculus (arrow).

Figure 11  Multimodal imaging of a limbic glioblastoma: (A) axial T2-weighted image showing right temporal lobe tumor and extensive edema (arrow); (B) color-coded relative cerebral blood volume map showing elevated perfusion within the lesion (arrow); (C) multivoxel MR spectroscopy acquired over the lesion, the green voxel is enlarged in (D) and shows elevated Cho level, reduced NAA level, and a lipid or macromolecule peak; and (E) functional MRI localizing language function to the left hemisphere. Cho, choline; NAA, N-acetyl aspartate.
Figure 12 Inferior right MCA infarction in a 23-year-old patient with acute confusion: (A) axial T2-weighted image showing cortical and subcortical signal hyperintensity; (B) DWI image showing restricted diffusion in the right insula and frontal and temporal opercula; (C) follow-up axial T2-weighted image showing mature damage in the regions of diffusion restriction; and (D) coronal FLAIR image showing severe loss of hippocampal or medial temporal lobe tissue. The patient had severe anterograde amnesia. MCA, middle cerebral artery.

Figure 13 Bilateral ACA territory infarction: (A) volume-rendered catheter angiogram image of anterior communicating artery aneurysm (arrow); (B) axial T2-weighted image showing bilateral superior frontal and cingulated cortical infarction (arrows); (C) axial T2-weighted image showing T2-hypointense hematoma in the anterior interhemispheric fissure (arrow), and (D) maximum intensity projection of time-of-flight MR angiography of the circle of Willis showing absence of flow in the ACAs bilaterally (arrow)—there is subtle “T1 shine through” from the interhemispheric hematoma. ACA, anterior cerebral artery.
Figure 14  Transient global amnesia: (A) axial DWI image showing a tiny focus of diffusion restriction in the left hippocampus (arrow) and (B) ADC map showing hypointense signal change (arrow), confirming diffusion restriction. It is relatively rare to see any abnormality at all in such patients. ADC, apparent diffusion coefficient.

Figure 15  Herpes simplex encephalitis: (A) axial T2-weighted image showing diffuse signal hyperintensity and swelling of the right temporal lobe and frontotemporal region; (B) axial gradient echo T2* image more superiorly showing hemorrhagic change in the right insular cortex (arrow); (C) coronal T1 postcontrast image showing hyperintense signal in the right insular cortex and mildly increased meningeal enhancement; and (D) coronal FLAIR image showing abnormal signal hyperintensity (arrow) in the contralateral left insular cortex.
Both low- and high-grade astroglial tumors have infiltrative patterns of spread. Knowledge of the preexisting anatomical connections outlined earlier should allow focused assessment of the MRI study to assess the full extent of disease. As with any infiltrative lesion, complete resection is not surgically feasible. The role of the radiologist in the preoperative setting is to try and identify the highest grade or most aggressive component for biopsy. Gliomas have typically low signal on T1-weighted imaging and high signal on T2 and FLAIR and may show intralesion hemorrhage or calcification (Fig. 10). Regions of higher grade are associated with contrast enhancement and increased relative cerebral blood volume on perfusion-weighted imaging (usually owing to neovascular proliferation without effective blood-brain barrier formation), diffusion restriction (owing to increased cellularity), and evidence of necrosis (elevated lipid/lactate) and neuronal destruction (reduced N-acetyl aspartate) on MR spectroscopy (Fig. 11).

A multivoxel spectroscopic approach may help in identifying the most aggressive part of a large lesion.

**Acute and Subacute Confusional State**

**Acute**

Sudden onset of any neurologic dysfunction should always prompt consideration of a vascular etiology. However, sudden confusion is a relatively rare isolated presenting feature of stroke. There are 2 vascular territories (the middle and posterior cerebral artery) involving elements of the limbic system that may be accountable.

Inferior middle cerebral artery division occlusion leading to anterior temporal lobe and possible hippocampal infarction (Fig. 12). This mode of presentation appears more common when involving the left temporal lobe. Anterior cerebral artery infarction—this is particularly severe when bilateral involvement is demonstrated, as may be encountered in patients with an azygos anterior cerebral artery. Damage to the anterior cingulate cortex, the medial and orbitofrontal...
lobes, and critically the columns of the fornix may result in devastating behavioral alteration with features of abulia (poverty of speech and emotional apathy), severe anterograde amnesia and, particularly in the case of cingulate involvement, hypersexuality and agitation. DWI is clearly critical in stroke evaluation, allowing for detection of infarction within minutes of onset and providing reasonable estimation of age of infarct in patients with delayed presentation.

Transient Global Amnesia
This distinct, short-lived amnestic syndrome remains of unknown etiology, although occasionally, DWI-hyperintense lesions are encountered in the hippocampus, leading many to conclude a probable vascular etiology.

Subacute
Subacute presentations should prompt consideration of inflammatory or infectious causes. The infection that appears to show a particular tropism for the limbic system is herpes simplex (types 1 and 2). The typical presentation is with fever, confusion, and seizures. CT may show low density in the temporal lobes, but MRI is the most sensitive way of detecting subtle or early changes. There is T2 and FLAIR cortical or gray matter hyperintensity in the amygdala and hippocampus (often bilaterally). Detecting involvement of the insula and anterior cingulate cortex is helpful in unilateral cases to help suggest infection rather than tumor. Lesions may often be hemorrhagic and show contrast enhancement. DWI is sensitive at showing regions of involvement before T2-FLAIR signal alteration develops.

A more prolonged presentation tends to occur with autoimmune limbic encephalitis. This may be idiopathic but is frequently associated with an underlying systemic malignancy. The antibodies detected may help in directing the search for an underlying lesion: anti-Hu antibodies are associated with small cell lung cancer, anti-N-methyl-D-aspartate receptor antibodies with ovarian teratomas, and anti-Ma2 antibodies with testicular germ cell tumors. Anti-voltage-gated potassium channel antibodies are associated with thymic tumors. Imaging findings in limbic encephalitis may overlap with herpetic infection with bilateral T2-FLAIR-hyperintense swelling of the hippocampi and amygdala. A more symmetrical pattern of involvement and lack of meningeal enhancement, along with clinical features, may act as a clue to autoimmune rather than infectious etiology.

Cognitive Impairment
Given its role in memory formation, any disease that affects the hippocampus may present with problems with short-term memory in particular. Alzheimer disease affects the hippocampi preferentially, and although disproportionate hippocampal atrophy may be demonstrated on standard structural imaging, these features may not be apparent until late in the course of disease. In addition to focal atrophy, functional studies such as positron emission tomography perfusion scanning may show temporal hypoperfusion and newer ligands such as Pittsburgh Compound B allow detection of abnormal amyloid deposition.
Figure 18  Artery of Percheron infarcts: (A) axial ADC map showing bilateral medial thalamic and midbrain hypointensity; (B) axial DWI showing corresponding hyperintense signal; and (C) axial T2-weighted images showing matching T2-hyperintense signal. The patient presented with acute drowsiness and reduced conscious state. There is disruption of the mammillothalamic tracts and anterior thalamic radiations bilaterally. ADC, apparent diffusion coefficient.
noninvasive means of assessing hypoperfusion may be application of arterial spin labeling on MRI.27

Vascular dementia is highly prevalent in developed countries. Imaging usually reveals widespread small vessel ischemic change but focal ischemic involvement of the Papez circuit structures can account for severe memory impairment. Bilateral anteromedial thalamic infarcts (Fig. 18) damage the anterior thalamic nuclei (junction between the mammillothalamic tract and cingulum) and alone may suffice to diagnose vascular dementia (according to the National Institute of Neurological Disorders and Stroke and Association–Internationale pour la Recherché et l’Enseignement en Neurosciences criteria).28 Other vascular causes of thalamic damage, such as internal cerebral venous infarction, can have similarly devastating consequences.

Thiamine deficiency is most commonly encountered in cases of chronic malnutrition (eg, commonly in alcoholics) and the Wemicke-Korsakoff (involving anterograde amnesia) shows involvement of the Papez circuit structures. There is often T2-hyperintense mammillary body atrophy, and fornical involvement may be encountered (Fig. 19). Contrast enhancement may be encountered in the acute setting.29 Neurodegenerative disease in children may show involvement of the limbic structures with pathologic enhancement of the mammillary bodies and amygdala encountered in Alexander disease (Fig. 20).30 T1 hyperintensity of the amygdala is encountered in neurocutaneous melanosis.

Other Behavioral Disorders

The anterior temporal lobes are susceptible to traumatic injury and a specific behavioral syndrome may be encountered in severe bilateral injury with limbic neuroanatomical basis. Klüver-Bucy syndrome consists of fearlessness and placidity (owing to amygdaloid damage), hypersexuality (owing to

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Figure 19 Acute Wernicke encephalopathy: (A) axial T2-weighted image showing bilateral paramedian thalamic signal hyperintensity; (B) axial DWI image showing corresponding diffusion restriction, confirmed by the absence of hyperintensity on the ADC map (C), and (D) sagittal FLAIR image showing atrophy of the mammillary bodies (arrow) and hyperintensity of the massa intermedia (dashed arrow). ADC, apparent diffusion coefficient. (Case courtesy of Dr Adam G. Thomas.)
damage to the piriform cortex, a strong functional connection of the amygdala), and visual agnosia owing to damage of inferior temporal lobe structures31 (see Visual Pathways article in this issue).

**Conclusion**

The limbic system is critical in human memory, emotional experience, learning, and behavior. A wide variety of conditions may affect these structures, but most conditions present with epilepsy, confusion, memory impairment, or a combination or all of them. Knowledge of the connections of the limbic system allows detailed assessment of temporal lobe pathology but also allows one to detect possible limbic effects from more subtle lesions in distant locations. Standard structural imaging suffices in most cases but new information provided by even better DTI may provide new insights into the functional neuroanatomical consequences of disease.

**References**


**Figure 20** Alexander disease: (A and B) axial postcontrast T1-weighted images showing enhancement of the mammillary bodies (arrow, A) and amygdala (arrow, B).