

A CEREBRAL NETWORK REFLECTING REORGANIZATION IN MEDIAL TEMPORAL LOBE EPILEPSY

Hippocampal Atrophy in Temporal Lobe Epilepsy Is Correlated with Limbic Systems Atrophy

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Hippocampal sclerosis in temporal lobe epilepsy (TLE) is often associated with hippocampal atrophy. This study assessed whether such atrophy is correlated with loss of gray matter volume in other brain regions. In 16 patients with TLE and clear magnetic resonance imaging-based evidence of hippocampal sclerosis, hippocampal volumes were determined manually, and the local gray matter (LGM) amount was estimated throughout the entire brain using voxel-based morphometry. Voxelwise correlations between the volume of the sclerotic hippocampus and LGM were computed. The pattern of voxels whose LGM correlated with hippocampal volume outlined remarkably well the anatomy of the extended limbic system

and included the parahippocampal region, cingulate gyrus throughout its extent, basal forebrain, thalamic nuclei, medial orbitofrontal areas, and the insula. These correlations emerged mainly on the side ipsilateral to the affected hippocampus but were also found contralaterally. No such correlations were found in a group of 16 healthy controls. The present data show that hippocampal volume loss in TLE is associated with a widespread limbic systems atrophy. These findings are helpful to better understand the functional deficit and reorganization often found in temporal lobe epilepsy and will also provide a basis to assess neural plasticity in the limbic system for those patients who will undergo curative temporal lobe surgery.

Diffusion Tensor Imaging in Medial Temporal Lobe Epilepsy with Hippocampal Sclerosis

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Interictal diffusion imaging studies in patients with medial temporal lobe epilepsy (MTLE) accompanied by hippocampal sclerosis (HS) have shown an increased diffusivity in the epileptogenic hippocampus. In this study, we wanted to explore the whole brain to determine if MTLE could have an impact on the organization and the architecture of a large cerebral network and to identify clinical factors that could mediate diffusion abnormalities. Diffusion tensor imaging (DTI) and statistical parametric mapping of the entire brain were performed in 35 well-defined MTLE patients and in 36 healthy volunteers. SPM analyses identified three abnormal areas: an increased diffusivity was detected in the epileptic hippocampus and the ipsilateral temporal structures associated with a decreased anisotropy along the temporal lobe, a decreased diffusivity was found in the contralateral nonsclerotic hippocampus,

the amygdala, and the temporal pole, and finally, a decreased anisotropy was noted ipsilaterally in posterior extratemporal regions. Duration of epilepsy, age at onset, and the frequency of generalized tonic-clonic seizures or partial complex seizures did not correlate with the presence of diffusion abnormalities. Region of interest analysis in the hippocampus/parahippocampus demonstrated a correlation between lower ipsilateral diffusivity values and occurrence of epigastric aura and between higher anisotropy values in both hemispheres and history of febrile seizures. In conclusion, this study showed that diffusion abnormalities are not restricted to the pathologic hippocampus and involve a larger network. This pattern may indirectly reflect the epileptogenic network and may be interpreted as a cause or a consequence of epilepsy.

COMMENTARY

MTLE is the most common symptomatic partial or localization-related epileptic syndrome in adults and

the most frequent indication for epilepsy surgery (1–3). The pathological finding underlying the epileptogenic zone in these patients invariably includes hippocampal neuronal loss with associated gliosis (i.e., mesial temporal sclerosis) (2). Focal cell loss in patients with MTLE may be more widespread than just the hippocampal formation and also may be demonstrated in the amygdala, parahippocampus, and entorhinal cortex (1,3–5). Mesial temporal sclerosis includes prominent neuronal loss in the CA1, CA3, and CA4 hippocampal subfields (1,2). MTLE typically is a progressive disorder with focal neuronal loss that may be related to seizure activity and associated with the development of comorbidities, such as neurocognitive decline (1–3). Recurrent seizures may directly induce morphological alterations that are proconvulsant and increase susceptibility to network synchronization (1). The presence of mesial temporal sclerosis is of prognostic importance and strongly correlates with the presence of a pharmaco-resistant seizure disorder. Yet, patients with mesial temporal sclerosis may have surgically remediable epilepsy and be favorable candidates for operative intervention (2–6).

Structural MRI shows hippocampal atrophy (coronal or oblique coronal T₁-weighted images) and a signal intensity alteration (coronal or oblique coronal T₂-weighted or fluid attenuated inversion recovery images) in patients with mesial temporal sclerosis (2,3) MRI has been shown to be pivotal in the evaluation for treatment of patients with partial epilepsy of medial temporal lobe origin. The presence of MRI-identified mesial temporal sclerosis indicates a highly epileptogenic pathological substrate in patients being considered for surgical treatment (7). Atrophy of the hippocampus, as shown by quantitative MRI-based volumetric studies, is a surrogate for focal cell loss and correlates with the localization of seizure onset (3–6). In addition, studies using morphometric measurements have shown that extrahippocampal MRI structural abnormalities may occur in patients with MTLE (2–5). Using serial MRI studies, progressive hippocampal formation atrophy identified in patients with MTLE is thought to reflect a focal cell loss (1–4).

The study by Duzel et al. indicates that gray matter volume loss is more widespread than volume loss in the medial temporal lobe in 16 patients with MRI-identified mesial temporal sclerosis. The morphologic changes predominantly involved the extended limbic system. The findings were bilateral, but maximal ipsilateral to the epileptic medial temporal lobe. Similar gray matter volume loss was not evident in a control group of 16 healthy individuals. Thivard et al. indicated that diffuse tensor imaging and statistical parametric mapping was abnormal in the ipsilateral and contralateral temporal lobes as well as ipsilateral posterior extratemporal cortex in 35 patients with MTLE. Similar imaging changes were not evident in a control group of 36 healthy individuals. The authors concluded that the widely distributed alterations in diffusion tensor imaging (DTI) may

represent sequelae of recurrent partial seizure activity, reflecting an abnormal network associated with epileptogenesis.

The findings from these investigations provide compelling evidence that a neural network of functional and structural reorganization may occur in patients with MTLE both ipsilateral and contralateral to the epileptic brain tissue. The data complement previous observations that TLE may be associated with parahippocampal, entorhinal cortex, and extratemporal gray matter structural abnormalities (3–5). Previous reports also suggested that the anatomical relationship between the hippocampus and amygdala as well as between the entorhinal and perirhinal areas might explain the volume diminution ipsilateral to the epileptic temporal lobe (4–6). The potential mechanisms for the morphological changes include recurrent seizure activity of medial temporal lobe origin or the underlying etiological factors associated with the development of epilepsy. Diffusion imaging and DTI may permit detection of regions of the brain where the normal flow of water is altered (i.e., abnormal diffusion, indicating a potential functional or structural underlying abnormality) (8–10). DTI is a significant innovation of diffusion-weighted imaging that identifies areas of altered diffusivity and may show areas of disruption of the microstructural environment (8–10). White matter tracts can be reconstructed utilizing the information of directionality of diffusion in each voxel. DTI also may be useful to evaluate direct brain connectivity; a previous study indicated the presence of bilateral limbic system DTI alterations in patients with unilateral TLE (8). Fiber tracking also may be used to assess a white matter abnormality (9).

Issues that remain for further investigations include the prognostic importance of these widespread imaging alterations in patients undergoing surgical treatment for medial TLE and their association, if any, with comorbid conditions, such as depression and memory deficits. Whether or not the local gray matter (LGM) changes or the widespread limbic system DTI in patients with unilateral temporal lobe seizures is of any predictive value is unknown. The timing of the gray matter volume changes relative to seizure onset also needs to be clarified. It is not known if patients with MTLE rendered seizure-free on antiepileptic drug medication have similar structural changes. Understanding the neural network in epilepsy may be important in developing strategies to manage effectively both the seizures and the comorbid disorders. Serial MRI studies are needed to determine if the presence of limbic system morphological alterations are progressive and if there is any change in the extrahippocampal volumetric abnormalities after surgical treatment. Finally, it remains to be determined if the use of LGM changes, or DTI may increase the specificity and sensitivity of structural neuroimaging studies in patients, with normal MRI studies and intractable partial epilepsy, who are being considered for surgical treatment.

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