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Severe hippocampal atrophy is not associated with depression in temporal lobe epilepsy

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ABSTRACT

Depression in temporal lobe epilepsy (TLE) is common, is a strong predictor of subjective disability, and may have unique pathophysiological characteristics. Previous studies showed that reduced hippocampal volume is associated with significant depressive symptoms in patients with TLE. We utilized regions of interest analysis of high-resolution brain MRI and a reliable and valid measure of depressive symptoms to evaluate 28 consecutive adult subjects with video-EEG-confirmed TLE. Regions of interest were based on prior human and animal studies of mood and behavioral dysfunction. Forty-three percent of the entire group had significant symptoms of depression, defined by a Beck Depression Inventory (BDI) score of greater than 15. Total hippocampal volumes were significantly smaller in the group with BDI < 15, ($p < 0.007$). None of the subjects in the quartile with the smallest left hippocampal volume had a BDI score greater than 15 compared with 57% of the subjects in the upper three quartiles ($p < 0.008$). No other limbic brain structures (amygdala, subcallosal gyrus, subgenual gyrus, gyrus rectus), or total cerebral volume were associated with depressive symptoms. Adequate hippocampal integrity may be necessary to maintain depression symptoms in mesial temporal lobe epilepsy. This finding also supports the possibility of a unique mechanism for depression in mesial temporal lobe epilepsy, such as hyperexcitable neuronal influence on the limbic network.

1. Introduction

The hippocampus was initially described as a core component of the "emotional circuit" by Papez in 1937 [1]. He proposed a network with the concept that hippocampal hyperexcitation may activate negative mood states. Although smaller hippocampal volumes in humans have been associated with depression in psychiatric patients without other neurological disorders, the pathophysiology underlying these observations is not known [2,3]. In temporal lobe epilepsy (TLE), which is the most common type of epilepsy and often associated with depression [4], there is a much greater range of structural disturbances in the mesial structures, including the hippocampus [5]. An association of hippocampal volume with symptoms of depression remains controversial.

Although a decreased hippocampal volume is associated with mood disorders in some, but not all, studies of TLE [6,7], recent studies indicate that left hippocampal volume reduction is associated with depression [8,9]. The neuronal cell loss and synaptic reorganization observed in hippocampal sclerosis [10–12], which correlates with hippocampal volume on MRI [5], may provide an opportunity to study the association of structural variability with depression in a specific pathophysiological state. Many investigators described frequent spiking as a characteristic of the injured, epileptic hippocampus. These data support the concept of hippocampal sclerosis related to adjacent hyperexcitable neurons [10]. If hippocampal volume in temporal lobe epilepsy is associated with severity of depressive symptoms, a model of hyperexcitable hippocampal input into the limbic network in depression could be postulated. We evaluated the relationship of neuroimaging evidence of hippocampal injury with severity of depressive symptoms in consecutive patients with TLE.

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2. Methods

2.1. Participants

Patients with recurrent seizures receiving optimized pharmacological therapy in the outpatient clinic at the Washington University Comprehensive Epilepsy Center were offered presurgical evaluation that included long-term video-EEG monitoring and high-resolution brain MRI. A neuropsychologist assessed the patients' clinical mood state during presurgical evaluations, and we used the Beck Depression Inventory (BDI) for reliable and valid quantification of their depression symptoms. We enrolled 28 consecutive adults with confirmed TLE based on clinical semiology of their seizures, interictal EEG, and ictal video-EEG. All participants signed an informed consent document that was approved by the local Human Studies Committee.

We determined demographic variables for age, gender, and epilepsy-related factors (seizure type, localization of epileptogenic region, seizure frequency, age at first seizure, and epilepsy duration). Seizure classification was based on the definitions proposed by the International League Against Epilepsy (ILAE) [13]. Seizure type and localization were determined by long-term video-EEG monitoring. Seizure frequency was defined as the average number of complex partial seizures per month for the previous six months. We also looked at the type or number of antiepileptic drugs the subjects were taking at the time of their assessment.

2.2. Beck Depression Inventory

We utilized the BDI [14,15], which is a questionnaire commonly used for evaluation of depressive symptoms in persons with epilepsy [16]. A prior multicenter study determined that a cut score of 15 was based on an optimized receiver-operating characteristic curve of data for major depression in epilepsy [17].

2.3. MR acquisition

Magnetic resonance imaging was performed using an epilepsy-specific protocol on a 1.5-T Siemens machine (Siemens Medical Systems, Erlangen, Germany). The imaging included coronal T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequences [repetition time (TR) = 11.4 ms, echo time (TE) = 4.4 ms, inversion time (TI) = 300 ms, flip angle (FA) = 8°, resolution = 1 × 1 × 1.5, matrix = 256 × 256 × 108]. All parameters (calibration, window setting, etc.) were carefully monitored and optimized for best contrast and brightness. Sequence details of the coronal T1-weighted MPRAGE images were acquired from a high-resolution clinical test. Interscan and intrascan motion correction and averaging were accomplished off-line. Patients with hippocampal atrophy and/or signal change and patients with normal MRI were included. Since patients with normal MRI upon visual and volumetric analysis may have hippocampal sclerosis on pathological evaluation, we elected to determine the association of MRI volumetric quantification with severity of depression.

2.4. Image processing and regions of interest measurement procedures

Image processing prior to the region of interest (ROI) analysis included several image registration steps described earlier [2]. Multiple regions of interest were drawn using the Analyze AVW software (version 6.0, Biomedical Imaging Resource, Mayo Foundation) [18]. Images were displayed, and each ROI was manually outlined (HH and JS) in consultation with a neuroanatomist (JP) and guided by the previous reports. Manual outline of the regions of interest was blinded to clinical and BDI data. The volume estimation was performed using the Cavalieri's principle [19].

2.5. Anatomical definitions of regions of interest

2.5.1. Hippocampus

Anatomical boundaries were identified using prior definitions [2,20]. In the coronal plane, the tail of the hippocampus continues as the indusium griseum, a thin strip of gray matter overlying the surface of the corpus callosum. The most posterior slice for measurement was defined as the slice where the hippocampus first appeared adjacent to the trigone of the lateral ventricle. The gray matter with a boundary superiorly defined by the fornix–fimbria white matter junction, inferiorly by the parahippocampal gyrus white matter, medially by the subarachnoid spaces of the cisterns, and laterally by the lateral ventricle was included. The subiculum extending medially to the edge of the dentate gyrus was included in the measurement, but the alveus with the surrounding white matter, including the thin white matter border with amygdala, was excluded. Orthogonal views were consulted for all slices.

2.5.2. Amygdala

The amygdala was first visualized in a coronal plane. The anterior boundary of this structure was the first section in which the temporal stalk was connected to the white matter of the insula. The border was defined dorsally in the anterior sections by the entorhinal sulcus between the basal forebrain and temporal lobe and posteriorly in the sagittal section by a horizontal plane to the posteroinferior edge of the temporal stem with the temporal horn of the lateral ventricle. Ventrally, visualized in the sagittal section, the amygdala was restricted by the ventral–anterior edge of the hippocampus. Posteriorly, viewed also in the sagittal section, the amygdala was defined by its border with the hippocampus. Medially, best seen in the coronal section, the amygdala was bounded by a subarachnoid space. Laterally, also in the coronal section, the amygdala was bounded by the surrounding white matter [21].

2.5.3. Subcallosal gyrus (BA 25)

Tracing began at the slice where an anterior commissure was visible in a coronal plane. The mesial gray matter area of the prefrontal cortex in all slices anterior to the anterior commissure and extending to the last slice in which the internal capsule appeared was included.

2.5.4. Subgenual gyrus (BA 24)

This structure began as the first mesial gyrus in a superior to inferior plane in the prefrontal cortex on the coronal section. The gray matter included was between the first slice in which the internal capsule was visible and ended with the most anterior extension of the corpus callosum.

2.5.5. Gyrus rectus (BA 11)

The gyrus rectus was delineated in the coronal plane. It was defined by boundaries including the olfactory sulcus (lateral boundary), the olfactory trigone (posterior boundary), and, on the medial side, the cortex inferior to the horizontal line connecting the deepest point of the olfactory sulcus and the nearest point in the midline [22,23]. Tracing started in the plane where the most anterior part of the olfactory sulcus was visualized. Moving posteriorly, sagittal and axial views helped to identify the olfactory trigone. Tracing stopped at the point where the olfactory trigone was no longer visible.

2.5.6. Total cerebral volume

Brain tissue of the cerebral hemispheres, including both gray and white matter, was considered as the total cerebral volume. The midbrain superior to the pons was also included in the analysis. The volume was determined using an auto tracing module of the software in the coronal and transverse planes, with manual adjustments as needed to accurately define the border of the neocortex.

2.5.6.1. Statistical analysis. Volume of each ROI was analyzed as an absolute volume and as a ratio, i.e., volume of the ROI as a proportion of each