Hippocampal $^1$H-MRSI correlates with severity of depression symptoms in temporal lobe epilepsy

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Abstract—Objective: To investigate the association of an indicator of hippocampal function with severity of depression symptoms in temporal lobe epilepsy. Methods: We evaluated 31 patients with video/EEG-confirmed temporal lobe epilepsy using creatine/N-acetylaspartate ratio maps derived from a previously validated $^1$H magnetic resonance spectroscopic imaging ($^1$H-MRSI) technique at 4.1 T. We also assessed depression symptoms, epilepsy-related factors, and self-perceived social and vocational disability. We used conservative nonparametric bivariate procedures to determine the correlation of severity of depression symptoms with imaging and clinical variables. Results: The extent of hippocampal $^1$H-MRSI abnormalities correlated with severity of depression (Spearman rho = 0.65, p value < 0.001), but other clinical factors did not. Conclusion: The extent of hippocampal dysfunction is associated with depression symptoms in temporal lobe epilepsy and may be a more important factor than seizure frequency or degree of disability.

NEUROLOGY 2007;68:364–368

Depression is a common comorbid condition in many neurologic disorders and appears to have an increased prevalence in community and tertiary samples of persons with epilepsy. Depression contributes to poor health outcomes and increased health care costs in epilepsy. Although few studies have evaluated the association of depression with specific epilepsy syndromes, temporal lobe epilepsy is frequently implicated. Involvement of the limbic or ventral prefrontal structures is a possible explanation of the increased prevalence of depression in temporal lobe epilepsy, but the influence of regional brain dysfunction as opposed to social and psychological factors is not known. To evaluate the contribution of potential neuronal and psychosocial factors to depression in temporal lobe epilepsy, we determined the association of severity of depression symptoms with the extent of $^1$H magnetic resonance spectroscopic imaging ($^1$H-MRSI) hippocampal abnormalities, clinical variables, and self-perceived disability.

Methods. Patients. We studied a sample of adult patients who met the following criteria: 1) having had a diagnosis of temporal lobe epilepsy confirmed by recorded seizures during video/EEG monitoring, 2) capable of completing self-report questionnaires, 3) agreeing with and signing an informed consent document approved by our institutional review board (IRB), and 6) age 17 years or older. This lower age limit was used because the mood and health outcome variables had not been tested for reliability and validity in children and adolescents. Study questionnaires were administered by the study coordinator (M.V.) and were completed by patients in a private setting, usually in the outpatient neurology clinic. Magnetic resonance spectroscopic imaging acquisition and analysis. All adult patients undergoing presurgical evaluation for refractory temporal lobe epilepsy at the University of Alabama at Birmingham during the study period were offered $^1$H-MRSI through a National Institute of Neurologic Disorders and Stroke-supported protocol (NS033919). Details of the imaging protocol and examples of subject $^1$H-MRSI maps can be found in earlier publications. The subjects in the current study were a convenience sample who agreed to undergo $^1$H-MRSI and were able to obtain transportation at a time when the MR scanner was available. Briefly, all studies were performed in the interictal state, using a 4.1-T whole-body imaging/spectroscopy system and a quadrature-driven, tunable, matchable head coil. Sagittal and transverse scout images were acquired using inversion recovery gradient echo sequence (TR [repetition time]/inversion recovery time [TIR]/echo time [TE] 2,500/1,000/15). The transverse images were angulated to be parallel to the long axis of the hippocampi and used to select a rectangular region of interest (ROI) in the temporal lobes that included both hippocampal regions. Water- and lipid-suppressed spectroscopic images were acquired using a TR of 2,000, TE of 50 msec, a field of view of 240 × 240 mm, and 32 × 32 phase encodes with a slice thickness of 1 cm. Nominal voxel size was 0.5 cc. Scanning was not performed in the immediate postictal state.

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Supported by National Institutes of Health grants NS01794, NS033919, NS40808, NS047551, and a grant from the Epilepsy Foundation of America.

Disclosure: The authors report no conflicts of interest.

Received December 12, 2005. Accepted in final form October 9, 2006.

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the International League Against Epilepsy. 19 Subjects used
the Work/Driving/Social scale was one of four scales in the
Clinical and mood assessments. All mood, seizure, clinical,
each clinical variable with the POMS Depression scale. After Bon-
tonic-clonic seizures, no. (%) 11 (34)
Results. Patient characteristics. Demographic and sei-
Correlation of depressive symptoms, $^{1}H$-MRSI, and clinical
variables. The scatterplot comparing POMS Depres-
seizures, no. (%) 27 (87.5)
No. (%) of antiepileptic drugs
1 10 (33)
2 17 (55)
3 4 (12)
Mean (SD) no. of seizures/mo 14.7 (17.0)
Patients with simple partial
seizures, no. (%) 15 (48)
Patients with complex partial
seizures, no. (%) 11 (34)
patients with chronic illness and healthy subjects$^{21,22}$
and including previous studies of epilepsy patients.$^{18,23-25}$ The de-
pression subscale has been validated through extensive psycho-
metric testing and is scored 5-point Likert scale for which higher
values indicate greater mood disturbance.$^{21-23}$
Statistical analysis. We used Spearman rho correlations to
determine the bivariate association of the $^{1}H$-MRSI variable and
each clinical variable with the POMS Depression scale. After Bon-
neroni adjustment for multiple comparisons in the bivariate anal-
yses, significance was set at $p < 0.01$. We also applied linear
regression analysis to evaluate the independent associations of
the predictive variables with severity of depression symptoms. All
analyses were performed using SPSS version 10.0 (www.SPSS.
com; Chicago, IL).

Patients with complex partial
seizures, no. (%) 27 (87.5)
Patients with generalized
tonic-clonic seizures, no. (%) 11 (34)

Results. Patient characteristics. Demographic and sei-
zure characteristics of the 31 subjects are shown in table 1.
All subjects had at least one complex partial or generalized
tonic-clonic seizure in the previous 3 months at the time of
evaluation. Ten (32%) patients were on one antiepileptic
medication, 17 (55%) were on two medications, and four
(13%) were on three medications.

Correlation of depressive symptoms, $^{1}H$-MRSI, and clinical
variables. The scatterplot comparing POMS Depression scale scores with the extent of the abnormal
$^{1}H$-MRSI Cr/NAA ratio maps is shown in figure 2. The
results of bivariate nonparametric correlation analyses are presented in table 2. No association with laterality

Figure 1. An example of a $^{1}H$ magnetic resonance spectro-
scopic imaging ratio map in a patient with mesial tempo-
al lobe epilepsy. The map of the region of abnormality
was determined by inclusion of all voxels within the hip-
campi that had an abnormal creatine/N-acetylaspartate
ratio defined as >2 SDs beyond normal. The degree of ele-
vation of Cr/NAA is color coded and corresponds to the ab-
normal ratios; values of 1.3 to 1.6 by increments of 0.1.

every voxel within the hippocampi, and those that were 2 SDs
higher than normal were tagged as abnormal. The extent of ab-
normal voxels is a surface measurement (square millimeters), ex-
cluding voxels containing the cerebellar vermis, using software
developed by our group.$^{15}$ An individual patient ratio map image is
presented in figure 1.

Clinical and mood assessments. All mood, seizure, clinical,
and social and vocational disability assessments were per-
formed as part of a protocol supported by the National Institute
of Neurological Disorders and Stroke (NS001794), and ap-
proved by our IRB.$^{18}$ Onset of epilepsy was defined as the age at
the second unprovoked, nonfebrile seizure. For the purpose of
the logistic regression analysis, employment was defined as
working for a salary more than 20 hours per week; homemakers
and students were also included in this category. Education
was classified as years in a formal educational program of any
type.

We used the method of seizure classification recommended by
the International League Against Epilepsy.$^{15}$ Subjects used
monthly calendars to record seizure occurrences. After each type
of seizure was identified and classified through interviews by the
epileptologists, a letter was used to designate each seizure type
(i.e., simple partial, complex partial, or generalized tonic-clonic)
for the patient calendars. The seizure variable was coded and
analyzed as a continuous variable based on the number of each
seizure type per month.

The Work/Driving/Social scale of the Quality of Life in Epi-
lepsy Inventory-89 (QOLIE-89) was designed to assess the nega-
tive impact of vocational disability, driving restrictions, and social
isolation from the patients' perspective. The test-retest reliability
was 0.86 and Cronbach’s α was also 0.86 for the scale, as defined
in a large ($n = 304$), prospective multicenter study of psychomet-
ric characteristics.$^{20}$ Factor analysis of the 18 subscales showed
that the Work/Driving/Social scale was one of four scales in the
epilepsy-targeted composite factor, as opposed to mental health,
cognition, or physical health factors. The scale score ranges from 0
to 100, with higher scores indicating better self-perceived
functioning.

Mood status was determined by the Depression scale of the
Profile of Mood States (POMS). The POMS is a checklist of adja-
ces describing six mood conditions. The instrument has under-
gone extensive reliability and validity testing in a variety of
samples of patients with chronic illness and healthy subjects$^{21,22}$
and including previous studies of epilepsy patients.$^{18,23-25}$ The de-
pression subscale has been validated through extensive psycho-
metric testing and is scored 5-point Likert scale for which higher
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Statistical analysis. We used Spearman rho correlations to
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regression analysis to evaluate the independent associations of
the predictive variables with severity of depression symptoms. All
analyses were performed using SPSS version 10.0 (www.SPSS.
com; Chicago, IL).

| Table 1 Demographic and clinical characteristics of the study sample of patients with video/EEG confirmed temporal lobe epilepsy |
|----------------------------------|-----------------|
| Clinical characteristics (n = 31) |                 |
| Gender, F/M, %                   | 55/45           |
| Race (white/black/other), %      | 90/10/0         |
| Mean (SD) age, y, at evaluation, y | 35.4 (10.8)    |
| Mean (SD) age at epilepsy onset, y | 15.0 (12.0)    |
| Mean (SD) years of education     | 13.1 (2.1)      |
| Employment                       |                 |
| Employed (>20 hr/wk, includes     | 15 (49)         |
| homemaker or student), no. (%)   |                 |
| Unemployed (0–20 hr/wk), no. (%) | 16 (51)         |
| No. (%) of antiepileptic drugs   |                 |
| 1                               | 10 (33)         |
| 2                               | 17 (55)         |
| 3                               | 4 (12)          |
| Mean (SD) no. of seizures/mo     | 14.7 (17.0)     |
| Patients with simple partial     | 15 (48)         |
| seizures, no. (%)                |                 |
| Patients with complex partial    | 27 (87.5)       |
| seizures, no. (%)                |                 |
| Patients with generalized        | 11 (34)         |
| tonic-clonic seizures, no. (%)   |                 |

January 30, 2007  NEUROLOGY 68  365

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Discussion. The hippocampus is a critical component of the temporolimbic-frontal-subcortical network involved in major depressive disorders. Although hippocampal dysfunction in temporal lobe epilepsy might be anticipated to be associated with depression, few clinical studies have directly supported this plausible relationship. Depression symptoms are reported to be greater in temporal lobe epilepsy patients with MRI-identified mesial temporal lobe epilepsy than in those without MRI evidence of mesial temporal sclerosis. This variability may explain previous observations of extremes of interictal hyper- and hypometabolism in different regions in mesial temporal sclerosis. This variability may also explain the lack of correlation of hippocampal metabolism with depression severity in temporal lobe epilepsy.

The discrepancy of our 1H-MRSI findings with the previous reports of the lack of association of FDG-PET results with depression in temporal lobe epilepsy may be of relevance for understanding clinical correlates of metabolic deficits in the hippocampus. In a detailed comparison of 1H-MRSI to FDG-PET in temporal lobe epilepsy, hippocampal Cr/NAA measures did not correlate with glucose metabolism; indicating that alterations in glucose uptake and NAA concentrations represent different mechanisms of cellular metabolic dysfunction. Rate of brain glucose metabolism is largely dependent on pyramidal neuron activation and subsequent glutamate release, and recent studies indicate that glucose utilization is directly related to glia uptake of glutamate. The wide variability of hippocampal neuron/glia ratios commonly described in temporal lobe epilepsy may explain previous observations of extremes of interictal hyper- and hypometabolism in different regions in mesial temporal sclerosis.

We found a significant correlation of severity of depression symptoms with extent of voxels containing an abnormal Cr/NAA ratio in the hippocampi of persons with temporal lobe epilepsy. To our knowledge, this is the first description of a correlation of severity of depression symptoms with spatial involvement of a biomarker of neuronal dysfunction within a limbic structure. The strength of this correlation may be in part due to the high signal-to-noise ratio provided by the 4.1-T magnet, which allows smaller voxel size and precise identification of hippocampal gray matter to minimize partial-volume effects. Also, compared to other methods of metabolic imaging, NAA may be more closely associated with the mechanisms of hippocampal dysfunction that contribute to limbic system–dependent mood disturbance. However, we could not identify other studies of hippocampal NAA using 1H-MRSI in unipolar depression to further support this supposition. Because sampling of 1H-MRSI was limited to the temporal lobes in our study, correlation of dysfunction in other brain regions with depression symptoms cannot be determined; involvement of other components of the limbic-frontal-subcortical network in temporal lobe epilepsy remains a plausible hypothesis.
glucose metabolism with symptoms of depression. Alternatively, NAA synthesis is dependent on mitochondrial enzymes, including l-aspartate N-acetyltransferase, and coenzyme A, which may be more sensitive to clinically significant limbic dysfunction in temporal lobe epilepsy than is glucose-dependent basal energy maintenance. It should be recognized that postictal effects of seizures and chronic effects of antiepileptic drugs could confound the results of imaging of metabolic variables in epilepsy patients.

Previous investigations suggest that increased Cr/NAA ratios in temporal lobe epilepsy are not due solely to cell loss in the hippocampus. Atrophy is an unlikely explanation of our findings because we evaluated the extent of abnormal Cr/NAA ratios in voxels within the hippocampi. Decreased NAA is associated with cerebral regions of interictal spiking and seizure onset, which in combination with our results suggests the plausible hypothesis that depression symptoms in temporal lobe epilepsy may be due to the influence of hyperexcitable hippocampal neurons on the limbic network.

The role of the hippocampus in depression is not clearly defined, although recent investigations have identified hippocampal abnormalities. Hippocampal volumes are found in most studies to be smaller in neurologically normal patients with a history of depression compared to euthymic controls. Results of functional imaging studies, predominantly FDG-PET, are less consistent in the hippocampus during major depressive episodes, but the hippocampus has been less thoroughly investigated than the amygdala and ventromedial frontal cortex. Putative mechanisms of injury include chronic exposure to cellular stressors, including corticotropin-releasing factor and cortisol. An investigation of 17 patients receiving long-term corticosteroid therapy found abnormal Cr/NAA ratios in the medial temporal region as well as greater depression rating scores vs normal controls; these findings suggest that chronic exposure to elevated corticosteroid levels could induce dysfunction in limbic structures and subsequent depression. Additional data are necessary to more fully understand the role of the hippocampus in the genesis and maintenance of clinical depression, especially in specific neurologic disorders such as epilepsy.

References


Reversible Kernohan notch

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A 55-year-old patient experienced episodic headaches, left facial twitching, and increasing falls over 2 years. Multiple yearly brain MRs (figure 1, top panels) revealed a large right frontal arachnoid cyst with evolving contralateral brainstem notching against the left tentorium1,2 (tentorial arrows, figure 1, top panels). The lesion was marsupialized into the Sylvian fissure. Histology confirmed an arachnoid cyst (figure 2). Postoperatively, the patient’s symptoms abated, remaining asymptomatic after 1 year. MRI follow-up at 7 months demonstrated mild residual left peduncle gliosis with resolution of the Kernohan notch (figure 1, bottom panels).

Figure 1. Preoperative (upper) and postoperative (lower) images document chronic reversible Kernohan notch brainstem compression.

Figure 2. Histology confirmed an arachnoid cyst.

Disclosure: The authors report no conflicts of interest.

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Reversible Kernohan notch
Neurology 2007;68:368
DOI 10.1212/01.wnl.0000248190.45078.e6

This information is current as of January 29, 2007

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