Neuroimaging in Affective Comorbidities of Epilepsy

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Frank Gilliam, MD, MPH
Professor of Neurology and Neurosurgery
Penn State University
Disclosure

Name of Commercial Interest | Type of Financial Relationship
-----------------------------|-----------------------------
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American Epilepsy Society | 2013 Annual Meeting
Learning Objectives

• To understand the structural and functional imaging of emotional dysfunction and depression in temporal lobe epilepsy.
“The specialties of *clinical neurology* and *psychiatry* and *neurosurgery* should always be considered parts of a functional whole.”

Wilder Penfield, *No Man Alone* (autobiography), 1976
Association of serotonin transporter promoter (5-HTTLPR) and intron 2 (VNTR-2) polymorphisms with treatment response in temporal lobe epilepsy

Hecimovic Hrvoje\textsuperscript{a,*,} Stefulj Jasminka\textsuperscript{b}, Cicin-Sain Lipa\textsuperscript{b}, Demarin Vida\textsuperscript{a}, Jernej Branimir\textsuperscript{b,1}

Depression + AED Toxicity ➔ Health Status

NDDI-E
Adverse Events Profile

## Epilepsy, Affective Disorder, and Suicide

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Epilepsy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2.4 (2.0-2.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Epilepsy +</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective Disorder</td>
<td>32.0 (20.8-49.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>11.4 (4.16-31.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>12.5 (8.05-22.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Review Article:
The Molecular Neurobiology of Depression

## Depression and Epilepsy: Neuroimaging Studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>FINDINGS</th>
</tr>
</thead>
</table>
| Bromfield et al, 1990                | • ↓ $^{18}$FDG-PET  
  • Inferior frontal                     |
| Victroff, 1994                       | • ↓ $^{18}$FDG-PET  
  • Left temporal                           |
| Quiske et al, 2000                   | • Structural MRI  
  • Hippocampus atrophy                     |
| Giovacchini et al, 2005              | • ↓ 5-HT1A ($^{11}$C-WAY) PET  
  • Hippocampus                              |
| Savic et al, 2004                    | • ↓ 5-HT1A ($^{11}$C-WAY) PET  
  • Cingulate Gyrus                         |
5-HT$_{1A}$ Receptors Are Reduced in Temporal Lobe Epilepsy After Partial-Volume Correction

Serotonin Binding and BDI in TLE: MPPF BP

Lothe et al. *Brain*, 2008
FDG-PET and Depression in Epilepsy

NINDS Grants NS01794, NS40808, and NS047551

Gilliam et al. *Epilepsia* 45(s2):28-33, 2004
$^1$H-MR Spectroscopy and Depression in TLE

Spearman rho = 0.65, p<0.001  Gilliam et al. Neurology 68:364-368, 2007
<table>
<thead>
<tr>
<th>Variables</th>
<th>Spearman rho</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1)H-MRSI</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of epilepsy</td>
<td>0.17</td>
<td>0.37</td>
</tr>
<tr>
<td>Work/driving/social scale(^*)</td>
<td>−0.23</td>
<td>0.22</td>
</tr>
<tr>
<td>GTC seizure rate</td>
<td>−0.05</td>
<td>0.23</td>
</tr>
<tr>
<td>Gender</td>
<td>−0.17</td>
<td>0.37</td>
</tr>
<tr>
<td>Complex partial seizure rate</td>
<td>−0.12</td>
<td>0.52</td>
</tr>
<tr>
<td>No. of antiepileptic drugs</td>
<td>−0.11</td>
<td>0.57</td>
</tr>
</tbody>
</table>

MRS and Depth Electrode Findings in Temporal Lobe Epilepsy

Interictal Spike Frequency and H-MRSI-Measured NAA/Cr

Increased Hippocampal Glutamate/Creatine Contributes to Depression in Epilepsy

Kindling in Rats Leads to Persistent Depressive Behavior

For centuries the functional significance of the hippocampus has remained unknown. The hippocampus is by no means a vestigial structure; it may vary greatly in development in different persons. Retzius, commenting on this, stated that the varied development of the hippocampus is independent of age, sex or special prominence of any known psychic function. Ferrier was the first to test the matter experimentally. He destroyed the hippocampus in monkeys and described the depressive effect it produced on cutaneous sensibilities. He expressed the belief that it is the center for these sensibilities. What

leaving the functions of the hippocampus in obscurity

Subsequent observations have placed the zone of cutaneous sensibility in the parietal lobe, leaving the functions of the hippocampus in obscurity.

Since the Negri bodies, the essential lesions of rabies, or hydrophobia, have their site of predilection in the hippocampus and the cerebellum, this area of the brain was studied in many cases due to the probable location of the emotive mechanism. The prodromal symptoms—insomnia, irritability and restlessness—usher in the stage of excitement and profound emotional perturbation. There is extreme

intense emotional, convulsive, and paralytic symptoms

Archives of Neurology and Psychiatry. 38: 725-734, 1937.
Papez’ Circuit of Emotion

Papez JW. Archives of Neurology and Psychiatry. 38: 725-734, 1937
Deep brain stimulation for treatment-resistant depression

Mayberg HS et al. Neuron 45(5):651-60, 2005
BA 25 and Hippocampal Connextions: Cingulate Bundle and Uncinate Fasciculus

Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (*Macaca fascicularis*)

R. Insauti and M. Muñoz
Human Neuroanatomy Laboratory, Department of Health Sciences, University of Castilla-La Mancha, School of Medicine, Benjamin Palencia Building, Campus Universitario s/n, 02071 Albacete, Spain
Functional Connectivity of the Hippocampus and Anterior Prefrontal Regions Predict Depression in TLE

Kemmotsu et al. Epilepsy and Behavior. 29(3):552-9, 2013
Orbitofrontal Cortex Thickening in Depression and TLE

Hyperexcitable Hippocampal Effects on BA 25 in Temporal Lobe Epilepsy?
What About H.M.; did he have depression?
LOSS OF RECENT MEMORY AFTER BILATERAL HIPPOCAMPAL LESIONS

BY

WILLIAM BEECHER SCOVILLE and BRENDA MILNER

From the Department of Neurosurgery, Hartford Hospital, and the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute, Canada
“whose cheerful placidity does not differ from his preoperative status”
Hippocampal injury modulates depressive symptoms in TLE

Hecimovic, submitted
Future Directions

• Repeated Imaging in Prospective Cohort Studies
• Multimodality Imaging in Single Cohorts
• Imaging of Treatment Response
Impact on Clinical Care and Practice

• Affective Disorders and Depression are common in epilepsy and associate with poor QOL and suicide.

• Neuroimaging research offers the opportunity to better understand the role of brain dysfunction in epilepsy and depression.

• Neuroimaging studies suggest that hyperexcitability of the hippocampal-BA 25 – Insular axis is associated with depression in temporal lobe epilepsy, and may explain why surgical removal of the hippocampus can improve depression in this syndrome.
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