Connectivity by MR spectroscopic imaging
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American Epilepsy Society | Annual Meeting
Disclosure

Name of Commercial Interest: None

Type of Financial Relationship: None
Learning Objectives

• Correlation analyses of using MR spectroscopic imaging of bioenergetics and metabolism in MTLE show many limbic regions to be metabolically correlated

• Stimulator therapies are likely to be partially effective through modulating network activity
Collaborators and acknowledgements

- HP Hetherington
- R Kuzniecky
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- A Cohen-Gadol
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- N Avdievich

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  - R01-EB009871

- Swebilius Foundation Trust
Functional connectivity in epilepsy

• No surprise! Epilepsy is a network disorder
  – Seizure propagation network that can include abnormal and/or normal paths

• The notion of a stereotyped seizure event, i.e., a consistently propagated path— is important:
  – Semiology important for identification and planning resection
  – Brain stimulator devices: SANTE
  – Multiple subpial transections

• Can we more systematically make use of the network nature of epilepsy?
  – Defining the network is challenging: highly dependent on methodology
  – Consistency of network between patients and within a patient
There are many ways to define connectivity in the human brain

- Structurally: diffusion tractography MRI (not the same as diffusion weighted) attempts to define what physically connects $A \leftrightarrow B$
- Physiologically: uses correlation statistics to identify regions which are linked in slow (~once/10sec) moment-to-moment changes in blood flow, volume and metabolism—*not task dependent*
  - Pivots on neurovascular coupling
  - fluctuations of the gradient echo signal
  - fluctuations of the perfusion signal
- Metabolically: Correlation analyses performed with metabolic data from multiple loci
Metabolic dysfunction by FDG PET in epilepsy: a sampling of the literature

- Dlugos 1999: Hilar cell numbers correlated significantly with thalamic and basal ganglia FDG uptake (... not hippocampal FDG uptake)
- Benedek 2004: Thalamic FDG uptake is decreased in MTLE children-young adults
- Mazzuca 2011: Epileptic encephalopathy shows many regions of abnormality on FDG PET: bilateral temporal-parietal; orbito-frontal cortices
- → Significant interest to take such approaches to define connectivity in epilepsy
$^{31}$P spectroscopic imaging

- Direct measures of ATP, phosphocreatine (PCr), inorganic phosphate (Pi)
- A dynamic equilibrium between high energy phosphate production and consumption
- pH changes
  - Laxer 1992
- Bioenergetic impairment
  - Kuzniecky 1992
- Could be temporally varying: seizure-dependent
- Effective voxel size of the study is ~10cc

\[
\text{PCr} + \text{ADP} \leftrightarrow \text{ATP} + \text{Cr} \\
K_{eq} = (\text{PCr}/\text{ATP}) \times (\text{ADP}/\text{Cr})
\]
\( ^{31}\text{P} \) MRSI and Excitability

Compare pre-surgical in vivo hippocampal \( ^{31}\text{P} \) MRSI data with electrophysiology:

Membrane repolarization is slowed with decreased PCr/ATP

Inappropriate spiking is increased with decreased PCr/ATP

Williamson Brain  2005
$^{31}$P spectroscopic imaging in epilepsy

- N= 22 MTLE patients: Ipsilateral hippocampus significantly low compared to control ($P < 0.02$)
- More subtle changes seen in thalamus and striate

<table>
<thead>
<tr>
<th></th>
<th>Hip Amy</th>
<th>Hip Pes</th>
<th>Hip Body</th>
<th>Thal</th>
<th>Striatum</th>
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<tbody>
<tr>
<td>Ipsi</td>
<td>0.84±0.14*</td>
<td>0.87±0.10*</td>
<td>0.92±0.08*</td>
<td>0.90±0.09</td>
<td>0.77±0.13</td>
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<tr>
<td>Contra</td>
<td>0.86±0.20</td>
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<td>0.95±0.10</td>
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<td>Control</td>
<td>0.97±0.15*</td>
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<td>0.98±0.11*</td>
<td>0.96±0.10</td>
<td>0.83±0.13</td>
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</table>

*Pan Acta Neurol Scand. 2005*
Bioenergetic changes

- In spite of no significant group decrement in subcortical nuclei, downstream structures are metabolically correlated.
- The “downstream” (thalamus, basal ganglia) metabolic values correlate with gliotic pathology in the ipsilateral hippocampus.
Network correlations

• Ipsi hippocampus energetically *not* very well correlated
• But ipsi hippocampus does correlate with pathology
• Ipsi thalamus energetically *is* well correlated
• → A downstream network which is metabolically coherent

Pan, Acta Neurol Scand. 2005
Thus far: bioenergetics and MRSI in epilepsy

- **31P**: bioenergetic correlations in limbic system in MTLE
  - Volume size brings in substantial partial volume effect
- **1H MR spectroscopic measurements**: more sensitive and therefore smaller volume size
- **1H MR spectroscopic data**: informative on mitochondrial function
  - NAA synthesized in neuronal mitochondria (Goldstein JBC 1969)
- **Oxidative stress and mitochondrial dysfunction** are both a consequence and a cause of epileptic seizures.
  - Patel Free Rad Biol Med 2004
Healthy brain: there ought to be a relationship between high energy phosphates and NAA, Cr

There are inter-individual differences in NAA, Cr and high energy phosphates
Healthy brain: NAA concentrations positively correlate with ADP

- NAA responds to cellular energetic state
- Consider NAA similar to ATP synthesis rate, also under regulation by ADP

Pan Ann Neurology 2005
NAA and Epilepsy

Contralateral vs. Ipsilateral

P<0.05 highlighted
The meaning of hippocampal NAA/Cr

- Intracranial EEG measures of total power in MTLE relate significantly with NAA/Cr—but not in non-MTLE (presumably neocortical patients)

Pan, Epilepsy Res. 2009;
Encyclopedia Epilepsy Res 2010
The meaning of hippocampal NAA/Cr

- NAA/Cr values significantly correlate with the relevant SRT score - verbal (dominant) and visuomotor (non-dominant) based on hemispheric dominance (WADA)

Pan, Epilepsy Res. 2009;
Encyclopedia Epilepsy Res 2010
MR spectroscopic imaging of NAA/Cr in the limbic system: medial temporal lobe, thalamus and putamen
Networks of Neuronal Injury in TLE (correlations of NAA decrements)

Using a pairwise correlation approach, the ipsilateral hippocampus links well with many other limbic loci.
<table>
<thead>
<tr>
<th>Hippocampus</th>
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<th>3</th>
<th>4</th>
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<tr>
<td>Mean</td>
<td>1.26</td>
<td>1.34</td>
<td>1.31</td>
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<tr>
<td>SD</td>
<td>0.12</td>
<td>0.21</td>
<td>0.23</td>
<td>0.21</td>
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<tr>
<td>Patients, ipsi</td>
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</tr>
<tr>
<td>Mean</td>
<td>1.09</td>
<td>1.10</td>
<td>1.12</td>
<td>0.92</td>
</tr>
<tr>
<td>SD</td>
<td>0.21</td>
<td>0.16</td>
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<td>0.21</td>
</tr>
<tr>
<td>% change</td>
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<td>-18%</td>
<td>-14%</td>
<td>-25%</td>
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<td>p-value&lt;</td>
<td>0.001</td>
<td>0.001</td>
<td>0.014</td>
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<tr>
<td>Patients, contra</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.16</td>
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Hetherington Neurology 2007
### Hippocampal, thalamic, basal ganglia, insula

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<th>Thalamus</th>
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<tr>
<td>Mean</td>
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<td>1.29</td>
<td>1.61</td>
<td>1.43</td>
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<tr>
<td>SD</td>
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<td>0.18</td>
<td>0.21</td>
<td>0.26</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Patients, ipsi</strong></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>1.232</td>
<td>1.17</td>
<td>1.465</td>
<td>1.284</td>
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<td>0.2</td>
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<td>-9%</td>
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<td>p-value</td>
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<td>0.009</td>
<td>0.011</td>
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<td><strong>Patients, contra</strong></td>
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<tr>
<td>Mean</td>
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<td>0.165</td>
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<tr>
<td>% change</td>
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<td>-7%</td>
<td>-8%</td>
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<td>-15%</td>
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<tr>
<td>p-value</td>
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<td>0.351</td>
<td>0.026</td>
<td>0.068</td>
<td>0.250</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Hetherington Neurology 2007*
A plethora of data

• Many loci! we would hypothesize that somehow they are linked by both normal and/or epileptic networks

• As the networks of the resting brain have been detected from by ongoing fluctuations in BOLD and perfusion signal – neurovascular coupling – this suggests that such networks may also be seen with metabolic function

• → correlated NAA/Cr values across the network loci (more than two at a time)
Multivariate statistics

• Many limbic loci are potentially inter-dependent
• Pairwise correlations
  – A priori selection of two loci: applies a bias as to which loci are the most pertinent
  – Multiple pairwise correlations do not address how the loci are networked
• Multivariate analysis
  – Several different types of statistical analyses are possible
  – In this approach we define how the loci are correlated: a common factor analysis
Metabolic subcortical network: a common factor analysis

- Factor 1
  - Control and MTLE: co-variance of thalami
  - MTLE: some co-variance with the ipsilateral anterior hippocampus

Pan ISMRM 2009
Metabolic subcortical network: a common factor analysis

Factor 2
- control: dominant subcortical covariance
- MTLE: strong covariance of the ipsilateral insula, bilateral basal ganglia

Pan ISMRM 2009
Can the presence (or absence) of a metabolic limbic MTL network be useful?

- Linear discriminant analysis with the “pre-classified” MTLE and control groups: assess “unknown” neocortical epilepsy
  - Limbic loci: coherent metabolic network
  - n=12, w intracranial monitoring

- 2x2 contingency table
  - 6 with non-temporal involvement correctly classified as not showing MTLE
  - 4 patients with MTLE involvement correctly classified
  - 1 of 5: surgical MTLE but not metabolic MTLE—had AMTL surgery—pathology negative for HS
  - 1 of 5: metabolic MTLE but not surgical MTLE—did not undergo resection for cognitive function

<table>
<thead>
<tr>
<th>Prediction Group</th>
<th>MRSI +limbic</th>
<th>MRSI -limbic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned/completed surgery MTLE ± neocortical resection</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Planned/completed surgery neocortical resection only</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

P<0.05, Fisher exact test
Metabolic networks in epilepsy

• In MTLE
  – Ipsi hippocampus most metabolically abnormal
  – ipsi thal correlates with multiple subcortical loci, hippocampal gliosis
  – The downstream network can be more metabolically/energetically consistent than the seizure onset zone itself

• Multivariate analysis of subcortical loci
  – Controls: bilateral thal (ant, post) metabolically co-vary
  – MTLE: bilateral thal co-vary, also with anterior ipsi hippocampus
  – MTLE: co-variance between downstream loci: bilateral basal ganglia and ipsi insula
  – Potentially useful for detecting MTLE

• The thalamic network is very identifiable: likely to be modified with electrical stimulation, e.g., SANTE
Pt CA: 27yo RHF h/o sz onset age 2yo; Aura “woosh” sensation in head, LUE tingling sensation, then stiff elevation to flex over head, head to R, L arm clonic, hears but can't respond.
PET: L temp hypo
SPECT: L temp hypo
Developmentally normal.
Npsych: “bifr-temp dysfunction”
Frontal networks in neocortical epilepsy

S/p RmF resection; pathology dysplasia + balloon cells. Now 2.5y seizure free