Temporal Changes in the Structural and Functional Networks of Epilepsy

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Disclosure

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• Clinical Trials
  • Neurelis: Diaz.001.04 (Sub-I)
  • Neurelis: Diaz.001.05 (Sub-I)
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  • UCB Biosciences: EP0012 (Sub-I)
  • Sage Therapeutics: 547-SSE-301 (Sub-I)
A Diagnosis is Made
Seizure Freedom is not Achieved
Intractable Epilepsy
Outline and Objectives

1. Outline the typical clinical history of intractable epilepsy
2. Identify neuroimaging techniques used to assess pathological changes caused by epilepsy
3. Identify brain regions typically involved in the pathology of temporal lobe epilepsy (TLE)
4. Understand the role of structural and functional MRI in characterizing pathologic changes caused by epilepsy over time
Intractable Temporal Lobe Epilepsy

1. Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy in the adult population
2. At least 1/3 of TLE patients have intractable seizures
3. Uncontrolled seizures have a huge socioeconomic impact, with very significant morbidity, mortality, and financial and societal cost
4. While much of the impetus in intractable epilepsy research has been towards understanding and preventing epileptic seizures, specifically targeting the seizure onset area, uncontrolled seizures appear to have a much wider and deleterious effect on the brain
Spread of Temporal Lobe Seizures

Seizures in TLE spread well beyond the hippocampal region:

Hogan et al., 2006
Neuroimaging in the Study of Epilepsy

Neuroimaging is an integral part of assessing epilepsy:

1. Identify the etiology
2. Identify seizure zone
3. Parse out different epilepsy types/syndromes
4. Corroborate electrographic findings
Neuroimaging in the Study of Epilepsy

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5. Track disease progression?
   -> Seek a biomarker?
The Clinical History of Intractable Epilepsy

Epilepsy’s typical time course:

TIME

Seizure
The Clinical History of Intractable Epilepsy

Epilepsy’s typical time course:

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Seizure
Intractable Temporal Lobe Epilepsy

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TLE Ictal Onset Zone: The Hippocampus

Duvernoy, Cattin, Risold, 2013, The Human Hippocampus
MTS and Atrophy
The Hippocampus as a Closed Bounded Mesh

Hogan et al., 2004
Maccotta et al., 2015
MRI-negative TLE shows Significant Hippocampal Shape Abnormalities

Maccotta et al., 2015
MRI- vs. MRI+ TLE - Effect on Hippocampal Shape

Maccotta et al., 2015

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SCHOOL OF MEDICINE
Selective Temporal Effect on Hippocampal Atrophy

Maccotta et al., 2015
Selective Temporal Effect on Hippocampal Atrophy

Effect of Disease

Effect of Disease Duration
Selective Temporal Effect on Hippocampal Atrophy

Bernhardt et al., 2013
What about past the ictal onset zone?
Epilepsy as a Network Disease

- Is epilepsy a disease of **networks**?

- What does this mean? Many potential meanings:
  - A disease process that affects a region connected to a network of brain regions and as a result causes changes in other regions in the network
  - A disease process that changes the way different brain regions are connected
  - A disease process that results from, or whose main manifestation is a product of a change in the connections between brain regions
Epilepsy as a Network Disease

NORMAL
Epilepsy as a Network Disease
Epilepsy as a Network Disease

NORMAL
Epilepsy as a Network Disease
Epilepsy as a Network Disease
Epilepsy as a Network Disease
Epilepsy as a Network Disease

NORMAL
Epilepsy as a Network Disease
TLE leads to cortical thinning in extratemporal regions

Bernhardt et al., 2010
TLE leads to cortical thinning in extratemporal regions

Bernhardt et al., 2010
Cortical Thickness Effects of FCD Types by Disease Duration

FCD type-I vs controls
A. Short disease duration

FCD type-II vs controls

Ipsilateral Contralateral Ipsilateral Contralateral

Hong et al., 2016
Cortical Thickness Effects of FCD Types by Disease Duration

B. Long disease duration

Hong et al., 2016
Structural MRI can Track Temporal Effects of Epilepsy

- Structural MRI is able to detect fine pathologic changes caused by epilepsy that reflect disease duration and burden in cross-sectional studies.
- **Longitudinal** studies of epilepsy using structural MRI are further capturing the temporal component of the disease, but they are few and far between, and none with more than 2 timepoints.
- Structural MRI appears to have a use in separating different epilepsy syndromes and subtypes, hinting at the underlying pathophysiology.
- Structural MRI captures changes both within the ictal onset zone and outside of it, broadening our perspective of the effects of epilepsy on the brain as a whole.
Functional MRI
Functional MRI in TLE

Predicts Post Surgical change in Scene Memory Adequacy not Reserve

Rabin et al Brain 2004
Functional MRI in TLE

Functional MRI lateralization of memory in temporal lobe epilepsy

J.A. Detre, MD; L. Maccotta, BS; D. King, MD; D.C. Alsop, PhD; G. Glosset, PhD; M. D’Esposito, MD; E. Zarahn, BS; G.K. Aguirre, AB; and J.A. French, MD
Epilepsy as a Network Disease

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**Functional Connectivity**

REGION 1

REGION 2

\[ AVERAGE\ REGION\ 1\ TIME\ SERIES \]

\[ AVERAGE\ REGION\ 2\ TIME\ SERIES \]

\[ \rho \ (correlation) \]
The Correlogram

Raichle et al., 2011
Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

Andrew Ekstrom1,2, Thomas E. Nichols1,3, and Hans Knösing2


Edited by Emily N. Brown, Massachusetts General Hospital, Boston, MA, and approved April 17, 2011 (received for review February 10, 2010)

The most widely used functiontional magnetic resonance imaging (fMRI) analysis uses parametric statistical methods that depend on a variety of assumptions, in the most recent, we use real resting-state data and a total of 1.3 million random task group analyses to compute empirical significance maps using the FWE criteria. This is a powerful software package, SPM, FSL, and AFNI, as well as nonparametric permutation methods. In a novel, hypothetical situation in which 5% of the parameter statistical methods are shown to be conservative for fMRI inferences and model for electroencephalogram, our results suggest that the principal source of the usual cluster inferences is spatial autocorrelation functions that do not follow the assumed Gaussian distribution. By comparison, the nonparametric permutation test is found to produce smaller effects, as well as heteroskeleteral inferences. These findings speak to the need of validating the statistical methods being used in the field of neuroimaging.

Commentary on the article and a discussion thread can be found here.

Introduction

The fact that 20 years ago, functional magnetic resonance imaging (fMRI) has become a popular tool for studying the human brain, with some 4,000 published papers according to PubMed. Despite the popularity of fMRI as a tool for studying brain function, the statistical methods used have rarely been validated using real data. Validations have instead merely been performed using simulated data (3), but it is obvious that even very simple statistical tools can be misinterpreted when used on real data, coming from a living human subject, in an MRI scanner.

The introduction of modern data-sharing initiatives in the neuroimaging field (e.g., 18) it has become possible to evaluate the statistical methods using real data. Arp et al. (11), for example, used freely available anatomical images from 36 healthy controls to investigate the validity of parametric statistical methods for voxel-based morphometry (VBM) (12), Silver et al. (13) evaluated task images and genotypes data from 102 subjects in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (14, 15) to evaluate statistical methods in computer imaging. Another example of the use of open data is our previous work (16) where a total of 1,950 control subjects from the 1,000 Functional Connectomes Project (16) were used as null data for task-based single-subject (17) fMRI analyses with the SPM software. This work found a high degree of false positives, up to 78%, compared with the expected 5%. This is due to a simplistic material and statistical model in SPM. It is, however, not clear whether these problems would propagate to group studies. Another unresolved question was the statistical validity of other

Results

A total of 2,890,000 random group analyses were performed to compute the expected false-positive rates of SPM, FSL, and AFNI, these complete 100 simulated studies analyzed for 10 parameter combinations, three thresholding approaches, and

Significance

Functional MRI (fMRI) is 20 years old, yet surprisingly its most common statistical methods have not been validated using real data. Thus, we used simulated fMRI data from 485 healthy controls to compute 10,000 group task analyses. Using this null data with different experimental designs, we evaluated the incidence of significant results. In testing, we should find 5% false positives for a significance threshold of 5%. However, we find that the most common software packages for fMRI analysis (SPM, FSL, AFNI) can result in false-positive rates of up to 78%. These results question the validity of a number of fMRI studies and may have a large impact on the interpretation of numerous significant neuroimaging results.

http://www.arstechnica.com, 7/1/2016
Fig. 1. Results for one-sample t test, showing estimated FWE rates for (A) Beijing and (B) Cambridge data analyzed with 6 mm of smoothing and four different activity paradigms (B1, B2, E1, and E2), for SPM, FSL, AFNI, and a permutation test. These results are for a group size of 20. The estimated FWE rates are simply the number of analyses with any significant group activation divided by the number of analyses (1,000). From Left to Right: Cluster inference using a cluster-defining threshold (CDT) of $P = 0.01$ and a FWE-corrected threshold of $P = 0.05$, cluster inference using a CDT of $P = 0.001$ and a FWE-corrected threshold of $P = 0.05$, and voxel inference using a FWE-corrected threshold of $P = 0.05$. Note that the default CDT is $P = 0.001$ in SPM and $P = 0.01$ in FSL (AFNI does not have a default setting).

Eklund et al., 2016, PNAS
1. Epilepsy results in an overall **disintegration** of brain networks
Decreased Connectivity in Generalized Epilepsy

Song et al., 2011
1. Epilepsy results in an overall *disintegration* of brain networks

2. The **default mode network** is commonly affected
A default mode of brain function

1. Epilepsy results in an overall *disintegration* of brain networks

2. The *default mode network* is commonly affected

3. Network changes reflect *epilepsy type*
Connectivity is Selectively Increased Near the Ictal Focus

Maccotta et al., 2013
Epilepsy’s typical time course:
Epilepsy Continuum

Seizures/Year

Year

Epilepsy Continuum

Seizures/Year

Year


Epilepsy Surgery
Resting State Networks and Surgical Extent
Seizure Freedom Effect on Resting State Networks

A. Healthy
Seizure Freedom Effect on Resting State Networks

A. Healthy

B. TLE Preoperative
Seizure Freedom Effect on Resting State Networks

A. Healthy

B. TLE Preoperative

C. TLE Postoperative
Seizure Freedom Effect on Resting State Networks

D. TLE Preop - Healthy
Seizure Freedom Effect on Resting State Networks

D. TLE Preop - Healthy

E. TLE Postop - TLE Preop
Seizure Freedom Effect on Resting State Networks

TLE Preop vs. Healthy

Uncorrected Welch t-test
Seizure Freedom Effect on Resting State Networks

Uncorrected Welch t-test

TLE Preop vs. Healthy

TLE Postop vs. TLE Preop
Seizure Freedom Effect on Resting State Networks
Seizure Freedom Effect on Resting State Networks
Seizure Freedom Effect on Resting State Networks
Seizure Freedom Effect on Resting State Networks

- Healthy
- TLE Preoperative
- TLE Postoperative
TLE Connectivity Changes Are “Burned In” After Years of Disease
Epilepsy Continuum

Seizures/Year

Year

Total Seizures To Date

Epilepsy Surgery
Catching it Early

Functional and Structural Network Changes in Early Epilepsy

• NIH-funded, prospective, longitudinal study
  • Patients who are within 1 year of the first seizure of life
  • Study design:
    • 1st MRI at enrollment (structural and resting state functional sequences
    • Followed every 3 months in terms of seizures, AEDs, and relevant clinical history (EEG, etc.)
    • 2nd MRI after 2 years
Catching it Early

Seizures/Year

MRI

Total Seizures To Date

MRI

Year

Catching it Early

We want your patients! (we will be nice)

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Longitudinal Studies Are ... Hard

- Cross-sectional studies cannot do full justices to the temporal changes wrought by epilepsy or many other neurologic diseases
- Longitudinal studies are challenging
  - There are no good funding mechanisms for reasonably long longitudinal studies
  - Patients drop out
  - Scanners get upgraded ($#%#%)
  - Staff changes
- But they are a crucial part of understanding a disease such as intractable epilepsy that is actively smoldering along throughout a patient’s lifetime
Functional MRI can Track Temporal Effects of Epilepsy

- Functional MRI has the potential to track temporal effects of epilepsy, especially if pursued via longitudinal studies.
- Very few longitudinal fMRI studies exist in any discipline.
- “You can’t always trust fMRI”: Functional connectivity MRI is a noisy technique that requires lots of data, but with the appropriate strict artifact rejection it can provide quite stable data.
- Despite that caveat fMRI can capture a state of the brain that is different and complementary to structural MRI.
MRI as a Disease Biomarker

- Epilepsy is a paroxysmal disease that is hard to track using seizures counts alone.
- Structural and functional MRI have the potential to be used as a biomarker to track effects of treatment.
- They further provide a testable model of disease progression.
- In combination, they may provide even greater insight into the pathophysiology and progression of the disease.
FIG. 4. Individual-subject statistical activation maps for BOLD signal differences between RIGHT and LEFT trials. Atlas-transformed maps of activation are displayed for each subject as a horizontal section overlaid on the subject's corresponding structural image. Each section was chosen to be closest to the individual subject's peaks of activation in right and left motor cortex. Statistical significance is indicated as in the legend of Fig. 2 by the color range of the regions of activation (ranging from $P < 0.001$ to $P < 10^{-5}$). Task correlated activation in right and left motor cortex is found consistently in all 17 subjects, in addition to activation in SMA and cerebellum in many subjects. In the bottom right-hand corner of the figure, the panel labeled "GROUP" shows locations of the peaks of activation in right and left motor cortex for each subject overlaid on top of a group-averaged structural image (the superior-inferior coordinate for each peak was disregarded in this display).

Maccotta et al., 2001
1. Epilepsy adversely affects multiple brain regions, with an effect that preferentially affects specific brain regions.
2. Both structural and functional MRI can capture temporal effects of epilepsy on the human brain.
3. The adverse effect is both structural, leading to parenchymal loss, and functional, leading to abnormal connectivity (decreased or at times increased).
4. The adverse effect tracks disease burden and duration.
5. These changes have the potential to be used in predictive fashion when the disease is in its initial stages, and as a biomarker to assess disease progression and response to treatment.

Conclusions
Thank You

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