EPILEPSY CURRENTS

Current Literature
In Clinical Science

Functional Connectivity in Mesial Temporal Lobe Epilepsy: A Dynamic Concept

Patterns of Altered Functional Connectivity in Mesial Temporal Lobe Epilepsy.

Pittau F, Grova C, Moeller F, Dubeau F, Gotman J. *Epilepsia* 2012;53:1013–1023.

PURPOSE: In mesial temporal lobe epilepsy (MTLE) the epileptogenic area is confined to the mesial temporal lobe, but other cortical and subcortical areas are also affected and cognitive and psychiatric impairments are usually documented. Functional connectivity methods are based on the correlation of the blood oxygen level dependent (BOLD) signal between brain regions, which exhibit consistent and reproducible functional networks from resting state data. The aim of this study is to compare functional connectivity of patients with MTLE during the interictal period with healthy subjects. We hypothesize that patients show reduced functional connectivity compared to controls, the interest being to determine which regions show this reduction. METHODS: We selected electroencephalography-functional magnetic resonance imaging (EEG-fMRI) resting state data without EEG spikes from 16 patients with right and 7 patients with left MTLE. EEG-fMRI resting state data of 23 healthy subjects matched for age, sex, and manual preference were selected as controls. Four volumes of interest in the left and right amygdalae and hippocampi (LA, RA, LH, and RH) were manually segmented in the anatomic MRI of each subject. The averaged BOLD time course within each volume of interest was used to detect brain regions with BOLD signal correlated with it. Group differences between patients and controls were estimated. KEY FINDINGS: In patients with right MTLE, group difference functional connectivity maps (RMTLE - controls) showed for RA and RH decreased connectivity with the brain areas of the default mode network (DMN), the ventromesial limbic prefrontal regions, and contralateral mesial temporal structures; and for LA and LH, decreased connectivity with DMN and contralateral hippocampus. Additional decreased connectivity was found between LA and pons and between LH and ventromesial limbic prefrontal structures. In patients with left MTLE, functional connectivity maps (LMTLE - controls) showed for LA and LH decreased connectivity with DMN, contralateral hippocampus, and bilateral ventromesial limbic prefrontal regions; no change in connectivity was detected for RA; and for RH, there was decreased connectivity with DMN, bilateral ventromesial limbic prefrontal regions, and contralateral amygdala and hippocampus. SIGNIFICANCE: In unilateral MTLE, amygdala and hippocampus on the affected and to a lesser extent on the healthy side are less connected, and are also less connected with the dopaminergic mesolimbic and the DMNs. Changes in functional connectivity between mesial temporal lobe structures and these structures may explain cognitive and psychiatric impairments often found in patients with MTLE.

Commentary

Mesial temporal lobe epilepsy (m-TLE) is a network disease. Its manifestations extend beyond seizures that arise from a well-restricted and limited focus within the hippocampus to include a wide array of cognitive and psychiatric challenges. In patients with unilateral m-TLE, the most obvious explanation for such extensive disease implications relates to widespread structural cortical and subcortical abnormalities described within both temporal lobes and strategic extratemporal brain regions. Cortical atrophy is seen in the frontocentral, lateral temporal (mainly superior and middle temporal gyri), dorsal parietal, and mesiotemporal cortices bilaterally. Similarly, volume loss occurs in the ipsilateral mesial orbitofrontal cortex, cingulate, and thalamus in patients with drug-resistant unilateral TLE (1, 2). Many of these atrophied structures represent key components of the default mode network (DMN) (3) and the limbic network, together responsible for maintaining baseline brain activities related to cognition, self-awareness, episodic memory, and emotions. As such, it is not surprising that structural damage affecting critical components of these networks may disturb mood and cognitive function. "Space" is then a critical concept: With high-resolution *structural* brain imaging demonstrating, as detailed above, the extension of atrophy beyond the space of the hippocampus, we have expanded our appreciation of the space of the epilepsy to a network rather than an individual structure. Recent high-resolution *functional* neuroimaging studies using functional magnetic resonance imaging (f-MRI) or EEG-triggered f-MRI—including work by Pittau et al. chosen for this commentary—

Epilepsy Currents, Vol. 12, No. 6 (November/December) 2012 pp. 238–240

add yet another dimension to our understanding of a network: the dimension of "time." This concept of time as a key element of our appreciation of any network study may help explain some of the apparent discrepancies in the current literature on functional connectivity, mainly those pertaining to inconsistent characterization of the functional network components in different research studies, and can be appreciated in reviewing the following three main points:

First, brain structures that show increased connectivity in one research study may actually show reduced connectivity in another study, depending on the technique used because the results pertain to *timing* the measurement of this connectivity. Electrophysiological connectivity measures are obtained via intracranial recordings and, as such, rely on direct measurements of epileptiform EEG activity. These studies typically show *increased* electrical connectivity and synchronization among components of the mesial temporal epileptogenic network during both the ictal and interictal periods (4). However, functional connectivity measures obtained in the present paper by Pittau et al. and in other f-MRI studies (5) rely on assessing the blood oxygen level dependent (BOLD) signals and show *decreased* connectivity between the mesial temporal structures and other components of the same limbic network—including the posterior cingulate, precuneus, anterior mesial prefrontal cortex, superior frontal gyrus, and angular gyri bilaterally. How do we explain this apparent contradiction? Recognizing the limited temporal resolution of f-MRI may help. While EEG connectivity measures are a direct evaluation of electrical hypersynchronization among different components of the epileptogenic network, BOLD signal changes reflect the abnormal neurovascular coupling and the metabolic dysfunction thought to result from and temporally follow this hypersynchronization. The same structures may then appear hyperconnected electrically and hypoconnected functionally.

A second time-related dimension of connectivity may pertain to the frequency of the underlying electrical activity being evaluated. Recent work by Dalal et al. (6) suggested that cortical activities of different frequencies may activate different functional networks and that various sub-bands of high-frequency electrical activity across the 60–500 Hz range may, in fact, be specific for certain functional tasks. In this context, one can appreciate that both high-frequency gamma oscillations and slow cortical potentials (< 4 Hz) have been linked to BOLD fluctuations. Different functional networks may be activated depending on the firing frequency of a pacemaker, and different components of the same network may be activated depending, again, on the firing frequency of the structures involved. For example, in a recent study of the primary sensorimotor network, isometric contraction of the forearm showed dominant coupling within the β-band (13–30 Hz) between the primary motor cortex (M1) and the supplementary motor area (SMA), whereas fast repetitive finger movements were characterized by strong coupling within the γ-band (31–48 Hz), mainly seen in connections from lateral premotor cortex to SMA and M1 (7). All three structures—M1, SMA, and lateral premotor cortex—are components of the same sensorimotor network, yet they were activated to a different degree and connected differently in different motor tasks, with these variations in connectivity potentially gated by varying their underlying firing frequency. It is not entirely clear for patients with m-TLE whether similar variations in functional connectivity networks exist within the temporal lobe.

The last time-related connectivity concept is that pertaining to the timing of the functional connectivity measurement in relation to the duration of the epilepsy itself. While most resting state f-MRI studies, including the present paper by Pittau et al., have consistently shown reduced functional connectivity of the affected ipsilateral hippocampus in m-TLE (8–10), the state of connectivity of the contralateral hippocampus seems to vary among studies. In most cases, the contralateral hippocampus seems to show increased connectivity (both in strength and distribution) with other components of the limbic network, a finding that was speculated to account for compensatory cognitive mechanisms (5, 8, 10). In contrast, the paper at hand in this commentary showed reduced connectivity of the contralateral hippocampus. Work done by Morgan et al. may shed some light on this contradiction. In a study aiming to quantify cross-hippocampal connectivity using high temporal resolution f-MRI, investigators found that in the initial ten years of epilepsy, connectivity is highly variable and mostly disrupted between the two hippocampi. However, this interhemispheric hippocampal connectivity increases linearly with disease duration when epilepsy progresses beyond ten years (9). The practical implication of this observation is that some existing inconsistencies in the findings of f-MRI connectivity studies may be at least partly related to including patients of highly heterogeneous epilepsy duration, as is the case in the current report by Pittau et al. The mechanistic implication of this finding is that it supports the dynamic, time-dependent, nature of functional connectivity as an adaptive compensatory mechanism in chronic epilepsy.

In summary, our understanding of a network concept in epilepsy is still at its beginning. Elegant studies of resting state connectivity designed with an appreciation of both the spatial and temporal dynamic nature of functional networks are needed to advance this field.

by Lara E. Jehi, MD

References

1. Bernhardt BC, Bernasconi N, Kim H, Bernasconi A. Mapping thalamocortical network pathology in temporal lobe epilepsy. *Neurology* 2012;78:129–136.
2. McDonald CR, Hagler DJ, Jr, Ahmadi ME, Tecoma E, Iragui V, Gharapetian L, Dale AM, Halgren E. Regional neocortical thinning in mesial temporal lobe epilepsy. *Epilepsia* 2008;49:794–803.
3. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: Anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008;1124:1–38.
4. Guye M, Régis J, Tamura M, Wendling F, McGonigal A, Chauvel P, Bartolomei F. The role of corticothalamic coupling in human temporal lobe epilepsy. *Brain* 2006;129:1917–1928.
5. Bettus G, Guedj E, Joyeux F, Confort-Gouny S, Soulier E, Laguitton V, Cozzone PJ, Chauvel P, Ranjeva JP, Bartolomei F, Guye M. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. *Hum Brain Mapp* 2009;30:1580–1591.

6. Dalal SS, Vidal JR, Hamame CM, Ossandón T, Bertrand O, Lachaux JP, Jerbi K. Spanning the rich spectrum of the human brain: Slow waves to gamma and beyond. *Brain Struct Funct* 2011;216:77–84.
7. Herz DM, Christensen MS, Reck C, Florin E, Barbe MT, Stahlhut C, Pauls KA,Tittgemeyer M, Siebner HR, Timmermann L. Task-specific modulation of effective connectivity during two simple unimanual motor tasks: A 122-channel EEG study. *Neuroimage* 2012;59:3187–3193.
8. Pereira FR, Alessio A, Sercheli MS, Pedro T, Bilevicius E, Rondina JM, Ozelo HF, Castellano G, Covolan RJ, Damasceno BP, Cendes F. Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: Evidence from resting state fMRI. *BMC Neurosci* 2010;11:66.
9. Morgan VL, Rogers BP, Sonmezturk HH, Gore JC, Abou-Khalil B. Cross hippocampal influence in mesial temporal lobe epilepsy measured with high temporal resolution functional magnetic resonance imaging. *Epilepsia* 2011;52:1741–1749.
10. Zhang Z, Lu G, Zhong Y, Tan Q, Liao W, Wang Z, Wang Z, Li K, Chen H, Liu Y. Altered spontaneous neuronal activity of the default-mode network in mesial temporal lobe epilepsy. *Brain Res* 2010;1323:152–160.

American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the main contributing author, please check the box "no" and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 06/13/12

2. First Name Lara Last Name Jehi Degree MD

3. Are you the Main Assigned Author? ☒ Yes ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title: Functional Connectivity in Mesial Temporal Lobe Epilepsy: A Dynamic Concept

5. Journal Issue you are submitting for: 12.6

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	☒				
2. Consulting fee or honorarium	☒				
3. Support for travel to meetings for the study or other purposes	☒				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☒				
5. Payment for writing or reviewing the manuscript	☒				
6. Provision of writing assistance, medicines, equipment, or administrative support.	☒				
7. Other	☒				

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section #3 Relevant financial activities outside the submitted work.
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	☒				
2. Consultancy	☒				
3. Employment	☒				
4. Expert testimony	☒				
5. Grants/grants pending	☒				
6. Payment for lectures including service on speakers bureaus	☒				
7. Payment for manuscript preparation.	☒				
8. Patents (planned, pending or issued)	☒				
9. Royalties	☒				
10. Payment for development of educational presentations	☒				
11. Stock/stock options	☒				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	☒				
13. Other (err on the side of full disclosure)	☒				

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☒ No other relationships/conditions/circumstances that present a potential conflict of interest.
☐ Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
Epilepsy Currents Editorial Board