Vickie and Jack Farber Institute for Neuroscience
Jefferson Health®

OUTCOMES & RESEARCH: VOLUME 2

COGNITIVE FUNCTIONING
AND
THE LANGUAGE SYSTEM IN TEMPORAL LOBE EPILEPSY

A MESSAGE FROM THE CHAIR

Dear Colleagues,

Now is an exciting time at Thomas Jefferson University Hospital's Departments of Neurology and Neurosurgery and the Vickie and Jack Farber Institute for Neuroscience – Jefferson Health. I am pleased to share this brochure, which outlines some of the innovative work that we engaged in on many fronts for the treatment of epilepsy. Our clinicians and researchers are continuously looking at creative ways to treat neurologic disorders. One such technique, the use of dynamic network analysis tools, provides a new perspective on the reconfiguration of the language system in both a normative and language- deficient epilepsy population.

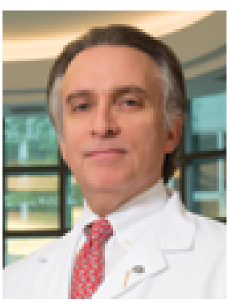
Joseph I. Tracy, PhD, Professor in the Departments of Neurology and Radiology and Director, Cognitive Neuroscience and Brain Mapping Laboratory, and Director, Clinical Neuropsychology Division, has contributed significant research in the area of epilepsy. His work focuses on functional and structural brain connectivity, with an emphasis on mapping in the brain key cognitive skills and behaviors, particularly as an aid to surgical planning and improving patient outcomes following clinical interventions, such as brain surgery. His findings help develop treatments that improve cognitive skills and, in particular, improve patient outcomes following brain surgery.

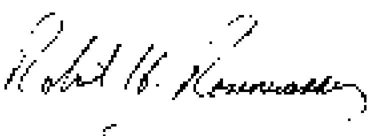
Research, such as that done on epilepsy, is the heart of the Vickie and Jack Farber Institute for Neuroscience, and it remains a crucial part of our mission. Each epilepsy-related department carries out basic, translational, and clinical research designed to understand fundamental mechanisms of the normal and diseased brain. Our specialists translate that understanding into treatments for our patients with epilepsy.

Jefferson Health's work on epilepsy is well-known, and Dr. Tracy has contributed significant research to the field, with many publications and epilepsy research on neurodegenerative and other devastating disorders. One of his research projects is illustrated in the following pages.

In the research highlighted, I believe you will find work on epilepsy that continues to improve patient lives.

Sincerely,





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Medical Director, Jefferson Neuroscience Network
Senior Vice President, Jefferson Enterprise Neuroscience

COGNITIVE FUNCTIONING AND THE LANGUAGE SYSTEM IN TEMPORAL LOBE EPILEPSY

Clinical Research on Epilepsy at Jefferson Health

Research into epilepsy under the direction of Joseph I. Tracy, PhD, focuses on functional and structural brain connectivity as measured by:

- Resting state functional connectivity
- Diffusion imaging and structural connectivity
- High-resolution anatomical MRI
- Task-based functional MRI

Applications to understanding and modeling the effects of seizures on cognitive networks are investigated, as well as the change and reorganization such networks undergo in response to treatment interventions. These consist of:

- Resective surgery
- Thermal ablation
- Brain electrical stimulation
- Neuroimaging correlates of seizure development and their cognitive impact

The Latest Treatments for Epilepsy

The Jefferson Comprehensive Epilepsy Center is one of the most experienced Centers for patients with epilepsy, performing 80 to 90 operations per year (more than all other area medical centers combined). Caring for patients who experience uncontrolled seizures is the work of our researchers, using the latest techniques in treatment, such as:

- Anterior temporal lobectomy
- Robotic Assisted Stereo EEG (since 2016)
- Laser Interstitial Thermal Ablation (since 2011)
- Responsive Neurostimulation (since 2008)
- Deep Brain Stimulation, both Asleep and Awake (since 2006)

Jefferson Health works with families and patients to offer diagnostic services to assess how epilepsy affects quality of life and to identify and treat cognitive or emotional difficulties. With appropriate treatment, about two-thirds of our patients are able to lead normal lives, including going to work or school and driving a car. We strive to help patients of all ages achieve freedom from seizures and offer medical treatment, care and counseling for pregnant women with epilepsy, including genetic and psychological counseling and, when required, surgery.

Ongoing Epilepsy Research

Epilepsy researchers at Jefferson Health regularly conduct MR scans that provide maps of brain structure and function utilized in pre-surgical planning, and during intraoperative neuronavigation in the surgical suite. Over 150 pre-surgical brain mapping studies are performed per year.

Using functional magnetic resource imaging and other MR techniques, such as functional connectivity and diffusion tensor imaging, Dr. Tracy and his colleagues utilize experimental cognitive and behavioral assessments to help patients. Some of their research includes but is not limited to:

- Language Lateralization and Cognitive Reorganization in Epilepsy
- Structural and Functional Connectivity in Epilepsy
- Memory Functioning in Epilepsy
- Prediction of Outcomes Following Epilepsy Surgery
- Cognitive Reorganization from Learning

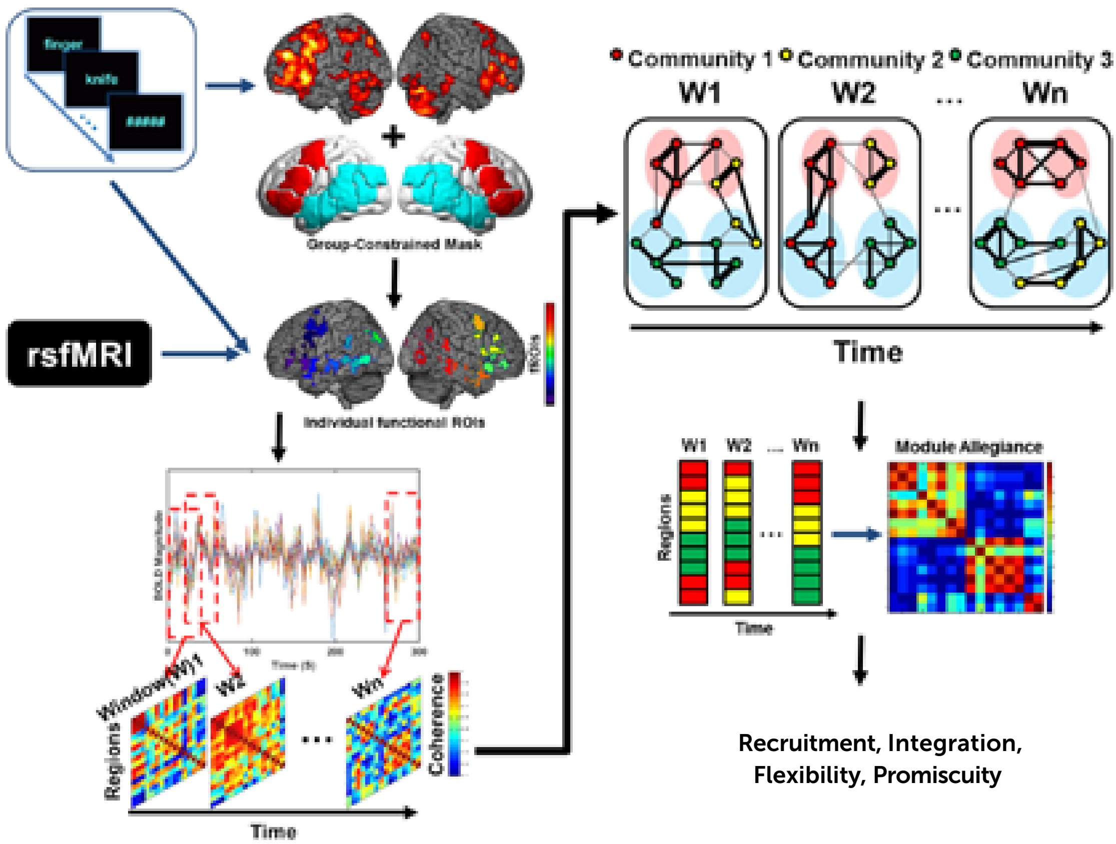

Figure 1. Schematic Overview of the Approach.

Sixteen language-related, group-constrained masks were used to define functional regions of interest by intersecting an individual's activation map with each mask and selecting the top 10% of the voxel. Most important, we partitioned the task into separate time windows, and looked for changes over time in the regional connections among brain regions. Such changes indicate that a particular area of the brain is changing "who it is communicating with" during the course of the task.

Source: Reproduced with permission Oxford University Press ©2018
Disrupted Dynamic Network Reconfiguration of the Language System in Temporal Lobe Epilepsy; Brain 141(5): 1375-1389, 1 May 2018, doi.org/10.1093/brain/awy042
Xiaosong He, Danielle S. Bassett, Ganne Chaitanya, Michael R. Sperling, Lauren Kozlowski, Joseph I. Tracy

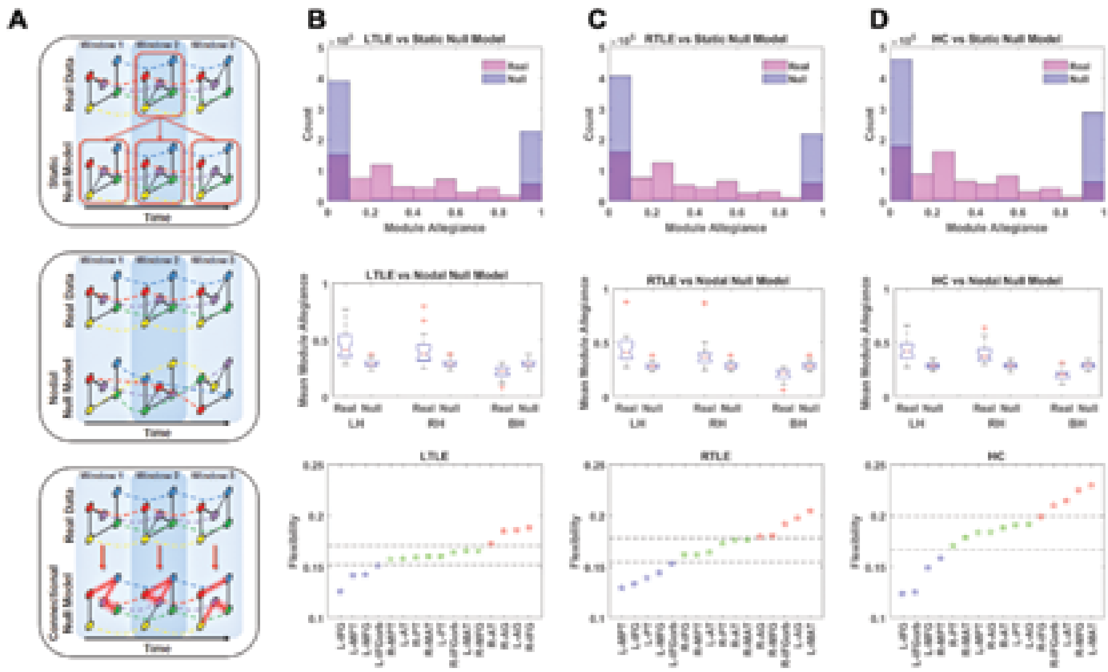

Figure 2. Schematic for all Three Models.

This figure shows the comparison between the real functional MRI data and corresponding null models in all three experimental groups, making the point that real dynamic changes occurred in the patients, not just random changes.

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Disrupted Dynamic Networks

Dr. Tracy and his team are currently working on the examination of disrupted dynamic network reconfiguration of the language and memory system in temporal lobe epilepsy (TLE). TLE tends to reshape the language system causing maladaptive reorganization that can be characterized by resting-state fMRI, diffusion imaging, and task-based functional MRI. These changes help explain the brain mechanisms that drive the cognitive and behavioral abnormalities seen in epilepsy. Understanding these mechanisms will greatly improve surgical decision making by reducing unwanted cognitive, emotional, and behavioral side effects.

The dynamic interacting nature of the brain as a complex system is often neglected, with many studies treating the language system as a static monolithic structure. Dr. Tracy's research demonstrates that as a specialized and integrated system, the language network is inherently dynamic, characterized by rich patterns of regional interactions, whose transient dynamics are disrupted in patients with TLE.

The research team applied tools from dynamic network neuroscience to functional MRI data collected from 50 TLE patients and 30 matched healthy controls during performance of a verbal fluency task, as well as during rest. (see Figure 1, Figure 2).

By assigning 16 language-related regions into four subsystems (i.e. bilateral frontal and temporal), and looking at changes in community (subsystem) membership over time, the team observed

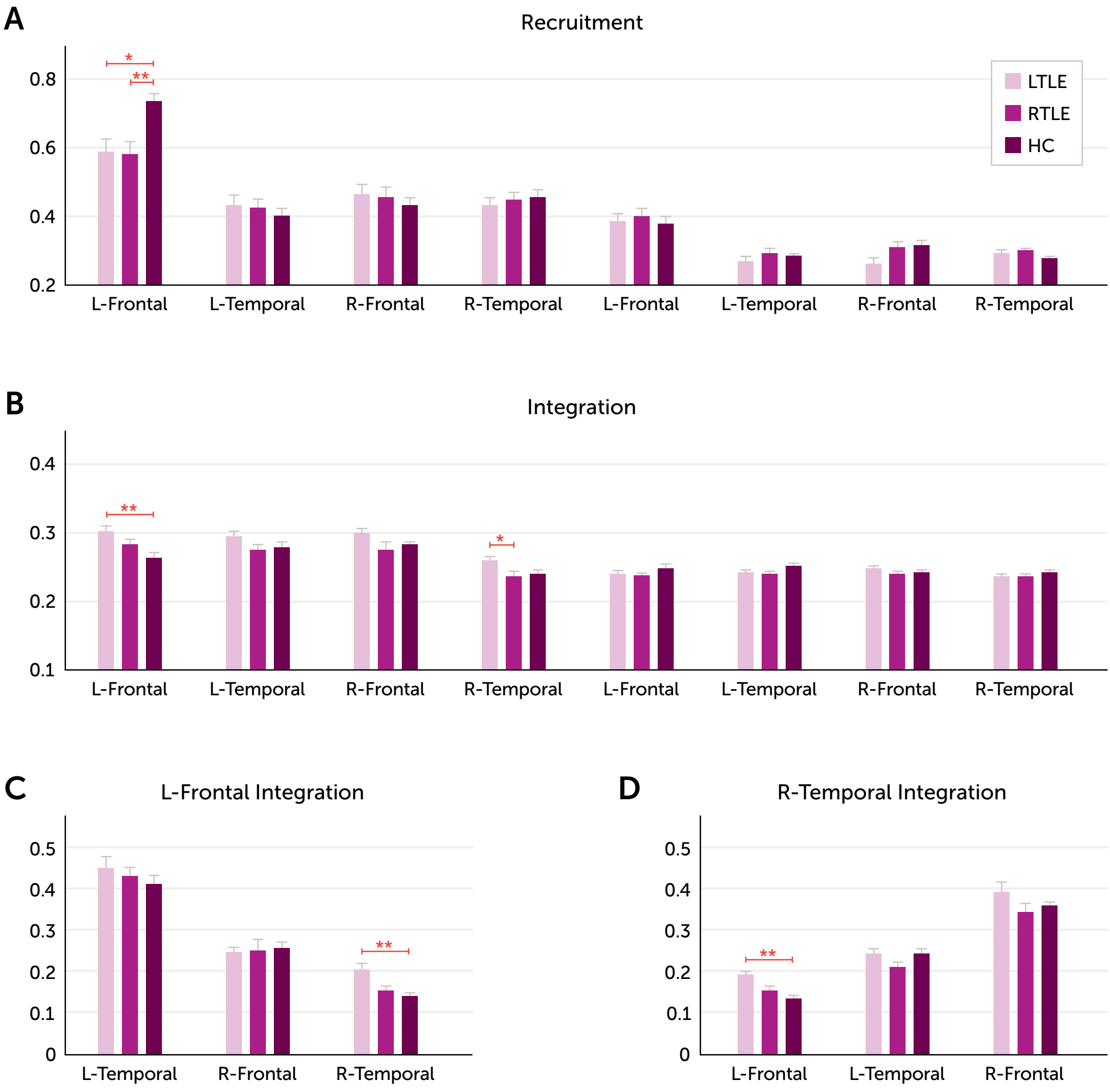

Figure 3. Summary of Results from Dynamic Analyses.

There were similar activation patterns during the verbal generation task for all three groups, whereas on the dynamic measures the patients differed from health controls. Most notably, the left temporal lobe epilepsy patients showed unique integration (communication) between the left frontal and right temporal lobe systems (see panels C and D).

Source: Joseph Tracy, PhD, ABPP/CN

regional specialization in both the probability of transient interactions and the frequency of such changes, in both healthy controls and patients during task performance but not at rest. The graphs in Figure 2 also makes clear that these interactions between regions are dynamic (changing over time) and not explained by various types of static (non-changing) models of inter-regional communication.

The study found that both left and right TLE patients displayed reduced interactions within the left frontal 'core' subsystem compared to the healthy controls. Also, both groups, overall, showed reduced flexibility during the task in 'peripheral' language subsystems involving the left temporal and right frontal lobe. Interestingly, despite these signs of reduced flexibility in network interactions, the left TLE

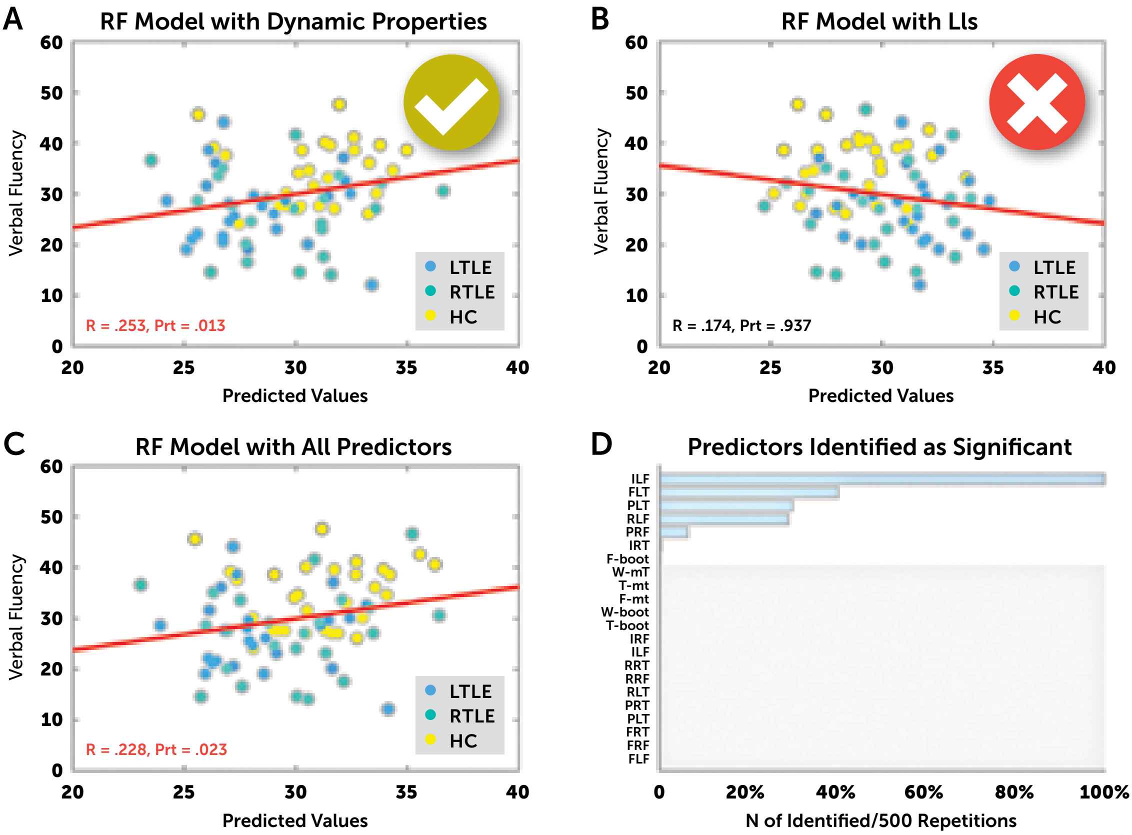

Figure 4. Dynamic Measures Predict Verbal Fluency; Static Laterality Indices Do Not.

A random forest model built with dynamic network properties can successfully predict verbal fluency while a model built with static network measures (e.g., laterality indices) cannot. Adding the latter to the former did not improve upon the dynamic model. When ranked, the importance of all the predictors with random forest showed that only the dynamic properties were selected as important.

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Disrupted Dynamic Network Reconfiguration of the Language System in Temporal Lobe Epilepsy; Brain 141(5): 1375-1389, 1 May 2018, doi.org/10.1093/brain/awy042
Xiaosong He, Danielle S. Bassett, Ganne Chaitanya, Michael R. Sperling, Lauren Kozlowski, Joseph I. Tracy

patients were unique in showing enhanced interactions between the left frontal 'core' and the right temporal subsystems. Importantly, such group differences were evident only during the task condition, (see Figure 3) not at rest, making clear that they are a task response, not just a background, baseline set of communications between these regions.

Finally, random forest regression showed that dynamic reconfiguration of the language system tracks individual differences in verbal fluency with superior prediction accuracy compared to traditional activation-based static measures. Results suggest dynamic network measures may be an effective biomarker for detecting the language dysfunction associated with neurological diseases such as temporal lobe epilepsy, specifying both the type of neuronal communications that are missing in these patients and those that are potentially added but maladaptive (see Figure 4).

Future work will continue to look for both maladaptive and adaptive, compensatory language network reorganizations.

Further advancements along these lines, transforming how we characterize and map language networks in the brain, have a high probability of altering clinical decision making in neurosurgical centers, thereby improving patient outcomes.

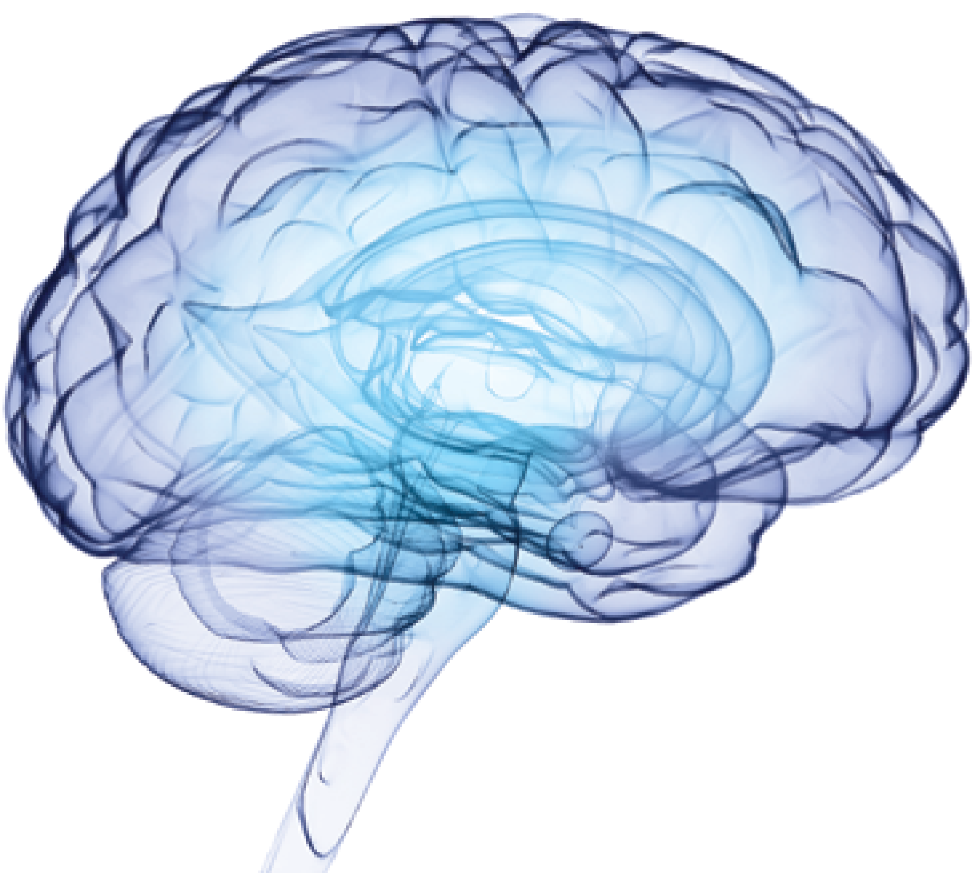
Abnormal interactions in both core and periphery subsystems reveal a lack of adaptive transient communications in TLE patients during an expressive language tasks, thereby providing a novel explanation for language deficits induced by these neurologic conditions.

As articulated by Dr. Tracy: "While it is likely that regional activity in the brain has some modular, static properties that are fairly constant across individuals and circumstances, it is also likely that much of the distinction between unique high-level skills and more mundane, automatic brain reactions (or between states of brain pathology versus health) come from differences in the way brain regions interact and dynamically change their function as a way of coping with environmental demands or the compromise foisted upon the brain by disease."

In summary, surgical decisions may be improved by application of this research, as it provides evidence that measures of brain network dynamics can be an effective biomarker for detecting language dysfunction in certain conditions, such as epilepsy. The results of this study open up a new window into the analysis of cognitive dysfunction, uncovering subtle changes in brain processing during tasks such as language, changes that would otherwise be invisible using standard static measure of brain imaging or neuropsychological status.

Reference

He X, Bassett DS, Chaitanya G, Sperling MR, Kozlowski L, Tracy JI. Disrupted dynamic network reconfiguration of the language system in temporal lobe epilepsy. Brain. 2018; 1;14 (15):1375-1389.



Other Figures

Dr. Tracy regularly conducts functional magnetic resonance imaging scans to map out key functions in the brain so that these can be preserved during brain surgery.

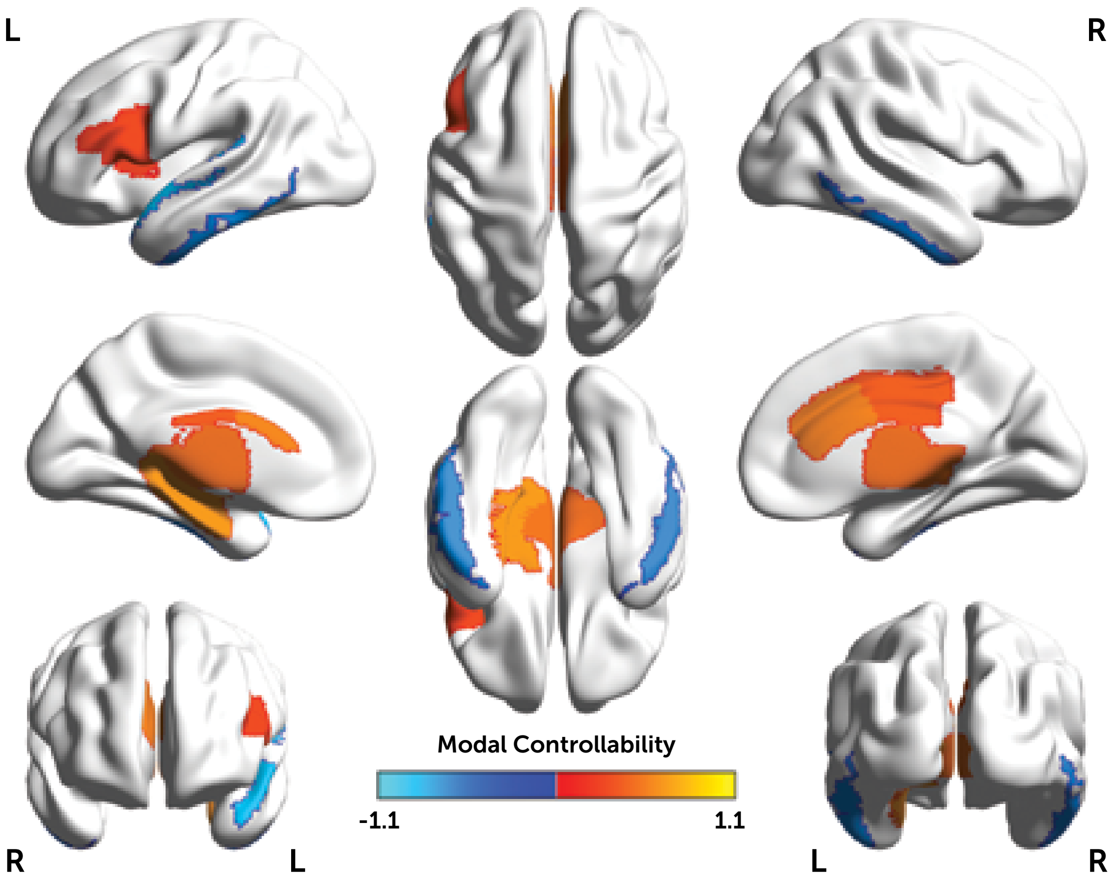


Figure 5. Demonstration of Mesial Temporal Lobe areas (in orange) that appear to be involve with shifting the brain into a "Seizure" state.

Source: Joseph Tracy, PhD, ABPP/CN

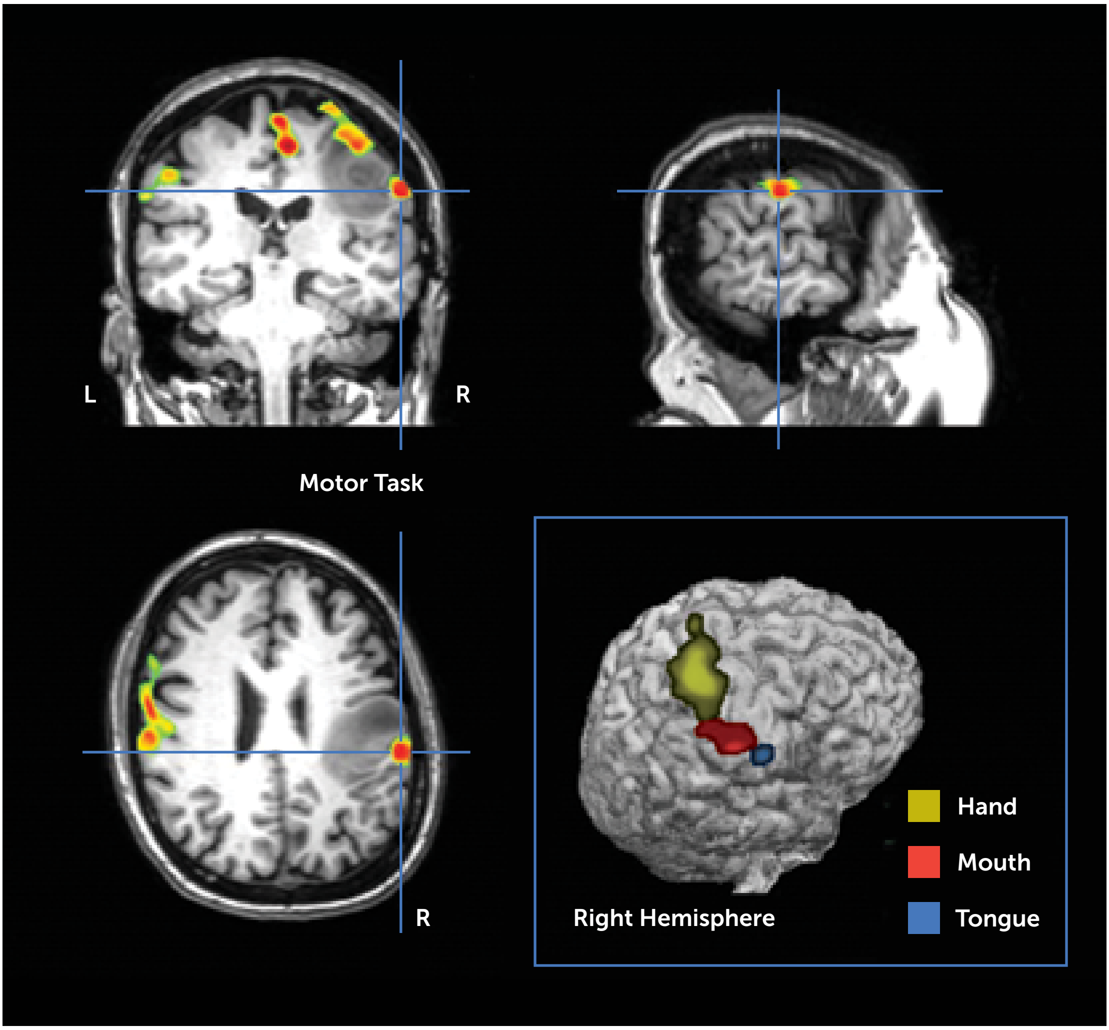


Figure 6(a). This image, particularly the right lower quadrant, provides a good visual depiction of the areas of the brain involved in left hand, mouth and tongue movements. The proximity of these functions to the pathologic area of the brain can also be seen.

Source: Joseph Tracy, PhD, ABPP/CN

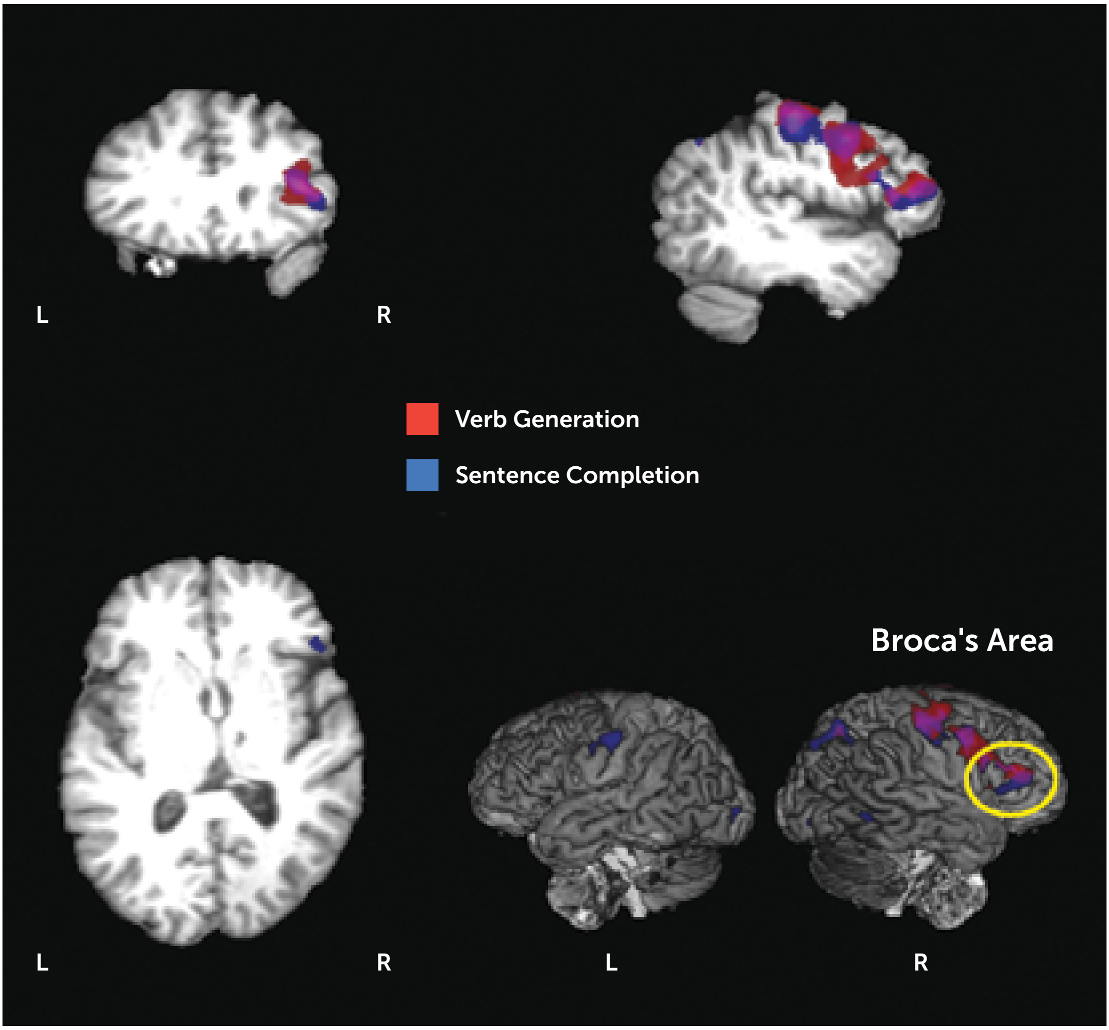


Figure 6(b). This image displays the brain activation involved in expressive language (verb generation) and receptive language (sentence completion). This particular patient shows an unusual and atypical pattern involving right hemispheric dominance for language. Understanding hemispheric dominance is an important factor when planning brain surgery interventions.

Source: Joseph Tracy, PhD, ABPP/CN

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