



Multimodal Evidenced Based Approach to Pediatric Epilepsy Neuropsychology: Past, Present & Future

Christine M. Salinas, PsyD

Michael Westerveld, PhD



Florida Hospital
for Children





Financial Disclosure

We **have no** financial relationships to disclose



Contact Information

- christine.salinas@childrens.harvard.edu
- michael.westerveld@flhosp.org



Outline

- Who are the surgical candidates? [how do kids differ from adults?]
- How has the role of epilepsy neuropsychologists evolved?
- What do we know about cognitive & behavioral outcomes? [what don't we know]
- How do we use evidence based clinical approaches? [nuts & bolts]
- What are some advances in functional mapping? [value added]
- How can you apply a multimodal approach? [case example]



**WHO ARE THE SURGICAL
CANDIDATES? [HOW DO KIDS
DIFFER FROM ADULTS?]**



Epilepsy surgery patients

- 50 million people worldwide (WHO)
- 3 million cases in US
- 200,000 new cases annually
- Highest incidence by age
 - At the extremes of the spectrum (under age 5 and over 70)
 - **30% may have drug-resistant epilepsy**



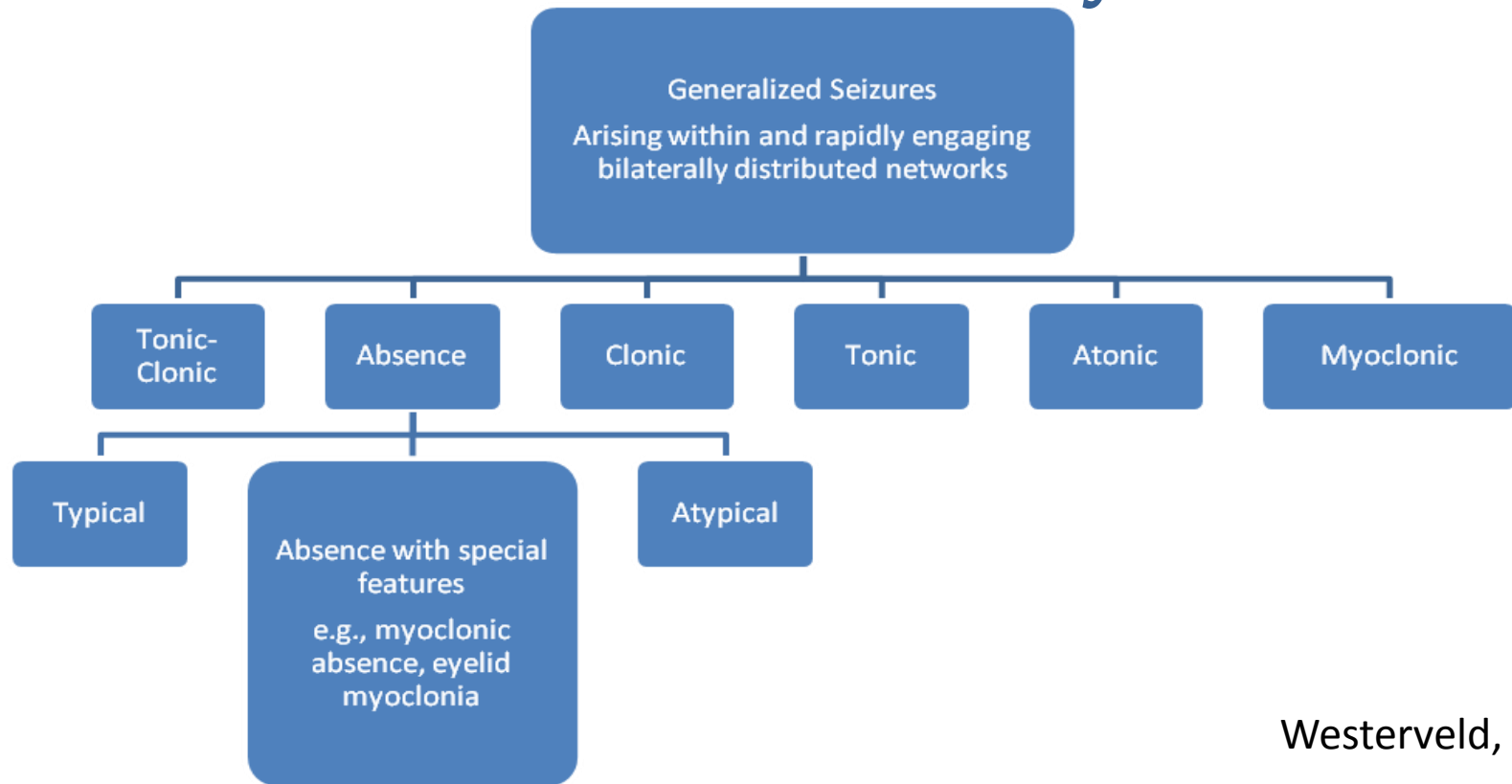
35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas

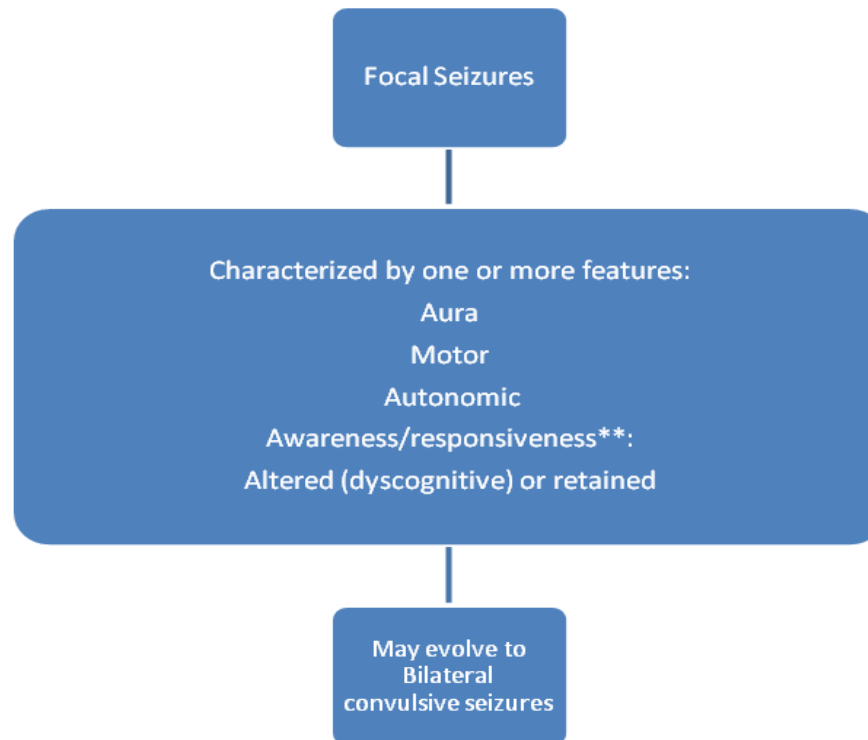
ILAE Classification System



Westerveld, 2012



ILAE Classification System





35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas

ILAE Classification of Epilepsies and Electroclinical Syndromes Arranged by Age of Onset

Neonatal Period	◦ Benign neonatal seizures ◦ Benign familial neonatal epilepsy ◦ Ohtahara syndrome ◦ Early Myoclonic Encephalopathy
Infancy	◦ Febrile seizures ◦ Benign Infantile epilepsy ◦ Benign Familial infantile epilepsy ◦ West Syndrome ◦ Dravet Syndrome ◦ Myoclonic epilepsy of Infancy ◦ Myoclonic Encephalopathy in non progressive disorders ◦ Epilepsy of infancy with migrating focal seizures



Childhood

- Febrile seizures, Febrile seizures plus
- Early onset childhood occipital epilepsy
- Epilepsy with myoclonic atonic seizures (formerly “astatic” seizures)
- Childhood Absence epilepsy (CAE)
- Benign epilepsy with Centrotemporal Spikes
- Late onset childhood occipital epilepsy
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Epilepsy with myoclonic absences
- Lennox Gastaut syndrome
- Epileptic encephalopathy with continuous spike and wave during sleep (CSWS; also referred to as Electrical Status Epilepticus during Slow Sleep (ESES))
- Landau Kleffner Syndrome



35th annual

CONFERENCE

November 4 - 7, 2015

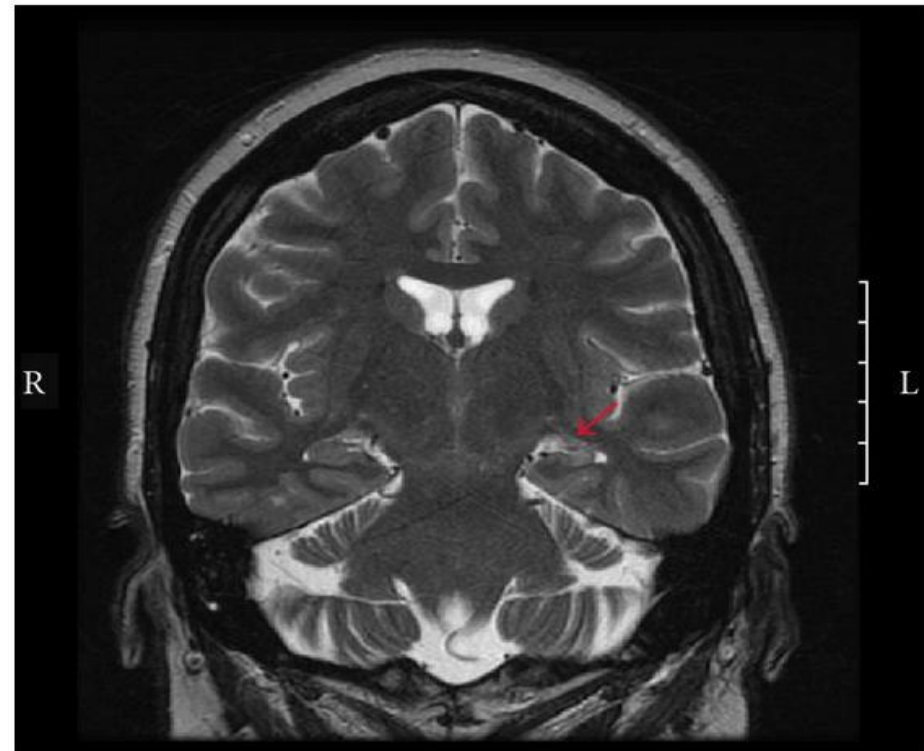
JW Marriott | Austin, Texas

Adolescence / Adult	◦ Juvenile Absence epilepsy ◦ Juvenile Myoclonic epilepsy (JME) ◦ Epilepsy with generalized tonic-clonic seizures alone ◦ Autosomal dominant epilepsy with auditory features (ADEAF) ◦ Other familial temporal lobe epilepsies	
Variable at Age of Onset	◦ Familial focal epilepsy with variable foci ◦ Progressive myoclonus epilepsies ◦ Reflex epilepsy	
Distinctive Constellations / Surgical Syndromes	◦ Mesial Temporal Lobe epilepsy with hippocampal sclerosis ◦ Rasmussen syndrome ◦ Gelastic seizures with hypothalamic hamartoma ◦ Hemiconvulsive-hemiplegic epilepsy	
Nonsyndromic Epilepsies	Epilepsy attributed to structural metabolic causes	◦ Malformations of cortical development ◦ Neurocutaneous syndromes (Tuberous Sclerosis Complex, Sturge-Weber) ◦ Tumor, infection, trauma, vascular, antenatal/perinatal insults, etc.
	Epilepsies of unknown cause	



Pathological Substrate in Adults

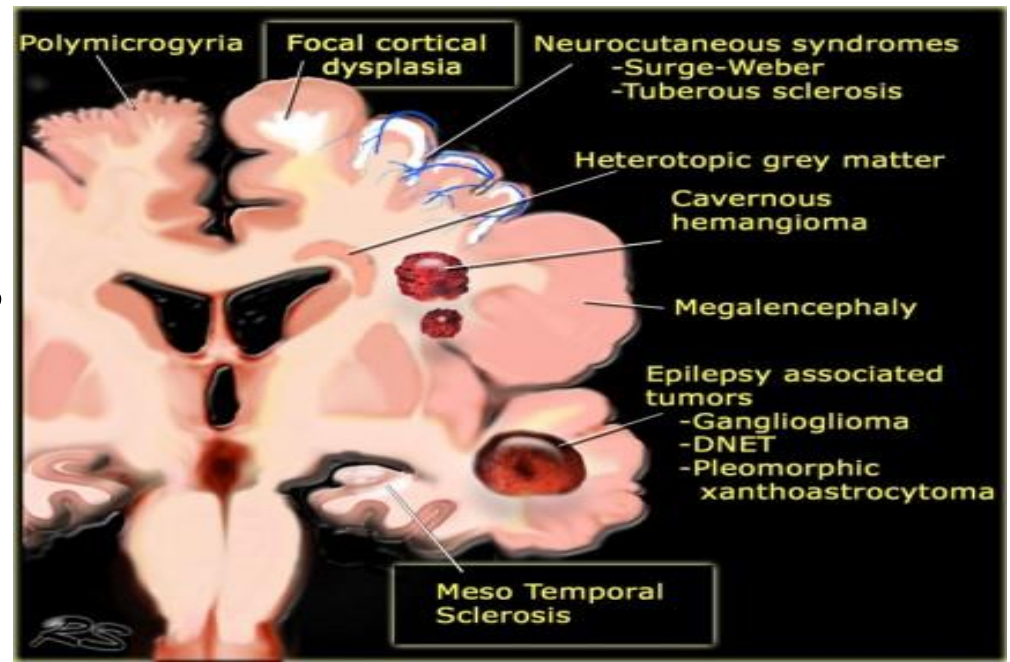
- Mesial TL structures
 - Amygdala
 - Hippocampus
 - Entorhinal cortex





Pathological Substrate in Children

- MCD/low grade tumors
 - 90% <3yo
 - 70% of school age
 - 57% of adolescents



Wylie, Comair, Kotagal et al (1998)



Treatment Options

- Opinions regarding surgery in children are evolving
 - More syndromes considered for surgery
 - Seizures previously thought to be unlocalizable (post-callosotomy localization)
- Palliative surgery is more common

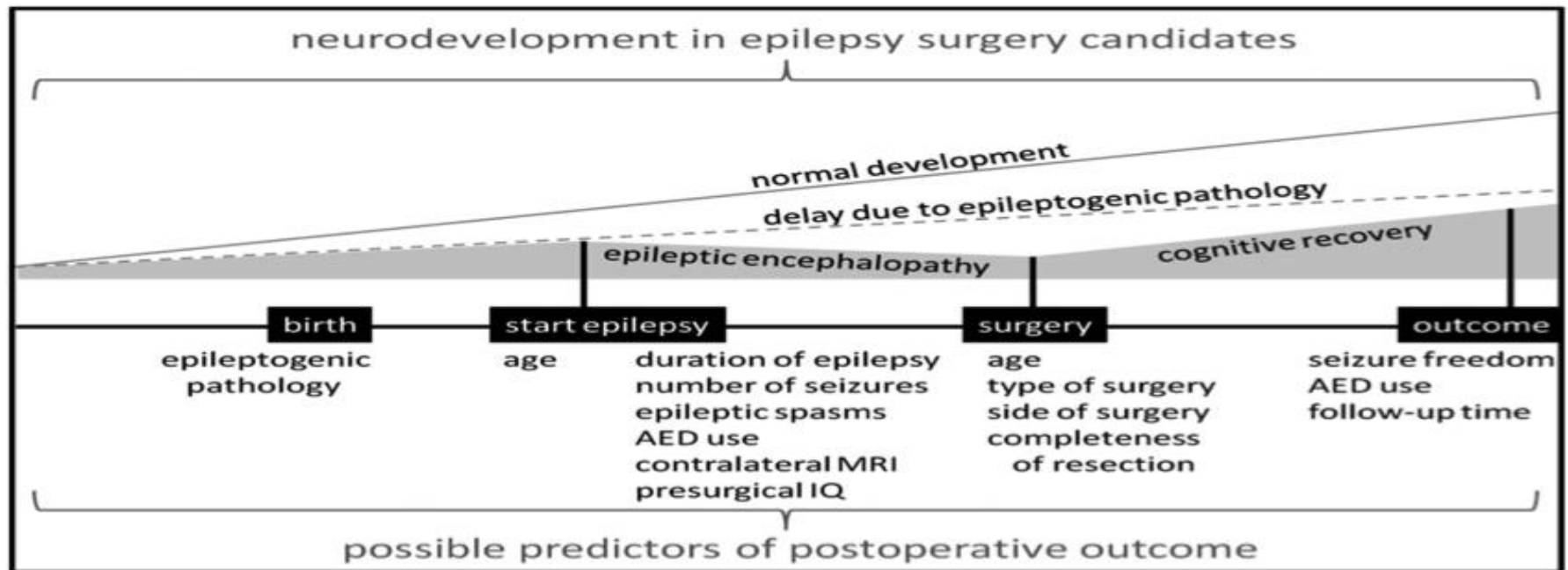


Developmental model is key

- Brain
- Context
- Development



Factors associated with outcomes



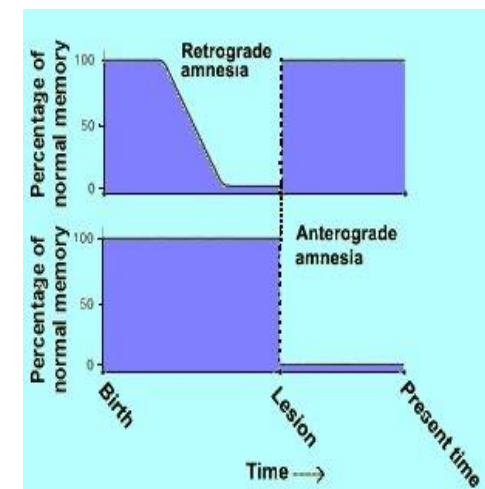
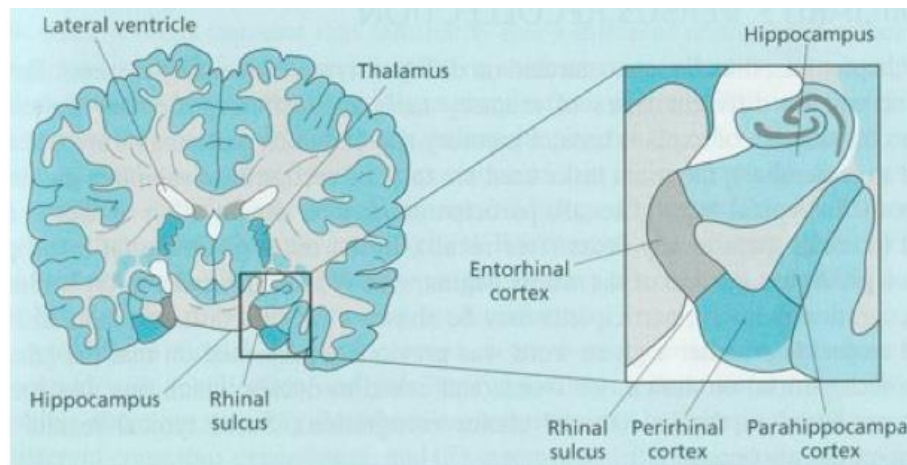


HOW HAS THE ROLE OF EPILEPSY NEUROPSYCHOLOGISTS EVOLVED?



35th annual

CONFERENCE





35th annual

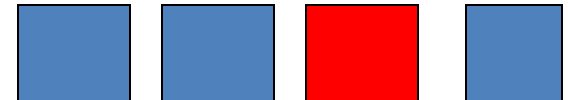
CONFERENCE

November 4 - 7, 2015

Marriott | Austin, Texas



Dr. Ward Halstead



Features Seen in Experimental Monkey



1. Visual agnosia
2. Increased oral tendency
3. Decreased emotional reaction
4. Hypersexuality
5. Hypermetamorphosis



35th annual

CONFERENCE

November 4 - 7, 2015
Marriott | Austin, Texas

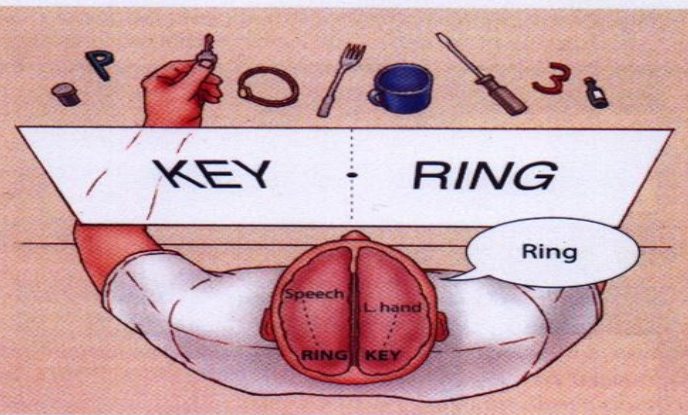
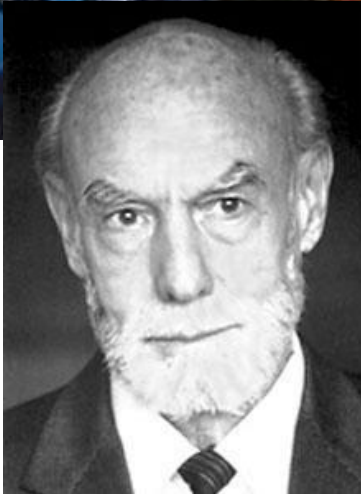
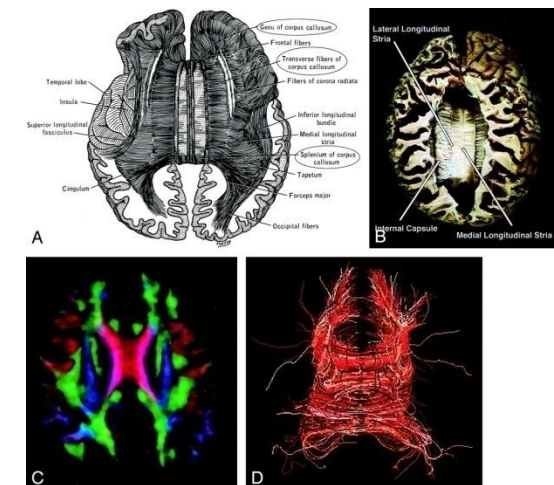
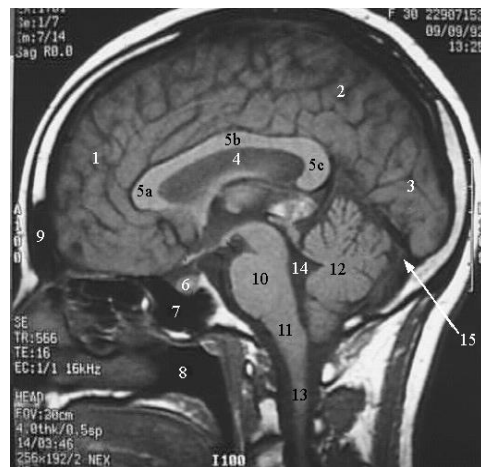


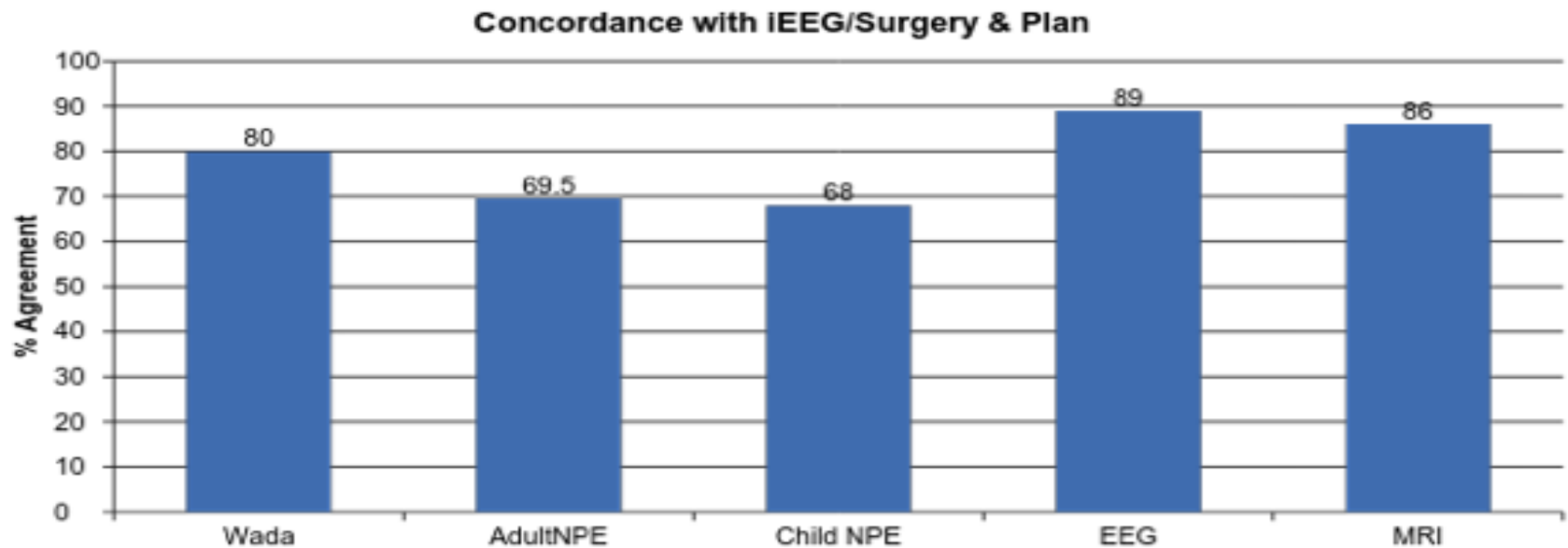
Figure 9.9 The split-brain patient reports through the speaking hemisphere only the items flashed to the right half of the screen and denies seeing left-field stimuli or recognizing objects presented to the left hand. The left hand correctly retrieves objects presented in the left visual field for which the subject verbally denies having any knowledge.



<http://youtu.be/ZMLzP1VCANo>



Neuropsychology's Role in Surgical Planning



(Moser et al., 2000; Loring et al., 1993; Kneebone et al., 1997; Kim et al., 2004; Ogden Epker & Cullum, 2001; (Salinas & Westerveld, unpublished)



Pediatric Epilepsy Neuropsychology

- Always have been/will be role in patient selection
- Early role was to assist with functional localization, add to concordance
- As technology improved, role evolved to predicting risk of cognitive morbidity
 - Also validating new technologies
- As pediatric surgery options increase, role of NP is once again taking center stage
 - Understanding development and plasticity
 - Assessing outcomes
 - Academic and behavior concerns
 - Early studies focused on global outcome; more recent studies (e.g., Smith and colleagues at Hospital for Sick Children; Sherman and colleagues)



**WHAT DO WE KNOW ABOUT
COGNITIVE & BEHAVIORAL
OUTCOMES? [WHAT DON'T WE
KNOW]**



IQ Outcomes

- Most likely outcome = No IQ change
- Younger age was predictor of 
- Bozeman consortium follow up study (~1 yr)
 - 82 TL patients (43L/39R)
 - Significant improvements (> 2 SEM) noted in 9% of children
 - Significant declines (> 2 SEM) noted in 10% of children
 - 82% had no change in VIQ; 82% had no change in PIQ

Westerveld et al (2000). *Neurosurgery*



Long Term IQ Outcomes

- 42 patients who underwent TL followed 9 years after surgery
- Group statistics show significant changes at 6-8 year and longer follow-up
 - 41% had increases of >10 FSIQ points compared with 10% of controls
 - Only 1 patient had decline of >10 FSIQ points
 - PIQ improved in both Left and Right TL groups
 - VIQ improved only in Left TL group

Skirro, Cross, Cormack et al (2011). *Neurology*



Verbal Memory Outcomes

- Risk in children is not as consistent and compelling as in adults

44 children (18 RTL/ 17 LTL/ 9 Extra-temporal)

-14-20 month f/u duration

-No lateralizing differences at baseline for verbal memory

-No significant declines observed in verbal memory following LTL, despite normal baseline performance

Mabbott & Smith (2003). *Neuropsychologia*



Visual Memory Outcomes

- Dependent on type of memory & surgery
 - Design reproduction showed no significant RTL-LTL baseline differences
 - No significant change in design recall after surgery
 - Face recognition deficits were noted preoperatively for RTL, but not LTL
 - At post-op, RTL showed significantly lower performance
 - Extra-Temporal lesions were not associated with baseline memory deficits or declines



Language outcomes

- Children who undergo TL vulnerable to naming deficits
- Younger age & congenital syndrome associated with 

Vega et al (2015). *Epilepsy & Behavior*; Boshuisen et al (2010). *Neurology*



Executive Functioning Outcomes

- Intractability associated with ↓ IQ ↓ EF

80 surgical candidates, average FSIQ=72, mean age 11 years

- 68% of sample had at least 1 sig. elevation on the BRIEF
- More frequent clinical elevations were found among children with ID

*Inhibit and Monitor scales were more likely to be elevated

*Least elevated clinical scale was Organization of Materials



Behavioral Outcomes

- Psychiatric diagnoses more common
- When present before surgery, disruptive behavior and developmental disorders tend to persist
- Affect/Mood disturbance closely related to seizure status and outcome
- Dependent on surgery type

McClellan et al (2005). *Dev Med & Child Neurology*; Micallef et al., (2010). *Epilepsia*; Ettinger et al; *Epilepsia*; Salinas & Klein (2015).



Academic skills may be slower to recover

	Surgical			Nonsurgical		
Measure	Time 1	Time 2	n	Time 1	Time 2	n
Reading decoding	92.2 (17.2)	90.7 (14.9)	29	86.1 (18.5)	84.5 (18.8)	20
Reading comprehension	90.6 (19.3)	88.4 (15.4)	26	91.2 (18.8)	89.1 (16.2)	19
Spelling	91.5 (15.8)	88.7 (15.3)	29	86.1 (18.5)	84.1 (18.3)	20
Arithmetic	83.3 (15.3)	78.2 (16.8)	29	79.8 (22.0)	77.3 (19.2)	20

Smith, Elliot, Lach, 2004 Epilepsia



Quality of Life Outcomes

- Improvements in social function observed for surgery patients at 2 yrs, declines for non-surgical controls
- Retrospective study of young adults who had surgery in childhood
 - 3 groups: seizure free post-op; post-op seizures in last 12 months; non-surgical control
 - Seizure free group had significantly better outcome (employment, community involvement)
 - No more likely to be involved in relationship

Smith et al (2008). Lach et al (2010).



Cognitive Comorbidity & QoL

- Parent reported executive dysfunction is significant predictor of poor QoL
-  BRIEF elevations: 2x risk of  QoL
- Significant difference in QOL between those with (M=64.87, SD=15.64) & without (M=47.53, SD=13.42) EF impairments; $t(32)=3.47$, $p=.002$.
- BRIEF scores provided a statistically significant prediction of the Overall QOLCE scores, $F(8, 42) = 6.830$, $p = .000$, $R^2 = .565$, adj. $R^2 = .483$.

Sherman, Slick & Eyrl (2006). *Epilepsia*; Love, Webbe, Kim, Lee, & Salinas (2015).



Hemispherectomy Outcomes

- Hemispheric syndromes (Rasmussen's, hemimegacephaly, Sturge-Weber, infantile hemiplegia) more likely to include study of language
- Worse outcome associated with progressive disorders (e.g., Rasmussen's) and contralateral MRI findings
 - Contralateral EEG findings not necessarily associated with worse cognitive/language outcome



NPE data predicts seizure outcome

- IQ disparities in left language dominant children predict sz freedom

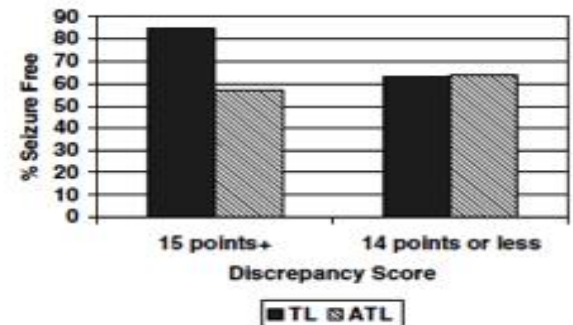


Fig. 3. Seizure outcome (Engel Class I) for the typical language (TL) and atypical language (ATL) representation groups by magnitude of VIQ/PIQ discrepancy. The presence, but not the direction, of the discrepancy was associated with increased likelihood of seizure control in TL subjects, but was unrelated to control in ATL subjects.

Blackburn, Lee, Westerveld, et al (2007). *Journal?*



NPE data predicts seizure outcome

<u>IQ Category</u>	<u>% Seizure-Free Children (n=156)</u> (Lee, et al., 2004)	<u>% Seizure-Free Adults (n=1,034)</u> (Chelune, et al., 1999)
Superior (≥ 120)	100%	83.3%
High Avg. (110 – 119)	89%	82.9%
Average (90 – 109)	78%	77%
Low Avg. (80 – 89)	71%	75%
Borderline (70 – 79)	59%	73%
Very Low (< 70)	40%	54%



State of Pediatric Outcomes

- Evidence is lacking!
 - Most studied population is temporal lobectomy, which is least common in children
- Strongest evidence for early surgery is in QoL domain
- Particular focus on domains such as attention/executive function & language is needed
- Adaptive functioning and contextual/familial factors are underemphasized
- Little to no emphasis on early assessment (preschool) to help understand long-term outcomes of very early intervention
- Minimal information on epileptic encephalopathies or related syndromes
- Small numbers at any given center make studies of outcome difficult



HOW DO WE USE EVIDENCE BASED CLINICAL APPROACHES? [NUTS & BOLTS]



Epilepsy Neuropsychology Tools

- History & Observations
- Pre- & post-operative assessment
- Multi-factorial approach
 - Age
 - Developmental/cognitive level
 - Referral
 - Role of family/ecological demands
- Interpretative analysis
- Specialty procedures



Review of NINDS CDEs



Evaluating the CDEs

Pros

- Evidence to support utility
- Useful for pooling data
- Easily accessible, with many in public domain

Cons

- Test limitations (QOLCE)
- Limited breadth and depth of assessment
- Does not address areas of concern to many parents/families

**Parent Packet**

- ☐ Background Questionnaire
- ☐ BASC-2: 2-5, 6-11, & 12-18
- ☐ BRIEF-P 2-5, 5-18
- ☐ ABAS-II: 0-5, 5-21
- ☐ QOLCE 4-18
- ☐ CDI-2 Parent (7-17)

Epilepsy Screening < = 2 yo

- ☐ Mullen Scales
- ☒ Peabody Motor

Epilepsy Screening 3 yo

- ☐ Mullen Scales
- ☐ WPPSI-IV Picture Naming
- ☐ WPPSI-IV Receptive Vocabulary
- ☐ WRAVMA Pegs
- ☐ CELF-4 Preschool
- ☒ Peabody Motor Scales
- ☒ D/W AA, Tactile, Object

Epilepsy Screening 4 yo

- ☐ WPPSI-IV including GLC
- ☐ WRAVMA Pegs
- ☐ CELF-4 Preschool
- ☐ Kiddie CPT
- ☐ WRAVMA Visual Matching
- ☒ Peabody Motor Scales
- ☐ D/W AA, Tactile, Object

Epilepsy Battery 5-13yo

- ☐ 5 WPPSI-IV including GLC
- ☐ 6+ WISC-IV short form
- ☐ 5+ CVLT-C
- ☐ 5+ CMS Dot Locations
- ☐ 5+ Boston Naming
- ☐ 5+ Grooved Pegs (norms 5-14)
- ☐ 5+ Kiddie CPT
- ☐ 6+ CPT-2
- ☐ 5+ CMS Stories
- ☐ 5-7 Word Generation
- ☐ 8+ DKEFS Verbal Fluency
- ☐ 7-13 TMT A & B Child Version
- ☐ 5+ TVPS-III Spatial Rel./Fig. Ground
- ☐ 5+ CELF-4 R. Sentences (+ complete)
- ☐ 7+ ToL-DX
- ☐ 5+ CMS Faces
- ☐ 5+ CMS Word Pairs
- ☐ 7+ Rey-O Copy, 10+ CopySD/LD/Rec.
- ☒ 5+ D/W Hand, Visual, AA, Object, Tactile, Gait, Romberg
- ☒ 5+ Calculation

Epilepsy Battery 14-17

- ☐ 14+ WASI-2 + WMI/PSI
- ☐ 14-15 CVLT-C
- ☐ 16+ RAVLT (metanorms)
- ☐ 14-16 CMS Dot Locations
- ☐ 14+ Boston Naming (use 15-18 norms for 14)
- ☐ 14+ GPB (5-14 norms, use 16+ for 15yo)
- ☐ 14+ CPT-2
- ☐ 14-16 CMS Stories
- ☐ 14+ DKEFS Verbal Fluency
- ☐ 14+ TMT Adult Version (adolescent norms)
- ☐ 14-17 TVPS-III Spatial Rel./Fig. Ground
- ☐ 14-17 CELF-4 R. Sentences (+complete)
- ☐ 14+ ToL-DX
- ☐ 14-16 CMS Faces
- ☐ 14-16 CMS Word Pairs
- ☐ 14+ WCST 64 Card
- ☐ 14+ Rey-O Copy/SD/LD/Rec.
- ☒ 14+ D/W Hand, Visual, AA, Object, Tactile, Palm, Finger, Gait, Romberg Calculation

Emotional/Behavior

- ☐ 6-18 RCMAS-II
- ☐ 7-17 CDI-II
- ☐ 11-18 QOLIEAD

Hemispherectomy/Callosotomy

- ☐ 0-3 Mullen
- ☒ Birth+ Peabody Motor Scales
- ☐ 2:6-5 WPPSI-IV Picture Naming
- ☐ 2:6-5 WPPSI-IV Receptive Vocabulary
- ☐ 4-5 WPPSI-IV including GLC
- ☐ 6+ WISC-IV short form
- ☐ 5+ CVLT-C
- ☐ 5+ CMS Dot Locations
- ☐ 5+ Boston Naming
- ☐ 5+ Grooved Pegs
- ☐ 5-7 NEPSY-II Word Generation
- ☐ 8+ DKEFS Verbal Fluency
- ☒ 5+ D/W Object

+Right Hemisphere

- Imitation of Facial Affect
- Production of Facial Affect
- Comprehension of Affective Facial Expression



Post-operative assessment

- Acute and long term approaches
- Typical follow up period based on evidence
 - Is there one? Should there be one?
- Goals/purpose
 - RCI
 - Return to baseline is not sufficient



**WHAT ARE SOME ADVANCES IN
FUNCTIONAL MAPPING?
[VALUE ADDED]**



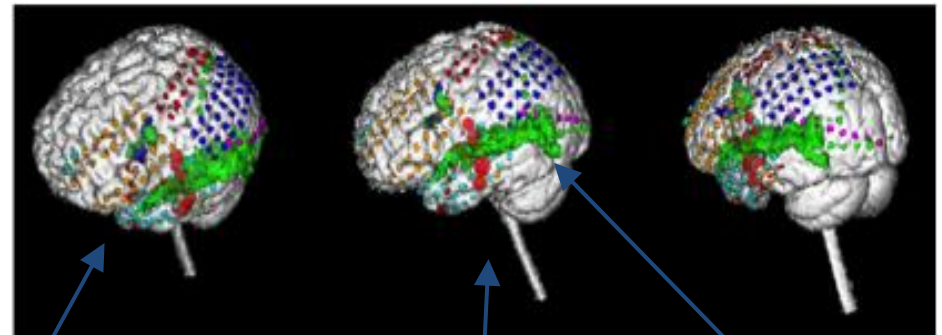
Functional mapping tools

BDE

“casket”



DE



Blue blob: fMRI auditory decision

Green blob: fMRI story listening

Red circle: MEG receptive language



Epilepsy: a window into language (re)organization

- Atypical language more common
- Language may be “pushed” to homologous areas contralaterally or shift within hemisphere; additional areas may be recruited
- Naming functions may reorganize anteriorly in left frontal lobe while phonemic decoding and comprehension may migrate more posteriorly and superiorly
- Visuospatial deficits may be observed (“Crowding Hypothesis”)

Woermann (2006). *Epilepsia*; Berl et al 2015



Epilepsy: understanding memory functions

- Functional adequacy
- Functional reserve



Overview of Wada procedure

- Unilateral anesthetization provides reversible model of surgical morbidity
- Stimuli presented during period of maximal hemispheric anesthetization
 - Assessment of expressive and receptive language, memory
- Vast literature supporting validity as predictor of surgical outcome



Wada predicts seizure outcome

- Memory asymmetry predicts sz laterality & sz freedom
 - Memory asymmetry predicted seizure laterality in both TL and extra-temporal lobe seizures, but less accurately than with adults
 - Memory asymmetries that were consistent with seizure laterality were significantly related to seizure freedom
 - Patients with no memory asymmetry or asymmetry disparate from side of surgery had less favorable seizure outcome

Lee et al (2002). Lee et al (2003).



Wada predicts cognitive outcome

- Memory asymmetry predicts  verbal memory
 - 132 children from 3 centers underwent surgery
 - 70% showed memory asymmetry in the expected direction
 - Group statistics showed significant improvement in verbal memory for patients with Wada asymmetry
 - Individual statistics showed majority 72/93 (77%) had improved verbal memory after surgery
 - 30% had no asymmetry or reversed asymmetry
 - This group had significant decline in verbal memory
 - 31/39 (80%) individuals showed decline

Lee, Westerveld, Blackburn, Park, & Loring (2005).



Electrocortical Stimulation Mapping

- Leave subdural electrodes in place during periooperative periods to determine epileptogenic zone and language or sensorimotor mapping can take place during this time.
- Method: Biphasic pulses of current on two adjacent contacts; stimulation may begin at 3-4mA with a train duration of 3-5 seconds. The stimulation intensity is increased until a physiological response is seen (speech arrest, motor or sensory response), AD is observed or seizure occurs
 - Stimulation directly interferes with language
 - Identifies areas that are critical to language vs. highlighting active areas that are part of a language network but not necessarily essential
 - Cons
 - Can only record activity in the gyri and not in the depth of sulci; only restrictive parts of the brain is exposed.
 - May provoke seizures
 - More difficult to conduct in children vs. adults



ESM Logistics/Setting

- Team waits for patient to have enough seizures first to determine epileptogenic zone
- When epilepsy focus has been identified, neuropsychologist is asked to do mapping by epileptologist (dependent)
- Dilantin dosing is usually administered first
- Nurse is asked to have additional medication on hand in case of seizure (Valium/Diastat)
 - IV administration
- Neuropsychologist explains rationale and procedure to patient and family
- Neuropsychologist usually works individually with patient and EEG tech
- Baseline testing is conducted first to ensure accuracy and reliability of patient responses



ESM stimuli

- Visual naming
- Auditory responsive naming
- Sentence repetition
- Recitation tasks (alphabet, counting)





Auditory Naming

- Round toy that bounces
- Person that flies planes
- A tall animal with a long neck



Repetition

- Limes are sour
- Santa's Short Suit Shrunk
- Awful Arthur's Oyster Bar



35th annual

CONFERENCE

November 4 - 7, 2015
JW Marriott | Austin, Texas

Language Mapping Protocol (core)

Examiners Present: _____

Tech: _____

- | | | |
|------------------------------|---------------------|---------------------------|
| 1. Speech Arrest-No response | 2. Hesitation/Pause | 3. Dysarthric/Slowing |
| 4. Perseveration/Intrusion | 5. Circumlocution | 5. Semantic paraphasia |
| 6. Phonological paraphasia | 7. Neologism | 8. Request for Repetition |
| | | 9. Comprehension |

	mA	Practice Items	Score	ADs
		Bird	+ -	
		Dress	+ -	
		Watch	+ -	

Electrodes	mA	Visual Naming/Auditory Naming/Repetition	Score	ADs
		Bear 1 2 3 4 5 6 7 8 9	+ -	
		Guitar 1 2 3 4 5 6 7 8 9	+ -	
		Star 1 2 3 4 5 6 7 8 9	+ -	
		Hamburger 1 2 3 4 5 6 7 8 9	+ -	
		Animal that oinks 1 2 3 4 5 6 7 8 9	0 1 2 3 4 + -	
		Animal that goes woof 1 2 3 4 5 6 7 8 9	+ -	
		Mary had a little lamb 1 2 3 4 5 6 7 8 9	0 1 2 + -	
		Jack & Jill went up the hill 1 2 3 4 5 6 7 8 9	+ - 0 1 2	



ESM results

ESM has shown intrahemispheric reorganization

- Anterior reorganization of expressive language in left frontal lobe

Less effective results with children less than 10 has been reported (19%)

Testing auditory rather than visual naming may be more appropriate for patients undergoing standard ATL resection

- AN sites located more anterior

Hamberger et al (2003). Kadis et al (2007); Shevon et al (2007)



ESM and outcomes

- Patients who undergo SLAH may still present with deficits
- Resection of identified language areas may not lead to persistent deficits*
- Resection of ESM+ sites associated with naming decline

Luders et al (1991) *Journal?* Hamberger (2001) *Journal?*



fMRI: Overview

- Indirectly measures neural activity in the brain by imaging the change in blood flow (hemodynamic response) related to energy use by brain cells
 - uses change in magnetization between oxygen-rich and oxygen-poor blood as its basic measure (BOLD signal).



fMRI paradigms

Verb generation seems to be reliable in determining hemispheric dominance

Tasks capturing wider network is optimal but ADT may be more helpful for surgical planning

Story listening with backward speech and/or modulated tone leads to stronger activation in dorsal plane and HG activations than with noise; and more specific than silence

fMRI concordance with Wada ranges from 70-91%; up to 14% discordance with atypical cases

Binder et al (2000) *Cortex* Szaflarski et al (2009) *Neurology*; Upadhyay et al (2008) *J Neuroscience*



35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas

[] Language – Story Listening (5:12) 5 cycles (12s fixation followed by 30s blocks)

Active (30s): Listening and understanding stories

Control (30s): Listening to a modulated sound similar to the “wind”

[] Language-Auditory Category (5:12) 5 cycles (12s fixation followed by 30s blocks)

Active: Word Matches Category (Animals, Food, People, Things in Nature) = Yes/Left Word doesn't match category = No/Right

Control: Backwards Speech Followed by Beep = Yes/Left Backwards Speech with no Beep = Right/No

[] Language - Semantic Decision (5:12 or 7:12 depending on task chosen-1 or 2)

Active: Animal Has 4 Legs = Yes/Left Animal does not have 4 legs = No/Right

Control: Two Consecutive High Pitch Sounds in Sequence = Yes/Left No = Right

[] Language – Verb Generation (5:12) 5 cycles (12s fixation followed by 30s blocks)

Active (30 s): Think of “action” words in response to presentation of nouns

Control (30s): Finger tapping bilaterally like “playing a piano” or “typing on keyboard”/####

[] Language-Auditory Description Test (5:12) 5 cycles (12s fixation followed by 30s blocks)

Active: True Description (“apple is a fruit”) = Yes/Left False description (“apple is for writing”) = No/Right

Control: Backwards Speech Followed by Beep = Yes/Left Backwards Speech with no Beep = Right/No

[] Language Reading (5:12) 5 cycles (12s fixation followed by 30s blocks)

Active: Reading Control: White/Black Box

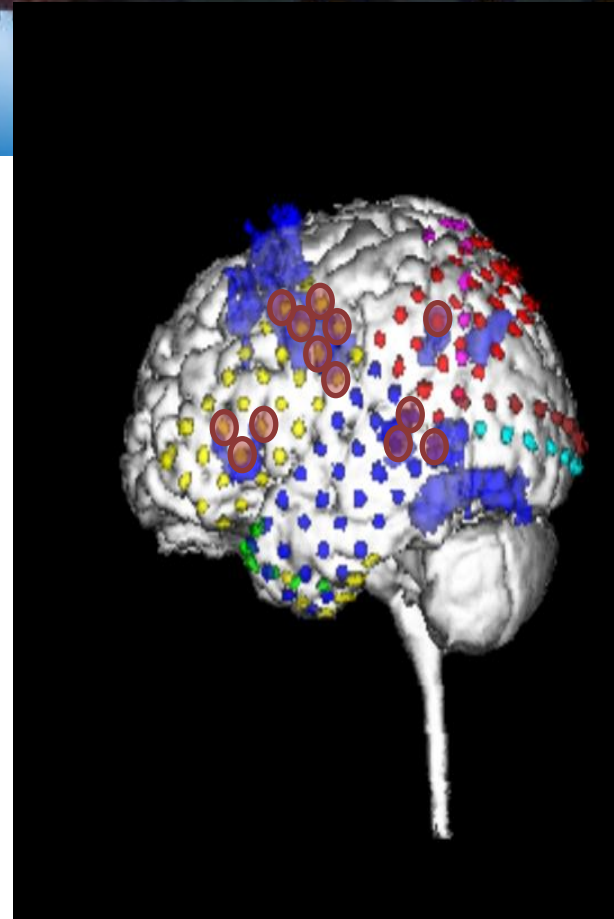
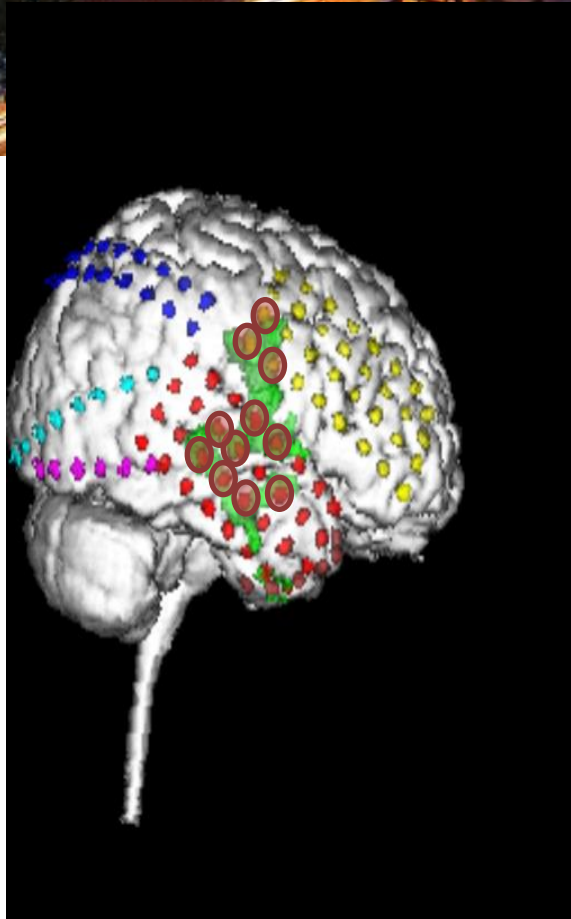


35th annual

CONFERENCE

- 7, 2015

stin, Texas





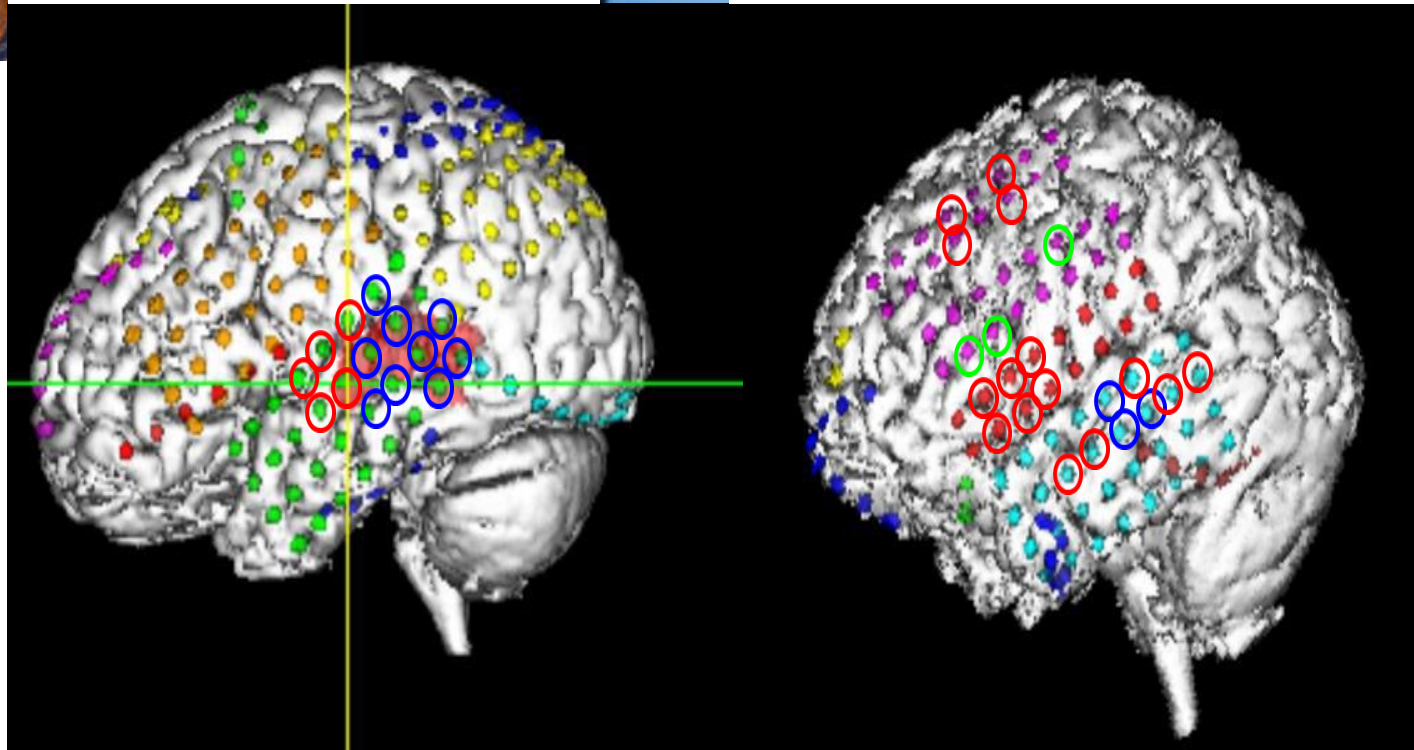
35th annual

CONFERENCE

7, 2015
n, Texas

Figure 1. Patient 8: Story

Figure 2. Patient 5: Story



- True positive
- True negative
- False positive
- False negative

Salinas, Chen, Korostenskaja, et al 2014



fMRI-ESM concordance

fMRI-VG & Story

LIFG activation in RH; BIFG or RIFG activation in LH

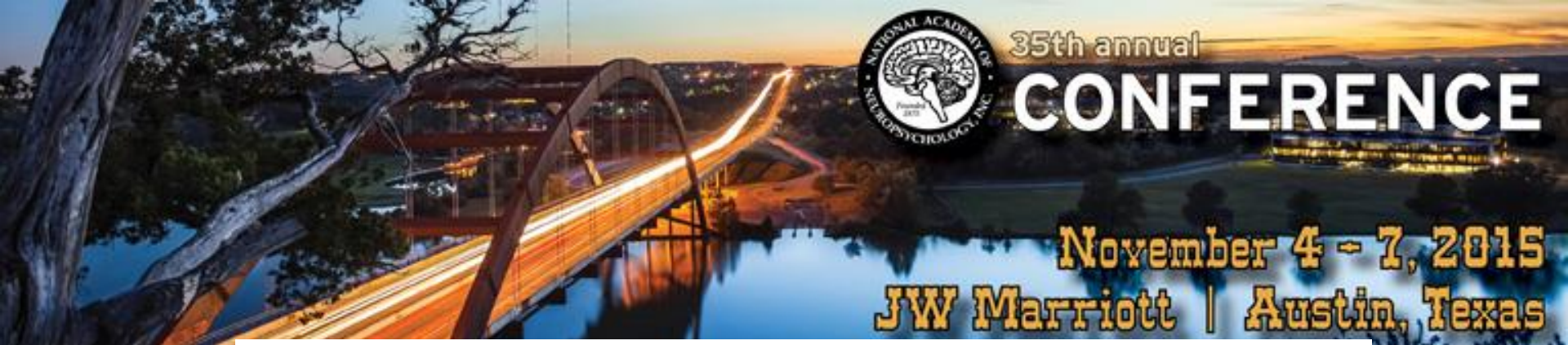
A total of 349 contacts were stimulated across patients; 117 produced a positive response.

43/117 positive contacts were located within an active fMRI cluster

Among the 232 negative contacts, 41 were located within an active fMRI cluster and 191 were not.

The overall **sensitivity of language fMRI was .36** and the **specificity was .82**.

The false positive rate (+fMRI activation; - ESM finding) was .17, and the false negative rate was .63.



Epilepsia, 53(4):639–650, 2012
doi: 10.1111/j.1528-1167.2012.03433.x

FULL-LENGTH ORIGINAL RESEARCH

Imaging language networks before and after anterior temporal lobe resection: Results of a longitudinal fMRI study

*†‡Silvia B. Bonelli, *†Pamela J. Thompson, *†Mahinda Yogarajah, *†Christian Vollmar,
*†Robert H. W. Powell, *†Mark R. Symms, §Andrew W. McEvoy, *†¶Caroline Micallef,
*†Matthias J. Koepp, and *†John S. Duncan

*Epilepsy Society MRI Unit, Epilepsy Society, Chalfont St Peter, Buckinghamshire, United Kingdom; †Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, United Kingdom; ‡Department of Neurology, Medical University of Vienna, Vienna, Austria; §Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom; and ¶Department of Neuroradiology and Neurophysics, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom

-In LTLE, ↑ LMFG activation ↓ naming (100% sensitivity)

-Contralateral reorganization to RMFG ↓ naming

-Activation in posterior remnant of L hippocampus ↔

-Ipsilateral reorganization to LMFG ↑ naming



fMRI under sedation

Table 2. Failure Rates (No Activation Obtained in Canonical (Auditory or Visual) Areas

Medication	Auditory Task	Visual Task
Pen	18% (3/17)	25% (4/16)
Pen +	38% (5/13)	15% (2/13)
Pro	21% (4/19)	39% (7/18)
Dex	25% (6/24)	46% (11/24)
Dex-Pro	28% (5/18)	11% (2/18)
Sev	44% (4/9)	44% (4/9)
Average	29%	31.5%

Table 4. Activation Intensity of Cases With Activation in Canonical Areas (Rank 2 to 4)

	Auditory - mean	Auditory - SD	Visual - mean	Visual - SD
Pen	3.5	0.85	3.58	0.67
Pen+	3.5	0.76	3.45	0.52
Pro	2.93	0.88	3.55	0.82
Dex	3.39	0.78	3.69	0.63
Dex-Pro	3.69	0.63	3.56	0.51
Sev	2.8	0.84	2.8	0.45
ANOVA	(A) P = 0.1			
Ho =	(V) P = 0.12			

The null hypothesis was not rejected for either group (Auditory: ANOVA P = 0.1; F = 1.95); (Visual: P = 0.17, F = 1.61).



MEG: overview

- predictions based on the activation/connectivity of Wernicke's area have high level of concordance with Wada
- local patterns of activation associated with cognitive operations that are critical for word comprehension (i.e., phonological and semantic processing).
- functional specialization is probably based in the existence of “two segments” of the Arcuate Fasciculus supporting phonological and lexico-semantic processing

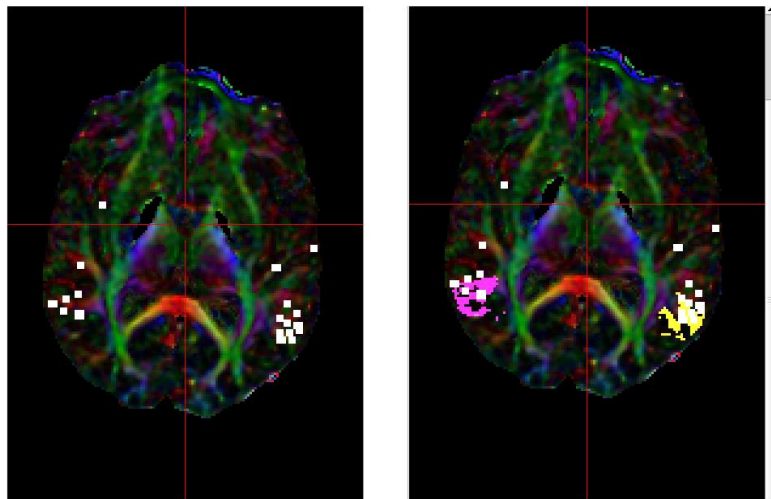
Papanicolaou et al. (2004); Glasser and Rilling, (2008).



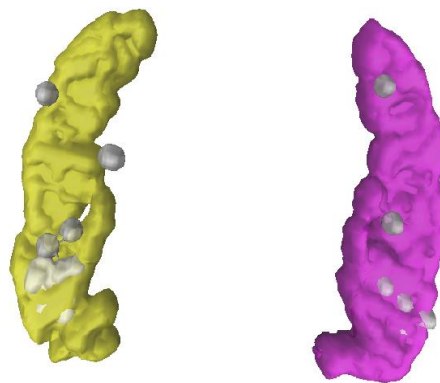
MEG-DTI

- tested the existence of specialized cortical regions and tracts within WA supporting specific word comprehension subprocesses (i.e., phonological vs semantic processing)
- Activity maps associated with word and pseudoword auditory processing were derived for the late components of the evoked magnetic fields (~180 to 800 msec)
- Active areas were used as a seed for MEG guided tractography analysis
- Regional patterns of activation of STG and MTG were derived for word and pseudoword processing

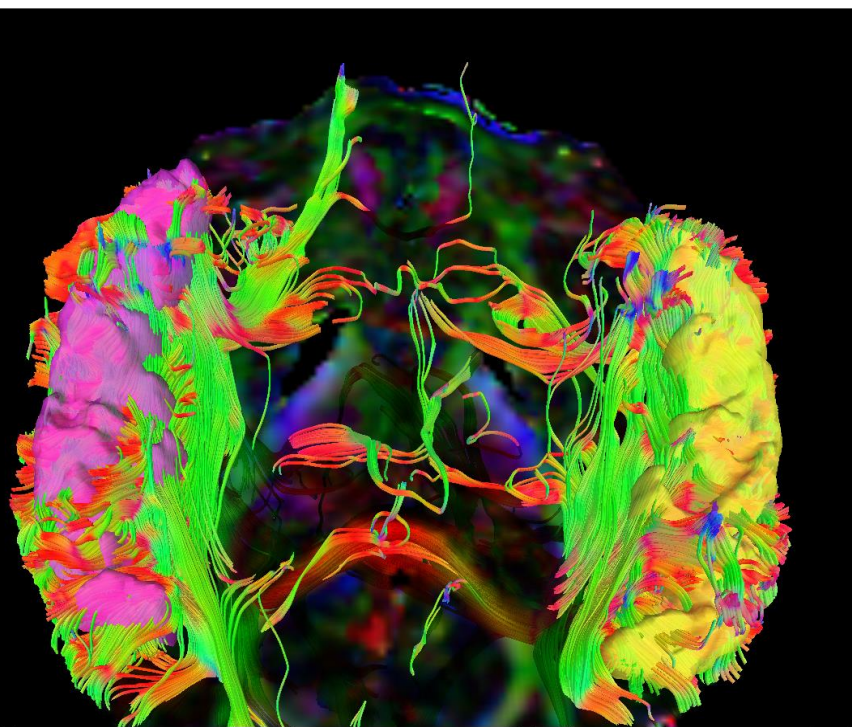
a



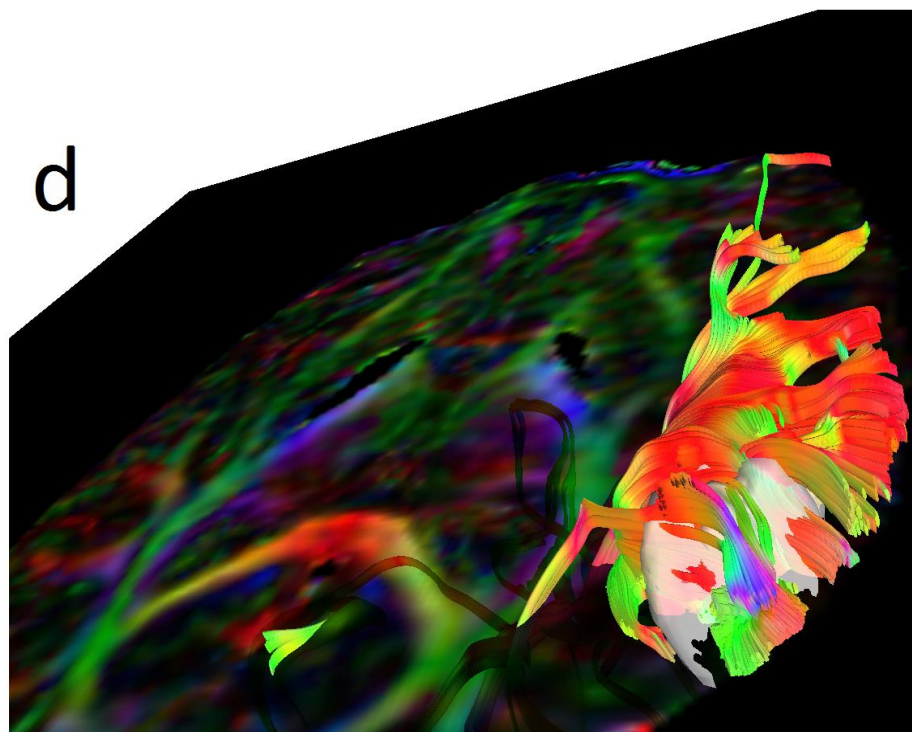
b



c

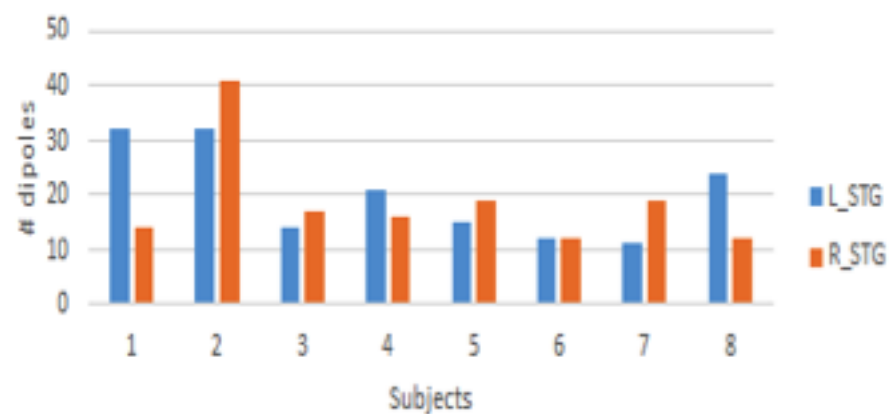


d



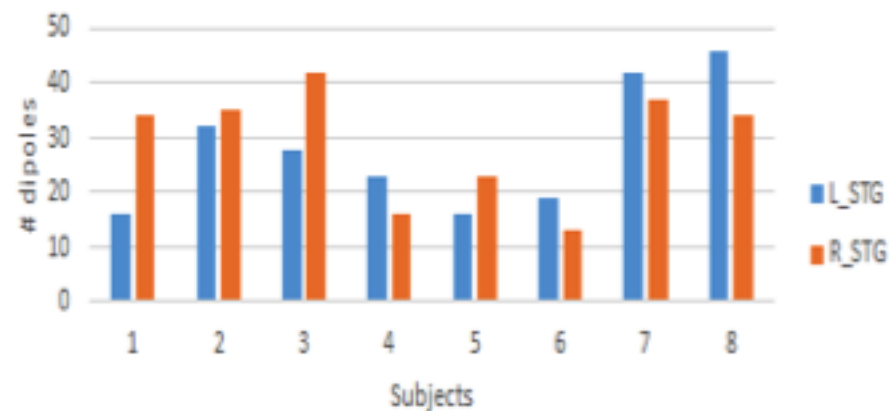
WORD

STG

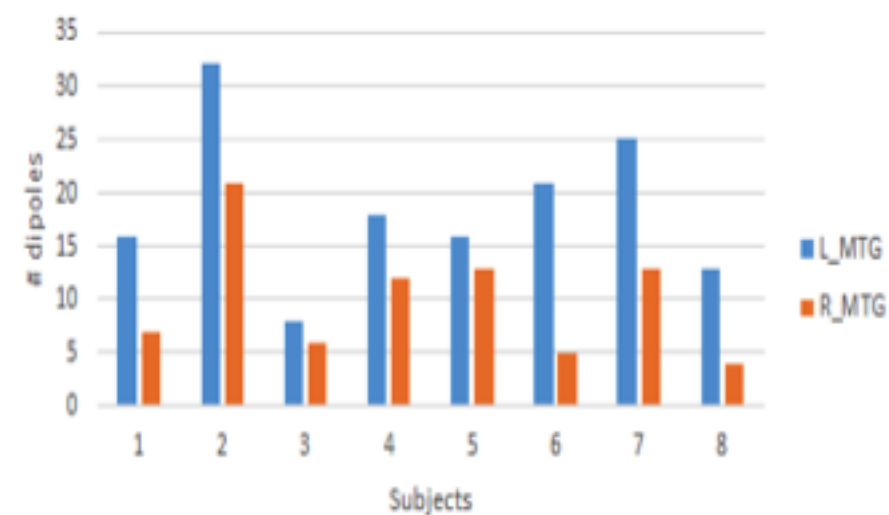


PSEUDOWORD

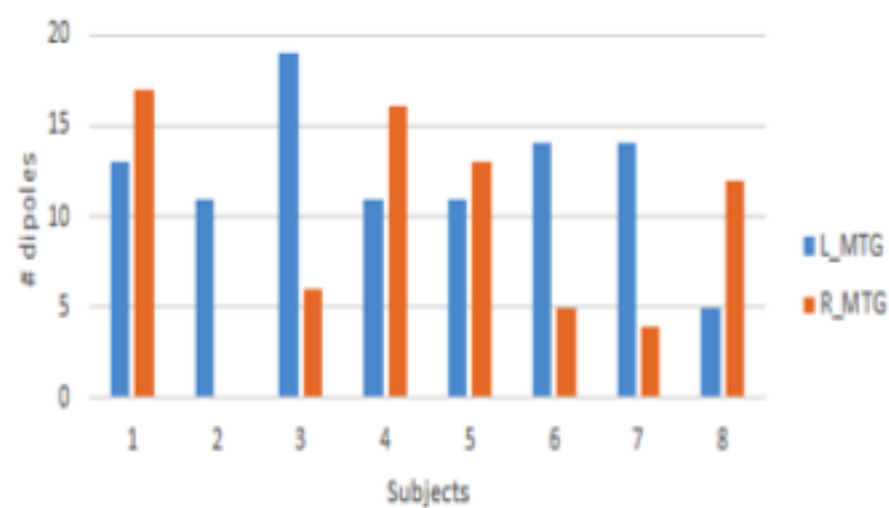
STG



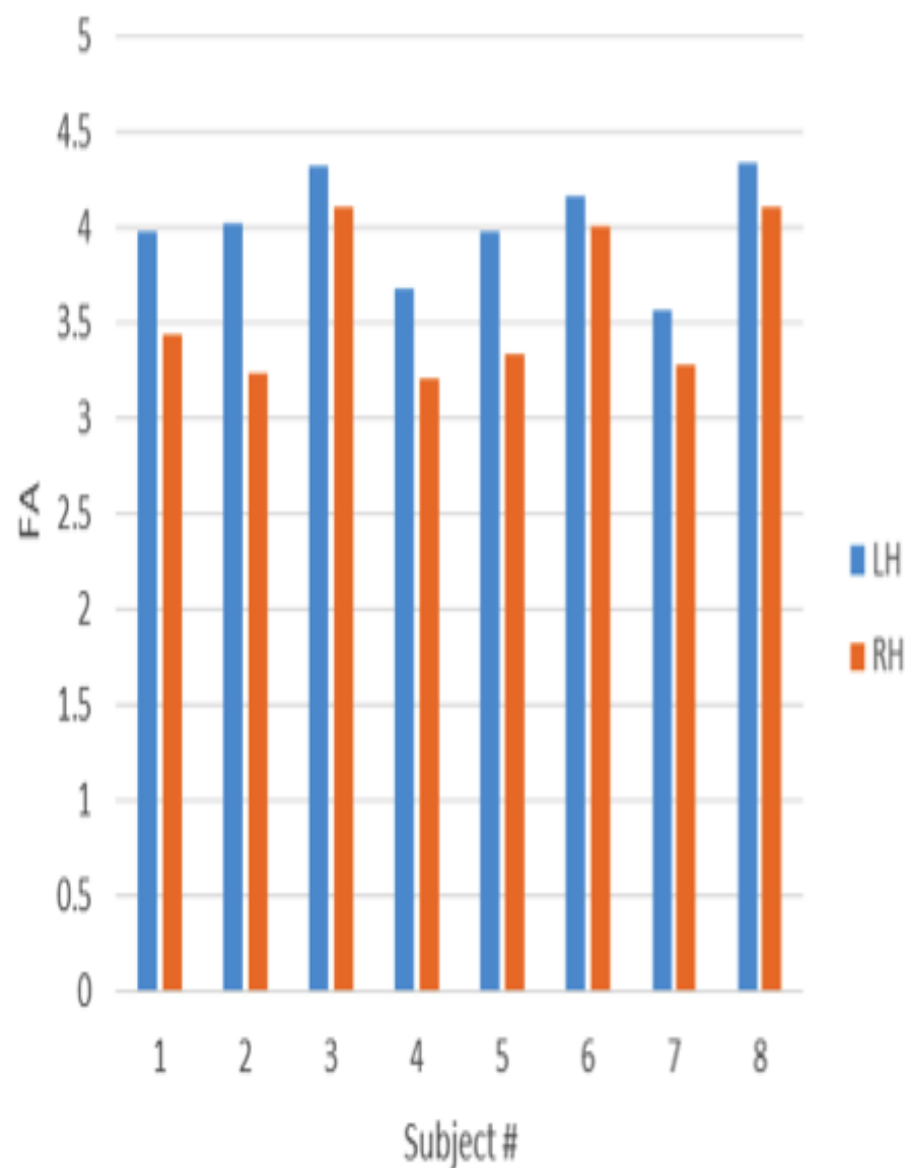
MTG



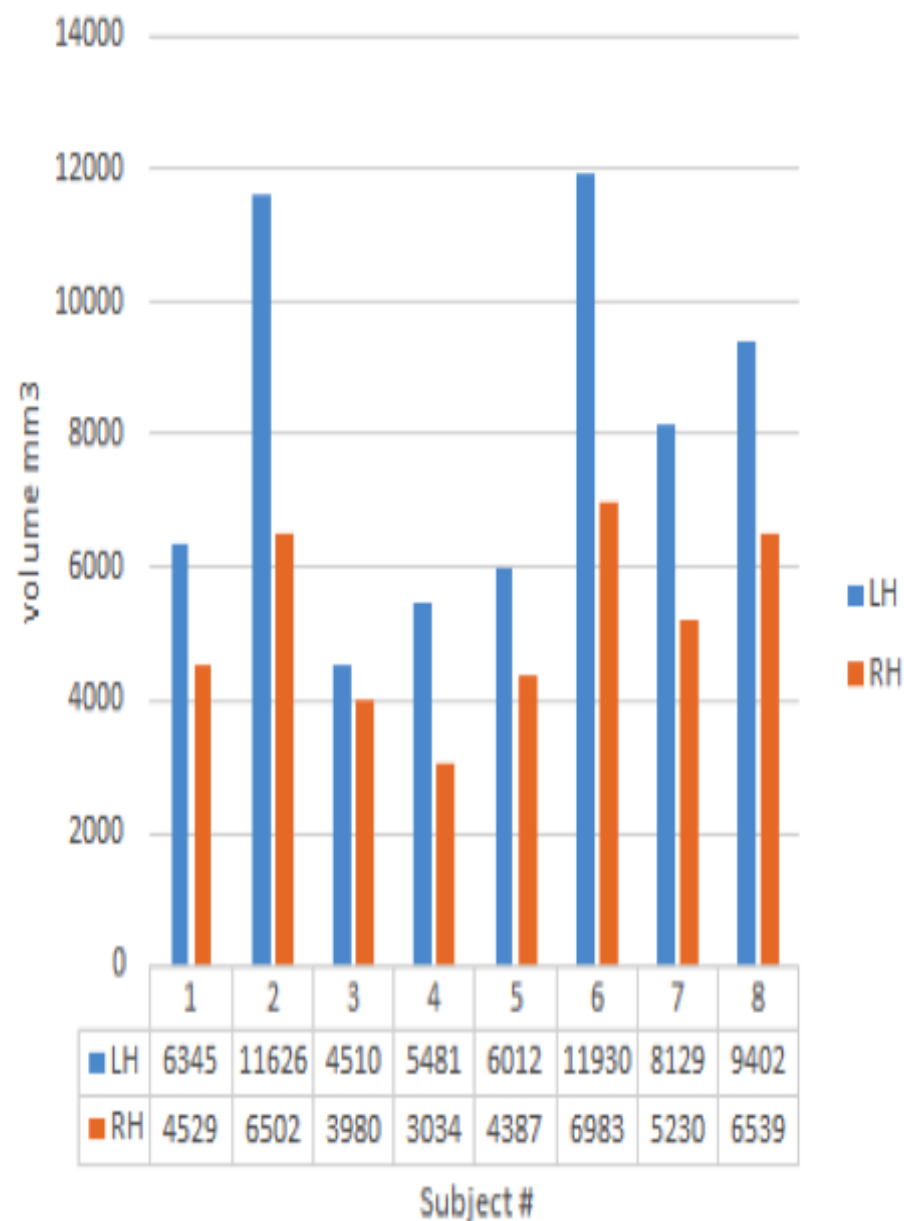
MTG



MEG-Guided Tract FA (Words)



MEG-Guided Tract volume (Words)





Emerging Technique: ECoG mapping

ECoG signal changes in the high gamma band (> 70 Hz) may be most valuable for assessing the task-related activity

Highly congruent results w/ ESM for hand motor cortex mapping (3.19 % false positives and 1.12% false negatives)

Spontaneous recording during typical behaviors (e.g., conversation) showed good consistent with ESM

Average sensitivity of ECoG was 0.62, while the average specificity was 0.75 in review of papers comparing to ESM

100% concordance for both sensitivity and specificity was observed compared to intra-op ESM for tumor cases

Korostenskaja M, Chen PC, Salinas CM, et al., 2014; Cho-Hisamoto, Kojima; Brunner et al. 2009; Arya, Wilson, et al 2015;



35th annual

CONFERENCE

November 4 - 7, 2015

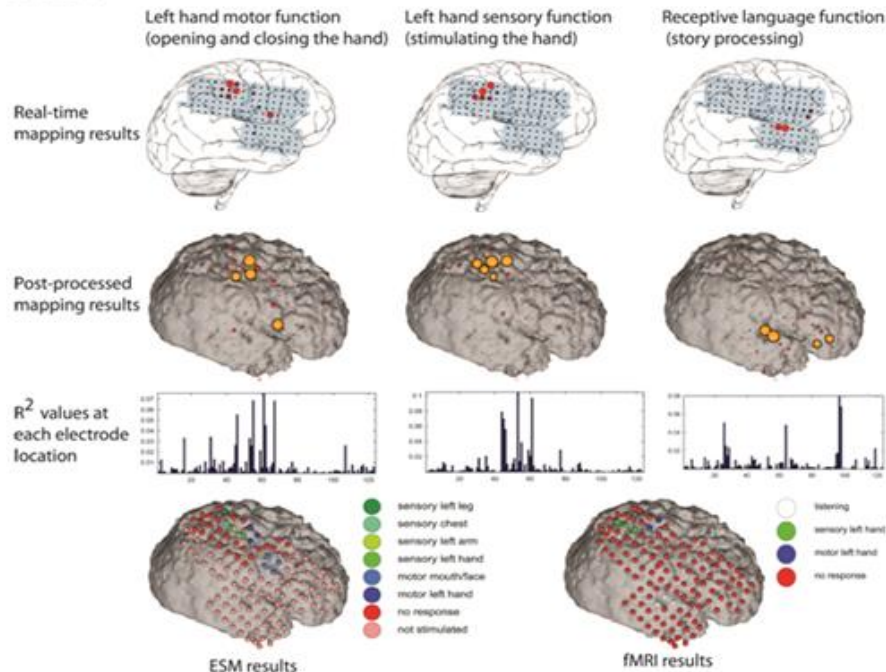
JW Marriott | Austin, Texas

CortiQ-based Real-Time Functional Mapping for Epilepsy Surgery

Christoph Kapeller,† Milena Korostenskaja,‡§|| Robert Prueckl,*† Po-Ching Chen,‡§||
Ki Hyeon Lee,|| Michael Westerveld,||¶ Christine M. Salinas,||¶ Jane Cook,||#
James Baumgartner,|| and Christoph Guger* C.*

a

SUBJECT 10





RTFM-ESM-fMRI concordance

- RTFM is 25% sensitive and 91% specific in determining language-specific cortex compared to ESM
- RTFM showed similar sensitivity and specificity of detecting eloquent language cortex (29% sensitivity and 92% specificity) when compared to fMRI

Predicting Language Outcomes

Equal predictive value of ESM and RTFM for overall language function

Higher ESM predictive value for expressive language (ESM/RTFM 50%/25%)

Higher RTFM predictive value for receptive language (ESM/RTFM 40%/60%).

Korostenskaja M, Chen PC, Salinas CM, et al., 2014



Functional Mapping Summary

- Atypical lateralization is common in epilepsy
- fMRI is useful for guidance of electrode placement
- fMRI predicts language outcomes in adults
- Contralateral reorganization is not always effective
- ESM is generally safe and effective; predicts expressive decline
- ESM results may be task dependent
- RTFM is an emerging technique with clinical promise; may be more effective in reducing risk for receptive decline



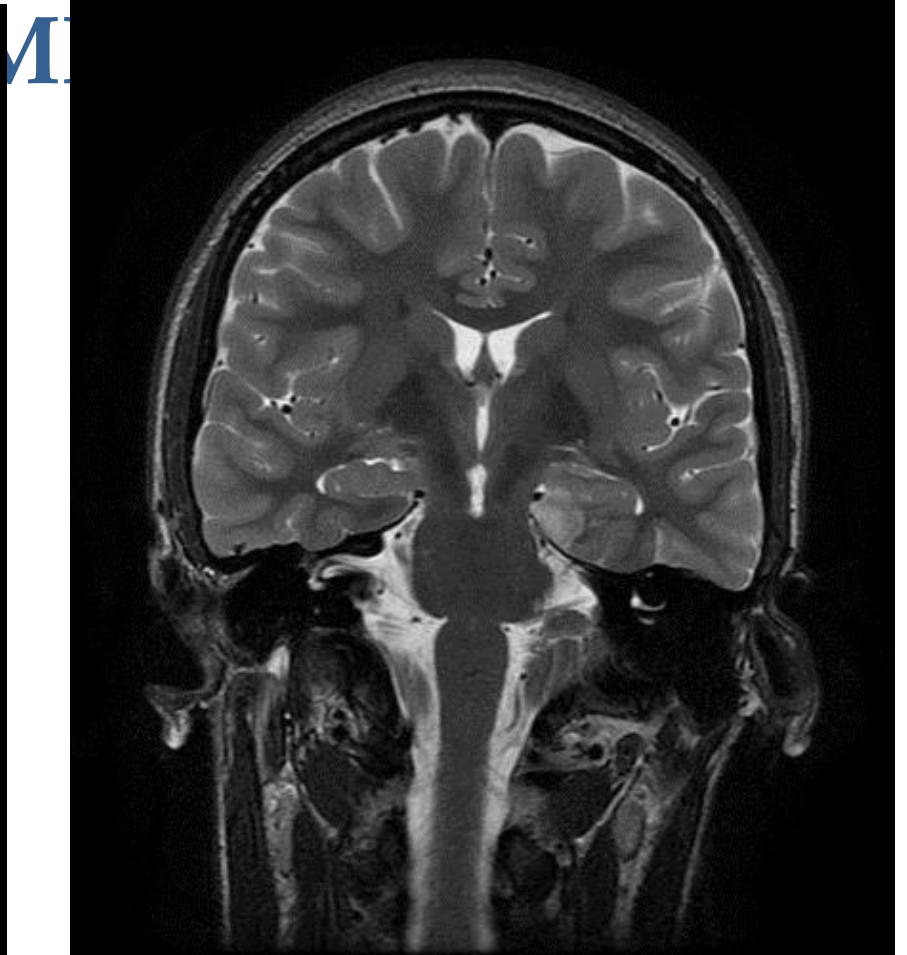
Identifying Patients for Functional Studies

- Wada?
- ESM?
- fMRI?



Patient Scenario #1: Wada

- 14 year old, right handed adolescent woman
- Seizure onset, age 9; initially thought to be panic attacks/anxiety so no imaging done until age 12 after “anxiety” did not resolve with multiple treatment efforts
- NP evaluation showed:
 - VCI=102; PRI=94
 - Verbal and nonverbal memory both WNL
 - Mild deficit in confrontation naming, otherwise normal NP





Patient Scenario #2: Wada

- 15 year old left handed female with one year history of seizures
 - Staring off, unresponsive, and incoherent speech
- NP Exam showed normal function
 - VCI=118; PRI=133
 - Normal verbal and nonverbal memory
 - All other cognitive function intact at above average to superior level

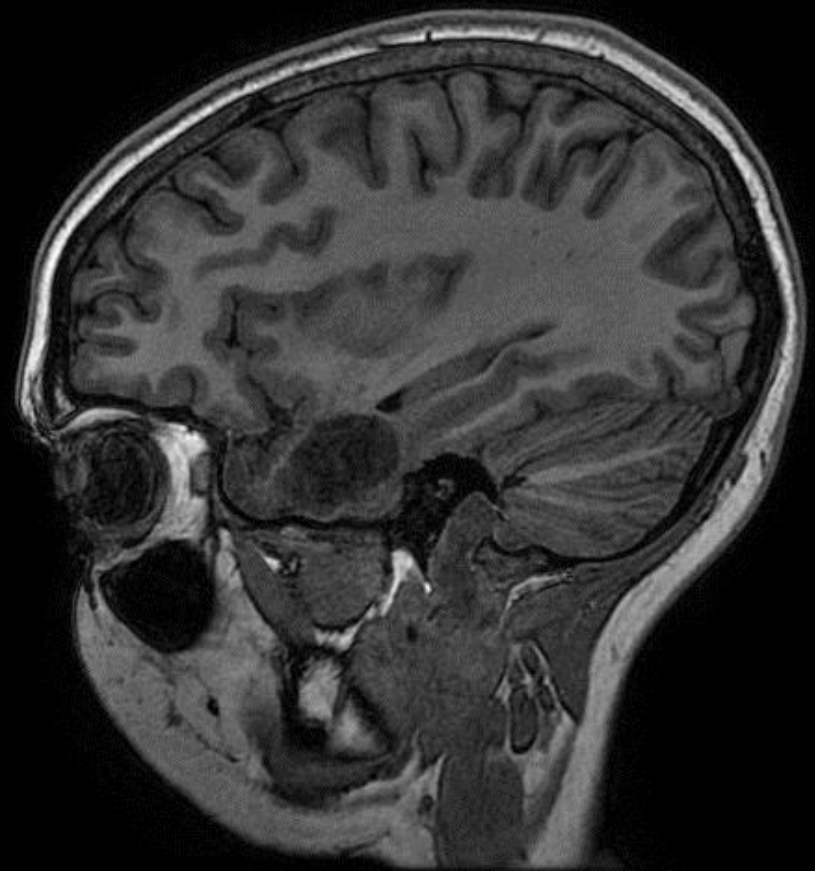
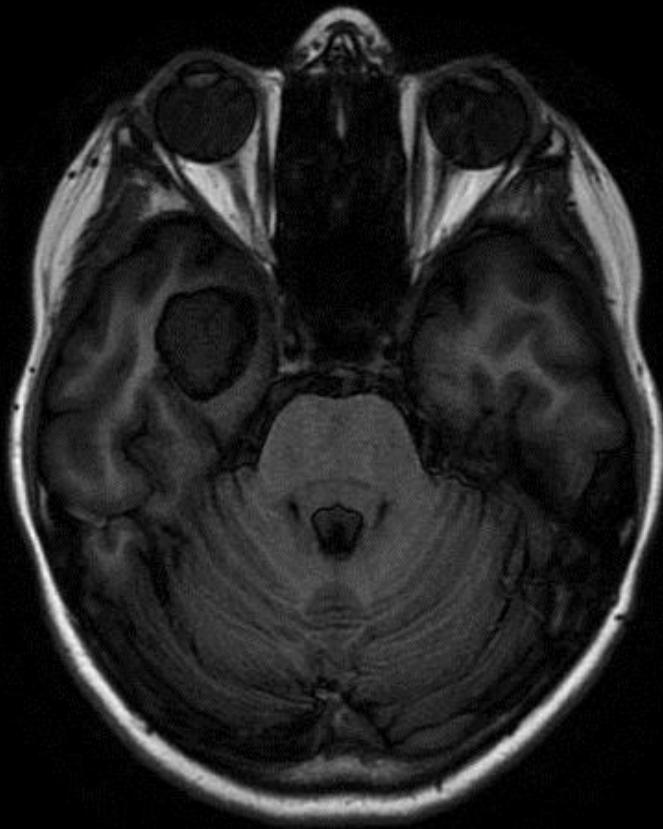


35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas





Patient Scenario #1: Decision

- Rationale
- Outcome



Patient Scenario #2: Decision

- Rationale
- Outcome



Epilepsy Surgery Case Example





35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas

Epilepsy Surgery Evaluation/Treatment

- Phase I
 - vEEG
 - MRI-epilepsy protocol
 - PET
 - Interictal/ictal SPECT (SISCOM)
 - MEG
 - **Neuropsychological Evaluation**
 - **fMRI**
 - **Wada**
- Phase II
 - Subdural grid/strips
 - ECoG
 - Functional Mapping
 - **ESM**
 - **RTFM**
- Phase III-Surgery
 - Temporal Lobectomy
- **Post-Op NPE Follow up**



Background History

15 year-old girl with seizure onset at 9 yrs old

Birth/Developmental History: wnl except for social functions

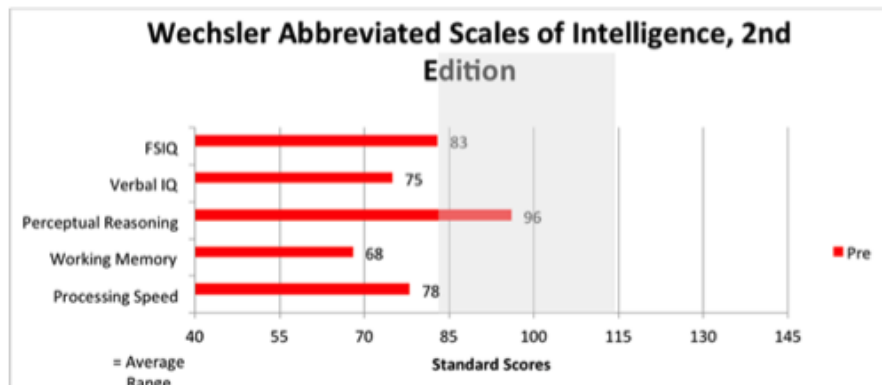
Educational History: B's and C's; retained in 3rd grade

Two seizure types

- Staring and humming lasting less than a min: x1 seizure/week
- Facial twitching, then generalized convulsive seizure
- Tried multiple AEDs, last on lamictal and vimpat



NPE



left fronto temporal pattern; ASD

Language: very low on all tasks (naming, sentence repetition, fluency, vocabulary)

Attn/Exec: poor sustained attention; very low auditory attention; very low novel problem solving

Fine Motor: normal bilaterally

Verbal/Visuospatial Memory

***very low acquisition with limited retention (10-20%); did not benefit from cueing or recognition testing across any tasks**

***Visuospatial: average learning and recall of visuospatial locations**

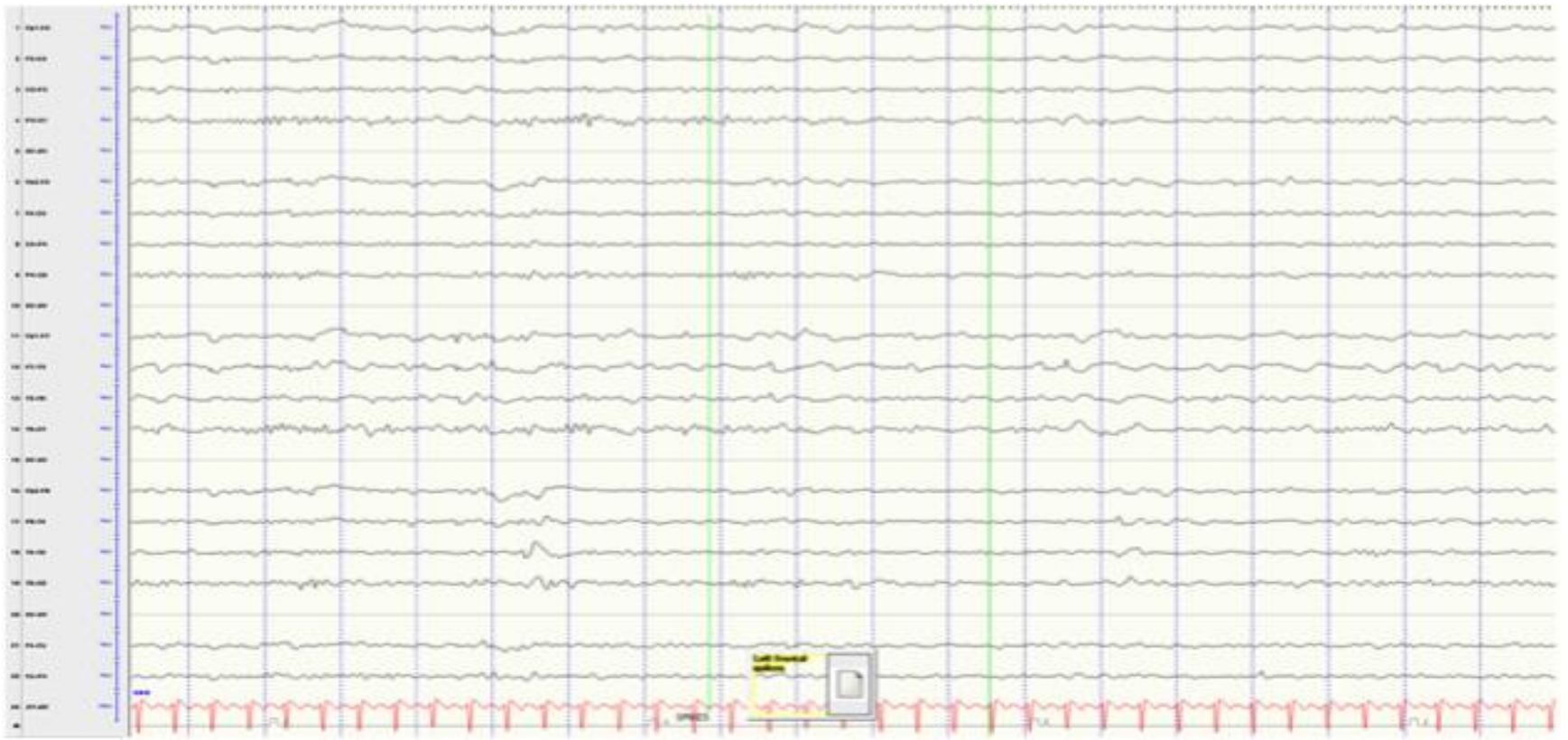


Ictal EEG

- Left parasagittal onset: medial parietal or posterior frontal with spread to the left temporal region noted

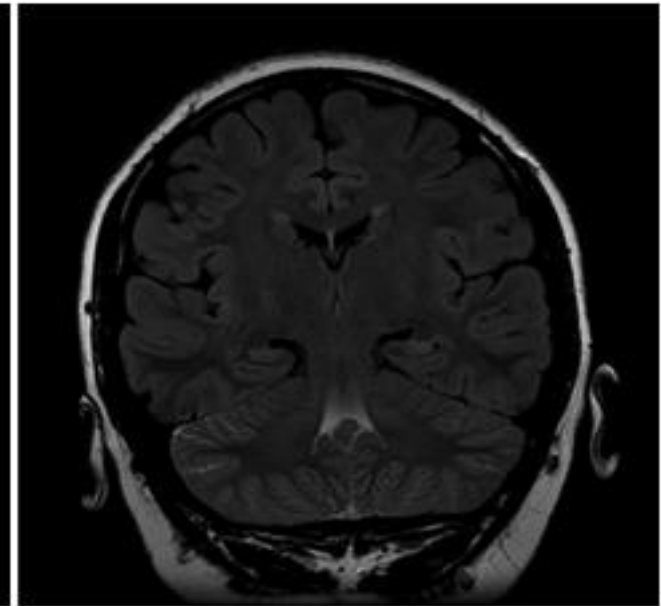
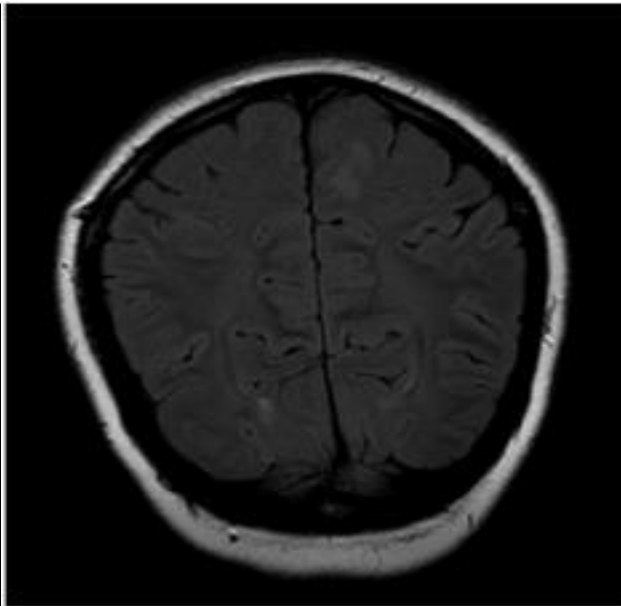
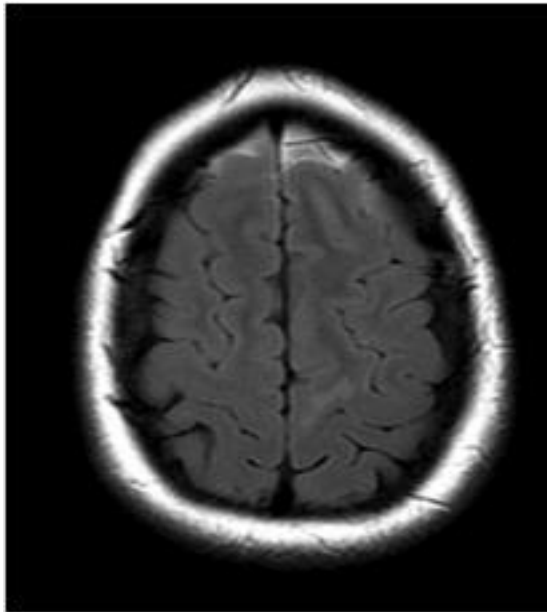


interictal spikes





MRI





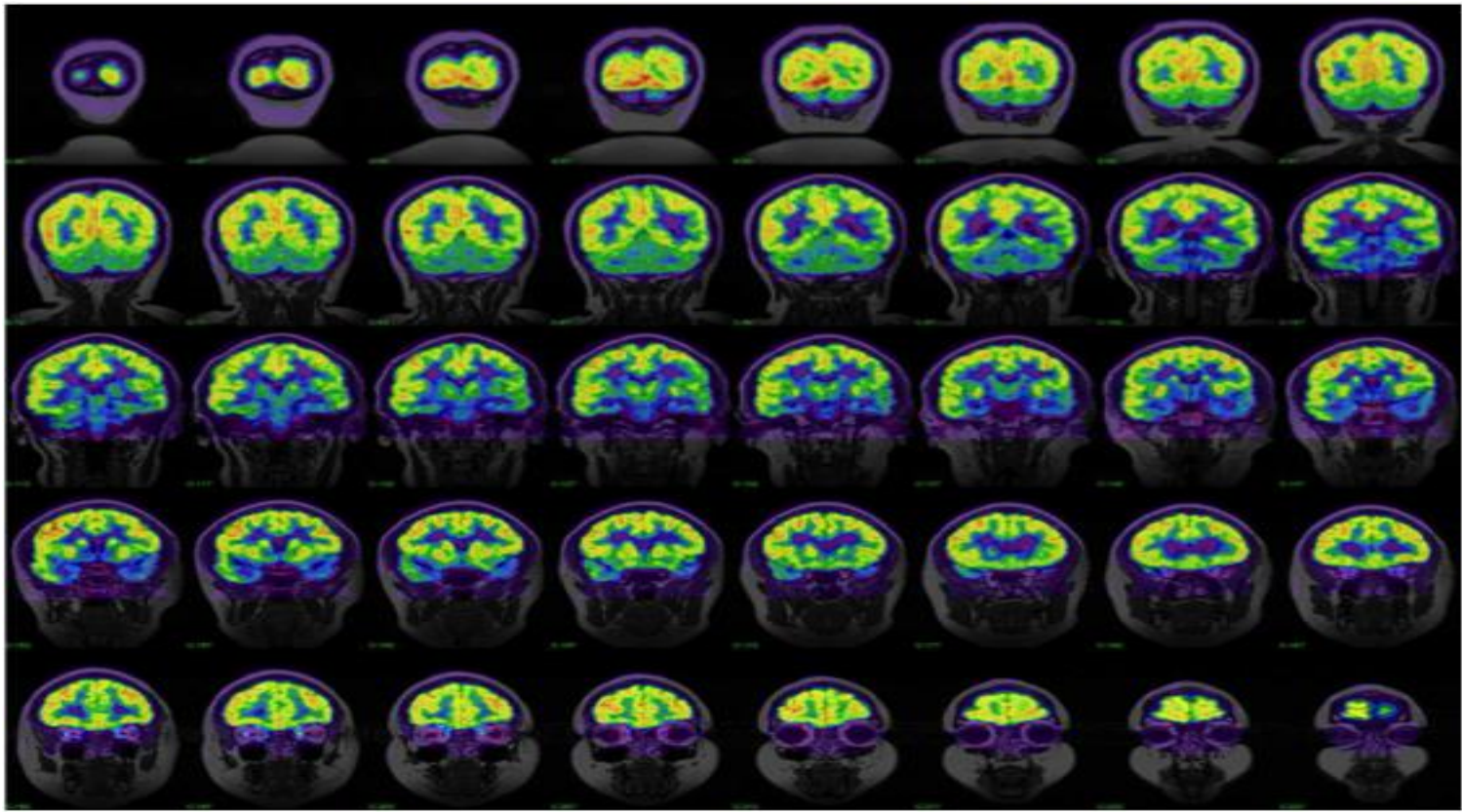
35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas

FDG-PET

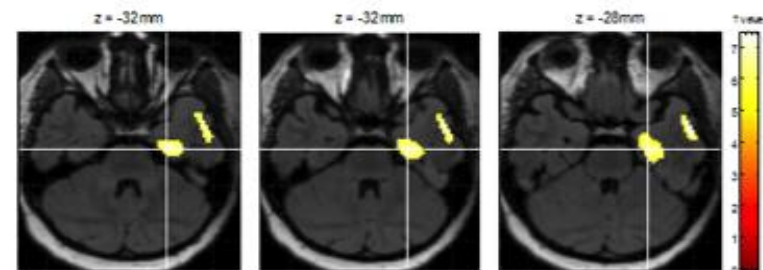
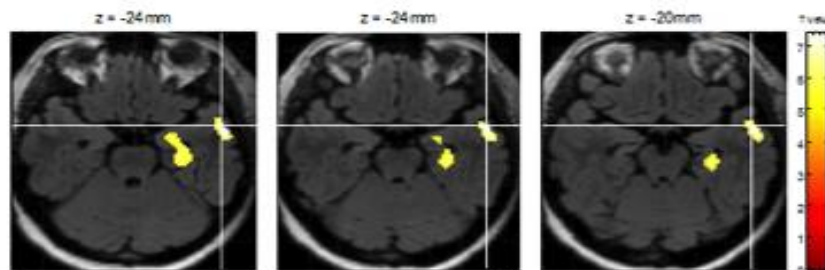
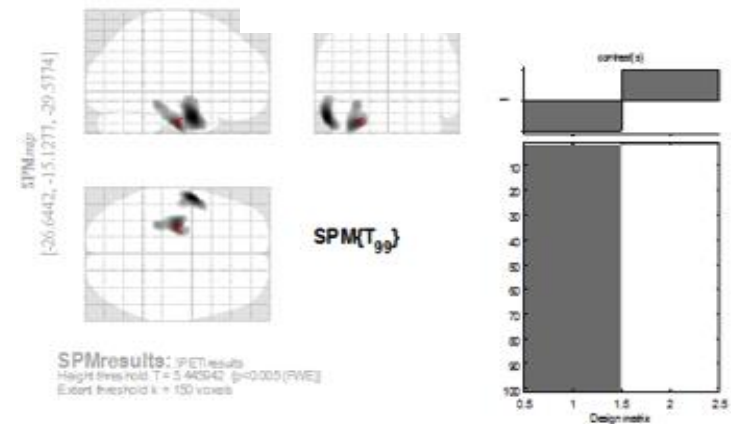
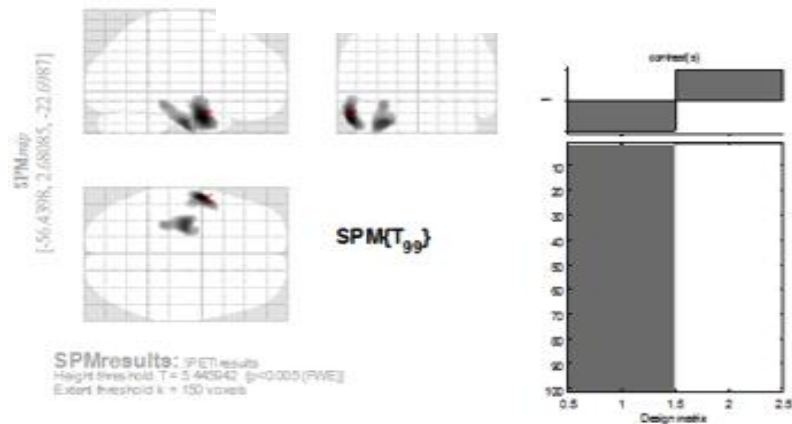




35th annual

CONFERENCE

November 4 - 7, 2015
JW Marriott | Austin, Texas





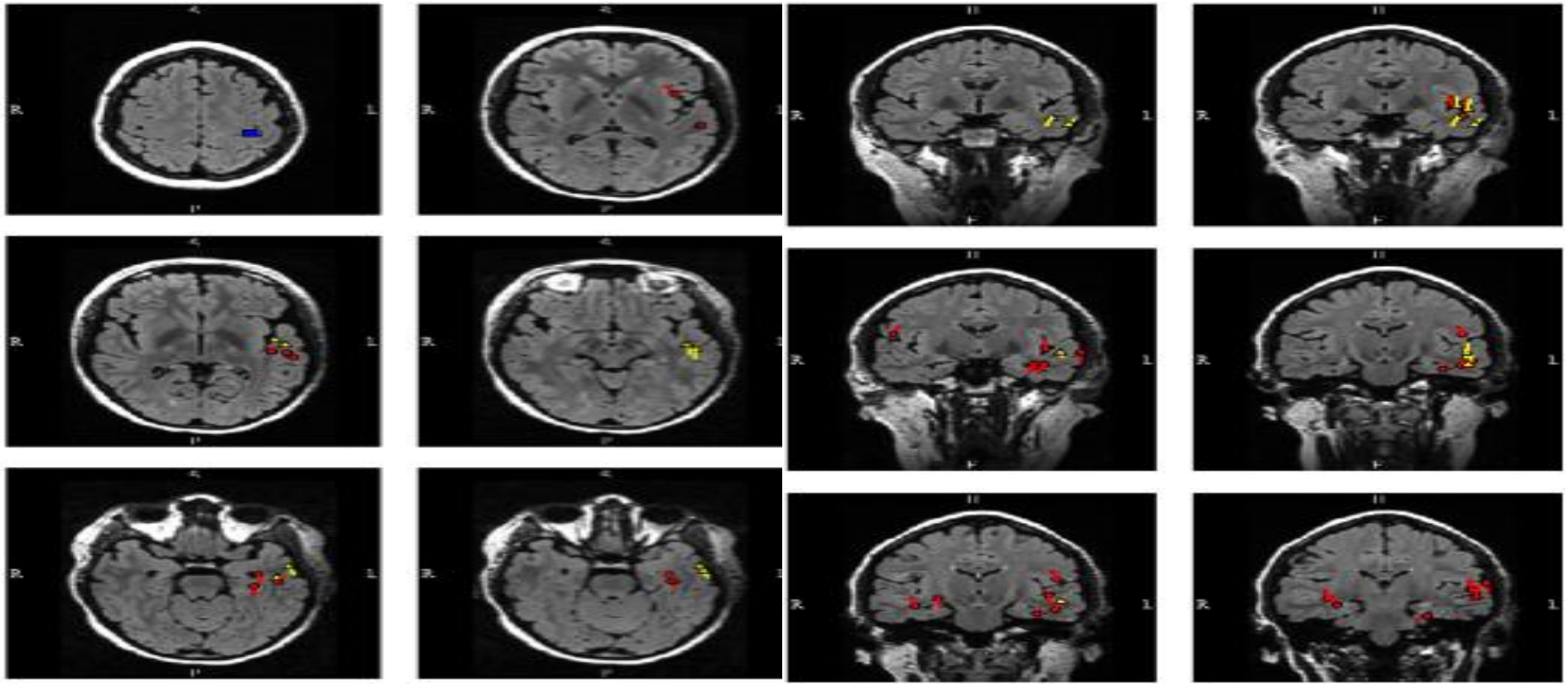
35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas

MEG





Hypothesis & Plan

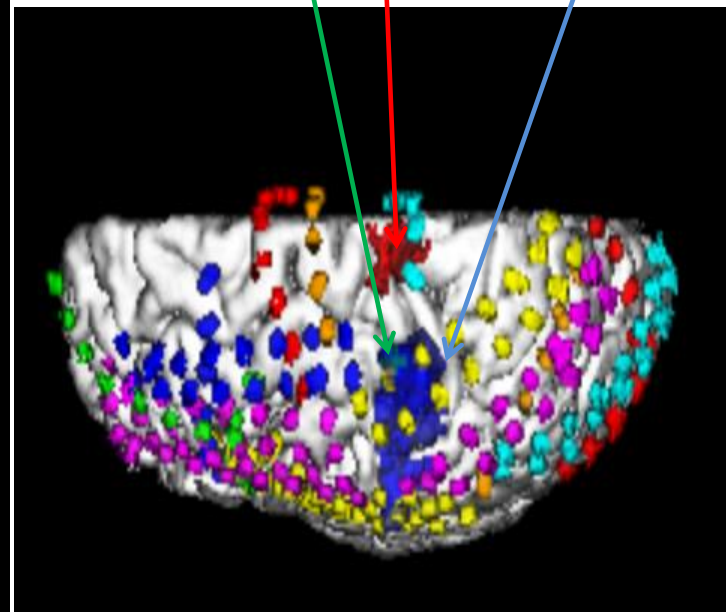
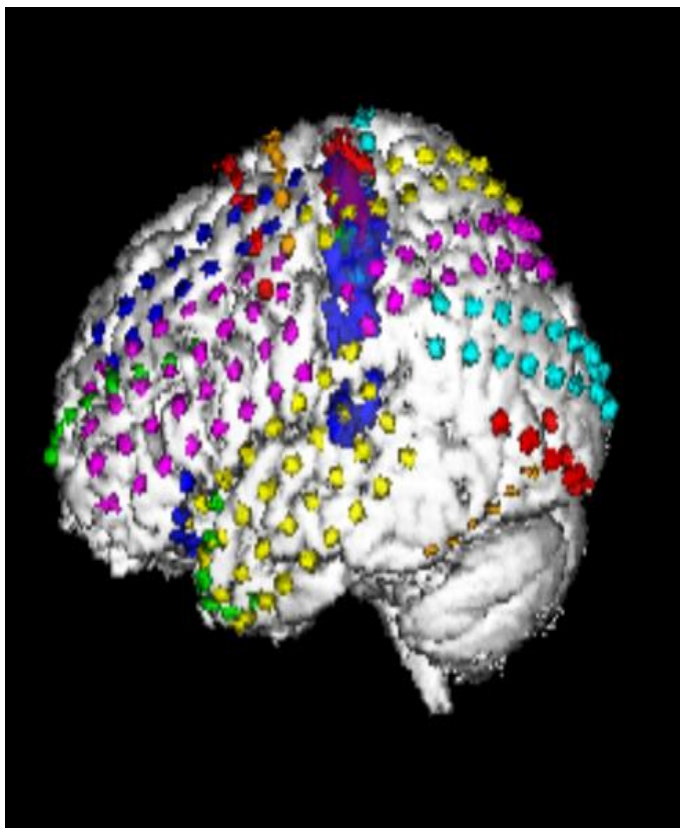
- Left hemisphere onset focal epilepsy
- Dual pathology
- Subdural grid coverage over the left hemisphere: left frontal lesion and the temporal lobe

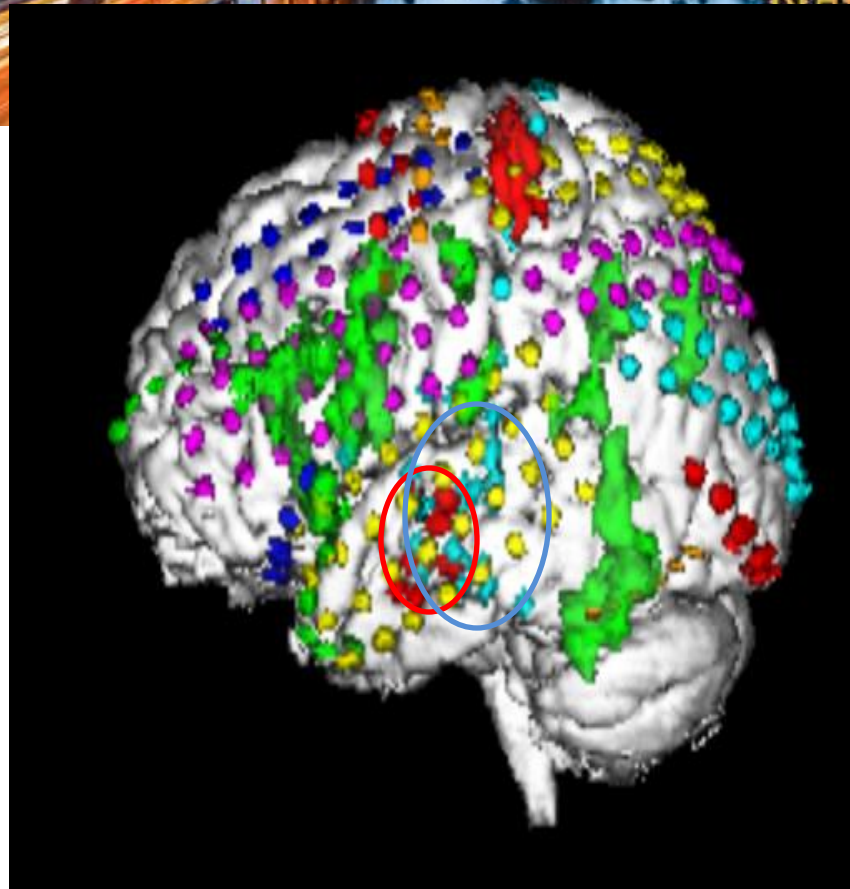
fMRI+Wada

ESM



Lesion (red blob)
MEG motor (green dot)
fMRI motor (blue blob)





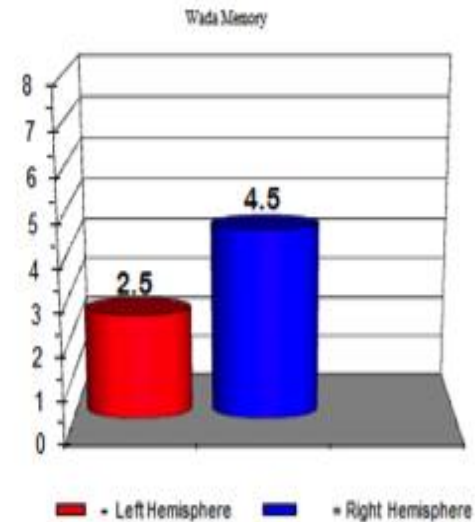
MEG receptive language (cyan dots)

MEG spike (red dots)



Wada

- L language dominant



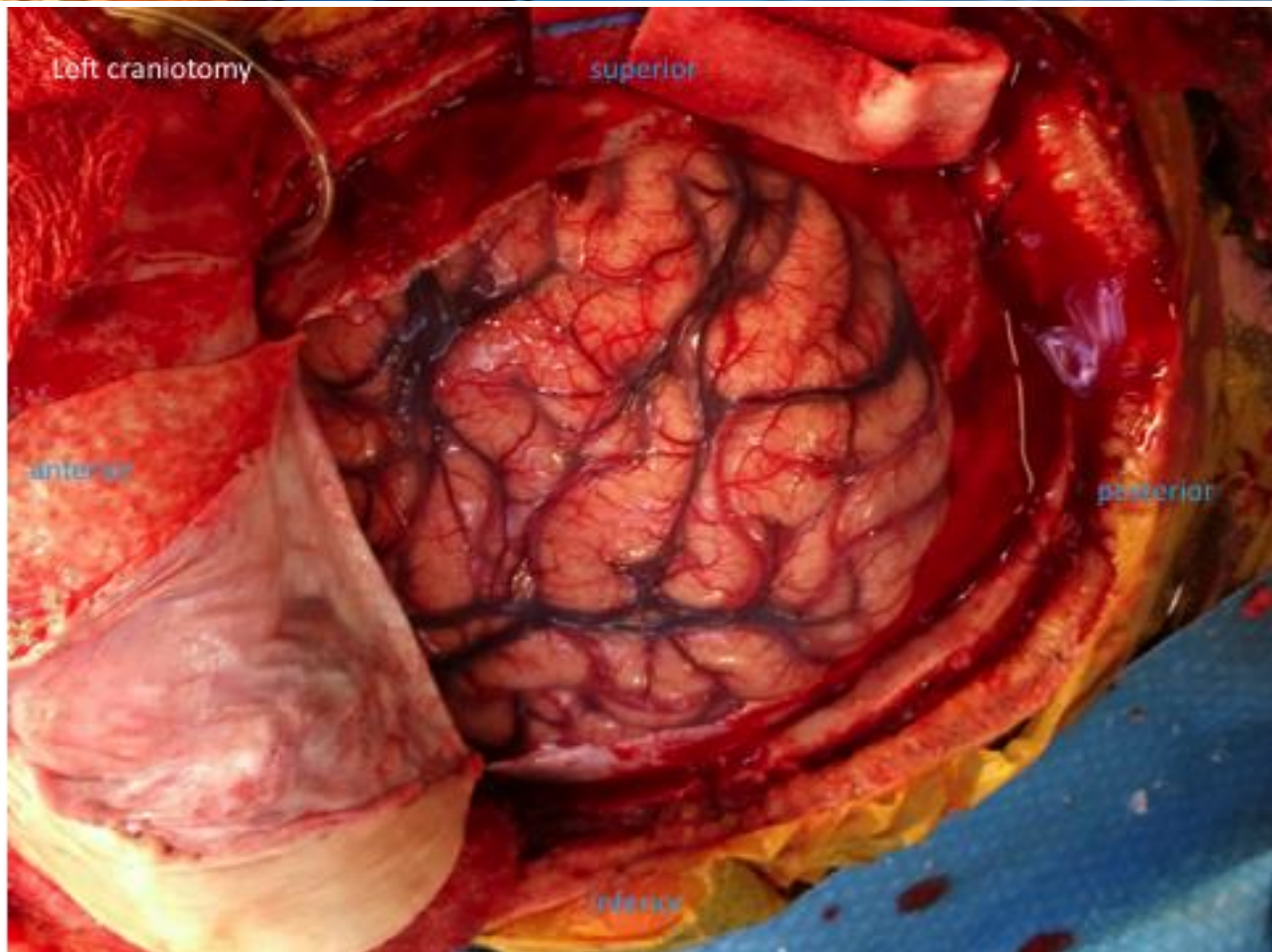


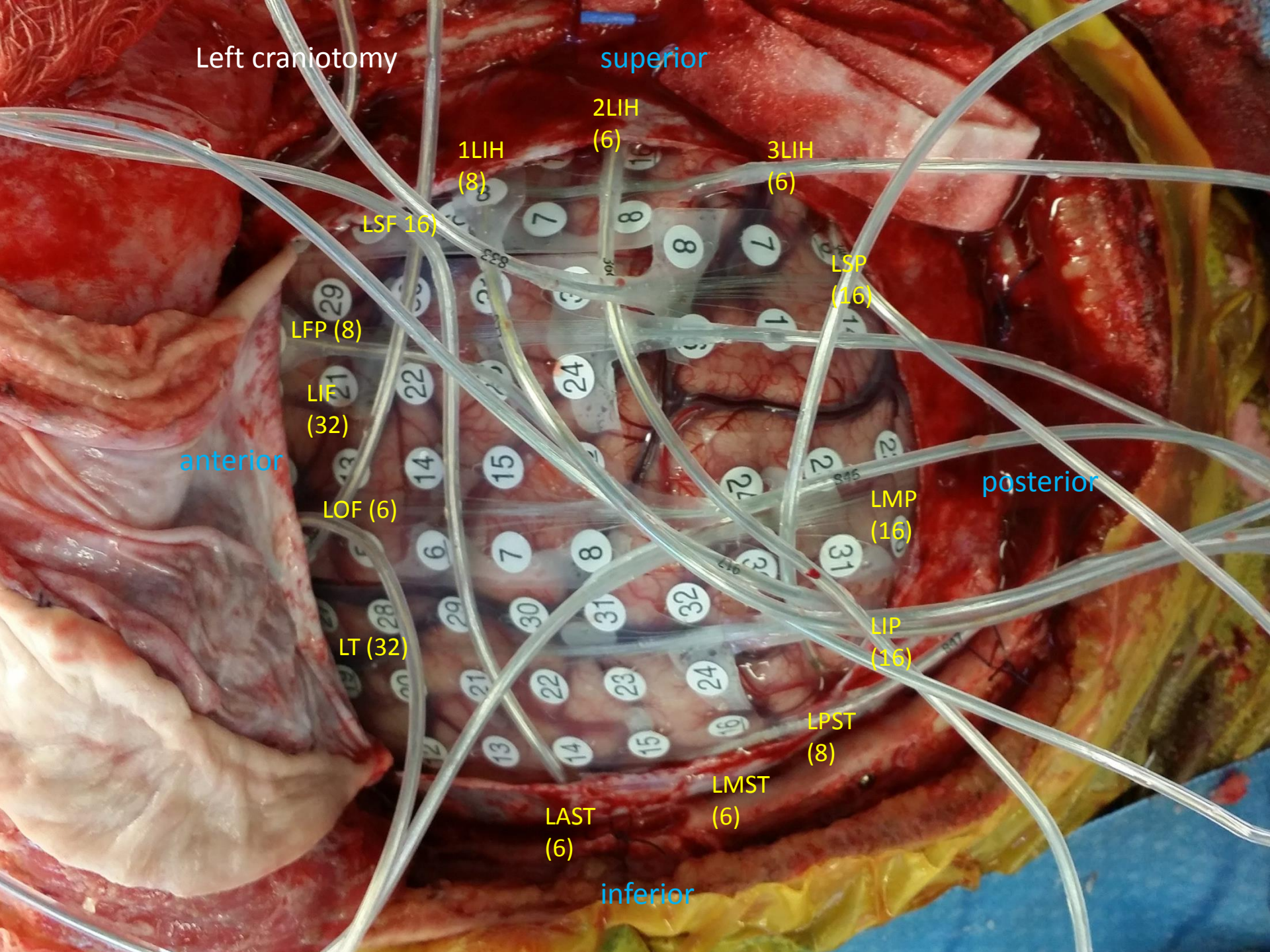
35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas





Left craniotomy

superior

2LIH
(6)

1LIH
(8)

3LIH
(6)

LSF 16)

LSP
(16)

LFP (8)

LIF
(32)

anterior

LOF (6)

LT (32)

posterior

LMP
(16)

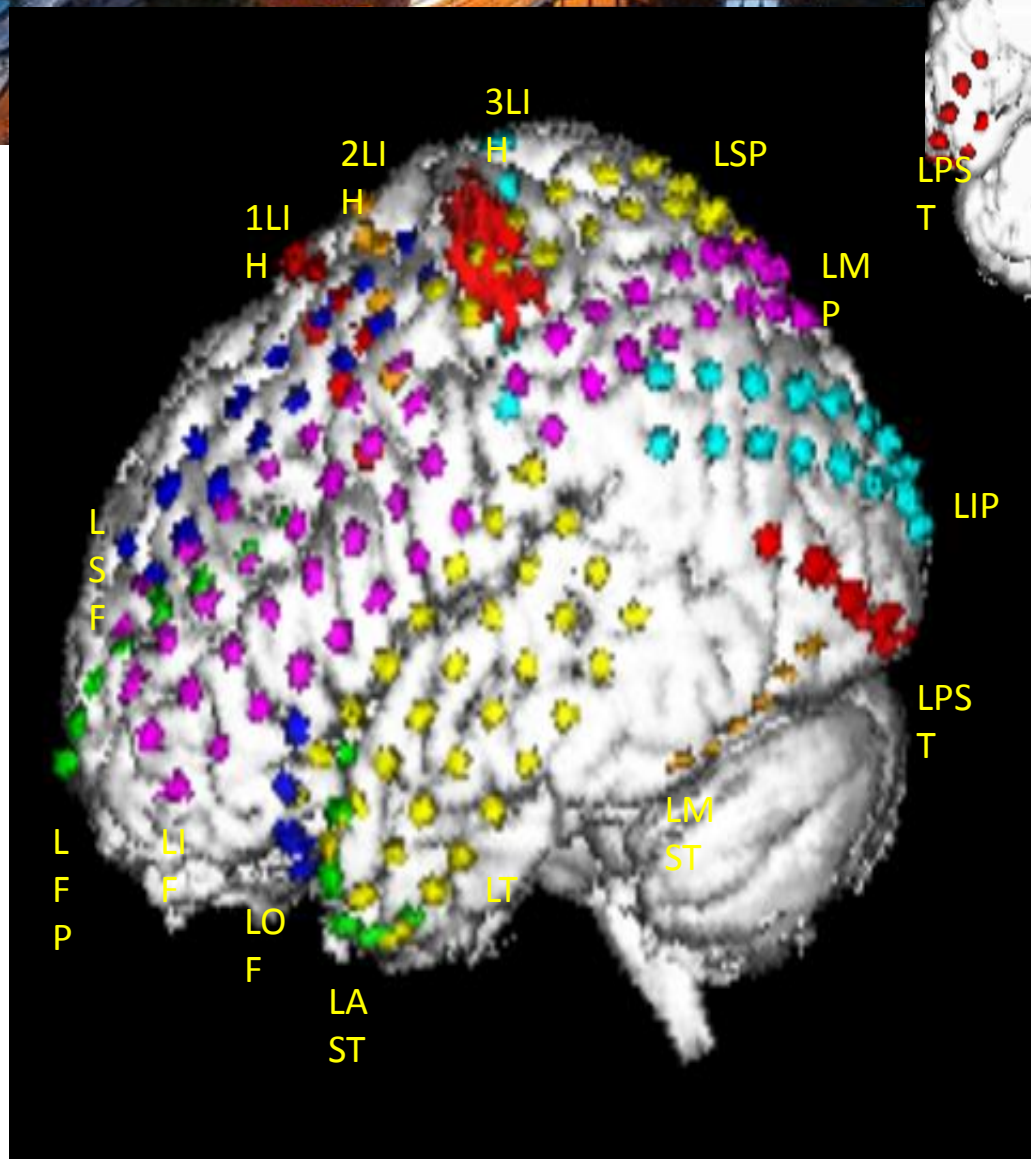
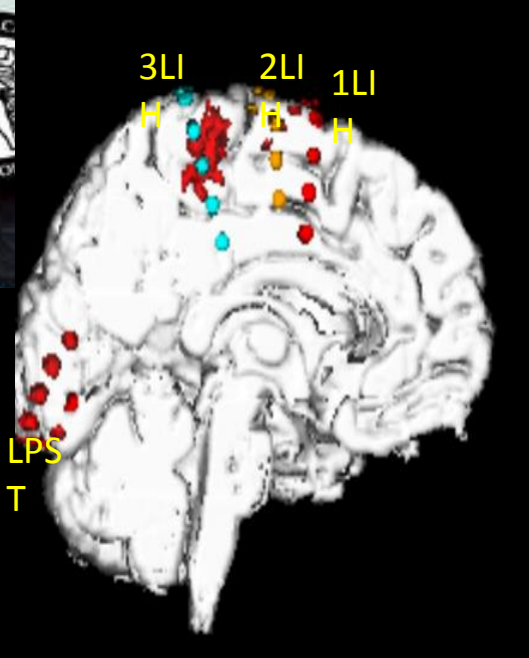
LIP
(16)

LPST
(8)

LMST
(6)

LAST
(6)

inferior



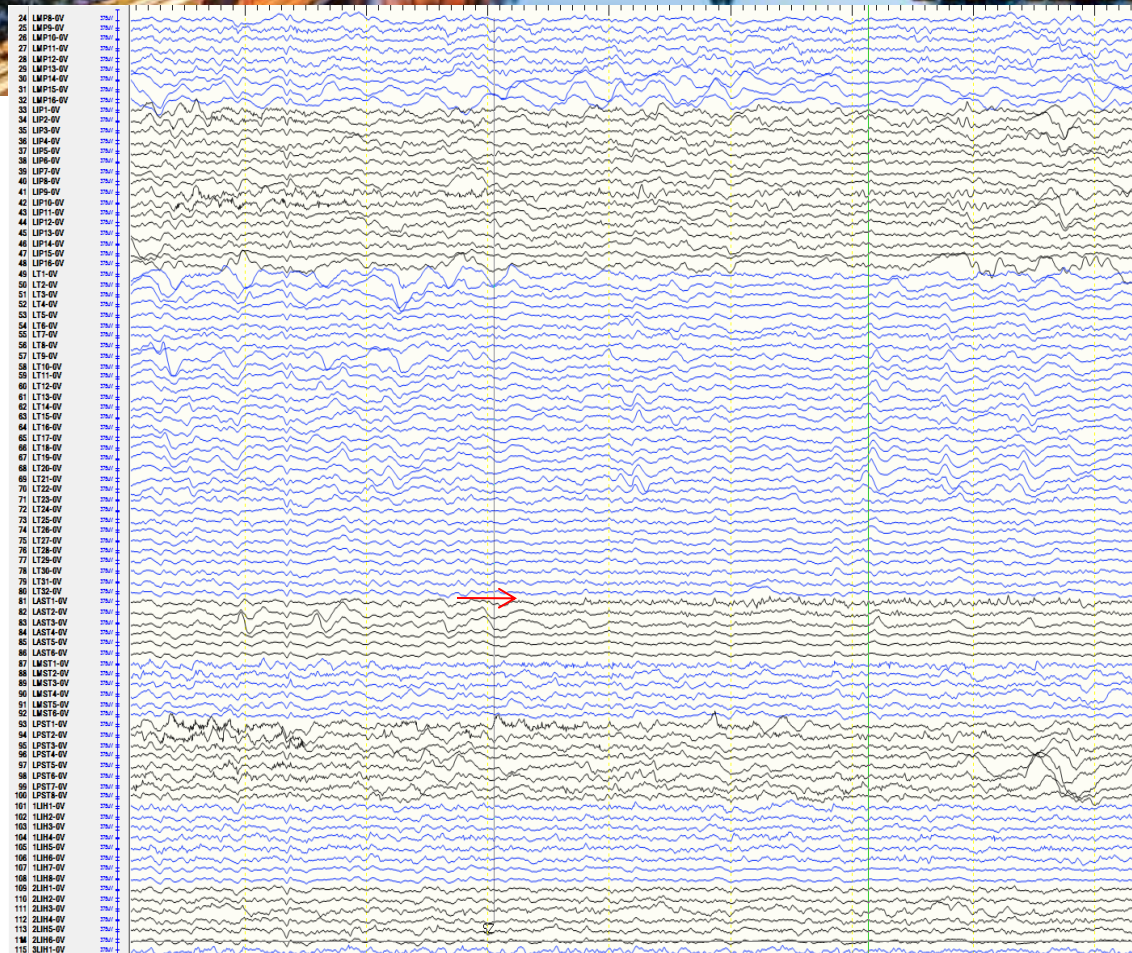


35th annual

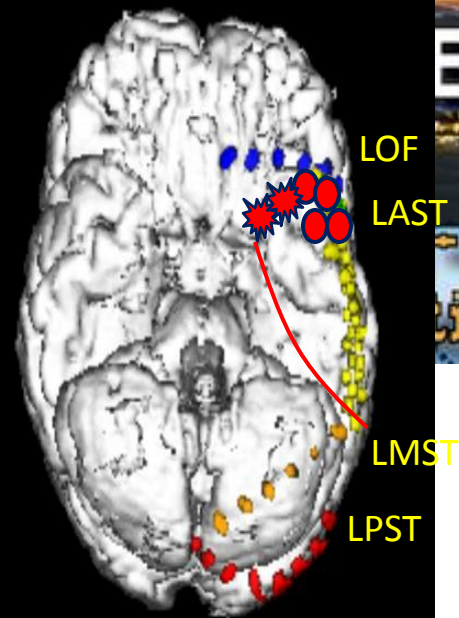
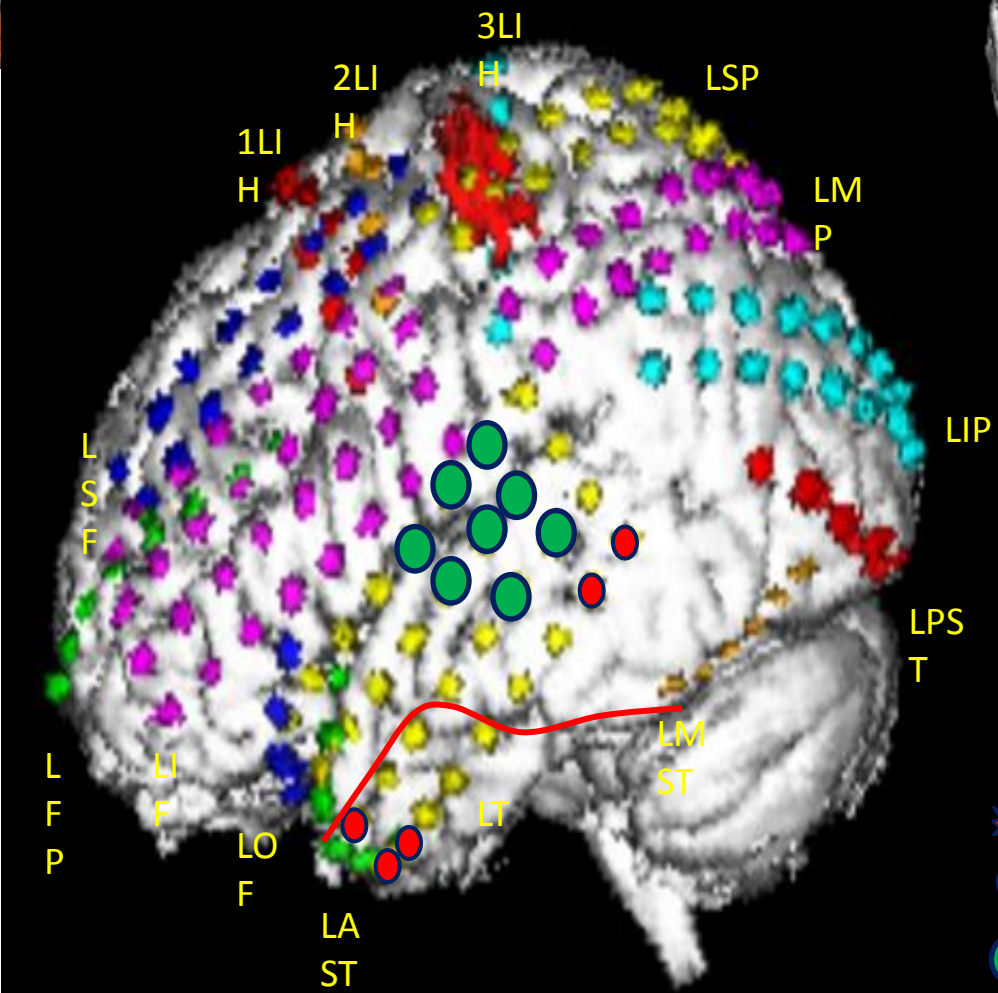
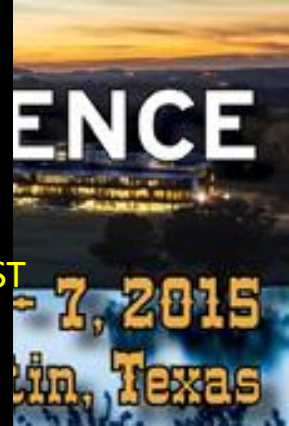
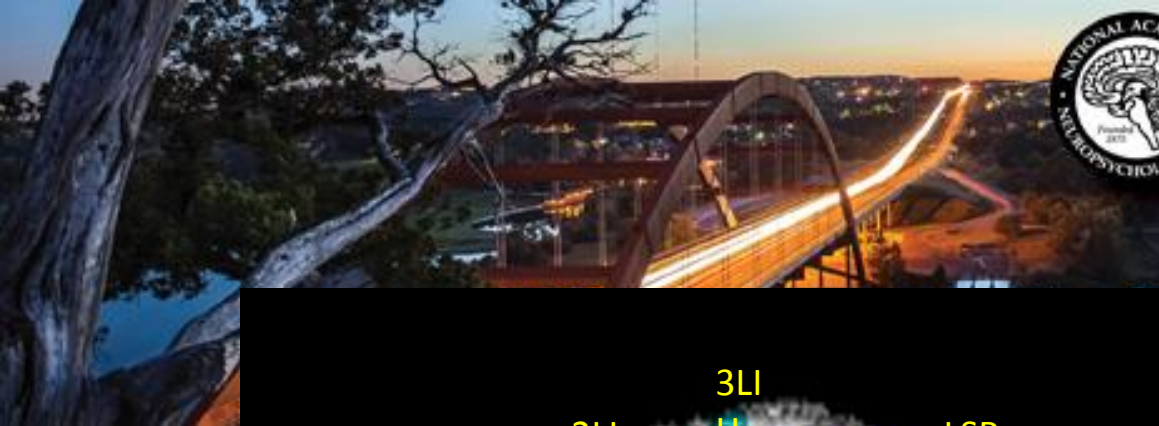
CONFERENCE

November 4 - 7, 2015

Austin, Texas



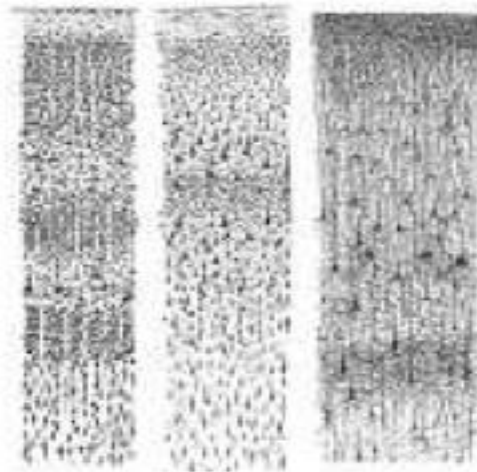
High frequency fast activities
in LAST 1



-  Ictal onset zone
-  Epileptogenic
-  Language cortex



**The brain is a world consisting of
unexplored continents and great
stretches of unknown territory**



Santiago Ramon y Cajal



35th annual

CONFERENCE

November 4 - 7, 2015

JW Marriott | Austin, Texas





Questions/Discussion

