A Clinical Trial of an Advanced Diagnostic Biomedical Device for Epilepsy Patients

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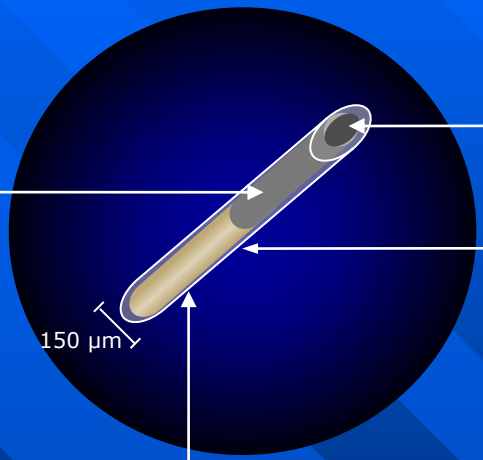
Introduction

- We are developing an advanced biomedical device for the diagnosis of epilepsy in patients during surgery.
- For the first time, the neurochemistry underlying normal and pathologic neuronal function in the intact brain of the epilepsy patient is studied, *in vivo*, in NYU Tisch Hospital under Inst. Review Board Approval, with unique BRODERICK PROBE® biosensors patented by CUNY and NYU.
- Using semiderivative and linear voltammetric circuits, Neuromolecular Imaging (NMI), with our biosensors, the selective detection of specific neurotransmitters and neurochemicals in discrete parts of intact brain are imaged within a temporal resolution of seconds.

The Indicator Sensor of the BRODERICK PROBE®



Carbon-base with several patented formulations

Interfacial surface of the sensor interactive with neurochemicals

Insulating Teflon sheath

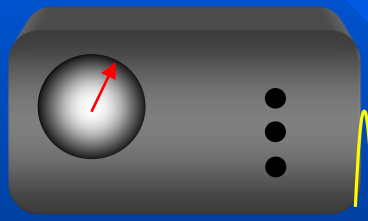
Connector to Potentiostat

Diameter: as small as 1nm
Voltage range: ±1000 mV
Scan rate: ~5-30 mV/sec

The BRODERICK PROBE®

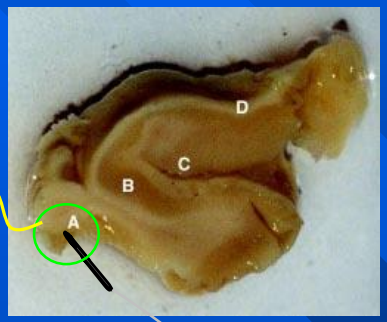
for human and animal studies:

Potentiostat



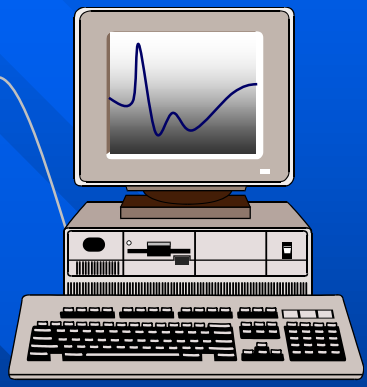
Applies potential to sensor

Implanted Sensor



***Sensor** detects neurochemical concentrations in subiculum*

Output Signal



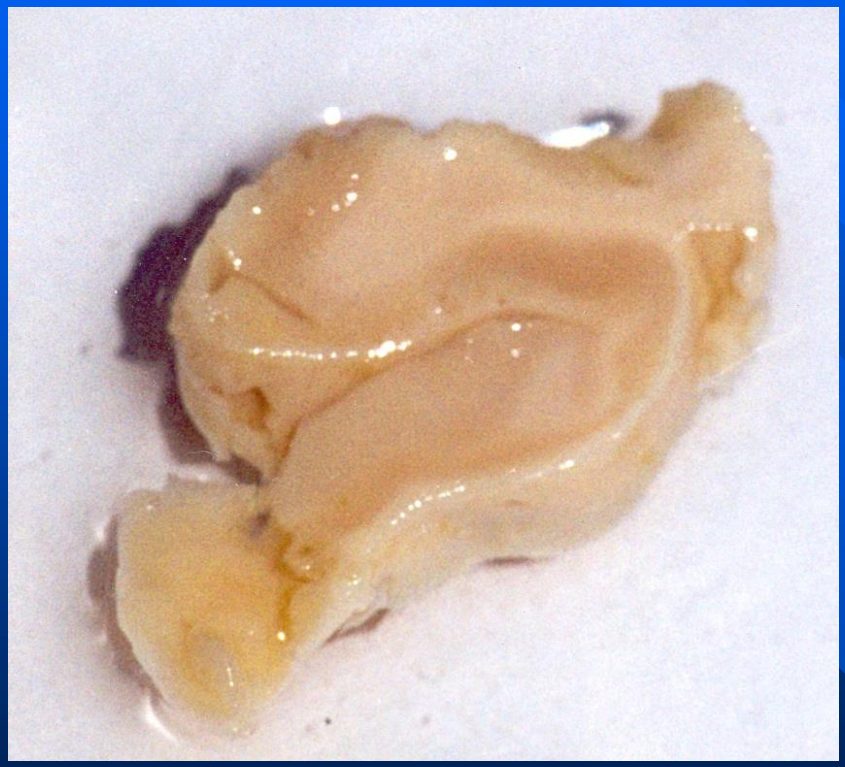
Neurochemical signatures at specific potentials imaged by hardware-software interface

Figure above: A longitudinal section of the human hippocampus resected en bloc from epilepsy patient, just prior to NMI. ***A**, subiculum; **B**, pyramidal cell layer; **C**, granular cell layer of the DG; **D**, alveus.*

NMI – *In Situ* Studies

- NMI studies were performed in resected hippocampus(HPC) *en bloc* in 9 MTLE and 5 NTLE patients.
  - NTLE patients : 28-44 y/o
  - MTLE patients :27-35 y/o
  - Gender ratio was equal
- Criteria for differential diagnosis was absence and presence of atrophy in HPC for NTLE and MTLE patients, respectively.
- Seizure focus in neocortex is necessary for NTLE patients.
- Patients who are refractory to pharmacotherapy seek elective surgery for resection.
- Purpose for NMI during surgery: To define the neurochemistry of the epileptogenic zone for better seizure-free outcome in our epilepsy patients.

Results *In Situ* Studies:



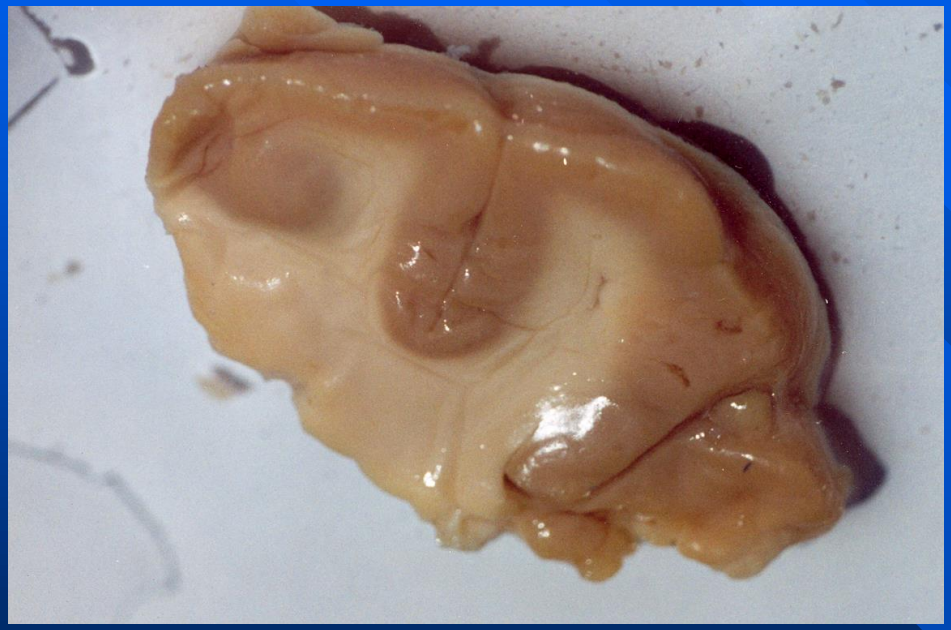
- **Hippocampus(HPC):**
- ***Norepinephrine(NE):***
  - **MTLE > NTLE**
- ***Serotonin(5-HT):***
  - **NTLE > MTLE**

  Broderick, et al., *Brain Research* 878: 42-63, 2000.

  Tryptophan(L-TP):
  - **MTLE > NTLE**

  SV Pacia & PA Broderick. *Bioimaging in Neurodegeneration*. Eds: PA Broderick, DN Rahni, EH Kolodny, Humana Press (now, Springer) 2005. Totowa, NJ: 141-147.

Results *In Situ* Studies:

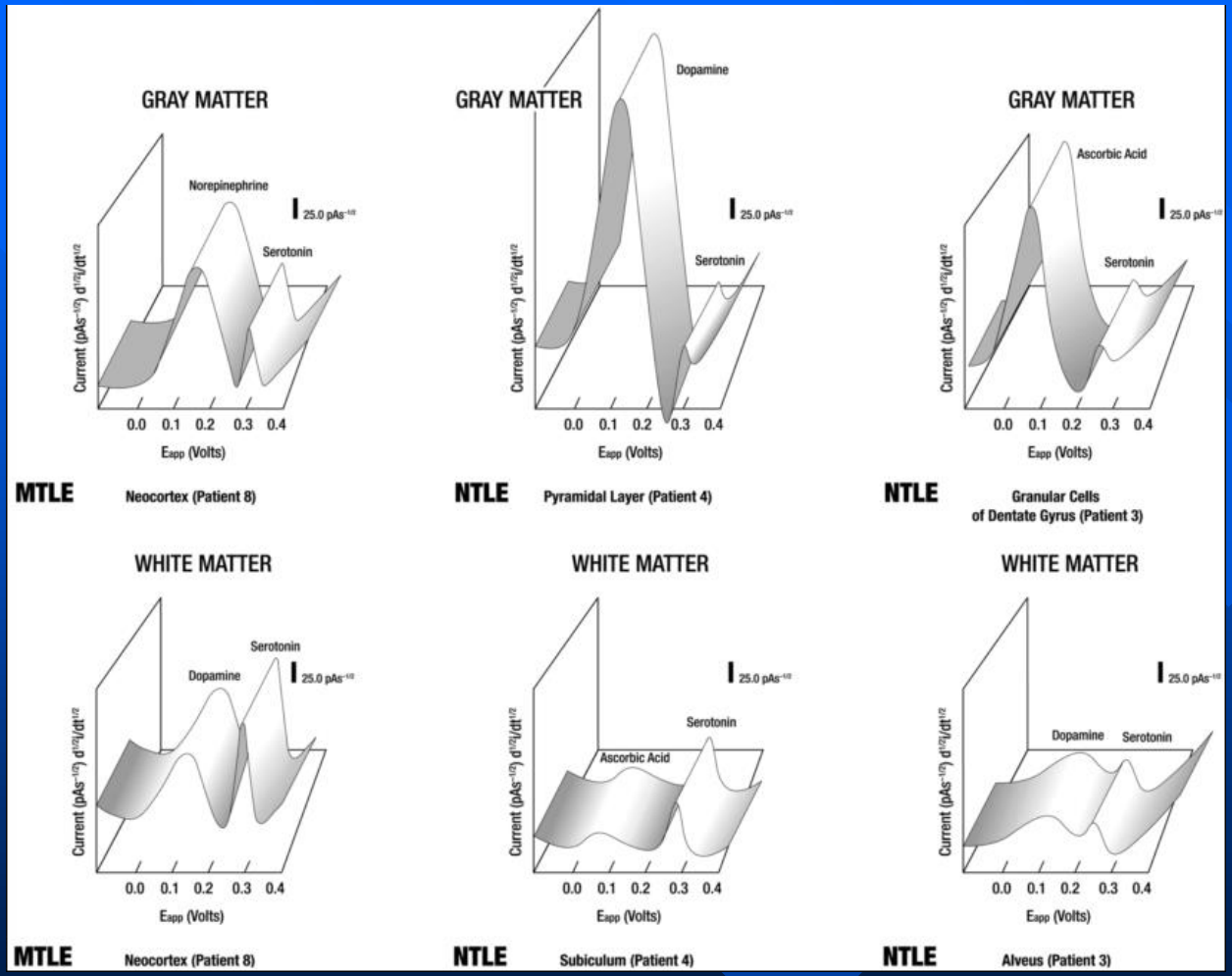


- **Neocortex:**
- **MTLE:*Norepinephrine (NE)***
- **NTLE: *Dopamine(DA),Ascorbic Acid(AA),NE depletion***
- ***Serotonin(5-HT),*** similar: Pacia et al., *Brain Research* 899:106-111, 2001.

Tryptophan*(L-TP):* **MTLE > NTLE;**

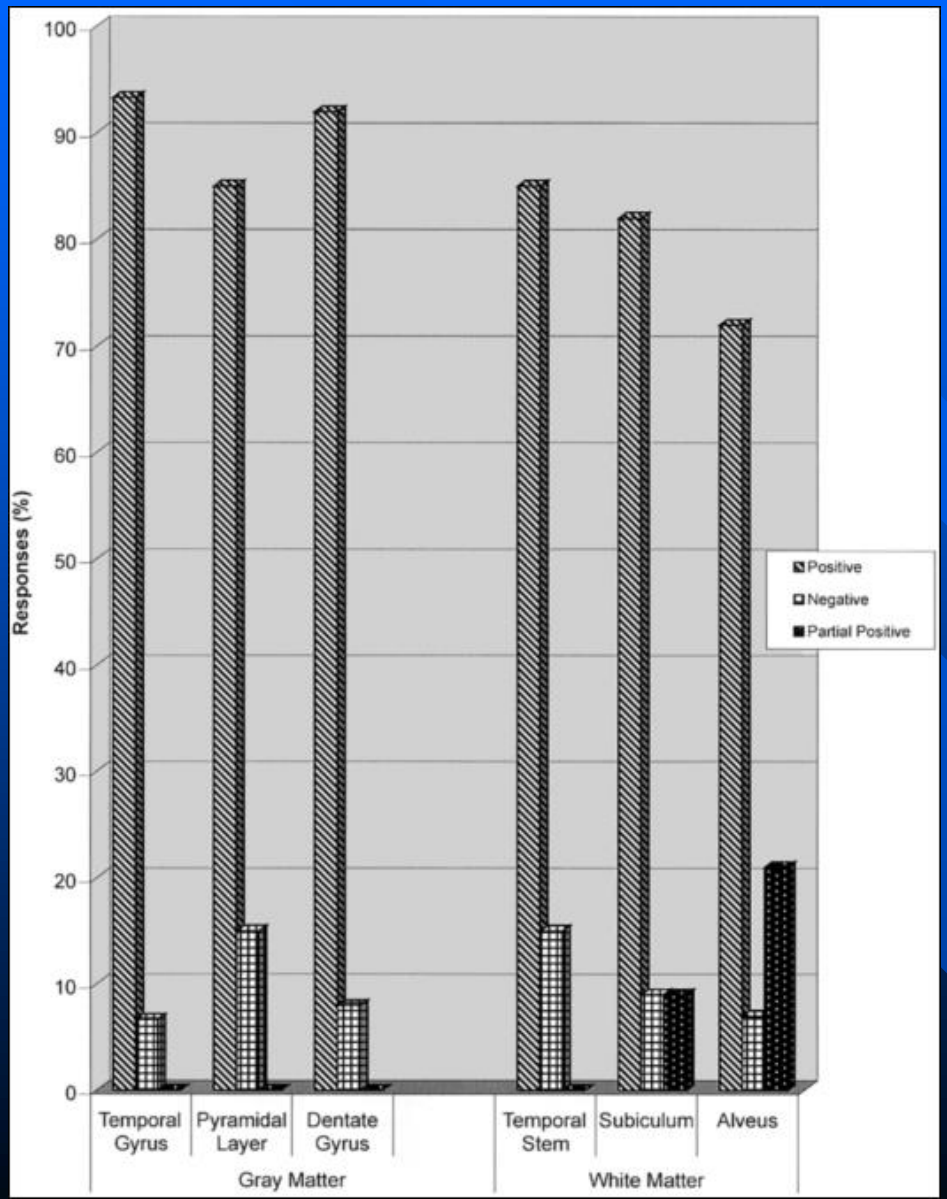
SV Pacia & PA Broderick. *Bioimaging in Neurodegeneration* (Eds: PA Broderick, DN Rahni, EH Kolodny) Humana Press (now Springer) (2005) Totowa, NJ: 141-147.

NMI *In Situ:*



- Slide 8: NMI profiles distinguish between white and gray matter in seconds.

NMI *In Situ:*



- Slide 9: Histograms showing % analysis of white matter profiles vs gray matter profiles.

Multi-Disciplinary Conference (MDC)

- History
- Age of Onset
- Epilepsy risk factors
- Family History
- Past Medical/Surgical History
- General Examination
- Neurological Examination
- Seizure Description
- Medications
- Neurophysiology Studies
- Video EEG
- EEG
- Neuroimaging/ Radiology Studies
- Neuropsychological Evaluation
- MDC Impression
- MDC Recommendation

Patient RH1 – Page 1/3

- Patient: Age-42, gender-female
  - Age of Onset: 39.
  - Epilepsy Risk Factors: No known risk factors
  - Family History: non-contributory
  - Past Medical/Surgical History: depression, asthma, anemia
  - General Examination: Normal
  - Neurological Examination: Normal

- Seizure Classification: Complex Partial with secondary generalization
  - Aura: No aura is reported.
  - Seizure Semiology: fearful, confused with decreased responsiveness, shaking of all extremities with tongue biting
  - Post-Ictal Semiology: confused, speech difficulties
  - Seizure Frequency: 5-10 per month

Patient RH1 – Page 2/3

- Seizure Classification: Generalized Tonic Clonic (GTC)
  - Aura: No aura is reported
  - Seizure Semiology: Clonic and Tonic Convulsions

- Current Epilepsy Treatment:
  - Lamictal® (lamotrigine)
  - Trileptal® (oxcarbazepine)

- Video EEG:10/3/2005 – 10/8/2005
  - Events: Three events captured which had left anterior temporal focus. Two events involved right head deviation, right limb tonic, activity, one of which secondarily generalized. The third event involved speech and behavioral arrest.
  - Clinical Impression: This VEEG study is consistent with partial epilepsy arising from the left anterior temporal region.

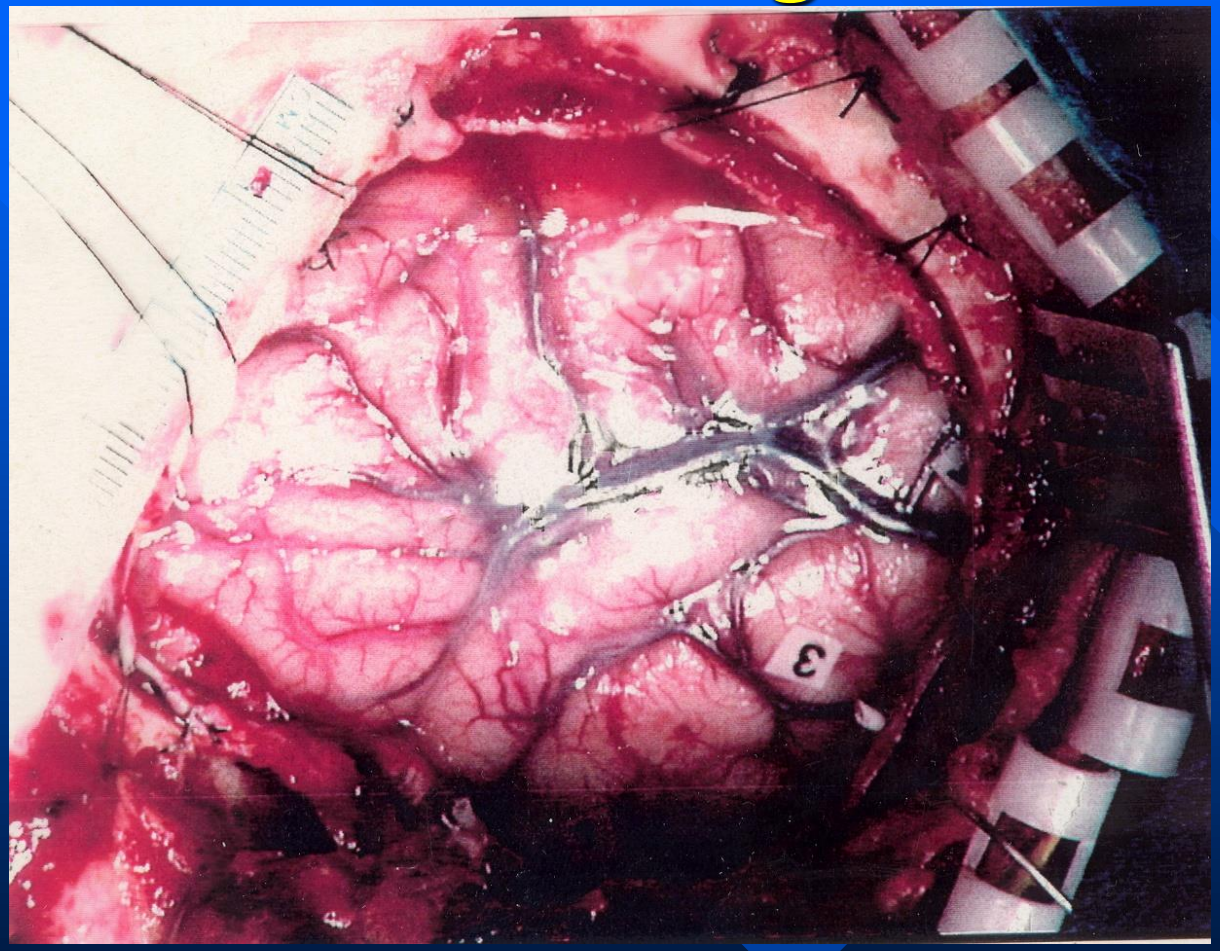
Patient RH1 – Page 3/3

- EEG: 05/23/2005
  - Clinical Impression: Normal 24 hours ambulatory digital EEG recording during wakefulness and sleep
- EEG: 05/12/2005
  - Clinical Impression: This is an abnormal EEG due to the presence of left frontotemporal slow delta background activity and epileptiform activity. The latter could be secondary to a structural lesion.
- Multi-disciplinary Conference Impression: (MDC):
  - Localization-related epilepsy with a left temporal focus
- Multi-disciplinary Conference Recommendation: (MDC):
  - 1. Repeat neuropsychological testing
  - 2. Wada- memory test
  - 3. Left temporal subdural grid and subtemporal strip study

NMI Intra-Operative Studies

- *In Vivo* studies with NMI and BRODERICK PROBE® biosensors begin with EEG monitoring wherein the site of cortical resection is defined with subdural grid epilepsy electrodes which are placed on the surface of the brain and epilepsy strip electrodes are placed subtemporally.

Exposed Temporal Lobe of Epilepsy Patient During NMI



- Slide 15: Patient is recommended for surgical resection.

NMI Intra-Operative Studies

- Then, biosensors, with a diameter five times less than epilepsy depth electrodes for invasive EEG, are placed by direct visualization in the exposed cortical region with and without epileptic spike activity in regions destined for resection.

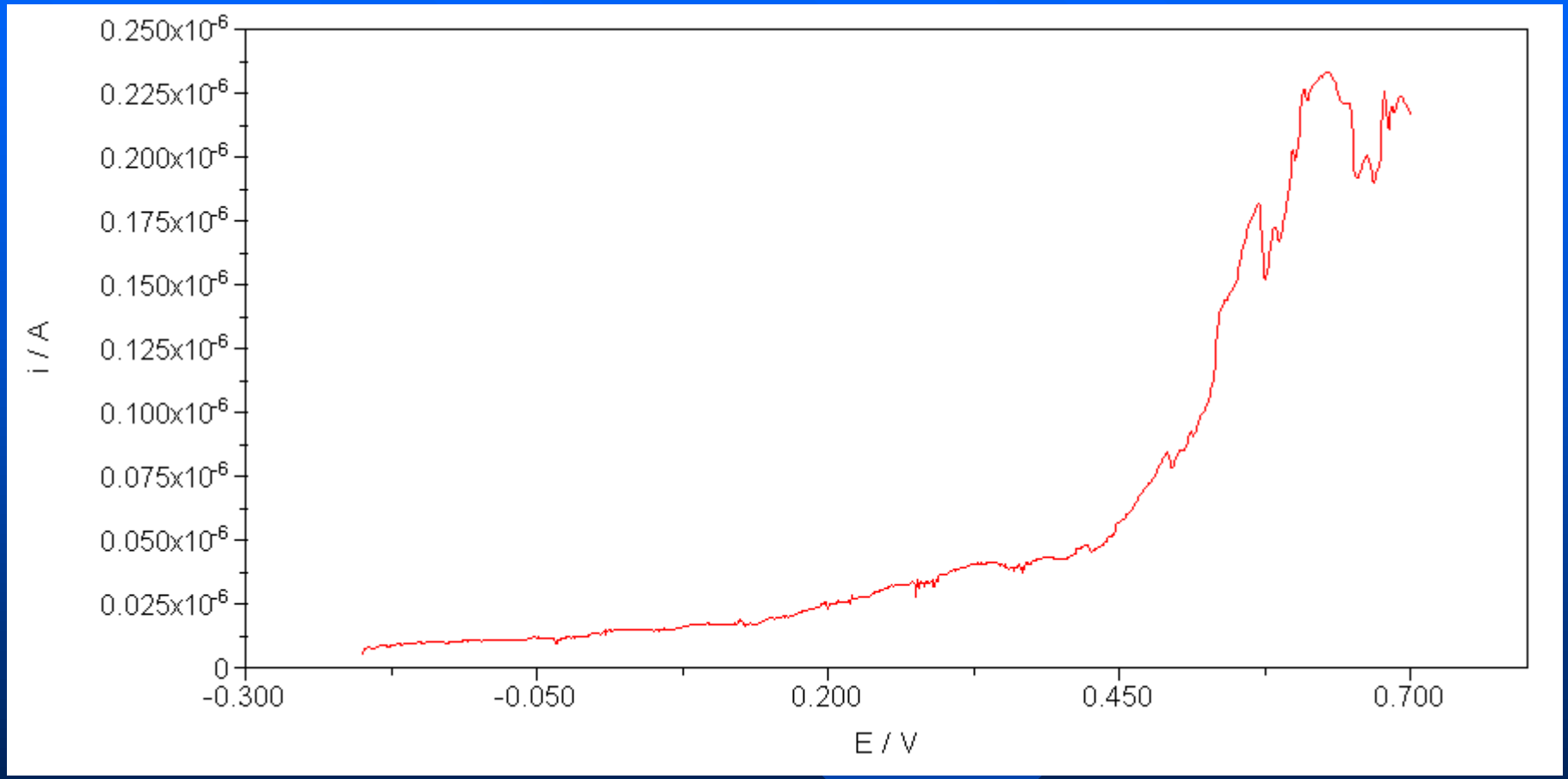
- About six to ten recordings with γ-irradiated (11.6-12.7 kilograys (kGys), laminar biocompatible carbon-based BRODERICK PROBE® laurate biosensors are taken at a cortical depth of microns to less than 2 mm for a 20-30 min time period.

Results – Intra-Operative Studies

- In our first anterior temporal lobe epilepsy patient, preliminary results showed that catecholamines, a metabolite of dopamine(DA), homovanillic acid(HVA), tryptophan(L-TP), precursor to serotonin(5-HT), dynorphin(DYN), and somatostatin(SRIF) were imaged in neocortex.

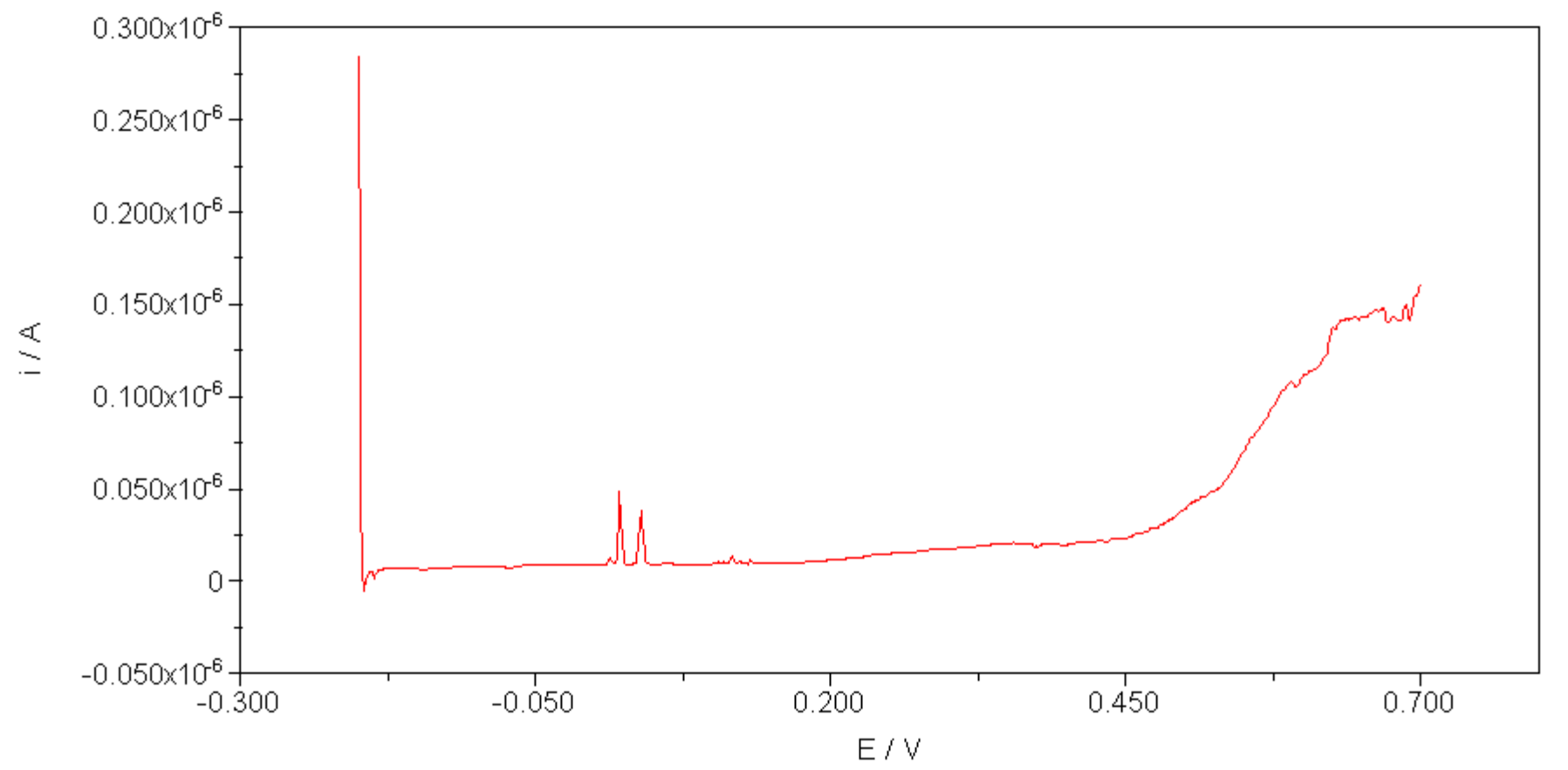
- The presence of L-TP and Peptides and DA metabolites were greater than the presence of monoamines or indoleamines.

Intra-Operative NMI *In Vivo*



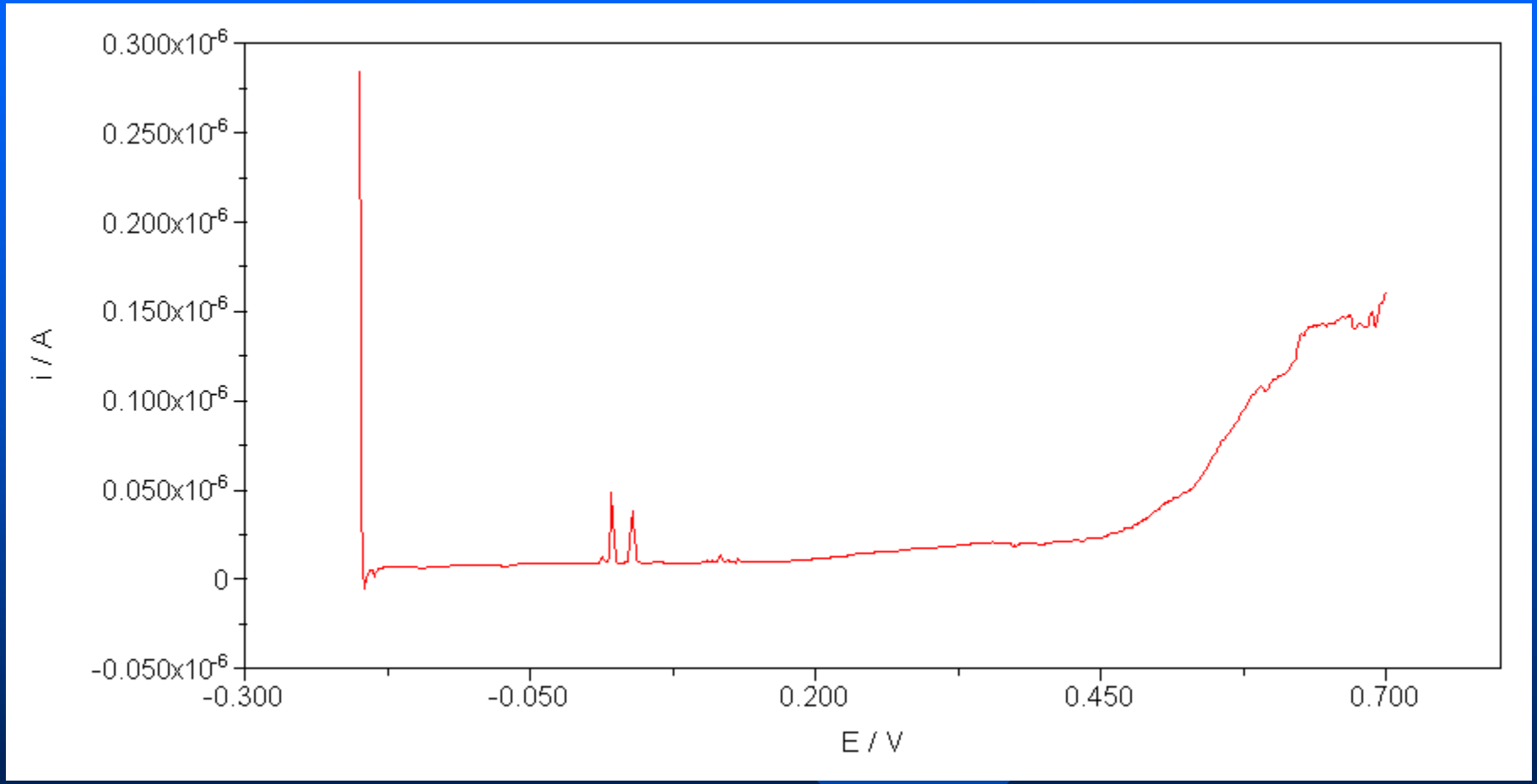
- **<u>Slide 18:</u> Linear circuit: Patient (RH) studied on 10-23-08. On the x-axis: oxidation potential in mvolts. On the y-axis: current in *u*amps: catecholamines, 5-HT, HVA, L-TP, DYN, & SRIF were imaged during surgery. L-TP and Peptides exist in greater abundance than are the monoamines or indoleamines.**

Intra-Operative NMI *In Vivo*



- **Slide 19: Linear circuit: Patient (RH) studied on 10-23-08. On the x-axis: oxidation potential in mvolts. On the y-axis: current in uamps. HVA, L-TP, DYN, & SRIF were imaged. L-TP and Peptides were present in higher concentration than the monoamines or indoleamines.**

Intra-Operative NMI *In Vivo*.

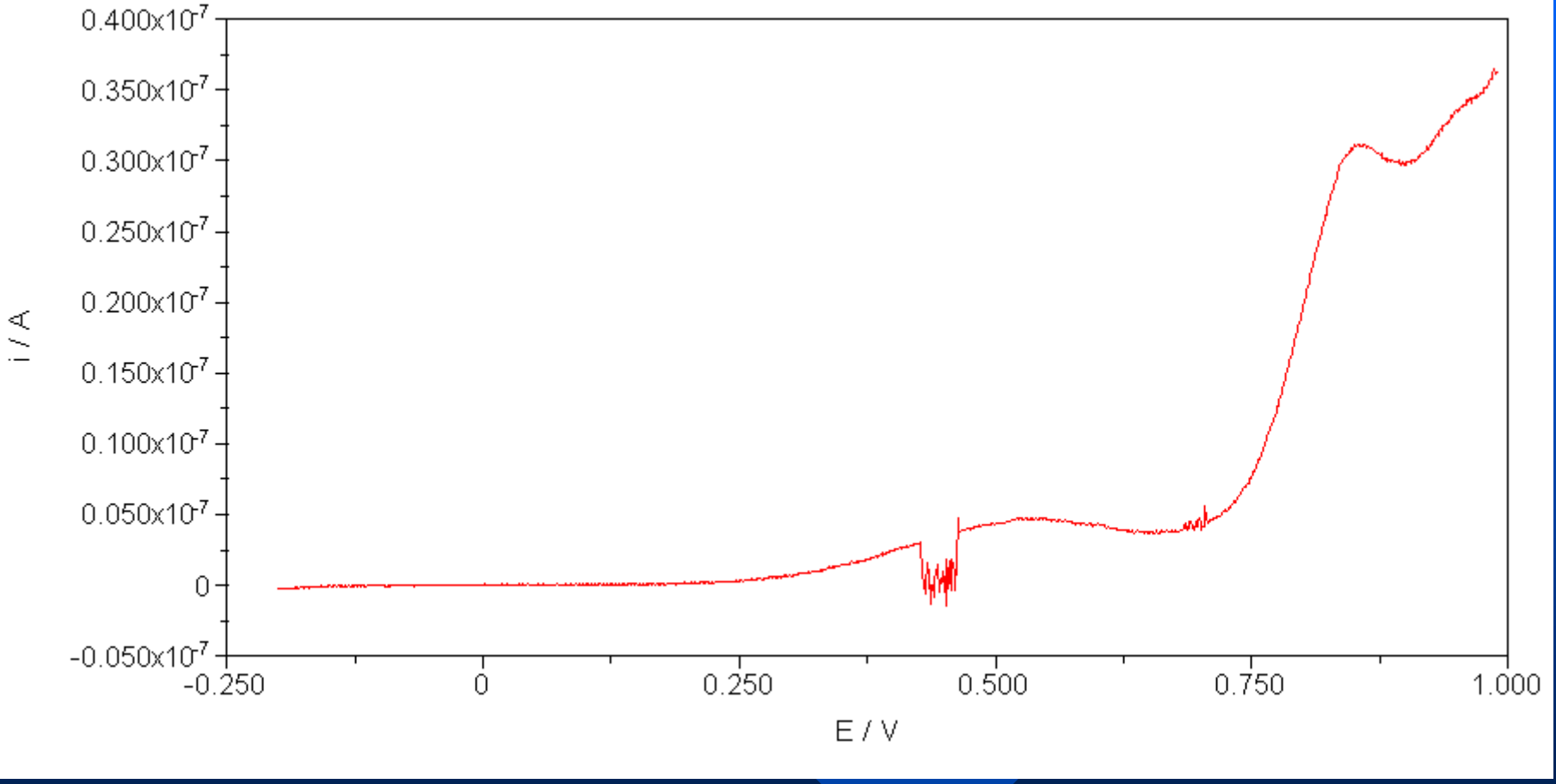


- **Slide 20: Linear circuit: Patient (RH) studied on 10-23-08. On the x-axis: oxidation potential in mvolts. On the y-axis: current in uamps. HVA, L-TP, DYN, & SRIF were imaged. L-TP and Peptides were present in higher concentrations than monoamines or indoleamines.**

Molarity-Preliminary Data

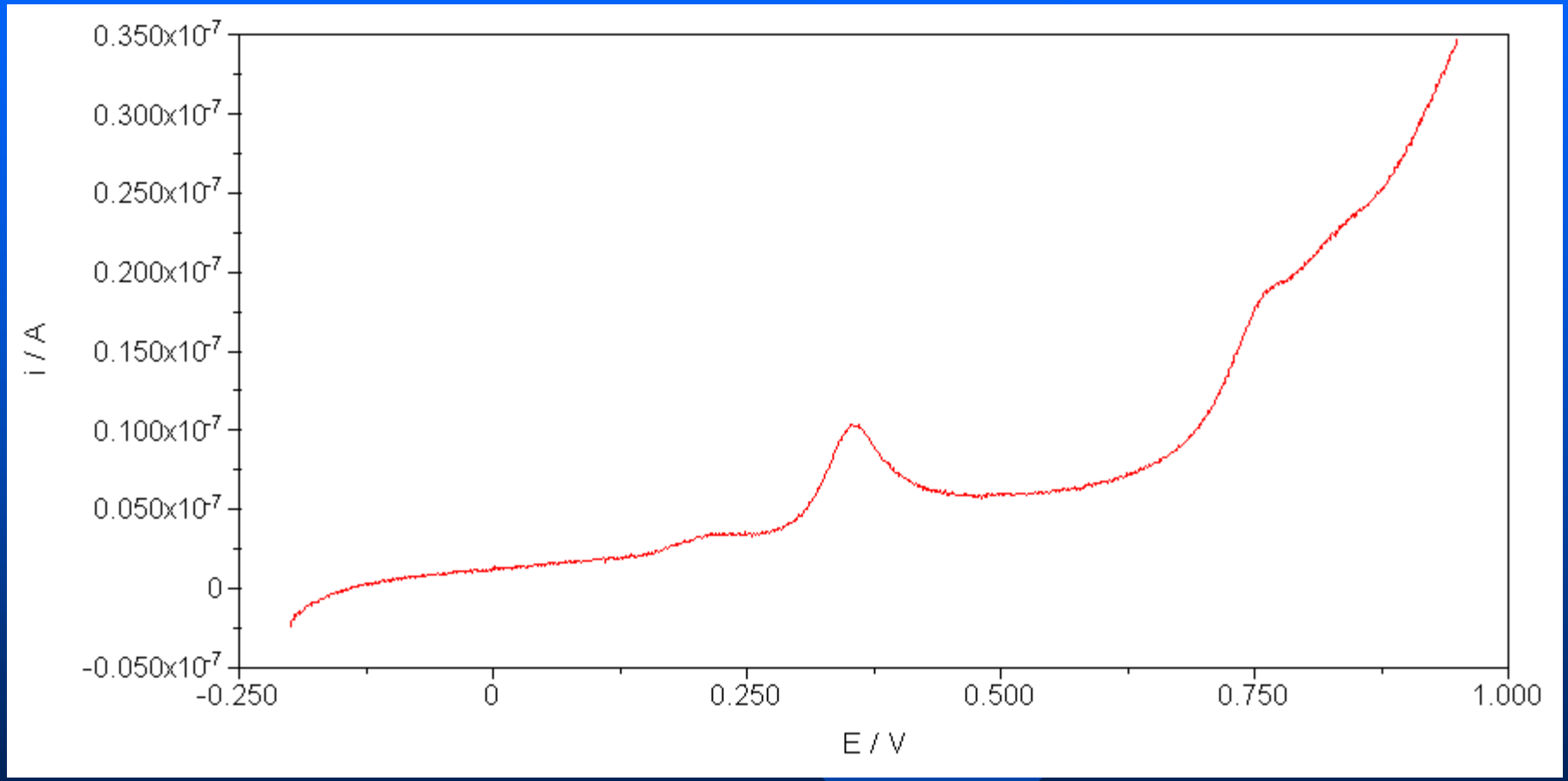
		Detection Limits - *In Vitro*	Detection Limits - *In Vivo*	Approximate Neurochemical Concentration
Catecholamine	DA/NE	2nM	20nM	~.2nM
Serotonin	5-HT	1nM	10nM	~.5nM
Homovanillic Acid	HVA	20nM	0.2*u*M	7nM
Tryptophan	L-TP	20nM	0.2*u*M	1*u*M
Dynorphin	DYN	4nM	40nM	2*u*M
Somatostatin	SRIF	3.7nM	37nM	4*u*M

Intra-Operative NMI *In Vivo*



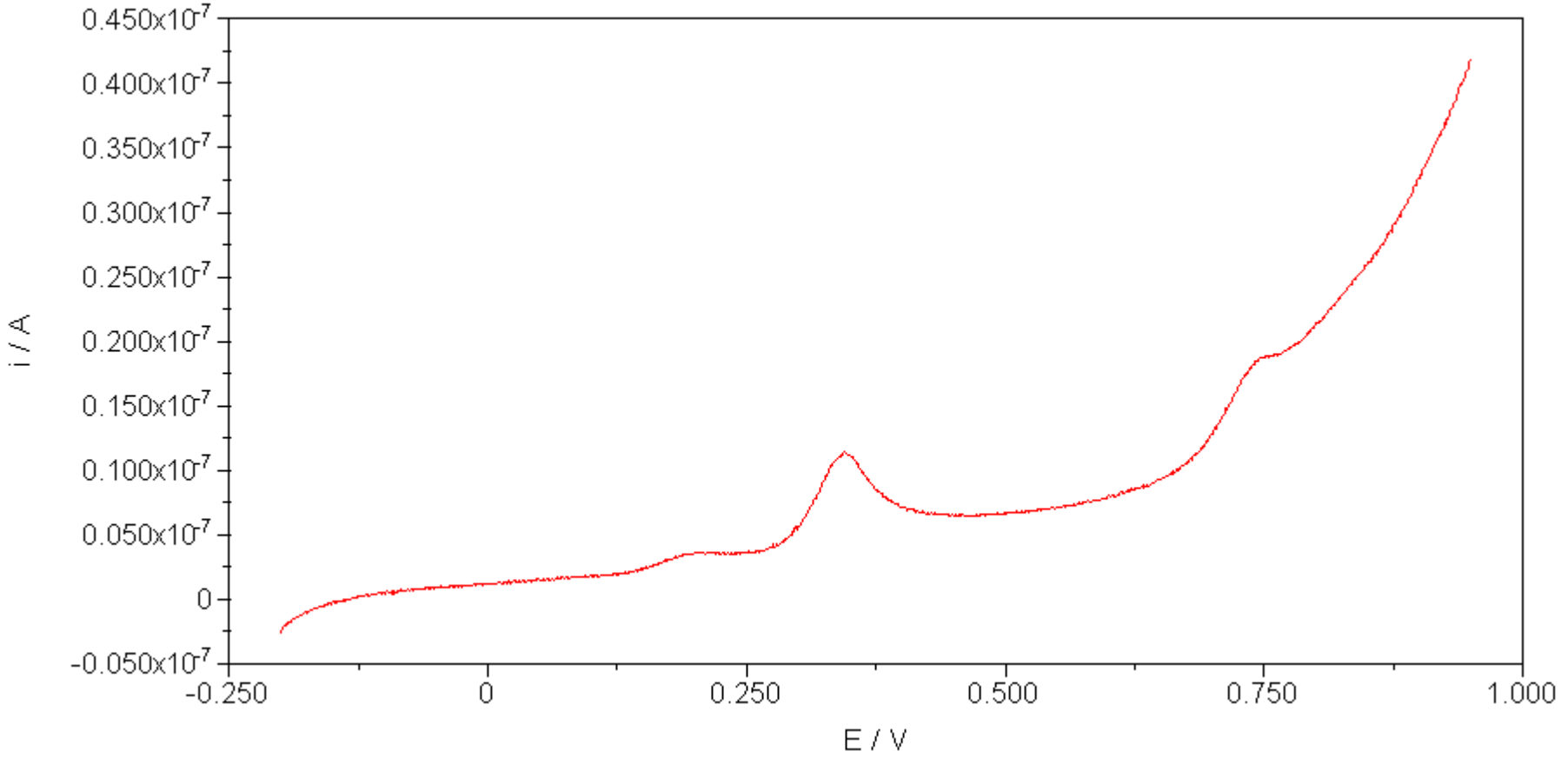
•Slide 22: Linear circuit: Patient studied 1-8-09. On the x-axis: oxidation potential in mvolts. On the y-axis: *u*amps times 10. HVA, L-TP, DYN, & SRIF were imaged. L-TP and Peptides were present in highest amounts.

NMI *In Vitro*



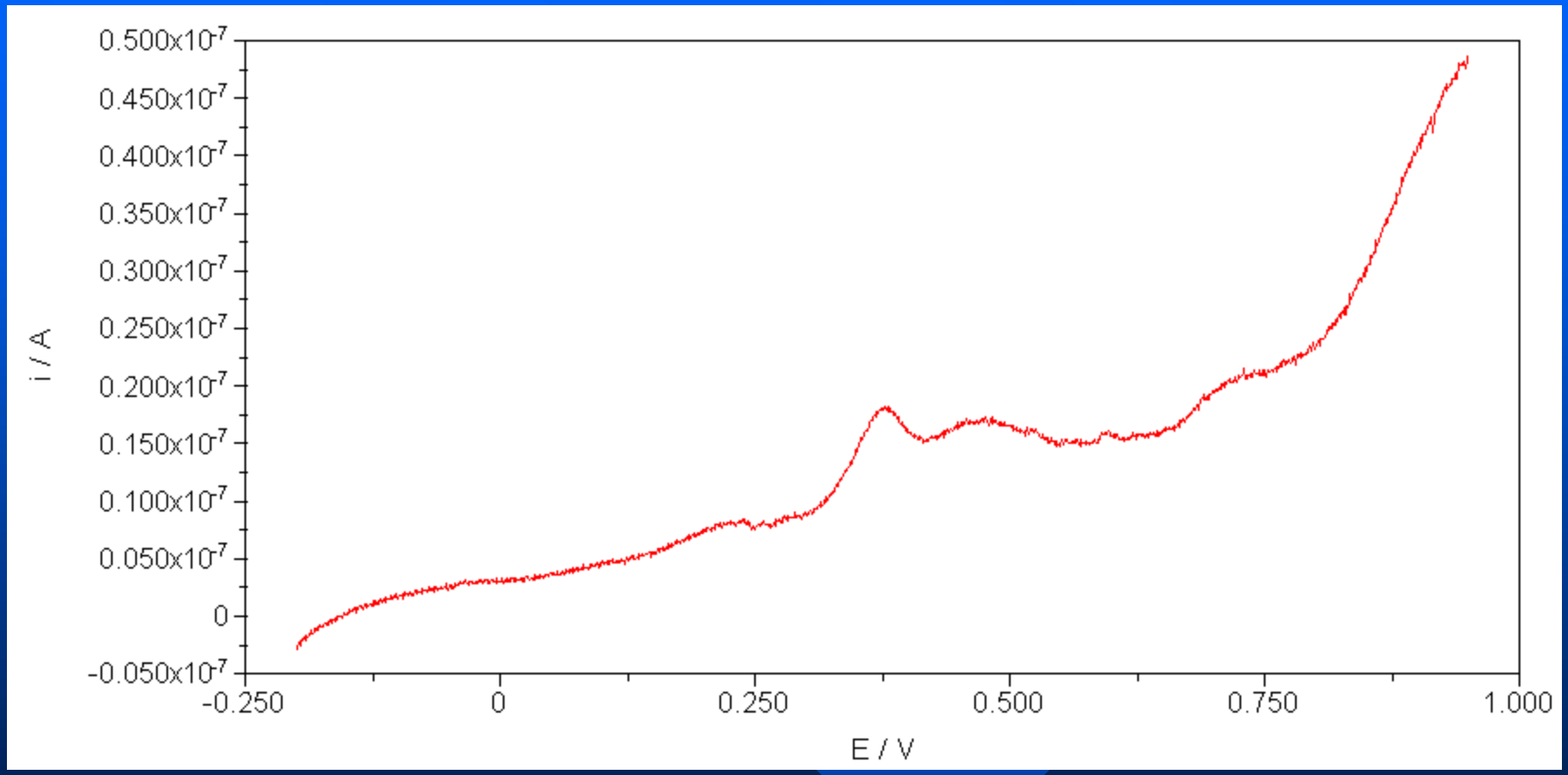
- Slide 23: Linear circuit: On the x-axis: oxidation potential in mvolts. On the y-axis: current in *u*amps times 10. DA, 5-HT, L-TP, DYN, & SRIF were pipetted into phosphate buffer and imaged.

NMI *In Vitro*



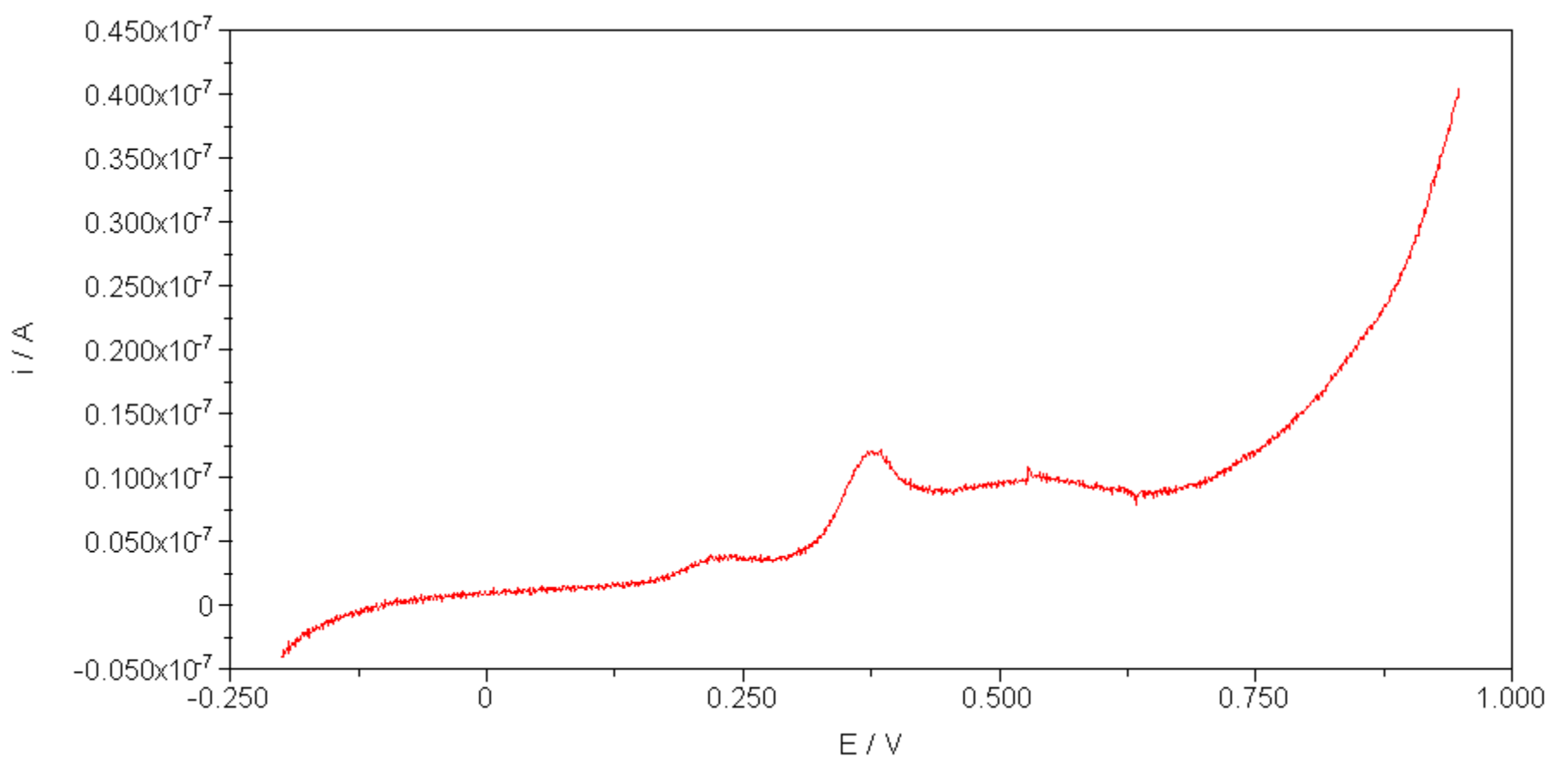
- Slide 24: Linear circuit: On the x-axis: oxidation potential in mvolts. On the y-axis: current in *u*amps times 10. DA, 5-HT, L-TP, & DYN were pipetted into phosphate buffer and imaged.

NMI *In Vitro*



- Slide 25: Linear circuit: On the x-axis: oxidation potential in mvolts. On the y-axis: current in *u*amps times 10. DA, 5-HT, HVA, and L-TP were pipetted into phosphate buffer and imaged.

NMI *In Vitro*



- Slide 26: Linear circuit: On the x-axis: oxidation potential in mvolts. On the y-axis: current in *u*amps times 10: DA, 5-HT, and HVA were pipetted into phosphate buffer and imaged.

Pathology: (RH) Page 1/2

- Brain, left temporal lobe, excision:
  - White matter hypercellularity, mild
  - Cortical dysplasia, moderate
  - White, matter neuronal heterotopia, moderate
  - Gliosis, Intraparenchymal subpial (chaslin type), severe
  - Histiocytic infiltration and vascular profileration, focal, consistent with hypoxic/ischemic injury, subarcuate,
  - Meningitis, chronic, mild, probably related to placement of subdural epilepsy EEG recording device; vascular hyalinization, moderate.
- Brain, left hippocampus, excision:
  - Neuronal loss
  - Gliosis, severe

*The immunostains performed on the specimen labeled "hippocampus" including GFAP, highlight gliosis and neuronal loss, respectively.

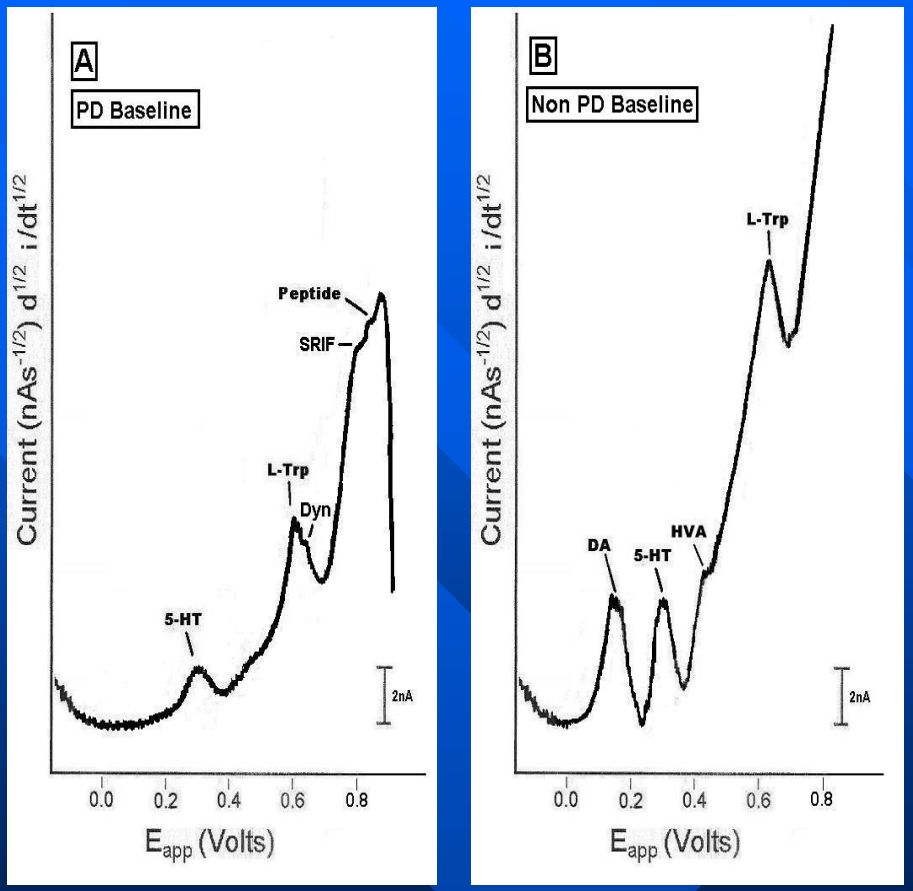
Pathology: (RH) Page 2/2

- "With regard to the pathology report: If you were to look at dozens of pathology reports following grid/strip studies in patients, you would find some strong similarities between the reports. One of the most enduring of these findings is the meningitis, mild, chronic (at least mild dysplasia and gliosis is also seen in virtually all studies). These findings are believed to be related to the subdural epilepsy electrode placement. Because this is seen in MANY patients in which the BRODERICK PROBE® has not been placed, I would not assume that it is related in any way to this finding – although causality can never be truly proven or disproven.

- The histiocyte infiltration consistent with hypoxic/ischemic injury is not seen as often in grid studies, but has been seen previously. The fact that it is designated as subacute strongly votes against it being related to the BRODERICK PROBE® . The probe is utilized and then very quickly thereafter, the tissue is excised; this would preclude the time to develop vascular proliferation that characterizes it as a subacute process." – Chad Carlson, M.D. Epileptologist, NYU.

THUS, BRODERICK PROBE® biosensors do not cause gliosis, sclerosis, brain/neuronal damage, or histiocyte infiltration.

Parkinson Animal: PD vs non PD



Slide 29: Semiderivative circuit: Representative NMI neurochemical signature profiles in dorsal striatum of (left) PD and (right) the non-PD animal, endogenous (baseline) images. (2namps/10mm). L-TP and Peptides-present in PD.

Conclusion

(1) The amino acid, L-Tryptophan (L-TP) and Peptides were present in high concentrations in neocortex of epilepsy patients during surgery.

(2) The monoamines, dopamine (DA) and norepinephrine (NE) and the indoleamine, serotonin (5-HT) were present to a significantly lesser extent in the neocortex of epilepsy patients during surgery.

(3) Parkinson's animals have abundantly more L-TP and Peptides than animals who did not have the Parkinson's syndrome.

THUS, L-TP and Peptides may serve as markers for pharmaco-and or gene therapy for neurodegenerative processes!

Present & Future Studies

- The present studies chart a course for safe and cutting-edge opportunities to characterize neurochemical profiles for epilepsy patients with partial seizures and for the development of new strategies to alleviate the burden of seizures in our patients.

- Future studies involve the prolonged use of BRODERICK PROBE® biosensors in patients undergoing intracranial EEG studies in our intensive care unit.

BRODERICK PROBE® biosensors:

Applications

BRODERICK PROBE® biosensors have direct potential for application in several areas of clinical and preclinical medicine!

- **Spinal and cranial surgery**
- **Deep brain stimulation**
- **Drug delivery systems**
- **Neurostimulation**
- **Pain management**
- **Neurosurgery**
- **Tumor resection**
- **Biopsy**
- **Functional Neurosurgery**
- **Shunts**
- **Image-guided surgery**
- **Spinal cord stimulation**
- **Head Trauma**
- **Epilepsy**
- **Human Uterine Cervical Cancer**

- **Disorders: Neurodegenerative, Neuropsychiatric, Cardiovascular,**
- **Cognitive and others such as autism and ADHD**
  - **Depression**
  - **Psychosis**
  - **Anxiety**
  - **Cocaine addiction**
  - **Hypotension**
  - **Hypertension**
  - **Hypoxia**
  - **Stroke**
  - **Dementia**
  - **Breast Cancer**

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