EE 791 Lecture 9

Therapeutic Brain Stimulation

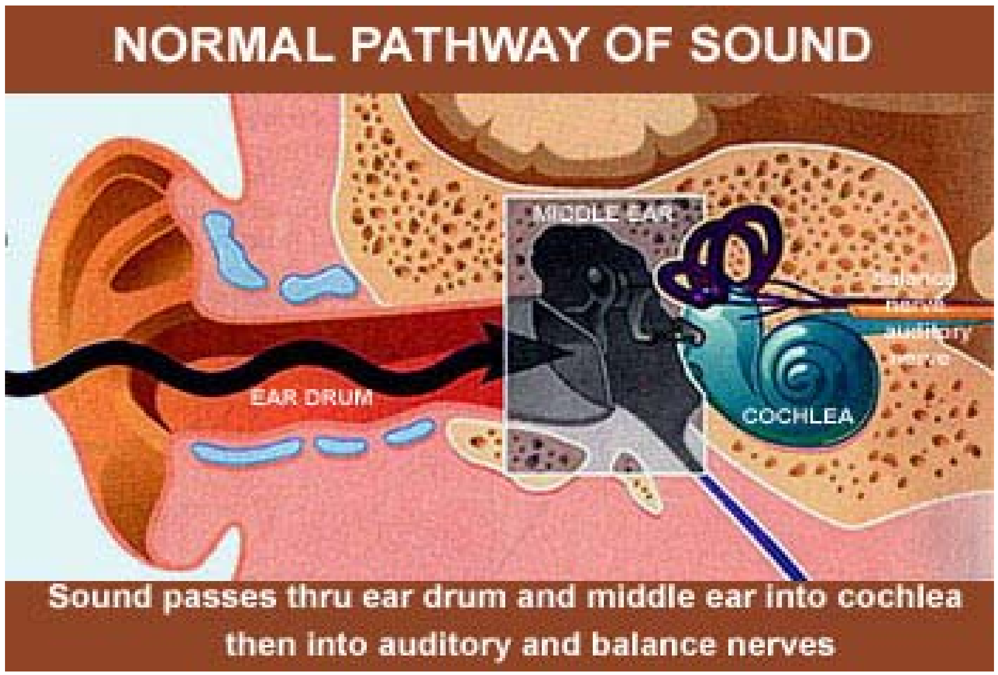
March 25, 2019

What BME Contributions?

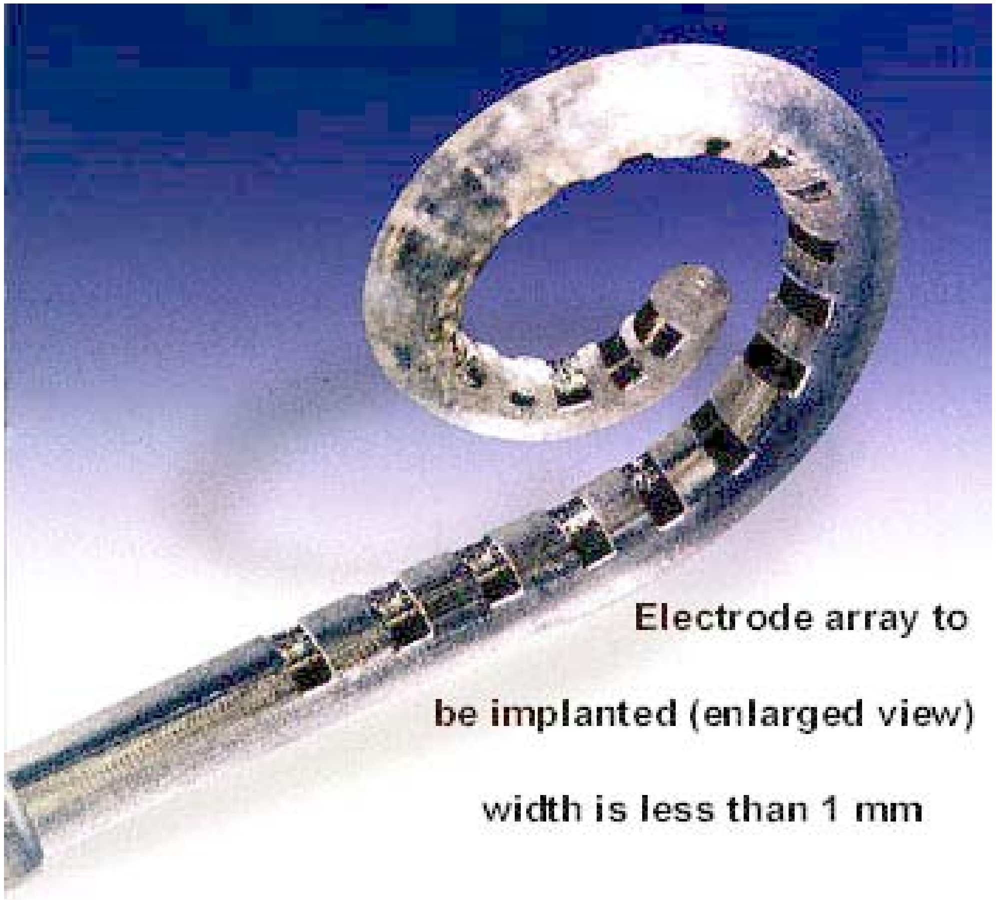
- Basic Research (technology to understand physiology or anatomy better)
- Therapeutic (maintain health and function)
- Prosthetic (artificial organ or part)
- Improve normal function

Prosthetic Advances

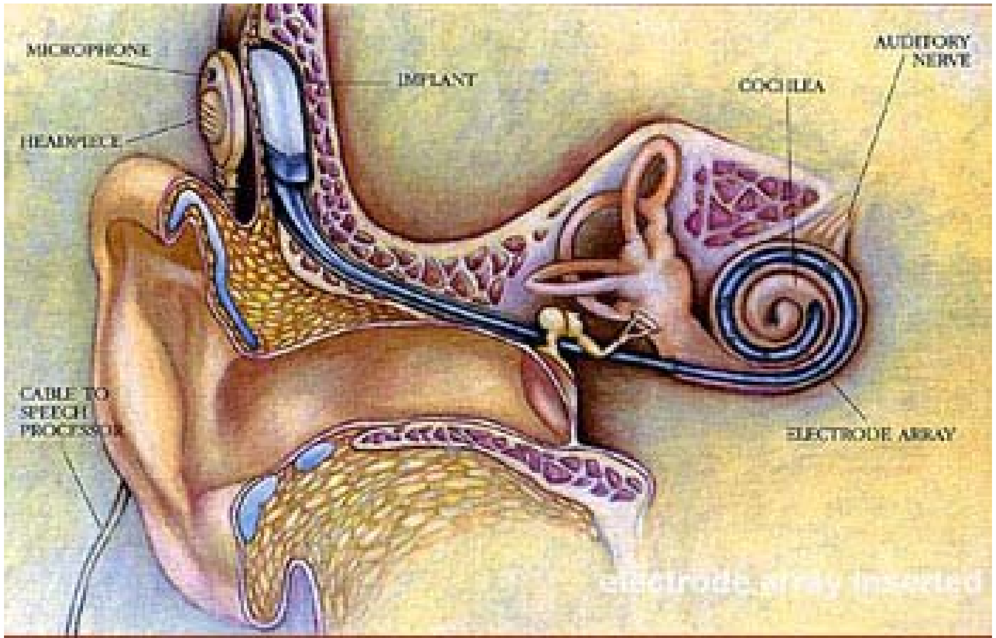
(Cochlear Implant)



Cochlear Stimulating Electrode

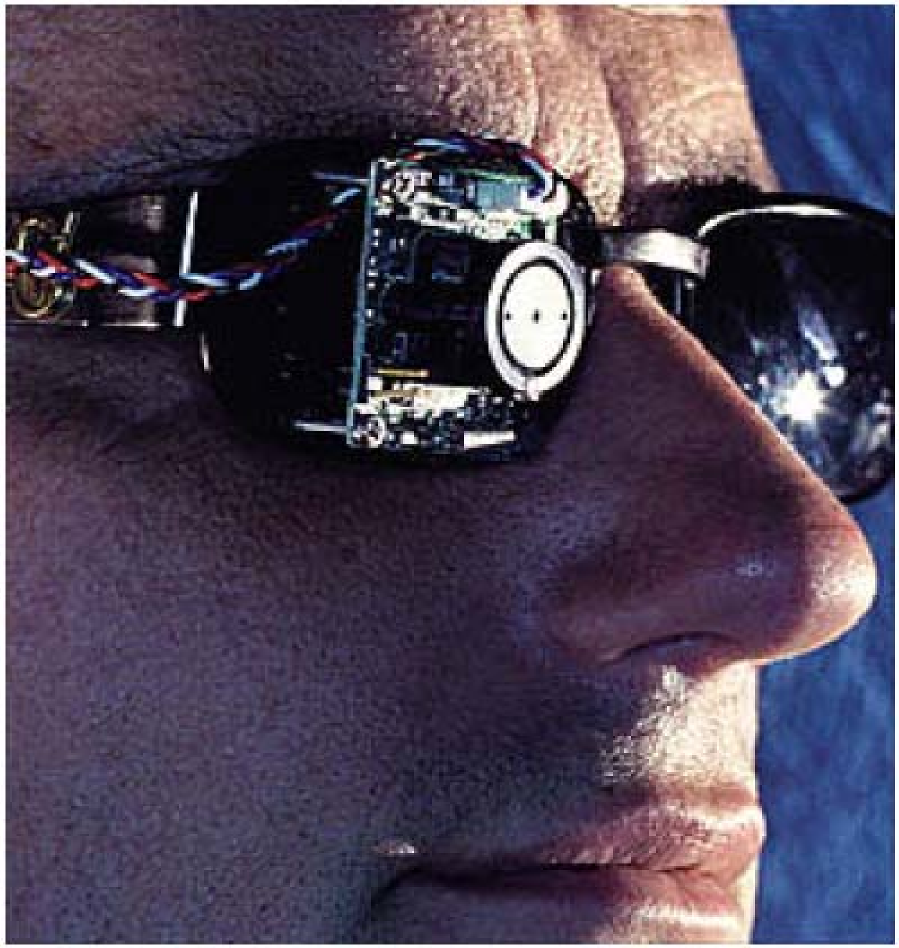


Implanted System



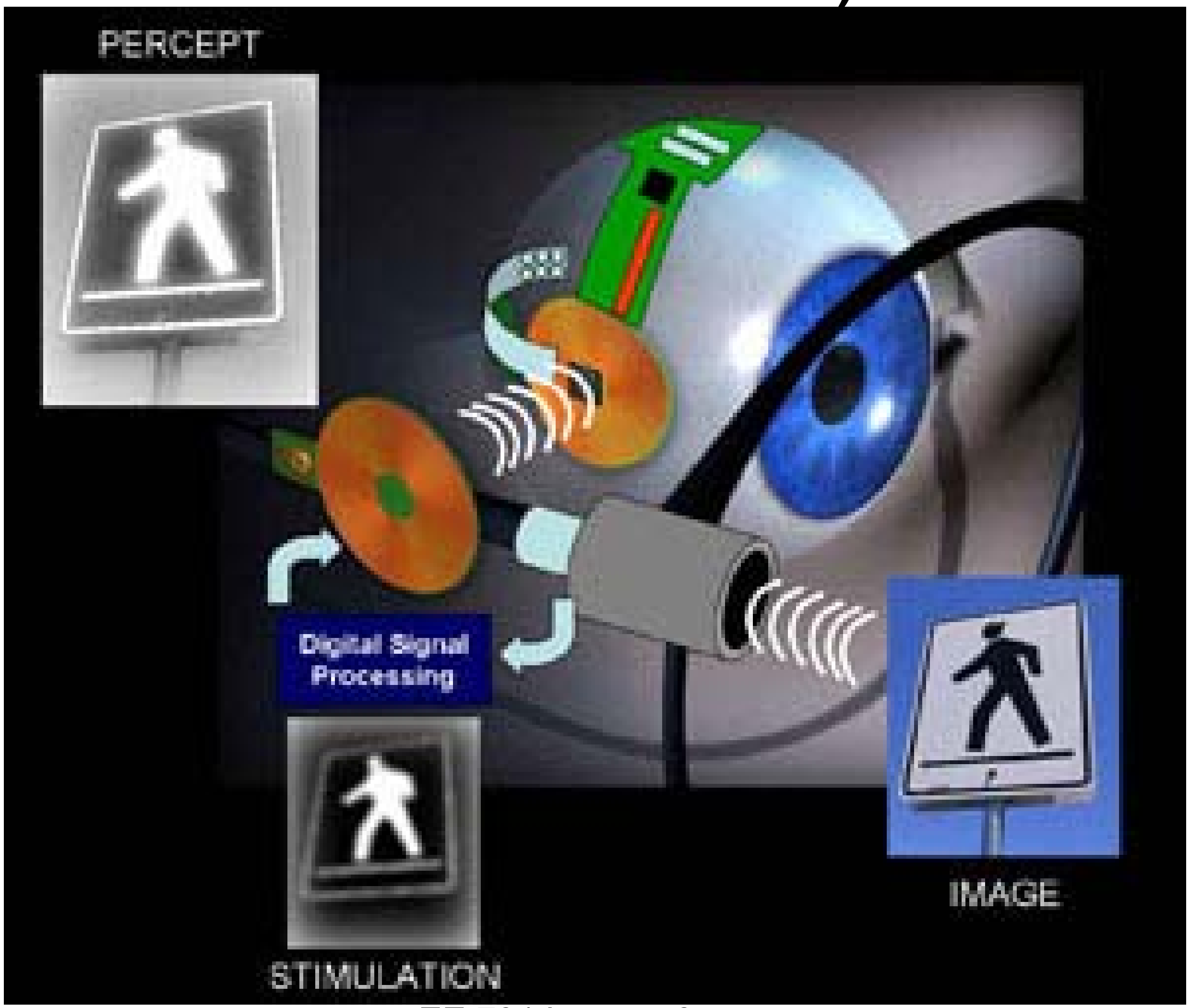
Schematic of cochlear implant; note electrode array inserted into cochlea.

Prosthetic Advances
(Visual – Artificial Retina)

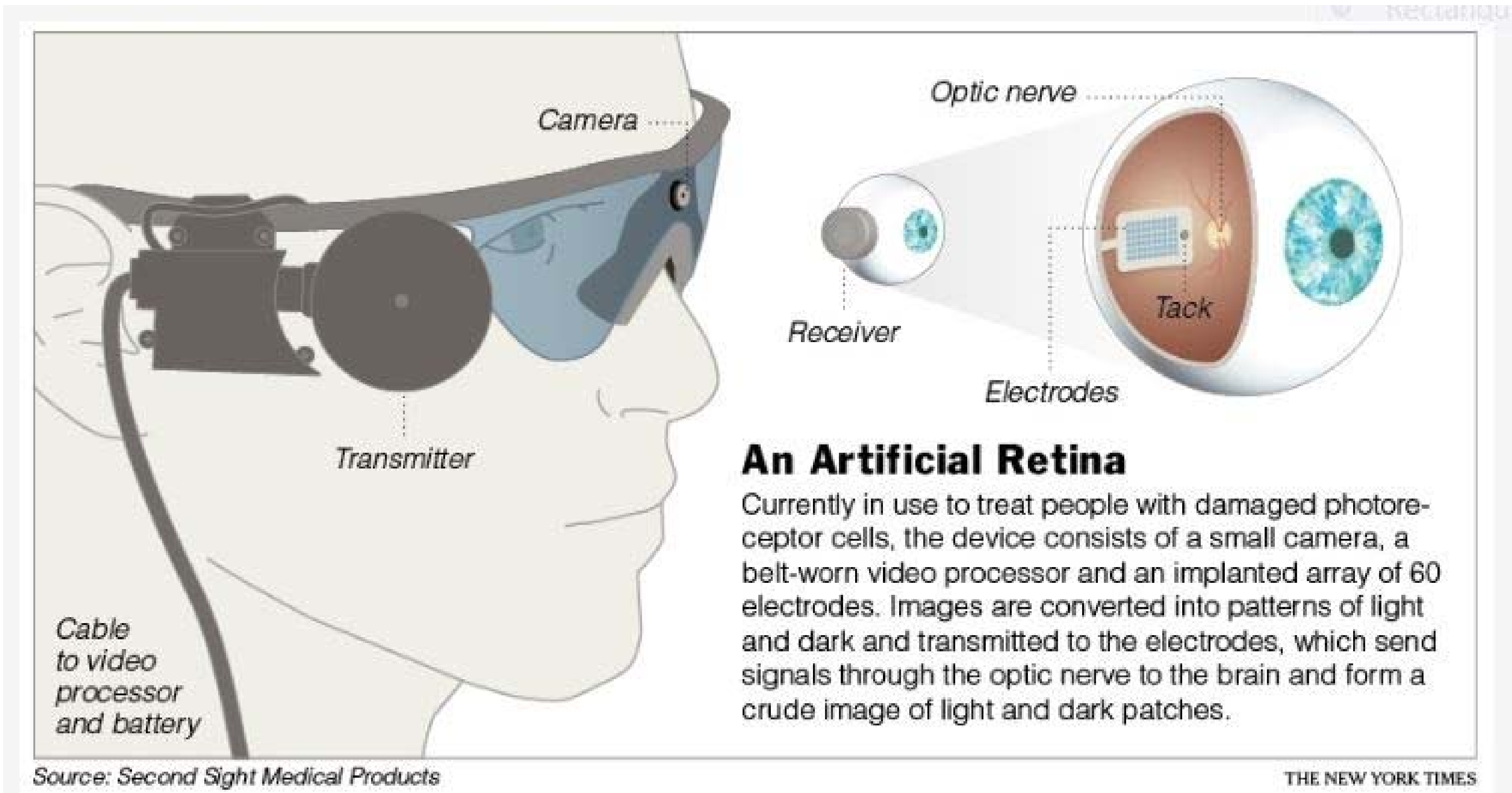


Direct Brain Stimulation

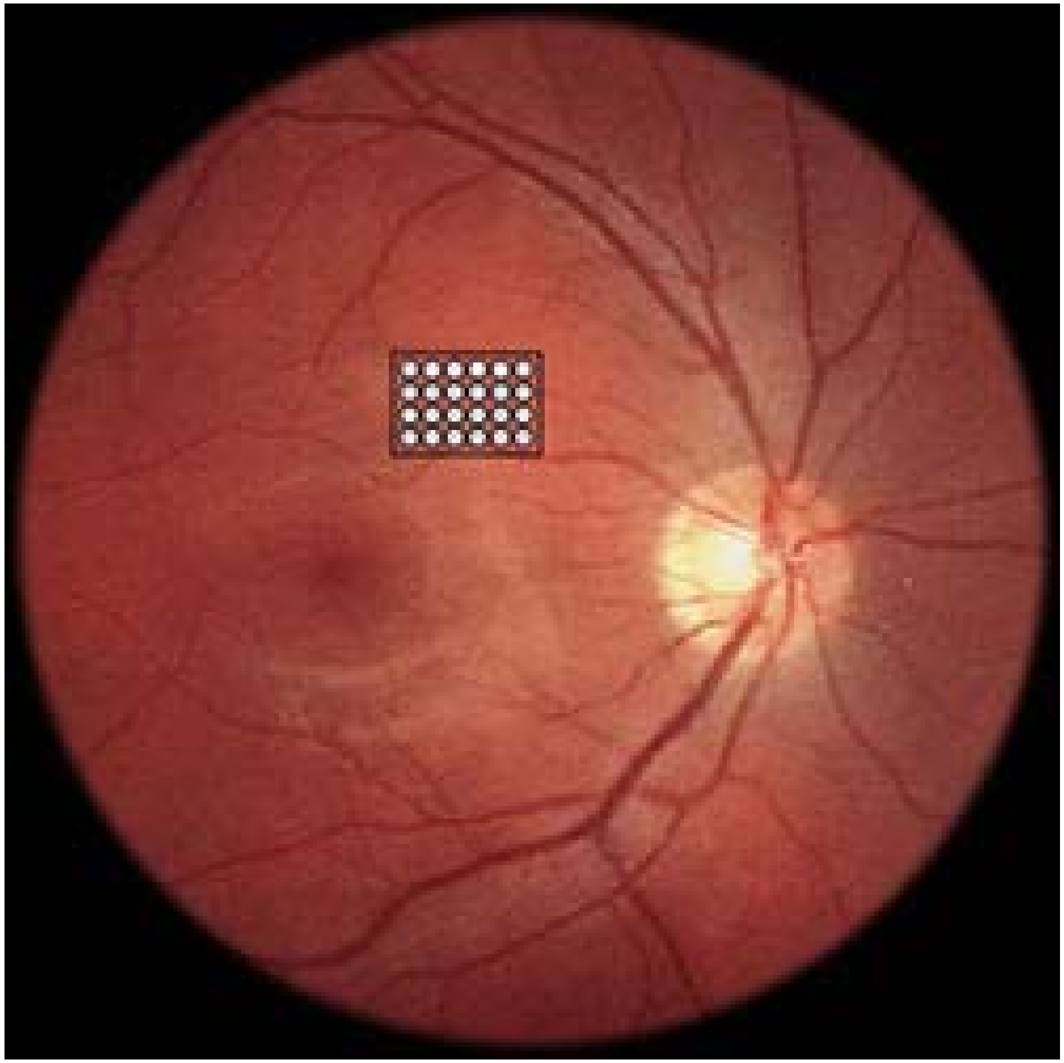
Advances in Vision (Retinal Stimulation)



Argus II Implant



Advances in Vision (Retinal Implant)



Therapeutic Brain Stimulation

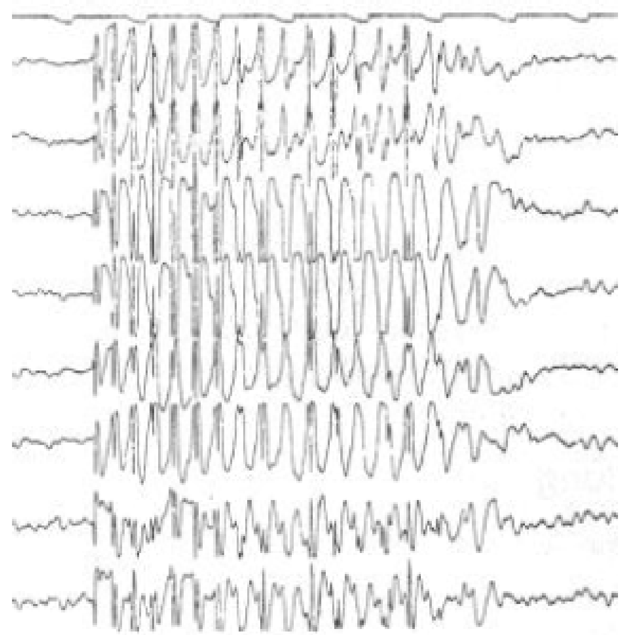
- Intracranial cortical stimulation (e.g. epilepsy)
- ECT (transcranial electrical stimulation e.g. depression)
- Deep brain stimulation (e.g. Parkinsonism)
- Vagal stimulation (epilepsy, depression)*
- Transcranial magnetic stimulation (depression, schizophrenia)*

Problems Encountered

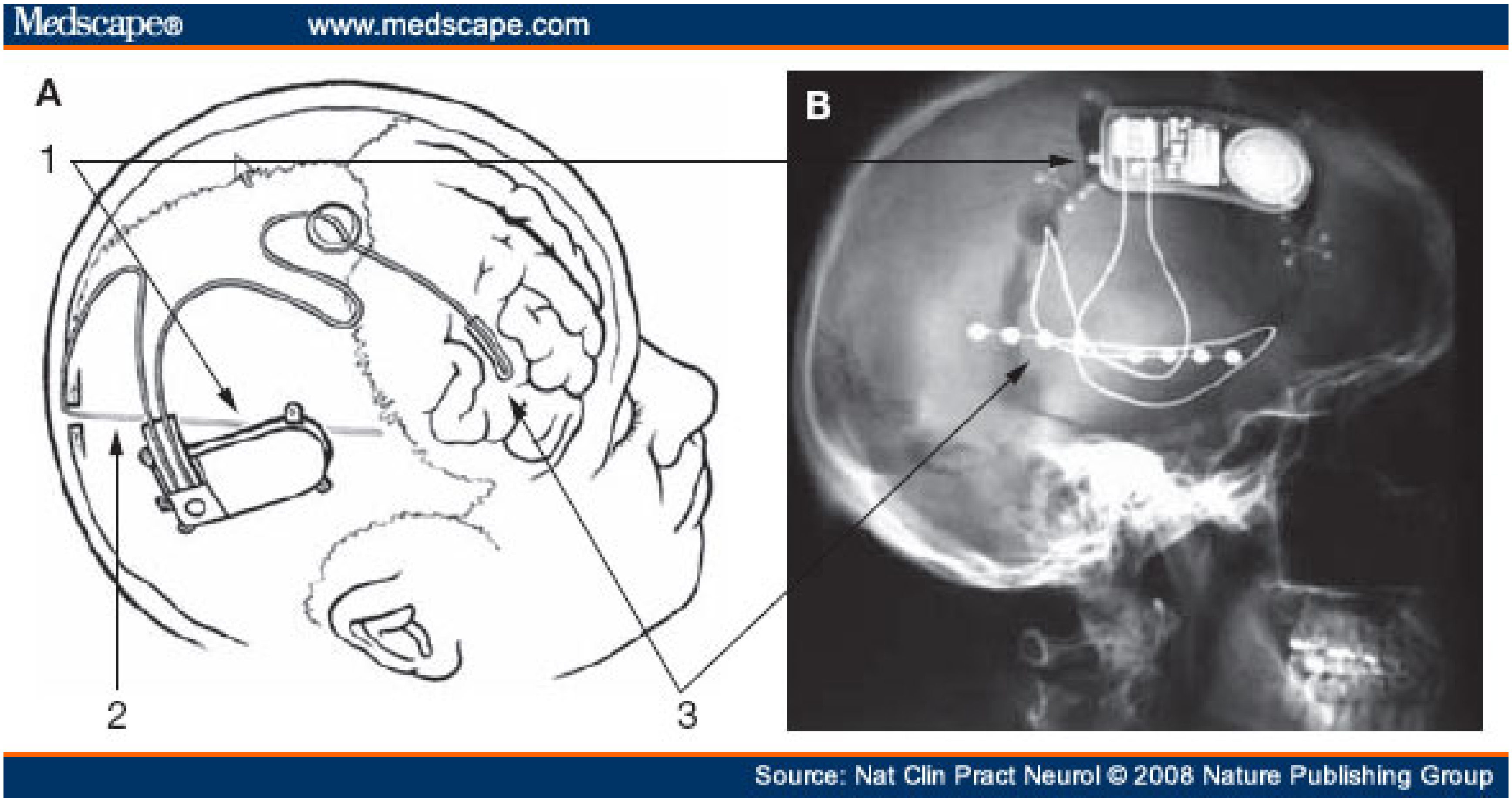
- Complexity of Brain (anatomical, neurophysiological) especially of frontal lobes
- Treatment mechanisms little understood (animal research suggests some mechanisms but human mostly hypotheses)
- Hardware well developed and flexible but treatment protocols either too rigid or too flexible
- Patient selection

Epilepsy EEG Signal

- Spikes
  - response to stimuli
  - Epileptic seizures
  - higher frequency content
  - Up to 100 Hz



Closed Loop Epilepsy Treatment



Movement Disorders
(Parkinsonism)

- Resulting from loss of neurons in substantia nigra (SNc) which produces dopamine
- Treated with dopamine agonist (short lived), monoamine oxidase inhibitor (less effective), dopamine precursor L-DOPA (gold standard)
- Biggest challenge is dose regulation (half-life of L-DOPA is 90 min)
- Less and less effective as deterioration of substantia nigra continues

Basal Ganglia

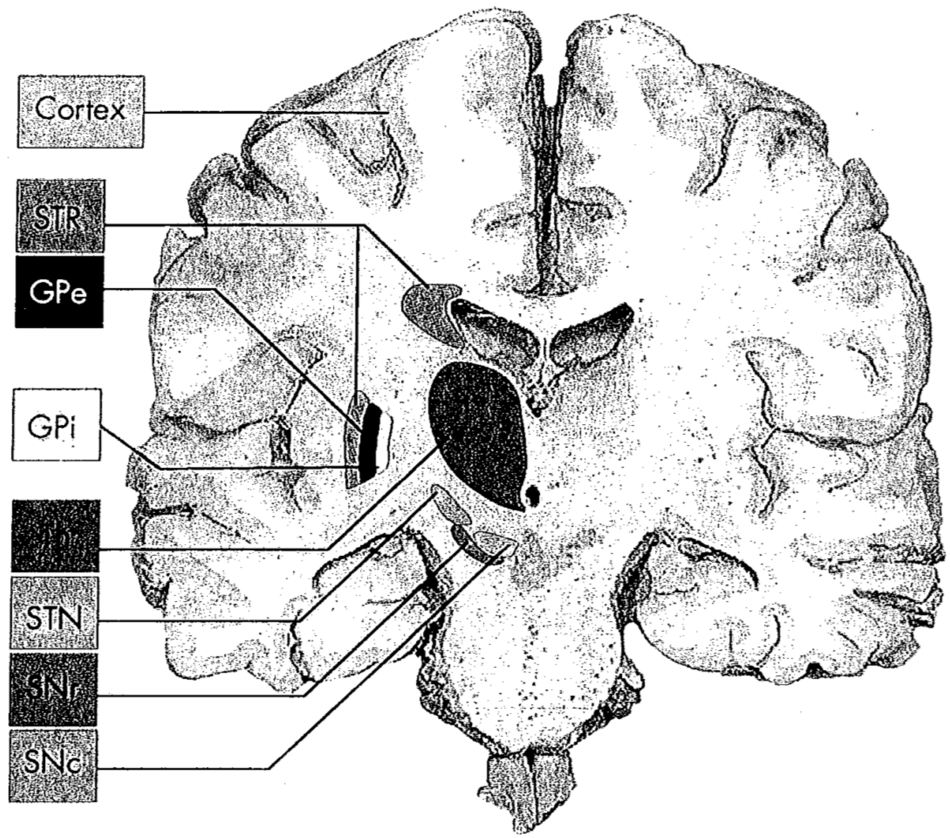
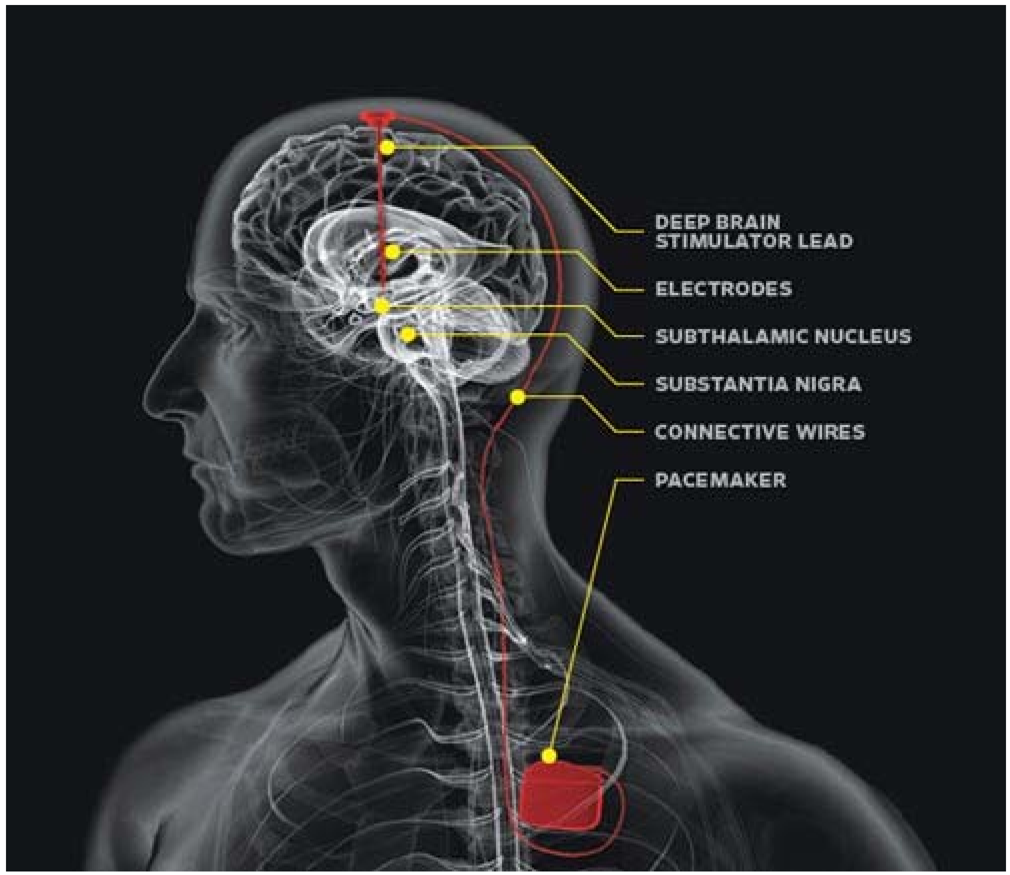


Figure 1 - Coronal (frontal) section of the brain showing the different structures in the basal ganglia. STR, striatum; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; Th, thalamus; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata[14].

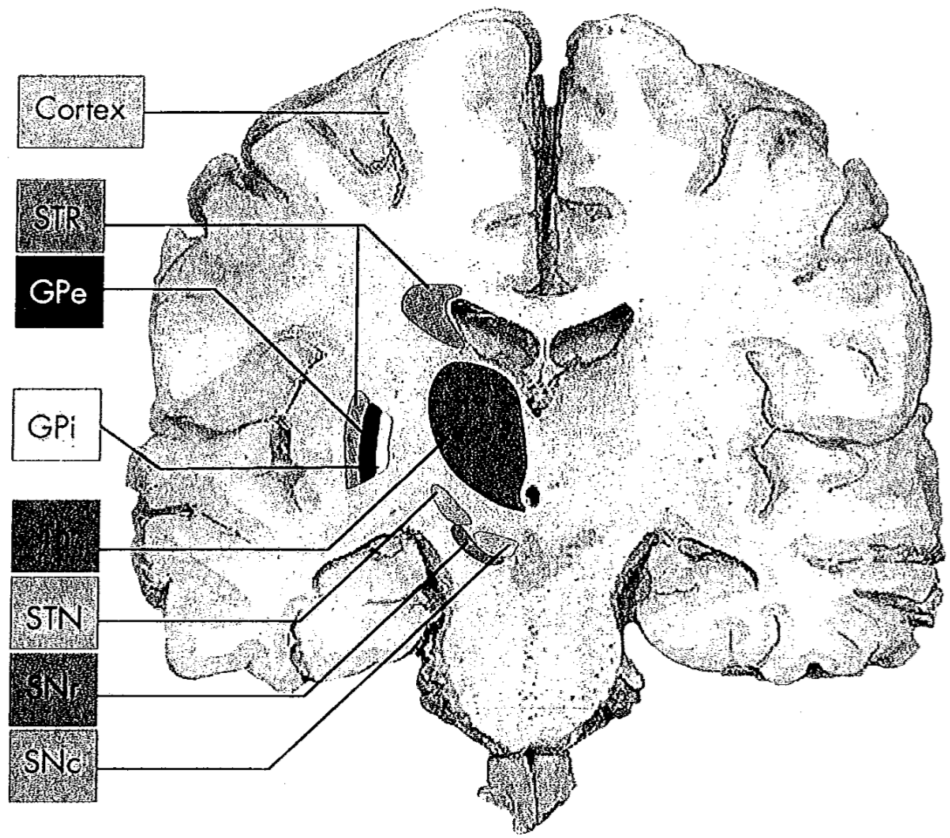
System to Control Movement Disorders



Deep Brain Stimulation

- Instead of ablation (to relieve tremor)
- First reported in 1987 with thalamus stimulation
- Globus pallidus next site with some success
- Subthalamic nucleus (1998) most successful with immediate relief of symptoms when stimulator turned on
- Stimulation of 60–200 μs pulses at >100 Hz
- Hypothesized result is inhibition, same as ablation

Basal Ganglia



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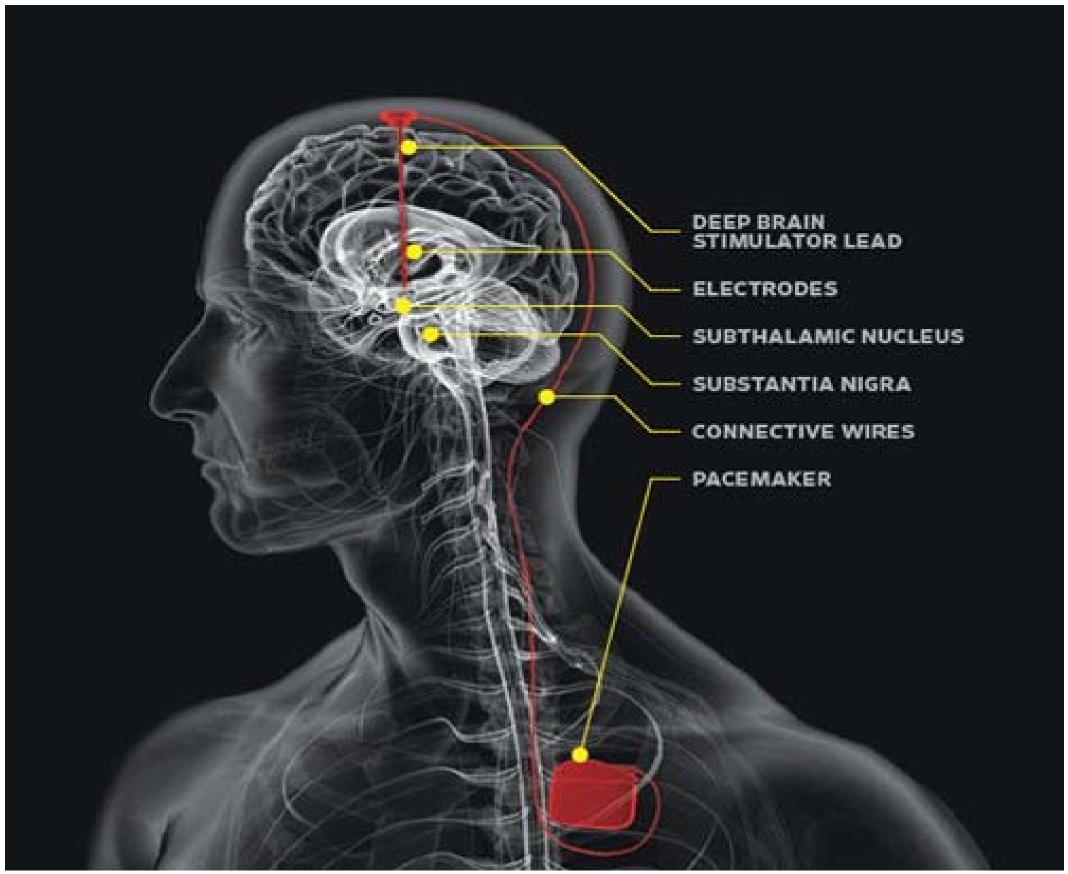
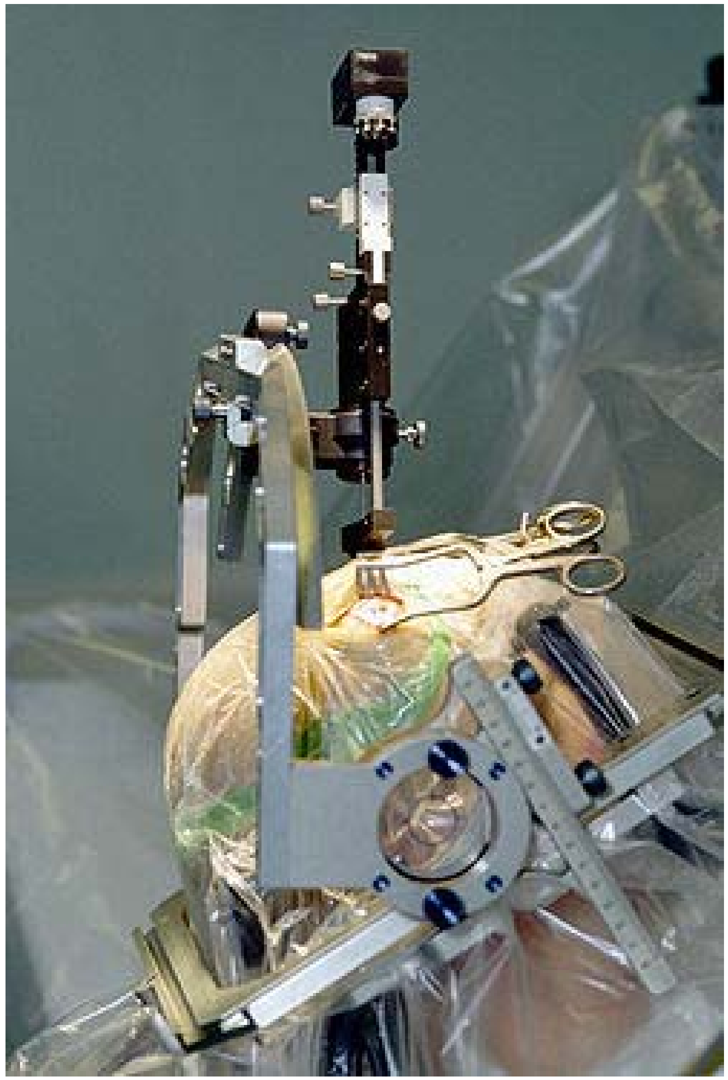
Basic Stimulator

- Medtronic Kinetra Stimulator
- Treat Parkinson or other Movement Disorders

System to Control Movement Disorders



Electrode Insertion



Electrodes for Depression

EM Treatment of Depression

- Acute and Maintenance ECT “gold standard”? Maintenance (10 treatments) as effective as medication but 46% relapse
- Vagal Nerve Stimulation (implant) Mixed results
- Repetitive Transcranial Magnetic Stimulation (“non-invasive”) Mixed Results

Problems Encountered

- Complexity of Brain (anatomical, neurophysiological) especially of frontal lobes
- Treatment mechanisms little understood (animal research suggests some mechanisms but human mostly hypotheses)
- Hardware well developed and flexible but treatment protocols either too rigid or too flexible
- Patient selection

VNS: Vagal Nerve Stimulation
Possible Mechanisms

- Alters CSF concentrations of neurotransmitters (e.g. GABBA) or their metabolites
- Alters functional activity of orbital frontal cortex, insula, thalamus, hypothalamus, etc.
- Anticonvulsants have been shown to have therapeutic value in mood disorders

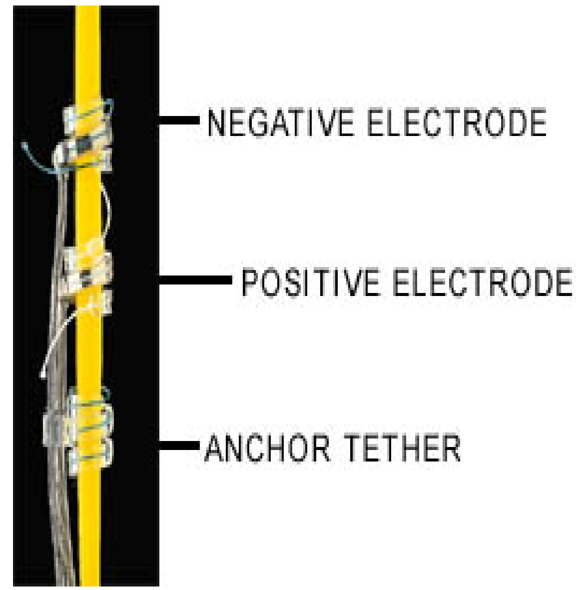
VNS: Vagal Nerve Stimulation Clinical Results

- Reduction in epileptic seizures (29,000 Cyberonics implants by 2005) few side effects
- 21 centre trial for major treatment-resistant depression 222 patients (Rush et al, Biol Psychiatry 2005)
- After 10 weeks 15% responded (≥ 50% improvement in HRSD) in treatment group vs 10% responded in sham group (not sig.)
- Longer term response rates more encouraging

Cyberonics VNS System

- Pacemaker similar to cardiac pacemaker
- Cuff electrodes on left vagal nerve
- Patient or caregiver parameter adjustment via magnetic field

Pacemaker and Electrodes



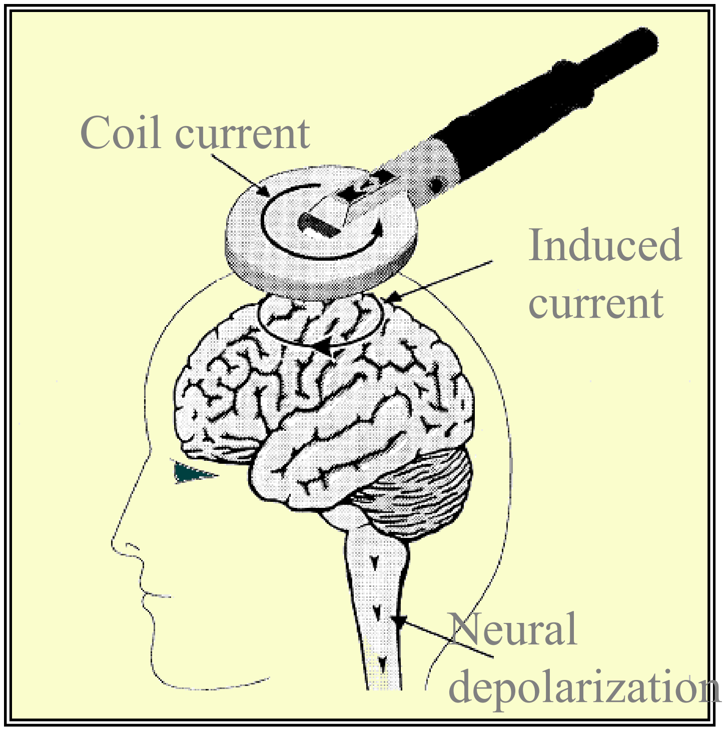
Treatment Settings

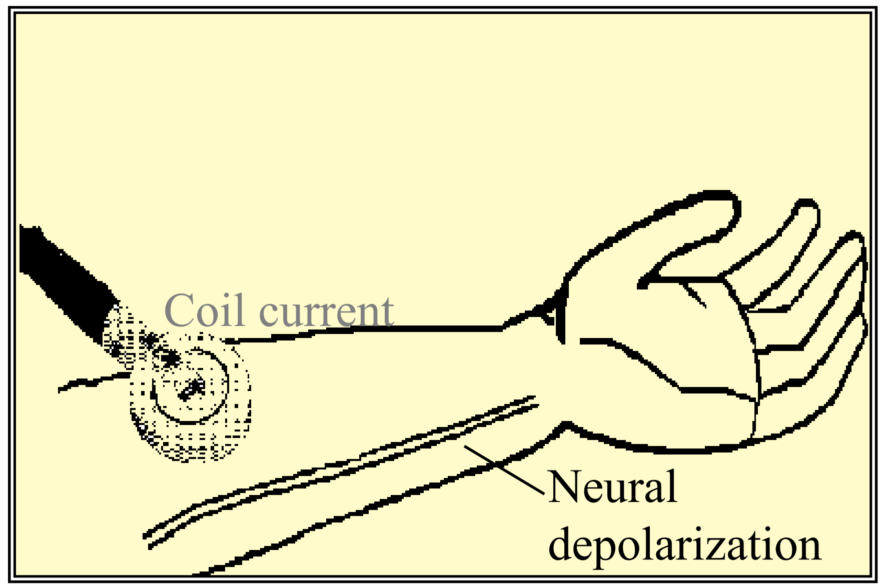
- Output current 0 -3.5mA: median last visit .75 ma, range .00 – 1.5 mA; start .25 mA (Rush)
- Signal frequency 1 – 30 Hz: median 20 Hz, range 10 – 20 Hz; start 20 Hz (Rush)
- Pulse width 130 – 1000 µsec: median 500 µsec, range 130 – 500 µsec; start 500 µsec (Rush)
- On time 7 – 60 sec, median 30 sec, range 14 – 30; start 30 sec (Rush)
- Off time .2 – 180 min: median 5 min; start 5 min (Rush)

rTMS: Repetitive Trans-Cranial Magnetic Stimulation

- Treat severely depressed patients who are resistant to pharmacology
- Alternative is periodic applications of electro-shock (ECT) treatment
- 30% of patients respond
- Would like to increase percentage of responders

Magnetic Nerve Stimulation (MNS)

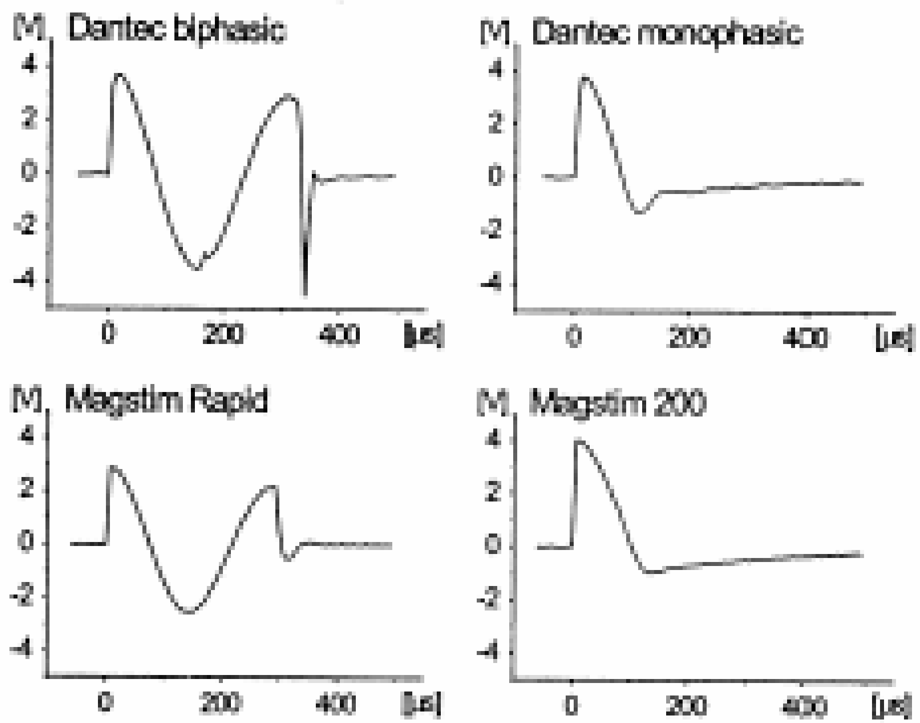




Current Commercial Machines

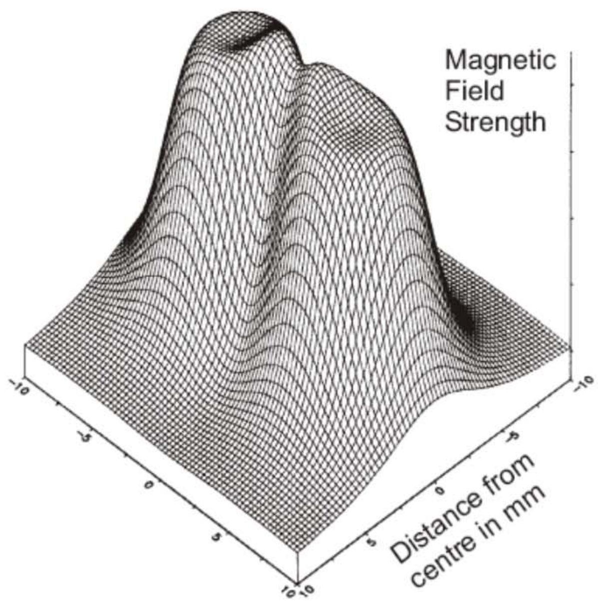
- Example Magstim

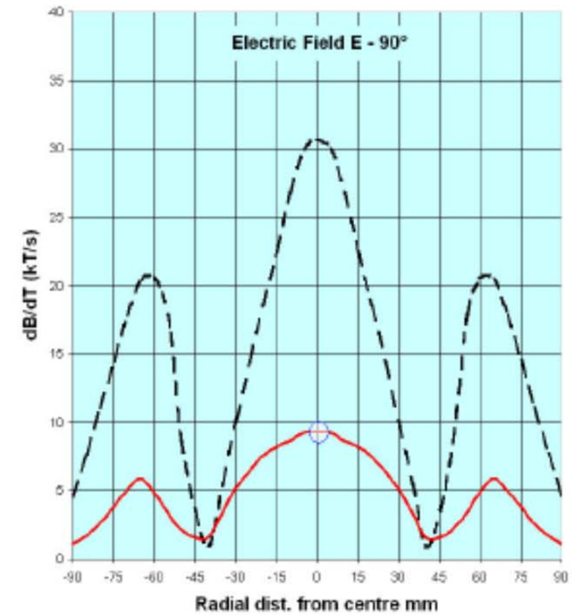
Stimulus Waveforms



Magnetic Field

Source: Medtronic, 2004





Source: Medtronic, 2004

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Treatment Protocol

- Find left thenar (abductor pollicis brevis) motor cortex stimulation point by monitoring M-wave of right thenar muscle
- Stimulate left frontal lobe (F3) at point 5 cm anterior to this site on a sagittal line
- Using a fixed % (80 – 120) of thenar threshold amplitude stimulate at 8 to 10 Hz for fixed periods up to 1800 stimuli; several clinics 3000 stimuli
- Repeat 4 to 5 times/week for 5 weeks

Clinical Treatment

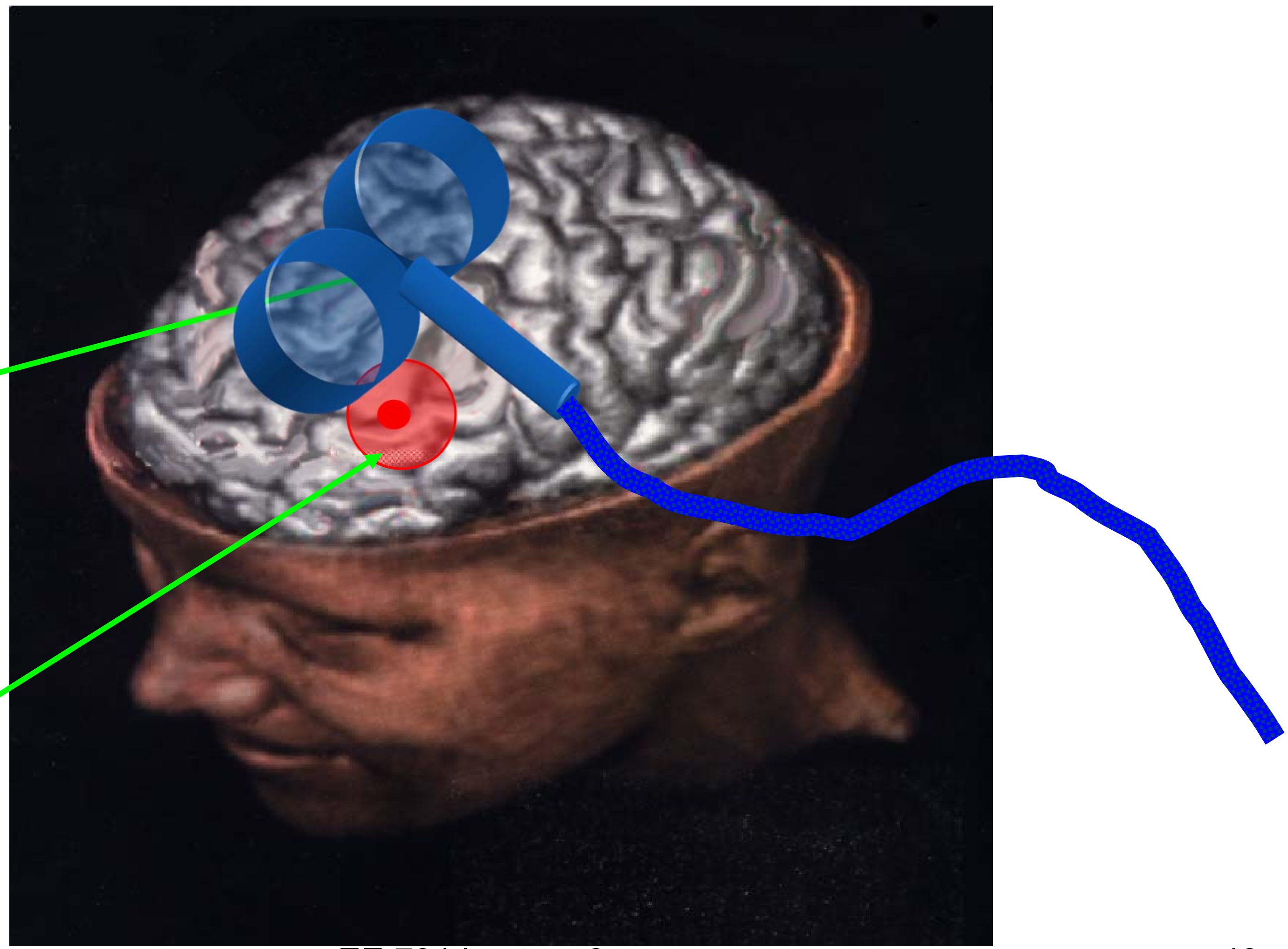
Research Challenges (Objectives)

- Develop quantitative method for predicting which patients will respond to rTMS (use pre treatment EEG parameters, QEEG)
- Develop quantitative method for determining best site of stimulation
- Determine effects of changing stimulus amplitude and frequency

Can We Predict Who Will Respond?

	ACTUAL RESPONSE **Chi square = 4.866, p = .0227**	
PREDICTED RESPONSE	RESPONDER	NON-RESPONDER
RESPONDER	6	4
NON-RESPONDER	1	8

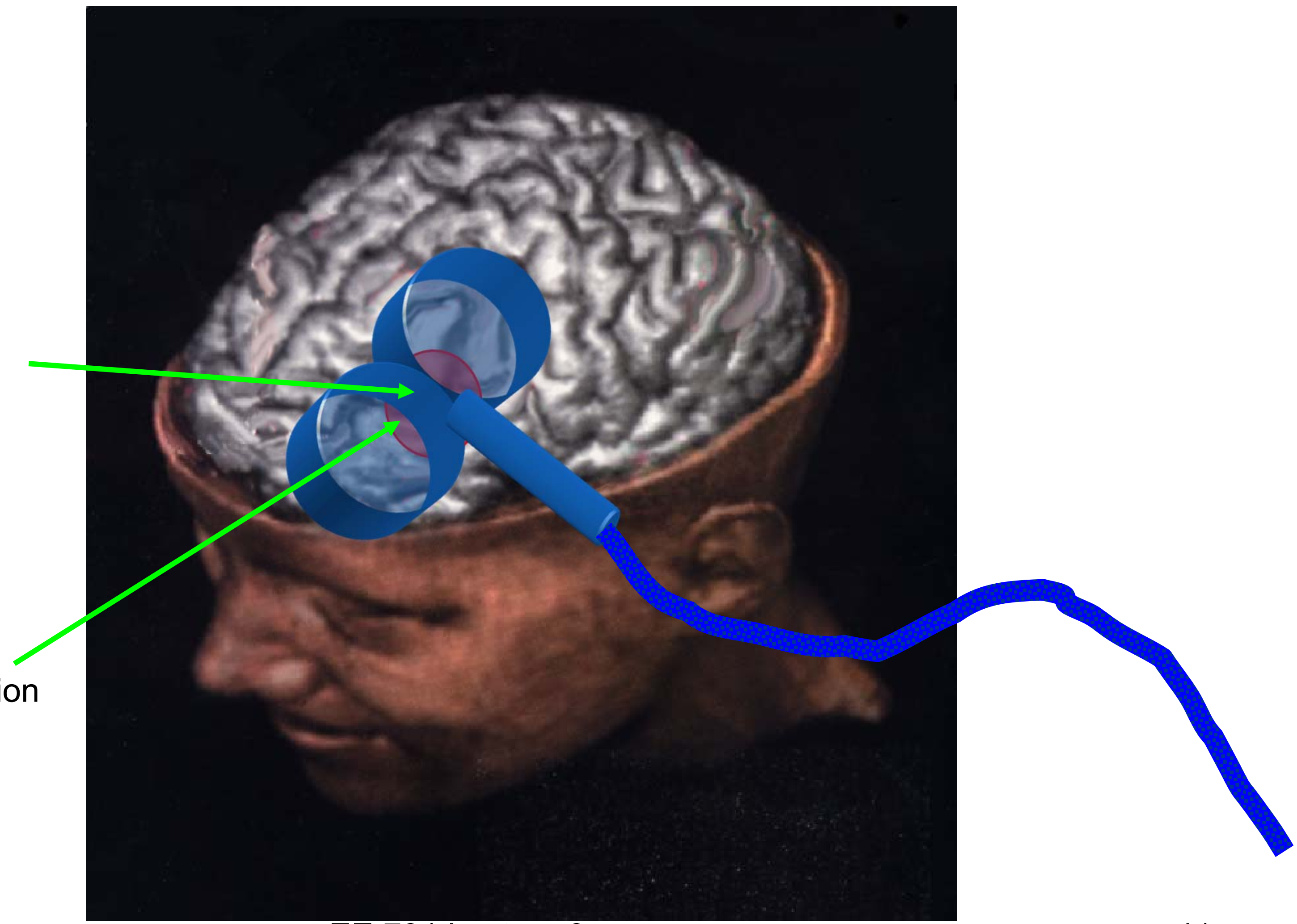
Those with correctable pathophysiology may not respond as standard methods place the coil in the wrong spot (we are not very good at predicting RESPONSE using QEEG)



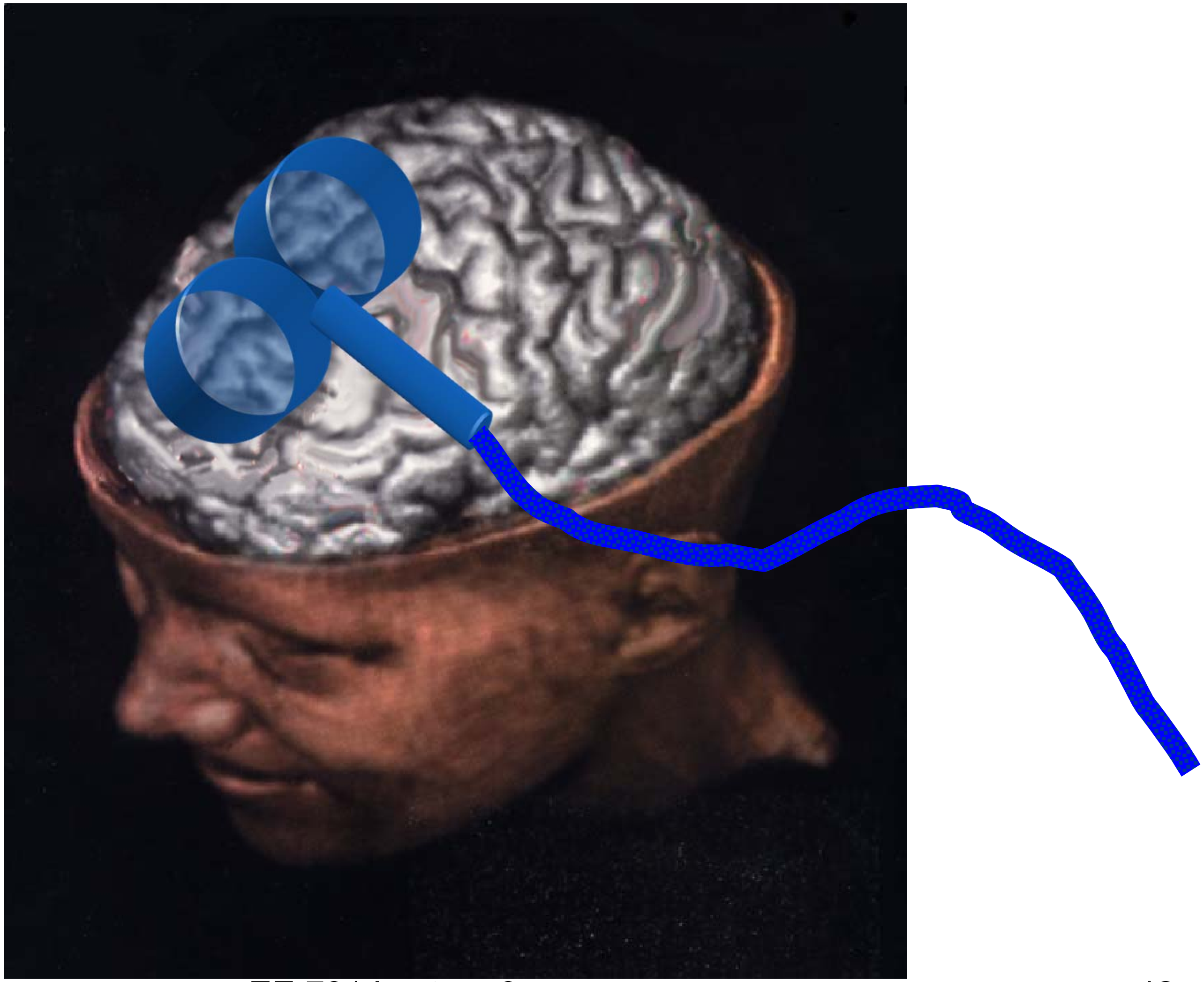
Other subjects respond as their head size and brain anatomy is such that standard methods place the coil over the site of possible dysfunction (detectable using QEEG)

Standard positioning method correctly places coil at the appropriate site to effect an antidepressant response

Possible site of correctable dysfunction



Those without correctable pathophysiology will not respond no matter where we put the coil(we are quite good at predicting NON-RESPONSE using QEEG)



No rTMS correctable dysfunction present therefore coil positioning is not important

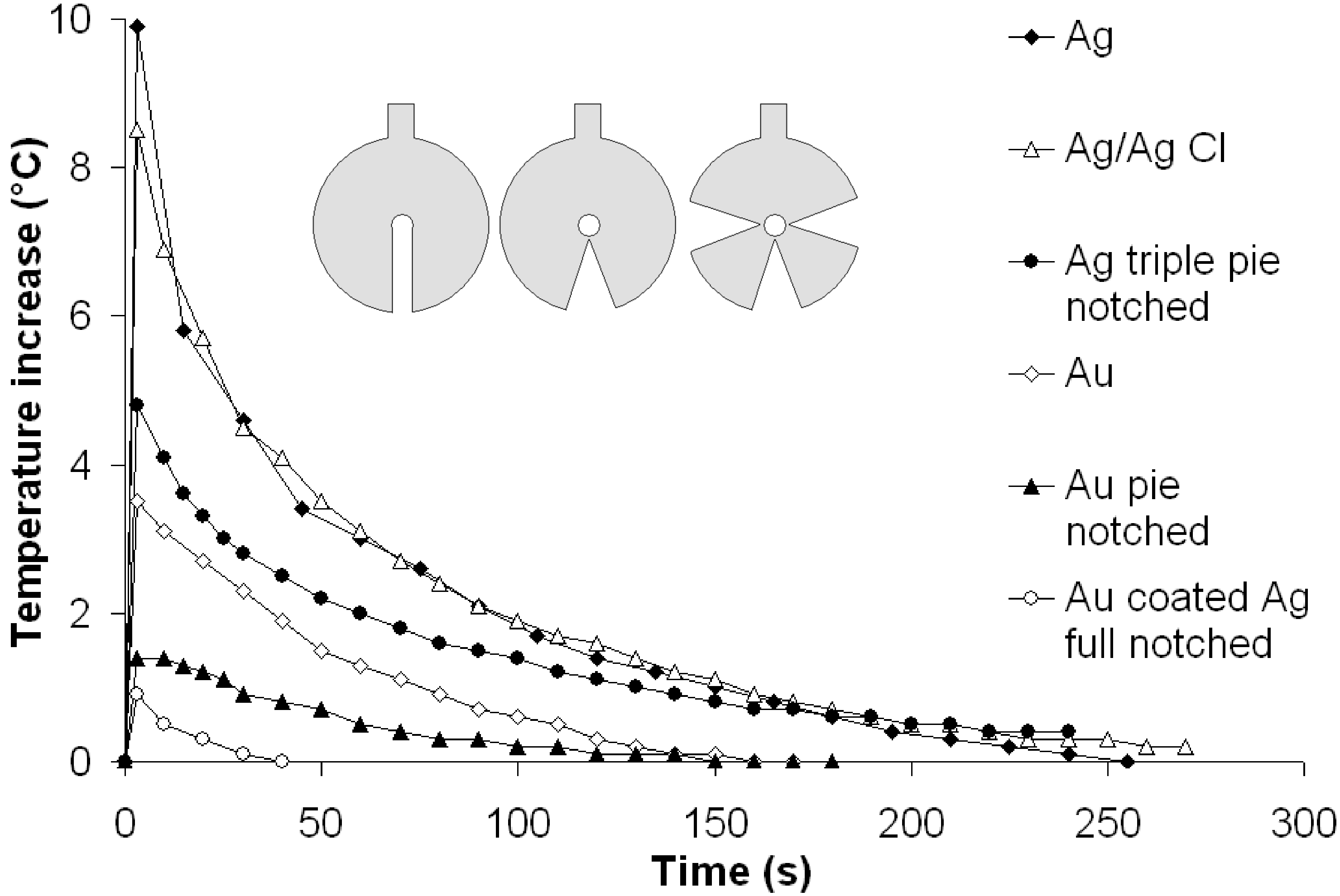
Current Status for EEG Processing

- Significant results for simple Alpha and Theta power ratios in determining potential responders (50 – 60%)
- Considerable improvement when using more EEG parameters in a learning algorithm (80%, N = 54)

Magnetically Evoked Potentials (MEP)

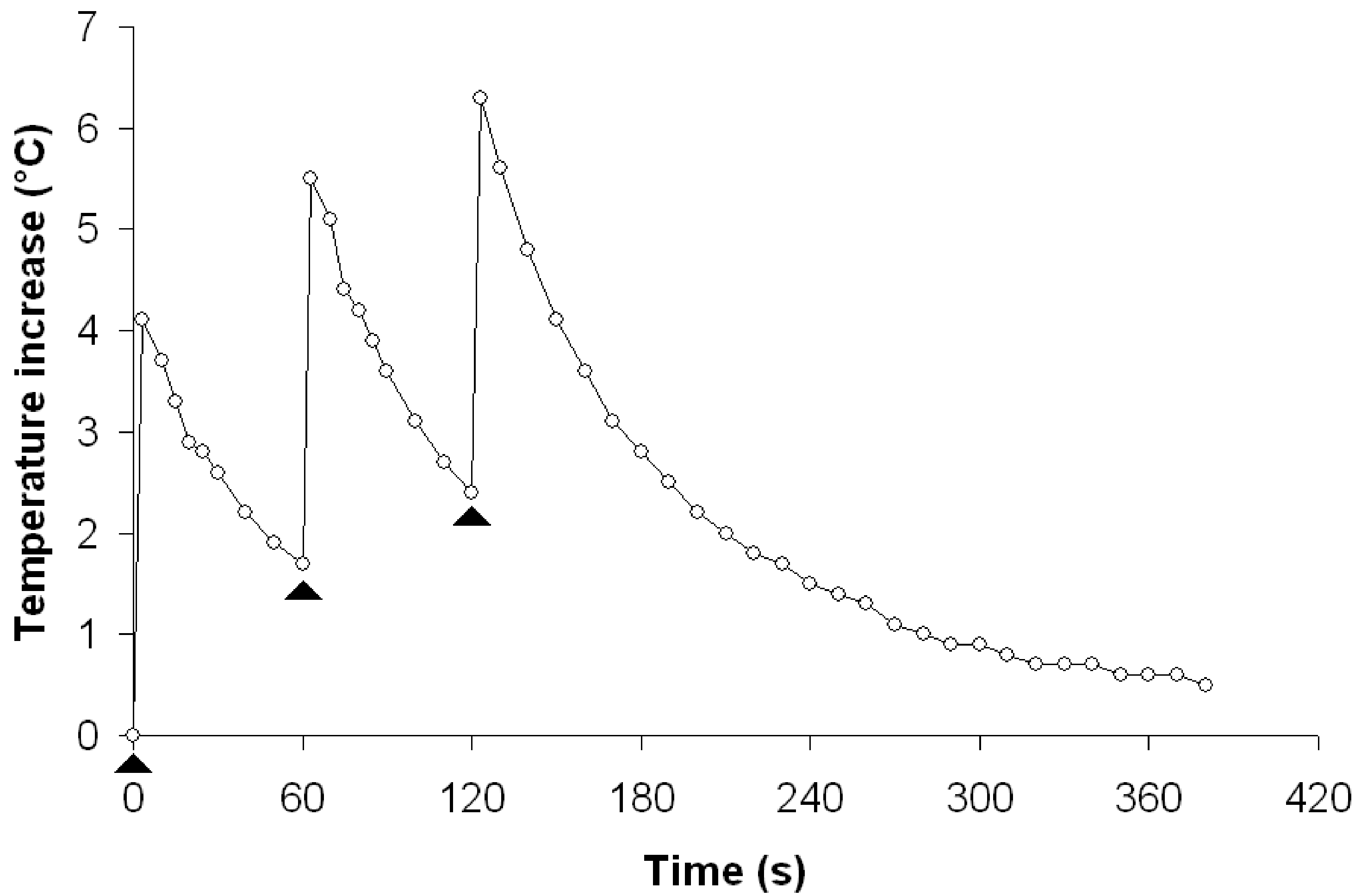
- Assume the neural tissue is a stochastic system
- Require multiple stimuli and synchronous averaging of evoked potentials
- Heating of EEG electrodes during stimulus train
- Saturation of amplifiers by magnetic stimulus artifact

Electrode Materials



3s at 20Hz at 85% intensity, r = -30mm

rTMS Trains of Stimuli

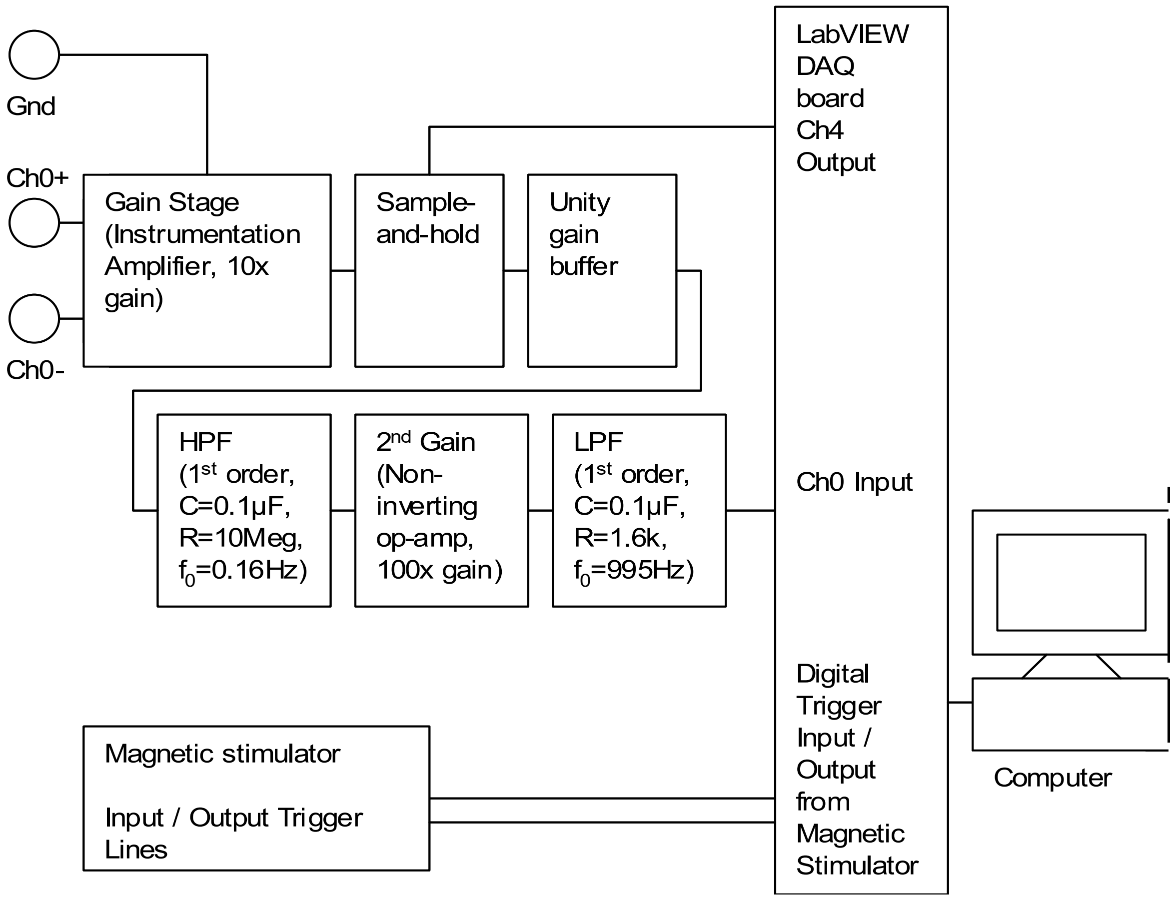


Au electrode, 3s at 20Hz at 85% intensity, trains at 0, 60, 120s

Artifact Blocking

- Various methods have been used:
  - Low slew rate amplifiers (Thut, 2005, Ives, 2006)
    - First 30ms of signal lost and bandwidth reduced
  - High bandwidth amplifiers (Fuggetta, 2005)
    - First 15ms of signal lost
  - Switching off the amplifiers (Shutter, 2006)
    - First 200ms of signal lost
  - Sample-and-hold circuit (Ilmoniemi, 1997)
    - Works, published results ignore or mask first 10 ms

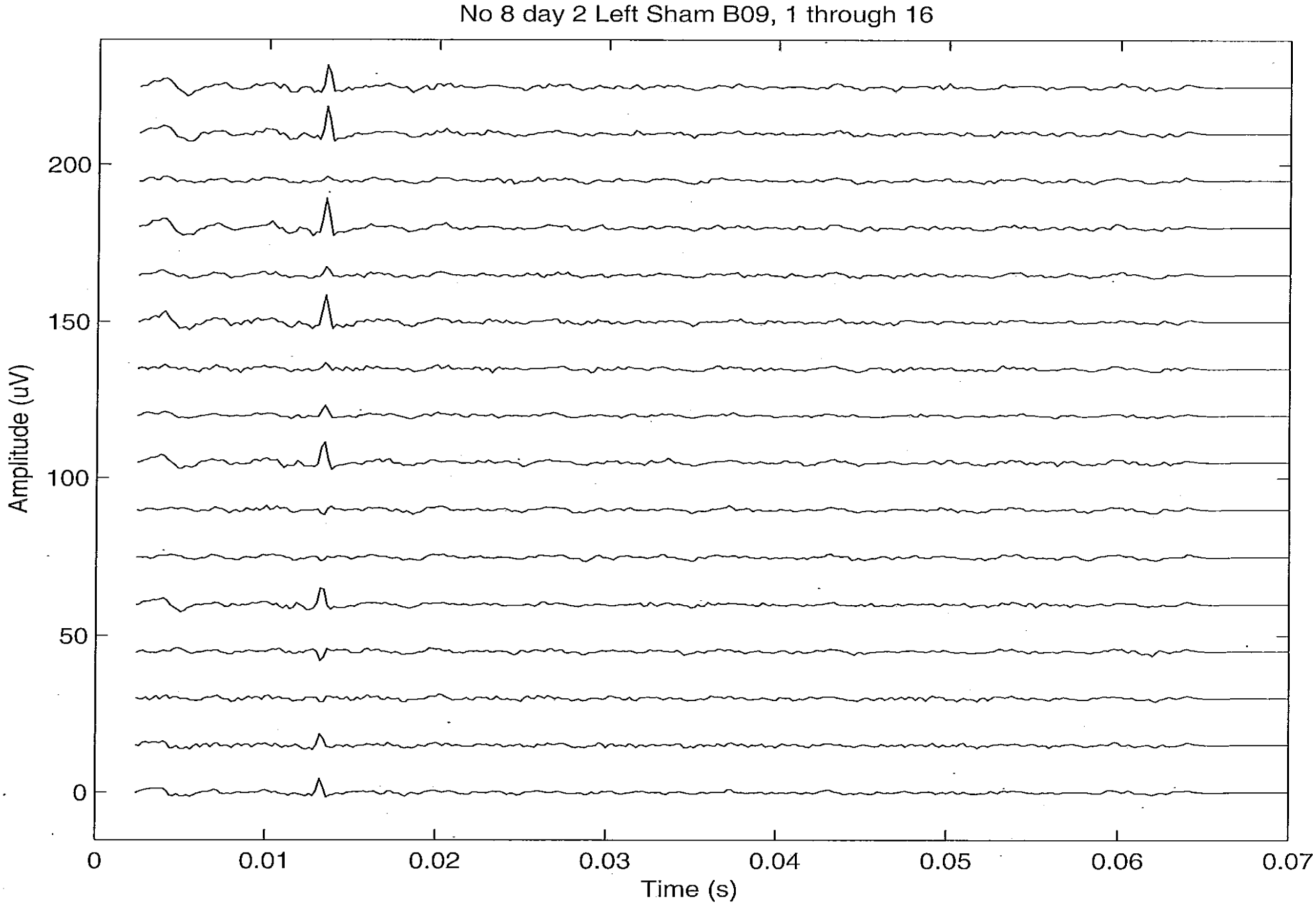
Systems Approach



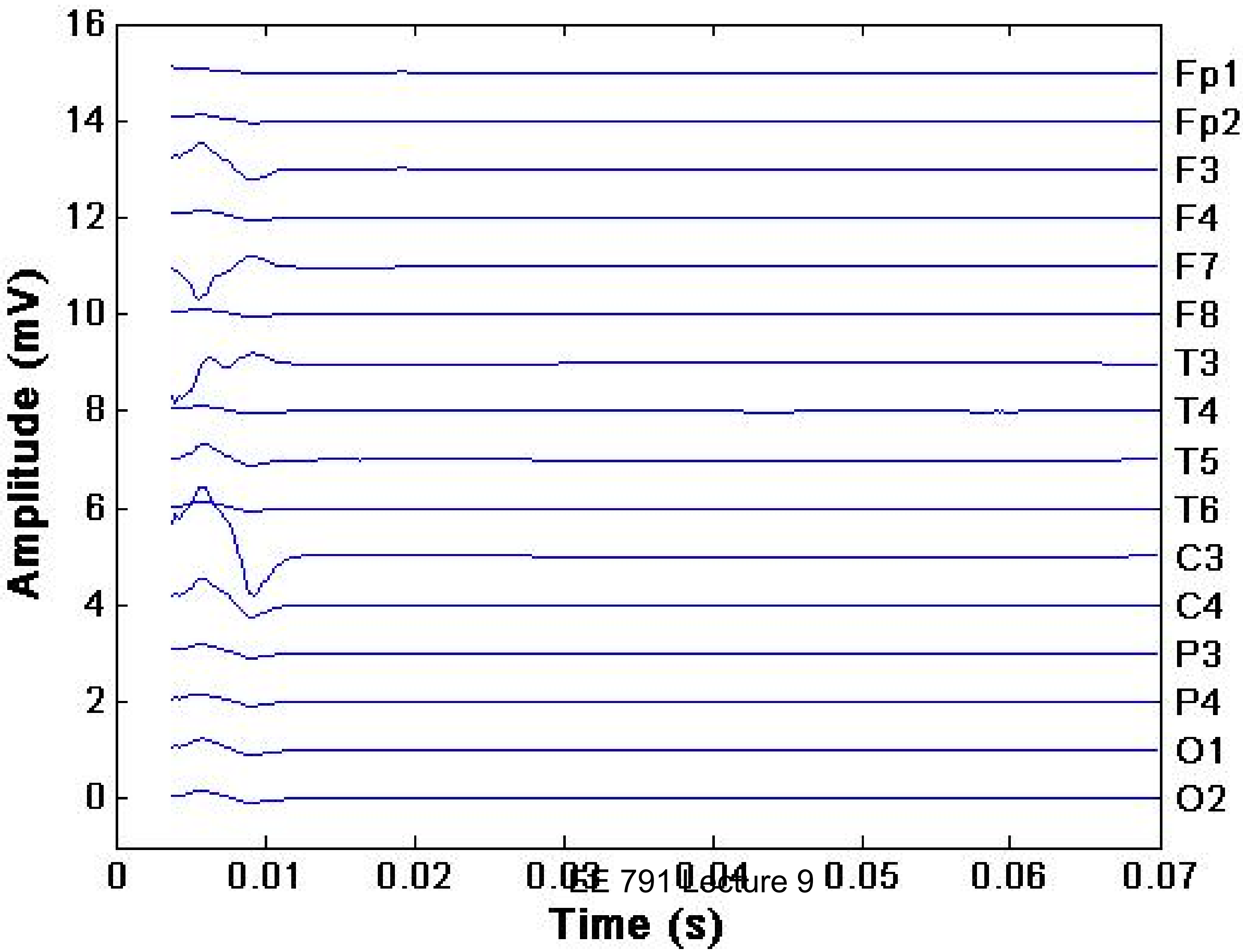
Left Side vs Right side Stimulation

- Only analyzing response in bandwidth 250 Hz - 2 KHz for short latency responses
- Series 1 is left side stimulation at 10 Hz for 8 sec at 110% MT
- Series 2 is right side stimulation at 1 Hz for 60 sec at 110% MT
- Ratio is True/Sham Response (avg signal power in 7.4 – 30 ms window) for left
- Right ratio corrected for residual background activity

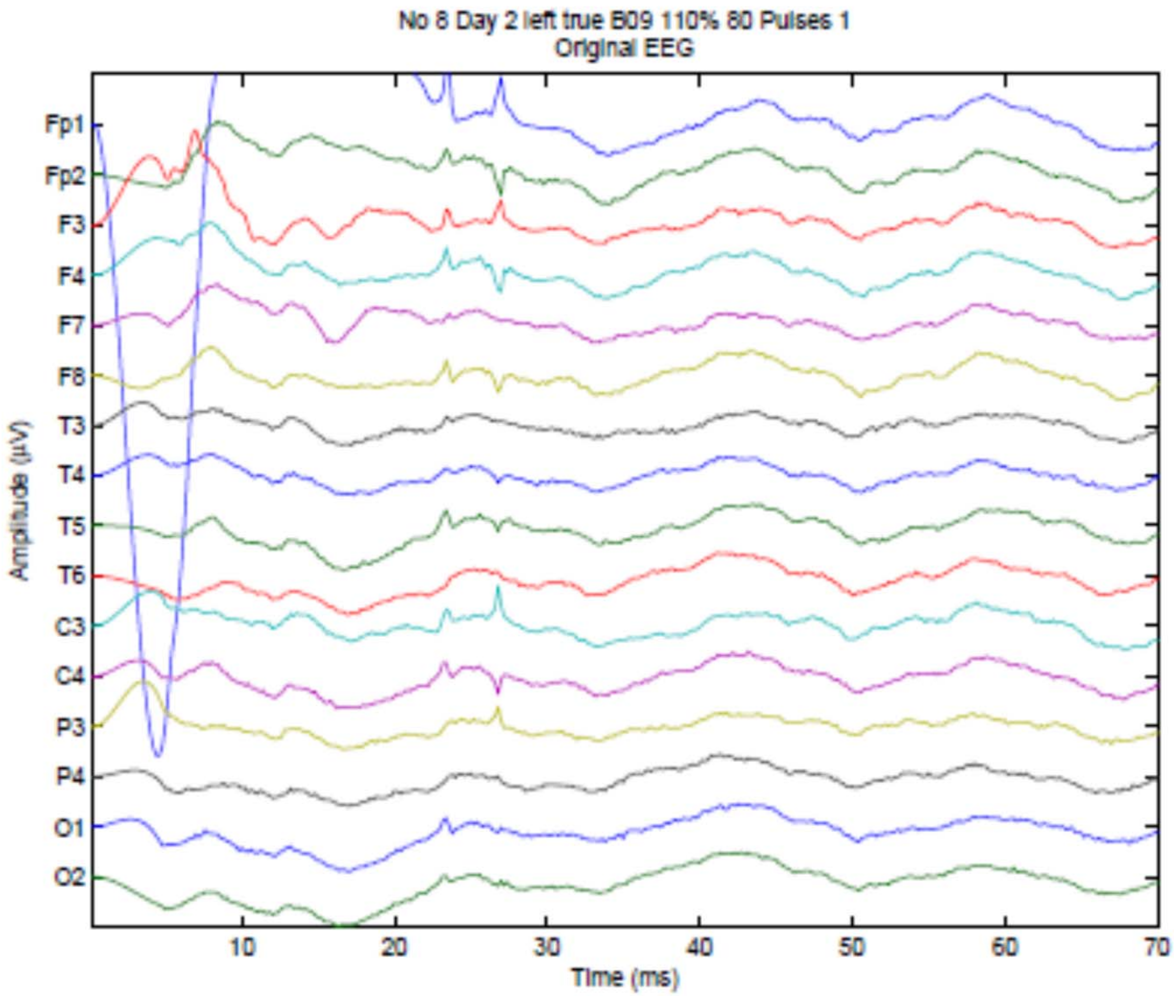
Typical Left 10 Hz Sham Response



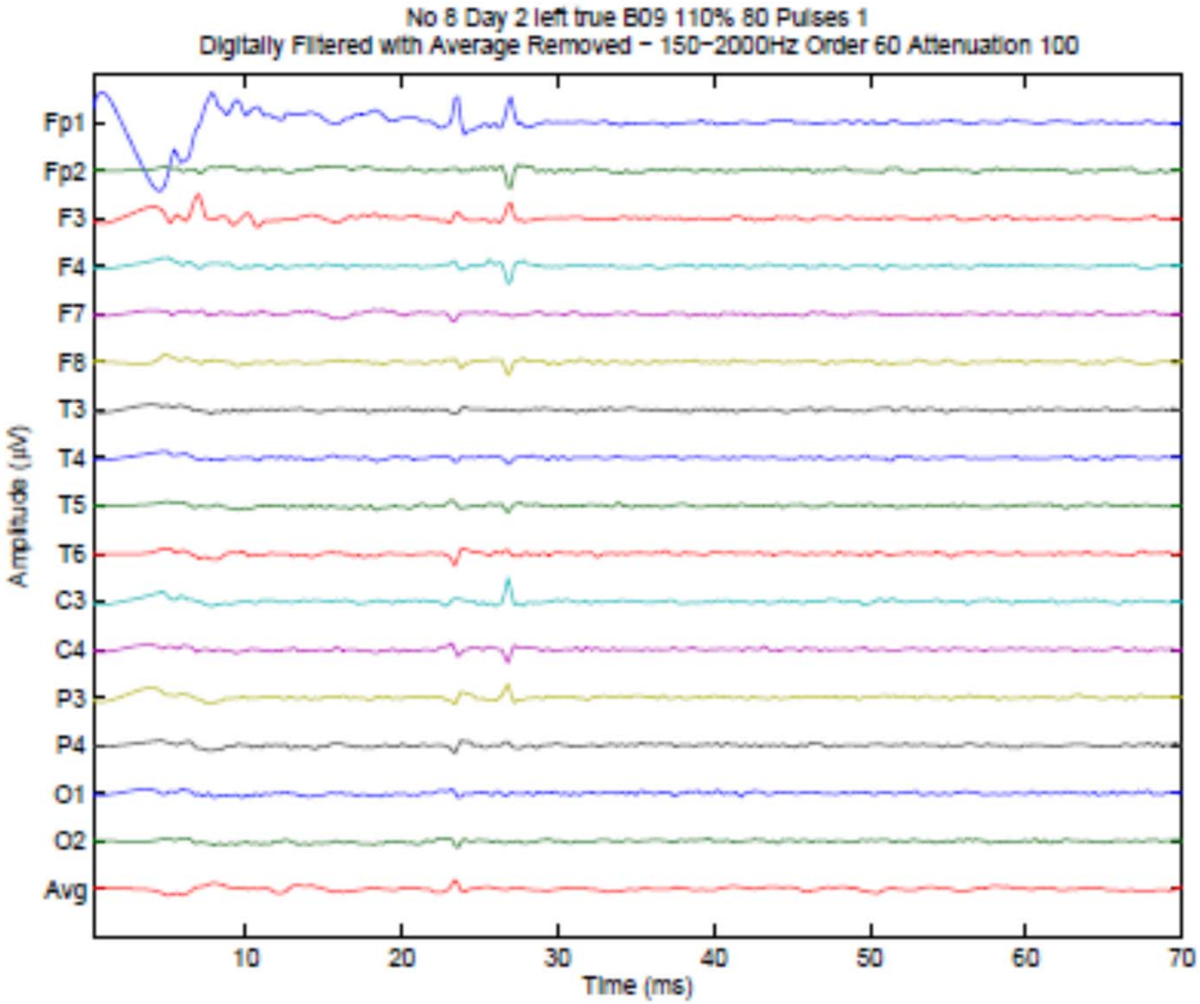
Scalp Muscle Response



Results of Day 2 Position Study (Typical Subject)



Using Digital Filtering



Noise-free Response

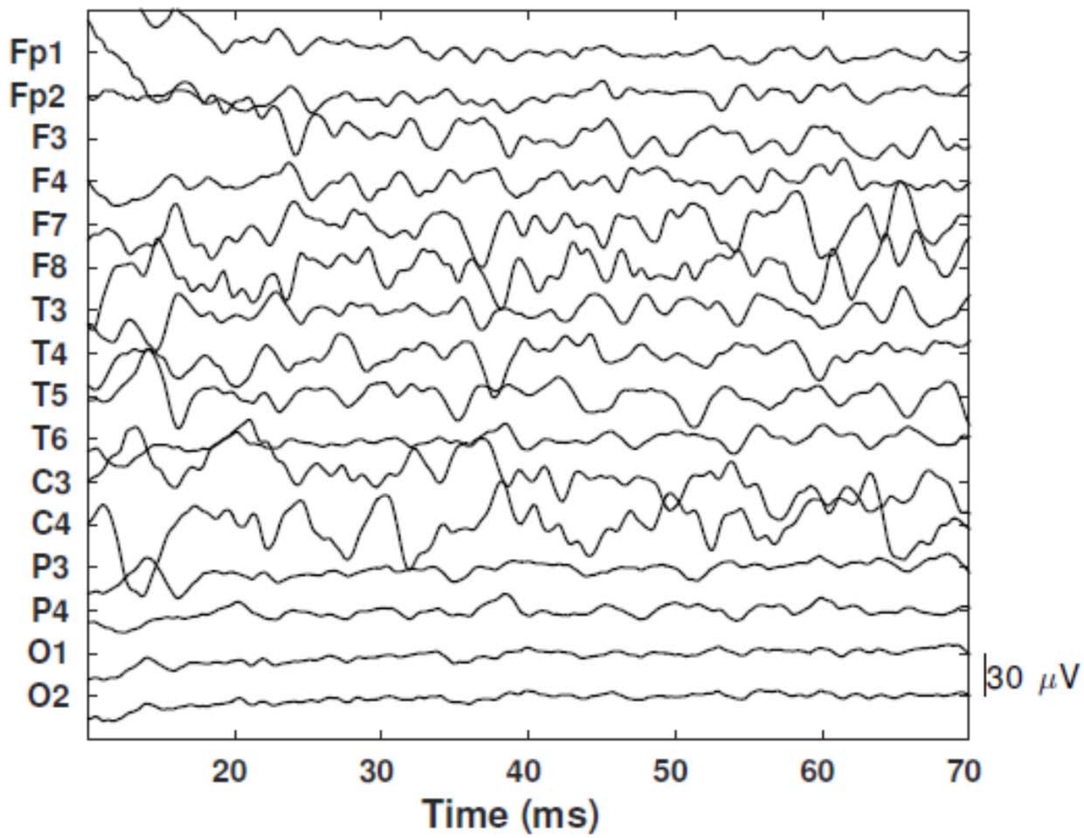


Fig. 1. Average response for 80 stimuli at 10 Hz to Brodmann area 10 for a 33 year old male, with data bandpass filtered from 25 to 2000 Hz.

Testing with Simulated Signal

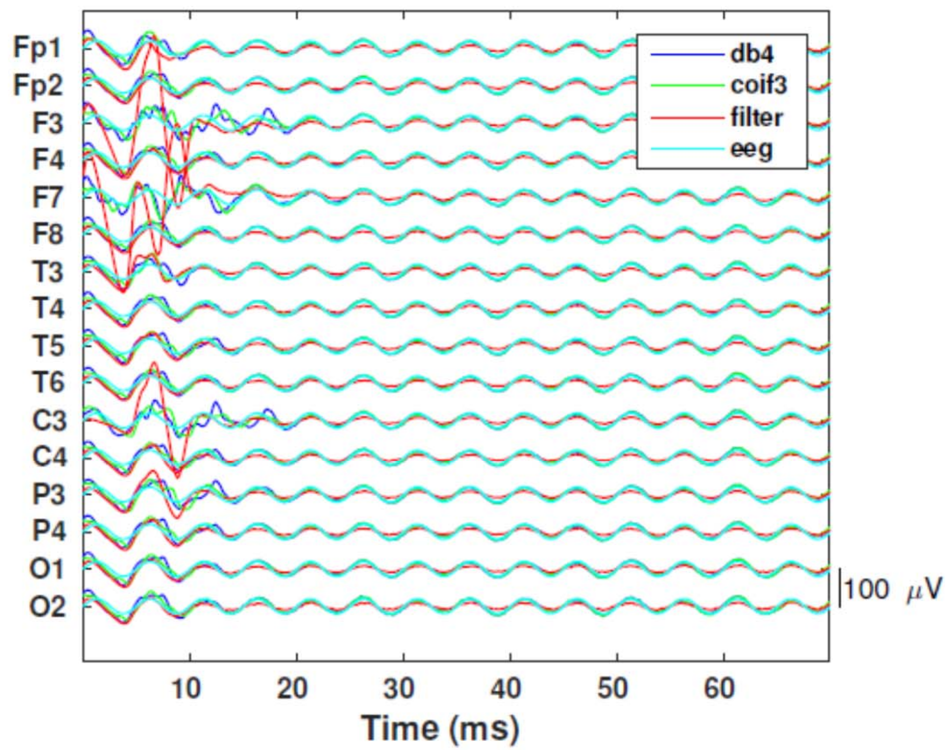


Fig. 3. Residual from denoising simulated EEG contaminated by an electrically stimulated CMAP using wavelet denoising and digital filtering, (150-2000 Hz).

RMSE for Simulated

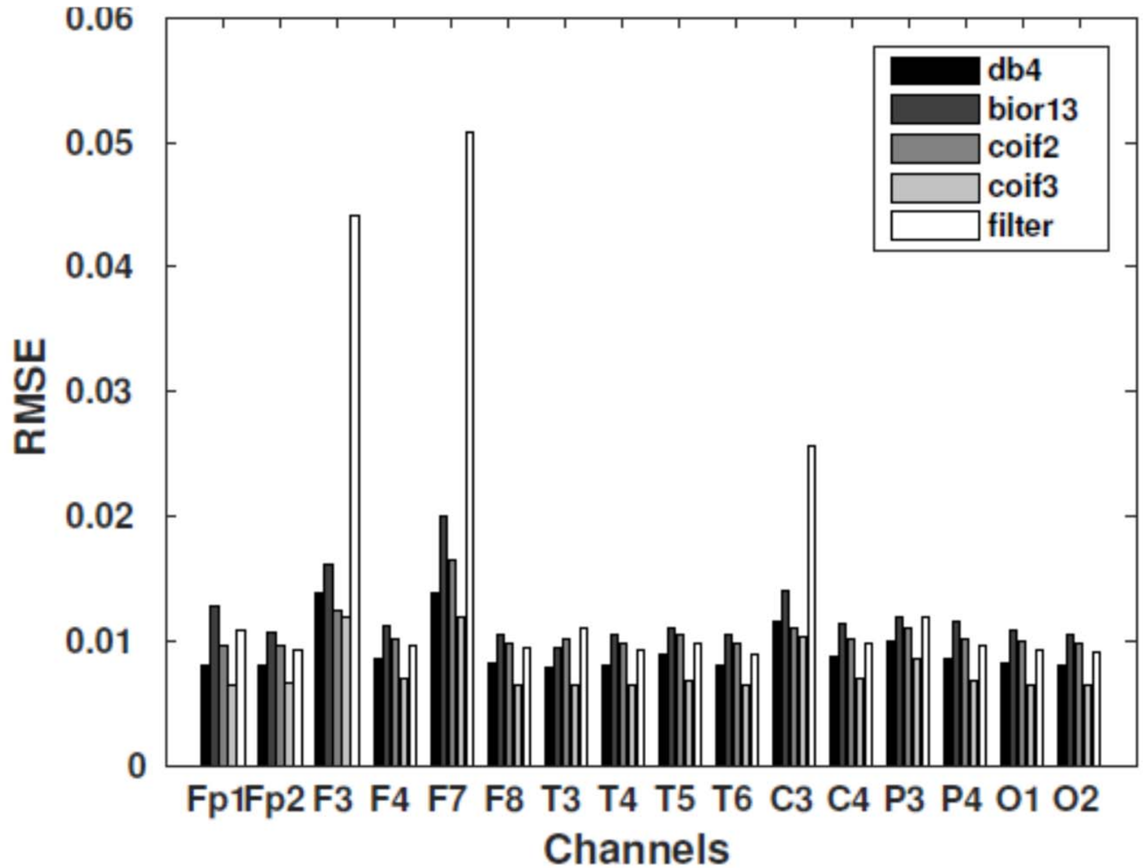


Fig. 4. Comparison of root-mean-squared error (RMSE) in recovering the original simulated EEG signal for digital filtering and the proposed method.

Real Results

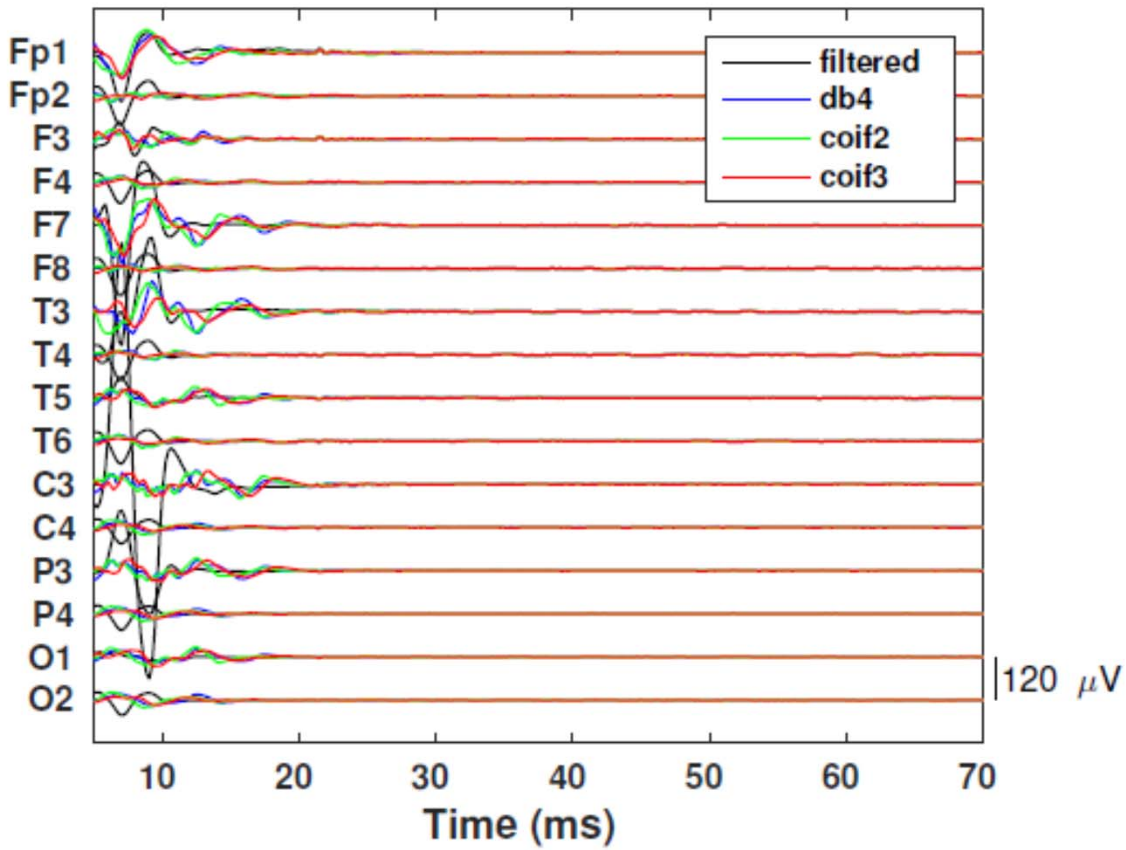


Fig. 5. Residual of wavelet denoising with various mother wavelets and digital filtering (150-2000 Hz). Original data is shown in Figure 2.

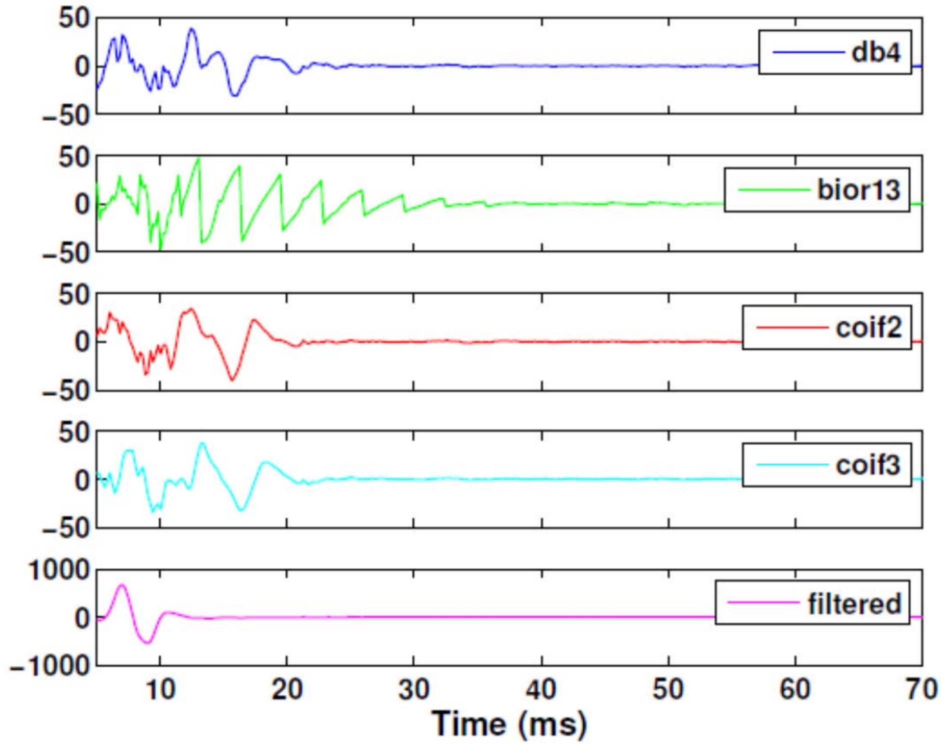
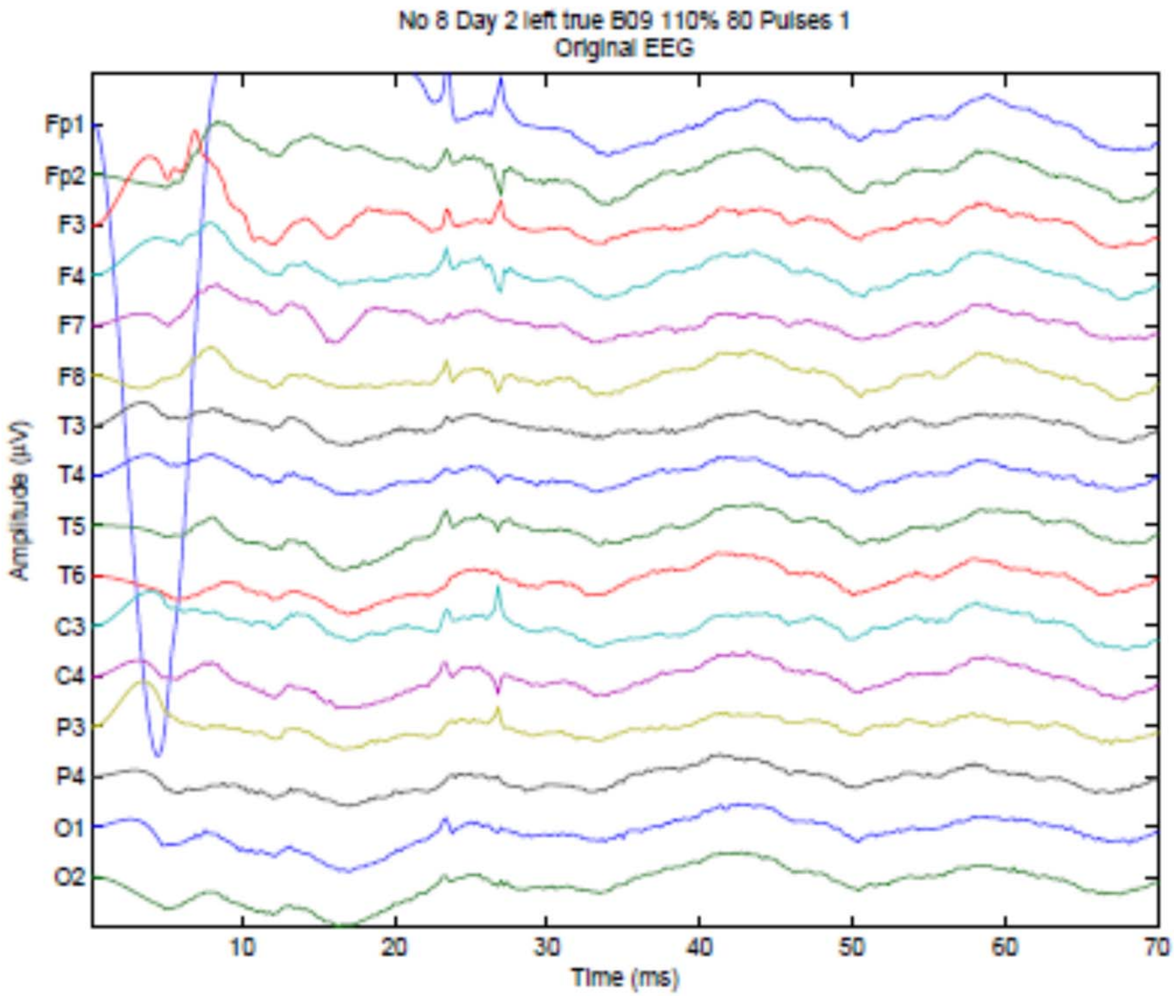
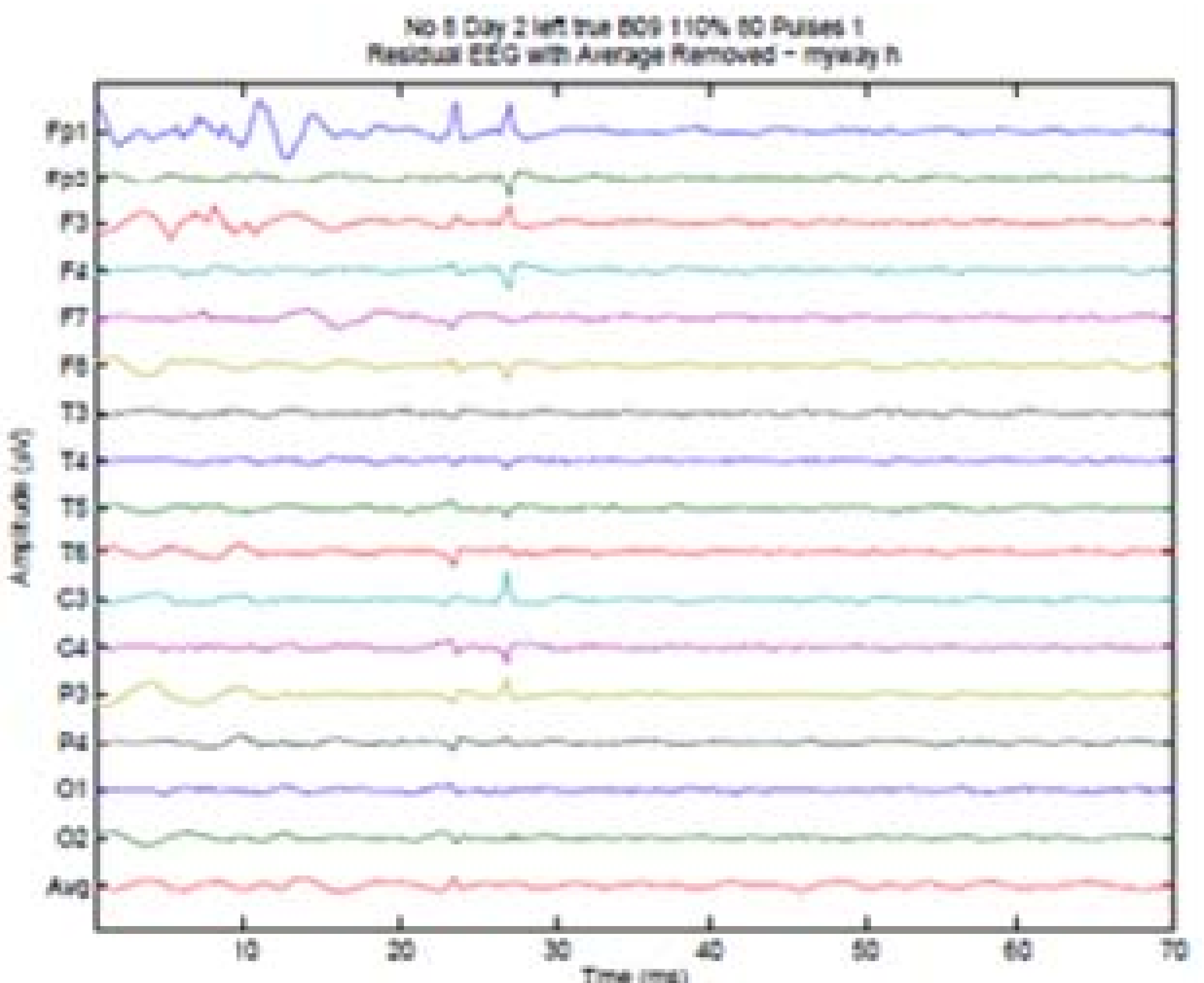


Fig. 6. Residual of wavelet denoising with various mother wavelets (from top: Daubechies 4, Biorthogonal 1.3, Coiflet 2, Coiflet 3) and digital filtering (150-2000 Hz) at C3. Original data is shown in Figure 2.

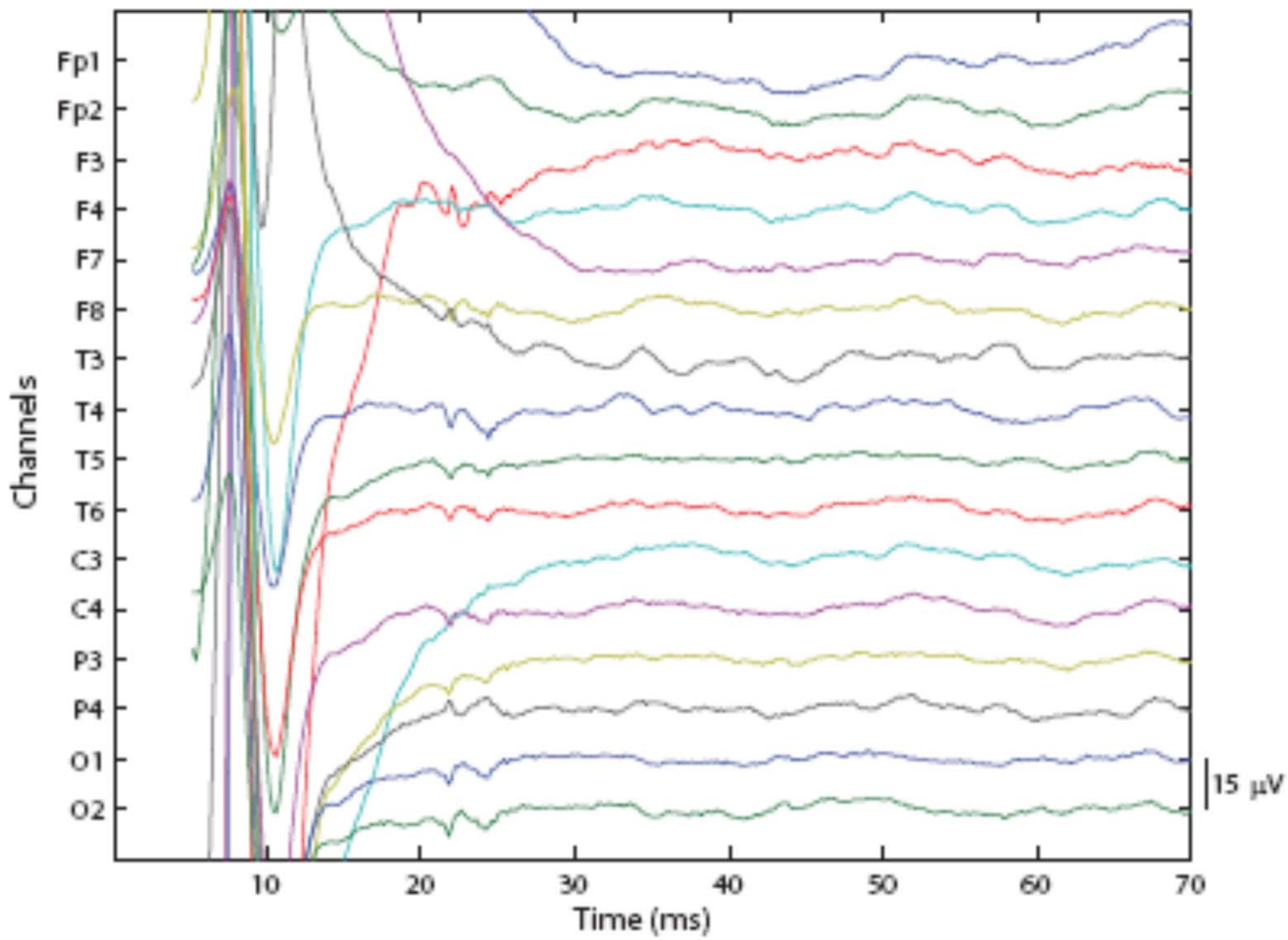
Results of Day 2 Position Study (Typical Subject)



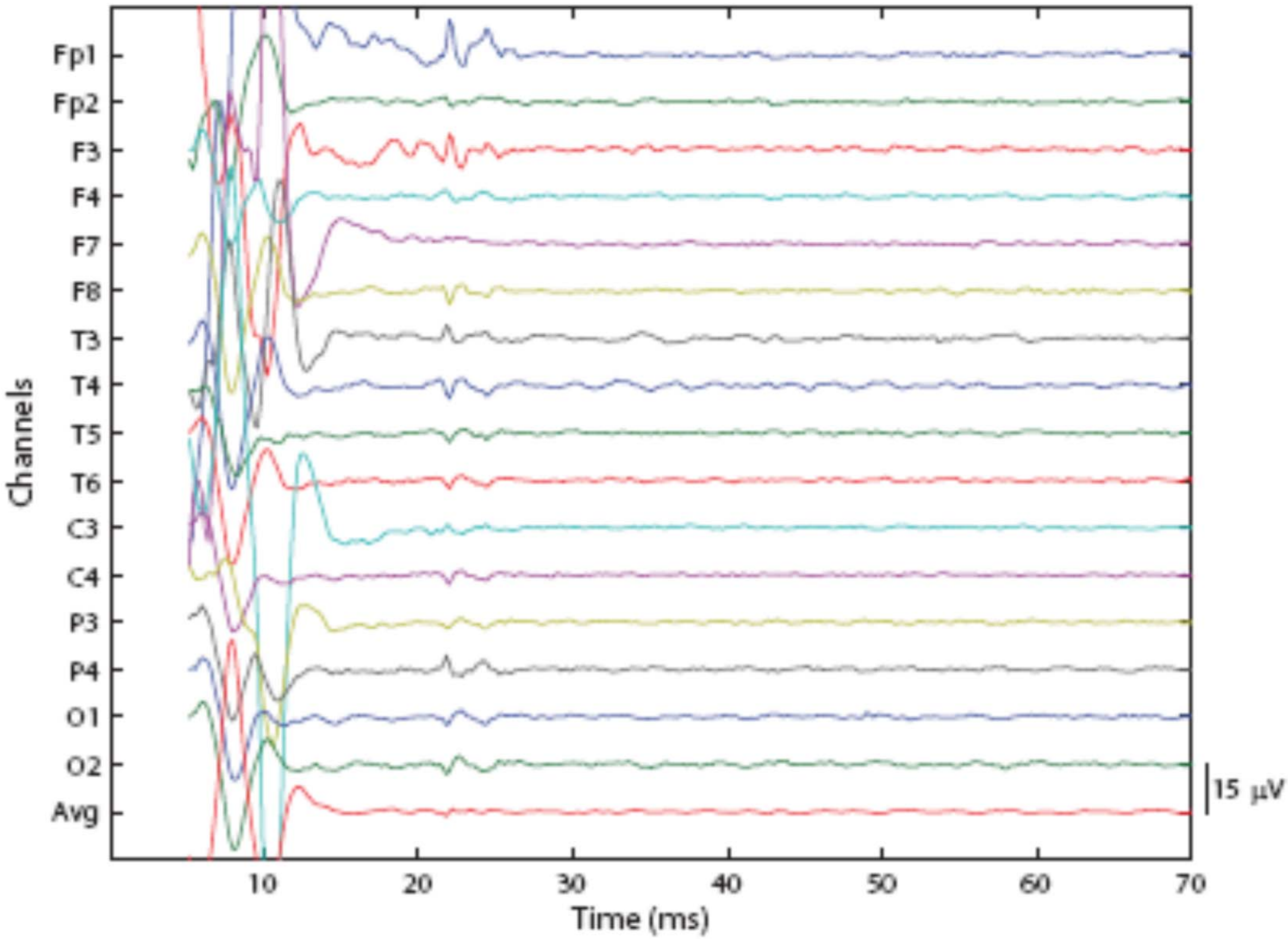
Using Wavelet Denoising



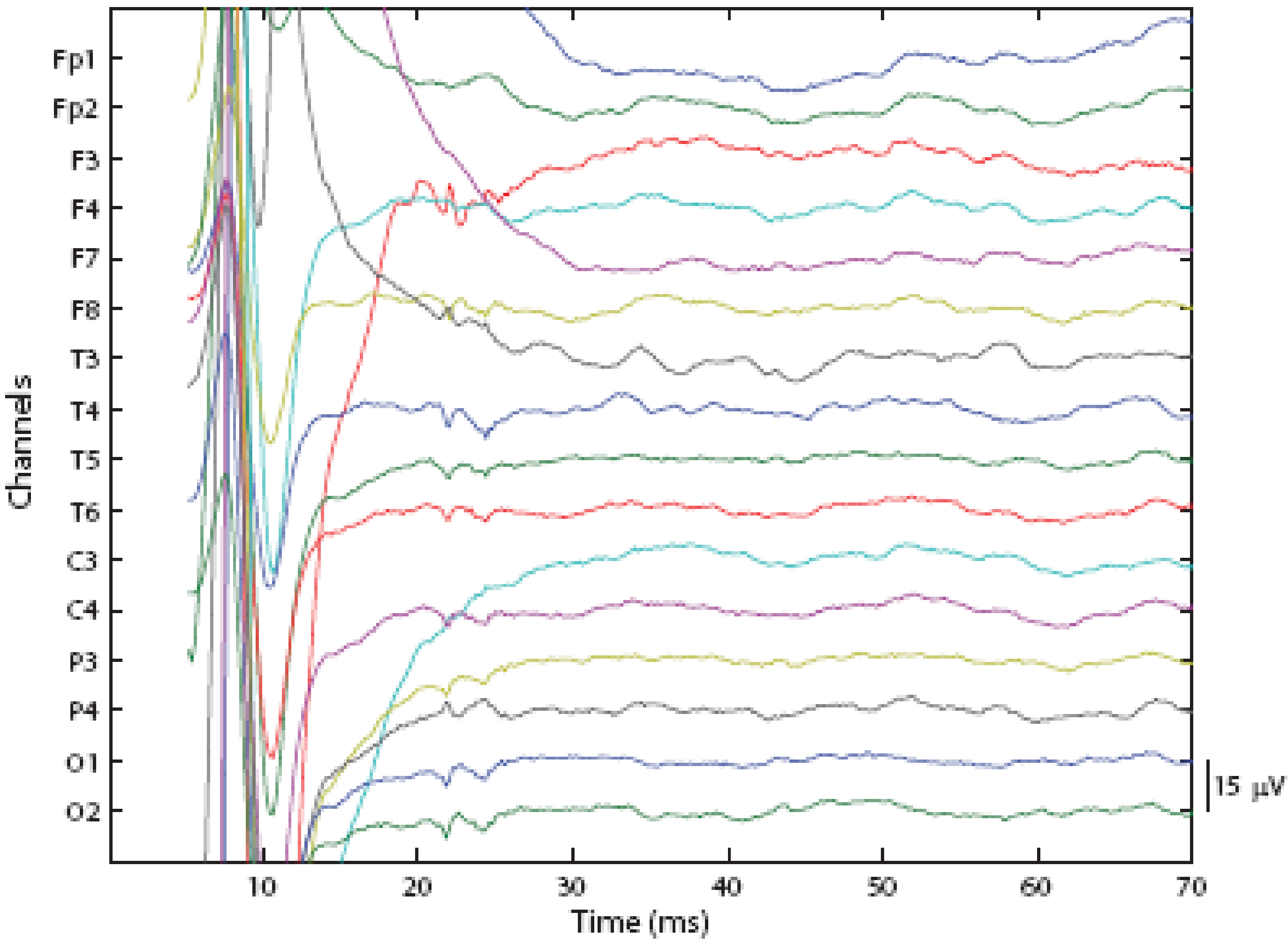
Unfiltered B10 Response to 10 Hz at B10, 80 Pulses



150 – 2 kHz Filtered Response for Slide 56



Brain Response Recorded on Scalp



Responses Following Processing

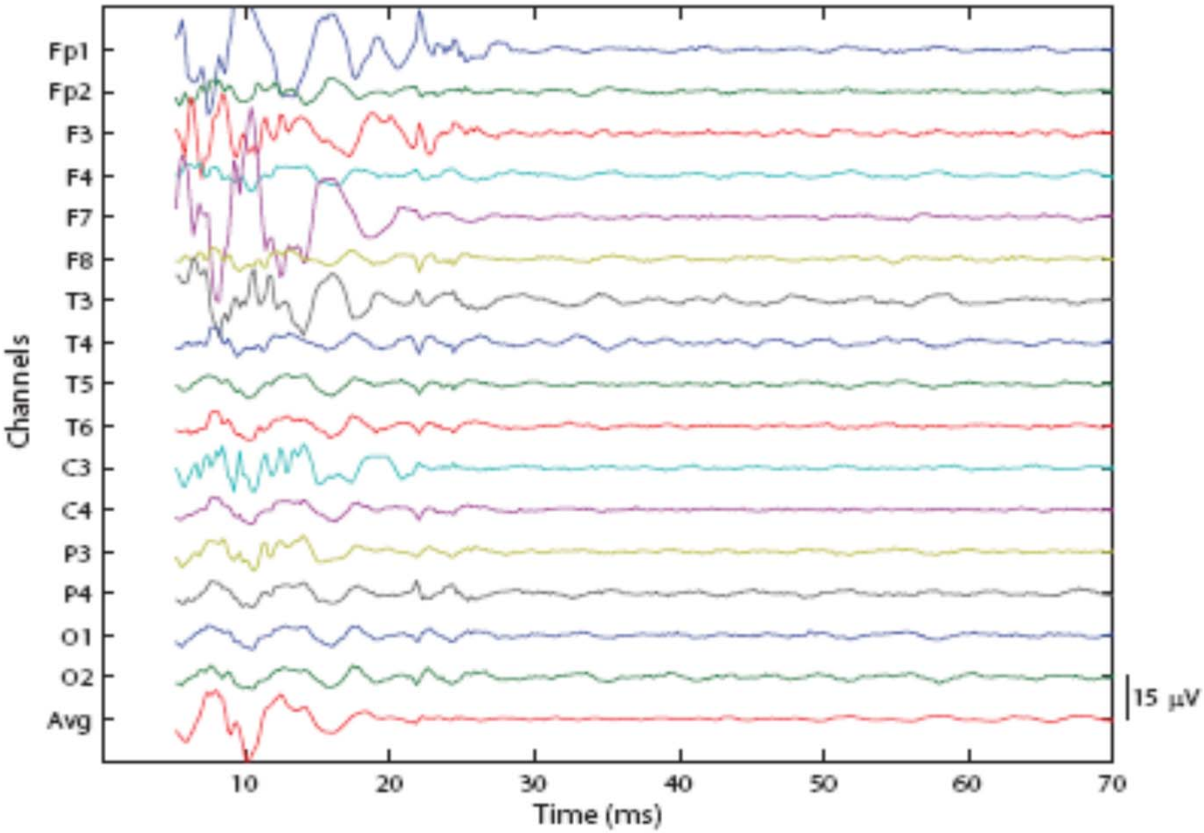
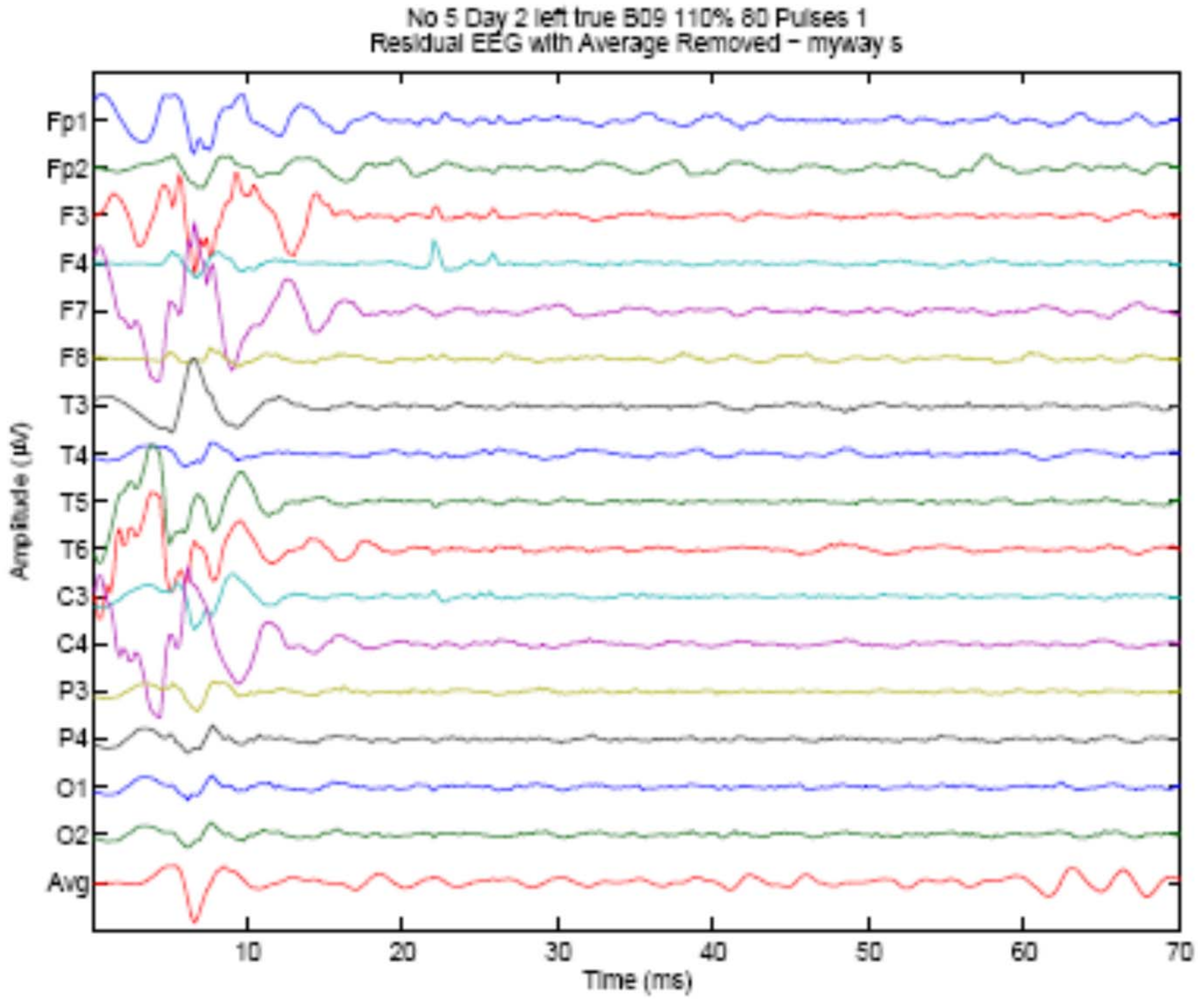


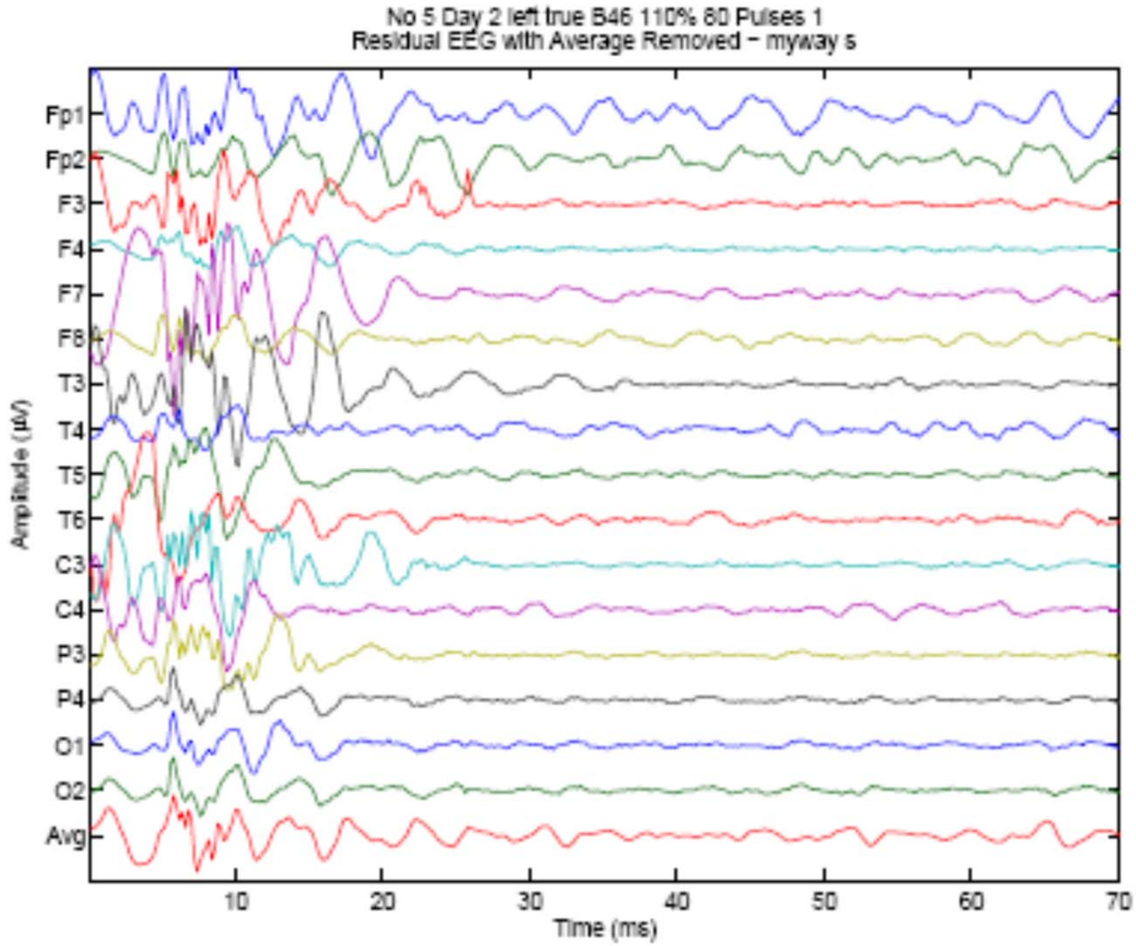
Fig. 3. Residual of wavelet denoising by soft thresholding

Left 10 Hz B09



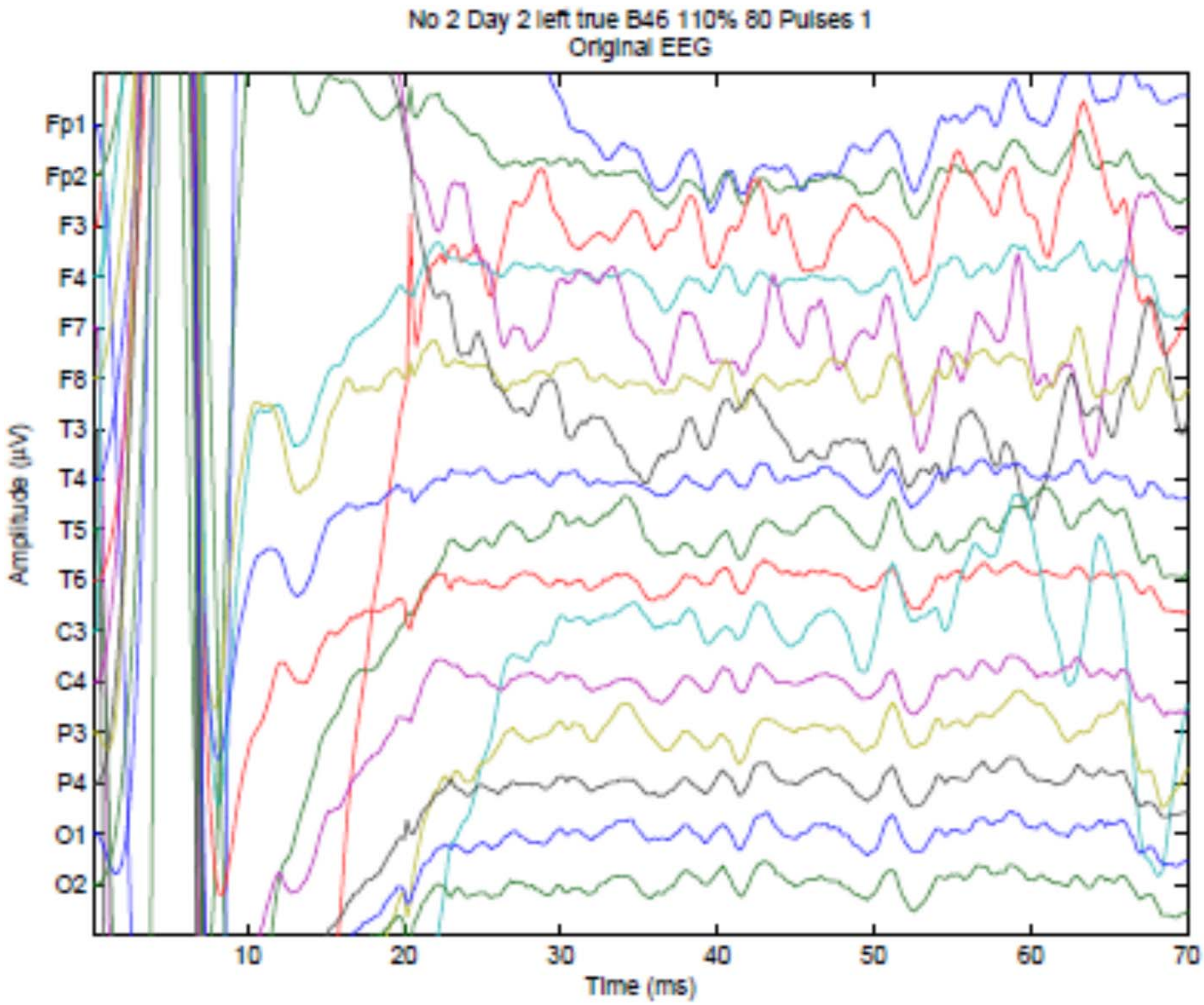
(b) Residual EEG, Soft Thresholding, Average Removed

Left 10 Hz B46

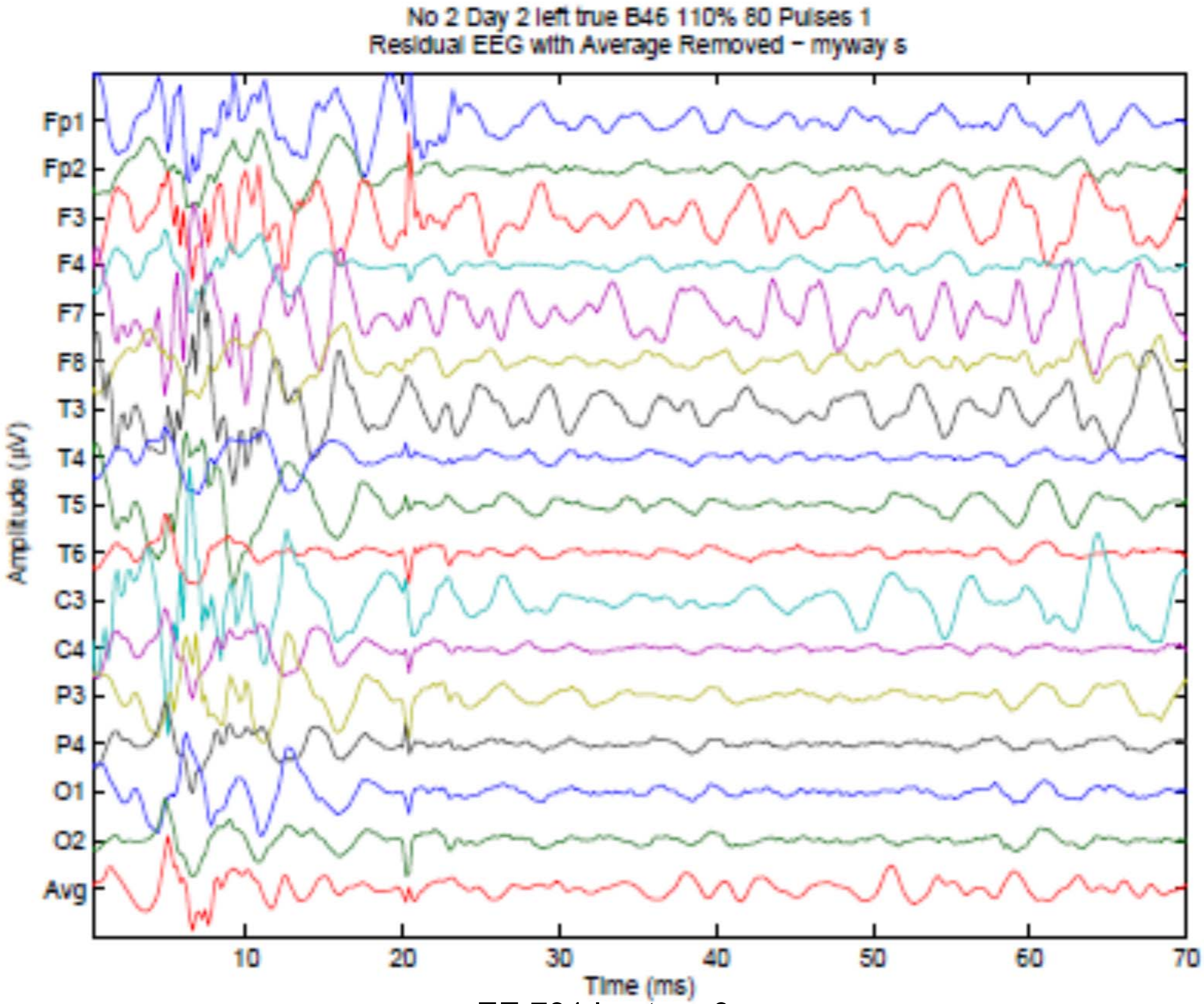


(b) Residual EEG, Soft Thresholding, Average Removed

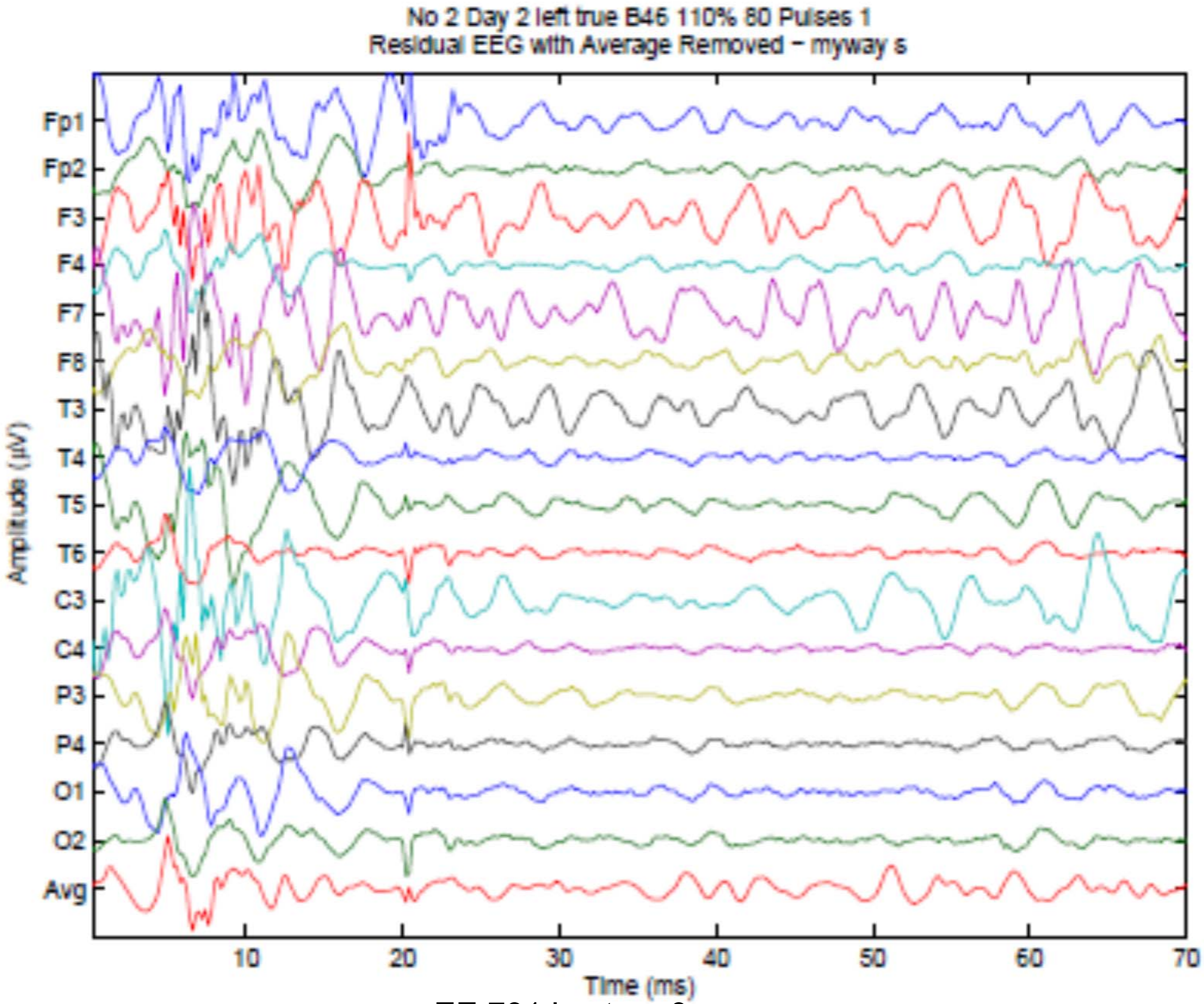
Brain Response for Sensitive Subject



Wavelet Denoised Response



Wavelet Denoised Response



Right Side Denoised Response