



**ARAŞTIRMA MODELLERİ**

---

**FONKSİYONEL NÖROLOJİK BİLİMLER  
&  
TARİH BOYUNCA GELİŞİMİ**

---

**Prof. Dr. Ali Savaş  
Ankara Üniversitesi  
Beyin ve Sinir Cerrahisi Anabilim Dalı**



# Nörolojik Fonksiyonel Araştırma

---

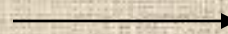
## Temel, Amaç & Metod:

- Sinir sisteminin fizyolojisini anlamak

- İlişkili bir çok disiplin var

Fizyoloji, Farmakoloji, Radyoloji, Nöroloji, Nöroşirürji ...vb.

- Basit Gözlemler



İnsanın varoluşu

Dış Dünya'nın varoluşu

- Ontolojik bakış: Felsefe, Metafizik



## FONKSİYON:

- Bir organın, bedenin tümü veya bir parçasının özel aksiyonu
- Nöronal Fonksiyonların Gözlenmesi:
  - Biyokimyasal & Nöronal membran fonksiyonları
- Organizmanın davranışı





## **Gerçek ve Veri Toplama :**

- 1) Deneysel Yöntem Temeldir  
En güvenilir veriyi sağlar**
- 2) Bazı nöronal fonksiyonlar insanda daha iyi  
gözlenebilir: – algı, dil, affekt**
- 3) Nörolojik sistem hastalıkları ve nöroşirürji girişimleri  
Fonksiyonel sistemin gözlemi için pencere açar**



**Gerçek ve Gözlemler :**

**4) Nörolojik Fonksiyonel  
Buluşlar:**

**Amprik  
veya  
Kaza ile**

**gözlemler**



# *“I am an experimental neurosurgeon”*

## **Cooper**

### **Cooper’ın Deneyimi :**

- Ansefalit-parkinsonizmde kraniotomi
- anterior choroidal arterin kopması
- Posoperatif tremorda durma  
(pallidum ?---otopsi-talamus-talamotomi)



**Hareket bozukluklarında çağdaş dönem**



## Tarihi Perspektif :

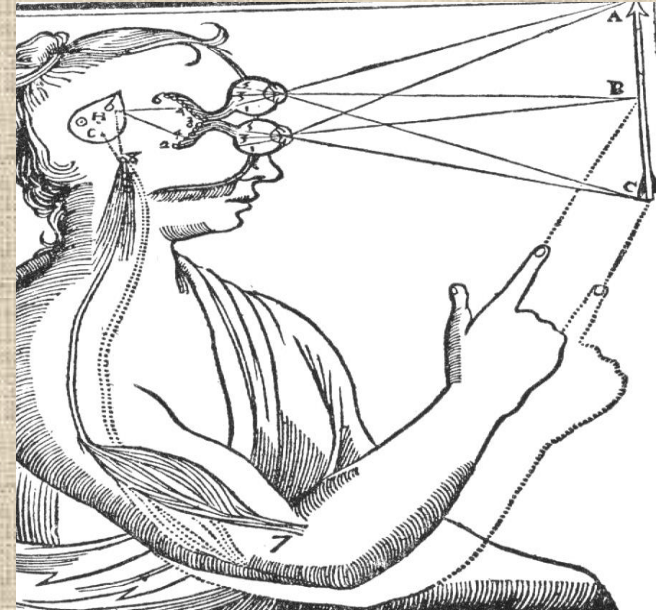
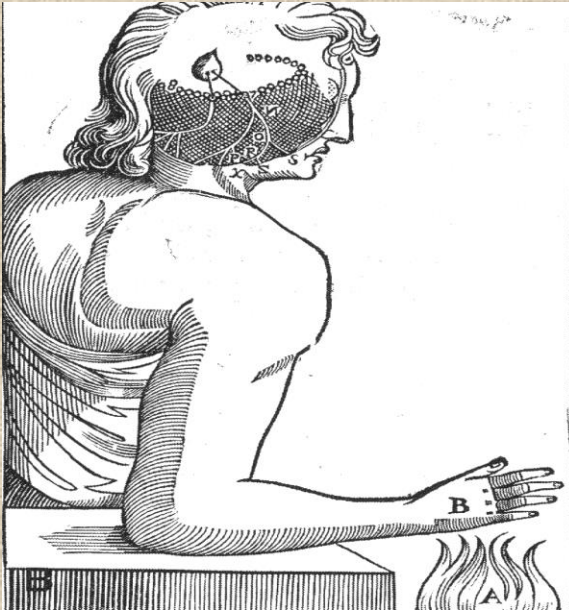
- Yarı bilimsel & günlük yaşam deneyimleri
- Rönesans- Matematik ve Fizik
- Iatrophysicists: Entellektüel uyanış

**Organik fonksiyonların  
mekanik zeminde açıklanması**

## RENE DESCARTES

### . Refleks teorileri

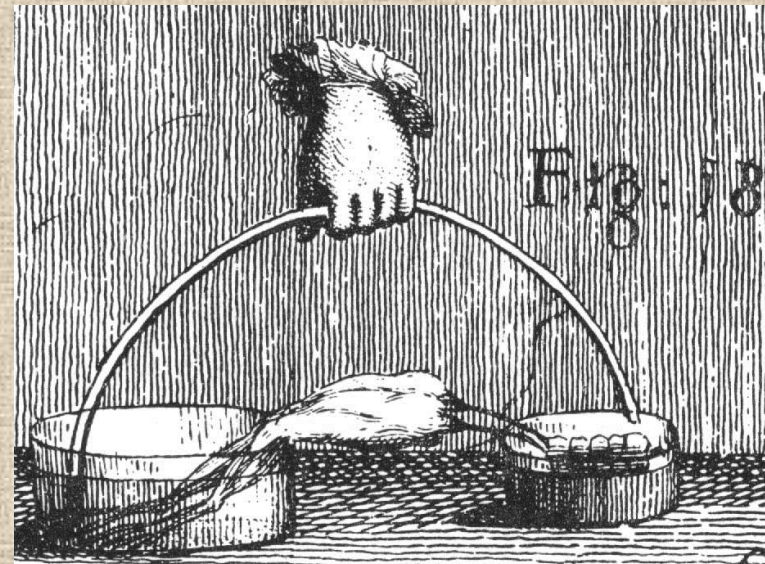
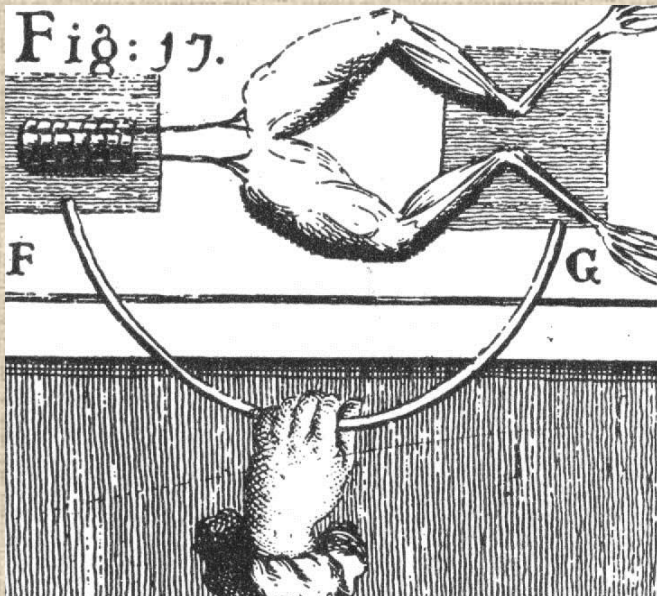
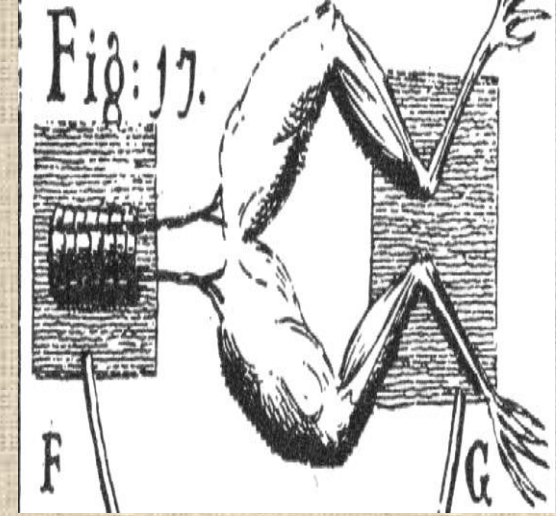
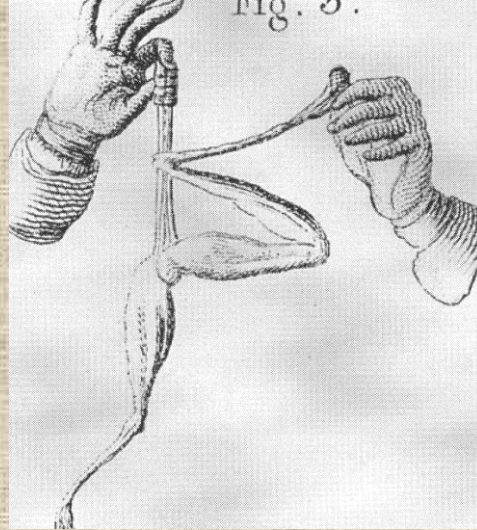
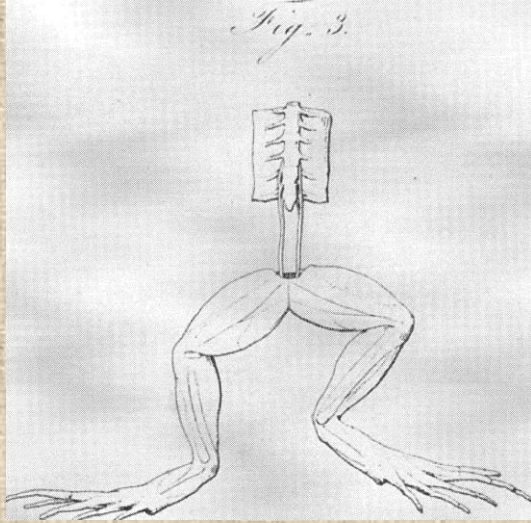
- Sinirler boyunca ileti kavramı
- Beyin uyarıların işlenmesini ve hedef organın hareketini sağlar





# LUIGI GALVANI (1737-1798)

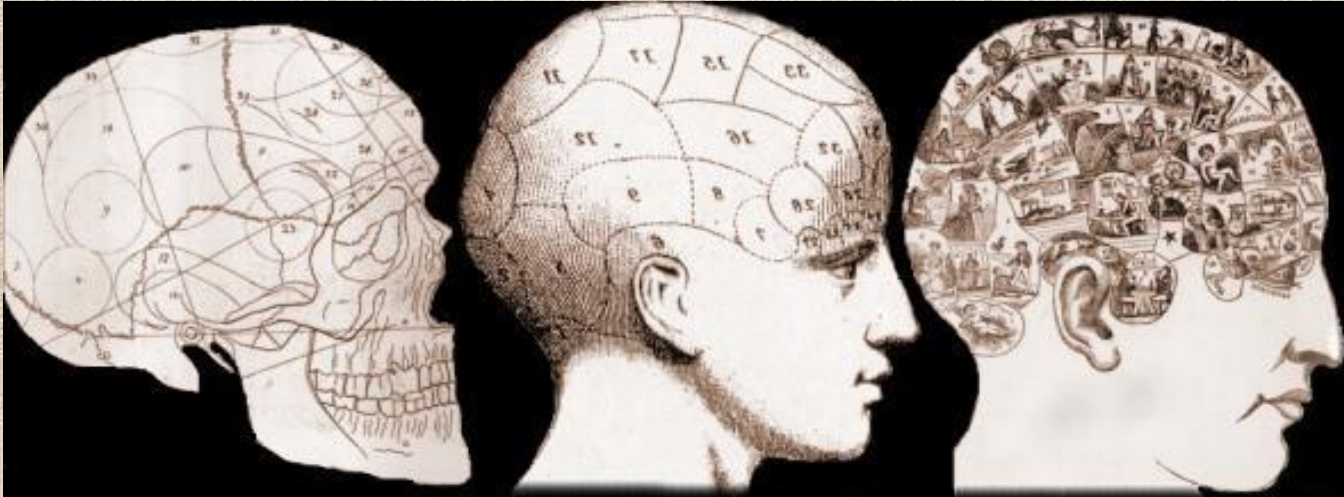
## . Hayvansal Elektrik- Kurbağa deneyleri





# FONKSİYONEL LOKALİZASYON TEKNİKLERİ TARİHÇE

- **Phrenology – Pseudo-Science**



- **Marie Jean Pierre Flourens**
  - Güvercin Deneyleri
  - Hemisferektomi
  - Kontr-lateral Görme Kaybı



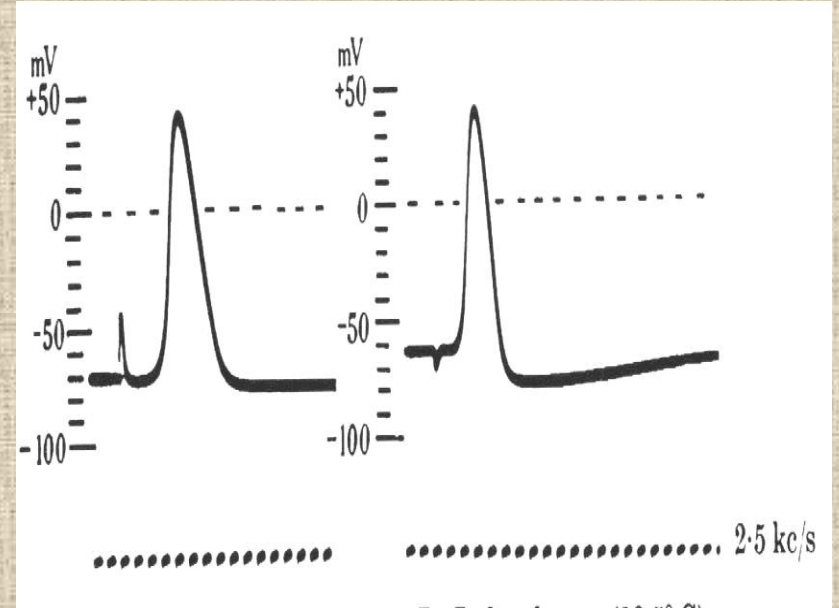
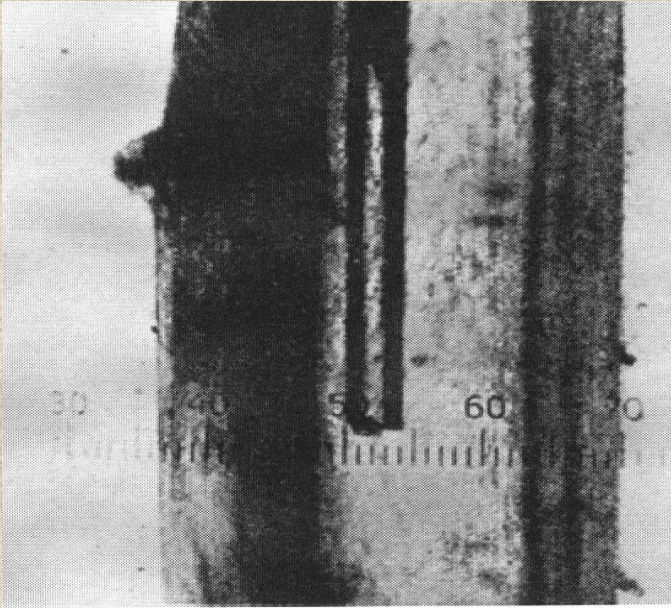
**Tarih :**

- **Johannes Müller (1801-1858)**  
-Spesifik Sinir Enerjisi yasası –Spesfik Duyum için spesfik ileti
- **L.F. Hermann (1821-1894)**  
Sinir impuls hızı:
  - 20 m/sec -frogs
  - 100 m/sec - humans
- **Francis Gotch**  
– Sinir akımı için kapiller elektrometre
- **Keith Lucas**  
- Refrakter period; hep ya da hiç fenomeni



Tarih :

- Alan Lyod Hodgkin
  - Sinir ii mikroelektrodlar (0.5 mic)
  - İmpuls iletisi sırasında iyon deęiřimi
  - Dinlenme potansiyeli: -70 mV





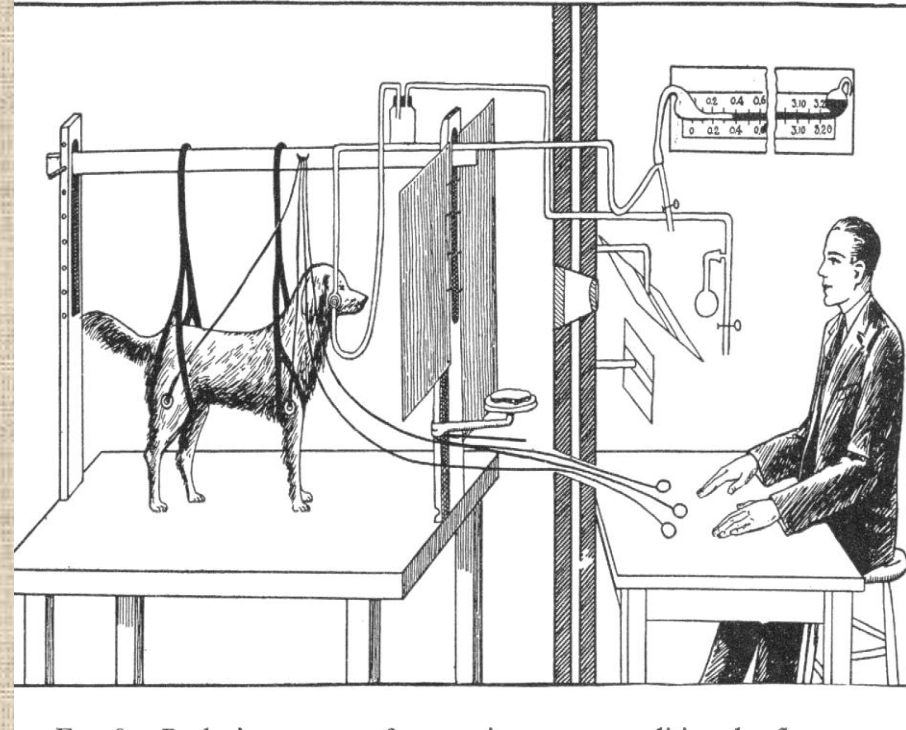
**Tarih :**

- **Ivan Pavlov (1849-1936)**

**Stimulus & Sekresyon Modeli**

**Kondisyone olmayan refleksler (ağız)**

**Kondisyone refleksler (görme)**

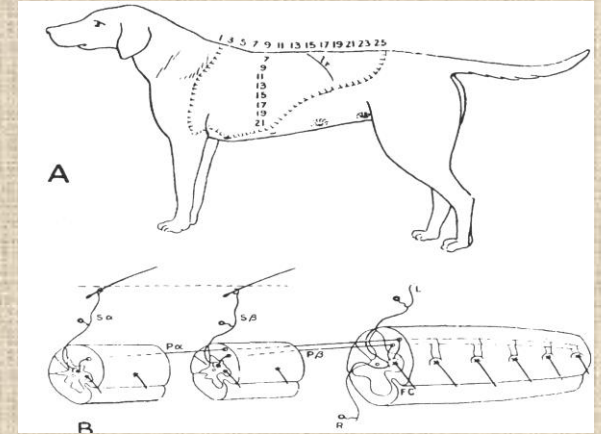


Tarih :

- **C. S. SHERINGTON**  
(1857-1952)

Deneysel Çalışmalar:

- Refleks arkında birden fazla nöron bulunur
- Sinir iletisi hem sinir içi hem de sinir dışından olur
- Refleks integre hareketin en basit yapısıdır

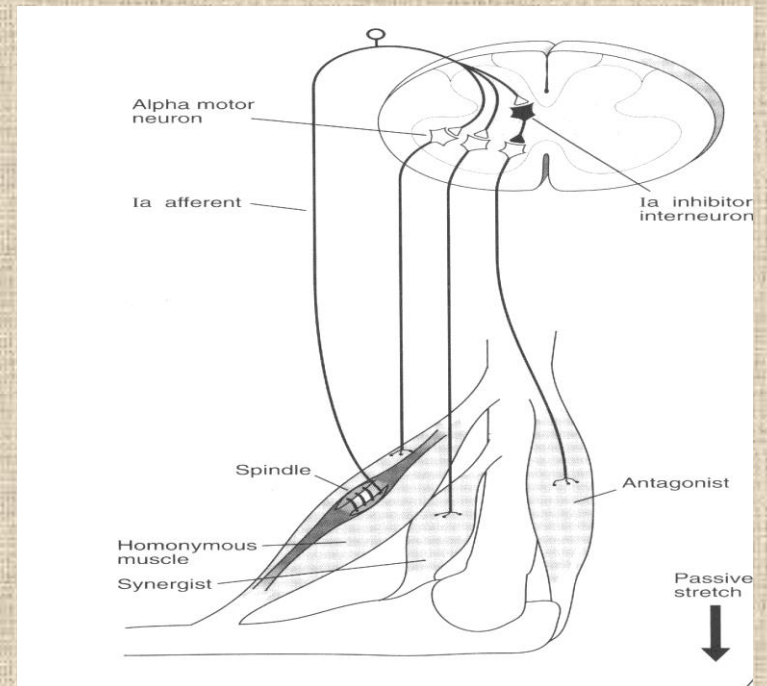




Tarih :

- **Schüller (1910)**  
Maymunda Anterolateral kordotomi
- **Martin (1911)**  
İnsanda kordotomi
- **Lars Leksell:**  
\* Neuroscience

Basınç modeli  
Intrafusul-Muscle Spindles  
Farklı innervasyon  
Gamma-motor Neuronlar

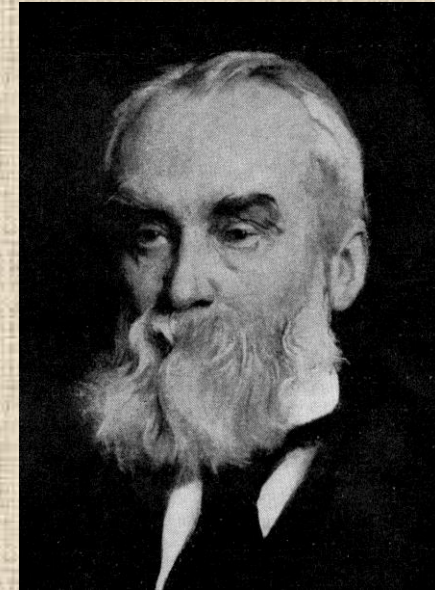
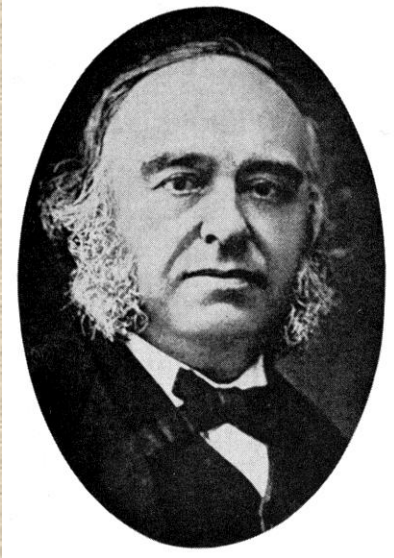




# TARİH

## KLİNİK GÖZLEMLER-APHASIA-DİL

- Pierre Paul Brocka  
– 1824-1880

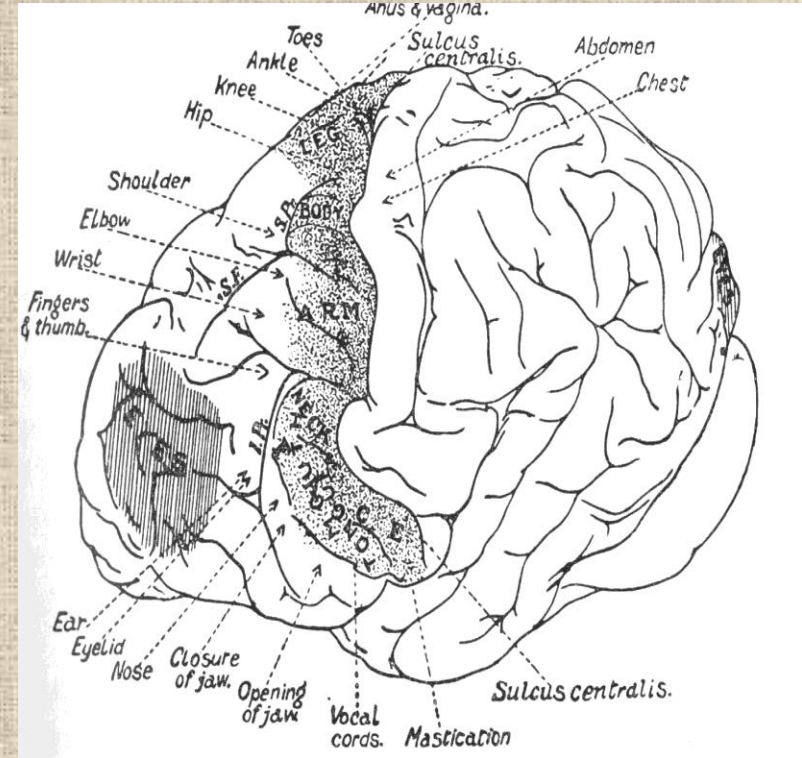


- Hunglings Jackson  
– 1835-1911





- Frisch & Hitzig  
Köpekte korteks stimulasyonu  
kontralateral hareket
- Robert Bartholow  
Human Cortex Stimulation
- Edward Sherrington  
Maymunda Kortikal Fonksiyonel Topografi





## KORTİKAL ELEKTRİKSEL AKTİVİTE

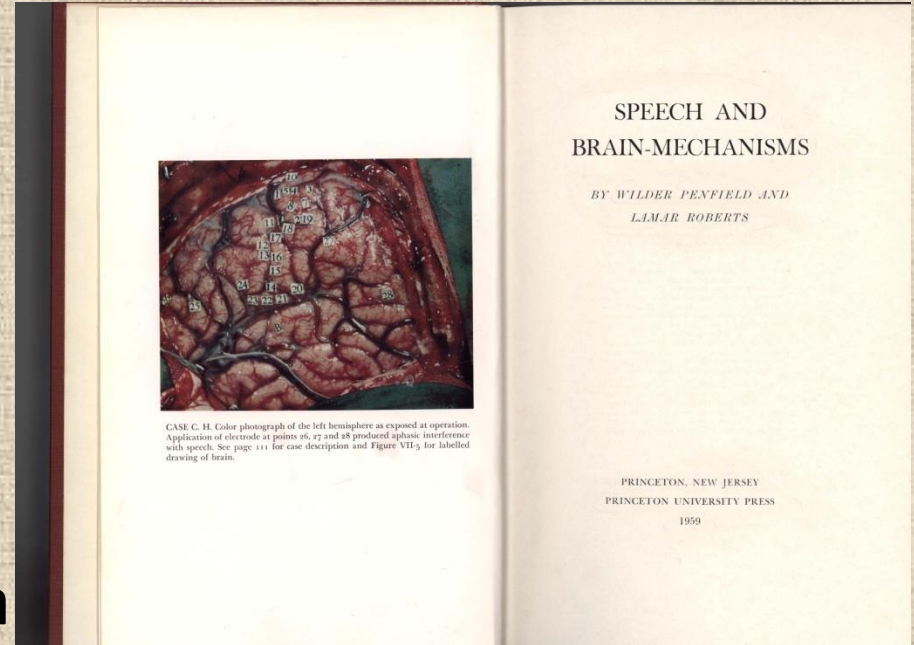
- **Caton**  
Kedi, Tavşan, Maymun  
Korteksten Aksiyonla ilişkili kayıtlar
- **Hans Berger**  
İlk İnsan Elektroencefalografisi
- **Wada- Intracarotid Amytal Test-**  
Hemispheric Dominance



# KORTİKEL FONKSİYON LOKALİZASYONU

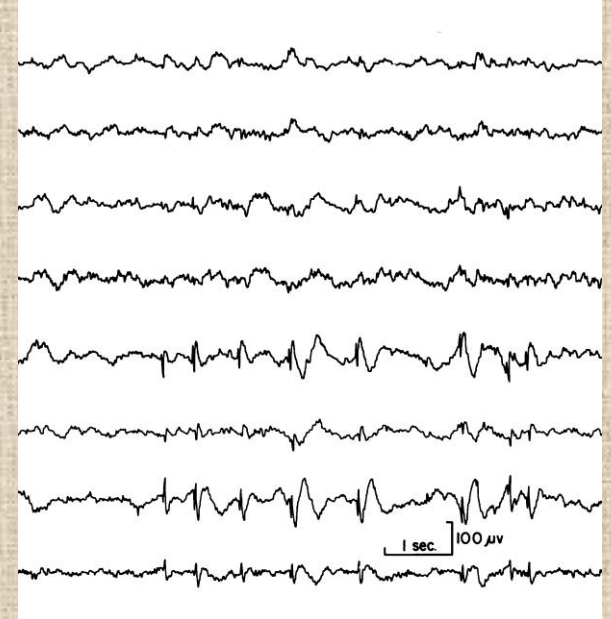
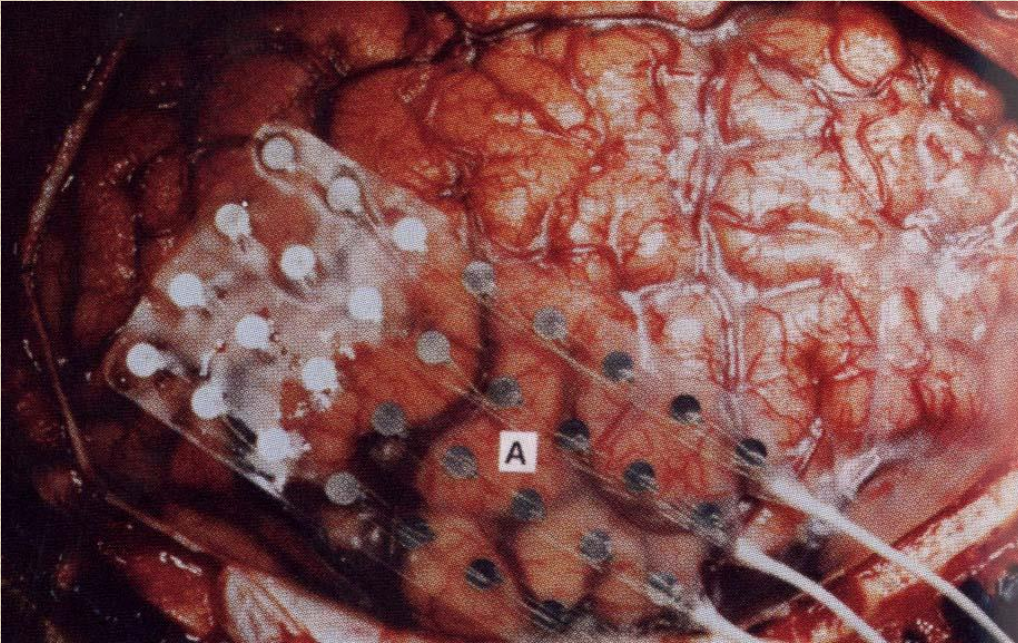
- **WILDER PENFIELD**  
MONTREAL NEUROLOGY INSTITUTE  
\* Neuroscience

- **Electrocorticography**
- **Epilepsi Cerrahisi**
- **Serebral Lokalizasyon**



# KORTİKAL FONKSİYONEL LOKALİZASYON

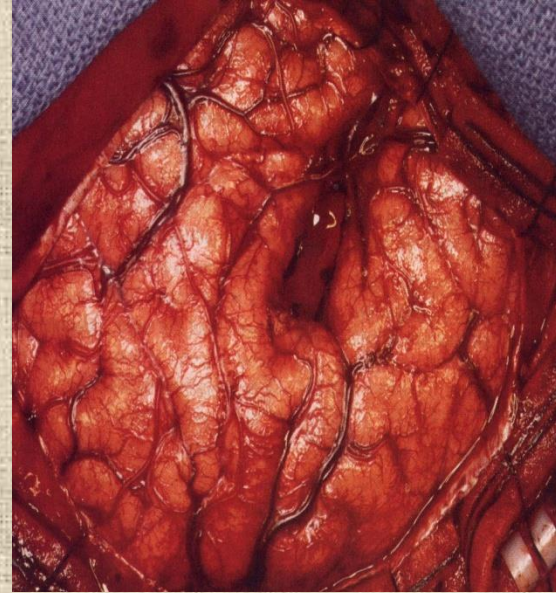
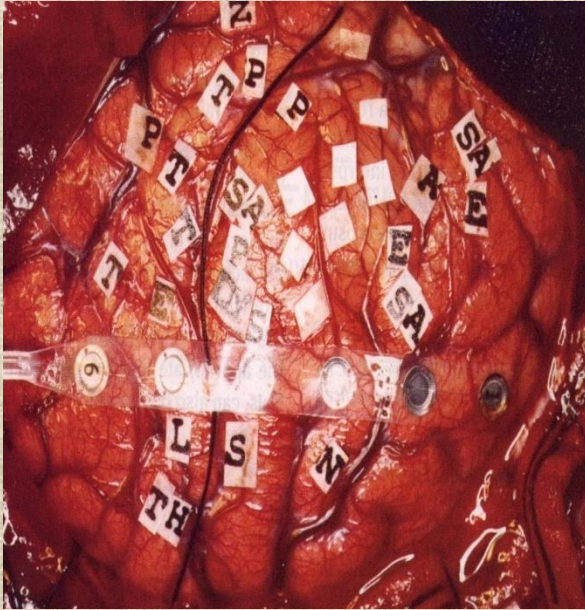
- Elektrokortikografi





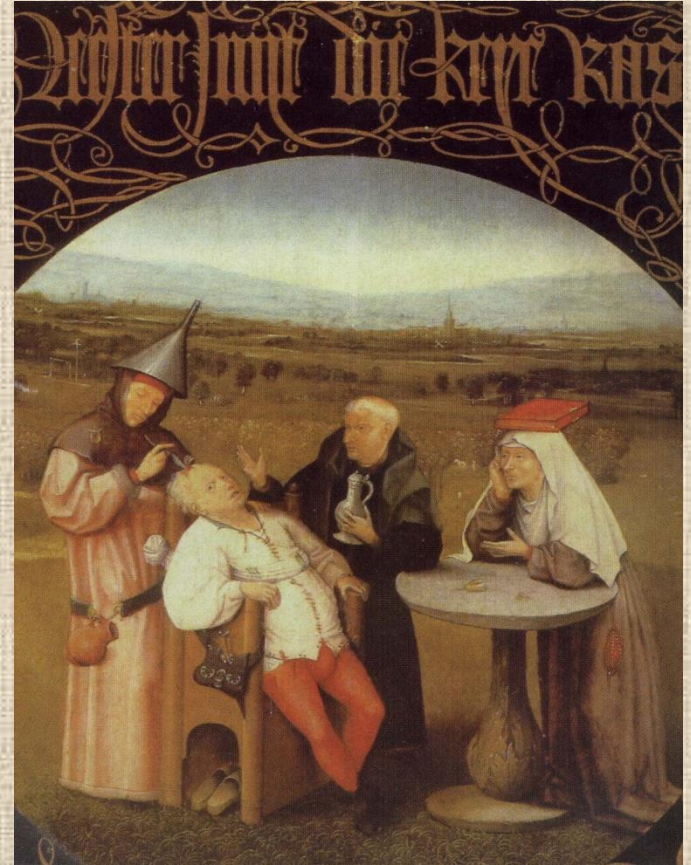
# KORTİKAL FONKSİYONEL LOKALİZASYON

- **ELEKTRİKSEL STİMULASYON-**
  - Kontraksiyon
  - Konuşma arresti
  - 0.5-15 mA, 50-60 Hz, 0.3-1 msec, 1-5 sn



# PSİKOŞİRÜRJİ

- **Fulton (1935)-**  
Şempaze  
Frontal lezyonla sakinleşme
- **Egas Moniz**  
Prefrontal Lobotomy

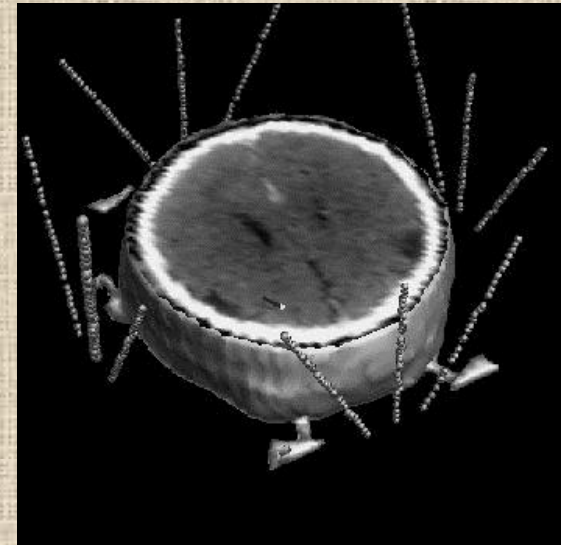
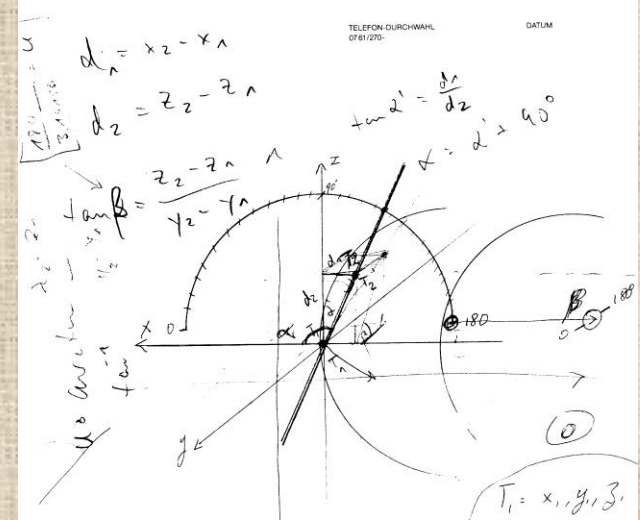




# İNSAN ÇALIŞMALARI

- **Fonksiyonel Nöroşirürji:**  
\*NÖRON CERRAHİSİ\*

- Hareket Bozuklukları
- Spastisite
- Ağrı
- Epilepsi
- Davranış Bozuklukları
- Lezyon teknikleri
- Elektriksel kayıt teknikleri
- Elektriksel stimülasyon teknikleri
- Stereotaktik teknikler
- Etc.





- **Fonksiyonel Lokalizasyon Teknikleri:**

- **I- Kortikal Haritalama:**

- **Elektrokortikografi**
- **Korteks stimulasyonu**
- **Uyanık Hastada Kraniotomi**





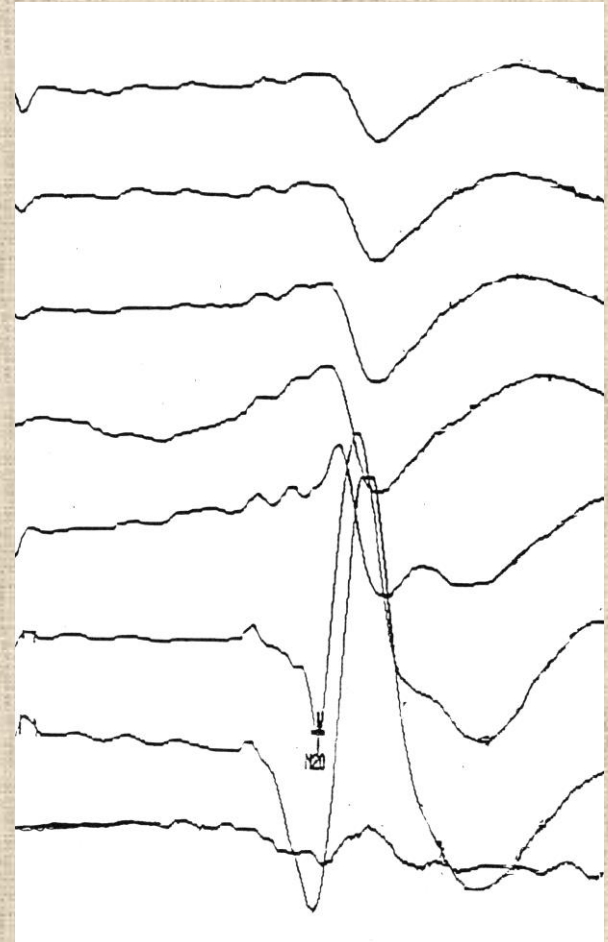
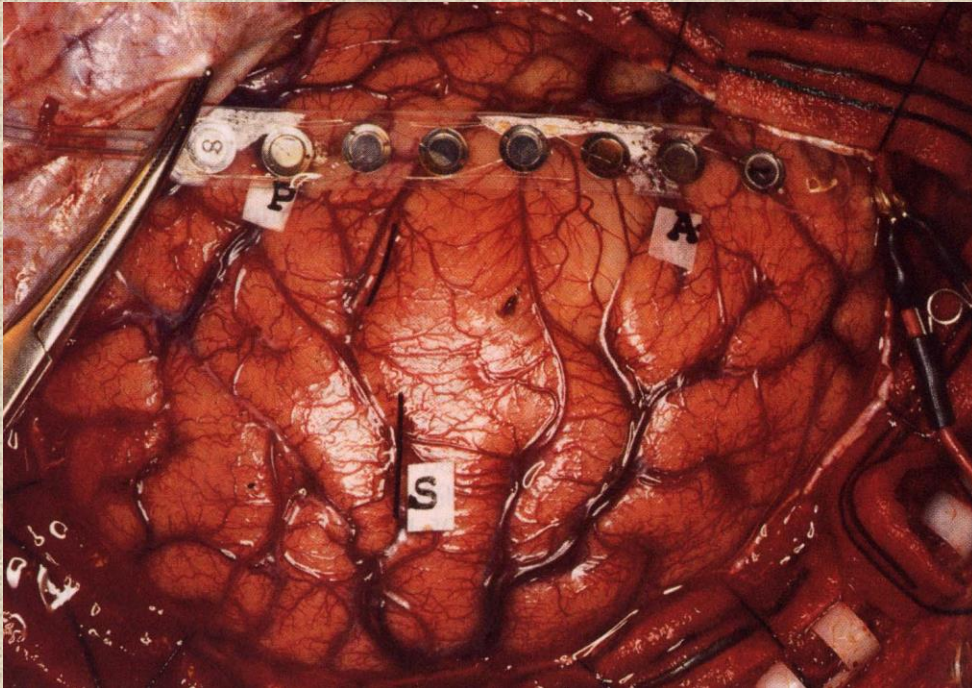
- **Fonksiyonel Teknikler:**

## **II- Evoked Potentials:**

- a) **Somatosensory evoked potentials:**  
descending somatosensory tracts  
localization of somatic sensory and motor cortex.
- b) **Thalamic-SEP**
- c) **Visual Evoked Potentials:**  
function of the visual pathway
- d) **Brain stem-Auditory Evoked Potentials:**  
function of brain stem and auditory pathways

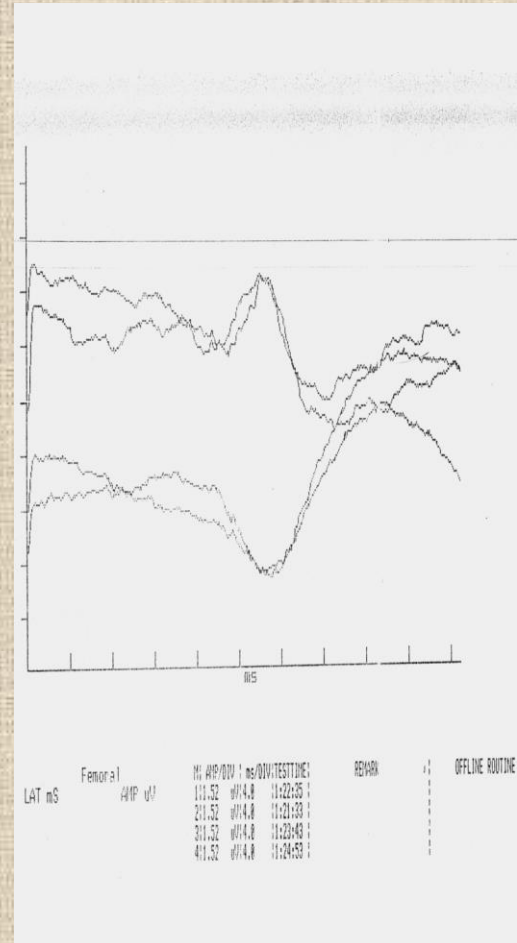
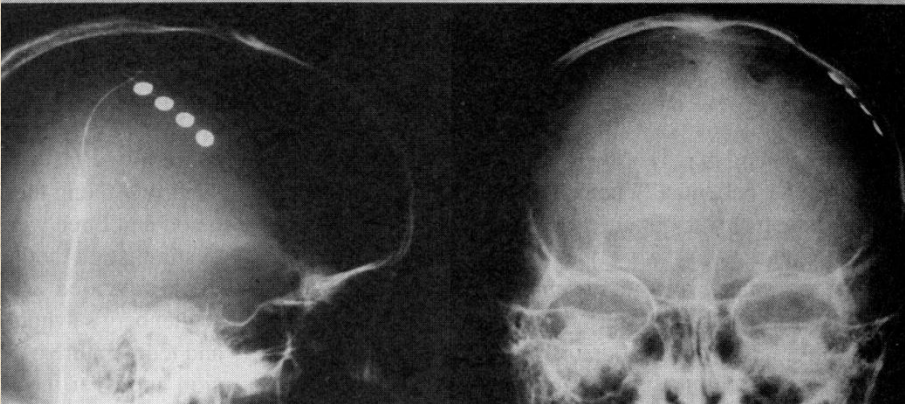
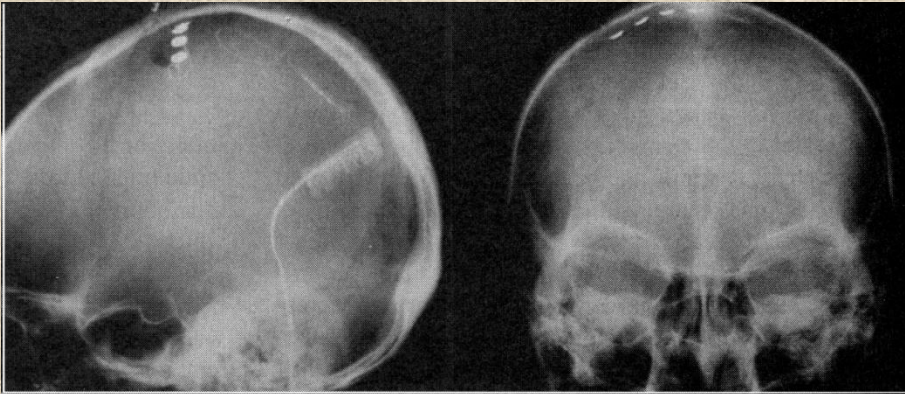


- SEP
- Median Nerve-Cortex- N20
- Invert Phase



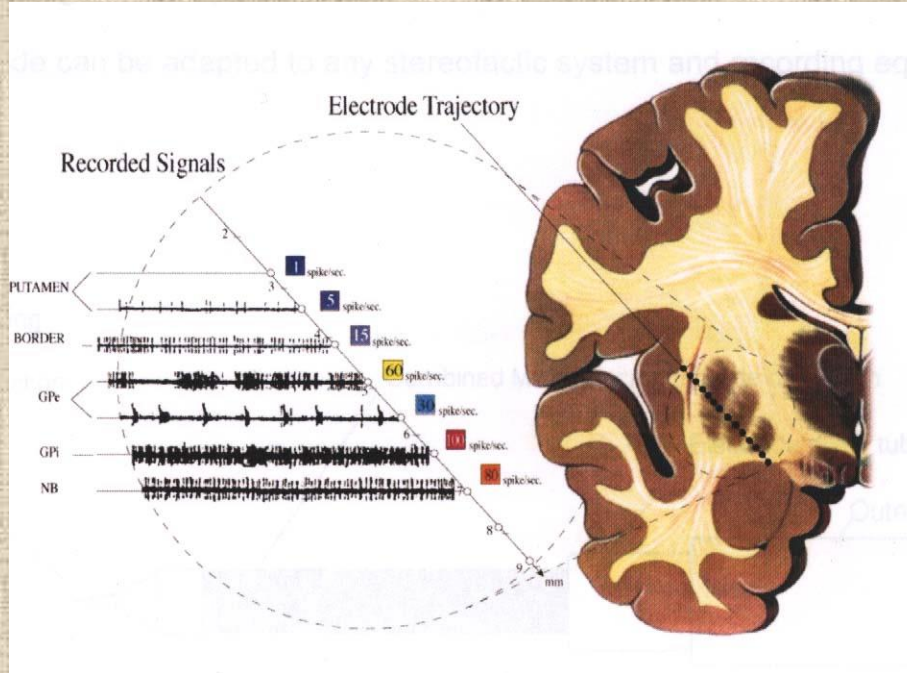


- SEP-Motor Cortex Stimulation- Analgesia



- **Fonksiyonel Teknikler:**

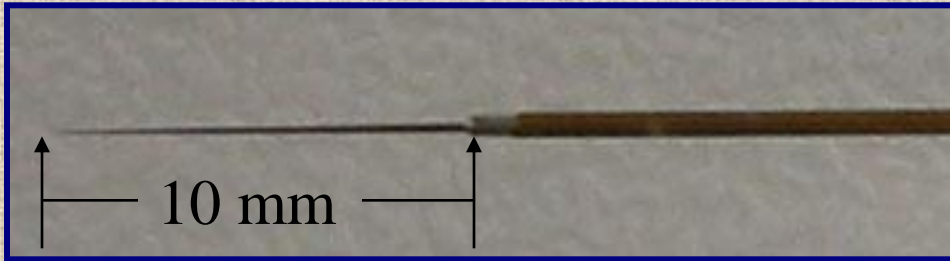
### III- Derin Beyin Haritalaması Stimulasyon Mikroelektrod Kayıt



## **† Nörofizyolojik Lokalizasyon:**

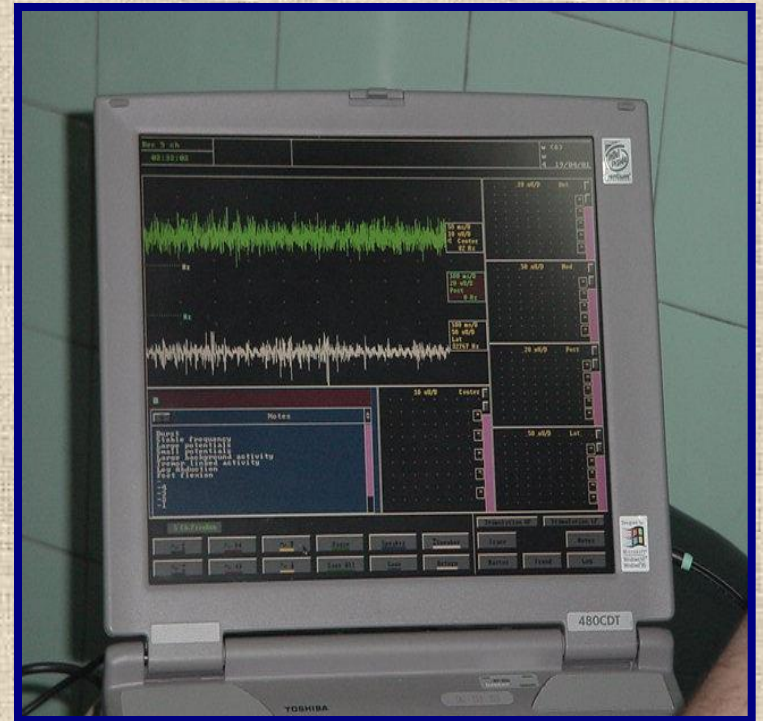
### **† Mikro-elektrod Kayıt**

Single-unit neuronal activite- uç-10  $\mu$  m



### **† Tremor-EMG**

### **† EP**



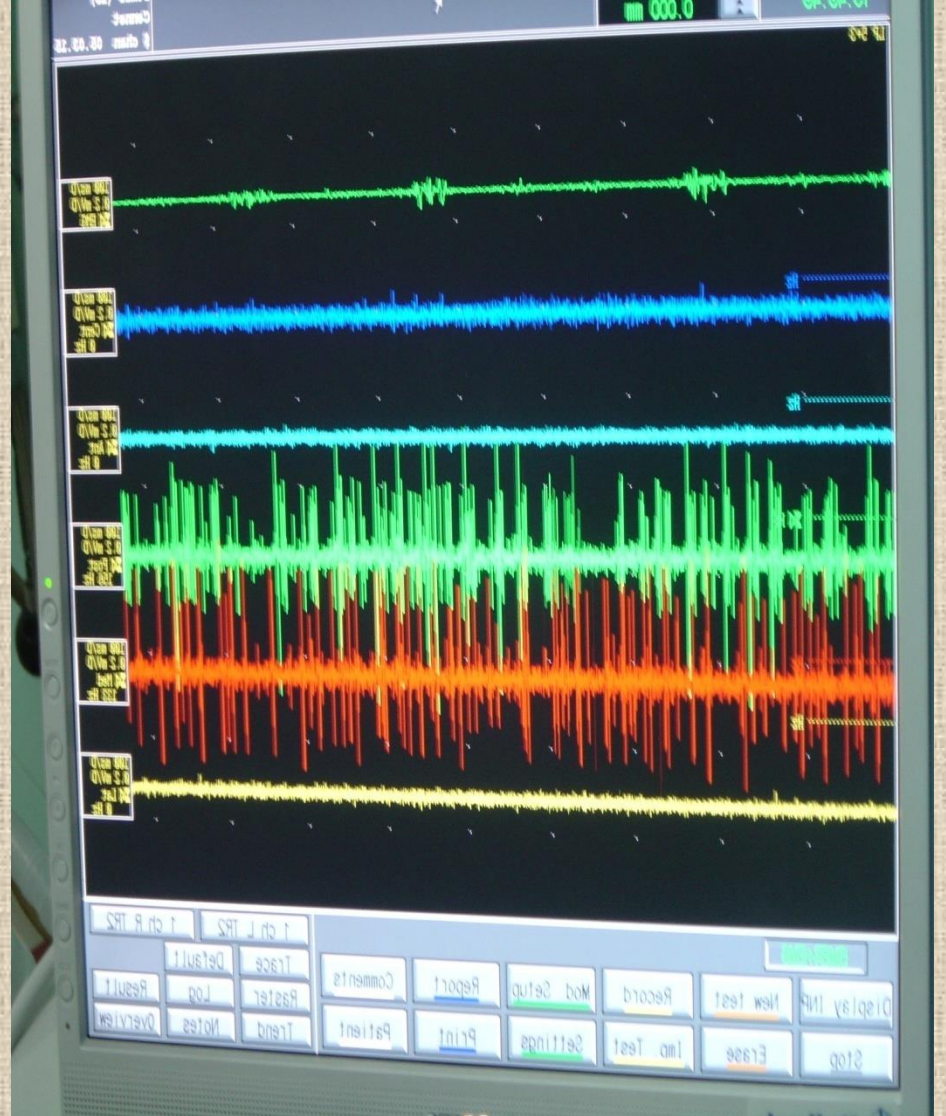
**(Medtronic, Leadpoint™ 2/4)**



## 5 Kanal (+3) Mikro-elektrod Kayıt Single-unit neuronal activite- uç-10 $\mu$ mm

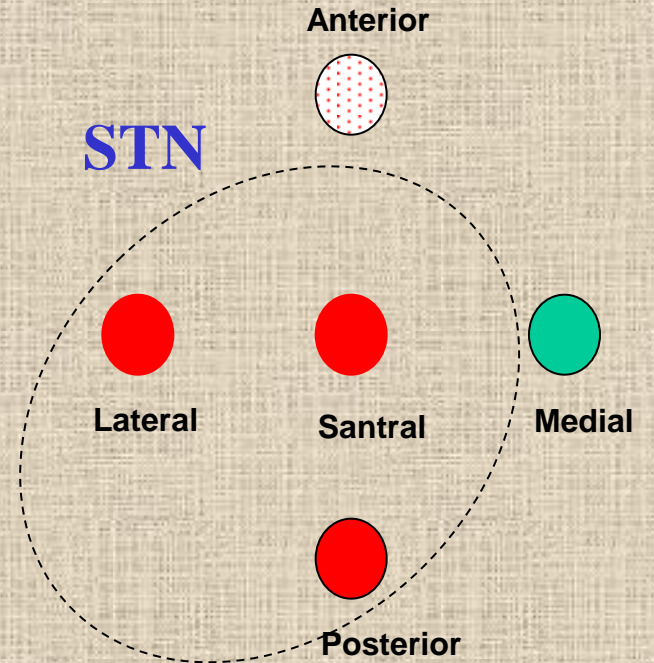
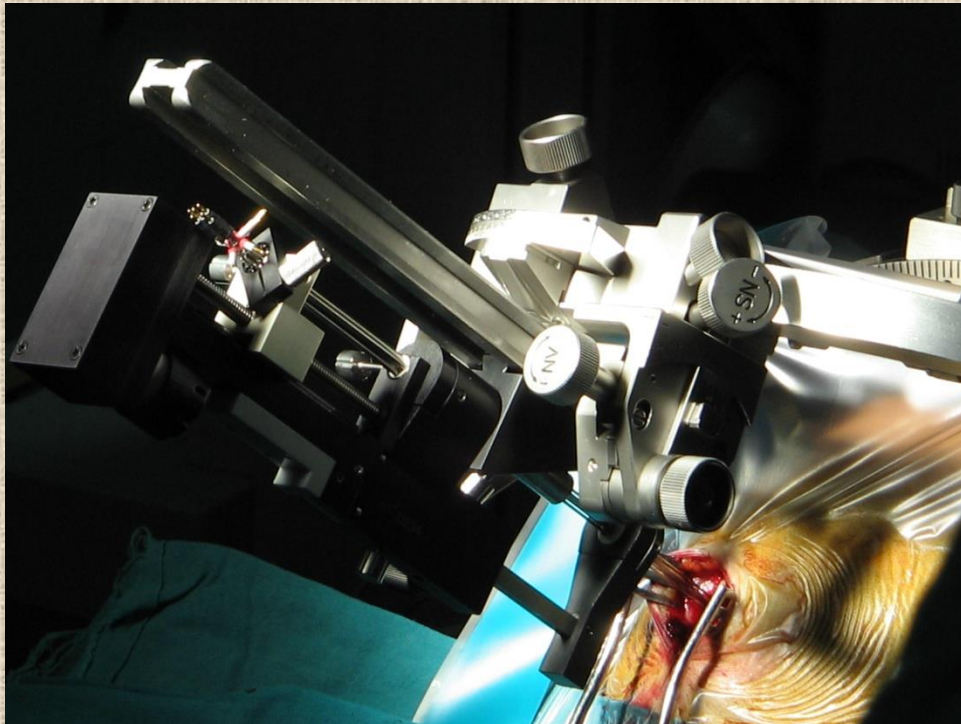


5 Kanal (+3) Mikro-elektrod Kayıt  
Medtronic-TM 5.04





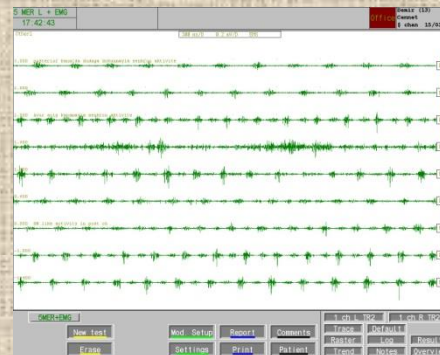
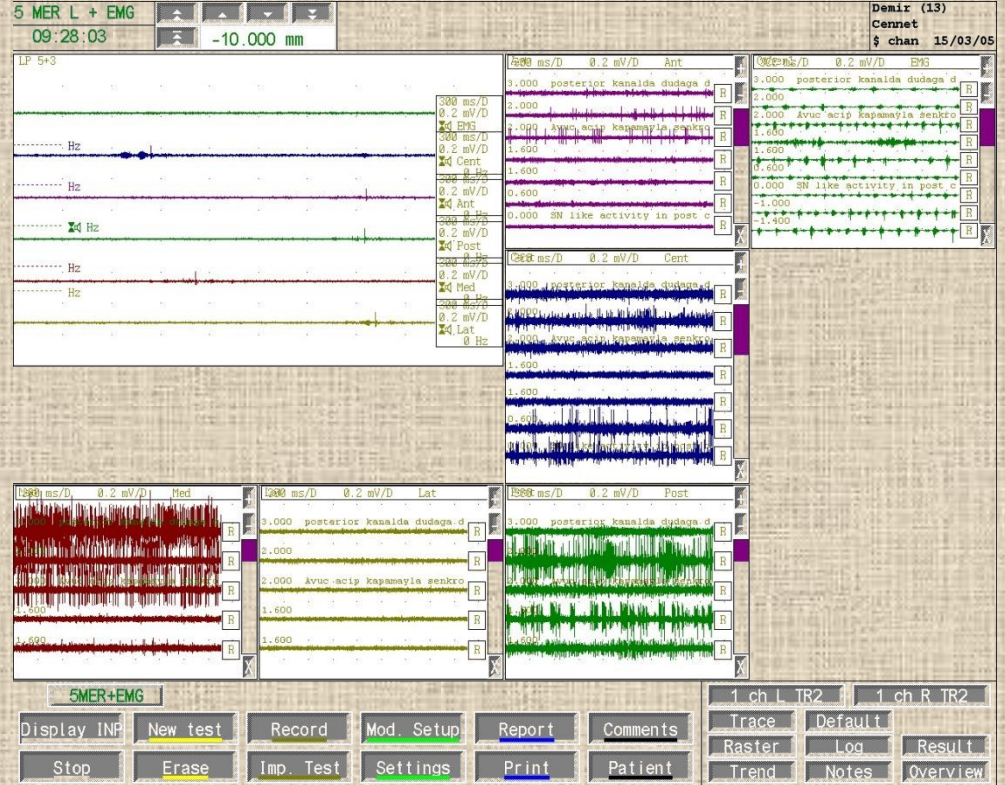
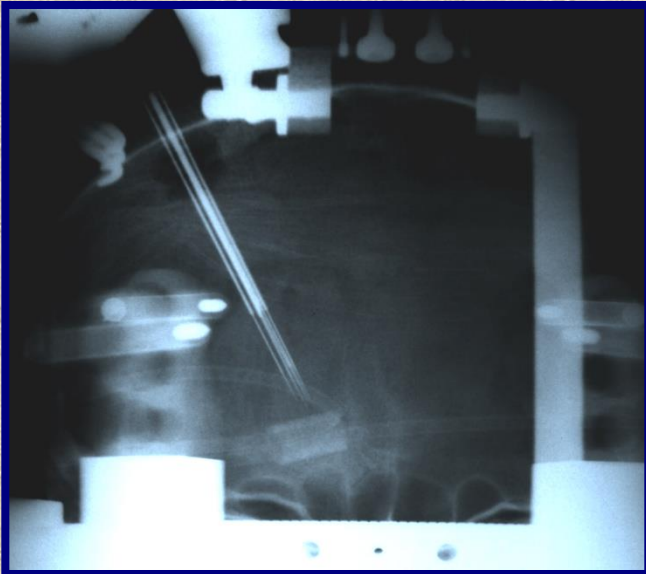
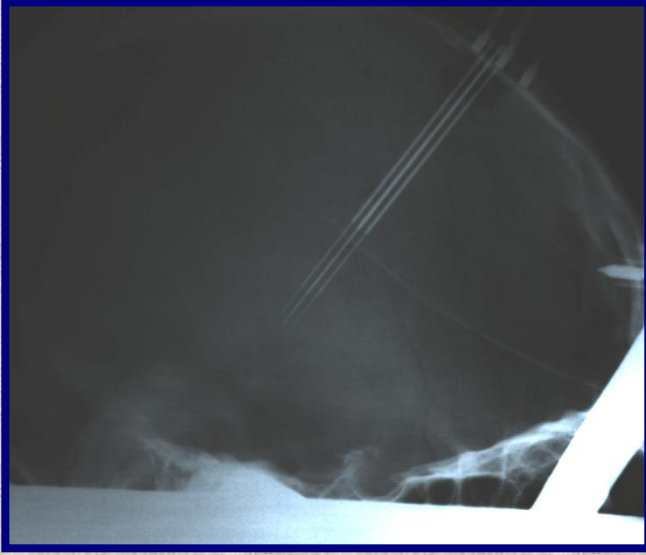
# 5 Kanal (+3) Mikro-elektrod Kayıt Single-unit neuronal activite- uç-10 $\mu$ mm



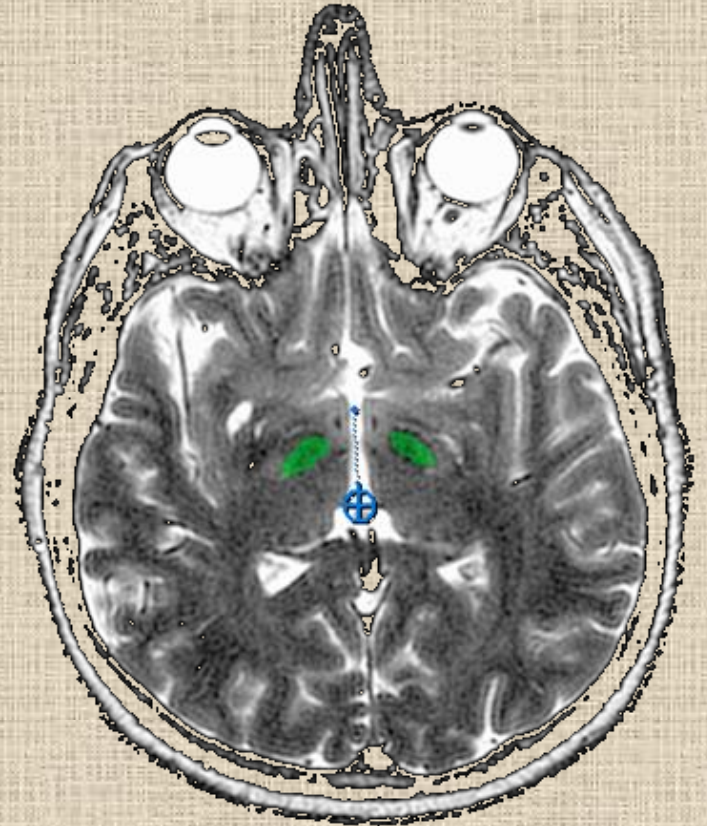
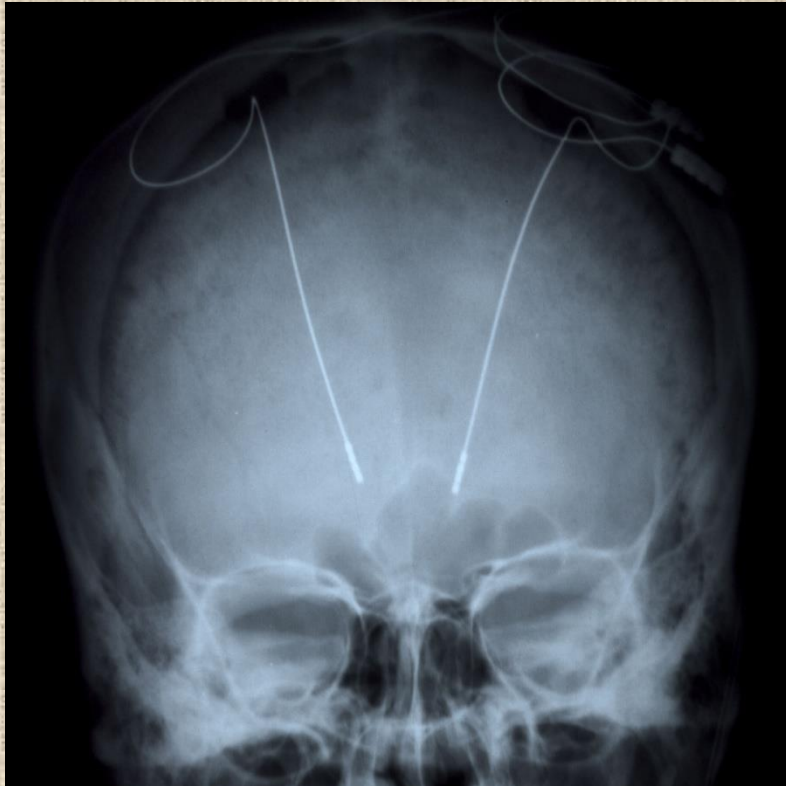


# 5 Kanal (+3) Mikro-elektrod Kayıt

## Single-unit neuronal activite- uç-10 $\mu$ mm





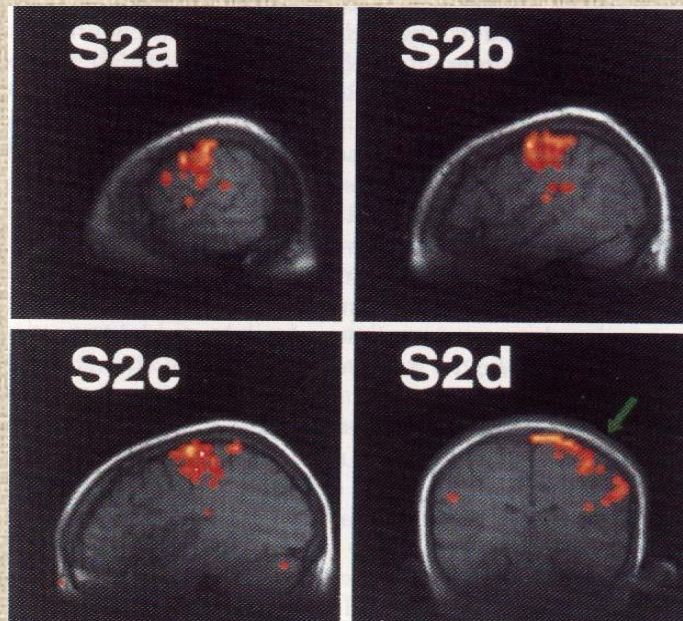




- **Fonksiyonel Teknikler:**

**IV- Fonksiyonel MRI:**

**capillary blood deoxyhemoglobin – blood flow**

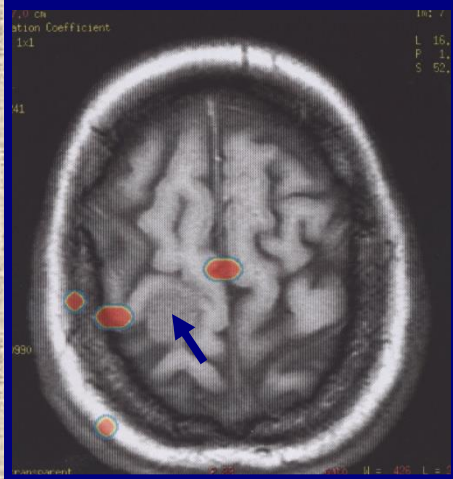




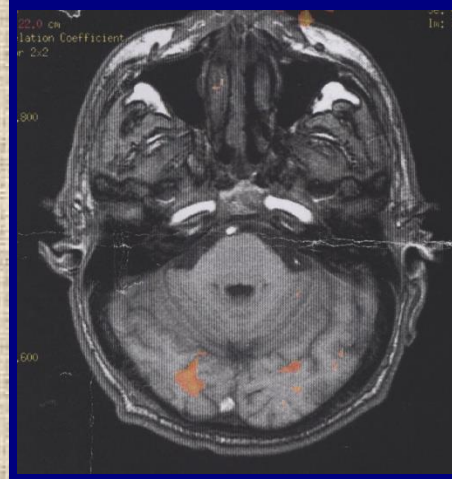
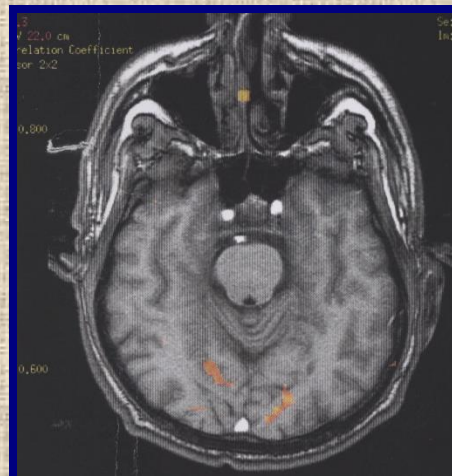
# MATERIAL & METHOD

## Preoperatif F-MRI ----- BOLD Technique

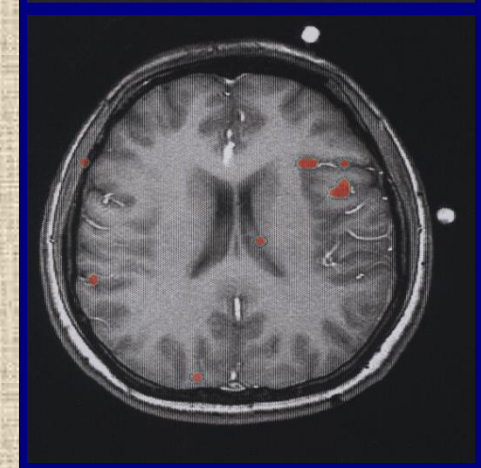
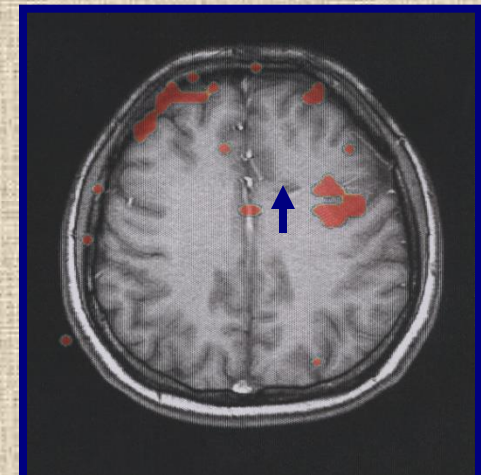
### Motor



### Vision

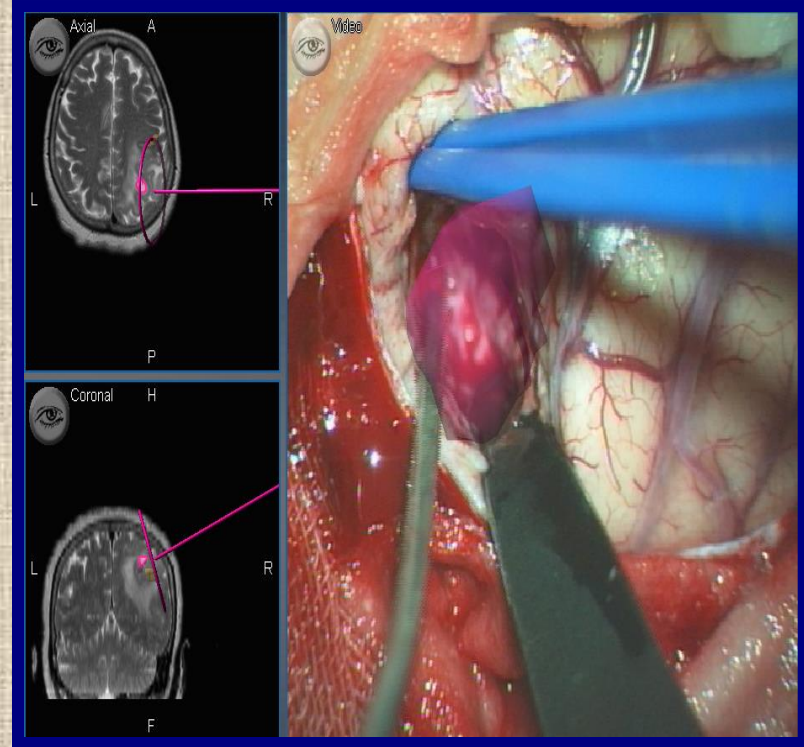
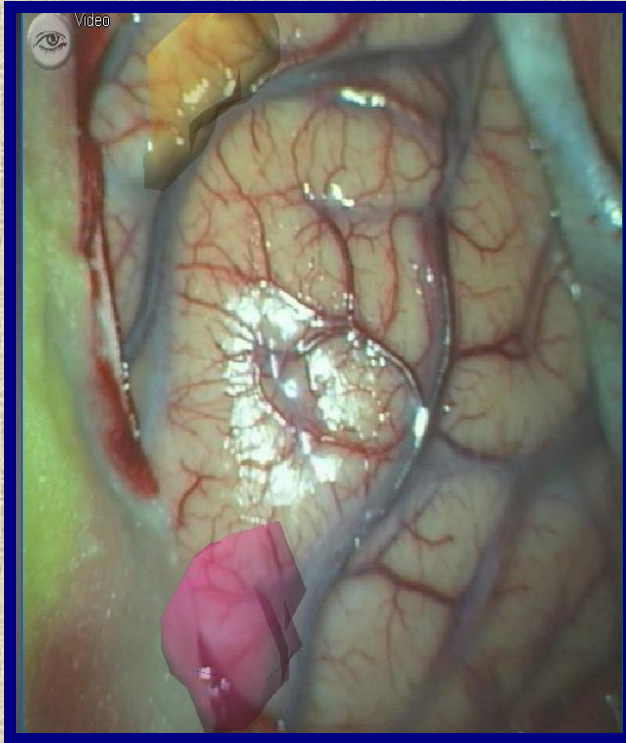


### Language



# FONKSİYONEL NÖRONAVİGASYON

- + Tumor ve fonksiyonel alanların lokalizasyonu
- + Tumorün çıkartılması
- + Motor alan

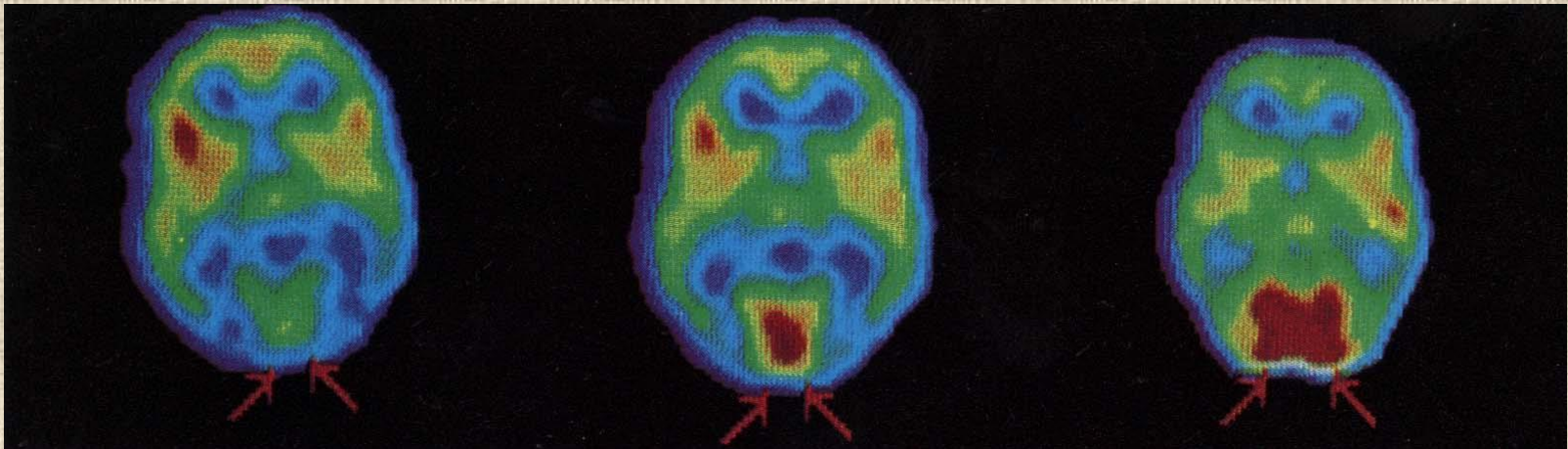




- **Fonksiyonel Teknikler:**

- IV- Pozitron Emission Tomography:**

- (18F)fluorodeoxyglucose consumption - metabolism, blood flow**



- V- Magnetoencephalography**



# DENEYSEL ARAŞTIRMA:

## Hayvan Kullanımı:

- Periferik sinirler, refleksler ve Spinal Kord:  
Amphibia, alt vertebralılar
- Fonksiyonel Beyin Araştırmaları:  
Memeliler  
Sıçanlar & Tavşanlar  
Kedi ve Köpekler,  
Antropoid Maymunlar





## **DENEYSEL ARAŐTIRMA:**

### **Temel Teknikler:**

#### **I- Destruktif Teknikler:**

- a) Mekanik veya Cerrahi Destruksiyon**
- b) Termal lezyon: radyofrekans veya koterizasyon**
- c) Radyasyon**
- d) Kimyasal Ajanlar: fenol, alkol, kainik asit**
- e) Kriyojenik lezyonlar**





## **DENEYSEL ARAŐTIRMA:**

**II- Elektriksel stimulasyon teknikleri**

**III- Elektro-fizyolojik kayıt teknikleri**

**IV- Nörofarmakolojik teknikler**

**V- Transplantasyon**







## **DENEYSEL ARAŐTIRMA:**

**VI- Hareketin Gzlenmesi:  
yrme paterni, ađrı reaksiyonu vb.**

**VII- Organizmanın genel davranıŐının  
gzlenmesi: uzaysal hafıza, đrenme**

**VIII- zel teknikler:  
hayvanlar iin stereotaktik baŐlıklar**





## PERİFERİK SİNİR DENEYLERİ

- Electromyography
- Electroneurography
- Motor Nerve Conduction
- Sensory Nerve Conduction
- Refleksler: H-reflex
- Cevaplar: F-response
- Somatosensory Evoked Potentials
- Fentanyl





# PERİFERİK SİNİR DENEYLERİ

- Sıçanlar
- Tibial sinirin kesilmesi ve Mikrocerrahi onarımı-
- Otograft
- Fonksiyonel Düzeltme Parametreleri



-Hepgöl K, Savaş A, Sporel; Özakat E, Edwards P, Hoop Gispens W: The Effects of Org 2766 On The Recovery From Nerve Graft. Turk Med Biol Res Vol. 4 Number 1: 35-42, 1993

-- Sporel-Ozakat RE: Peripheral nerve damage and repair: A Pharmacological Therapeutical Approach. Doctoral Thesis. Rijksuniversiteit Utrecht (Utrecht, Holland), 1990

-- Sporel-Özkat R E, Edwards P M, Hepgöl K T, Savas A, Gispens WH: A simple method for reducing autotomy in rats after peripheral nerve lesions. Journal of Neuroscience Methods, 36: 263-265, 1991



# PERİFERİK SİNİR DENEYLERİ

## Fonksiyonel Düzeltme:

- **Foot-sole sensitivity:**

Electrical current  
– 0.2-0.5 mApm  
Foot withdraw

- **Walking Pattern**

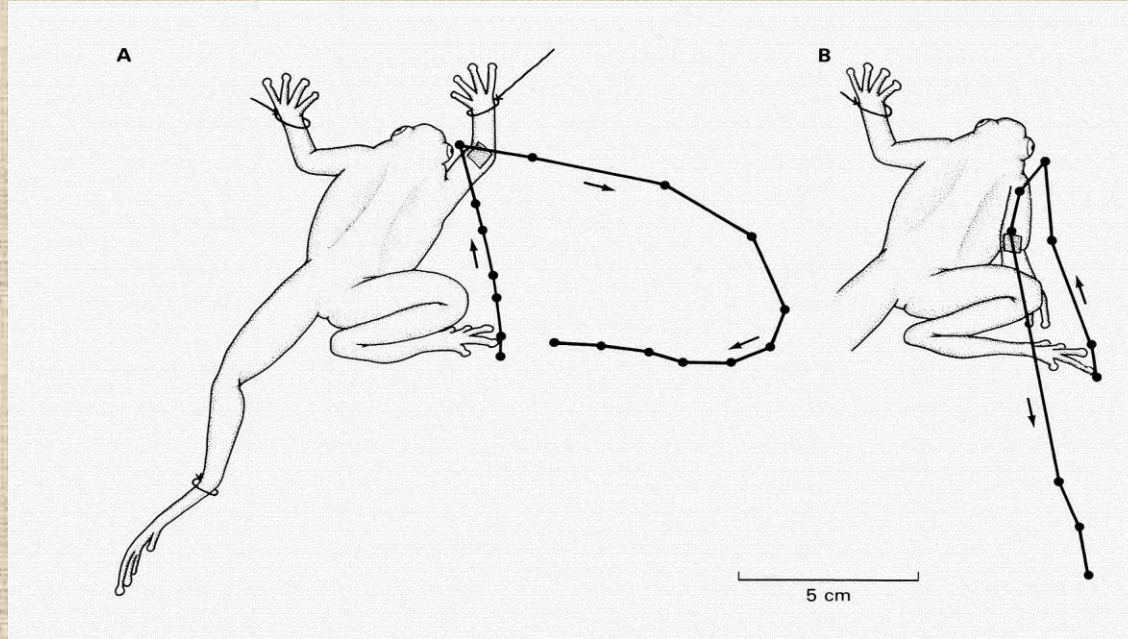
plantar surface-  
indigo traces  
length  
print angle



- **Motor and Sensory nerve conduction velocity**

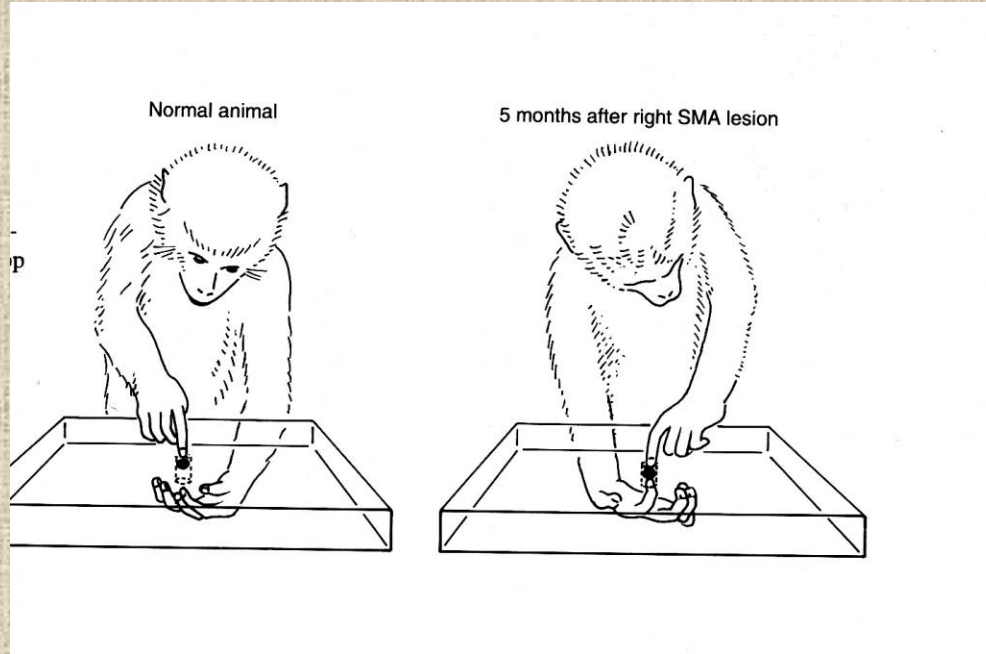
## SPİNAL REFLEKS DENEYLERİ

- Kurbağa-spinal transseksiyon
- Video çekim-hareketin değişimi



# KORTİKAL DESTRUKSİYON DENEYLERİ

- Maymun-Destek motor alan tahribi
- Bimanuel koordinasyon

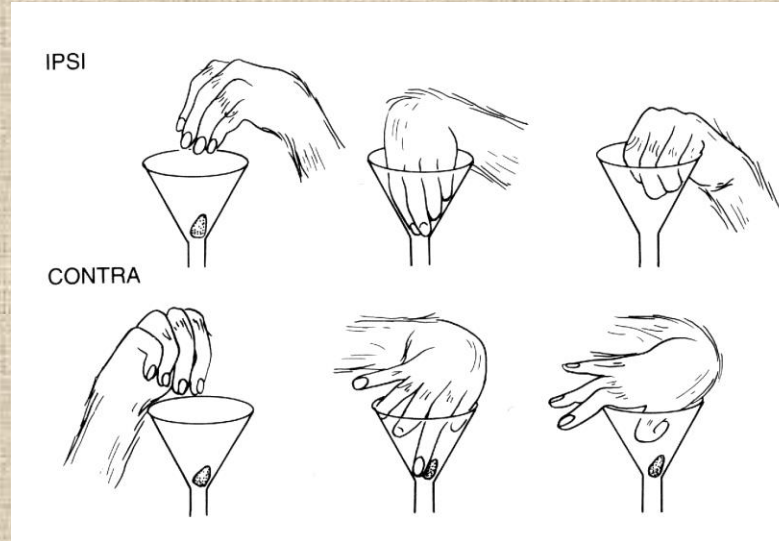


- Brinkman C: J Neurosci 4: 918-929, 1984

# MUSCIMOL (GABA AN.)

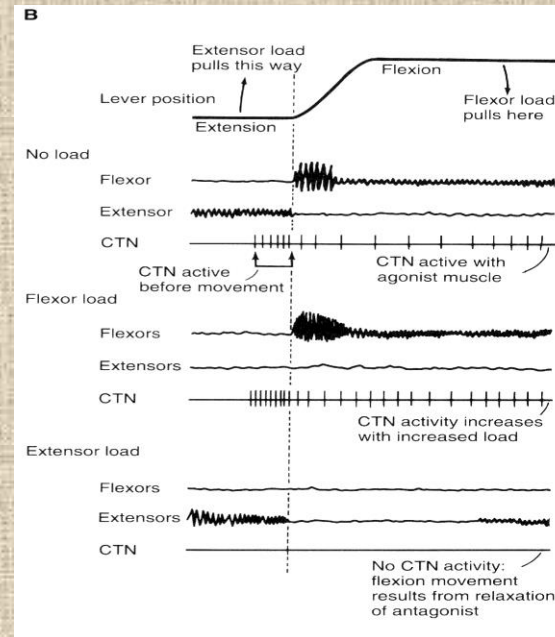
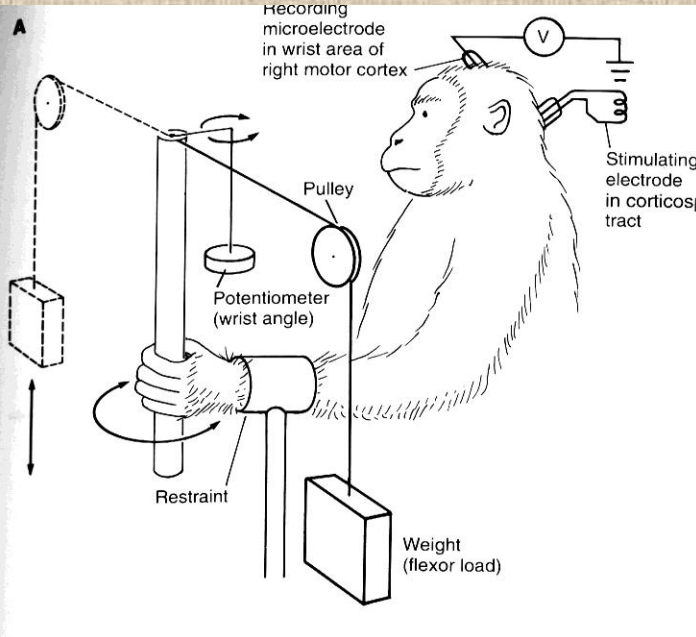
## Maymun-İntrakortikal injeksiyon

- Somatosensory korteks
- Parmak koordinasyonu
- Koniden cismin alınması



# KORTİKAL KAYIT DENEYLERİ

- Maymun-Kortikal Mikro-elektrod kayıt
- Aktivite kodunda değişiklik – yer değiştirme değil

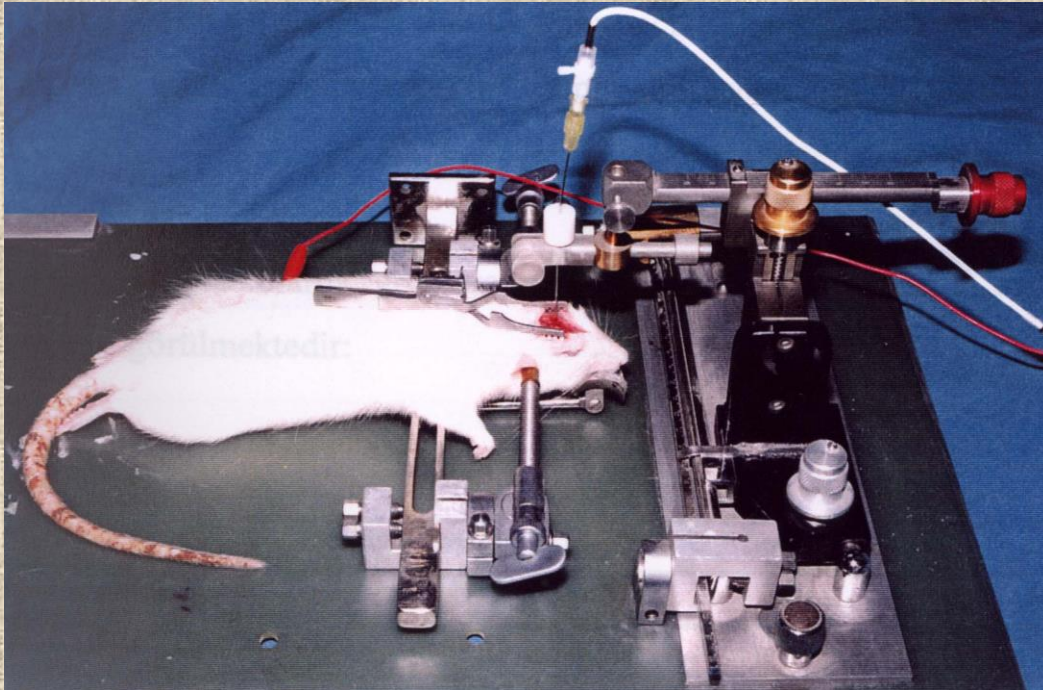






## HAYVANLAR İÇİN STEREOTAKTİK BAŞLIKLAR:

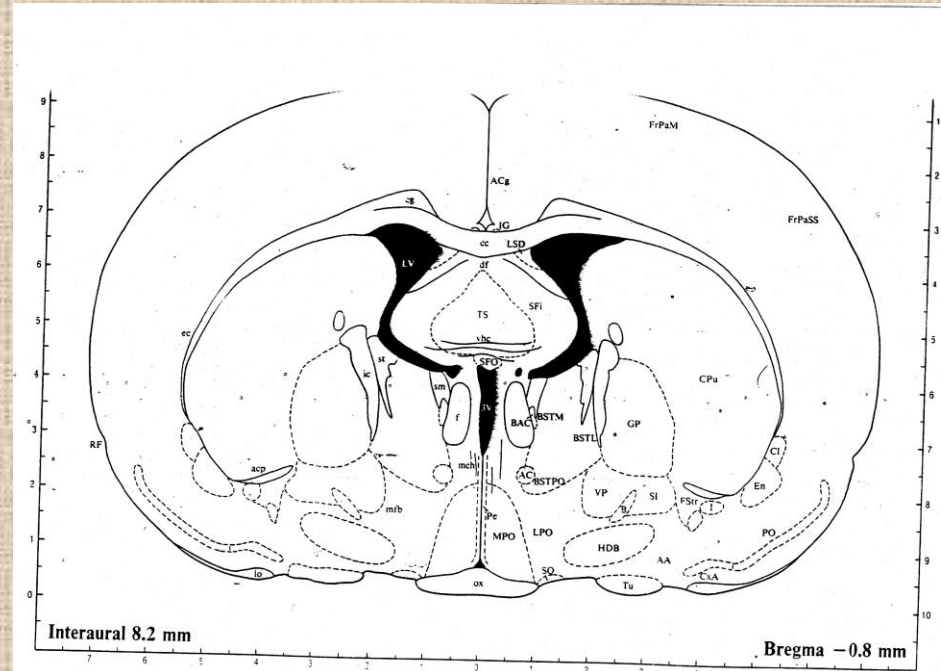
- Selektif lezyonlar: RF, Kainic acid
- İlaç enjeksiyonları Hamilton Needle
- Transplantation vb.



# STEREOTAKTİK ATLASLAR İnsan & Hayvan Referans Noktaları

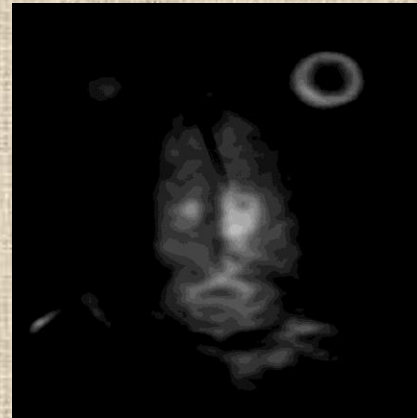
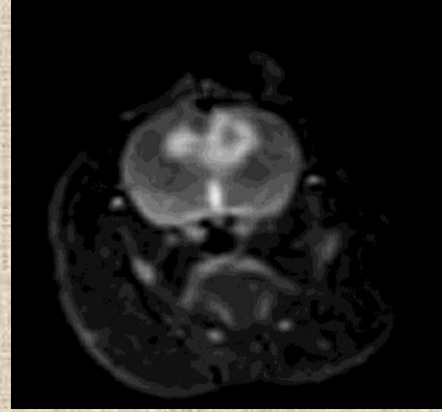
## Komissürler

## Bregma





# STEREOTAKTİK BEYİN LEZYONLARI SIÇAN





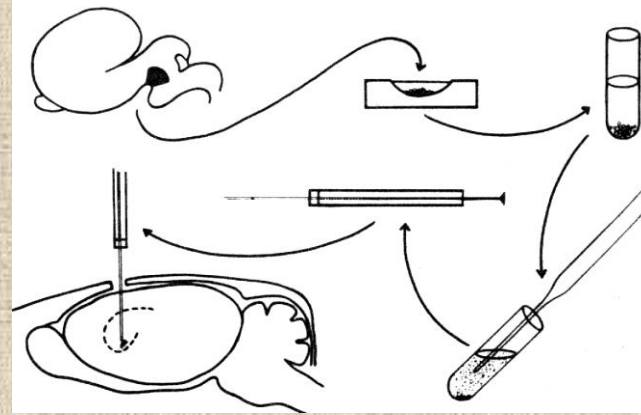
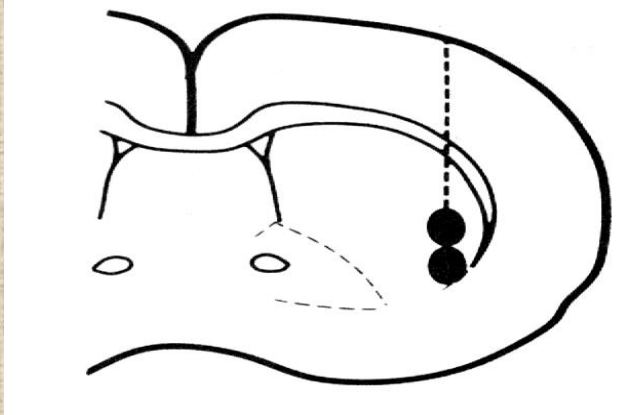
# DEMANS MODELLERİ

## STX Lezyonlar-Nöronal Transplantasyon

Sıçan

Nucleus Basalis Magnocellularis of Meynert Lesionları  
kainik acit- Stereotaktik Teknik

Fötal ön-beyin hücre süspansiyonu enjeksiyonu-  
frontal korteks

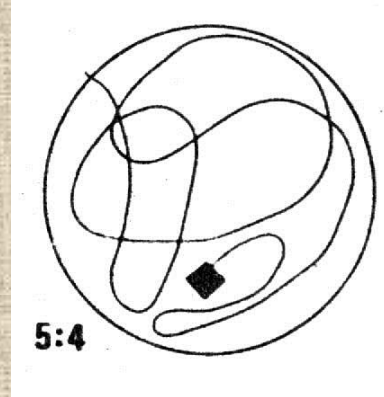
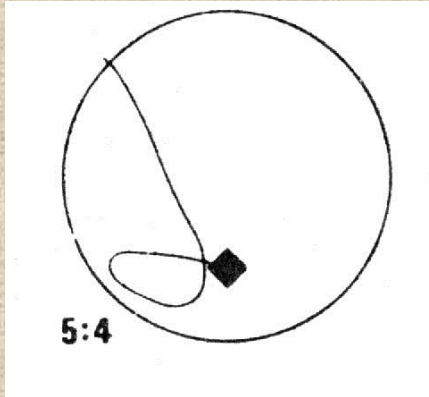




## DEMANS MODELİ

### Morris Water Maze test

Su tankı + Süt tozu + Platformu bulma zamanı



Can MS, Barlas O, Savas A: Amelioration of spatial learning and memory impairment by foetal cholinergic neuronal grafts in rats with lesions of the nucleus basalis magnocellularis. Turkish Neurosurgery 3: 6-10, 1993



## DENEYSEL PARKİNSON MODELLERİ

- **6-hydroxydopamine (6-OHDA)**

**Sıçanlar**

**Beyin içi-Topical, CSF**

- **1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)**

**Meperidine analogue-synthetic heroin-insan**

**Maymun**

**Sistemik uygulama- Nigro-striatal dejenerasyon**

- **İstrahat tremoru**

**rijidite**

**Akinesia**

**Postural instabilite**





## EKSPERİMENTAL EPİLEPSİ MODELLERİ

- **Penicillin – Topikal**
  - **Deney**
    - **Kedilerde penisilinle epilepsi**
    - **Korpus kallosum kesisi**
- **Alluminium Oxide Kremleri-Topikal**
  - **Maymun deneyleri**

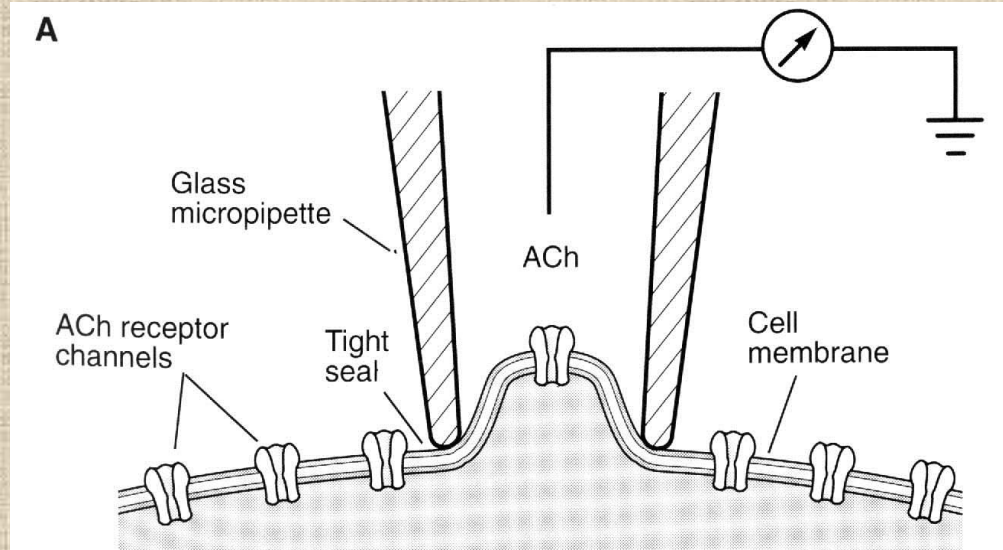


# PATCH-CLAMP TEKNIĐİ

## Membran Düzeyinde Fonksiyonlar

### İyon Kanalları

**Neher & Sakman: Nature 260: 799-802, 1976**  
Micropipette (1 mic)- elektrik akımı







# MEMBRAN DÜZEYİNDE NÖRON FONKSİYONLARI NÖROTRANSMİTTERLER PRECURSOR-UPTAKE-DENEYLERİ

- Tavşan- Hippokampal Doku Kesit Kültürleri
- High-affinity Choline uptake- Kolinerjik Nörona Spesifik
- Kolinerjik Nöron Fonksiyonel Marker'ı

-Savas A: The effects of continuous and single dose radiation on choline uptake in organotypic tissue slice cultures of rabbit hippocampus. Doctoral Thesis. Freiburg University, School of Medicine (Freiburg i. Br., Germany); 1994, pp.12-23

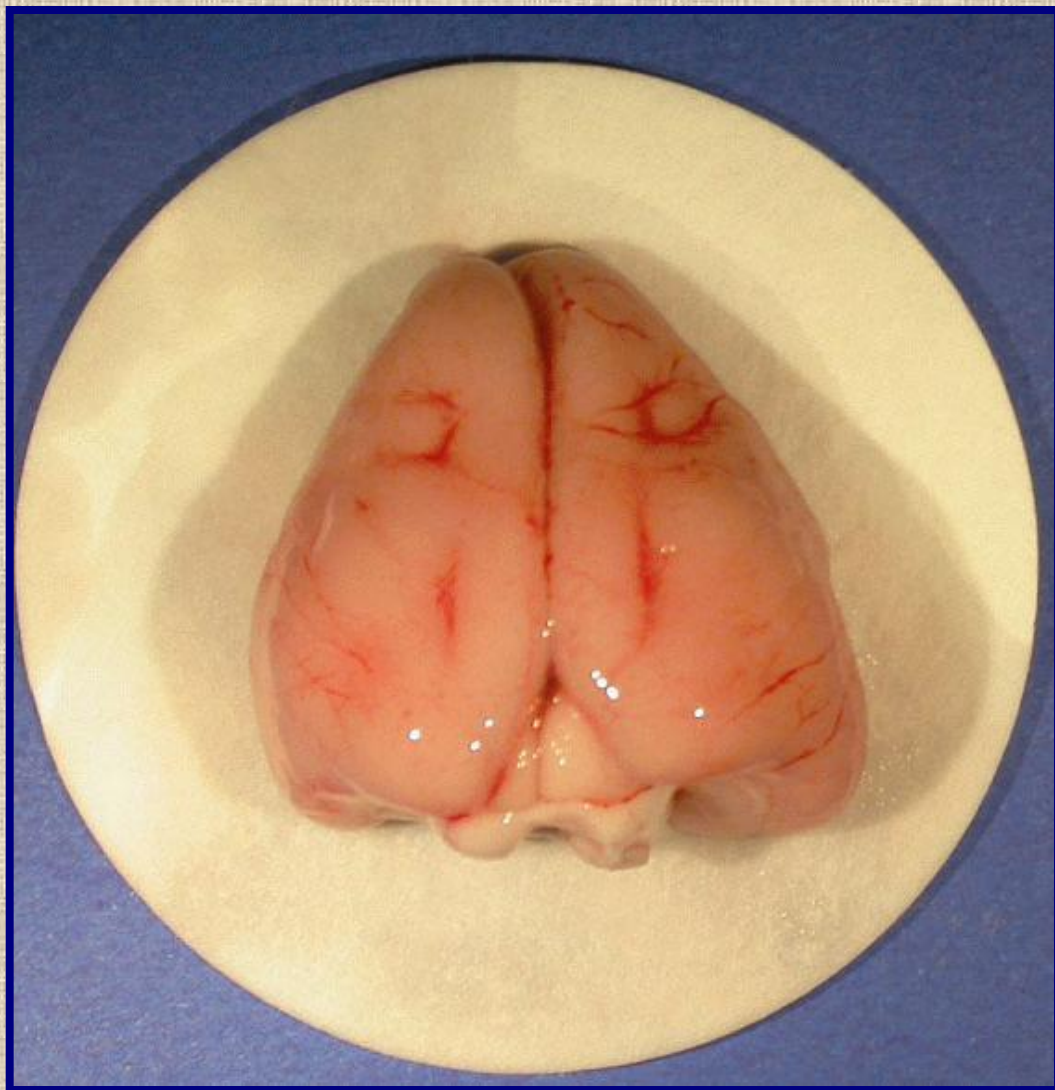
- Savas A, Warnke PC, Ginap T, Feuerstein TJ, Ostertag CB: The effects of continuous and single dose radiation on choline uptake in organotypic tissue slice cultures of rabbit hippocampus. Neurological Research, 2001



# Material & Method



- Hippokampal Diseksiyon



# Material & Method

- **Dinamik inkubasyon**



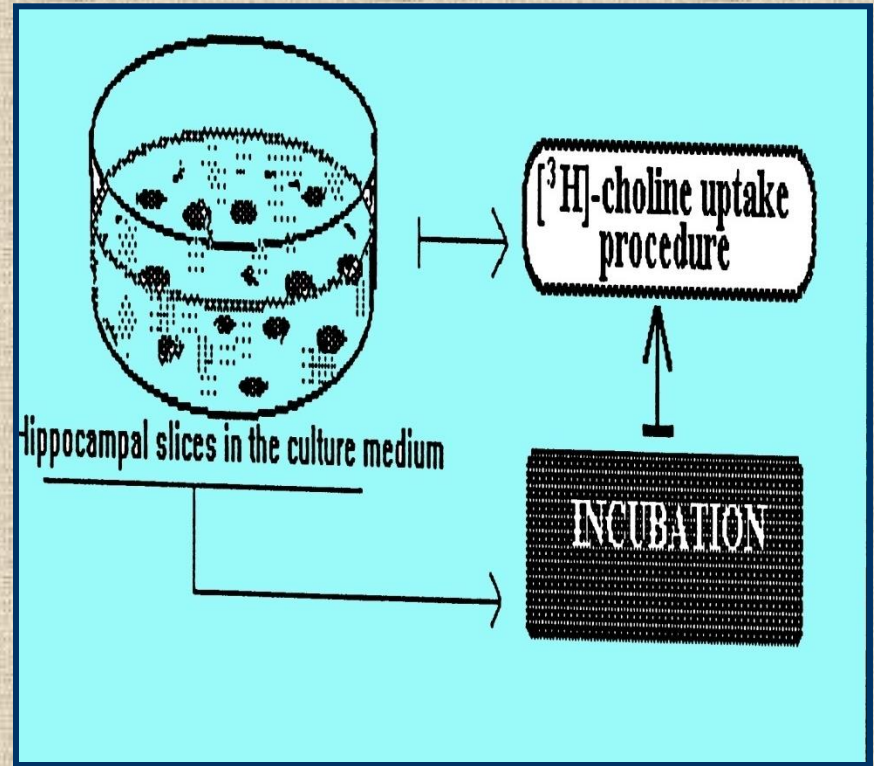
**72 saat**



# Material & Method

## Choline uptake prosedürü (longitudinal)

0, 14, 24, 38, 48, 62, 72 hours

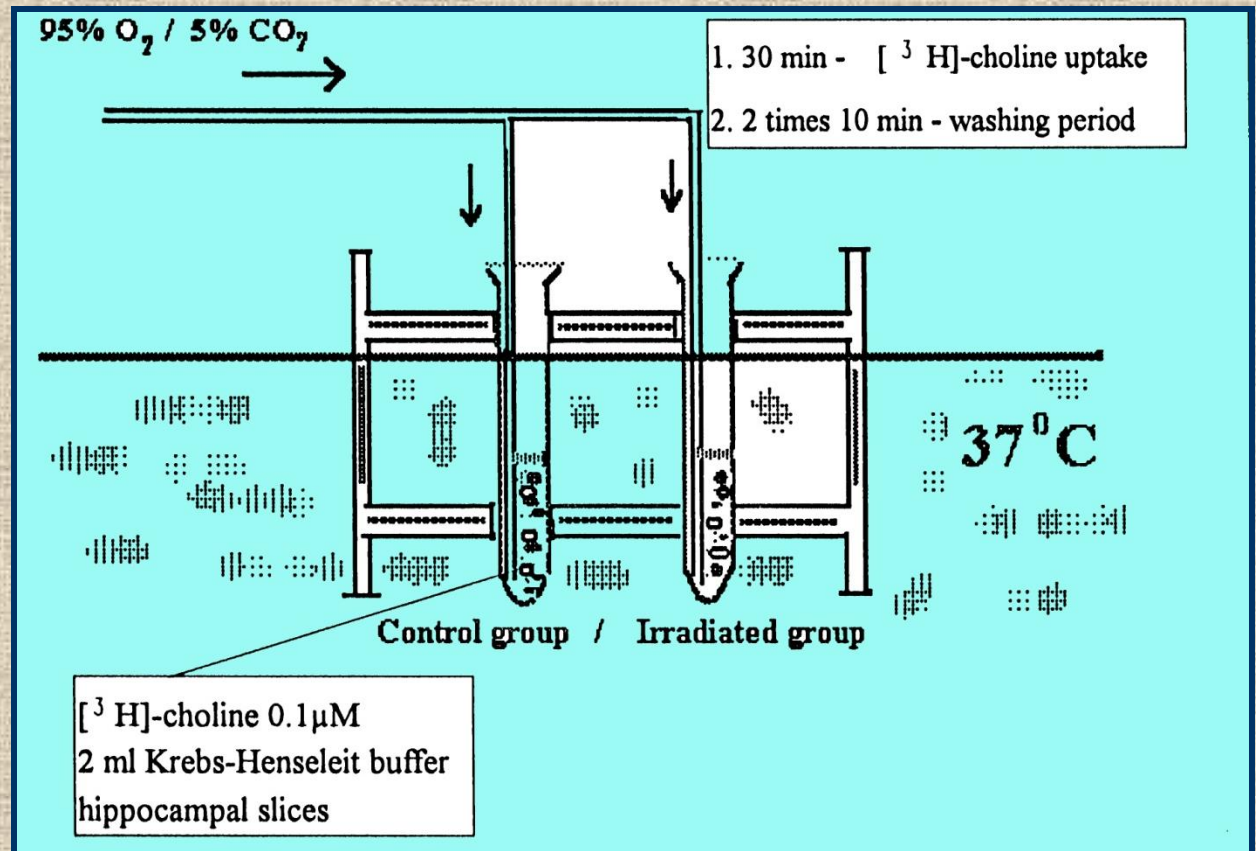
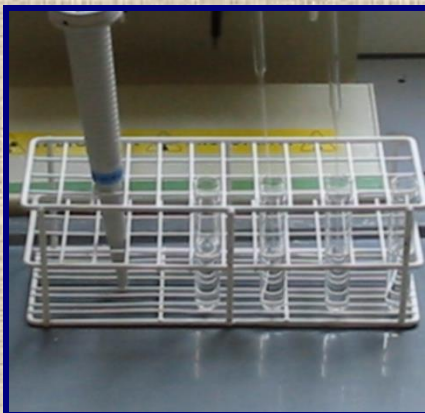


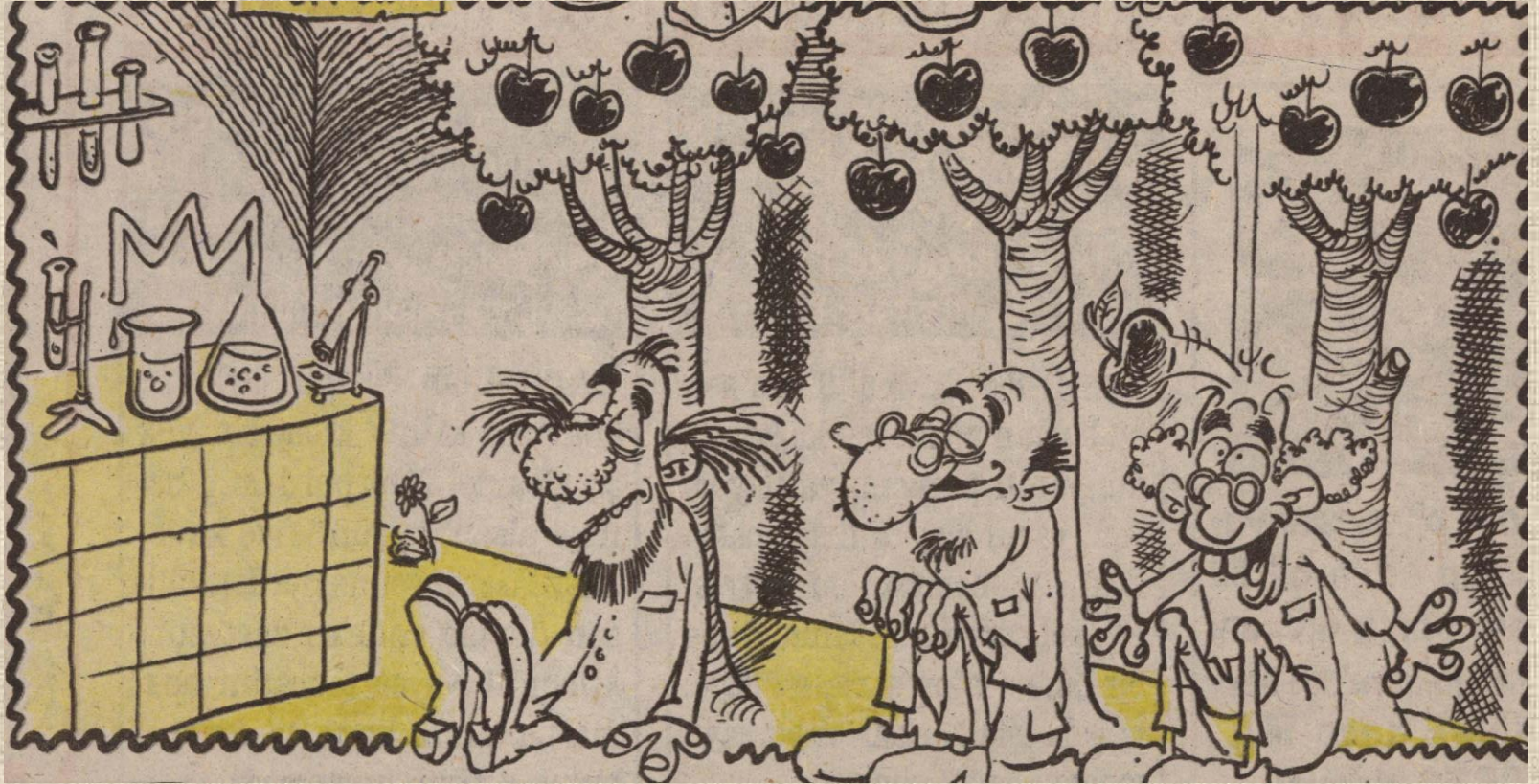
72 hours

(O<sub>2</sub> + rotasyon + kültür medium deęiřirme)

# Material & Method

- **Hemicholinium-3** (5 micro-M) kompetitif inhibitor- HACU





**Fonksiyonel nörolojik arařtırmalar  
neden önemlidir?**



- Klinik becerilerin gelişimini sağlar
- Bilimsel çevreleri etkiler
- İnsanların düşüncelerini etkiler
- Günlük yaşamı değiştirir
- Çağın felsefesini değiştirir