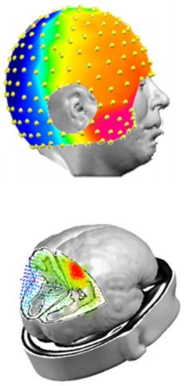
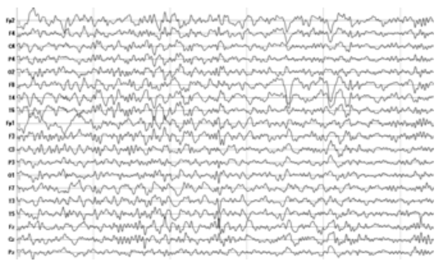
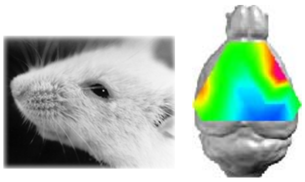
Cours à option 2ème-3ème années « Du neurone au patient »

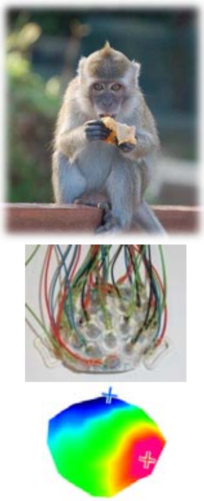
Cartographie fonctionnelle cérébrale

Charles.quairiaux@unige.ch









Cartographie fonctionnelle cérébrale

1. Cartographie fonctionnelle cérébrale chez l'homme

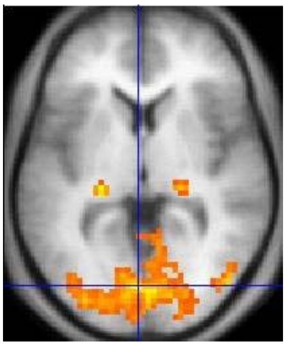
-Introduction:
Historique, concept de réseaux de neurones
- Méthodes de cartographie fonctionnelle:
  - A. Invasives: enregistrements intracrâniens
  - B. Non invasives: TEP, IRMf, EEG, MEG
    - → Bases physiologiques de l'EEG
    - → Potentiels évoqués et applications
    - → Localisation des sources de l'EEG
    - → Localisation: développement technologiques
    - → Application: épilepsie

2. Cartographie fonctionnelle chez l'animal
- → Pourquoi?
- → Un tour au labo

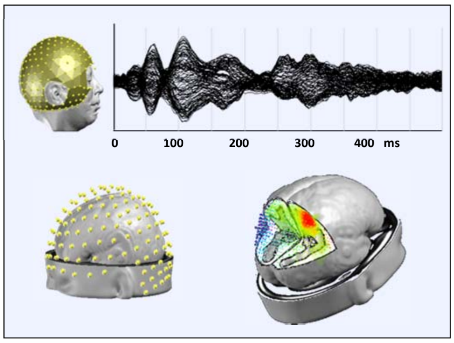
1. Cartographie fonctionnelle cérébrale chez l'homme

= localisation (spatiale et dynamique) de l'activité cérébrale durant les processus cognitifs par différentes techniques d'imagerie fonctionnelle

Exemples:



IRMf

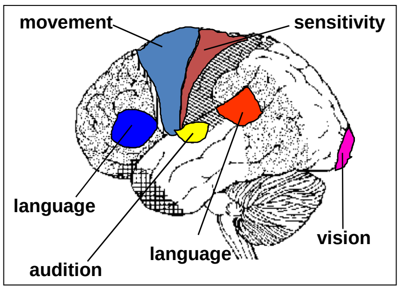


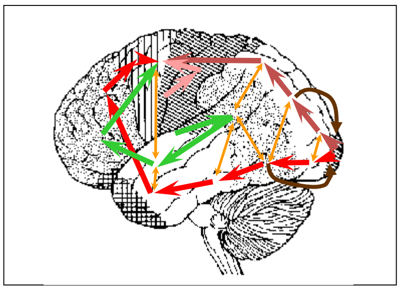
EEG and source localization

1. Cartographie fonctionnelle cérébrale chez l'homme

Localisation spatiale

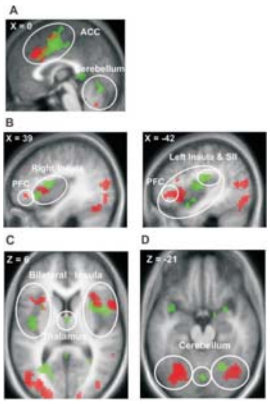
Dynamique



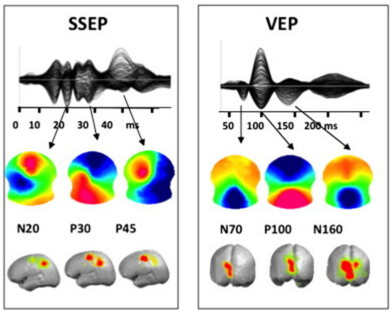


Régions fonctionnelles (=réseaux de neurones) ⟷ **"large-scale networks"**

1. Cartographie fonctionnelle cérébrale chez l'homme



IRMf: Zones du cerveau activées par la vision de la douleur chez une autre personne
= zones de l'empathie?



EEG et solution inverse: Zones du cerveau activées par un stimulus somatosensoriel ou visuel. Avantage: dynamique

Introduction: Historique

Où se trouve l'esprit?

- Hippocrates (460-370 av JC): → Cerveau, "par lui que nous pensons, concevons, regardons, entendons…"
- Platon (424-348 av JC): → Cerveau, "le siège de nos pensées"
- Aristote (384-322 av JC): →Coeur! Sensations, passions, affections….
  →Et cerveau : refroidit le sang et abrite l'âme rationelle
- Galien (131-201) et l'Eglise:→ Âme immatérielle, fonctions mentales dans les ventricules (vide!)

-Descartes (1596-1650): →Âme immatérielle, transmet ses ordres via la glande pinéale
→Cerveau=pompe musculaire

Introduction: Historique

Globalisme:

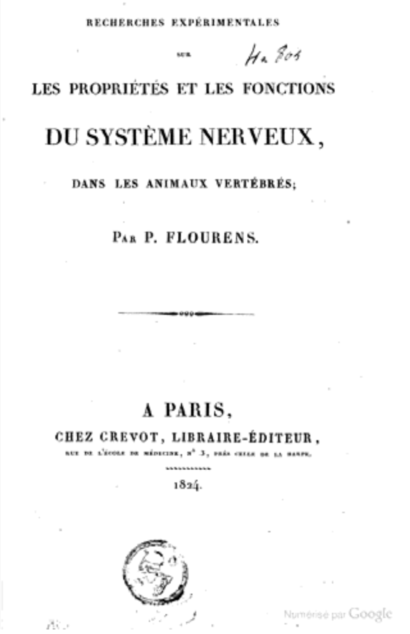
M. Rolando (1809) and M.J.P. Flourens (1824) made lesions in the CNS of animals and studied the results:

1. Nerves, spinal cord and medulla oblongata: directly excite muscles.
2. Cerebellum: coordination of movements
3. Hemispheres: initiate the voluntary movements

"Le nerf *excite*; la moelle épinière *lie*; le cervelet *coordonne*; les lobes cérébraux *veulent* et *sentent*. "

However within the hemispheres they found no single region responsible for memory or cognition!

→ Cognitive functions are globally distributed over the entire cortex= Globalism


RECHERCHES EXPÉRIMENTALES

SUR

LES PROPRIÉTÉS ET LES FONCTIONS

DU SYSTÈME NERVEUX,

DANS LES ANIMAUX VERTÉBRÉS;

PAR P. FLOURENS.

A PARIS,

CHEZ CREVOT, LIBRAIRE-ÉDITEUR,

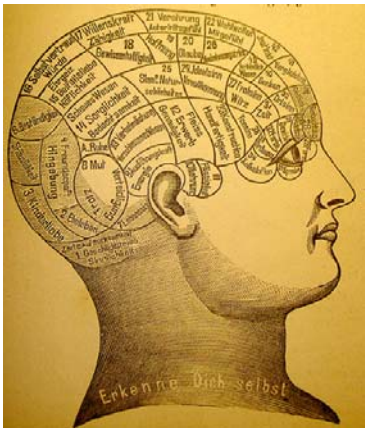
1824.

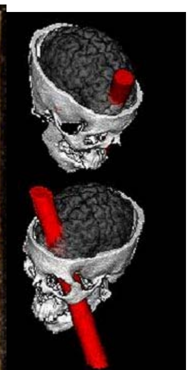
Introduction: Historique

Localisationisme: → Cognitive functions are localized to specific brain centers, cortical areas in particular

-Franz Joseph Gall (1758-1828): la bosse des maths….

-Phineas P. Gage (1823-1860): brain lesions and behavioral changes





Introduction: Historique

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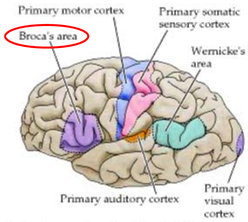
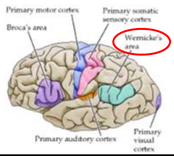
-Franz Joseph Gall (1758-1828): la bosse des maths….

-Phineas P. Gage (1823-1860): brain lesions and behavioral changes

- Paul Pierre Broca (1824-1880): Broca's aphasia: inability to produce speech; understanding not massively impaired



- Carl Wernicke (1848-1905): Wernicke's aphasia: inability to understand speech; speech production is possible but paraphasias, speech may be meaningless



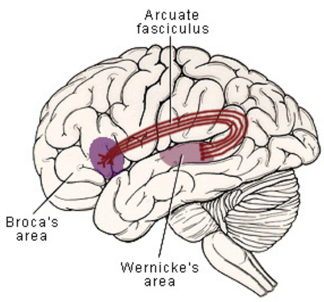
Introduction: Historique

Conduction aphasia= a disconnection syndrome

Not all language deficits are due to lesions in the cerebral cortex

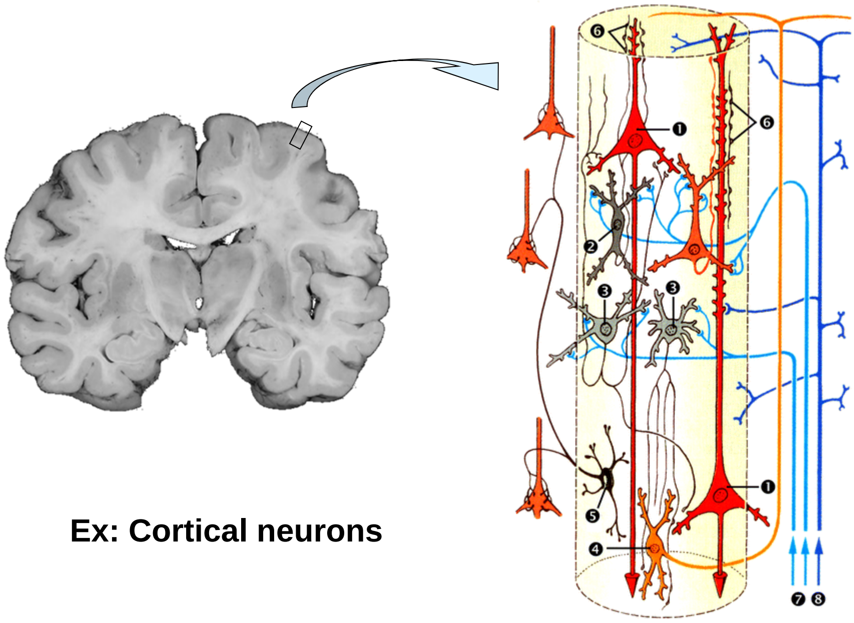
Conduction aphasia: inability to repeat speech directly, understanding unimpaired, production impaired with autocorrections

Interruption of fibre pathway: disconnection syndrome



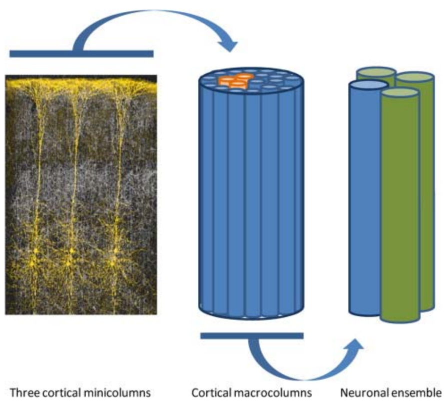
"large-scale networks"

Introduction: networks of neurons



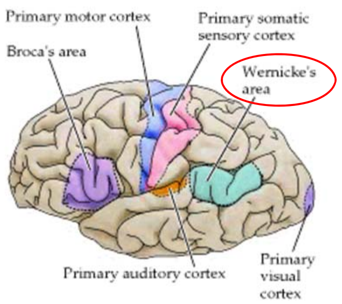
Ex: Cortical neurons

Introduction: networks of neurons

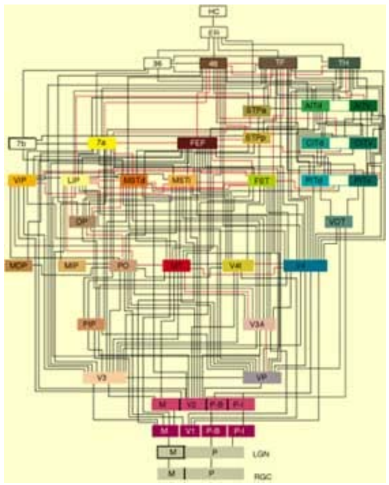


Introduction: networks of neurons

Large-scale functional networks



Simplified language network



Complete visual networks in the macaque brain (Felleman and Van Essen, 1990)

Introduction: networks of neurons

Résumé

Réseaux corticaux: concepts clés

•Le cortex contient des régions fonctionnelles spécialisées

•Les fonctions peuvent être latéralisées

•Les régions corticales spécialisées sont connectées par des projections cortico-corticales, formant des réseaux corticaux à large échelle.

•Les réseaux corticaux peuvent être interprétés comme des modules contribuant a plusieurs fonctions (multifonctionnalité)

•Les réseaux corticaux sont à la fois stables et « plastiques »

•Dynamique: le traitements de l’information par les réseaux est à la fois séquentiel et parallèle

Méthodes de cartographie fonctionnelle

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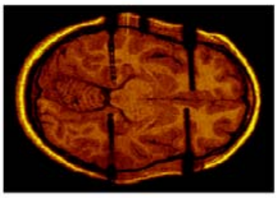
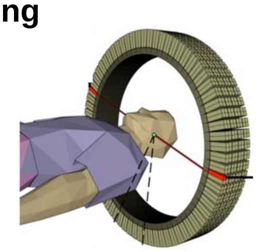
A. Invasive

- Intracranial electrophysiology



B. Non-invasive= functional brain imaging

- Positron-emission tomography (PET scan; 1952)
- Functional magnetic resonance imaging (~1992)
- Electroencéphalographie (EEG)



A. Invasive: enregistrements intracrânien

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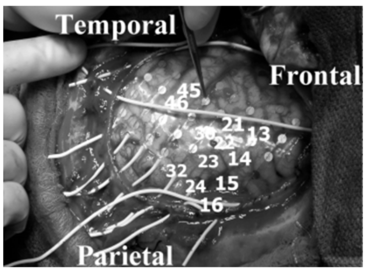
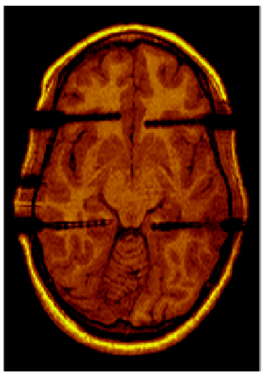
Electrical recordings and stimulation at the cortical surface or intracortically

Used in neurosurgical interventions where a mapping of cortical function is required (exeresis of potentially "eloquent", functionally important cortical areas)

W. Penfield (~1950) obtained the first "maps" of the primary somatosensory and motor cortices





B. Non-invasive: Tomographie par émission de positrons

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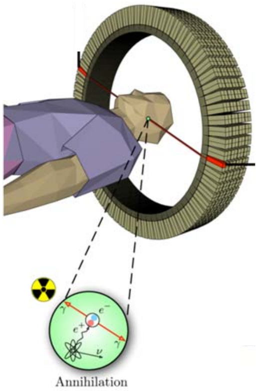
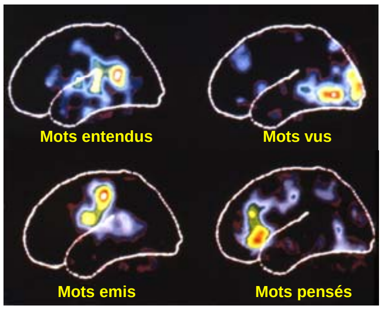
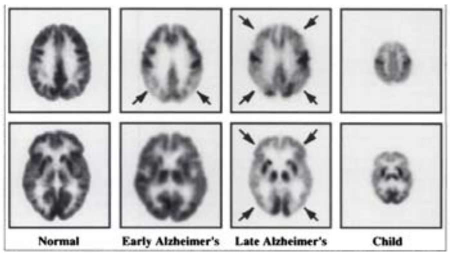
TEP (PET scan; 1952): accumulation de marqueurs radioactif émettant des positrons, rencontre avec un électron émettant un photon, détection des photons







B. Non-invasive: Imagerie par résonance magnétique

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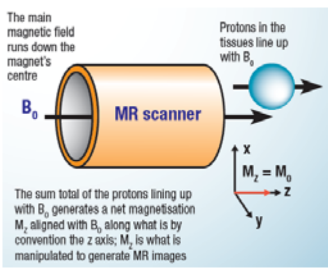
«Imagerie par Resonance Magnétique nucléaire des protons de l'eau » IRM (MRI, 1980)

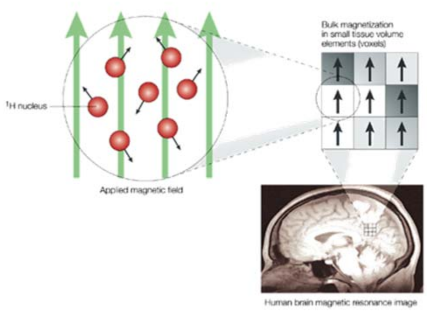
Physical principle:

▪The spin (=magnetic moment of a particle) of protons (especially hydrogen nuclei in water molecules) is aligned along a magnetic field (1 to 14 Tesla)

▪The alignment of the proton spin is briefly perturbed by a radiofrequency pulse

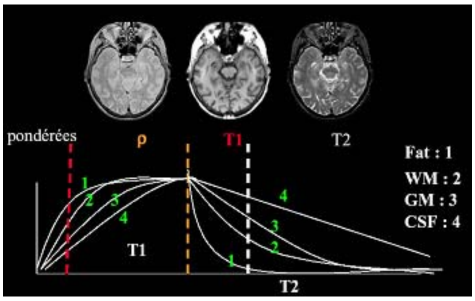
▪MRI measures parameters reflecting the realignment of proton spin along the main magnetic field: T1(longitudinal relaxation), T2 (transversal relaxation)





B. Non-invasive: Imagerie par résonance magnétique

Evolution de l'aimantation des tissus après application d'une radiofréquence (pulse)



T1: mise en evidence des tissus a variation d' aimantation rapide

-Hypersignal graisse (blanc)
-Hyposignal LCR (noir)

Substance grise grise (foncé)
Substance blanche blanche (clair) Donc anatomique!

Sang: noir

T2:mise en evidence des tissus a variation d' aimantation lente

-Hypersignal LCR (blanc)
-Graisse: foncé

Substance grise: clair
Substance blanche:foncé

Sang: noir (sauf oedeme)

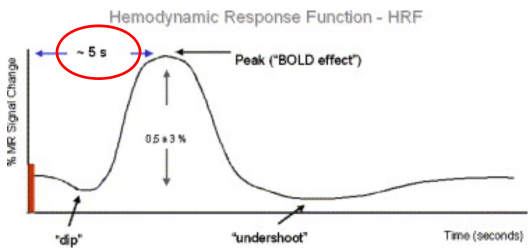
B. Non-invasive: IRM fonctionnelle

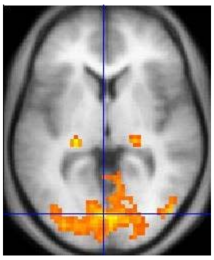
IRMf (fMRI, 1992)

Activité neuronale→ Effet BOLD (Blood Oxygenation Level-Dependant)

→ augmentation de consommation O2 →apport disproportionné de sang → <u>augmentation</u> de l'oxy-hémoglobine

Le rapport deoxy-Hb/oxy-Hb diminue ce qui augmente le signal IRM!





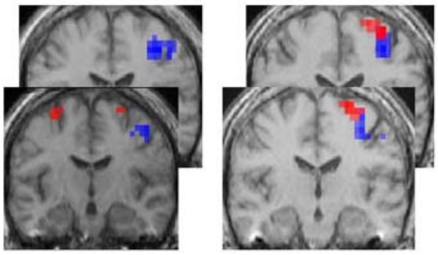
Zones activées en IRMf par stimulations visuelles

IRMf: applications

Plasticité après lésion dans le cortex moteur

→activation par "finger-taping":

20 days after stroke   4 months after stroke

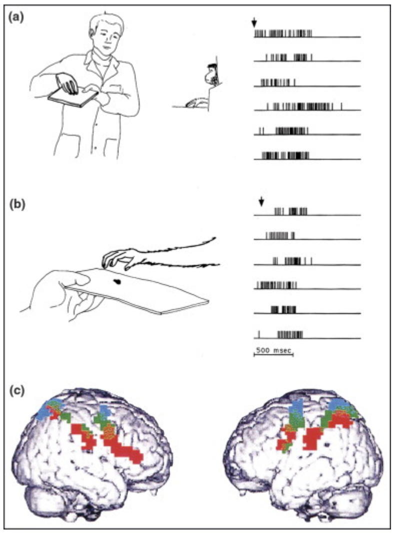


Jaillard et al, Brain 2005

Patient avec AVC

Sujet contrôle

Sciences cognitives: système miroir



Lacobani et al, PLoS Biol 2005

Méthodes de cartographie fonctionnelle

Résumé

- **Enregistrements électrophysiologique intracrâniens**
  - \+ activité neuronale, résolution temporelle
  - \- invasif, local
- **PET scan**
  - \+ étude de différents métabolites (glucoes, dopamine,…), résolution spatiale (250 mm3)
  - \- indirect, radioactif, résolution temporelle (100 sec!)
- **fMRI**
  - \+ résolution spatiale (1 mm3)
  - \- indirect, résolution temporelle (0.5 à 1.5 sec)
- **EEG!!**
  - \+ activité neuronale, résolution temporelle (microsec), «large-scale»
  - \- résolution spatiale

Electroencéphalographie (EEG)

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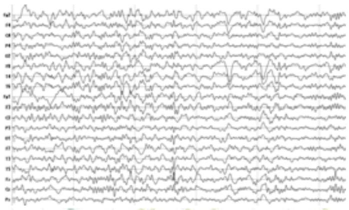
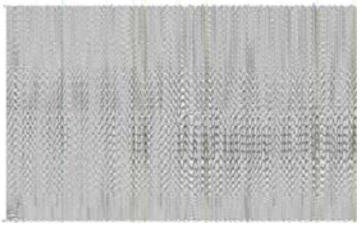
Applications:
- Monitoring des états de conscience (sommeil, coma)
- Epilepsie
- Pathologie des voies sensorielles
- Cartographie fonctionnelles





Evolution:
Augmentation des capteurs et imagerie par localisation de source

Electroencéphalographie (EEG)

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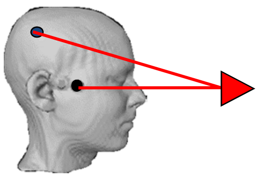
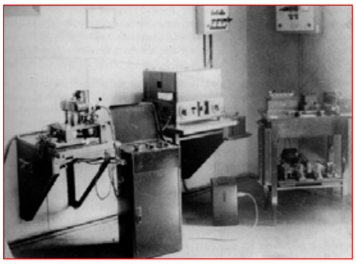
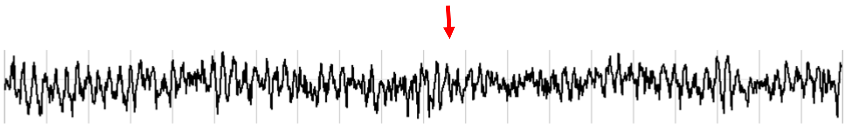




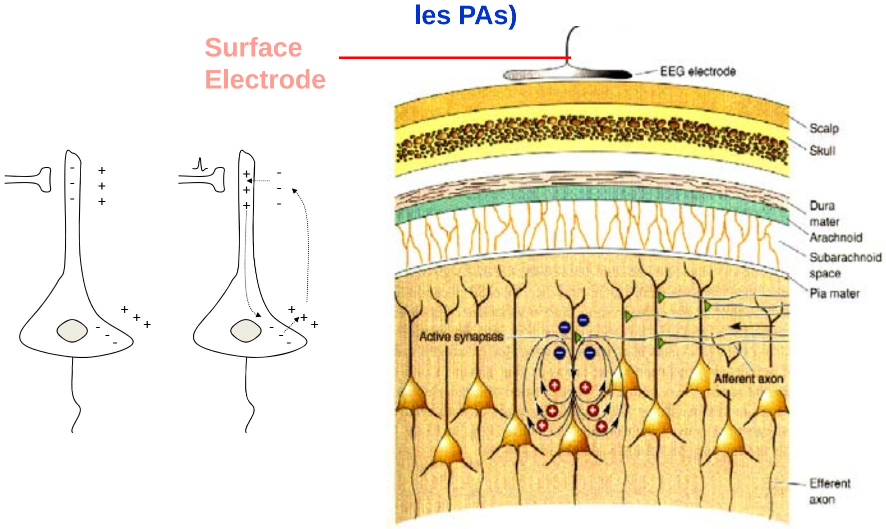
Hans Berger
(1926)



Les différences de potentiels ENTRE DEUX ELECTRODES (microvolts) enregistrés à la surface du scalp varient à haute vitesse (millisecondes)
→ <u>L'EEG mesure des changements d'activité électrique dans le cerveau</u>

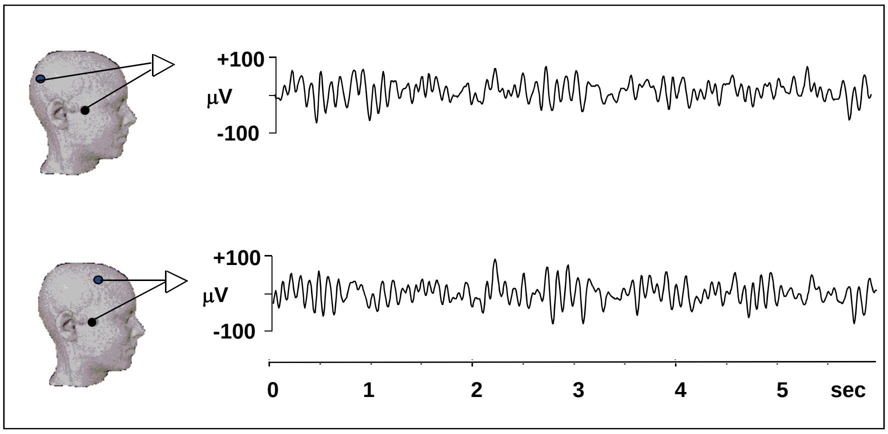
Bases physiologiques de l'EEG

Origine du signal EEG: dipôles créé par les courants synaptiques (et non les PAs)



→ l'activité synaptique de peu de neurones n'est pas visible sur le scalp

Bases physiologiques de l'EEG

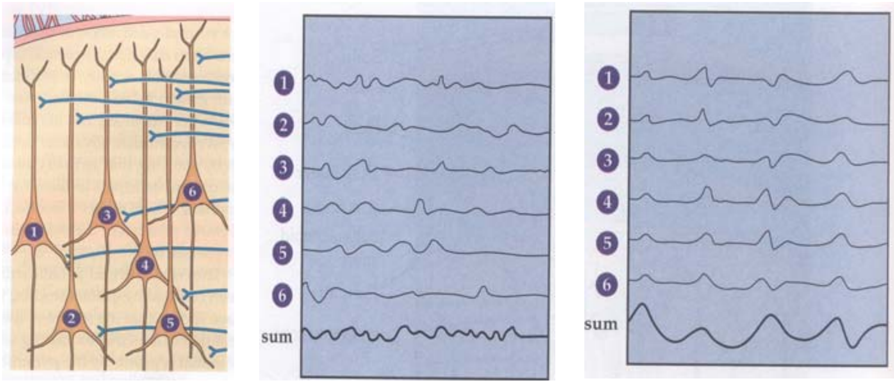


Chaque paires d'électrodes mesurent des tracés différents
→ L'EEG mesure des changements d'activité électriques locaux

Bases physiologiques de l'EEG

→ l'activité neuronale doit être synchronisée

irregular synchronised



Weak Synchronisation → irregular signal with small amplitude

Strong Synchronisation → regular signal with large amplitude

Purves: Neuroscience

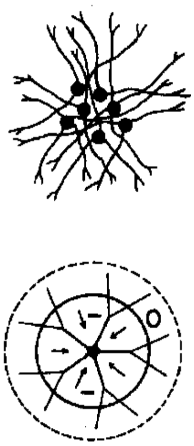
Bases physiologiques de l'EEG

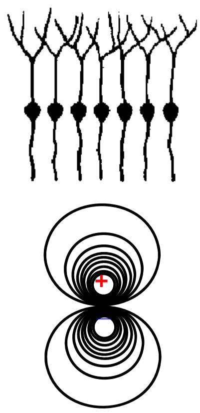
→Le signal EEG dépend de l'orientation des neurones

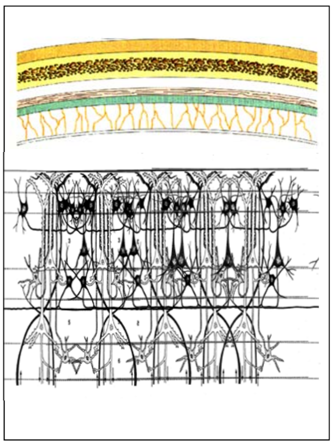
Radial orientation = Closed field

Parallel Orientation = Open (dipolar) field

Columnar organization of pyramidal neurons







Bases physiologiques de l'EEG

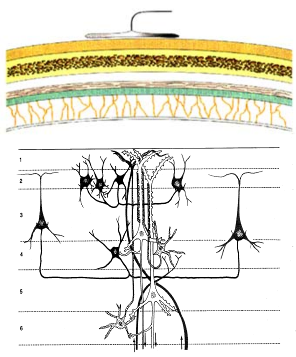
Résumé EEG1

- EEG records *postsynaptic potentials* and not action potentials.
- EEG records the activity of *pyramidal neurons* because of their parallel orientation.
- EEG records the *synchronous activity* of large number of parallel organized neurons that together generate a sufficiently strong dipolar field.

Electroencéphalographie (EEG)

Résumé EEG2

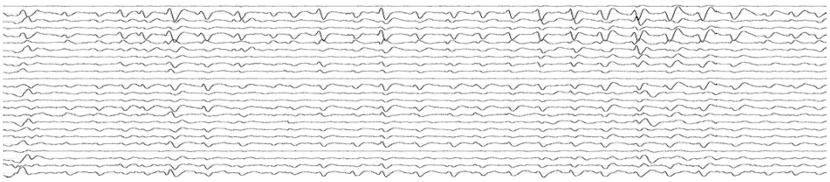
- Synchronous activity in neurons generates an electric and a magnetic field that can be detected using electrodes (EEG) or coils (MEG)
- In contrast to PET or fMRI, EEG and MEG measure direct correlates of neuronal activity
- Advantages: high temporal resolution allows studying synchronization between areas (useful in a large-scale network perspective!)
- Inconvenients: low spatial resolution



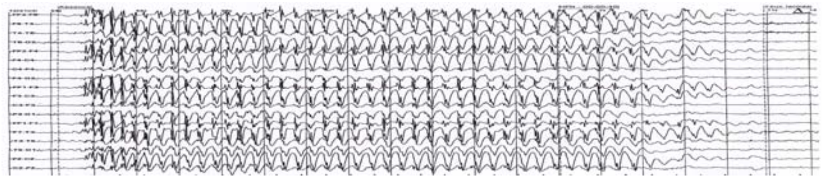
Grande distance entre electrodes et sources du signal
Nombre de sources plus importante que le nombre d'électrodes
→ Mauvaise résolution spatiale

Application: monitoring, épilepsie

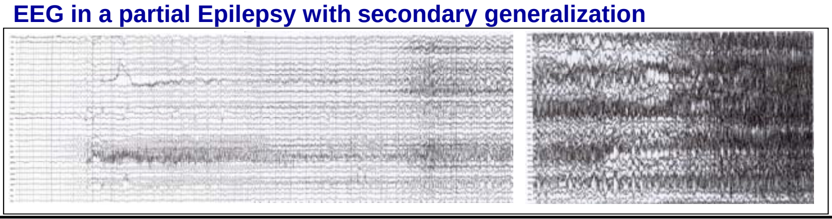
Interictal EEG (spikes)



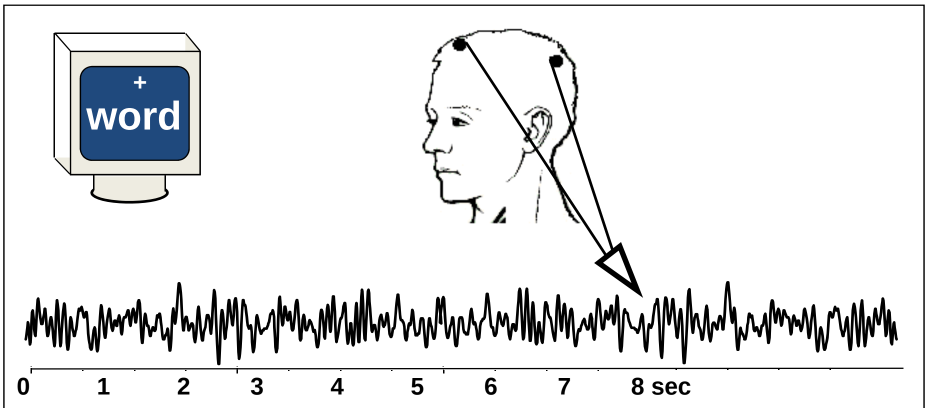
EEG in generalized Epilepsy (absence)



EEG in a partial Epilepsy with secondary generalization



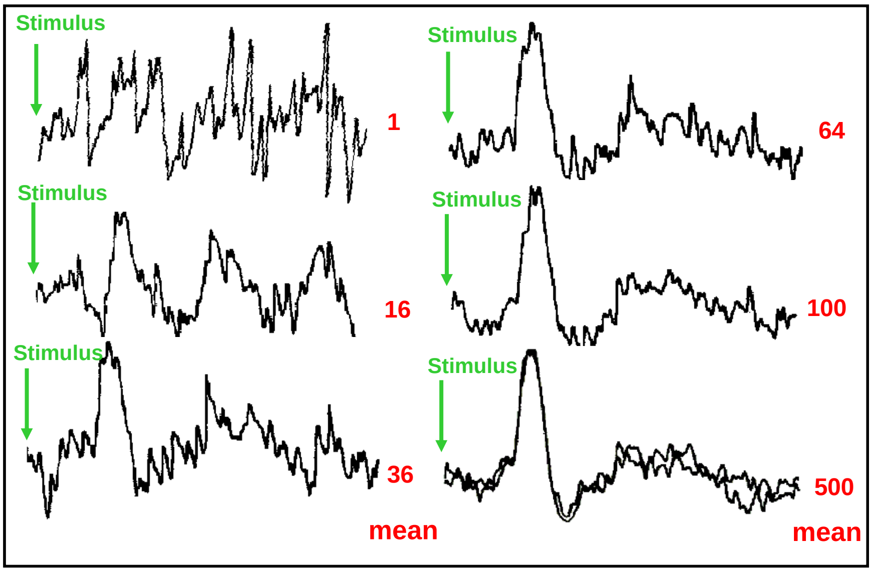
Application: potentiels évoqués



Cependant: la réponse neuronal à un seul stimulus n’est pas facilement visible dans l’EEG!

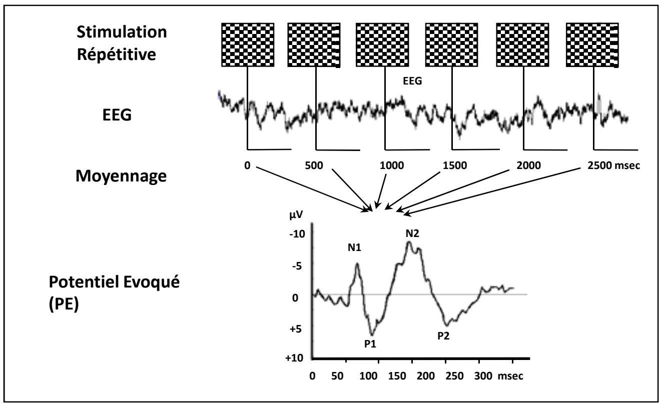
Application: potentiels évoqués

Moyennage du signal→ Potentiels évoqués



Regan, 1989

Application: potentiels évoqués

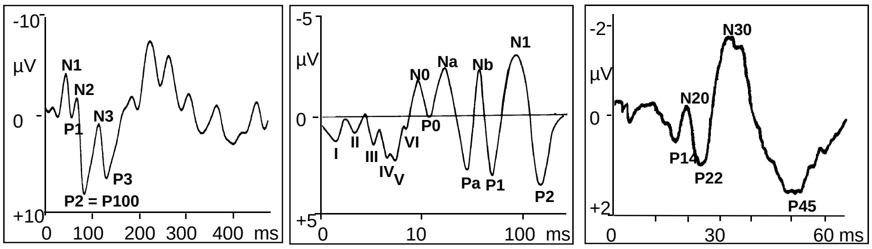


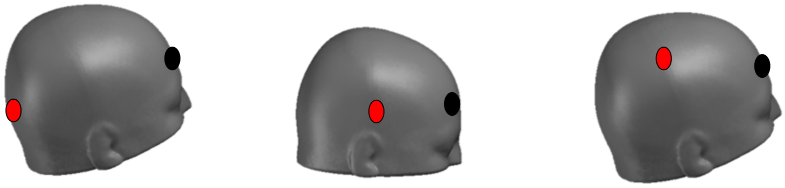
Les données sont moyennées à travers les répétitions de la condition expérimentale par rapport au Trigger de stimulation.

Les moyenne résultantes sont des courbes de différences de potentiel en fonction du temps.

Application: potentiels évoqués

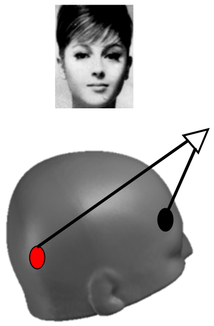
Visual VEP | Auditive AEP | Somatosensory SEP

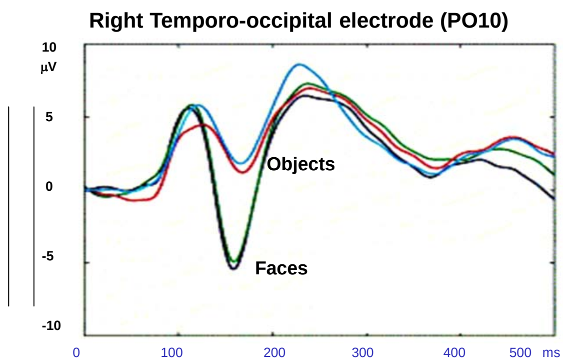




Regan, 1989 | *Hillyard et al., 1984* | *Desmedt et al., 1985*

Event-related potentials (ERP): visage



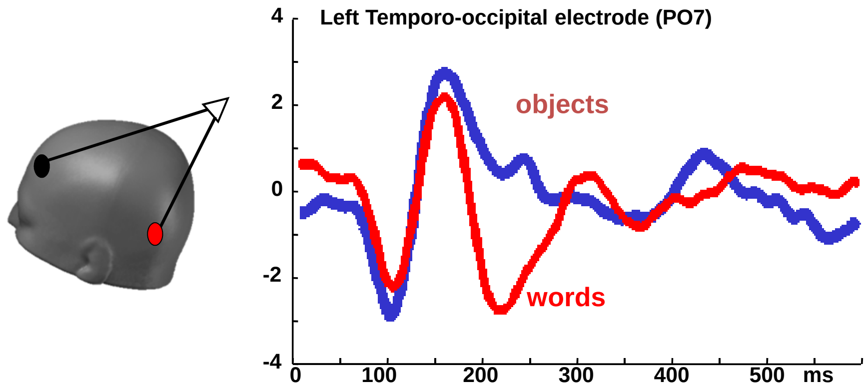


Caldara et al., 2003

Component at 170-200 ms : structural encoding of a face

(e.g. Bentin et al., 1996; Schendan et al., 1998, Allison et al., 1999; etc.

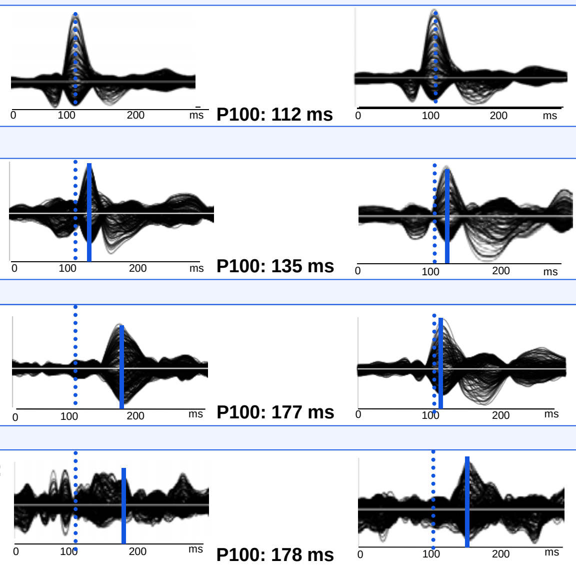
Event-related potentials (ERP): mot



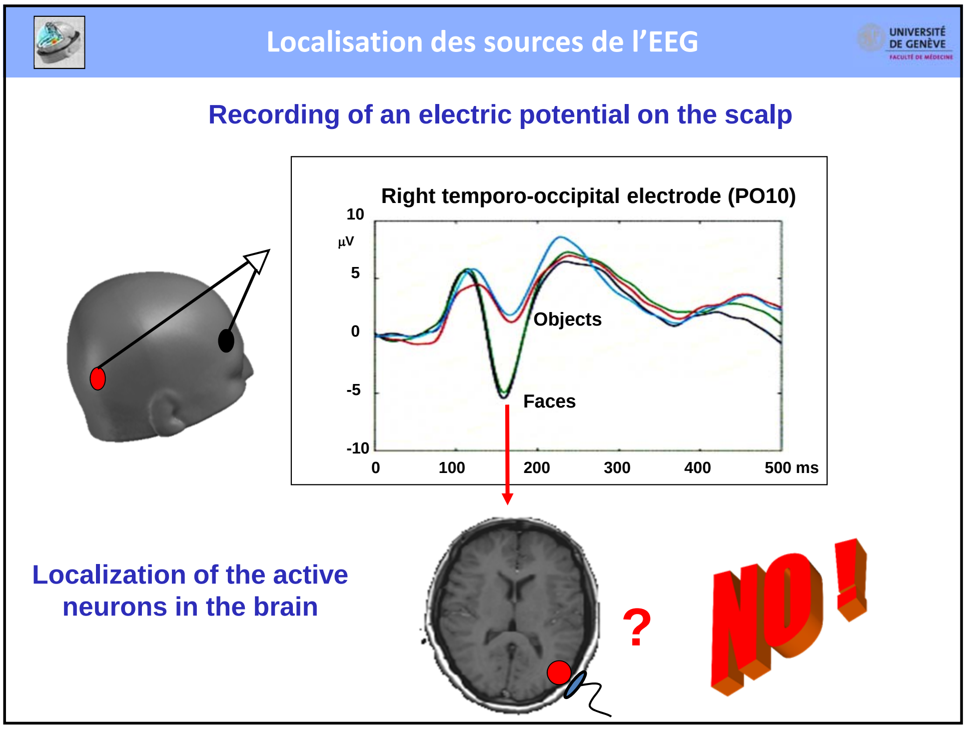
Khateb et al., 2003

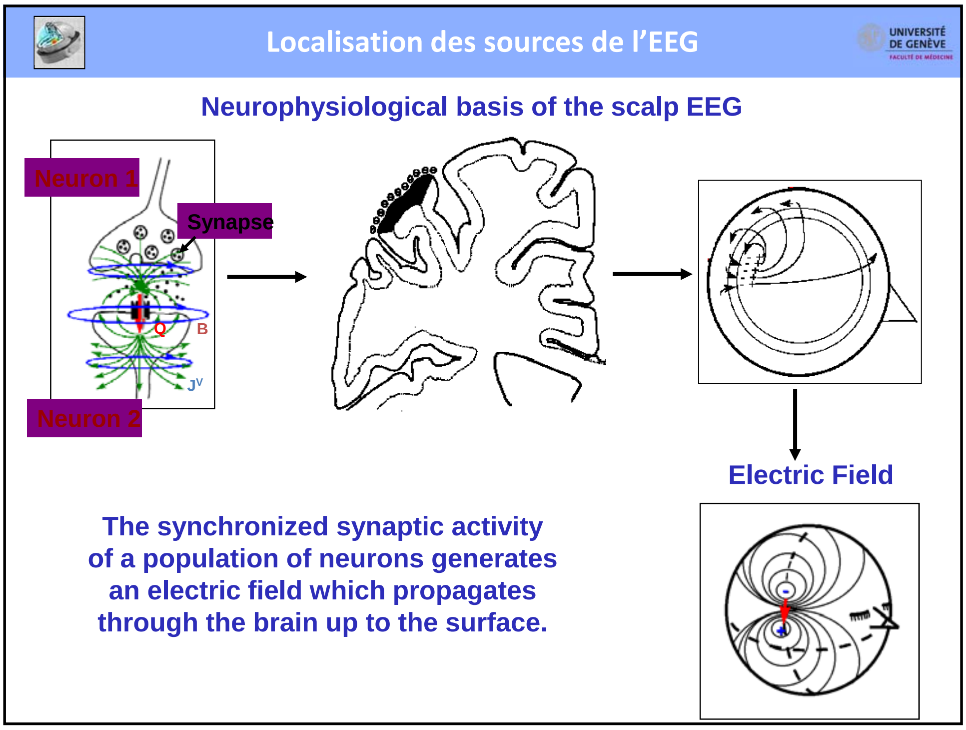
Component at 170-250 ms :
visual perceptual categorization of words; visual word formation
e.g. Nobre et al., 1994; Schendan et al., 1998, Cohen et al., 2000 etc.

Potentiels évoqués: cas cliniques, scléroses en plaques



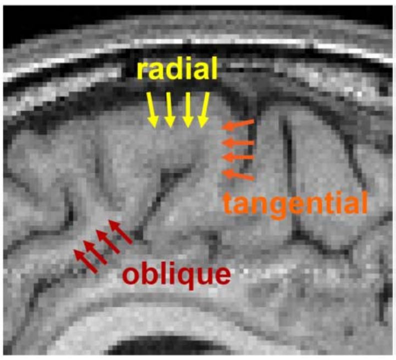
	Œil Gauche	Œil Droit
Normaux	**P100: 112 ms**	**P100: 111 ms**
I.H. (F, 25 ans): symptômes visuelles bilat. RRMS	**P100: 135 ms**	**P100: 124 ms**
C.A.G. (F, 27 ans): symtômes visuelles à G CIS	**P100: 177 ms**	**P100: 113 ms**
H. F. (M, 45 years): symptômes visuelles bilat. SPMS	**P100: 178 ms**	**P100: 141 ms**


Localisation des sources de l'EEG
UNIVERSITÉ DE GENÈVE
Recording of an electric potential on the scalp
Right temporo-occipital electrode (PO10)
10
µV
5
0
-5
-10
0
100
200
300
400
500 ms
Objects
Faces
Localization of the active neurons in the brain
?
NO !

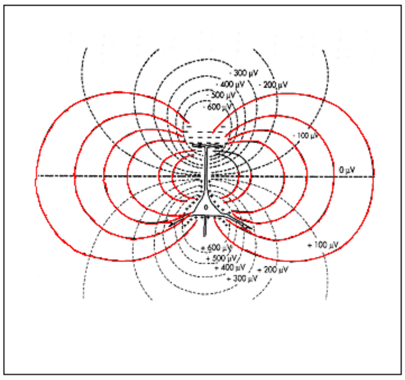

Localisation des sources de l'EEG
UNIVERSITÉ DE GENÈVE
Neurophysiological basis of the scalp EEG
Neuron 1
Synapse
Neuron 2
Q
B
Electric Field
The synchronized synaptic activity of a population of neurons generates an electric field which propagates through the brain up to the surface.

Localisation des sources de l'EEG

The orientation of the neurons with respect to the surface depends on the circumvolution of the brain



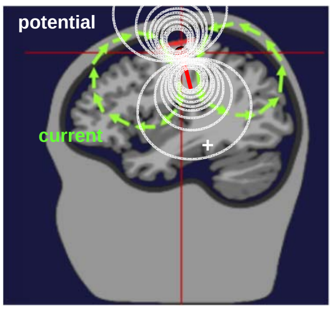
www.besa.de

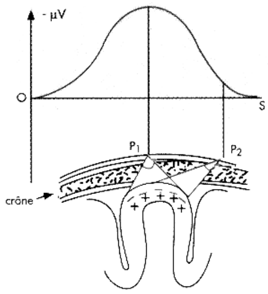


→The extracellular current flow depends on the orientation of the neurons

Localisation des sources de l'EEG

Vertically oriented dipole

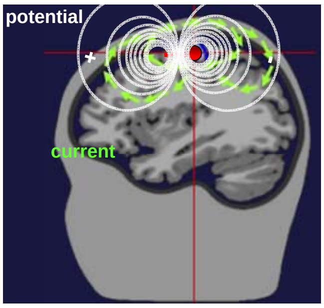


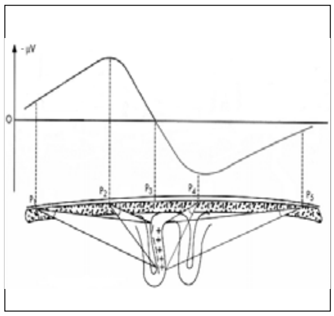


→ **The amplitude maximum is located above the electric source.**

Localisation des sources de l'EEG

Radially oriented dipole





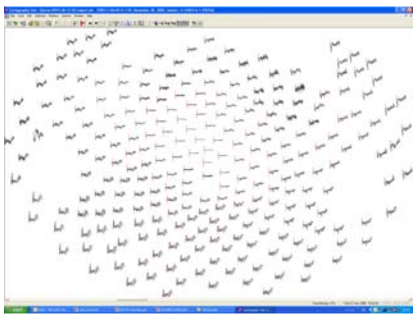
→The amplitude maximum localizes the generator not correctly.
It is in reality under the point of polarity inversion,
i.e. under the zero potential.

From: www.besa.de

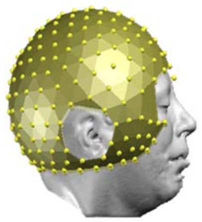
Localisation: Développements technologiques

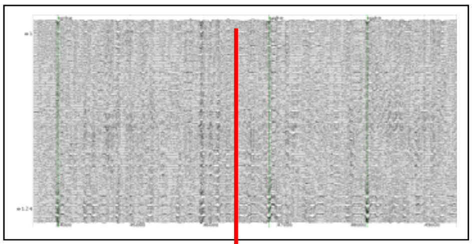
1980 →

2005 →

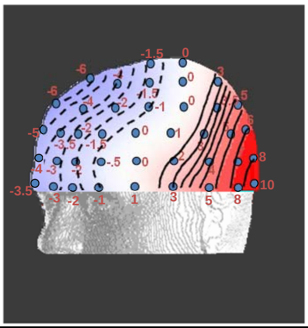


Localisation: EEG Mapping





1.
Recording of the EEG at many electrodes simultaneously

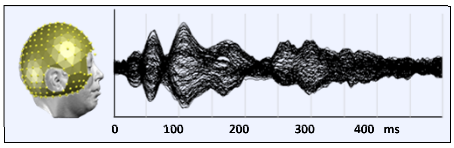


2.
Reconstruction of the electric field at each moment in time

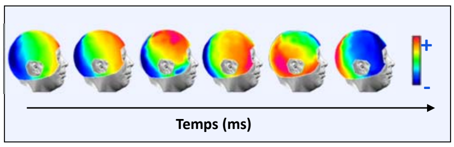
Lehmann, 1971

Localisation: EEG source imaging

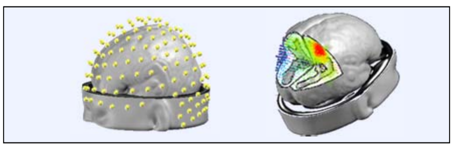
1. **EEG de Haute Résolution**: 64 jusqu'au 256 électrode



2. **Affichage Topographique avec interpolation**: Analyse spatio-temporelles du champ électrique par cartographie (brain mapping). Permet la visualisation instantanée de la distribution des potentiels améliorant la sélection de régions d'intérêts.



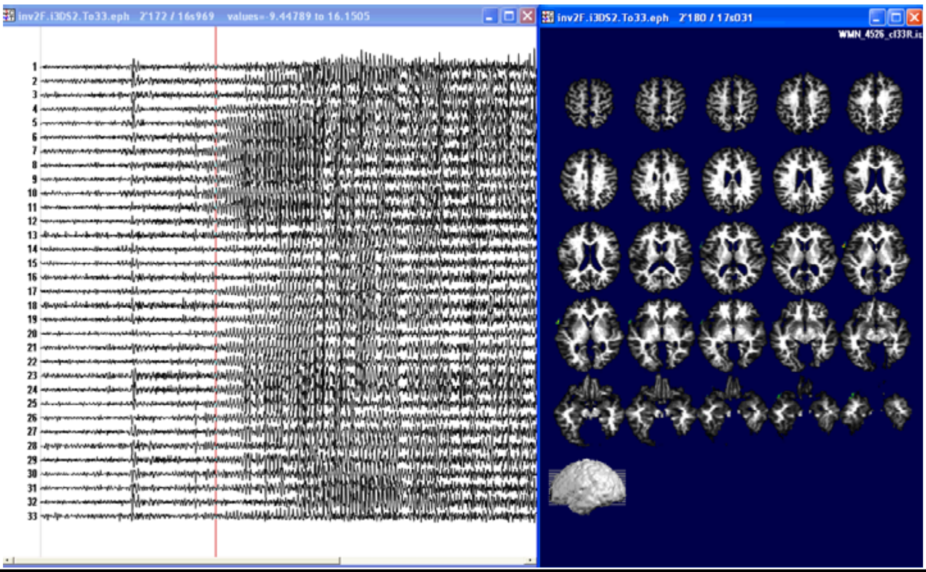
3. **Localisation de la source électrique**: Localisation-3D de la distribution de la source électrique dans le cerveau (idéalement dans l'IRM individuel) grâce à des modèles mathématiques de solution inverse. Ex: estimation de source de type LAURA: Local Auto-Regressive Average.



Dynamic ESI of interictal discharges

UNIVERSITÉ DE GENÈVE

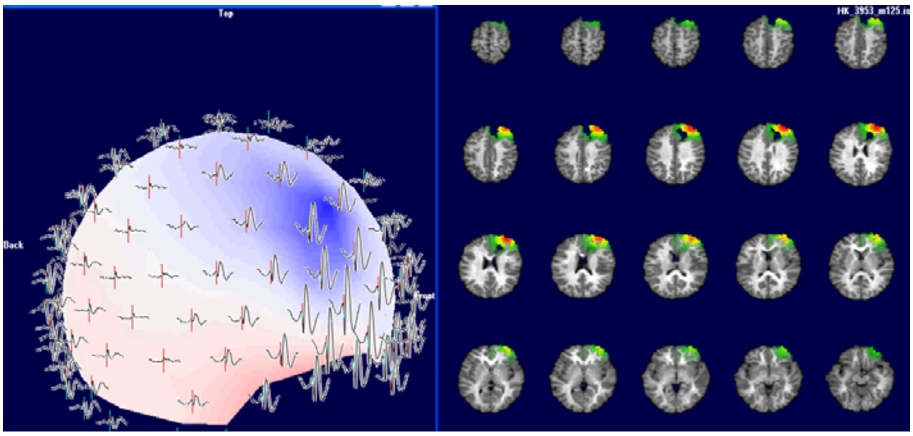
Seizure (33 channel recording)



Dynamic ESI of interictal discharges

UNIVERSITÉ DE GENÈVE

Averaged Spike (128 channel recording)



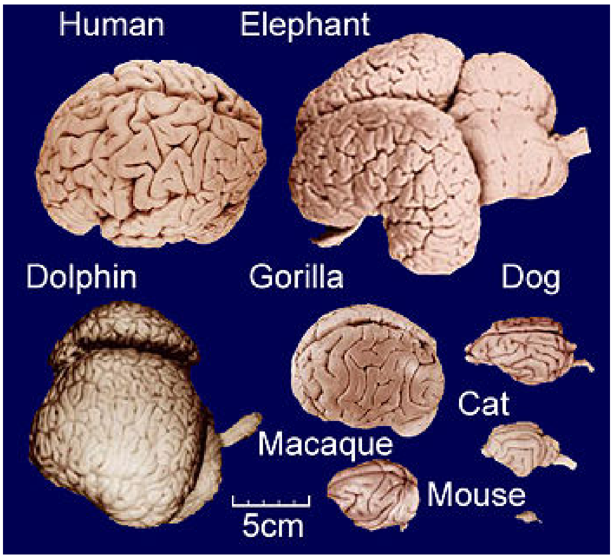
Electroencéphalographie (EEG)

Résumé EEG3

- L'enregistrements de potentiels évoqués requiert le moyenage de nombreuse réponses (faible amplitude de signal)
- La localisation des sources de l'EEG n'est pas directe:
  - l'activité électrique des générateurs voyagent jusqu'à la surface
  - la polarité du signal EEG à la surface dépendra de l'orientation des dipôles
- Important de caractériser l'EEG de surface par des enregistrements de haute densité couvrant l'ensemble du crâne
- Localisation des sources par solution inverse

1. Animal model for EEG studies?

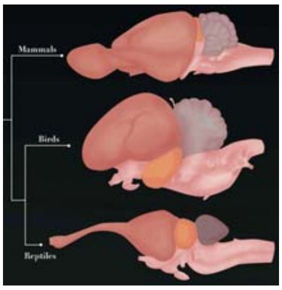
In general, is it a good model for neuroscience?

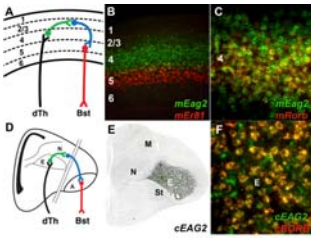


Size?
Cortex?
Circonvolutions?

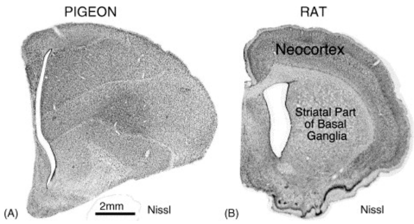
1. Animal model for EEG studies?

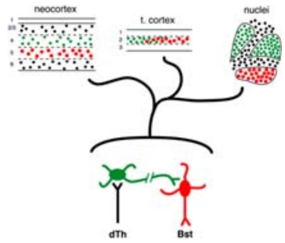
Mammifer vs birds



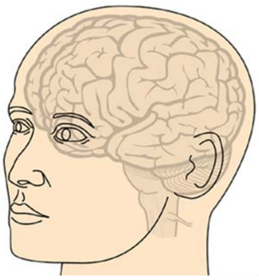


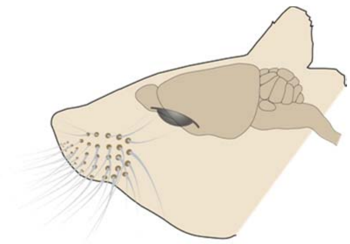
Dugas-Ford et al, PNAS 2012





1. Animal model for EEG studies?





Humans and rodents brains share fundamental physiological, histological and anatomical characteristics

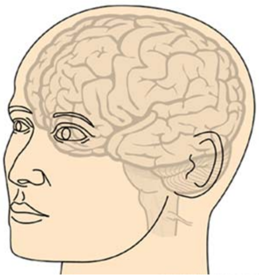
Fundamental neuroanatomy:

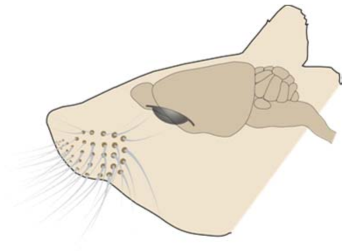
→Same embryologyc divisions:

rhombencephalon (medulla, pons, cerebellum), mesencephalon (midbrain), prosencephalon (di+telencephalon)

→ Same cortical types: paleocortex, archicortex, neocortex

1. Animal model for EEG studies?





Humans and rodents brains share fundamental physiological, histological and anatomical characteristics

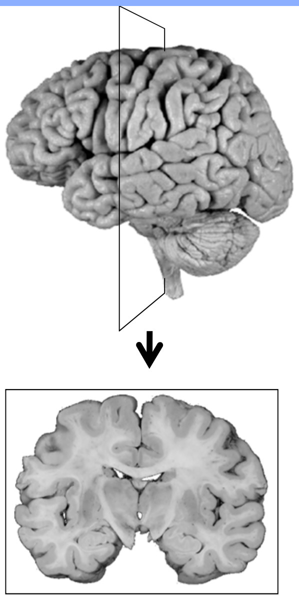
Fundamental units are neurons and astrocytes

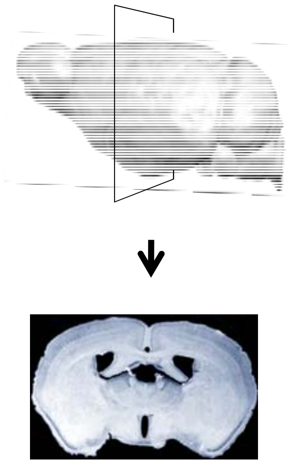
Human brain= 100 billion neurons
Human cortex= 12 billion

Rat cortex= 15-30 million
Mouse cortex= 4 million

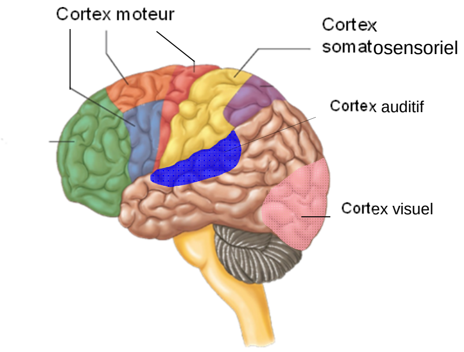
→ In both species, neurons make about 10.000 synapses each
→ No specific neuronal type in human

1. Animal model for EEG studies?

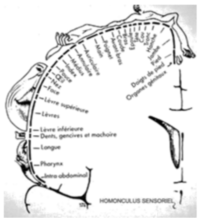




1. Animal model for EEG studies?

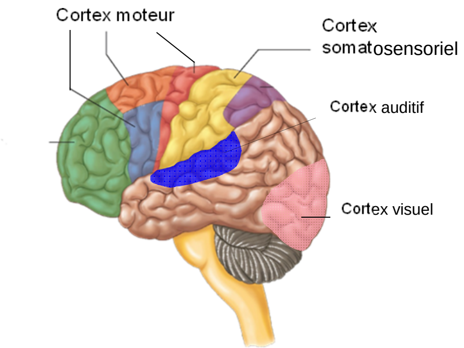


•Functional areas

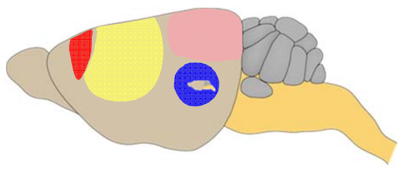


•Somatotopic maps

1. Animal model for EEG studies?



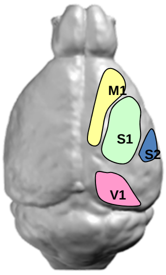
•Functional areas

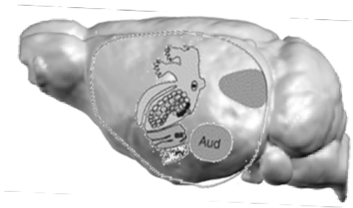


•Functional areas

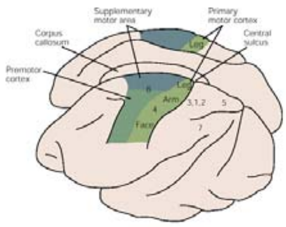
1. Animal model for EEG studies?

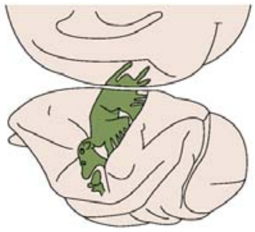
mouse





•Somatotopic sensory and motor maps





macaque

1. Animal model for EEG studies?

Summary:

- Very similar to the human one
- Similar fundamental physiological and histological characteristics
- Similar fundamental neuroanatomy: mostly crossed, brainstem and thalamic relays before cortex, cortex
- Cortex divided in similar functional areas
- Similar functional and anatomical organization: retinotopic, tonotopic and somatotopy

→Behavior? Conscious? Language? …

What to do with an animal model in neuroscience?

→ **To study the cellular and molecular basis for network function**

- invasive electrophysiology
- experimental lesions
- environmental manipulations
- pharmacological studies
- genetic manipulations to study molecular basis of networks function and pathologies: example→ Laurent!

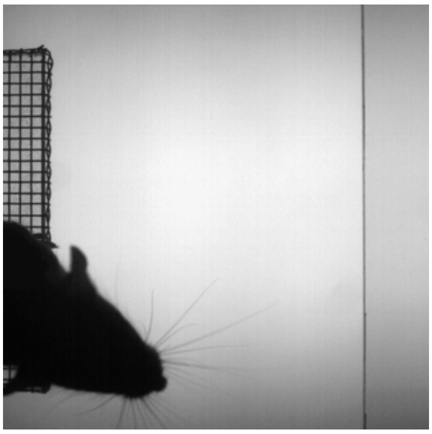
→**Questions/caveats:**

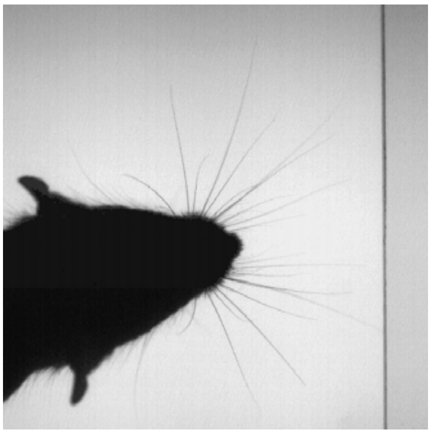
- **Anesthetized, awake head restrained, freely moving?**
- **Ethical debate:** **«** the benefit to humans does not justify the harm to animals **»**

→Animal care regulations, alternatives where possible, RRR= replacement-reduction-refinement

- **Can we transpose observations made in rodents to human?**

A brief introduction to the mouse/rat whisker-to-barrel cortex system





A brief introduction to the whisker-to-barrel cortex system

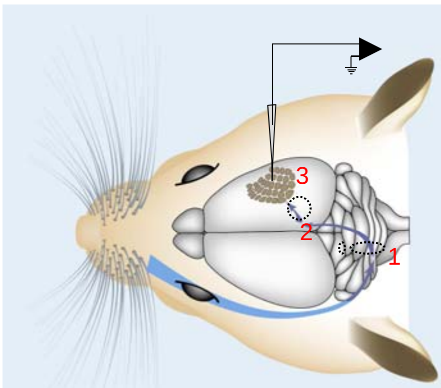
The somatosensory facial whiskers

Somatotopic « barrel » maps in S1

Ideal model to study:

- Experience and lesion dependant plasticity,
- development and maturation of neuronal networks,
- physiological bases of sensory processing,
- …

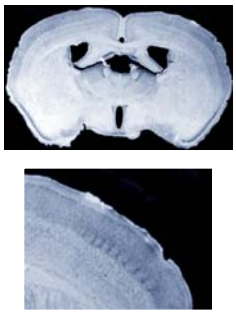
A brief introduction to the whisker-to-barrel cortex system



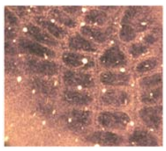
Schematic ascending pathway

1. Trigeminal nucleus
2. Thalamus
3. Cortex

Coronal section



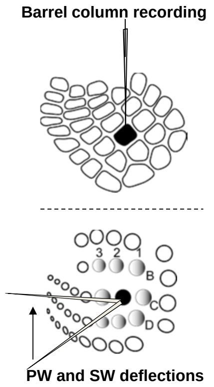
Tangential section

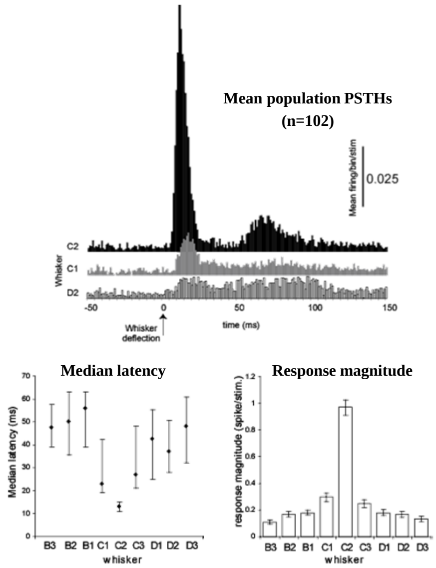


→Easy to study sensory processing at the neuronal level in vivo

A brief introduction to the whisker-to-barrel cortex system

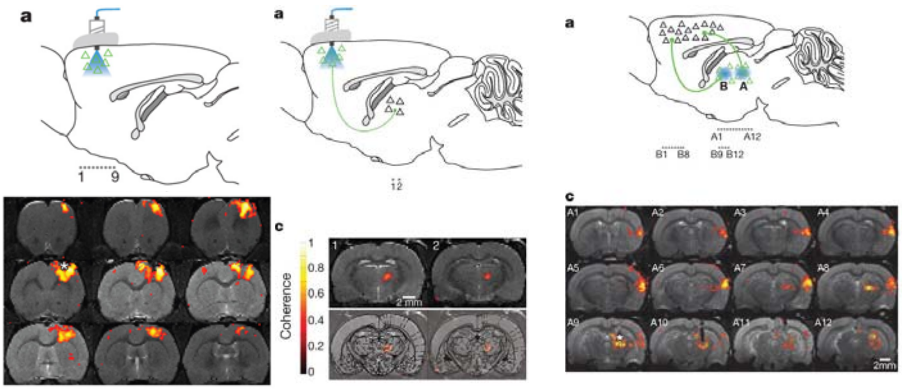
Example: layer IV unit responses





Tools

Simultaneous fMRI and optogenetics



Lee et al., Nature 2010

Tools

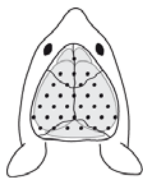
When you want to study large-scale neuronal networks, you especially want:

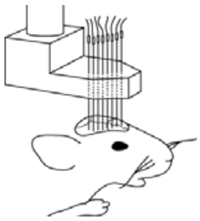
- Adequate spatial sampling
- High temporal resolution
- Minimal invasiveness: allows leaving the network intact and evaluating its function several times in the same individual animal (development? reversibility of plasticity? dynamic reorganization following brain lesion?)

→**Why not EEG mapping?**

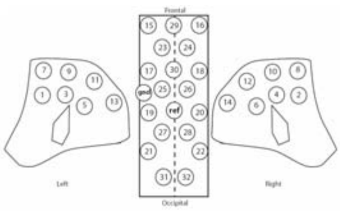
Mapping EEG in animals

32 CHANNEL MOUSE GRID
Epicranial





32 CHANNEL MACAQUE GRID
Scalp



Mapping EEG in animals

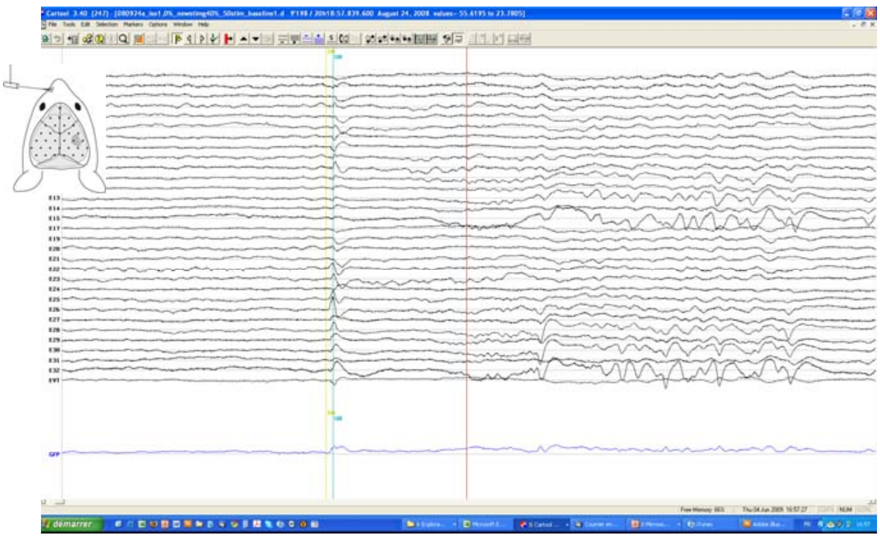
- •ANESTHETIZED
- •AWAKE, HEAD RESTRAINED
- •AWAKE, FREELY MOVING

Lab movie

Mapping EEG in animals

Epicranial somatosensory evoked potentials (SEP):

- Response of the brain to mechanical stimulation of the whiskers with 32e grid



Mapping EEG in animals

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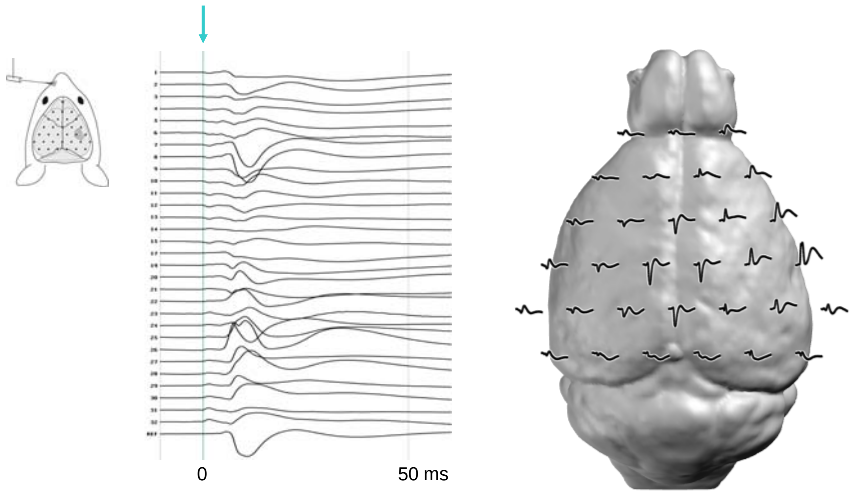

Mapping EEG in animals

Epicranial somatosensory evoked potentials (SEP):

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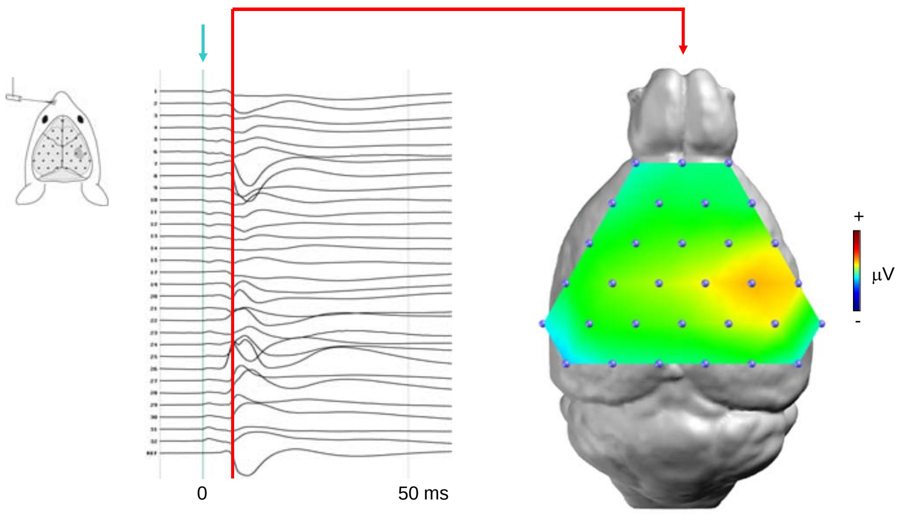
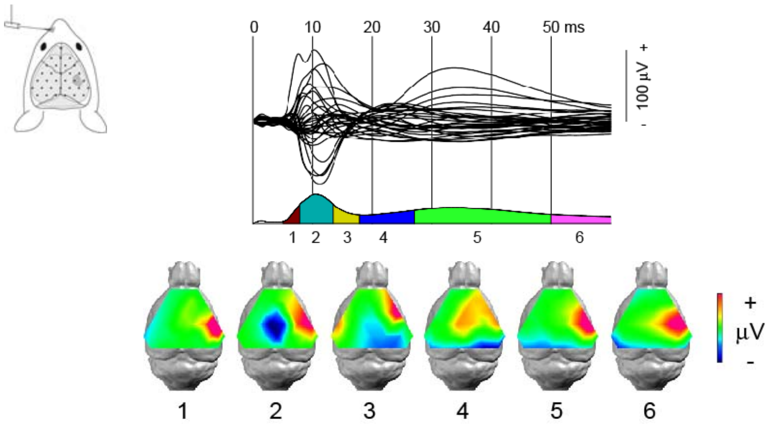


Mapping EEG in animals

The SEP component maps

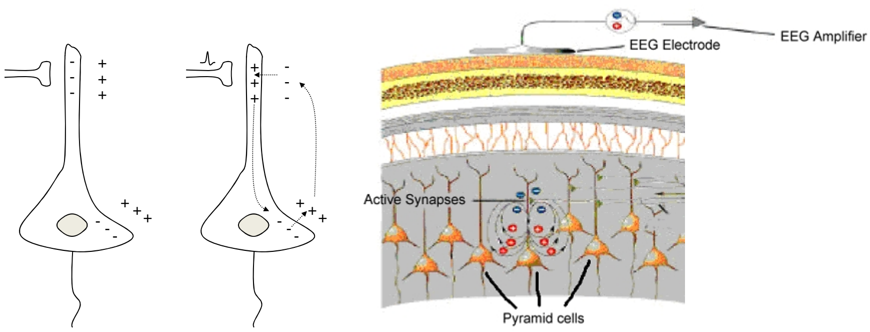


How do these surface maps relate to neuronal activity inside the cortex?

Mapping EEG in animals

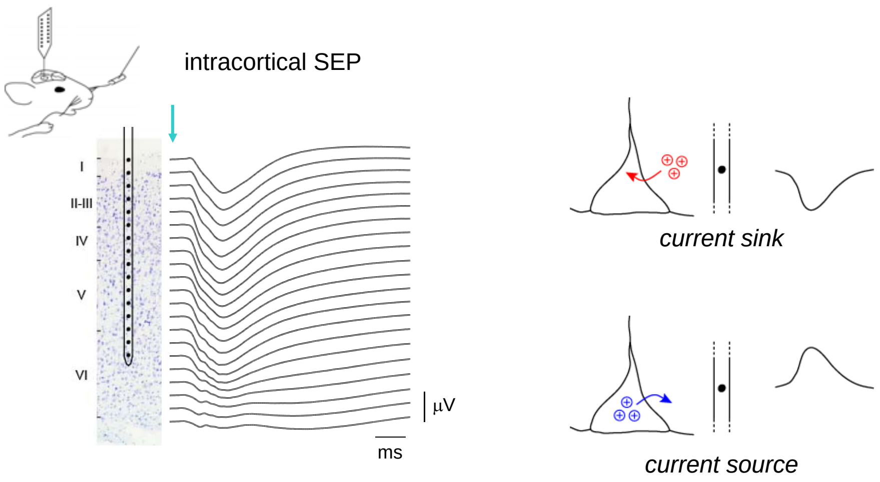
2. Intracortical sources of the epicranial maps?

Rappel: the lissencephalic cortex of rodents



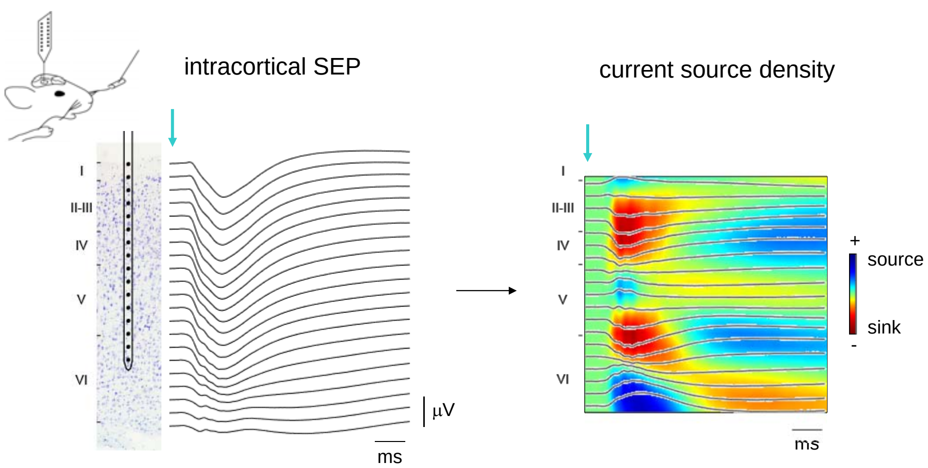
Mapping EEG in animals

Intracortical recordings



Mapping EEG in animals

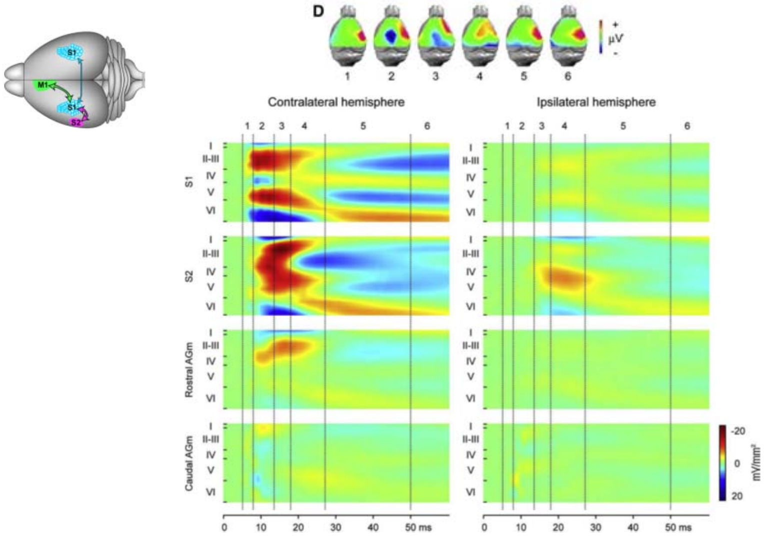
Current source density analysis (CSD)



Current sinks and sources indicate local neuronal activity

Mapping EEG in animals

2. Intracortical sources of the epicranial maps?



Mapping EEG in animals

→Epicranial ERP are reproducible in the same mice: allow for repeated measures (acute and chronic effects of lesions, recovery and treatment evaluation, plasticity)

What can be done with mouse epicranial ERP?

-Genetic manipulations

-Epilepsy models (heterotopic cortex)

-Functional recovery after brain lesions

-Functional maturation

-Functional plasticity

-Behavioral networks