Neurophysiology and neural engineering: from research to the development of functional biomarkers

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Fondazione I.R.C.C.S.
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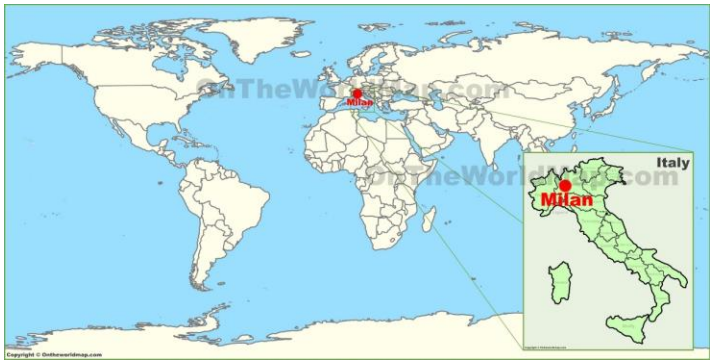
Sistema Socio Sanitario
Regione Lombardia

The Danyang-Kunshan Grand Bridge, China: longest bridge in the world 102 miles long. It runs between Shanghai and Nanjing in the Jiangsu province

Scientific breakthroughs often stem from ***bridging concepts across fields.***

Today we want to focus on the bridging concept across ***neurophysiology and engeneering***



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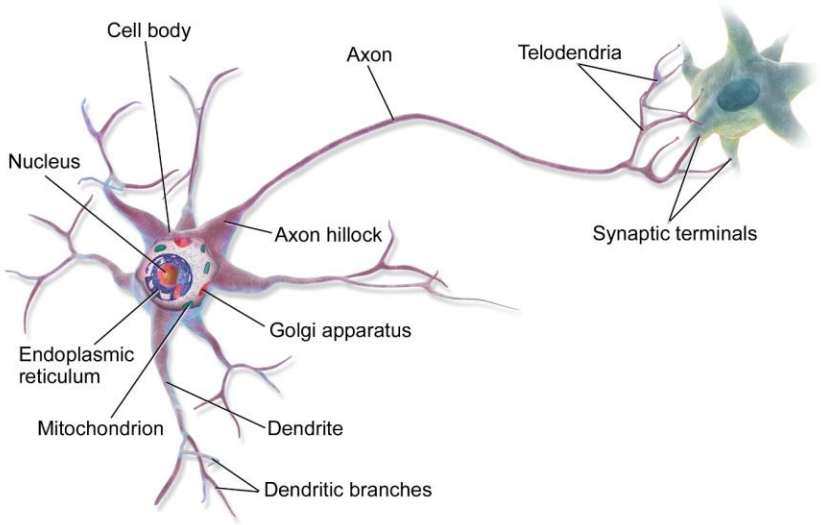
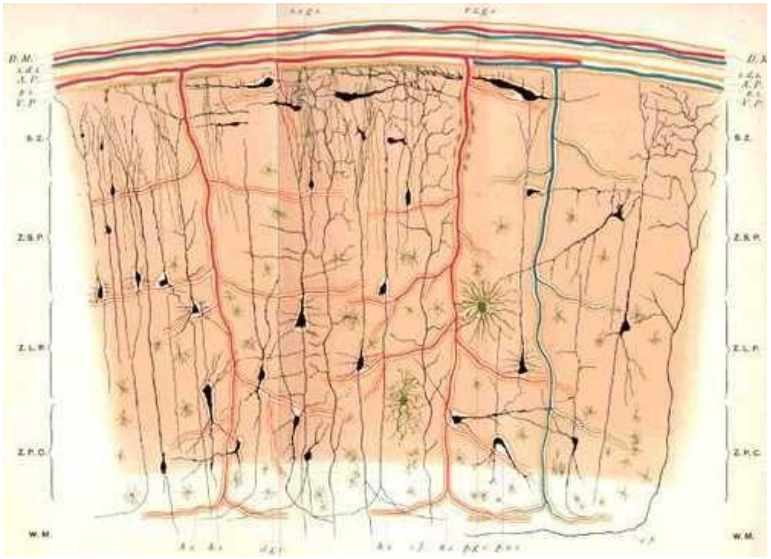


From a Single Neuron to Neural Ensembles

THE BASICS OF NEUROPHYSIOLOGY

Lebedev MA, Nicolelis MA.
Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation.
Physiol Rev. 2017 Apr;97(2):767-837. doi: 10.1152/physrev.00027.2016.

- **From a Single Neuron to Neural Ensembles**
- since the origins of modern neuroscience, researchers entertained physiological models of brain function in which populations of neurons performed the fundamental job of generating functions and behaviors.
-
- Camillo Golgi was the first to introduce the term **neural network**, as a way to describe the underlying **"functional module"** of brain operation proposed in his reticular theory (1875):
  - theory that nerve cells communicate with one another by means of an intricate network of anastomosing axonal branches contained in the neuropil intervening between cell bodies in the gray matter of the brain and spinal cord.



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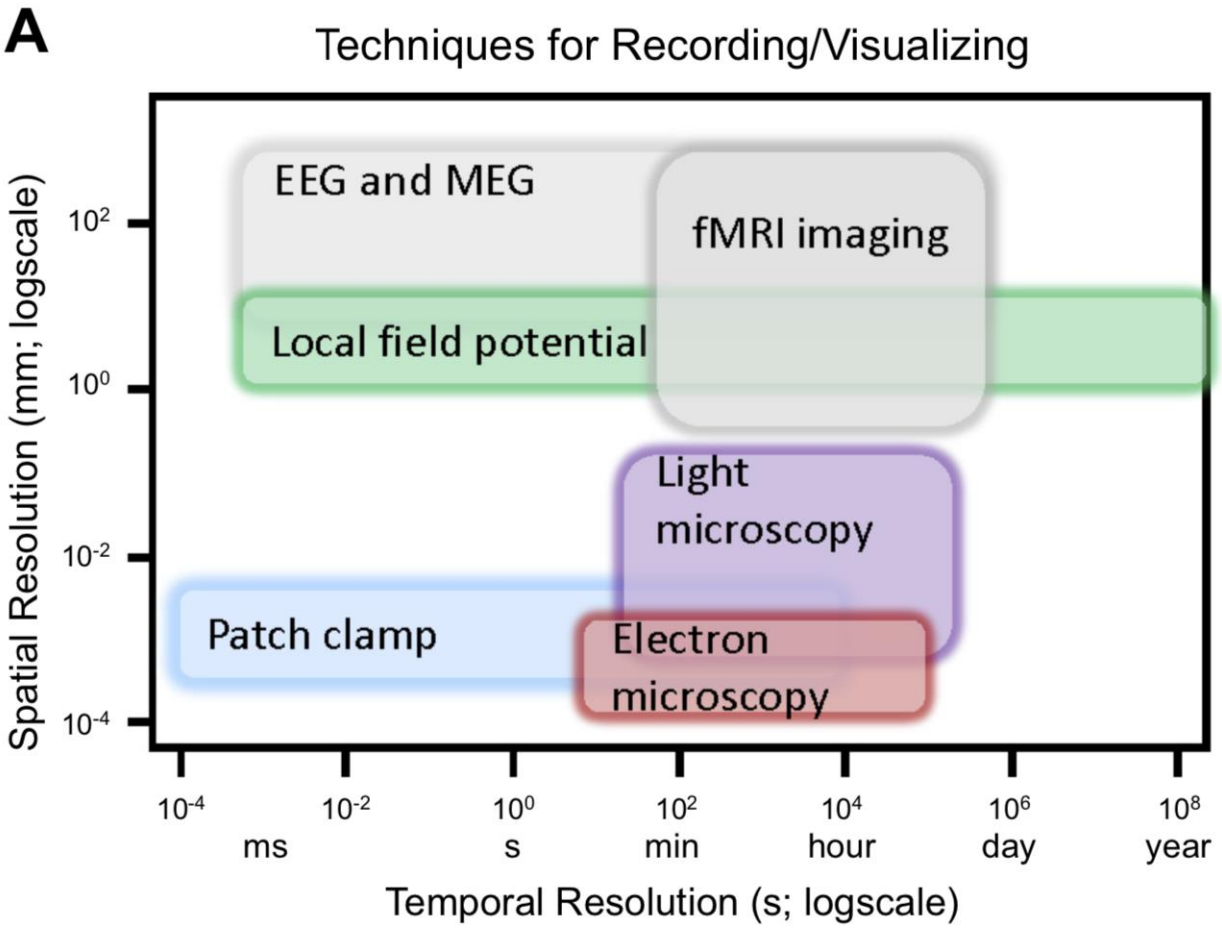

- During the century of intense work that followed the pioneering discoveries of Ramon y Cajal and Golgi, many other histological, electrophysiological, and imaging methods have been incorporated in the technical arsenal employed by neuroscientists to probe brain function at different levels of spatial and temporal resolution.

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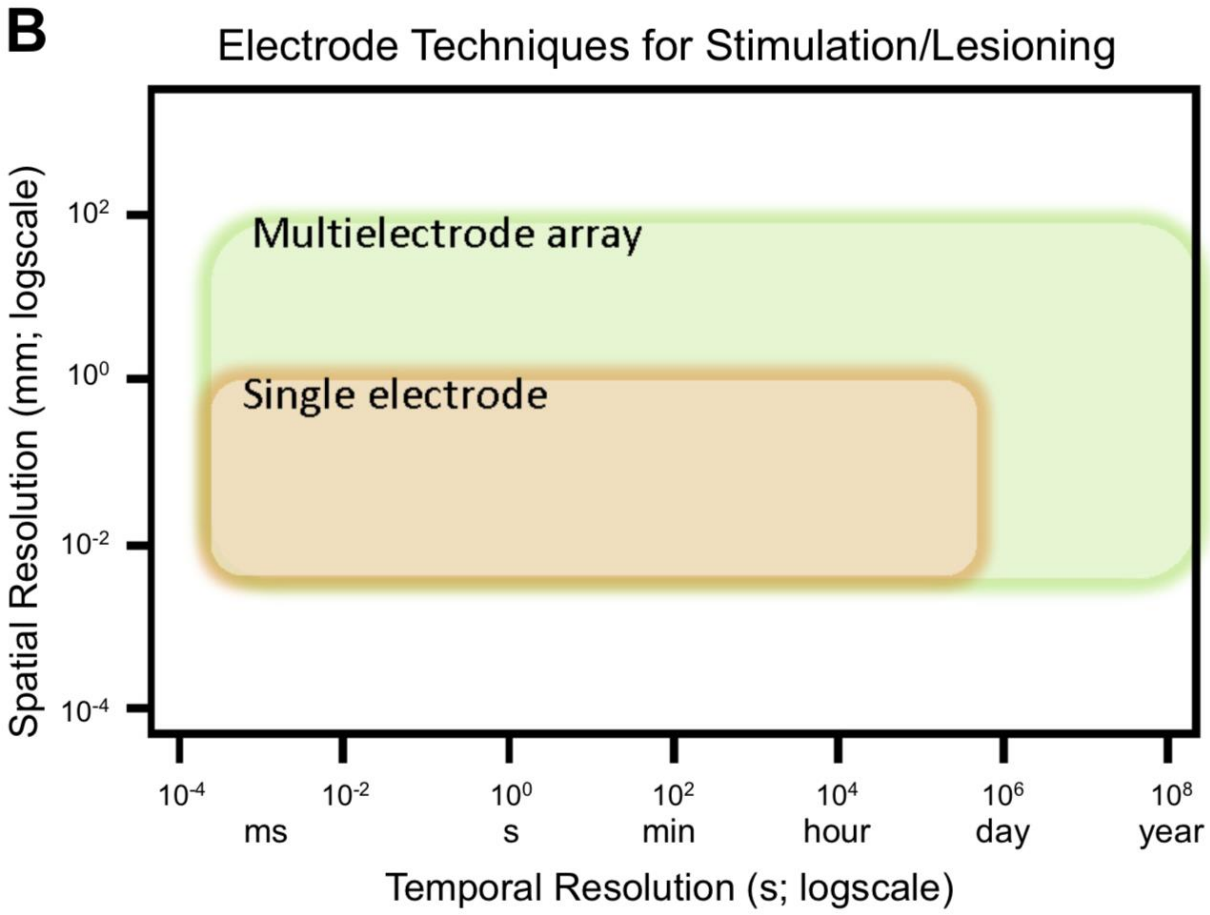

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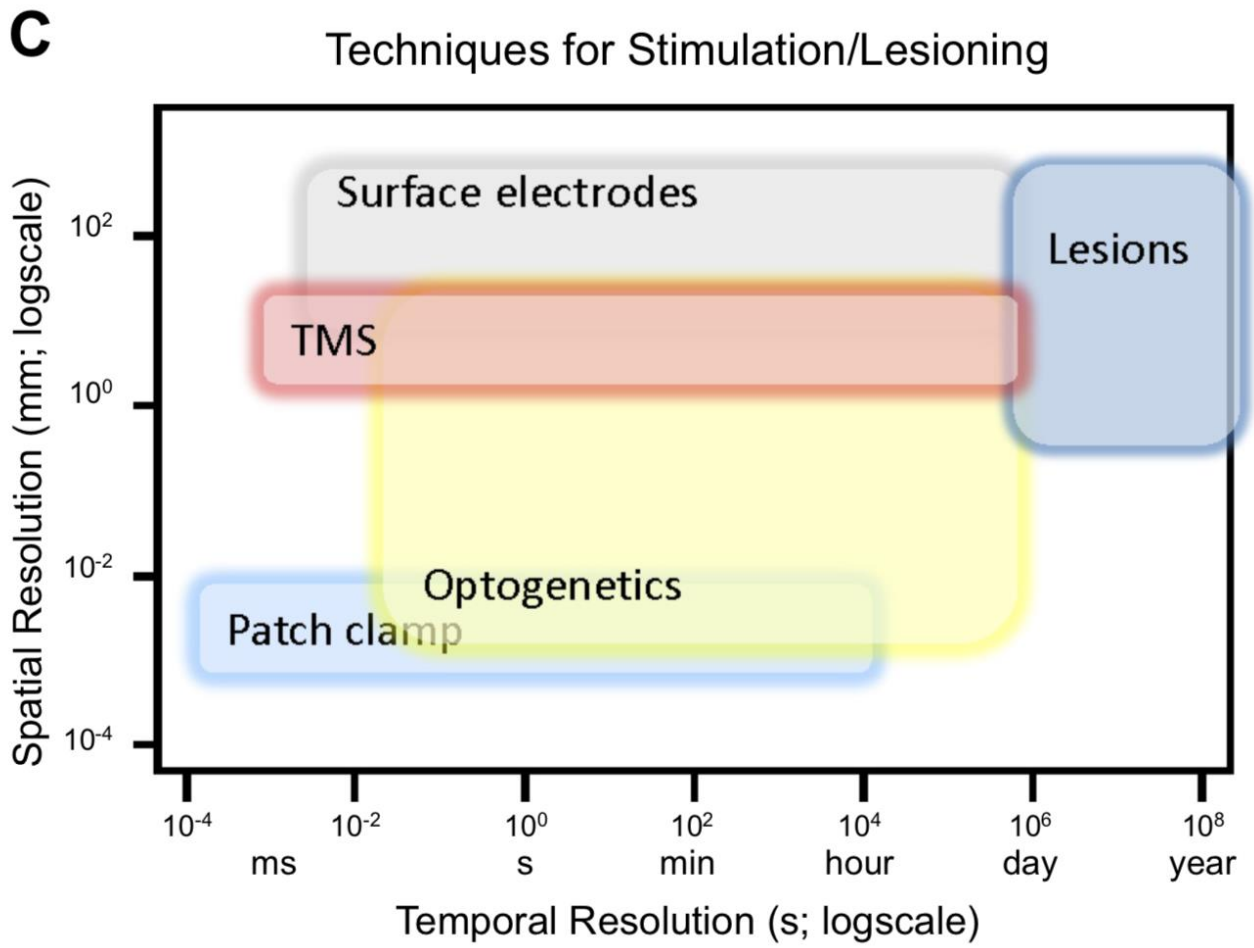

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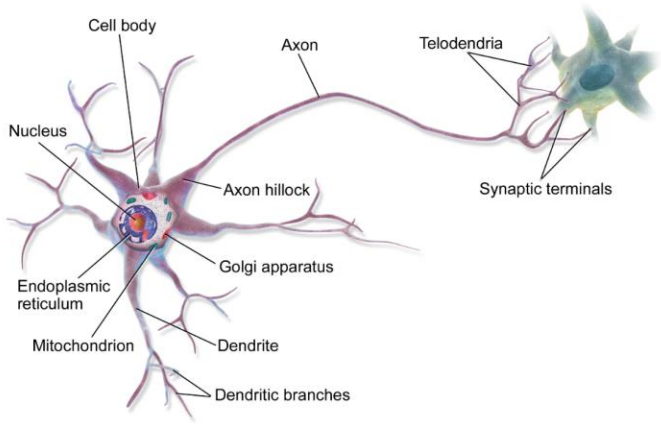
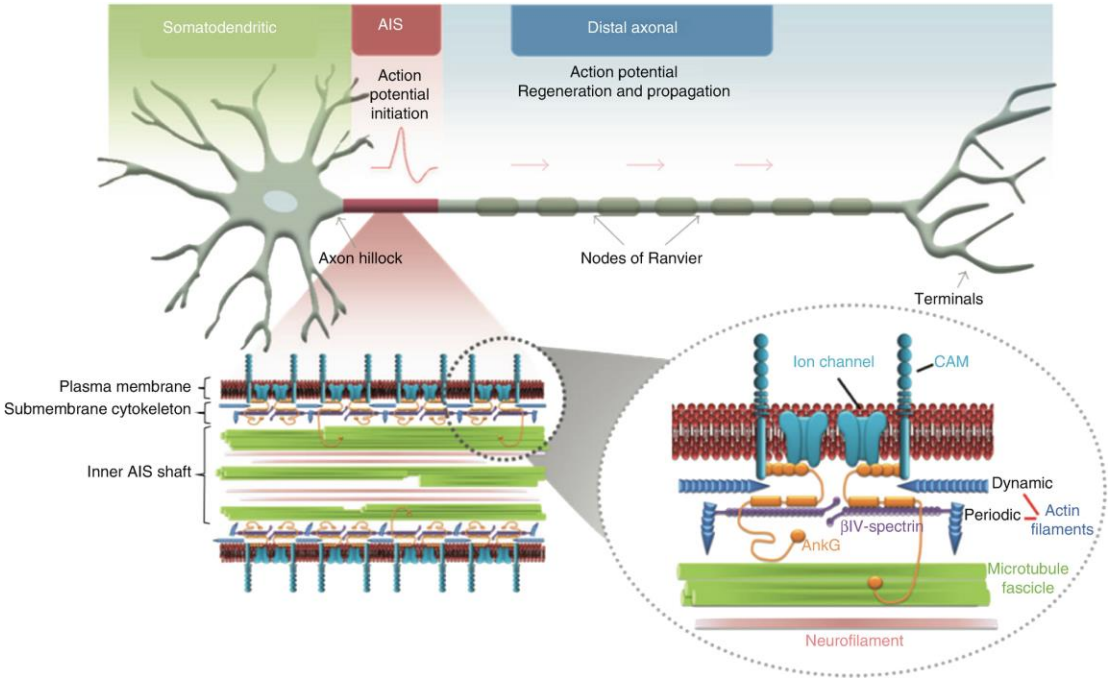
- in the early 19th century, theoreticians and neurophysiologists proposed that the **true functional unit of complex brains**, such as ours and those of other mammals, is represented, according to Hebb's own terms, by ". . . a diffuse structure comprising cells in the cortex and diencephalon, capable of acting briefly as a closed system, delivering facilitation to other such systems."

- neurophysiologists were primarily engaged in characterizing the **physiological properties of individual neurons**

- **a neural population view of brain function had to wait for four long decades before it could begin receiving serious experimental attention by neuro-physiologists (1980s, 1990s).**



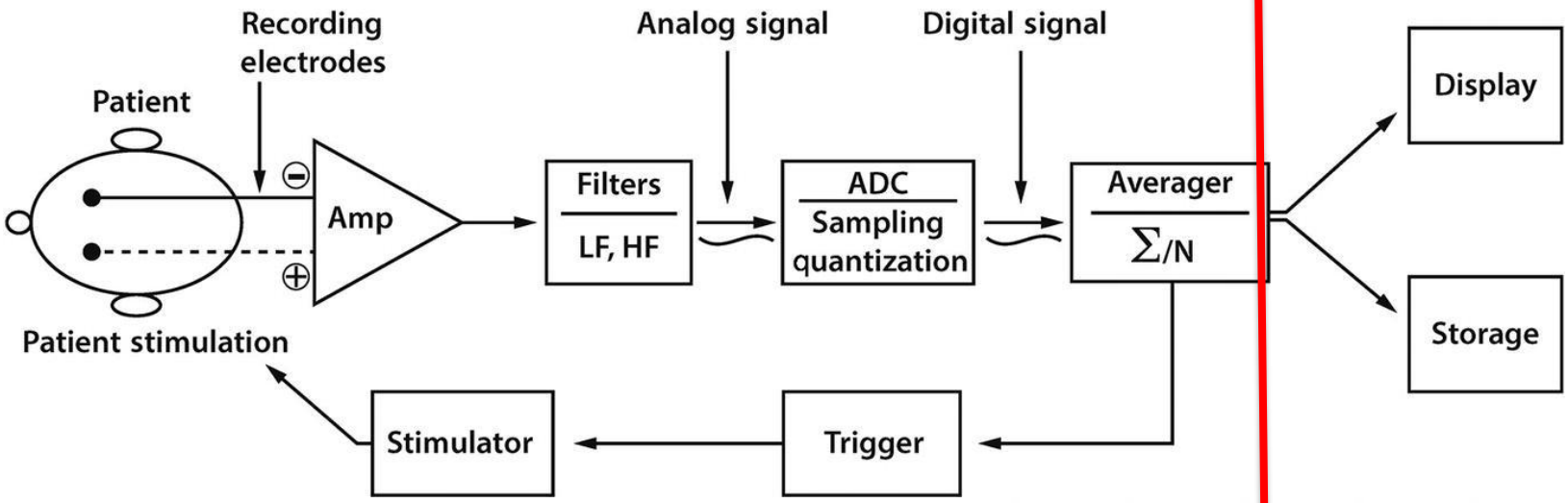
What is neurophysiology?



1. **Clinical neurophysiology** is a <u>medical</u> specialty that **studies the central and peripheral nervous systems up to the muscle fiber through the recording of bioelectrical activity, whether spontaneous or stimulated.**
2. It encompasses both research regarding the pathophysiology along with clinical methods used to diagnose diseases.

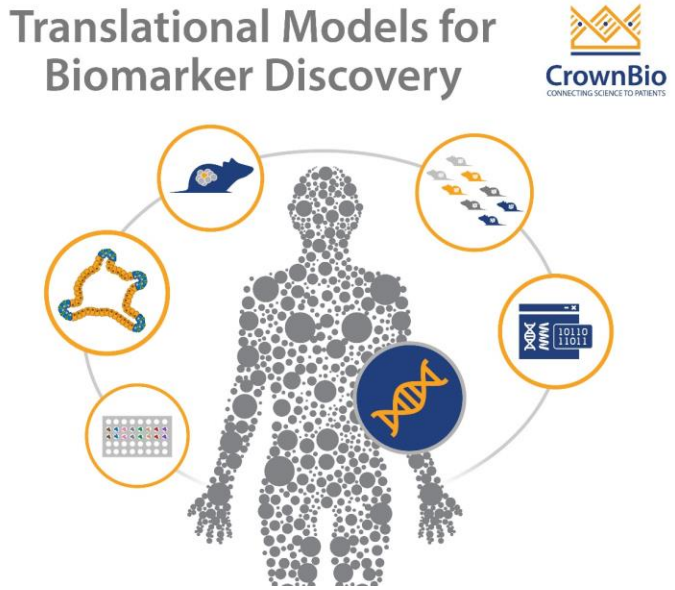
What is neurophysiology?

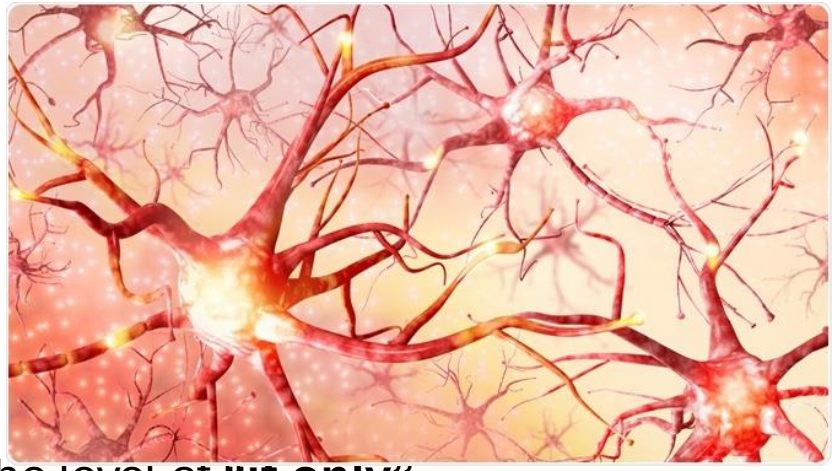
1. Tests are conducted and concerned with **measuring the electrical functions** of the brain, spinal cord, and nerves



BIOMARKER is “any substance, structure, or process that can be measured in the body or its products and **influence or predict the incidence of outcome or disease”**

In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a **biomarker** as **“a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”**





Biomarkers have recently ascended to the level of **"if only"**

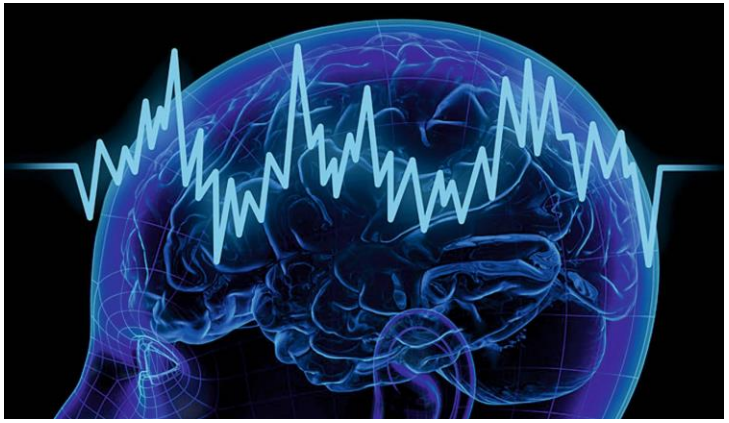
If only we had biomarkers for cognition, for language, for social skills, for memory …. and so on … we could understand the basic mechanisms of the main neurological functions, identify relevant disorders earlier, diagnose them more efficiently, and develop better treatments.

BIOMARKER

Levin AR, Ewen JB.

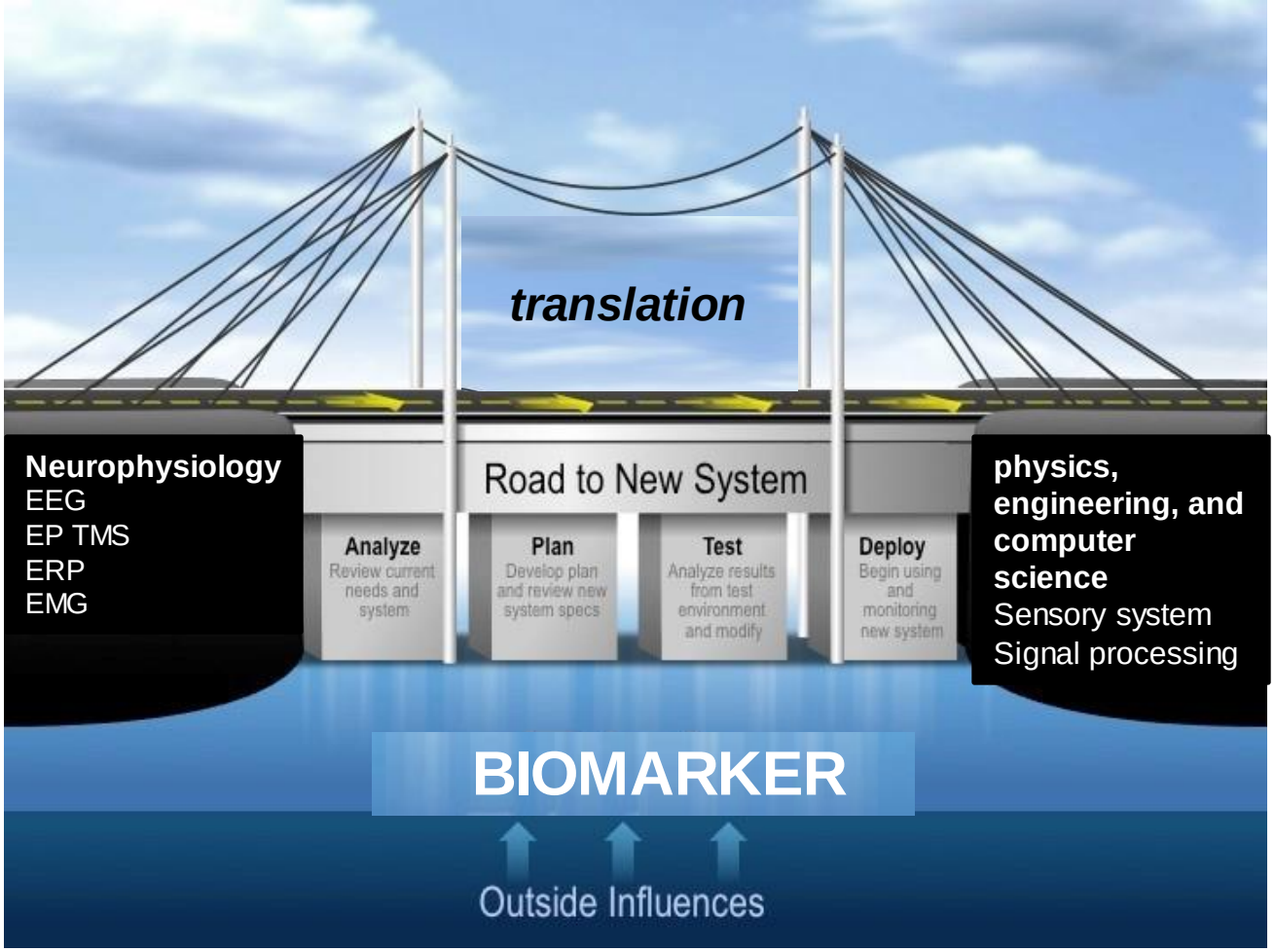
Clinical Cognitive Neurophysiology Bridges Through the Cloud: Towards Clinical Biomarkers of Cognitive Neurophysiology.

J Clin Neurophysiol. 2021 Aug 3.



*The challenge to building such bridges is **translation**:*

each field speaks its own language, and bridge-building requires a nuanced understanding of both languages and hence both fields.

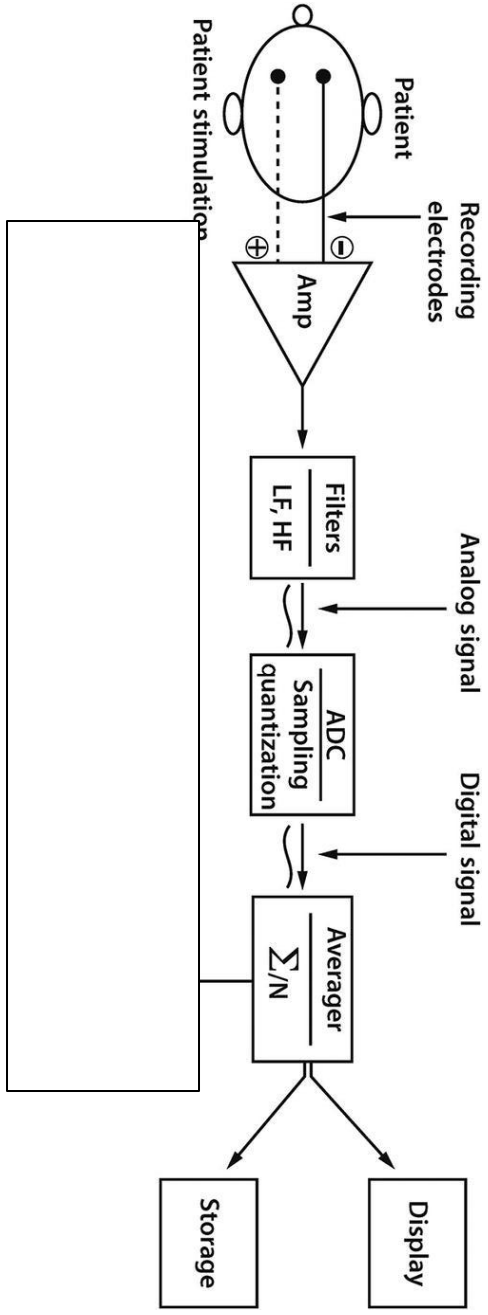


Yet translation itself has no one-way sign: It goes not only from bench to bedside but also from bedside to bench.

*It exists not only in the realm of researchers and clinicians but also in the **realm of humans and computers**, physics and psychology, genotype and phenotype, mind and brain, understanding and lack thereof.*

Which are the main neurophysiology tools?

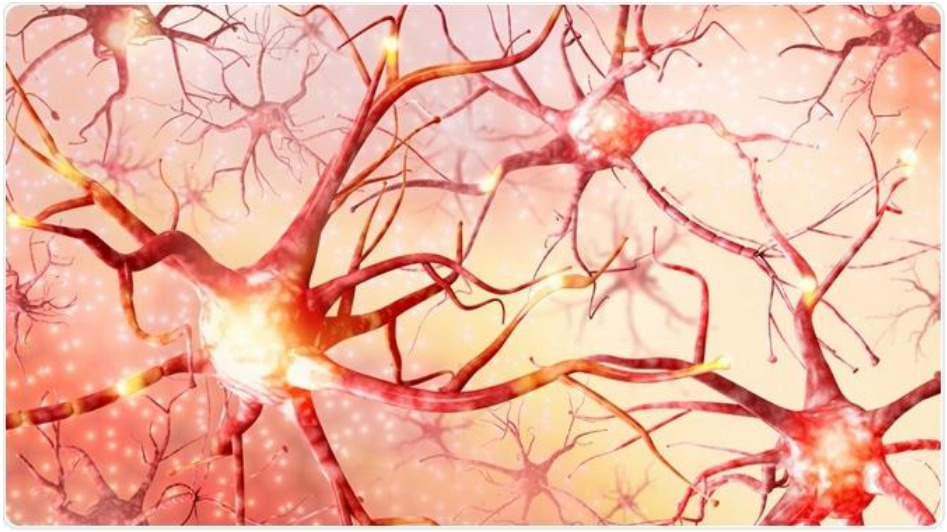
1. **Electro/Magnetoencephalography:** Diagnostic test of spontaneous thalamocortical rhythms (brain waves).
2. **Evoked potentials:** Diagnostic test evaluating specific tracts of the central and peripheral nervous system. These record the electrical responses of the brain and spinal cord to the stimulation of the senses.
3. **Event related potentials** Diagnostic test evaluating specific cognitive paradigms identified as event = an isolated occurrence of a presented stimulus, or a participant response recorded during a task.
4. **Electromyography and nerve conduction studies:** These diagnostic tests of the peripheral nervous system, especially useful in evaluating diseases of the muscles, nerves, and nerve roots.



Neurophysiology (**depending on the exact technique and analysis chosen**) can reflect mechanism, and **mechanism** is what we ultimately aim to identify and treat.

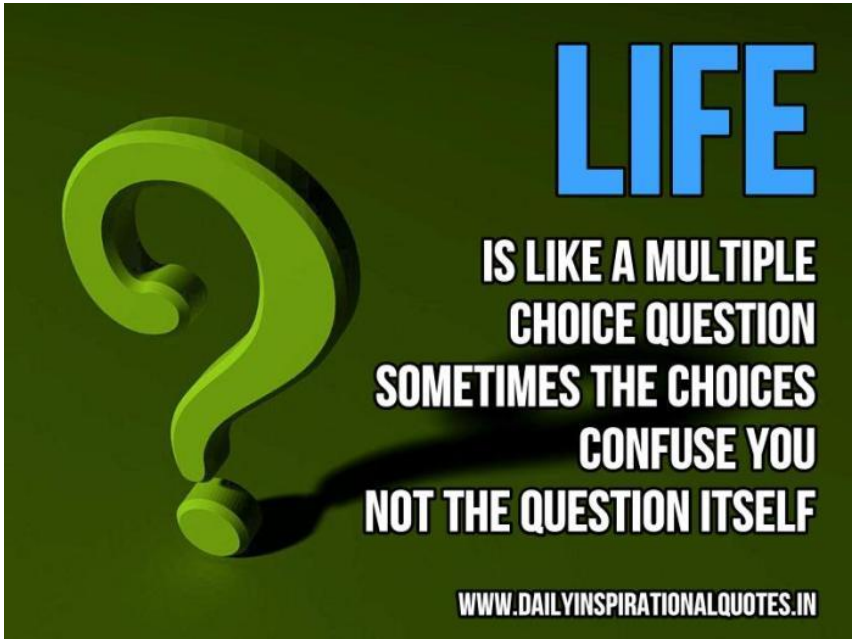
Perhaps, then what we need is not only biomarkers that mold to our current definitions of disease but rather **biomarkers that help us remold the definitions of diseases themselves**.

BIOMARKER

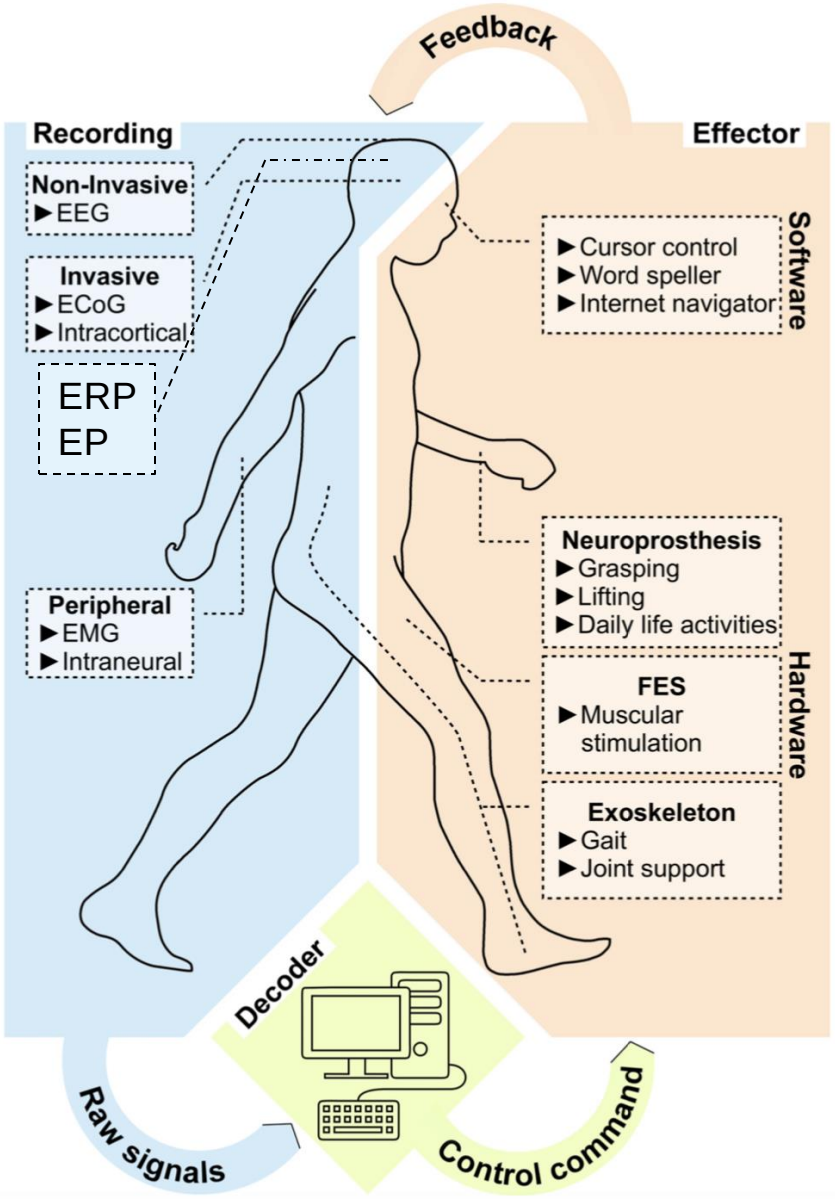


Signal processing

- Signal processing can help us maximize the potential of these methods.
- Within each method, **the choice of signal processing technique (from a myriad of possibilities) is not simply a technical decision**
- However, **the utility of signal processing depends on the clarity of its links to clinical disorders and their underlying mechanisms**.



Emergence of BMIs

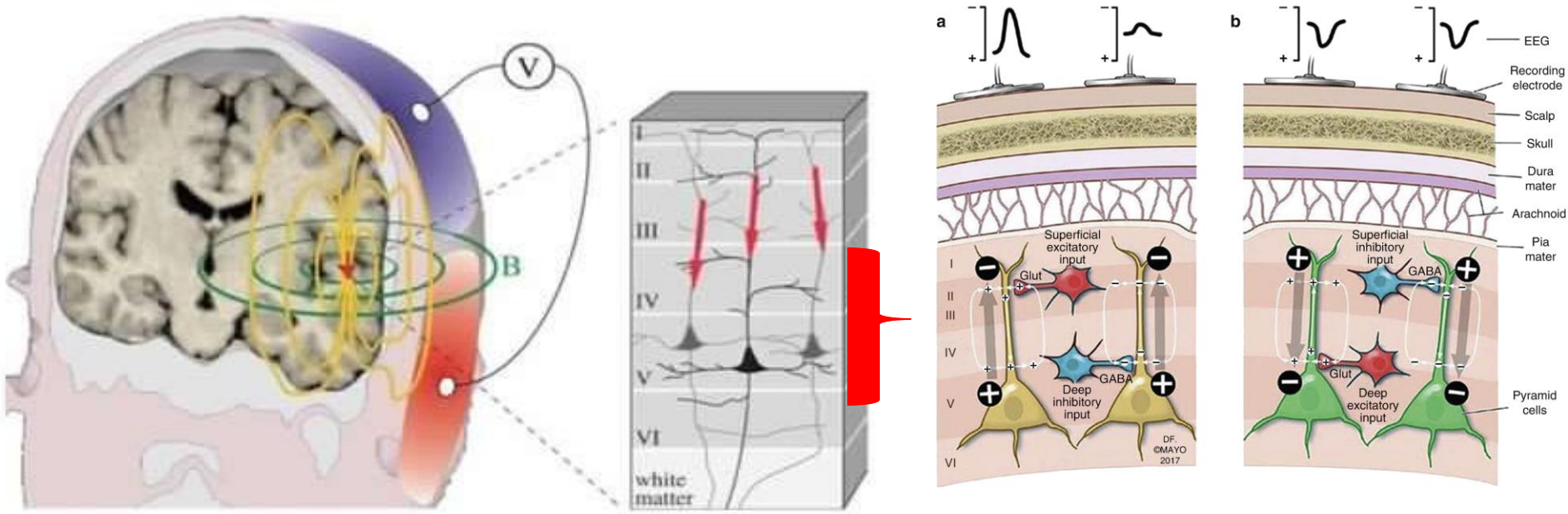


Pisotta I et al.

Hand-in-hand advances in biomedical engineering and sensorimotor restoration.

J Neurosci Methods. 2015 May 15;246:22-9. doi: 10.1016/j.jneumeth.2015.03.003.

- "Brain–Machine Interfaces" (BMIs). Despite the vast variety of BMI designs and applications, most of them follow a similar principle.
- Biological signals carrying neural information such as
  - EEG
  - ECoG
  - ERP
  - EP
  - EMG
  - Sensory nerve and compound motor action potentials
- are recorded either cortically or peripherally and are fed into a computer, which uses a decoding algorithm to translate the brain signals into computational commands.

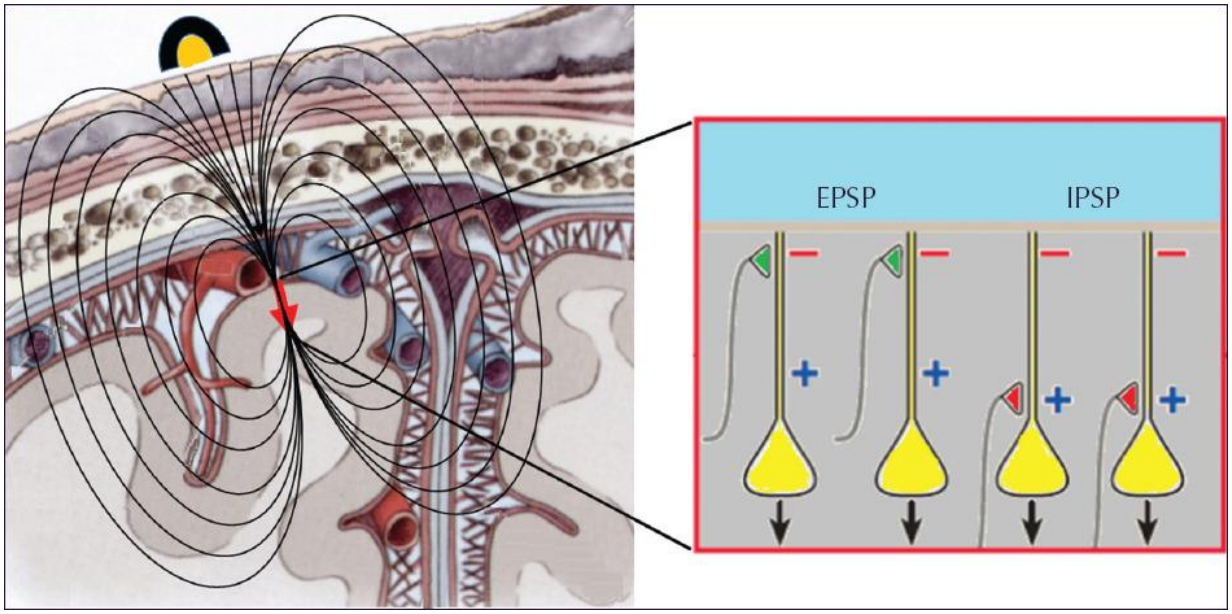


EEG signals are generated by the transmembrane ion currents in the pyramidal neurons (cortical layers IV-V).

EEG records currents flowing in the extracellular space.

ELECTROENCEPHALOGRAPHY

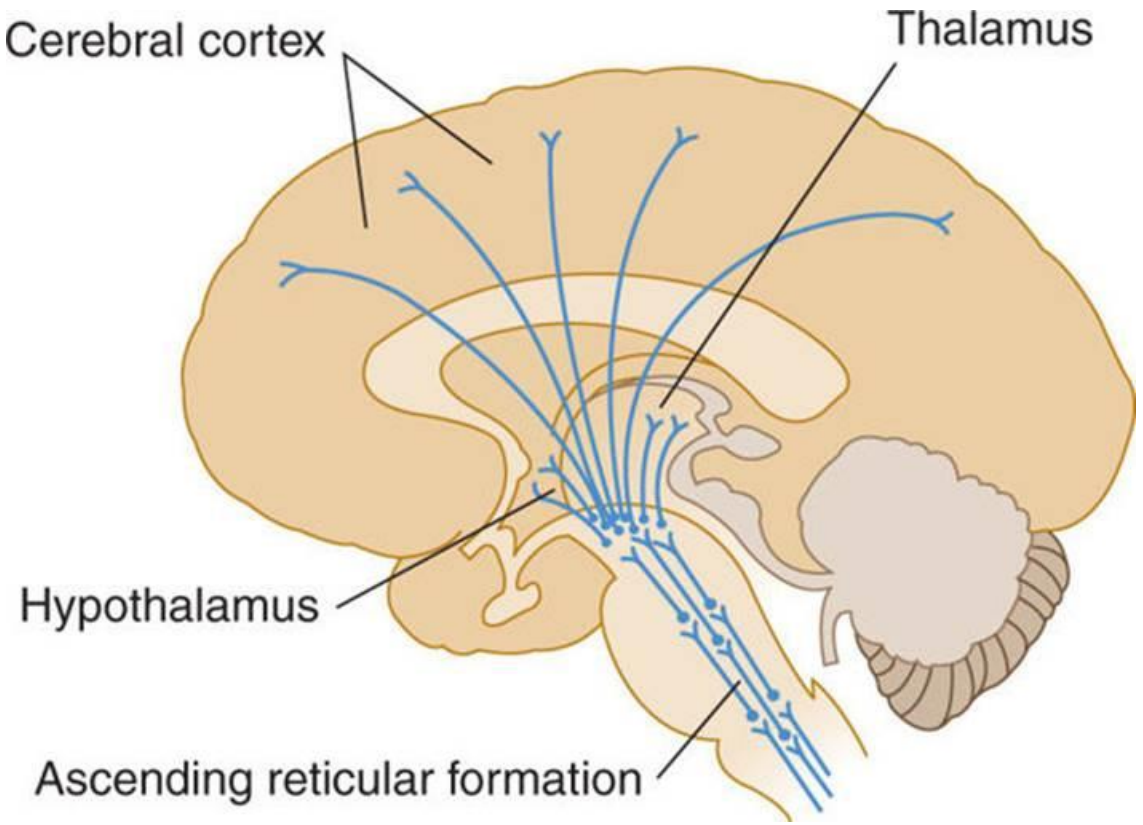
EEG

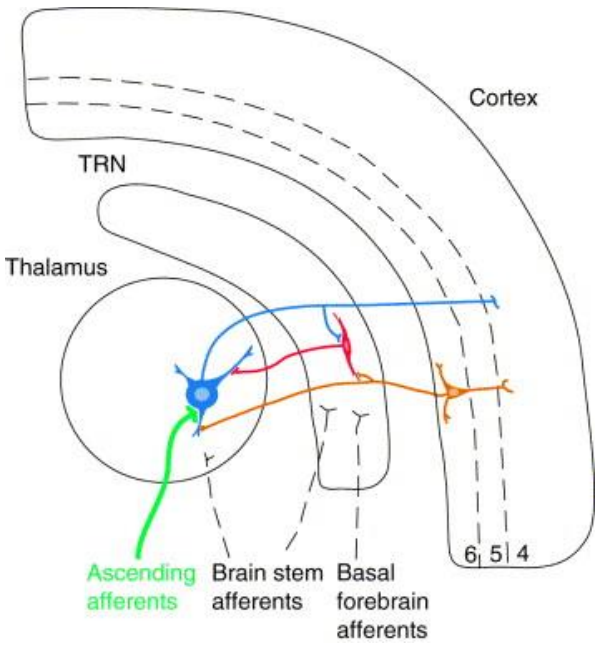


These local field potentials are produced by these extracellular neuronal generators, **excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs),** and flow through the **brain tissue and skull to the recording electrodes on the scalp**

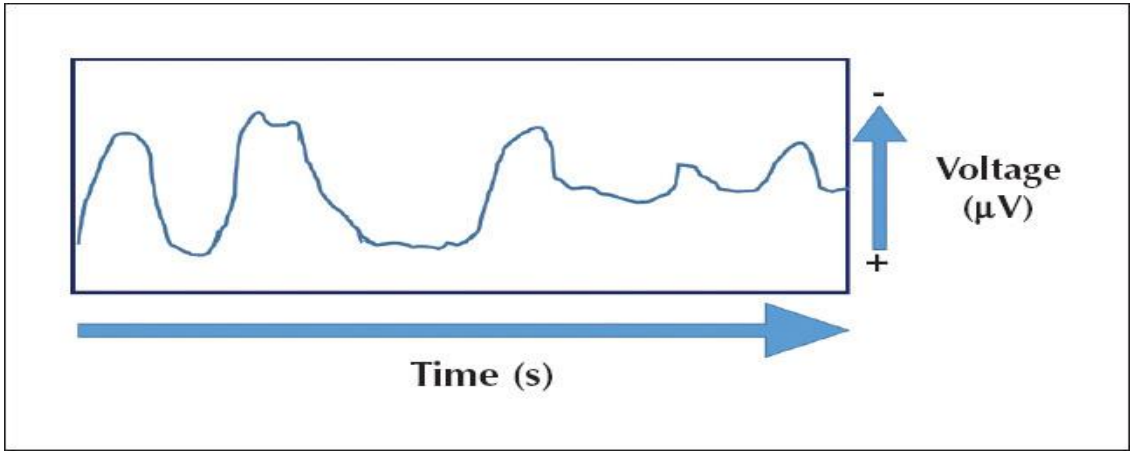
Activation of the dendrites or somas **can be synchronized to produce electrical potentials between the proximal and distal regions of a dendrite which produces an electrical dipole**.

EEG





The main inputs to the large neural mass generating resting state EEG (rsEEG) rhythms may include afferents **from thalamocortical and ascending reticular neurons.**



Babiloni C et al.

INTERNATIONAL FEDERATION OF CLINICAL NEUROPHYSIOLOGY (IFCN) - EEG RESEARCH WORKGROUP:

RECOMMENDATIONS ON FREQUENCY AND TOPOGRAPHIC ANALYSIS OF RESTING STATE EEG RHYTHMS. PART 1: APPLICATIONS IN CLINICAL RESEARCH STUDIES.

CLIN NEUROPHYSIOL. 2020 JAN;131(1):285-307. DOI: 10.1016/J.CLINPH.2019.06.234..

In clinical research, resting state electroencephalographic (rsEEG) rhythms are often recorded from the patient's scalp during short (i.e., minutes) eyes-closed and -open conditions.
mainly focuses on abnormalities in the frequency and topographical features of rsEEG rhythms to unveil neural dysfunctions in the regulation of quiet wakefulness

Frequency analysis aims to decompose the basic frequency bands forming the recorded EEG signals and relate them to brain general arousal and vigilance.

Babiloni C et al.

International Federation of Clinical Neurophysiology (IFCN) - EEG research workgroup: Recommendations on frequency and topographic analysis of resting state EEG rhythms. Part 1: Applications in clinical research studies.

Clin Neurophysiol. 2020 Jan;131(1):285-307. doi: 10.1016/j.clinph.2019.06.234..

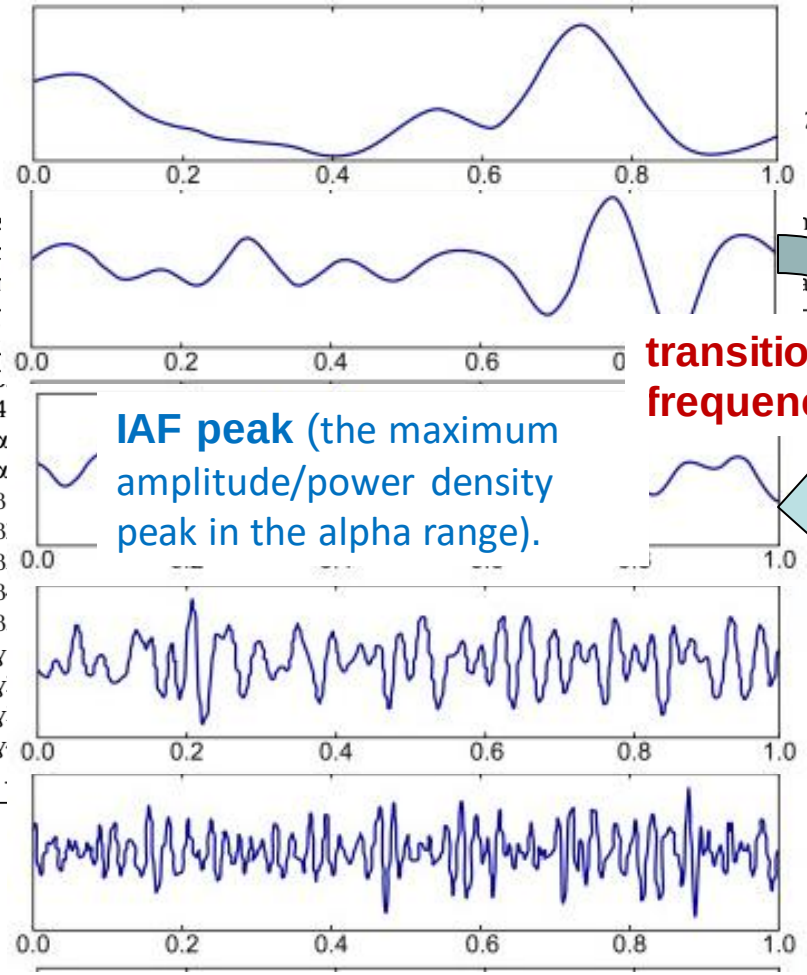
Table 1

Subdivision of the scalp-recorded resting ... nternational Federation of Clinical Neurophysiology (IFCN; Nuwer et al. 1999), International Pharmac... commonly used by clinical electroencephalographers (Kane et al., 2017). Note that the Guidelin... and ...

Frequency (Hz)		IFCN-2017 Glossary
Delta		0.1–<4
Theta		4–<8
Alpha		8–13
Beta		14–30
Gamma		>30–80

For components >70 Hz, the term high frequency oscillations (HFOs) is used.

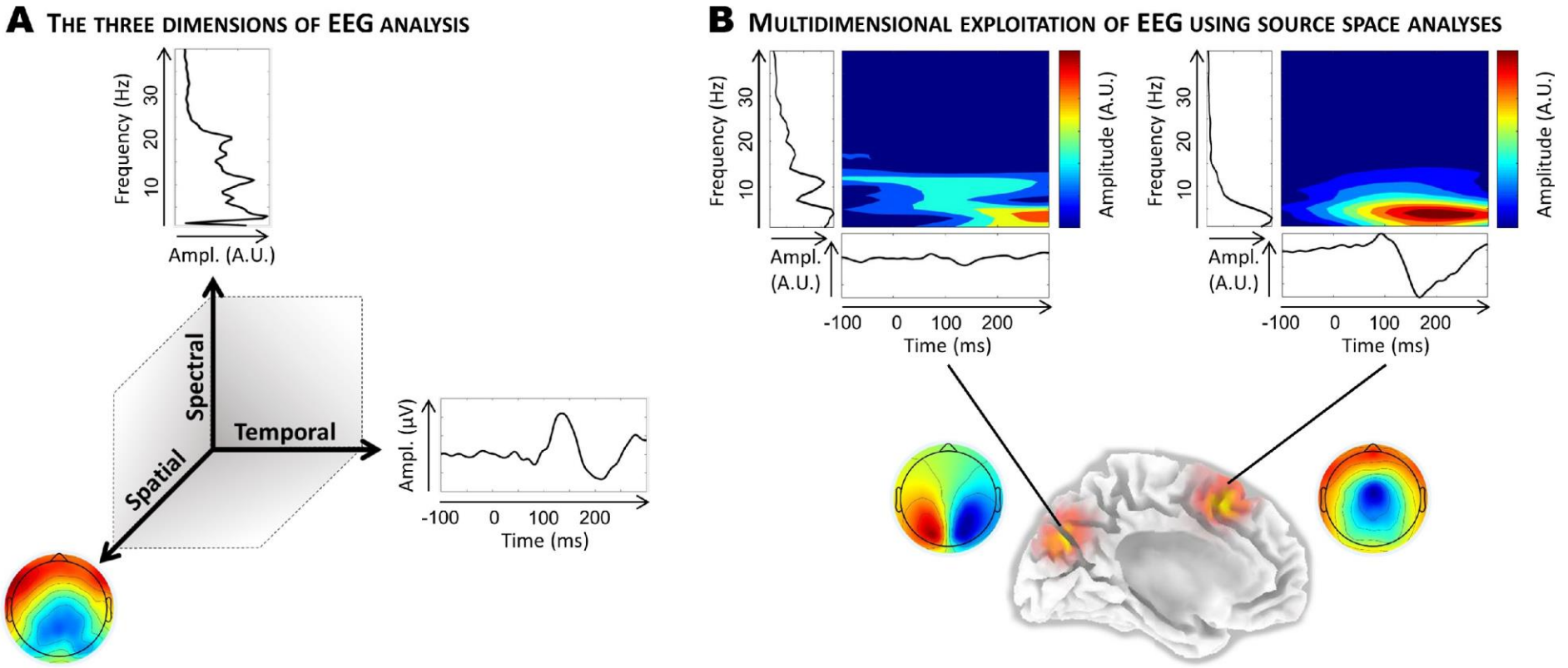
Empirical subdivision.



Garance M. Meyer et al

Electrophysiological underpinnings of reward processing: are we exploiting the full potential of EEG?

NeuroImage, 2021, https://doi.org/10.1016/j.neuroimage.2021.118478.



The discriminative power of EEG relies on the exploitation of three analytical dimensions. The EEG signal recorded at the sensors is a time-series, which can be resolved along different analytical dimensions.

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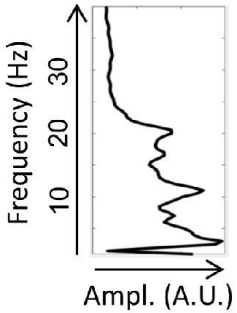
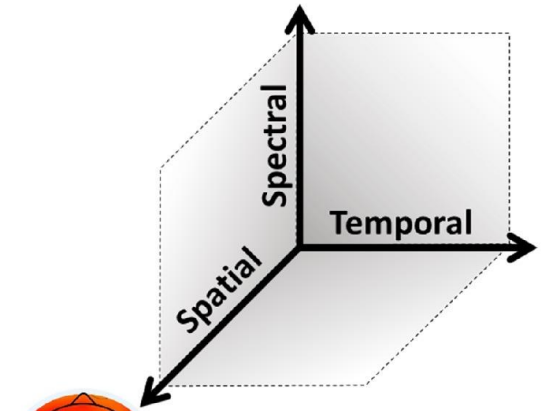
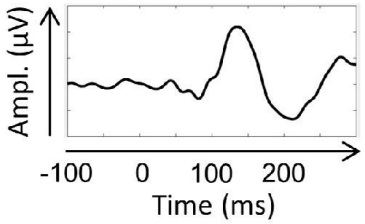
A THE THREE DIMENSIONS OF EEG ANALYSIS

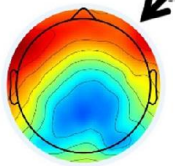


as well as its underlying **oscillatory rhythmicity** (***spectral* dimension**). Considering the spectral content of the signal **can help to distinguish brain processes or functions**, because these may occur in different frequency bands.





The **high temporal resolution** of the recorded time-series allows one to examine how it unfolds with time (***temporal* dimension**)



The third dimension, ***spatial***, is reconstructed from the known position of the different sensors on the scalp.

Yet, a range of solutions is available to take full advantage of the spatial information hidden in the scalp signal, including **source separation and source localization methods.**

Garance M. Meyer et al

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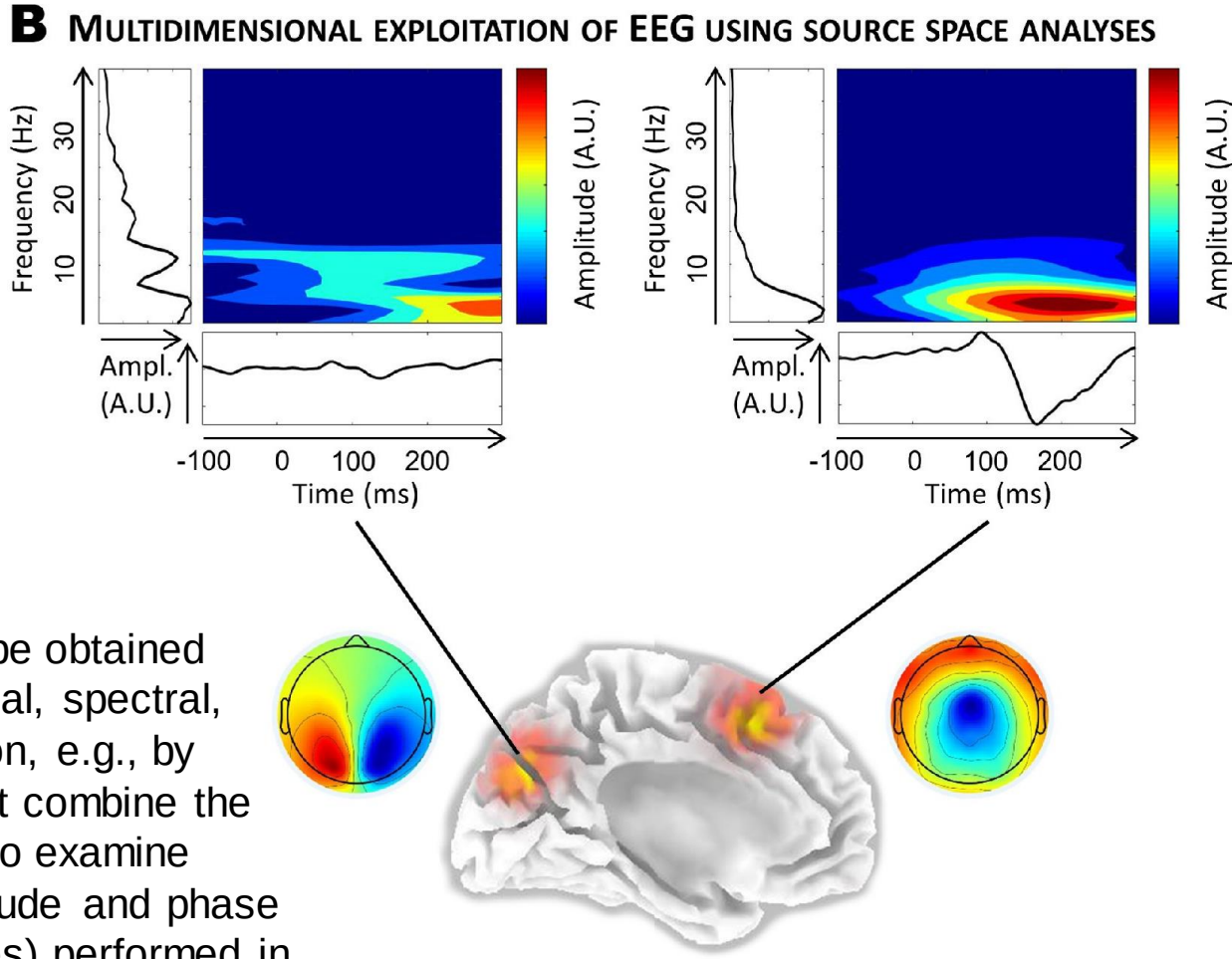
NeuroImage, 2021, https://doi.org/10.1016/j.neuroimage.2021.118478.



Optimal discriminative power may be obtained when the three dimensions -temporal, spectral, spatial- are leveraged in combination, e.g., by using time-frequency analyses (that combine the temporal and spectral dimensions to examine event-related changes in the amplitude and phase of oscillations at specific frequencies) performed in the source space.

Lefebvre A, et al.

Alpha Waves as a Neuromarker of Autism Spectrum Disorder: The Challenge of Reproducibility and Heterogeneity.

Front Neurosci. 2018 Oct 1;12:662. doi: 10.3389/fnins.2018.00662.

- Autism spectrum disorders (ASD), which aect 1–2% of the general population, are characterized by impairments in social communication associated with repetitive, stereotyped, or ritualistic behaviors
- ASD is a highly heterogeneous condition since patients with ASD display a variable clinical presentation ranging from mild to severe impairments and are frequently associated with comorbid disorders
- Besides, genetic and environmental causes and risk factors appear highly heterogeneous in ASD too.
- alpha oscillations may modulate the transfer of information in the thalamo-cortical and cortico-cortical networks but also facilitate and gate the external sensory perception
- in typically developing (TD) participants reported developmental trajectory of alpha waves with the frequency increasing and the power decreasing until around 10 years old.

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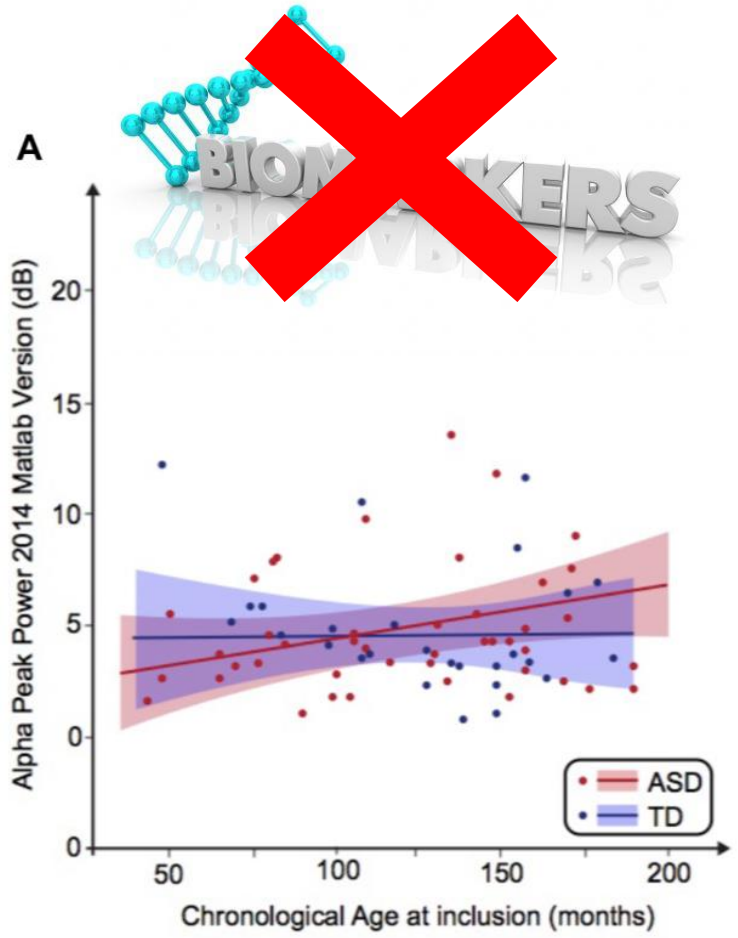
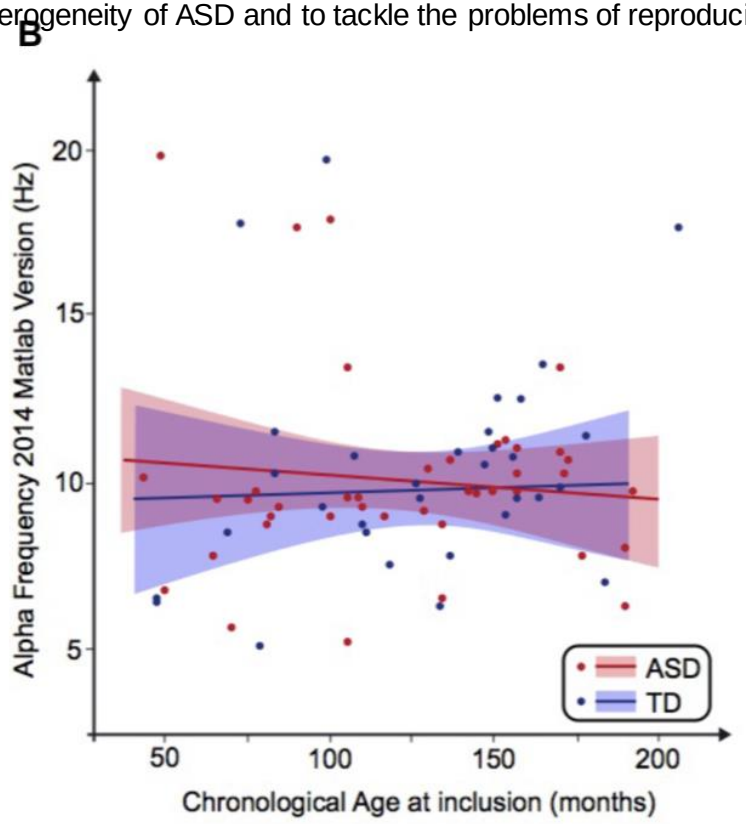


Our study **did not find evidence for abnormal alpha wave profiles in ASD.** We propose, however, an analysis pipeline to perform standardized and automatized EEG analyses on large cohorts. These should help the community to address the challenge of clinical heterogeneity of ASD and to tackle the problems of reproducibility.



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Clin Neurophysiol. 2020 Jan;131(1):285-307. doi: 10.1016/j.clinph.2019.06.234.

Frequency analysis

"synchronization" features ideally probe spatially local cortical neural oscillatory activity.

reflect the **temporal dynamics of the synchronized activity in local cortical neural populations**, showing a collective oscillatory behavior at a macroscopic spatial scale of a few centimeters

synchronized post-synaptic potentials showing an oscillatory behavior with phase, amplitude, and frequency features.

"connectivity" refers to an interareal interdependence of such activity as phase or amplitude.

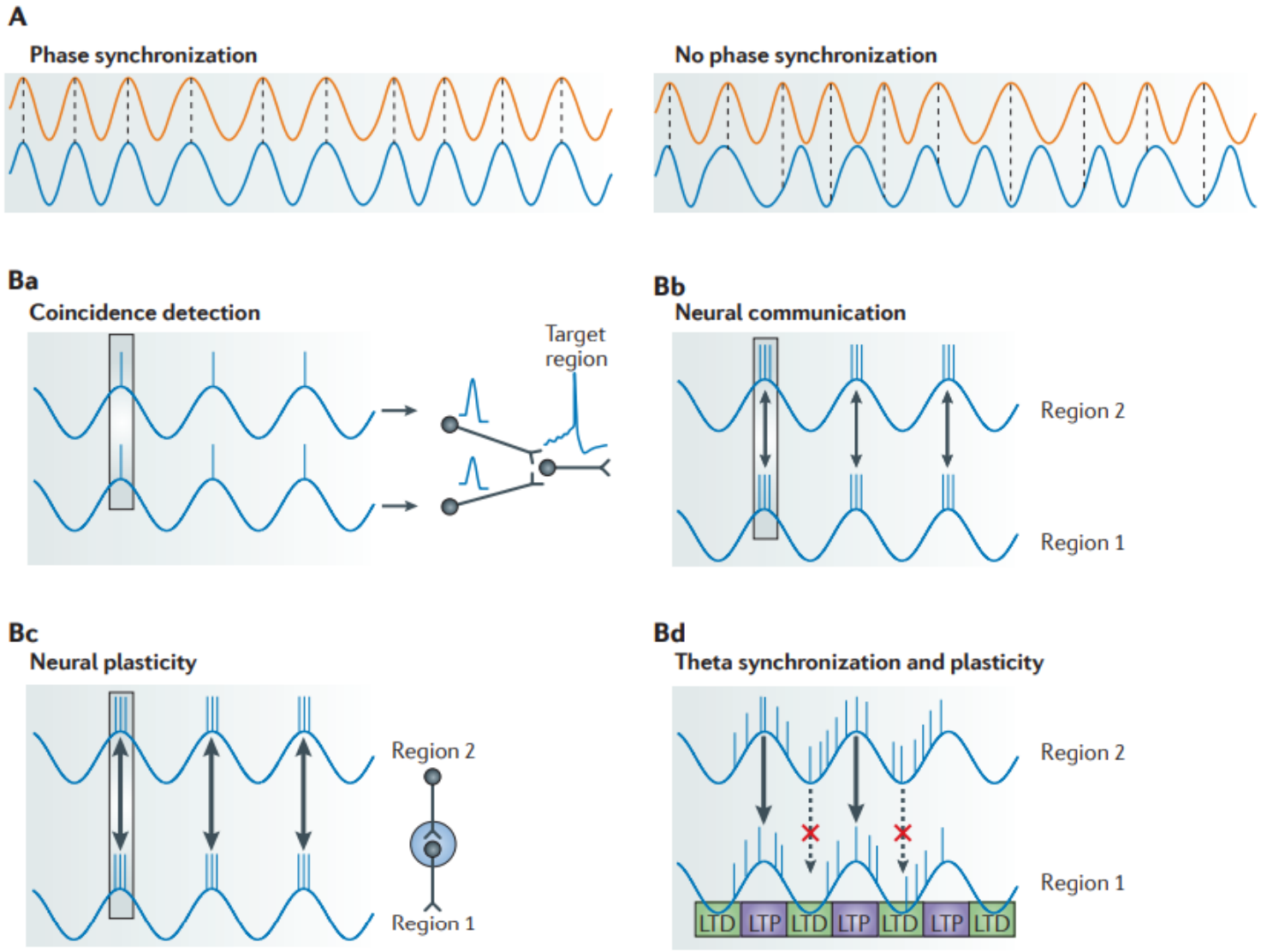
a key concept to describe the statistical interdependence between neural masses within and among brain networks, between two or more neural nodes of a brain network

EEG and magnetoencephalography (MEG) techniques have an ideal millisecond time resolution

Fell J, Axmacher N.

The role of phase synchronization in memory processes.

Nat Rev Neurosci. 2011 Feb;12(2):105-18. doi: 10.1038/nrn2979.



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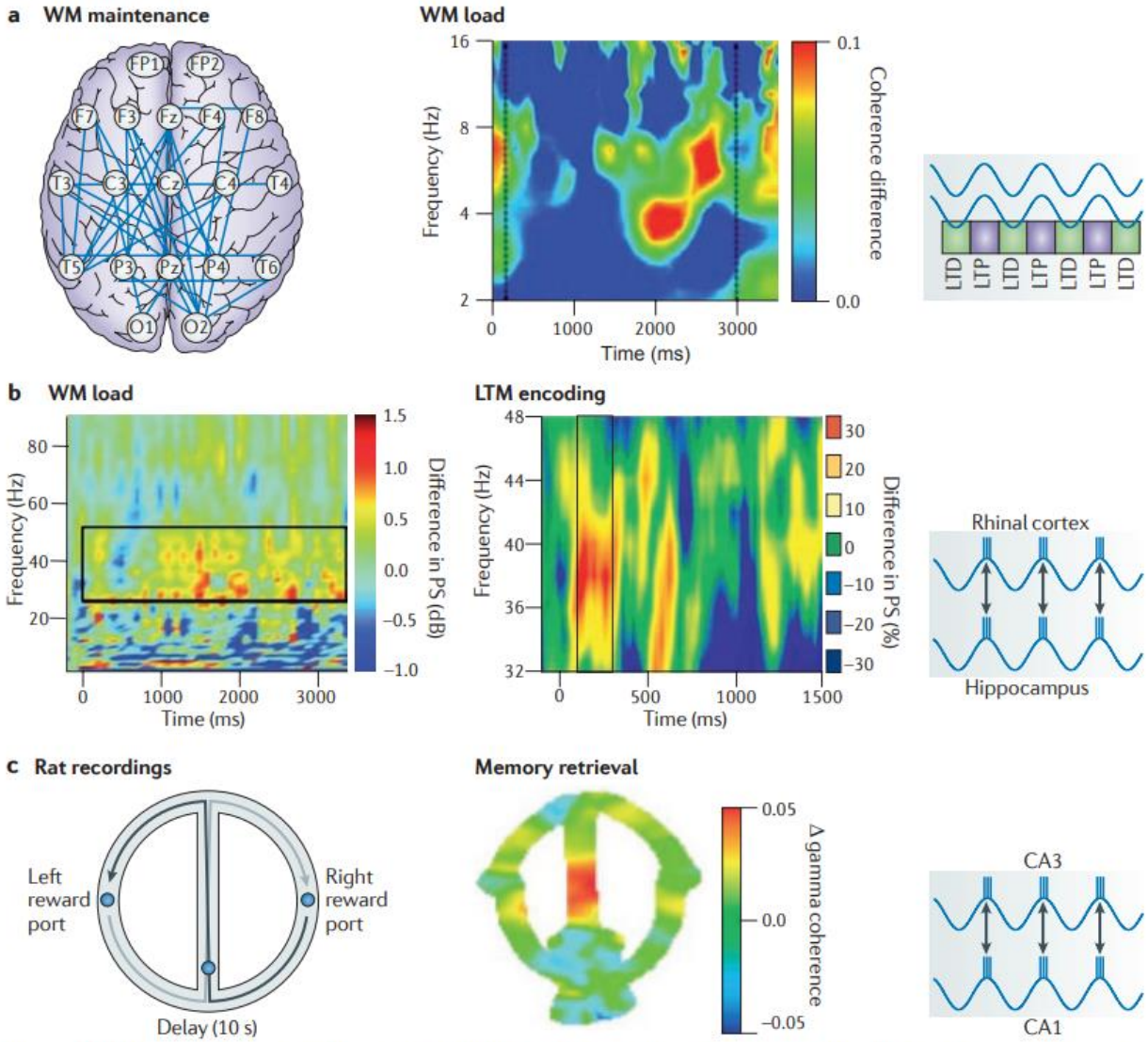


Rossini PM, et al.

Neurophysiological Hallmarks of Neurodegenerative Cognitive Decline: The Study of Brain Connectivity as A Biomarker of Early Dementia.

J Pers Med. 2020 Apr 30;10(2):34. doi: 10.3390/jpm10020034.

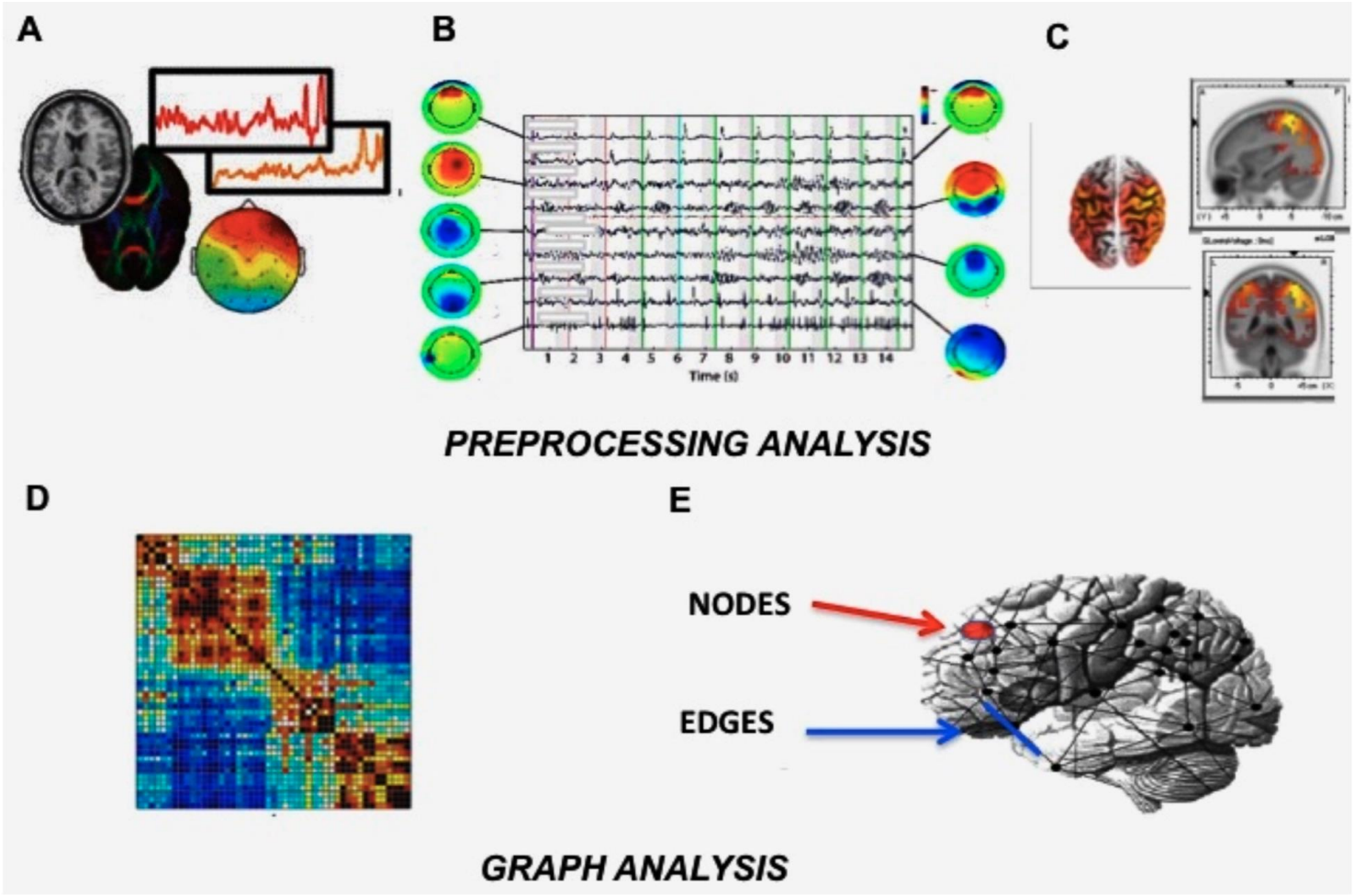
- The human brain can be represented as an anatomic-functional matrix (consisting of billions of neurons and their synaptic connections) of network structures at micro–meso–macro-scale levels.
- Within this matrix of networks, **nodes (neuronal assemblies) and links (connecting fibers) cooperate via dynamic aggregations or transient locking/unlocking** of their orchestrated firing oscillations

- **Phase synchronization (or coherence),** phase-locking, entrainment, cross-frequency (or power synchrony), and phase reset of EEG rhythms measure the degrees of functional and effective connectivity between different brain areas.

Rossini PM, et al.

Neurophysiological Hallmarks of Neurodegenerative Cognitive Decline: The Study of Brain Connectivity as A Biomarker of Early Dementia.

J Pers Med. 2020 Apr 30;10(2):34. doi: 10.3390/jpm10020034.



Rossini PM, et al.

Neurophysiological Hallmarks of Neurodegenerative Cognitive Decline: The Study of Brain Connectivity as A Biomarker of Early Dementia.

J Pers Med. 2020 Apr 30;10(2):34. doi: 10.3390/jpm10020034.

- by the application of artificial intelligence (i.e., learning-machine), **neurophysiological techniques represent valid biomarkers** for screening campaigns of the MCI population, mild cognitive impairment (MCI) an intermediate stage between dementia and normal brain aging.

Ewen JB.

Conceptual, regulatory and strategic imperatives in the early days of EEG-based biomarker validation for neurodevelopmental disabilities.

Front Integr Neurosci 2019;13:45.

- The question at the current time is whether new EEG approaches will have the reproducibility (reliability) and discriminatory ability (validity) to serve a useful purpose in trials for nervous system functions.

- **What to Measure**
- The EEG is a complex signal, and there is no end to the mathematical techniques that can be applied to it

TABLE 2 | FDA Biomarker Contexts of Use (COU).

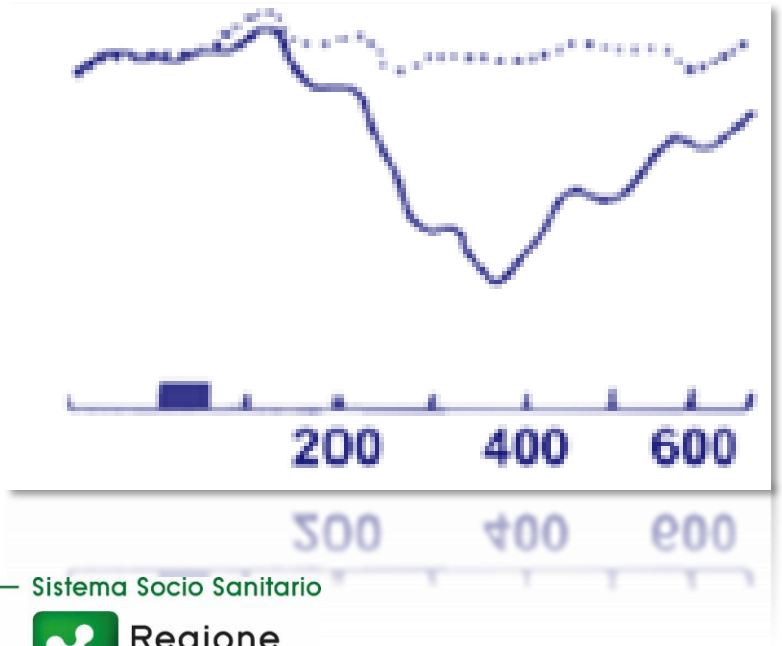
COU	Description
Diagnostic	Concurrent biomarker that specifies whether or not an individual has a disorder/pathologic process
Monitoring	Concurrent biomarker that concurrently reflects a change in a disease or in a side effect
Safety	Concurrent biomarker that reflects presence/degree of toxicity from an exposure
Response	Prospective biomarker that reflects a response to an intervention; when highly well validated, may serve as a *surrogate endpoint* in a clinical trial
Prognostic	Prospective biomarker that predicts clinical course
Predictive	Prospective biomarker that predicts response to an intervention
Susceptibility/Risk	Prospective biomarker that reflects potential for developing or disease sensitivity to a negative outcome following an exposure

Ewen JB.
Conceptual, regulatory and strategic imperatives in the early days of EEG-based biomarker validation for neurodevelopmental disabilities.
Front Integr Neurosci 2019;13:45.

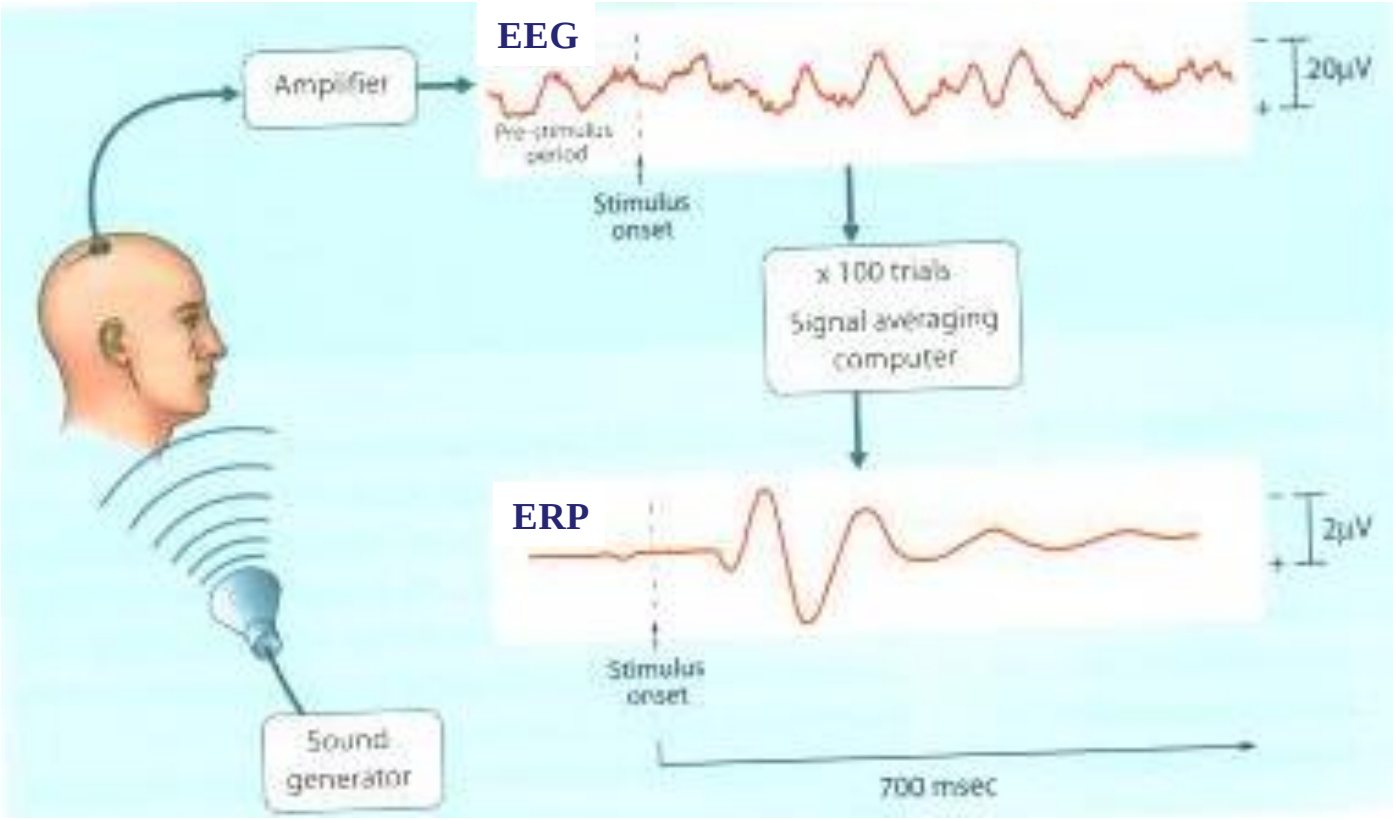
- However, to answer the question as to whether **EEG** as a technology holds promise as a basis for biomarkers, one need only consider that **EEG has been the technology par excellence (apart from the neurological exam and psychometric testing) for measuring CNS physiology in the clinical setting for the better part of a century.**

- An infinite number of parameters can be derived **from the EEG signal in both task-locked and spontaneous recordings:** time-domain evoked- and ERPs, spectral power, entropy, cross-frequency coupling, and a wide range of different connectivity metrics (Cohen, 2014).

Event-related potentials : mismatch negativity and P300



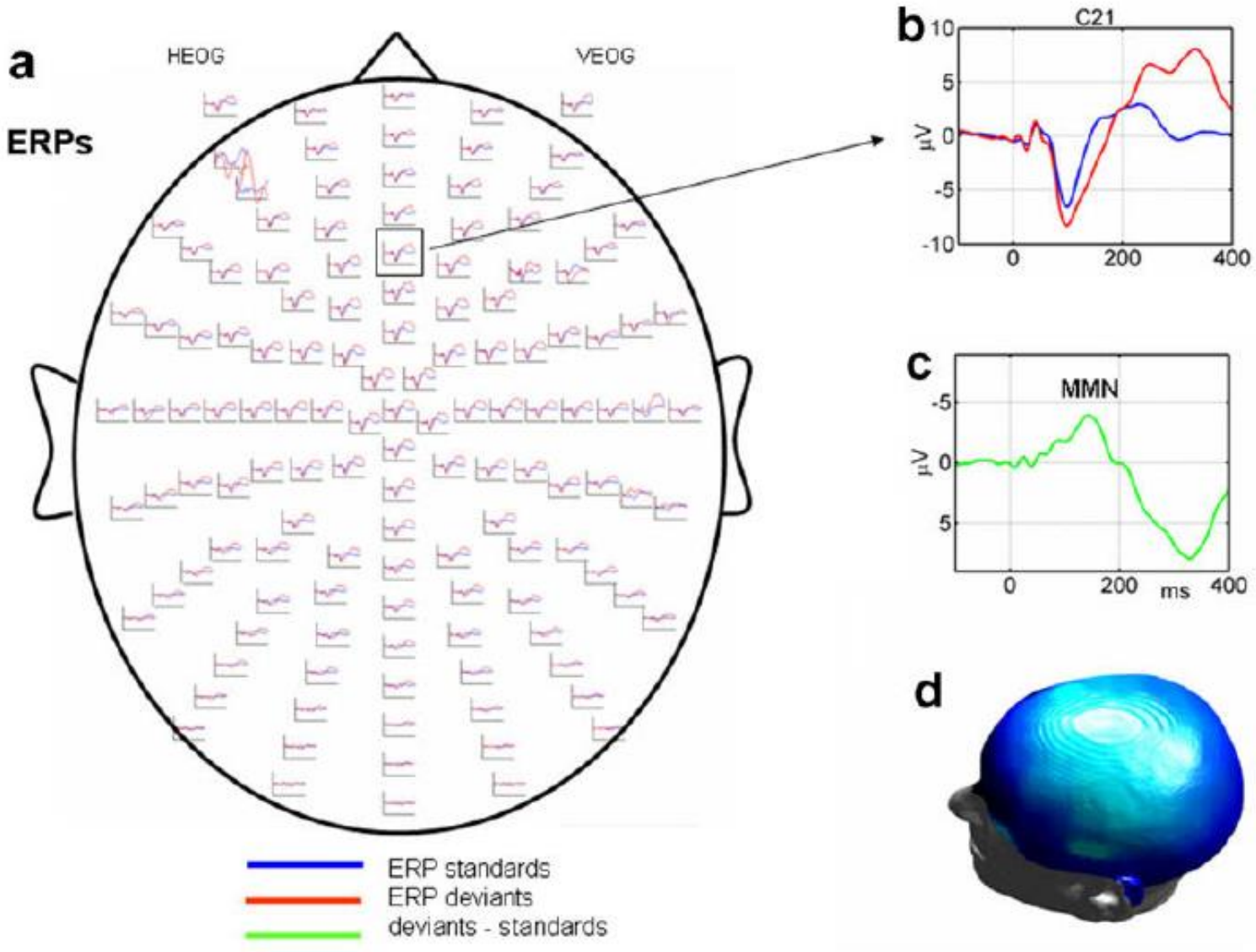
ERPs are linked in time with a physical or mental event, and are typically **extracted from the scalp-recorded electroencephalogram (EEG) by means of signal averaging**.



Mismatch negativity (MMN)

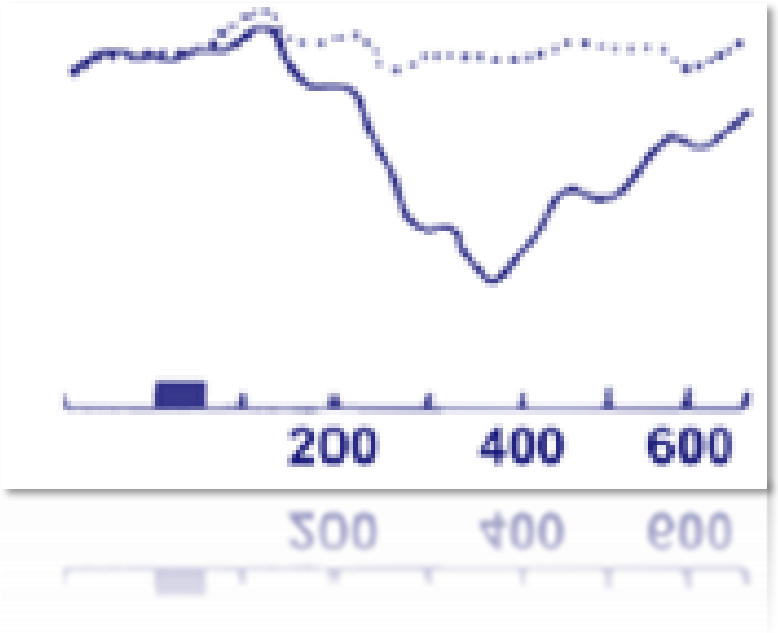
is a brain response **to violations of a rule**, established by a sequence of sensory stimuli (typically in the auditory domain)

to reflect an **automatic process** that detects a difference between an incoming stimulus and the sensory memory trace of preceding stimuli, even in the absence of the participant's attention.



Is the **negative component** of the waveform obtained by subtracting the event-related response to the standard event from the response to the deviant event. (From Garrido et al., 2007.)

P 300



The P300 (also known as P3 or P3b) is **a large, broad, positive component** in the ERP that typically **peaks 300 ms** or more after onset of a **rare, task-relevant stimulus.**

ELSEVIER

Clinical Neurophysiology 118 (2007) 2128–2148

www.elsevier.com/locate/clinph

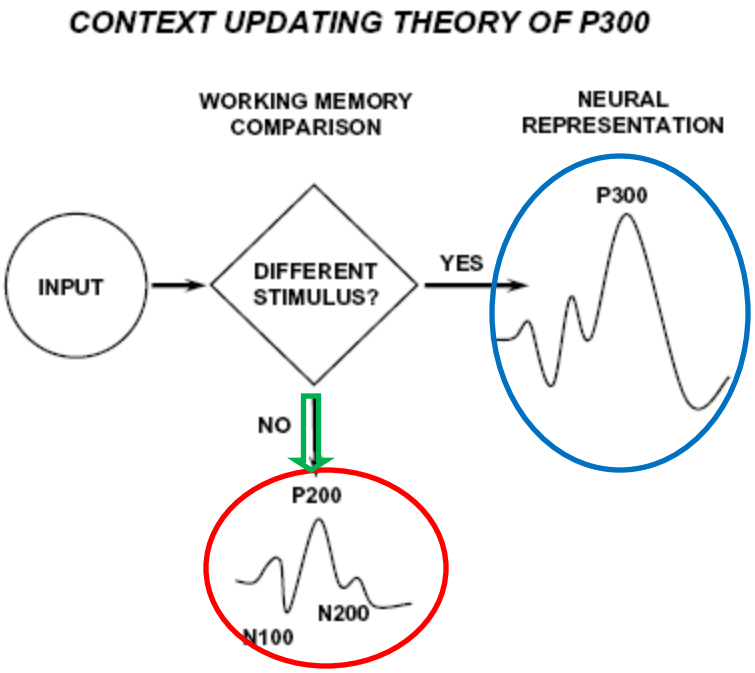
Invited review

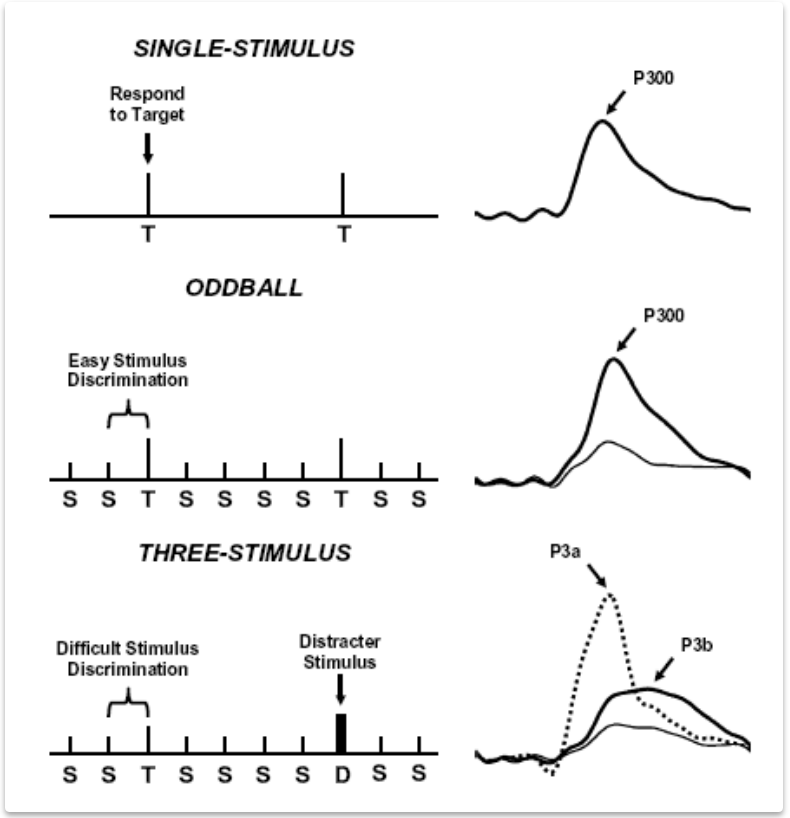
Updating P300: An integrative theory of P3a and P3b

John Polich *

Cognitive Electrophysiology Laboratory, Molecular and Integrative Neurosciences Department, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Accepted 28 April 2007
Available online 18 June 2007





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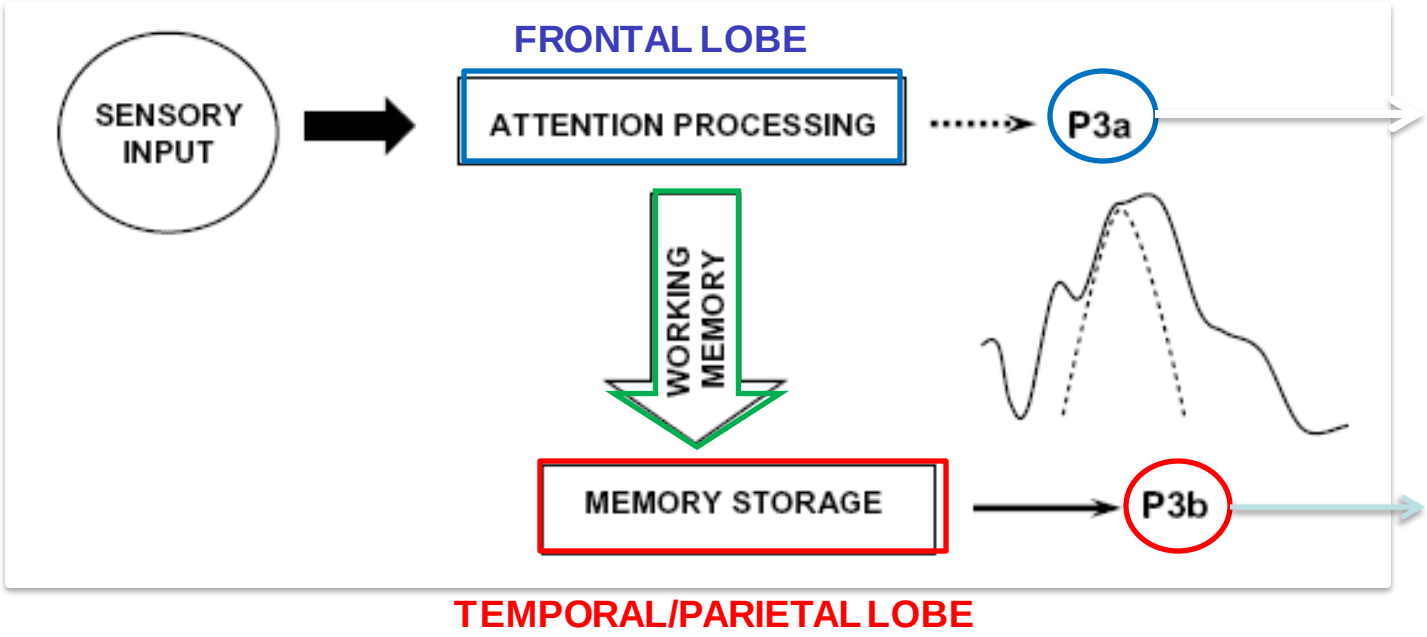
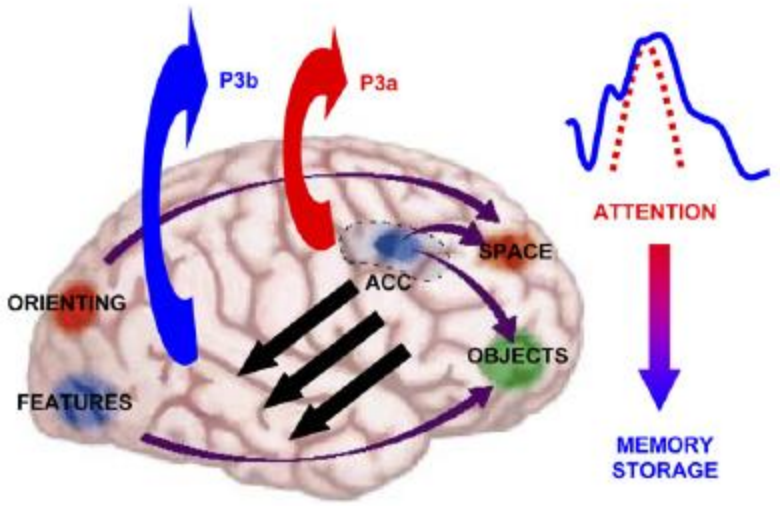


Schematic representation of brain activation patterns underlying P3a and P3b generation



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Accepted 28 April 2007
Available online 18 June 2007

The model suggests that stimulus information is maintained in **frontal lobe** working memory and monitored by **anterior cingulate structures.**

When focal attention for the standard stimulus is disrupted by the detection of a distracter or a target, **the P3a is perhaps generated by the activation pattern of the anterior cingulate** and related structures.

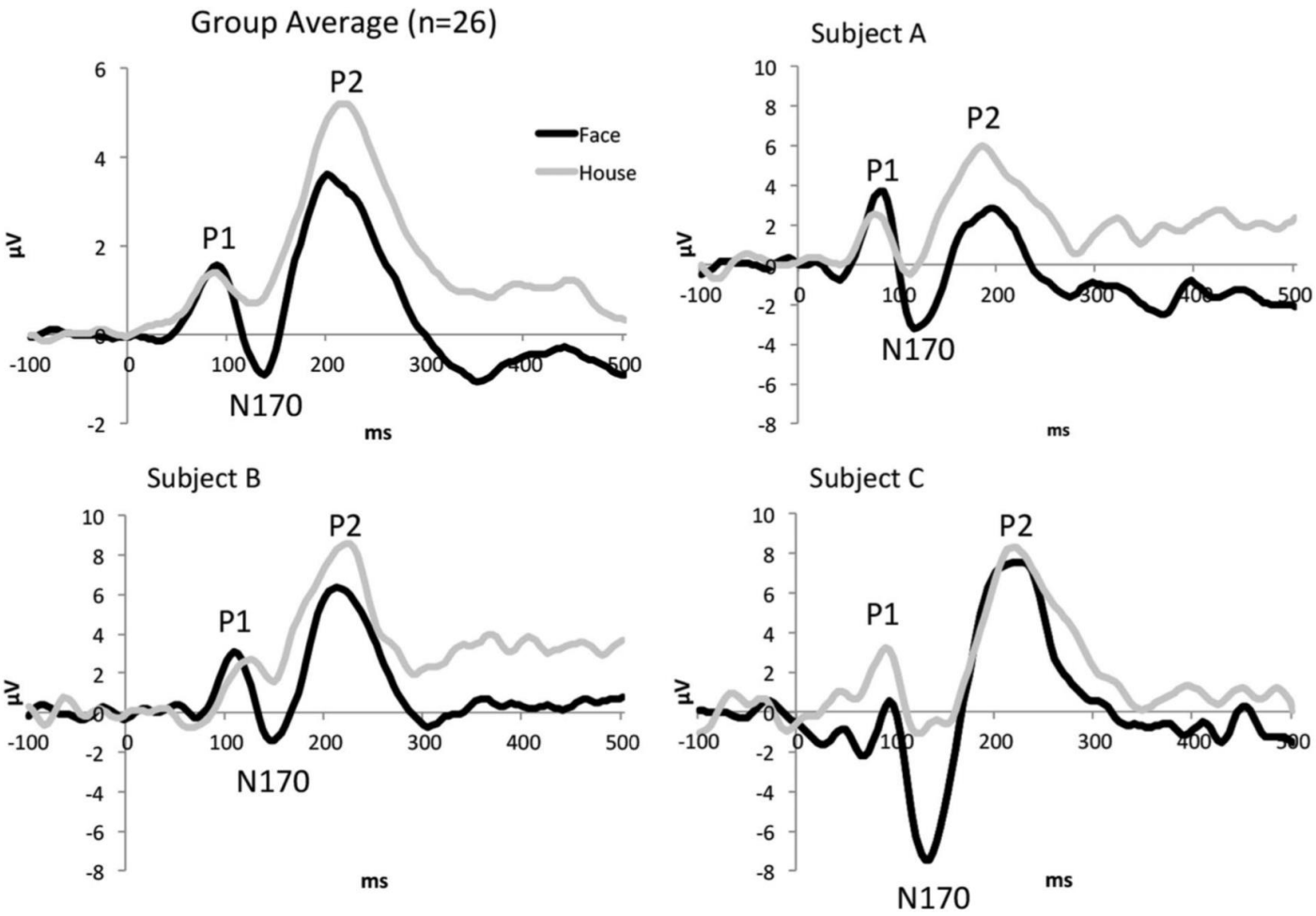
The attention-driven neural activity signal may be **transmitted to temporal–parietal areas**.

Memory related storage operations are engaged and **P3b is generated via temporal/parietal cortical structures**.

Key AP.

Searching for a "Brain Signature" of Neurodevelopmental Disorders: Event-Related Potentials and the Quest for Biomarkers of Cognition.

J Clin Neurophysiol. 2021 Aug 3. doi: 10.1097/WNP.0000000000000727.



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Searching for a "Brain Signature" of Neurodevelopmental Disorders: Event-Related Potentials and the Quest for Biomarkers of Cognition.

J Clin Neurophysiol. 2021 Aug 3. doi: 10.1097/WNP.0000000000000727.

- a task-based EEG recording to probe cognitive processes
  - Auditory Modality
  - Visual Modality
  - …..
- ERPS AS PREDICTORS OF RISK FOR POOR DEVELOPMENTAL OUTCOMES
- ERPS AS MARKERS OF TREATMENT EFFECTS
- Differences in the **amplitude, latency, and scalp distribution** of various ERP responses (peaks or latent components) are interpreted to **index neural processes underlying sensory–perceptual and higher-order cognitive processes**, from stimulus onset detection to identification and evaluation as well as response preparation and execution.

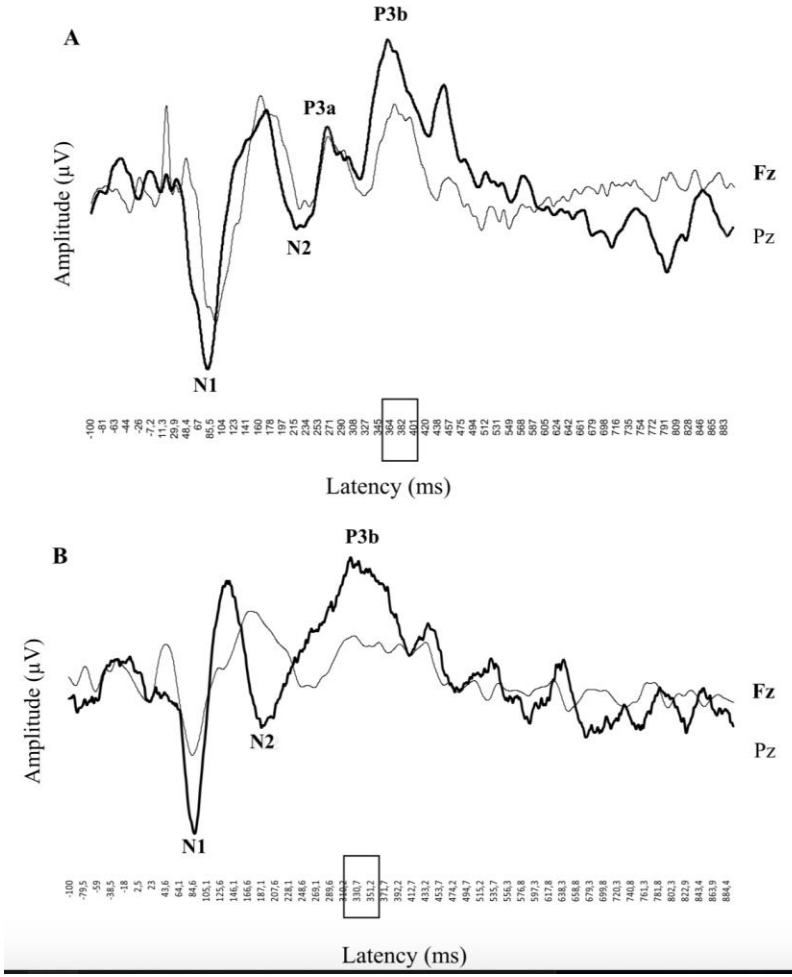
Karim Bennys et al

Cognitive Event-Related Potential, an Early Diagnosis Biomarker in Frail Elderly Subjects: The ERP-MAPT-PLUS Ancillary Study

Journal of Alzheimer's Disease 58 (2017) 87–97 87 DOI 10.3233/JAD-161012

- Synaptic dysfunction and/or early neurodegeneration with the presence of subtle cognitive symptoms defined the new diagnosis criteria for the preclinical stages of AD
- The ERP-P300 tool reflects synaptic dysfunction.

- the **P300 latency** is considered as a robust diagnosis marker of prodromal AD
- **topographical changes** in the distribution of P300 amplitudes might reflect neural compensation processes underpinned by a disconnection between frontal and posterior region in early phase of AD



Vicente Molina et al

Deficits of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder?

J Psychiatry Neurosci 2020;45(5)

- assessments of EEG modulation with cognition are of potential interest when studying the substrates of alterations in mental function, such as those found in psychoses.
- assessment of parameters that summarize EEG characteristics, such as spectral entropy, which quantifies the signal degree of uncertainty:
  - high spectral entropy corresponds to more uniform distribution of spectral content (a highly random signal), whereas low spectral entropy indicates a spectrum whose power is condensed to a narrower frequency range (a more regular signal).
- comparing spectral entropy values between the windows immediately before and after a target stimulus in a task: P300 task
- The auditory oddball task consisted of a 3-tone auditory oddball paradigm randomly presented:
  - target (500 Hz tone, probability 0.2),
  - distractor (1000 Hz tone, probability 0.2)
  - standard (2000 Hz tone, probability 0.6).

Spectral entropy modulation (factor scores): individual distributions and 95% confidence intervals (CI).

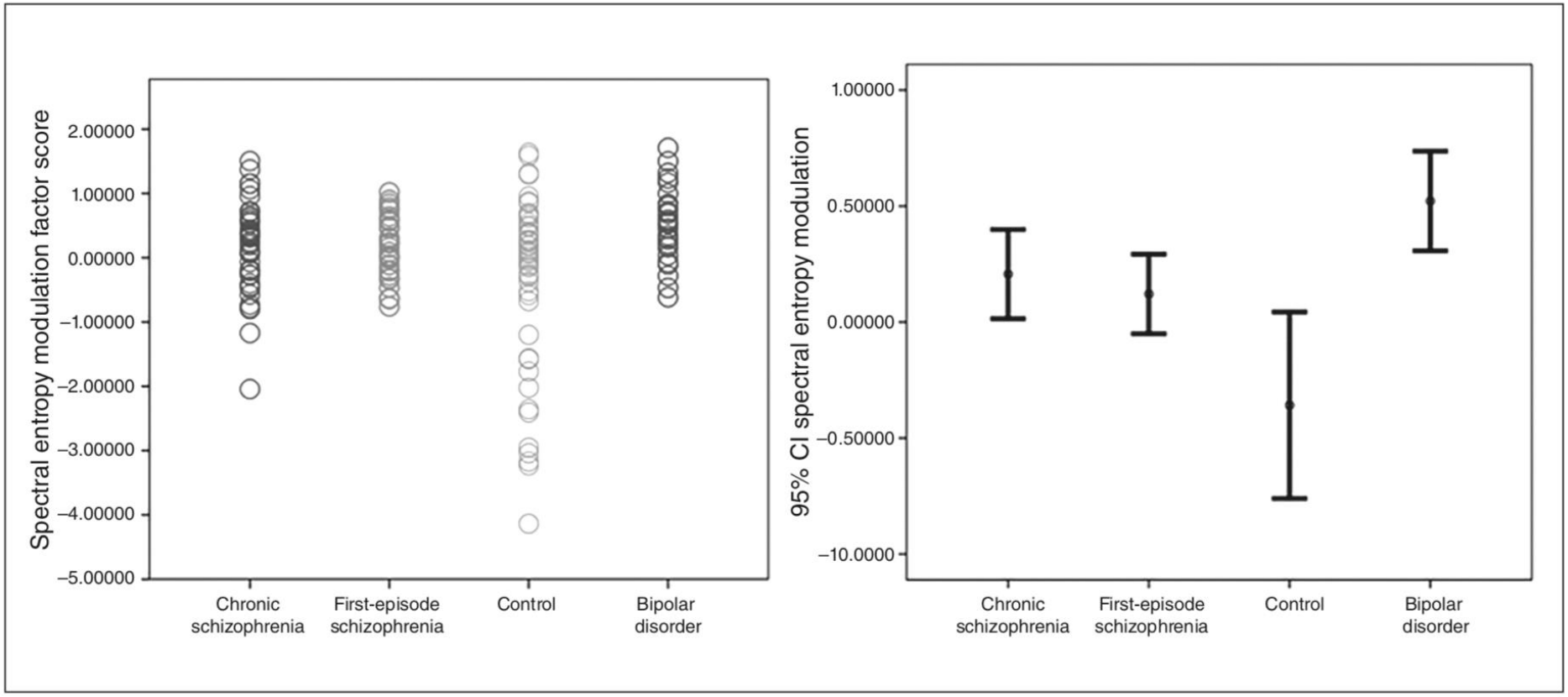
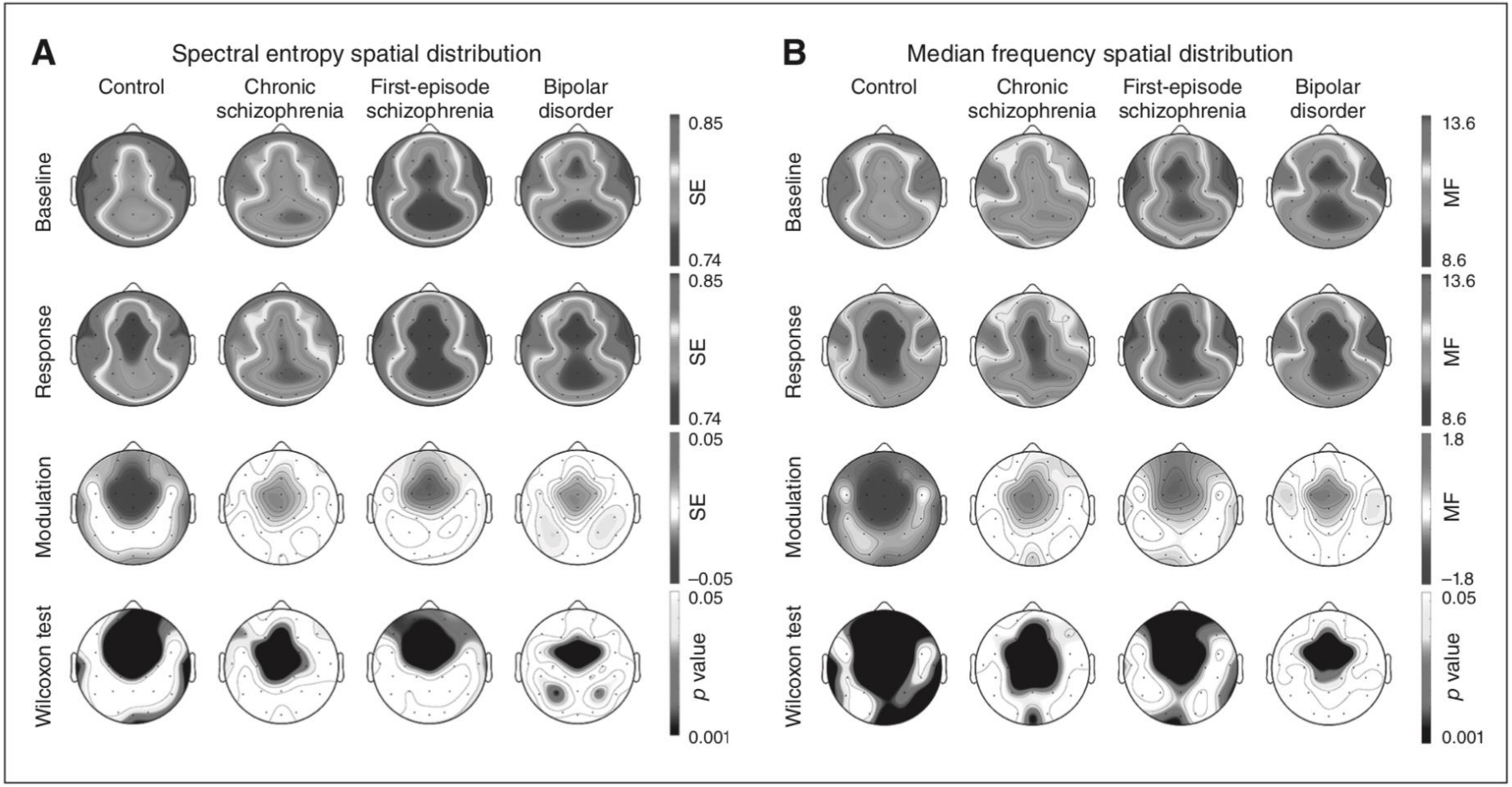
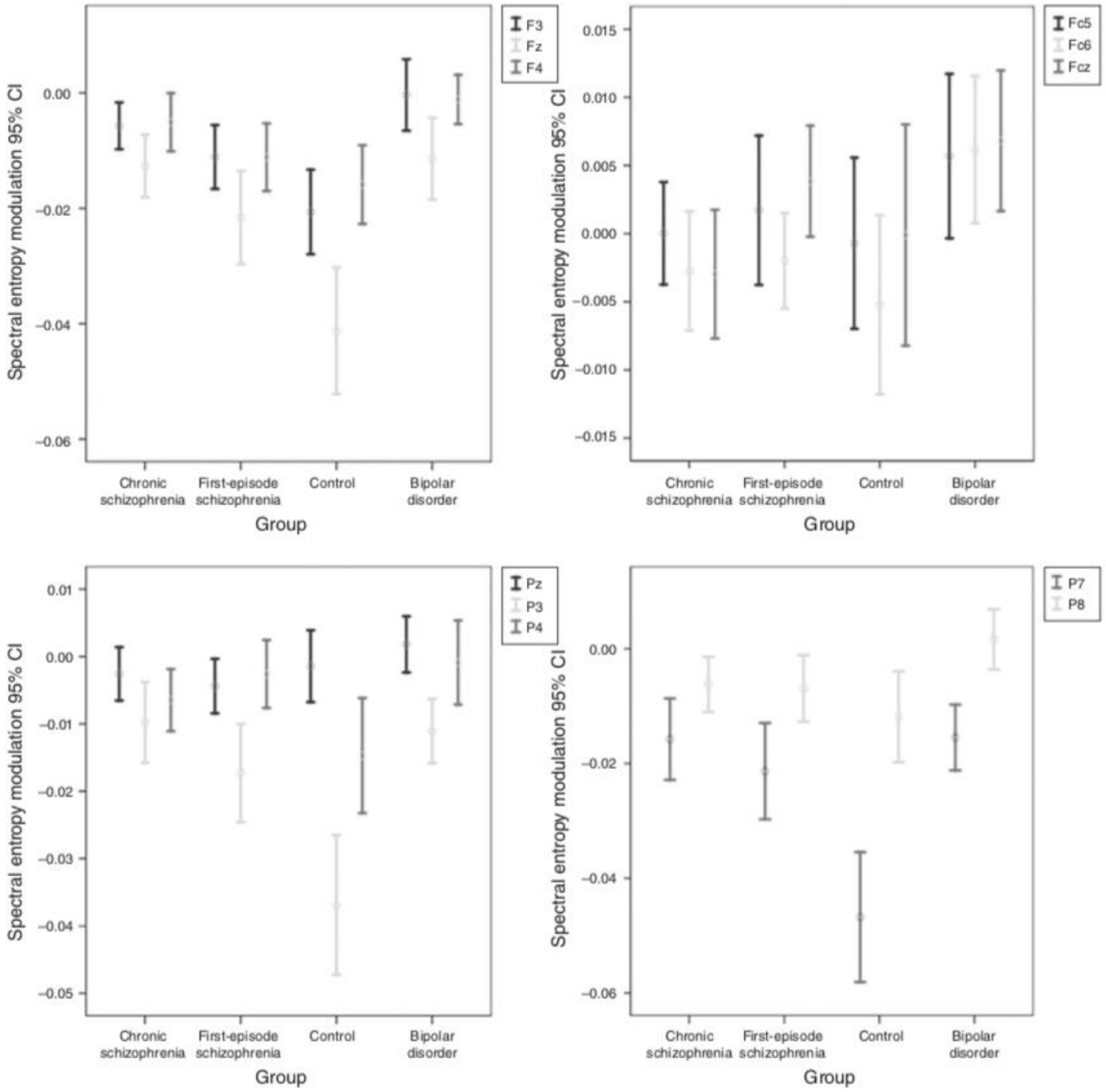


Fig. 1: Spectral entropy modulation (factor scores): individual distributions and 95% confidence intervals (CI).

Spatial distribution of spectral entropy (SE) and median frequency (MF) at baseline and response windows, and its difference (modulation) in each group, with corresponding intragroup statistical significance difference between windows (Wilcoxon test). Shading depicts the corresponding regional values in Hertz for median frequency.



Spectral entropy modulation 95% confidence intervals (CI) at frontal (F), frontocentral (Fc), and parietal (P) electrodes.



Vicente Molina et al

Deficits of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder?

J Psychiatry Neurosci 2020;45(5)

- a deficit in spectral entropy modulation occurs in patients with first-episode and chronic schizophrenia and euthymic patients with bipolar disorder.
- deficits in neural synchronization might contribute to psychoses.
- abnormal cerebral processing, reflected in a decreased EEG modulation during performance of a task with a small cognitive load, could contribute to aberrant mental representations in the form of the symptoms and/or cognitive deficits of psychosis. Therefore, deficits in spectral entropy (and median frequency) modulation could represent a marker of disease related to altered function in psychotic syndromes.
- global brain activity in schizophrenia and bipolar disorder shows a significant deficit in expected task-related modulation, which may hamper cognitive performance and mental representations under more demanding conditions.
- no significant differences in pre-stimulus spectral entropy, similar to previous reports, supporting the concept that the primary deficit in patients relates to modulation itself.

Sysoeva OV et al.

Atypical processing of tones and phonemes in Rett Syndrome as biomarkers of disease progression.

Transl Psychiatry. 2020 Jun 10;10(1):188. doi: 10.1038/s41398-020-00877-4.

- Rett Syndrome (RTT) is a neurodevelopmental disorder caused by a spontaneous mutation in the MECP2 gene located on the X-chromosome.
- Its primary clinical features include severe motor deficits and cognitive impairments. Verbal ability is typically also very restricted or absent.
- Early electrophysiological studies in RTT mostly focused on the auditory brainstem response (ABR), with findings indicating that initial subcortical stages of auditory signal processing appeared mostly unaffected. In contrast, AEP studies assessing later cortical stages of auditory processing have tended to show quite significant impairments.
- substantial delay in the mismatch negativity (MMN) response, an AEP component that is automatically generated when occasional deviant stimuli interrupt a stream of standard stimuli

Sysoeva OV et al.

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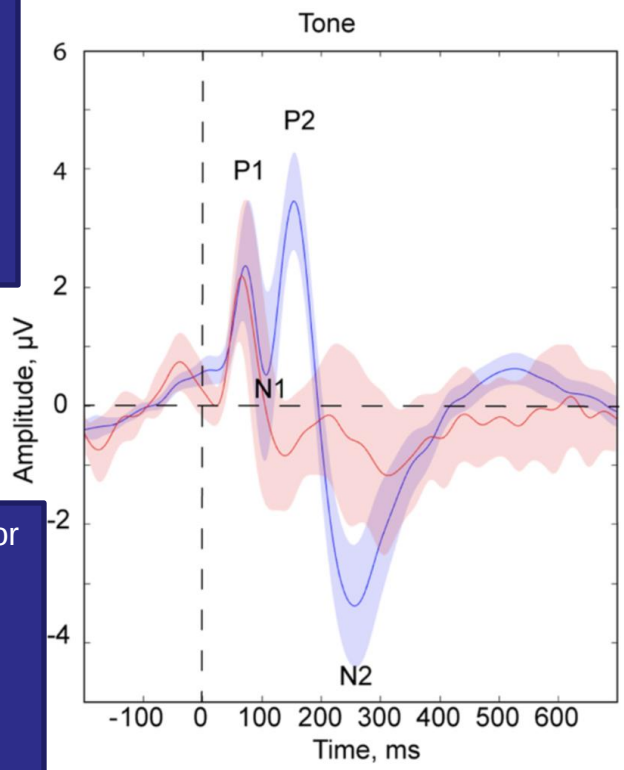
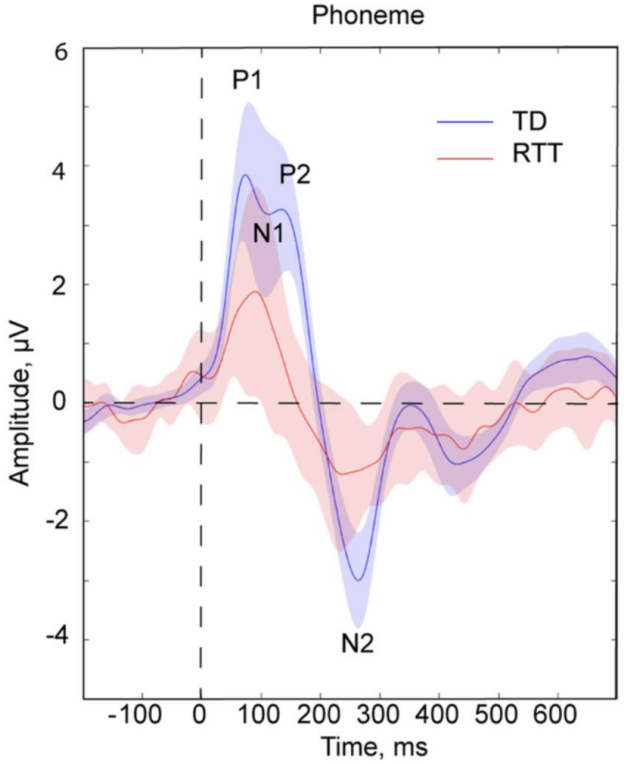
Transl Psychiatry. 2020 Jun 10;10(1):188. doi: 10.1038/s41398-020-00877-4.

to examine early auditory cortical processing of complex speech stimuli in RTT, and to compare these responses to those evoked by simple frequency-specific tones.

The initial AEP component (the P1 – 60–90 ms), which localizes in the region of primary auditory cortex, showed increased amplitude to the more complex phonemic inputs relative to pure tones in TD participants, in the RTT population, it did not show this modulation by stimulus type/complexity





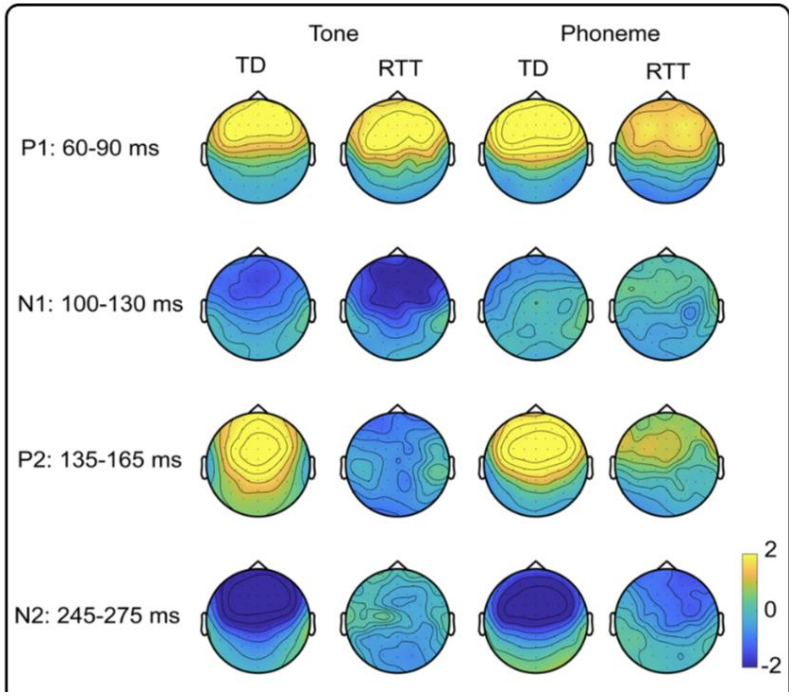
the P2 (135-164 ms), the following major deflection, was hugely diminished or even completely absent in the RTT group, regardless of stimulus type. The N2 (245–275ms) was also substantially reduced in amplitude in RTT and showed no modulation as a function of stimulus type.

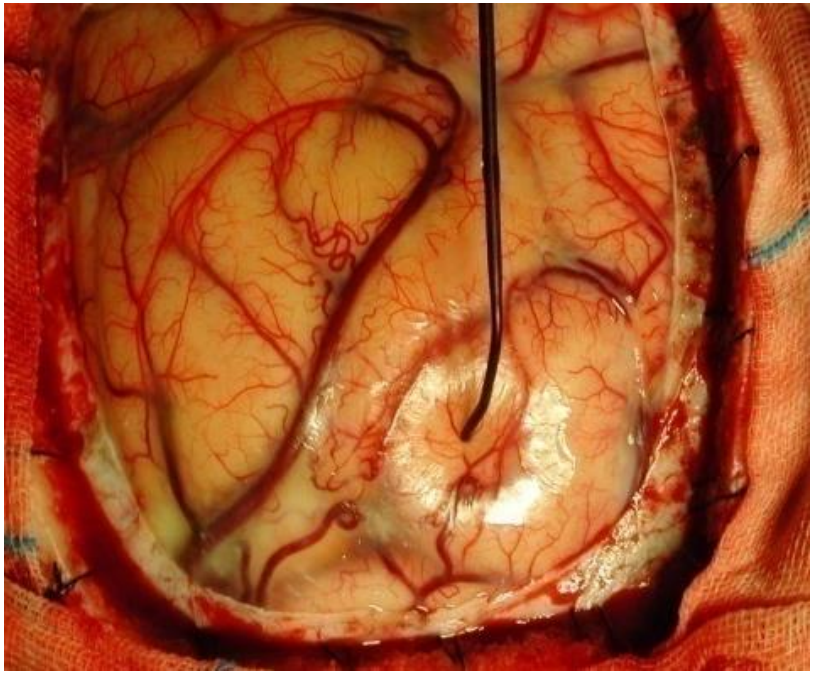
Sysoeva OV et al.

Atypical processing of tones and phonemes in Rett Syndrome as biomarkers of disease progression.

Transl Psychiatry. 2020 Jun 10;10(1):188. doi: 10.1038/s41398-020-00877-4.

- The **P2 effect** was remarkably robust in differentiating between groups with almost perfect classification into group despite the wide age-range of our samples.
- Given this robustness, the P2 has potential to serve as a monitoring, treatment response or even surrogate **endpoint biomarker**.



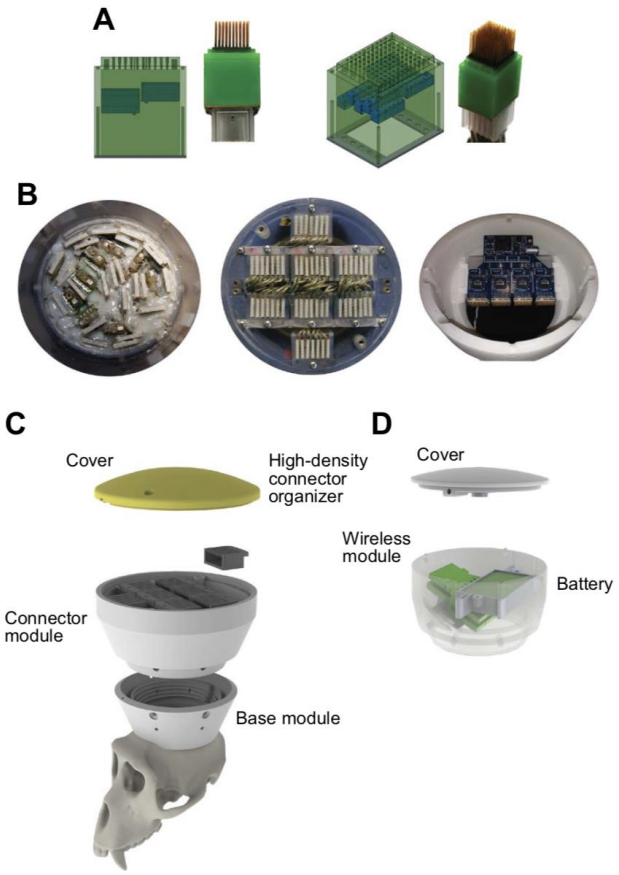


MOTOR ASSESSMENT AND CORTICAL/SUBCORTICAL RECORDING

Lebedev MA, Nicolelis MA.
Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation.
Physiol Rev. 2017 Apr;97(2):767-837. doi: 10.1152/physrev.00027.2016.

- the pioneering work of Apostolos Georgopoulos on directional coding in the primate motor cortex found that individual neurons in the primate primary motor cortex are broadly tuned to the direction of arm movement and that populations of such neurons, rather than an individual M1 neuron, have to be pooled together to compute the direction in which a monkey is about to move its arm.

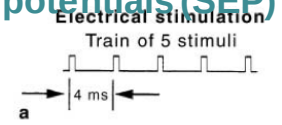
- By the mid-1990s, the introduction of new electrophysiological methods for chronic multielectrode recordings in freely behaving animals triggered a new phase of neural ensemble physiology, Multichannel, wireless recordings in rhesus monkeys.

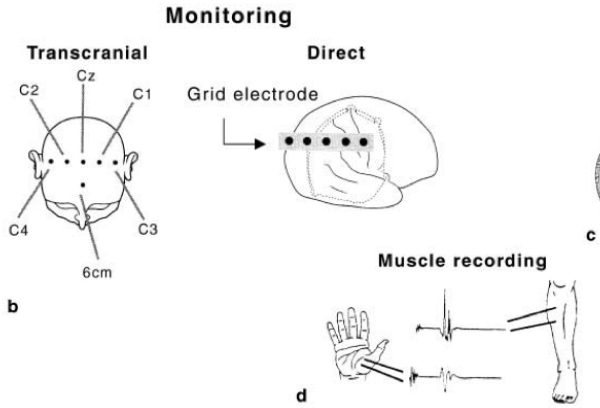


INTRAOPERATIVE NEURPHYSIOLOGY

MONITORING:

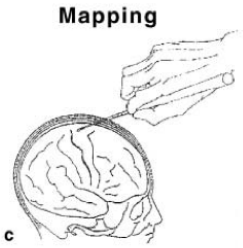
- Transcranial electrical stimulation or direct cortical stimulation motor evoked potentials (Tc-dMEP)
- Somatosensory evoked potentials (SEP)
- EEG-ECoG
- EMG
- PEV

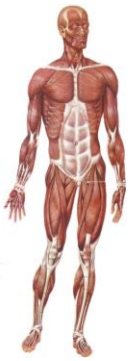




MAPPING:

- Direct electrical cortical and subcortical stimulation
- Phase reversal SEP

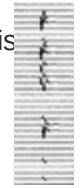




orbicularis oculi, oris

biceps,
extensor digitorum communis

abductor pollicis brevis (bilaterale)



tibialis anterior

Abductor hallucis

The modern field of brain stimulation owes much to the American Robert Bartholow (sometimes also referred to as Roberts Bartholow [4]), who was one of the first to report the effects of electrical current stimulation to the cortex in conscious humans [1]. He was therefore an important pioneer in translating bioelectricity research from animals to humans.

Robert Bartholow was born to Jeremiah and Pleasant Bartholow (née Peddicord) in New Windsor, Maryland [3] on 28 November 1931. Thanks to his parents' efforts he was able to study at Calvert College (now New Windsor College) in Maryland. Bartholow was a brilliant student and young assistant instructor of chemistry, and received the degree of Master of Arts in 1848 [3]. He was an excellent student in the Latin and Greek classics but he also devoted himself to the use of French and German with great success [5]. He enrolled in Medicine at the University of Maryland and received his degree in 1852. He started working as a private medical practitioner in Baltimore clinics and hospitals, but he then decided to join the Army Medical staff. In 1855, he finally realized his dream. He ranked first among the few selected from numerous candidates, as Assistant Surgeon in the U.S. Army, Recorder of the Board and Medical Purveyor for the Army of Potomac.

➢ELECTRICAL STIMULATION OF CROTICAL AND SUBCORTICAL BRAIN AREA

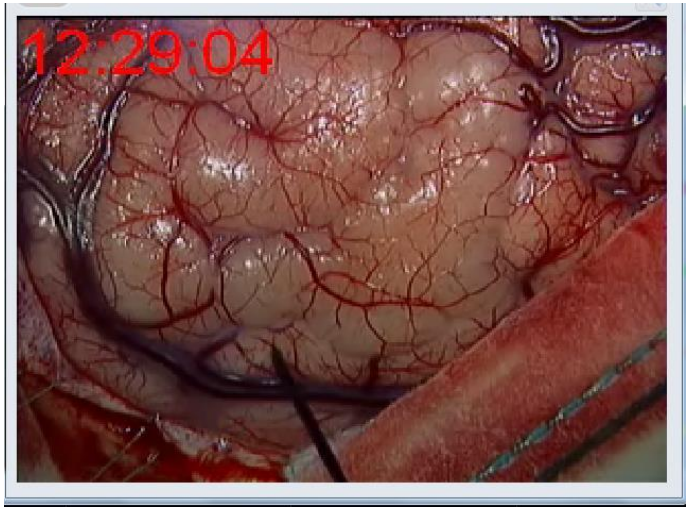
HYSTORY OF DIRECT CORTICAL STIMULATION

Historical perspective

- **1874** first description is attributed to **Robert Bartholow** et al.
- **1884** first application for **neurosurgical** purposes to **Victor Horsley and David Ferrier**
- **1888 William Keen**
- **1893**, Leonard Bidwell and Charles Sherrington in May and Fedor Krause in November.
- **early 20th century**: modern methods and principles by **Fedor Krause** who described the first **map of the human motor cortex**, which was then refined by **Harvey Cushing, Otfrid Foerster and Wilder Penfield (**routine procedure in **epilepsy** surgery**).**
- **in the seventies**: the technique was further refined by **Georges Ojemann**, by introducing a **biphasic current**, with **constant pulse** and by optimizing the intraoperative testing tasks.
- In **the nineties**, Mitchel **Berger** applied the direct electrical stimulation method for mapping eloquent cortical areas **for oncological neurosurgery** purposes and first described its application to the localization of **subcortical motor and sensory pathways.**
- **2000**: Hugues **Duffau** extended and codified the indication of direct electrical stimulation at cortical and subcortical levels to investigate intraoperatively the individual **functional connectivity of the brain**.
- In the last decade, popularized by the reported successes, **the technique has spread all over the world.**

Mechanisms of action of direct electrostimulation

- Direct electrical stimulation recruits more than a **thousand individual axons and cortical neurons** and may depolarize or hyperpolarize **local neurons** as well as also **neighboring axonal pathways**, and may induce local excitation or inhibition
- Determining the **net effect** of direct electrical stimulation thus requires both **local and distant neurophysiological measurements**
- For sensorimotor functions, direct electrical stimulation induces
  - a **"positive" effect which mimics sensorimotor function**,
  - whereas for **higher order cognitive processes** like language, arithmetic, or spatial awareness, the same stimulation induces **a stop of the function** as if the physiological signal was jammed

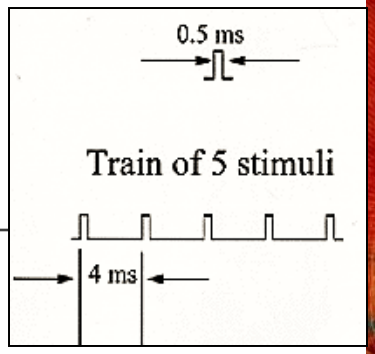


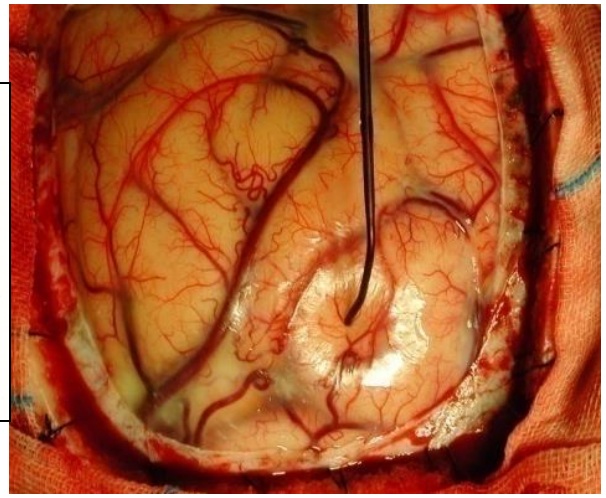
MEP short train technique

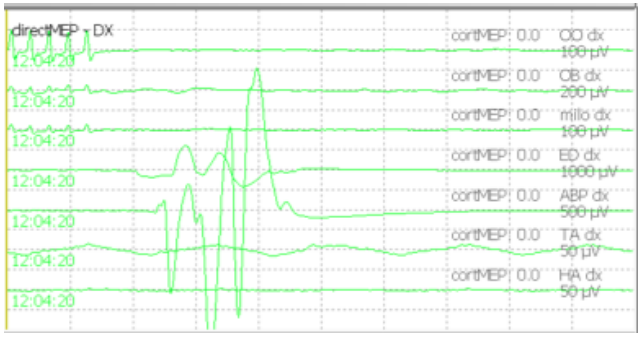
0.5 ms

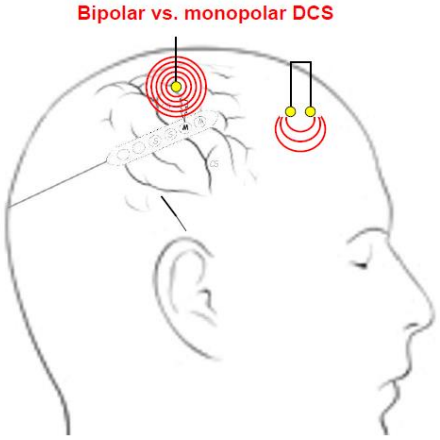
ISI = 4ms (250 Hz)

< 20 mA









Penfield technique (continuous stimulation for 3-4 sec.)

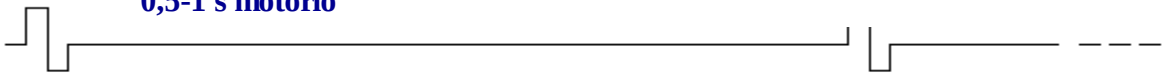
1 ms

2-8 mA 2-20 mA ("afterdischarge")

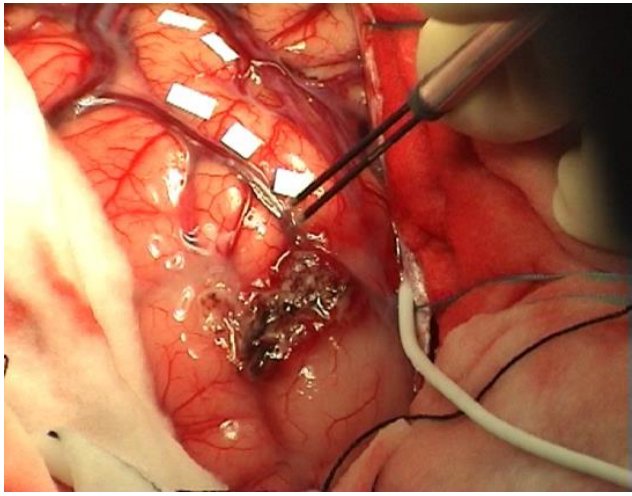
3-4 s linguaggio

0,5-1 s motorio

50-60Hz



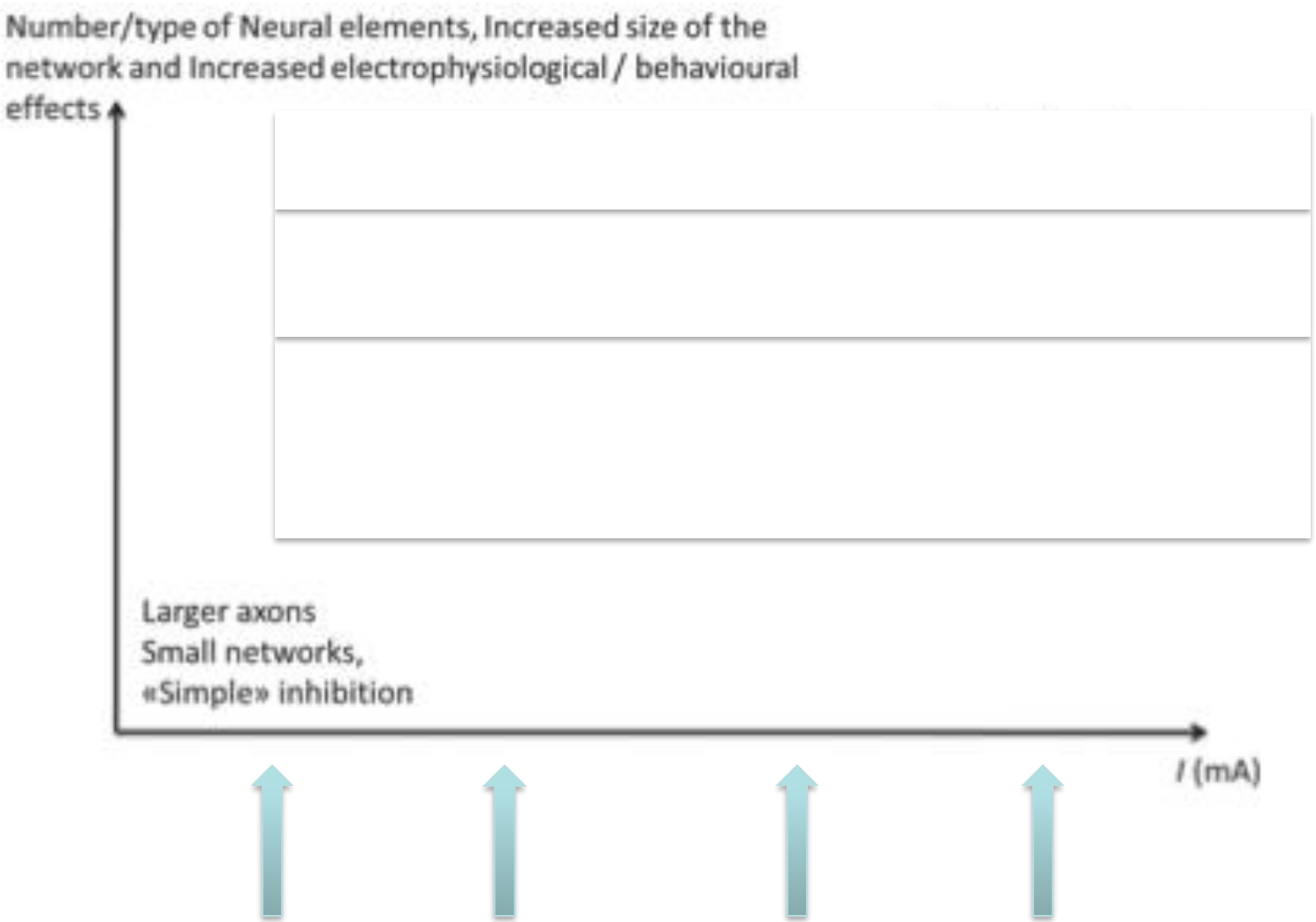
ISI = 20ms (50 Hz)

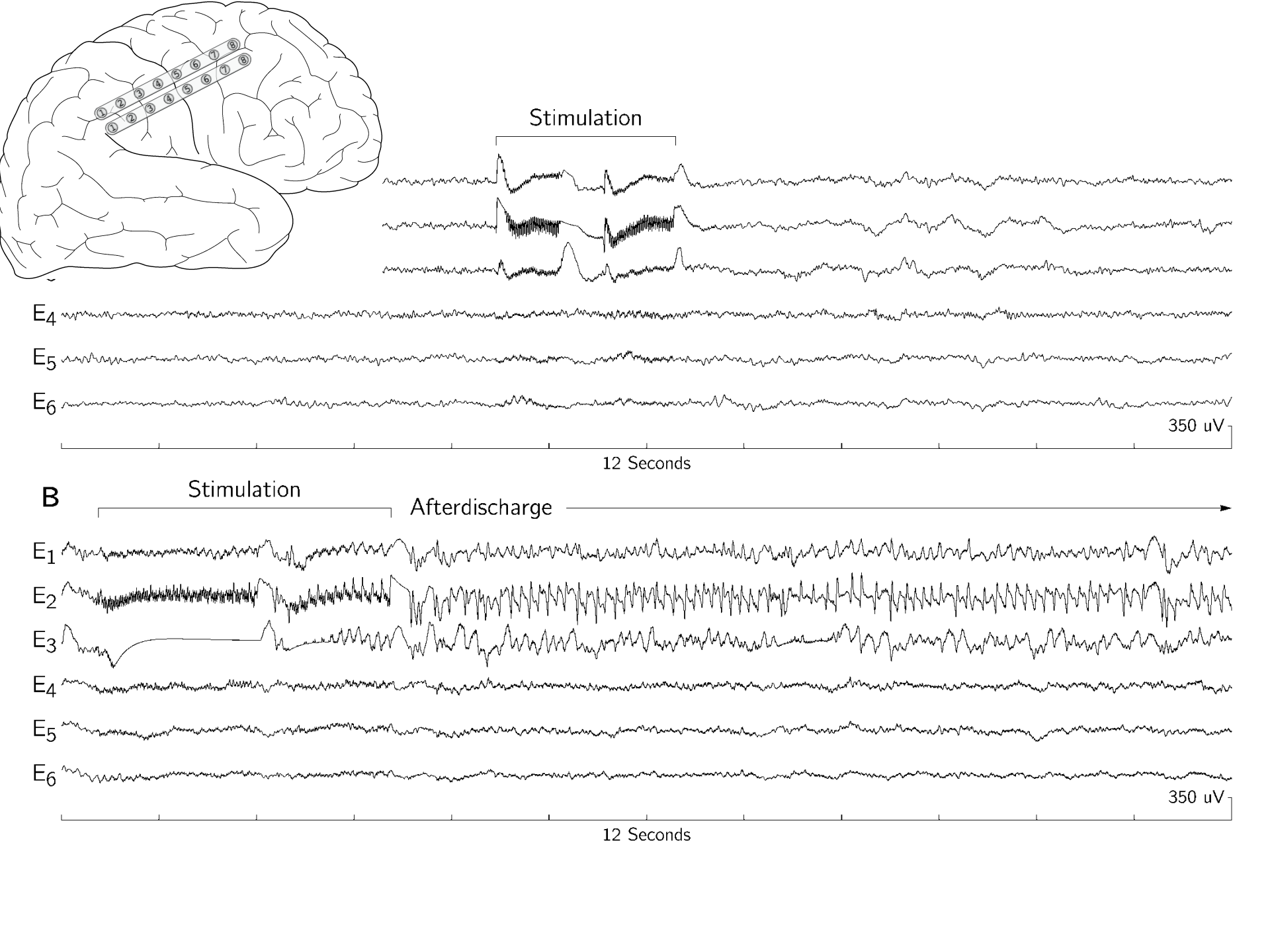


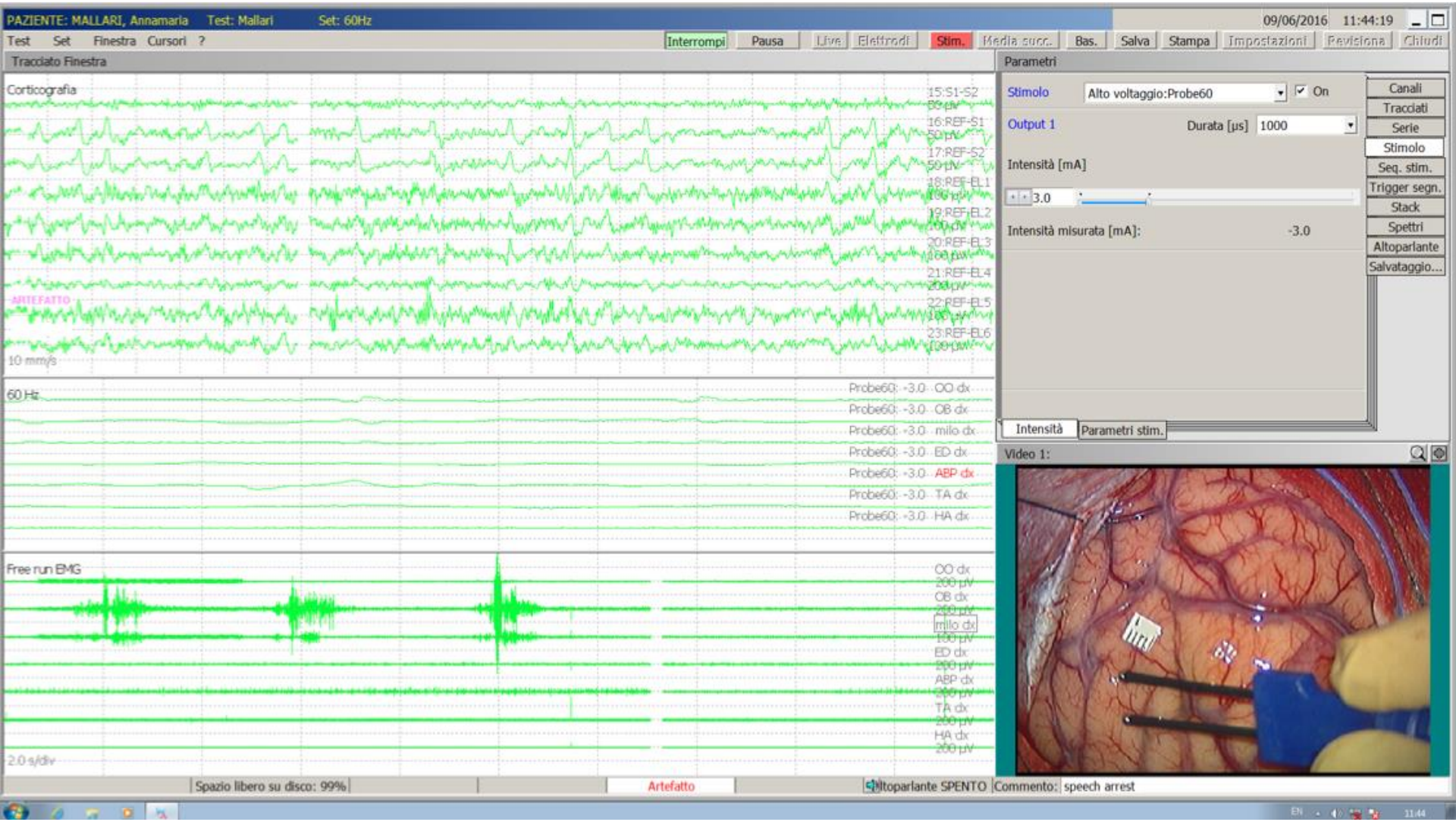
- Behavioural effects are more stereotyped when DES is applied subcortically and target a specific white matter fascicle.

A hypothesis concerning tl e recruitment of
neural elements. Conv sity by 1 mA
increases cortical spreadi to be confirmed

- Conversely, at the cortical level, the behavioural effects due to DES are more variable because of its isotropic spreading.

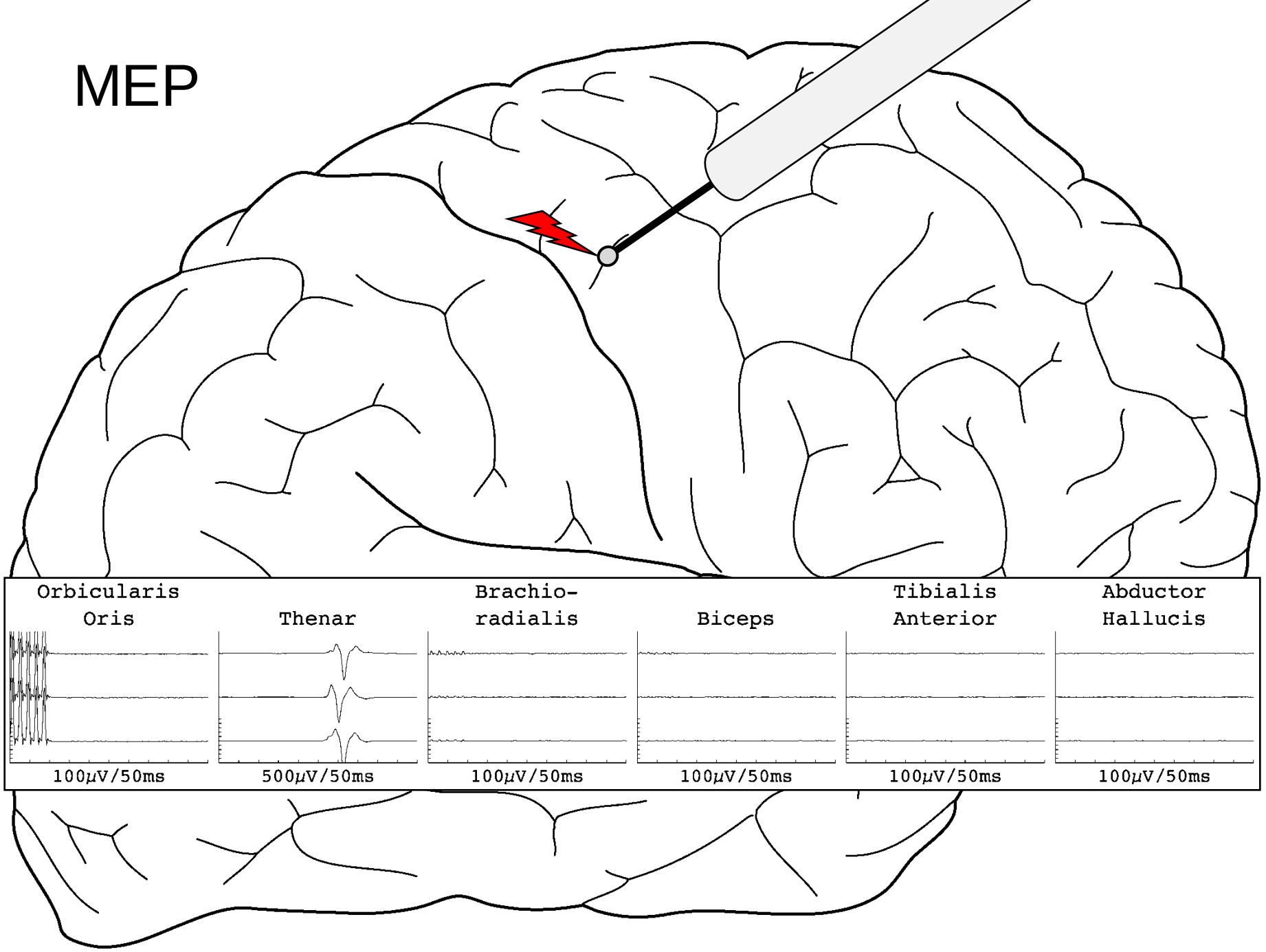



Stimulation
E4
E5
E6
350 uV
12 Seconds
B
Stimulation
Afterdischarge
E1
E2
E3
E4
E5
E6
350 uV
12 Seconds



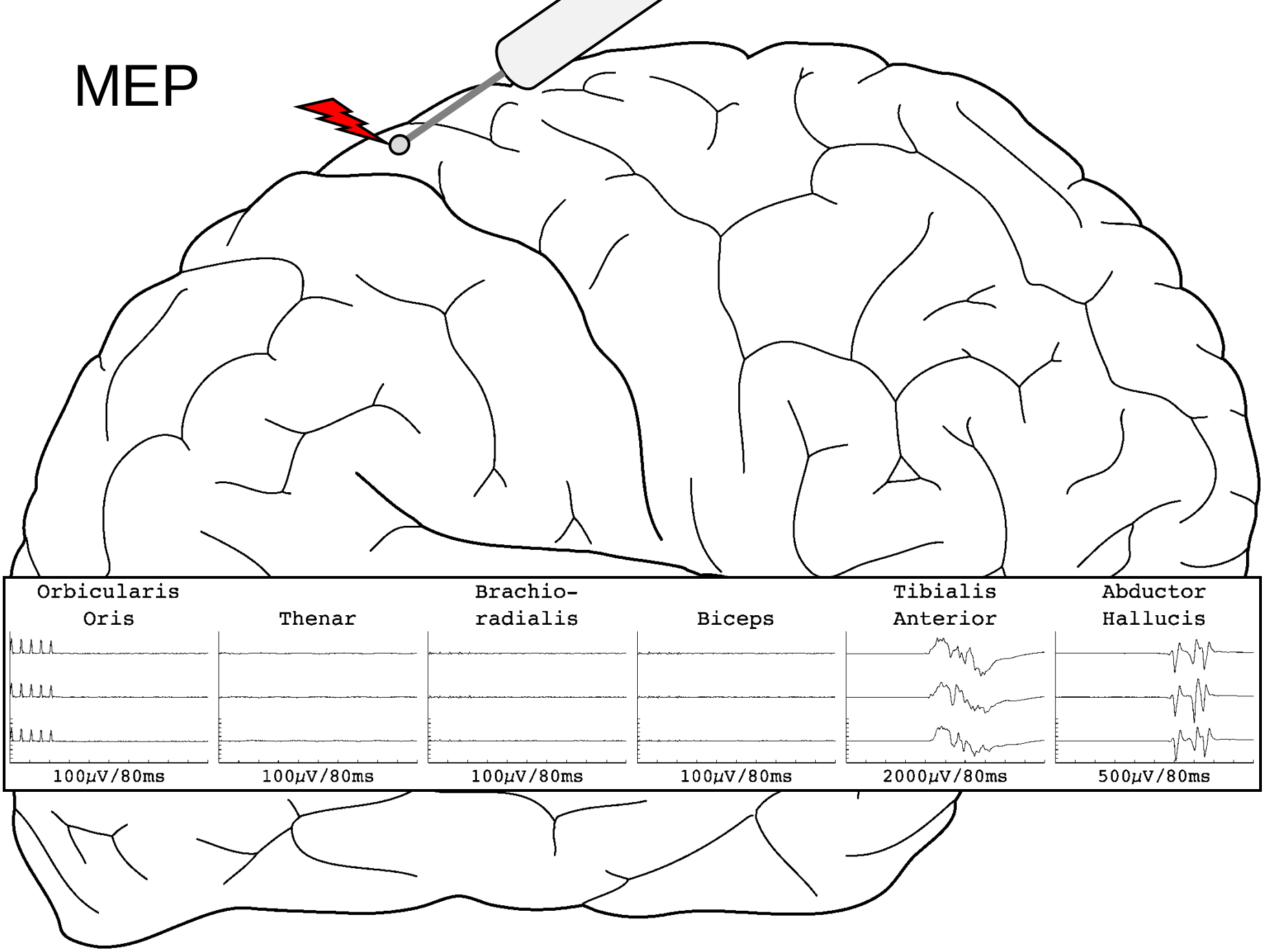
Speech arrest

MEP



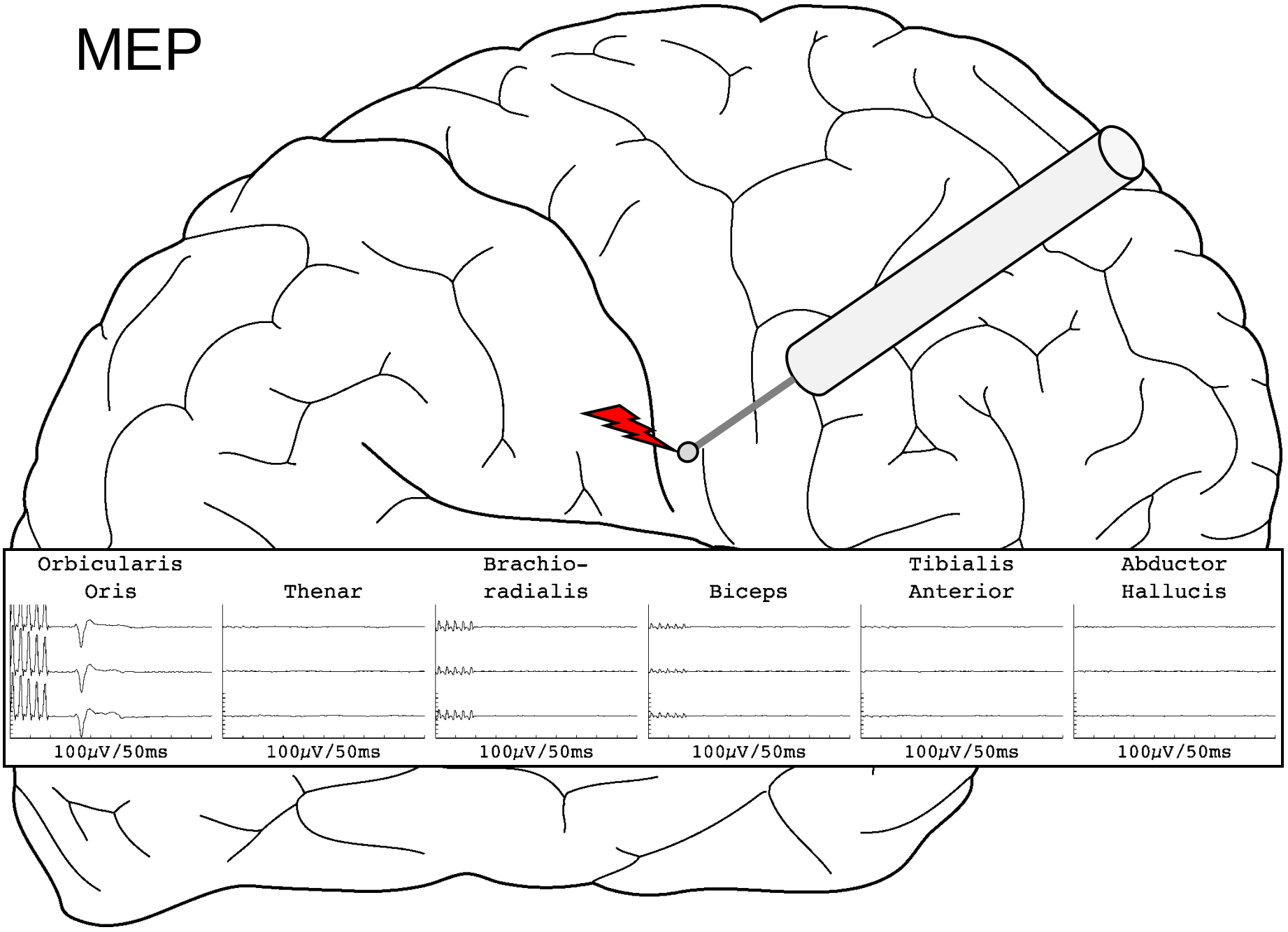
Courtesy of D. Mac Donald

MEP



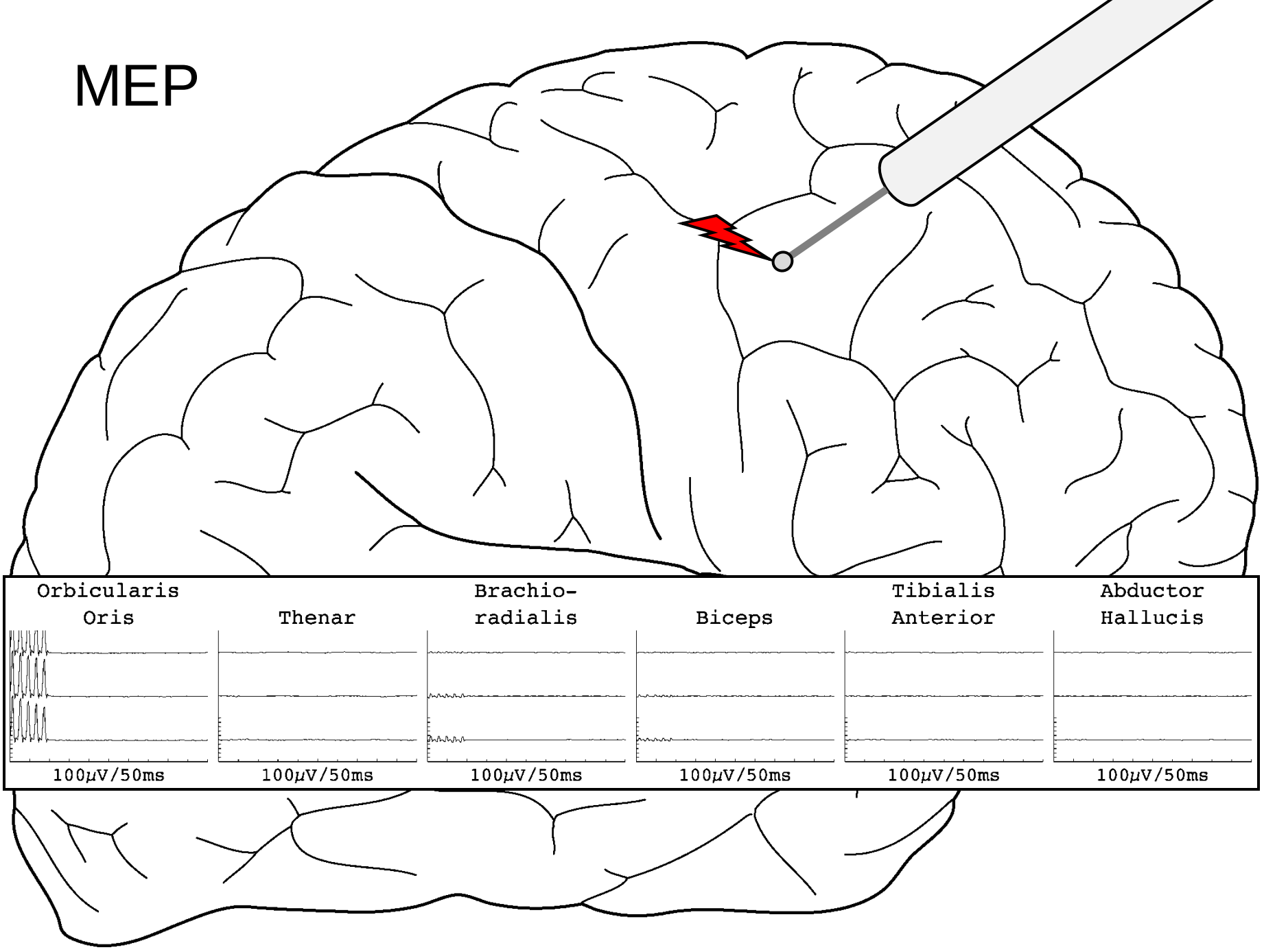
Courtesy of D. MacDonald

MEP

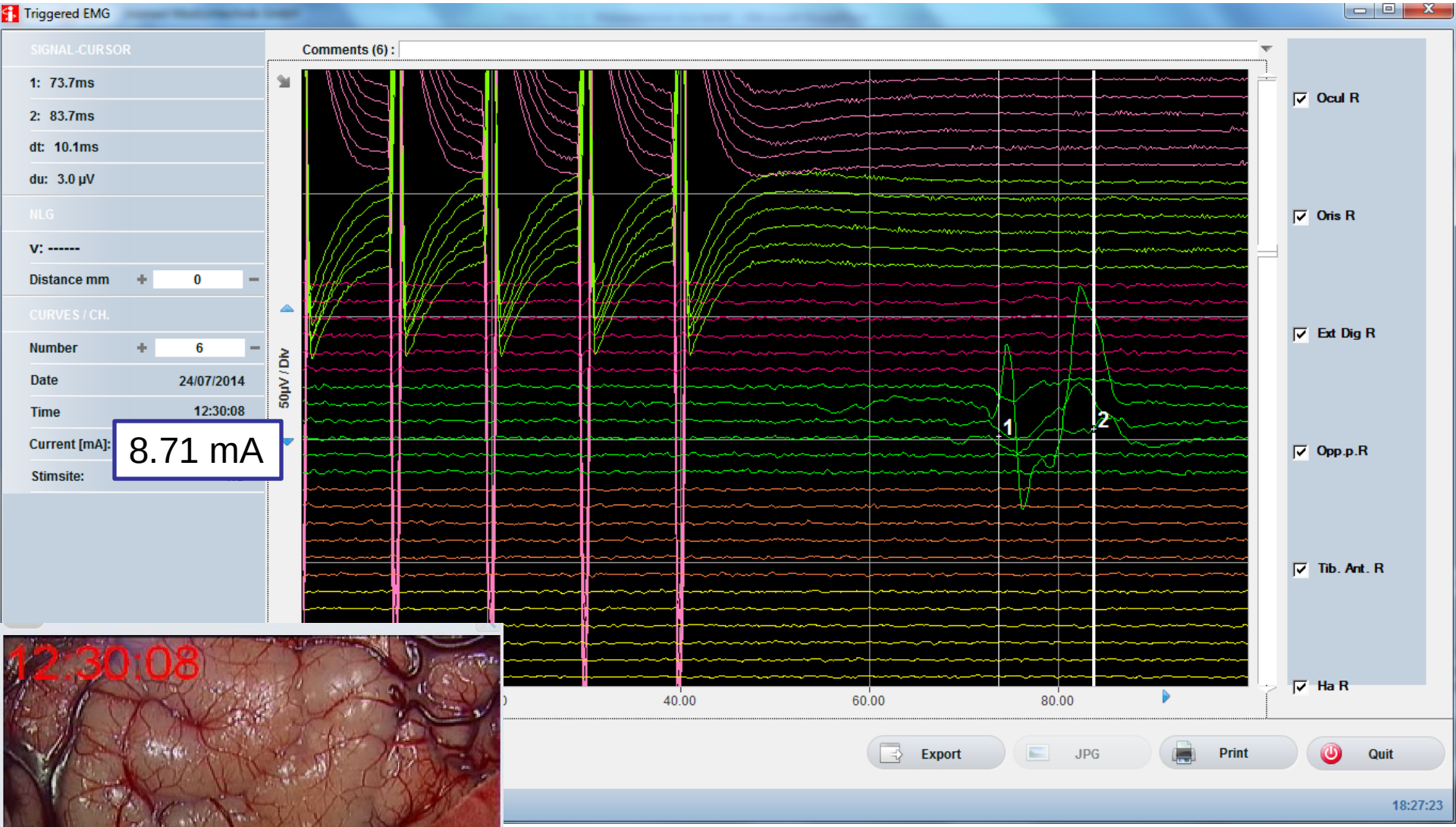


Courtesy of D. MacDonald

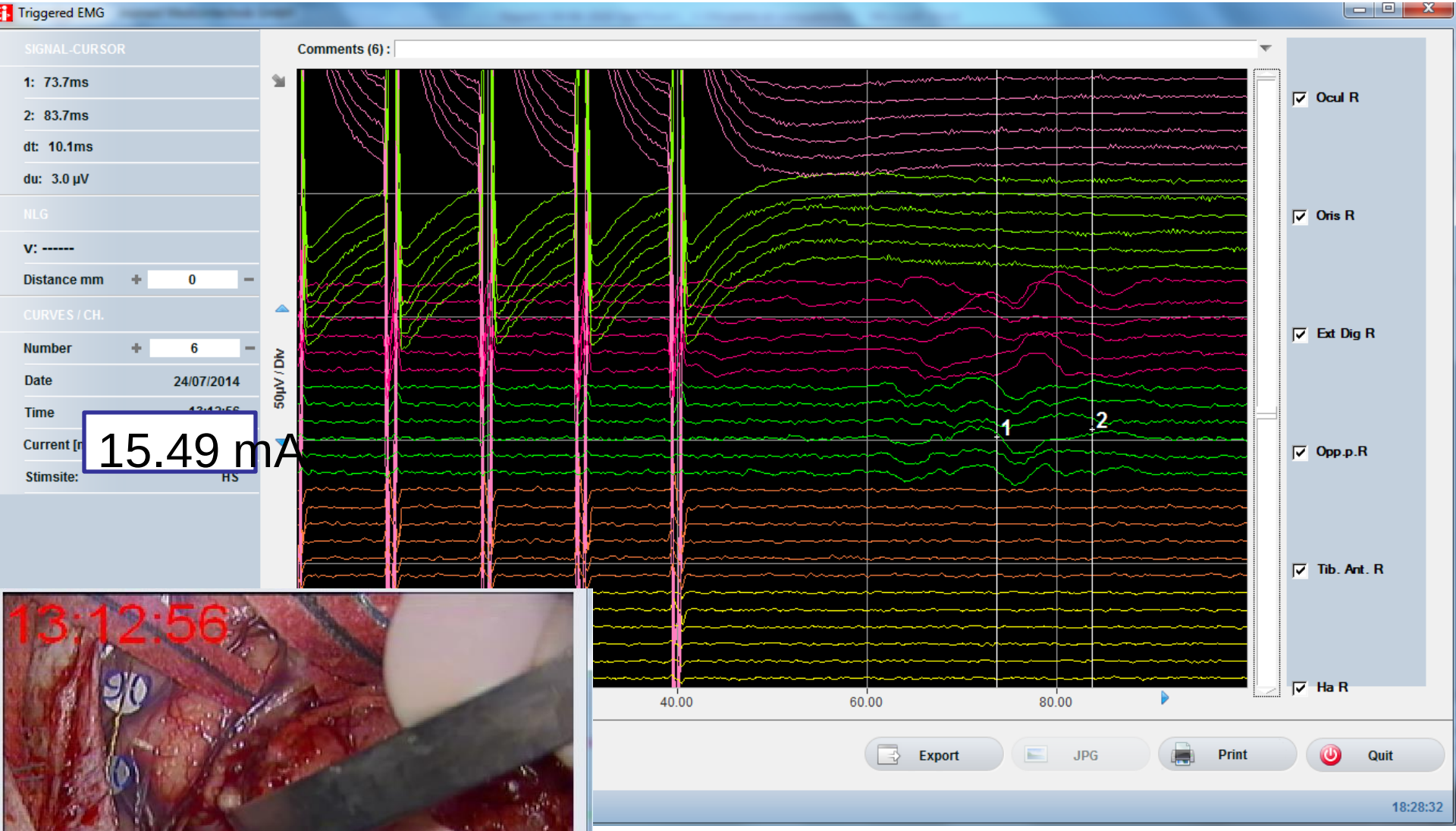
MEP



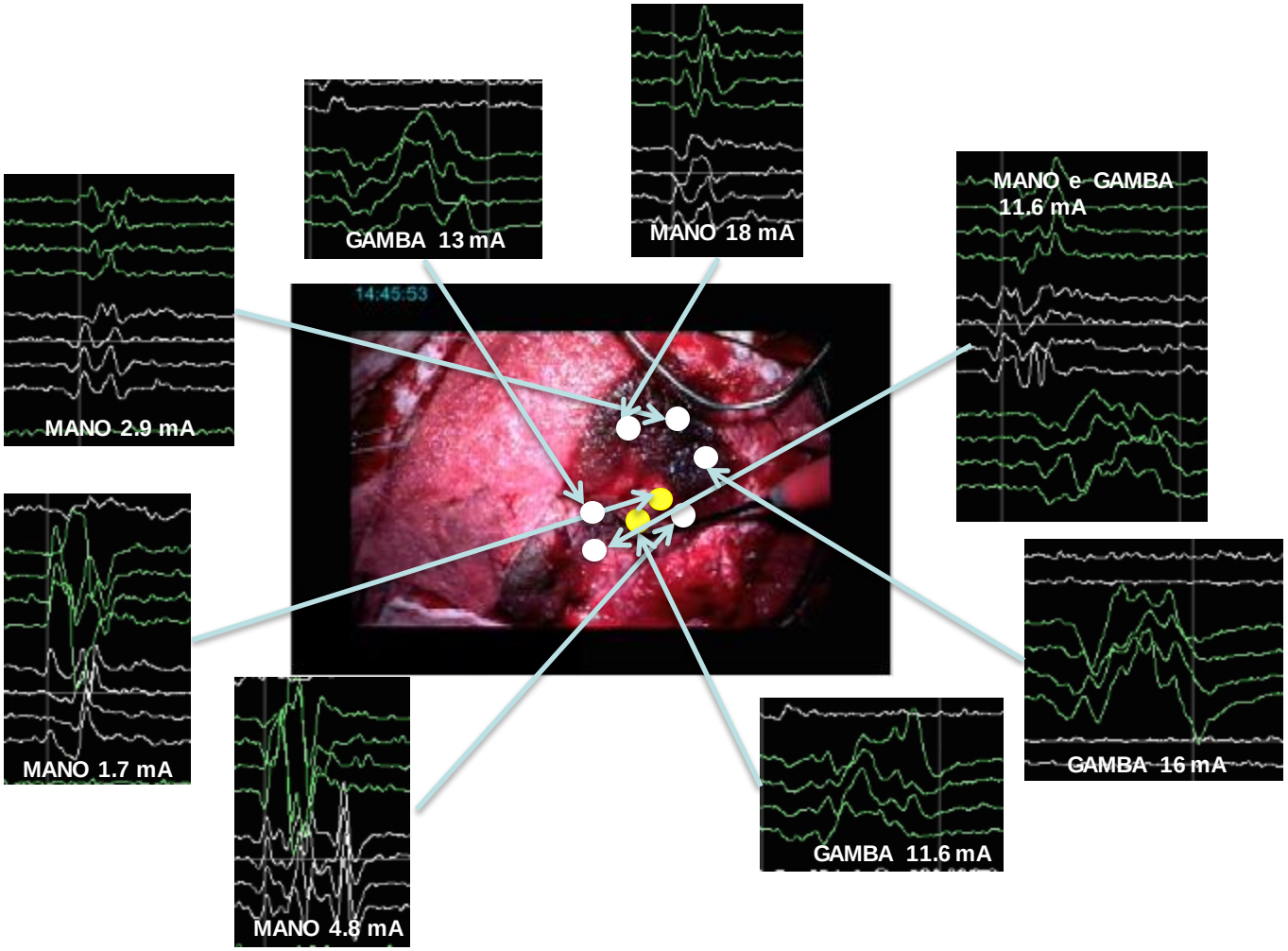
Courtesy of D. Mac Donald

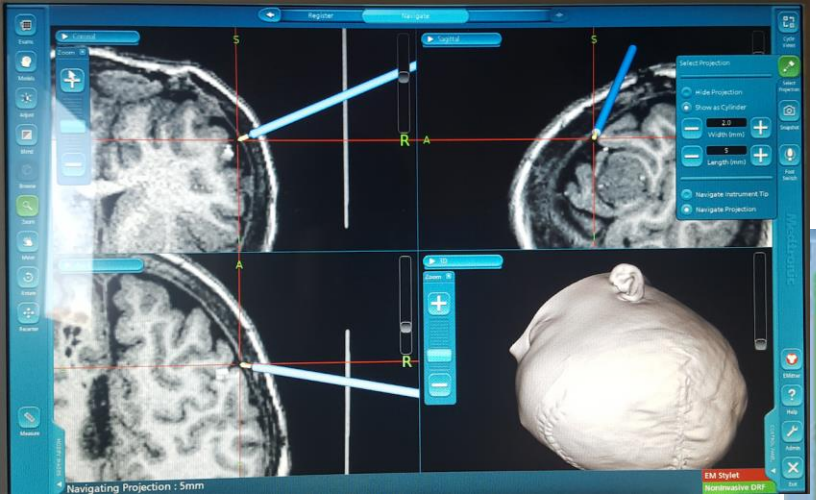

Triggered EMG
SIGNAL-CURSOR
1: 73.7ms
2: 83.7ms
dt: 10.1ms
du: 3.0 µV
NLG
V: ------
Distance mm 0
CURVES / CH.
Number 6
Date 24/07/2014
Time 12:30:08
Current [mA]: 8.71 mA
Stimsite:
Comments (6) :
50µV / Div
1
2
40.00
60.00
80.00
Ocul R
Oris R
Ext Dig R
Opp.p.R
Tib. Ant. R
Ha R
Export
JPG
Print
Quit
18:27:23

12:30:08

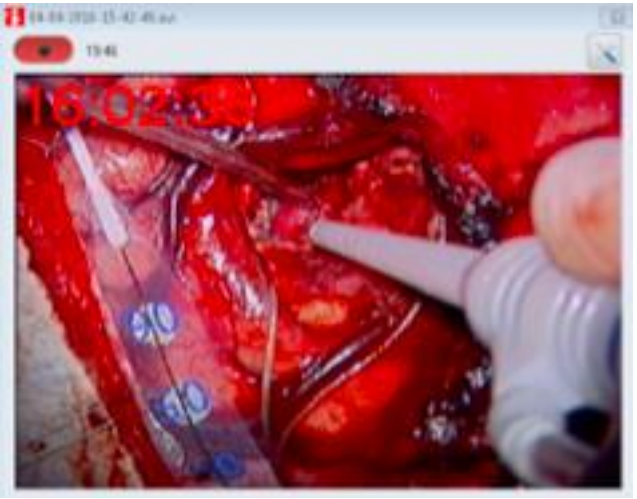

Triggered EMG
SIGNAL-CURSOR
1: 73.7ms
2: 83.7ms
dt: 10.1ms
du: 3.0 µV
NLG
V: ------
Distance mm 0
CURVES / CH.
Number 6
Date 24/07/2014
Time
Current [r
Stimsite: HS
15.49 mA
Comments (6) :
50µV / Div
1
2
40.00
60.00
80.00
Ocul R
Oris R
Ext Dig R
Opp.p.R
Tib. Ant. R
Ha R
Export
JPG
Print
Quit
18:28:32
13:12:56

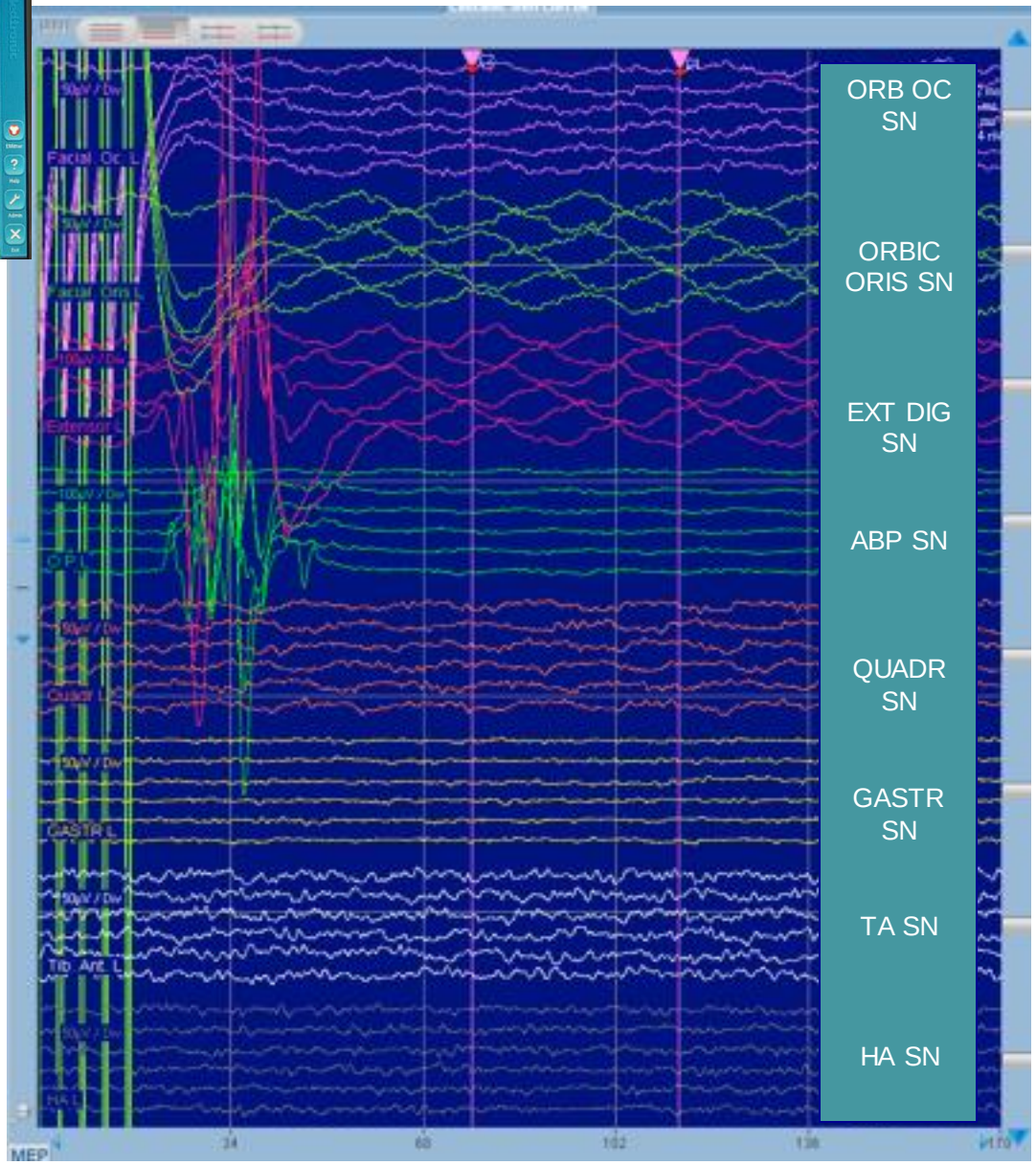
CORTICAL AND SUBCORTICAL MAPPING



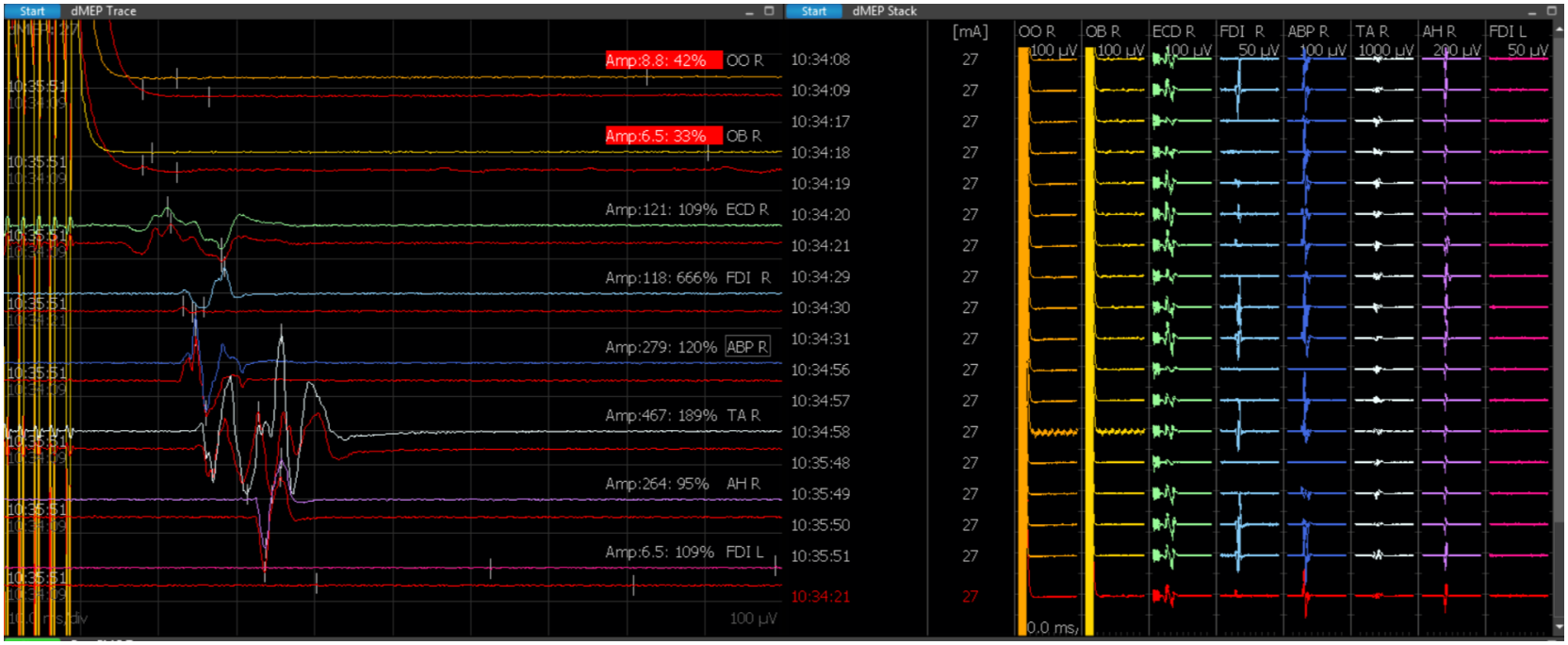

Navigating Projection : 5mm

#3-Fz 5 st 20 mA

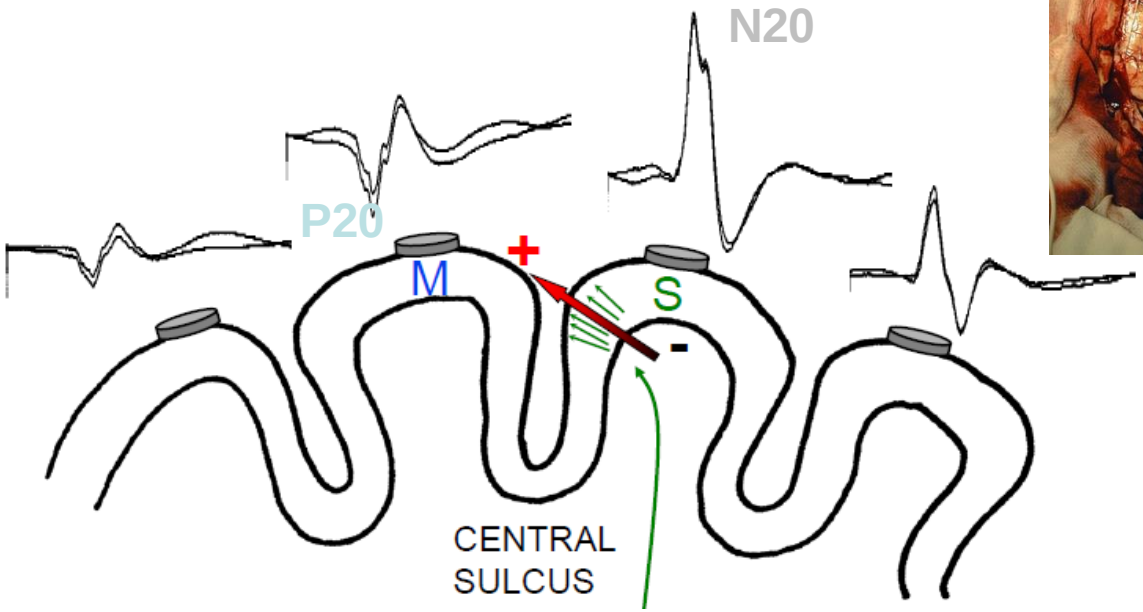


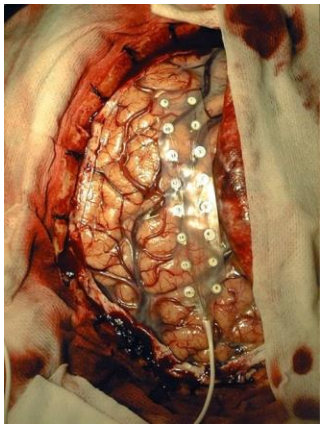

ORB OC SN
ORBIC ORIS SN
EXT DIG SN
ABP SN
QUADR SN
GASTR SN
TA SN
HA SN
MEP

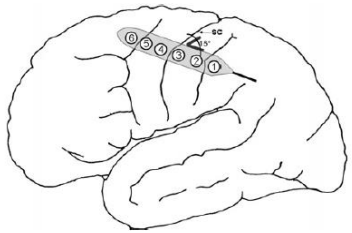
TcMEP - dMEP


Start
dMEP Trace
Amp:8.8: 42% OO R
Amp:6.5: 33% OB R
Amp:121: 109% ECD R
Amp:118: 666% FDI R
Amp:279: 120% ABP R
Amp:467: 189% TA R
Amp:264: 95% AH R
Amp:6.5: 109% FDI L
100 µV
Start
dMEP Stack
[mA]
OO R
OB R
ECD R
FDI R
ABP R
TA R
AH R
FDI L
100 µV
50 µV
1000 µV
200 µV
10:34:08
10:34:09
10:34:17
10:34:18
10:34:19
10:34:20
10:34:21
10:34:29
10:34:30
10:34:31
10:34:56
10:34:57
10:34:58
10:35:48
10:35:49
10:35:50
10:35:51
10:34:21
27
0.0 ms

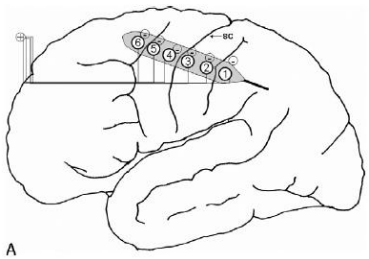
Median nerve cortical SEP





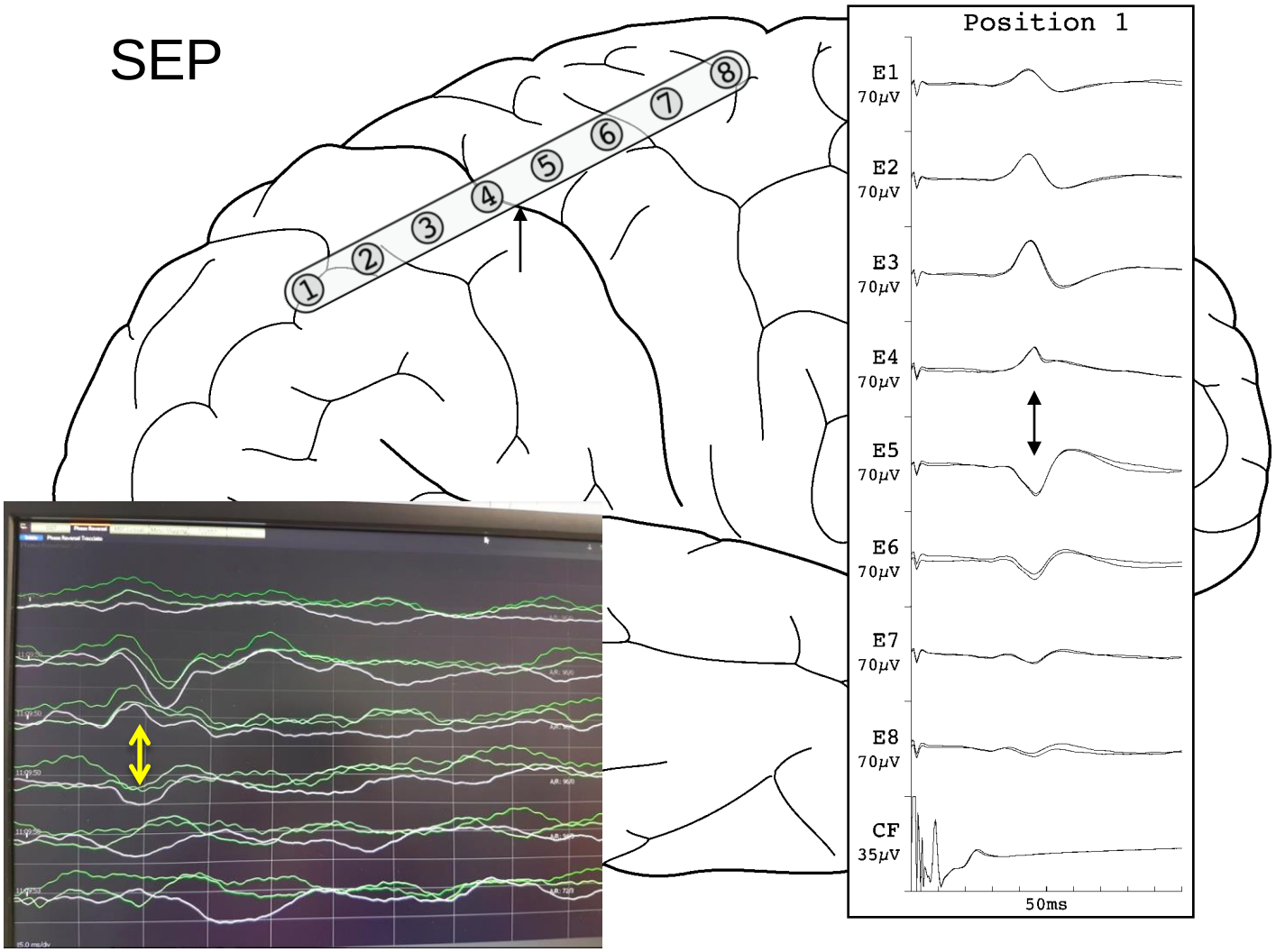


Optimal position must have a 15° angle to the central sulcus.

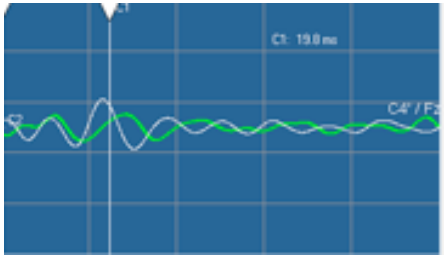


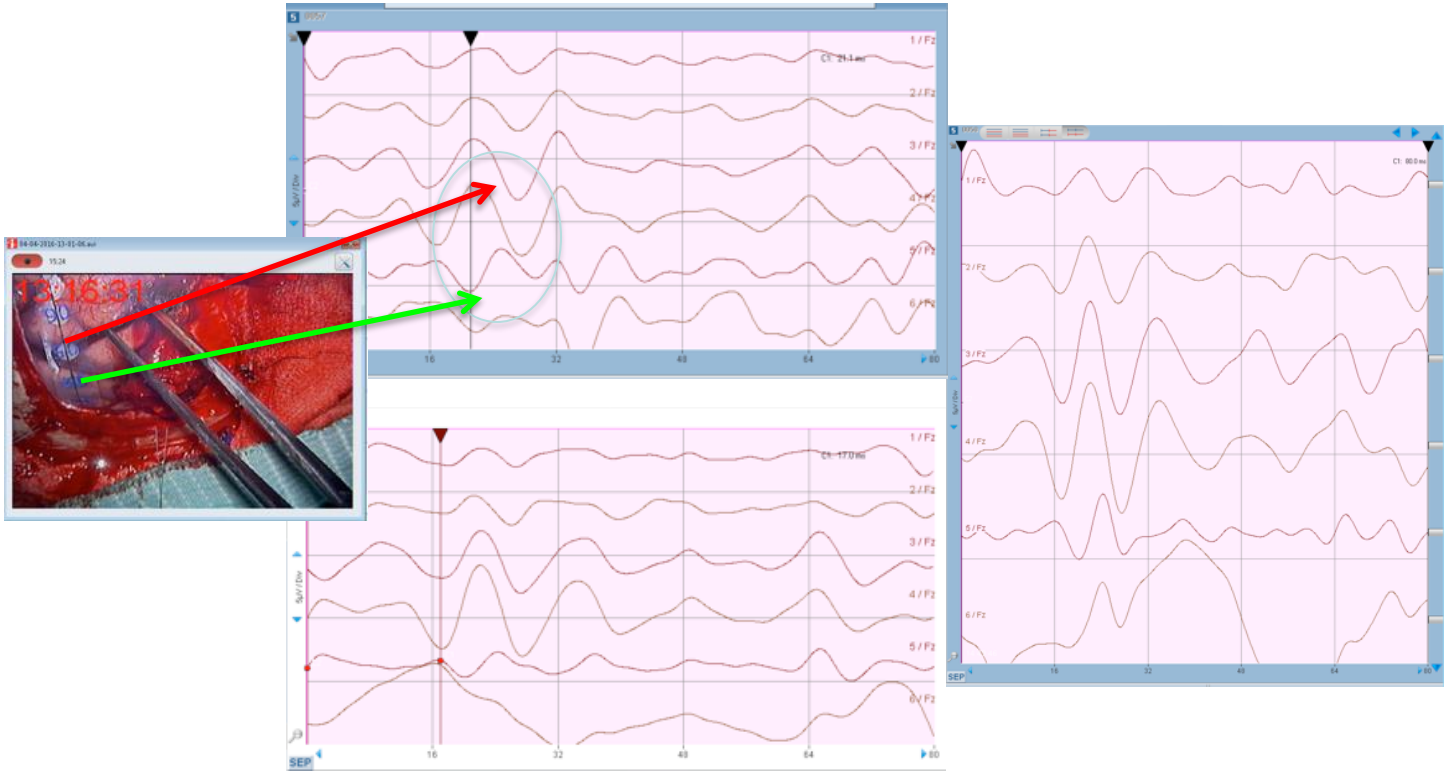
A

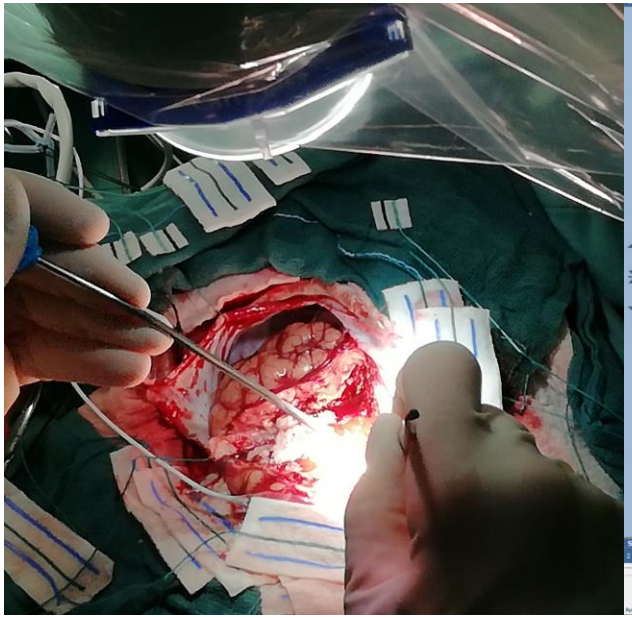
Courtesy of D. Mac Donald

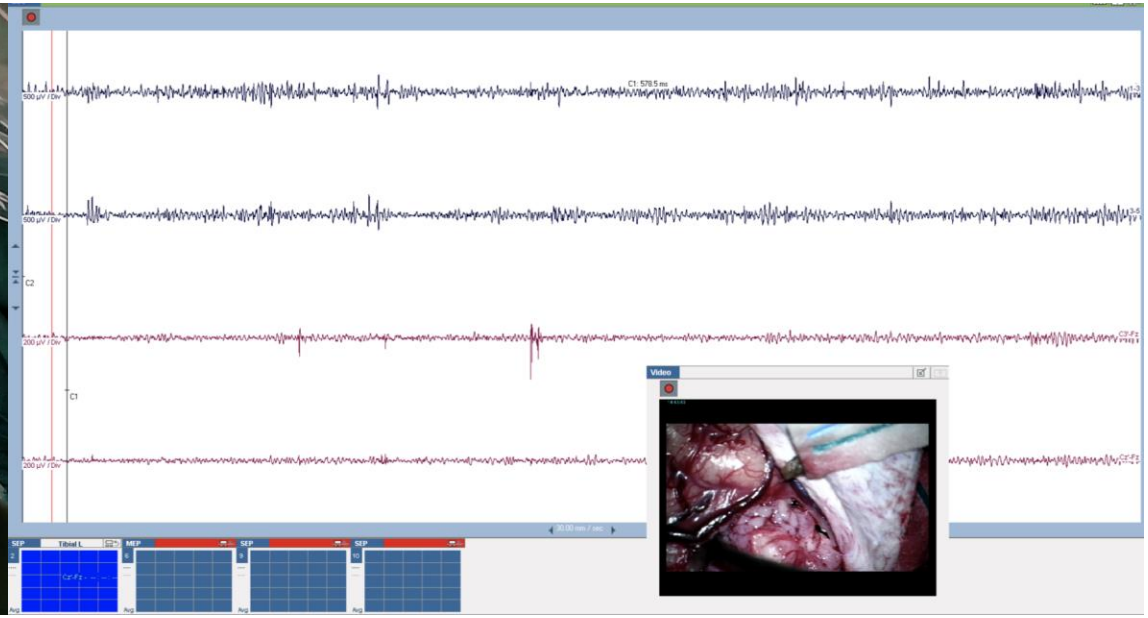

SEP
Position 1
E1
70μV
E2
70μV
E3
70μV
E4
70μV
E5
70μV
E6
70μV
E7
70μV
E8
70μV
CF
35μV
50ms
1
2
3
4
5
6
7
8

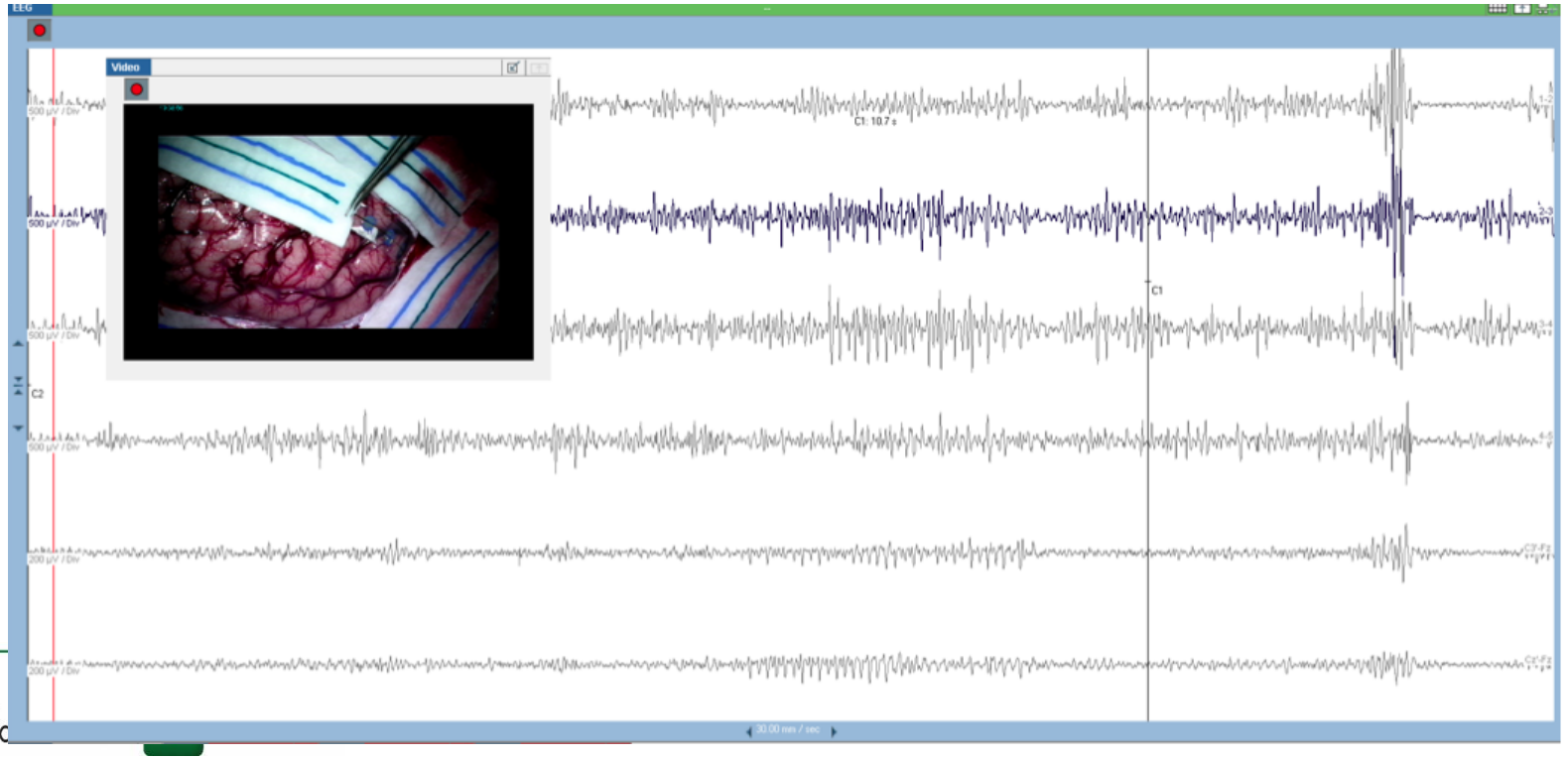
MEDIAN NERVE STIMULATION FOR IDENTIFICATION OF PHASE REVERSAL N20/P20 FOR FUNCTIONAL CENTRAL SULCUS POSITION



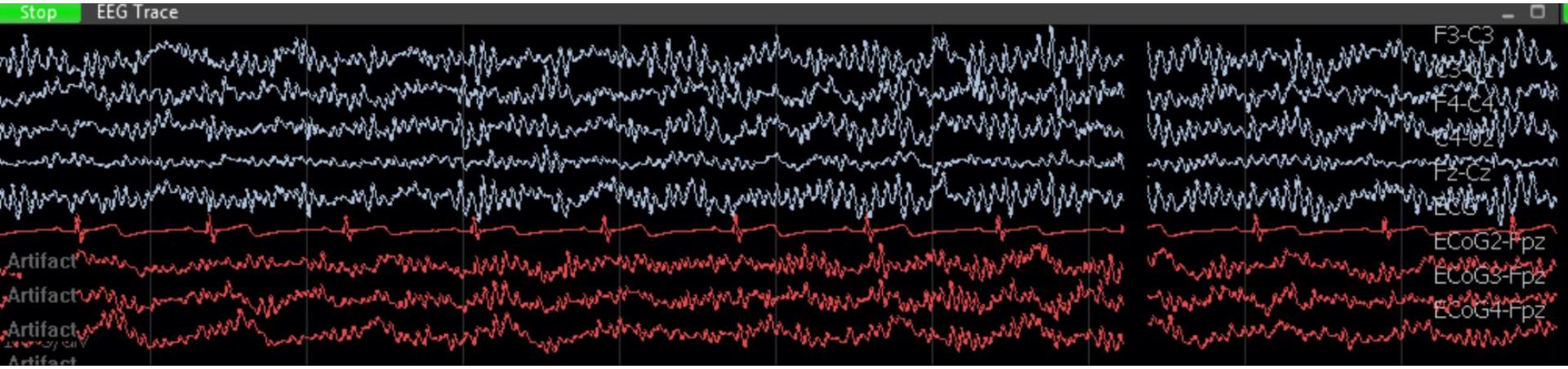




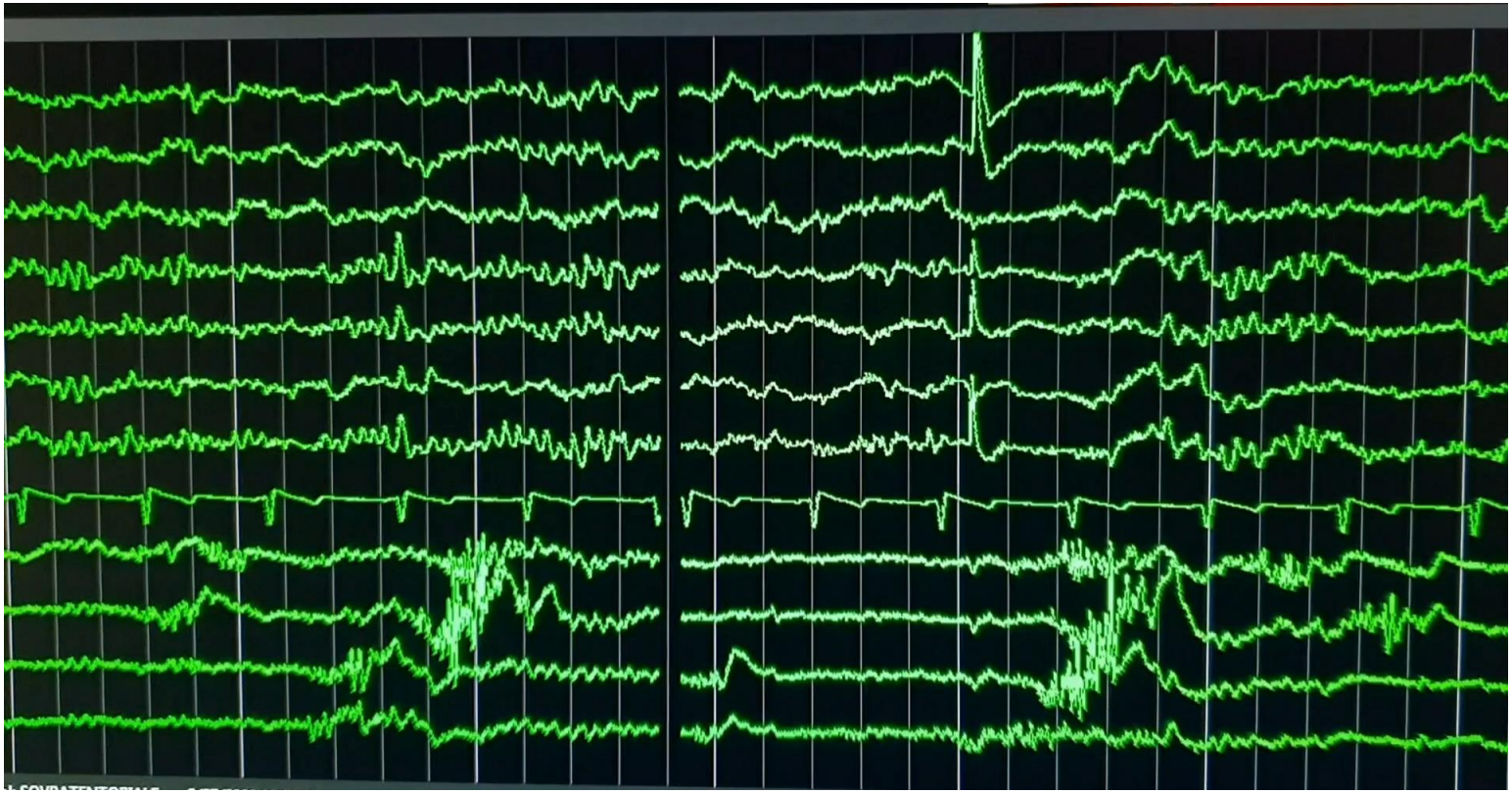

Video
SEP
Tibial L
MEP
SEP
SEP


EEG
Video
C1: 10.7 s
C1
C2
30.00 mm / sec

EEG - EoCG


Stop
EEG Trace
F3-C3
C3-O1
F4-C4
C4-O2
Fz-Cz
ECG
ECoG2-Fpz
ECoG3-Fpz
ECoG4-Fpz
Artifact
Artifact
Artifact

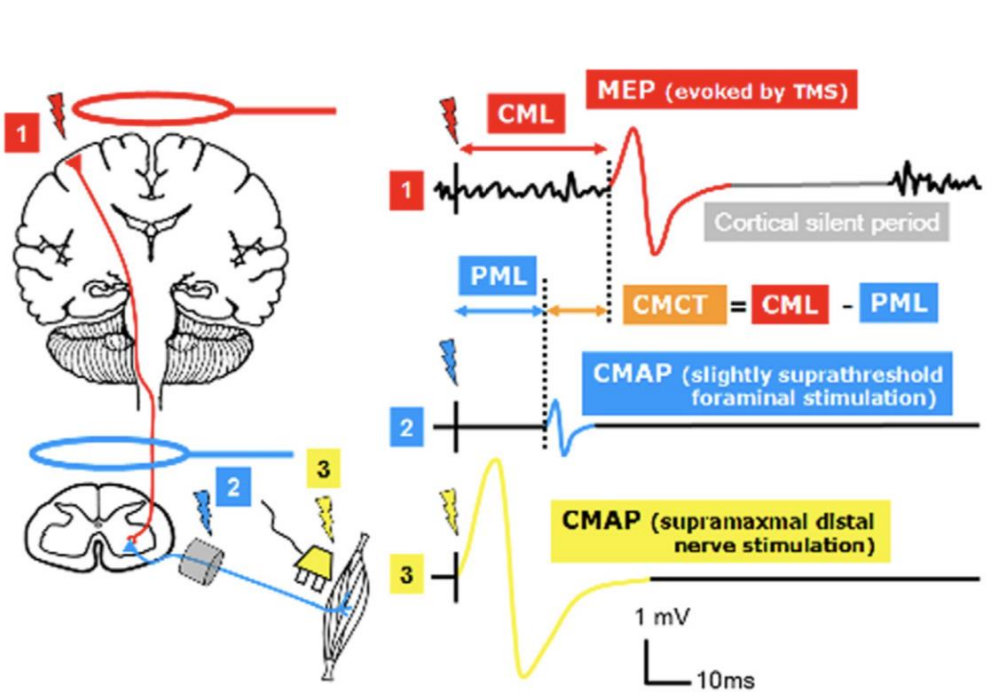
ECoG

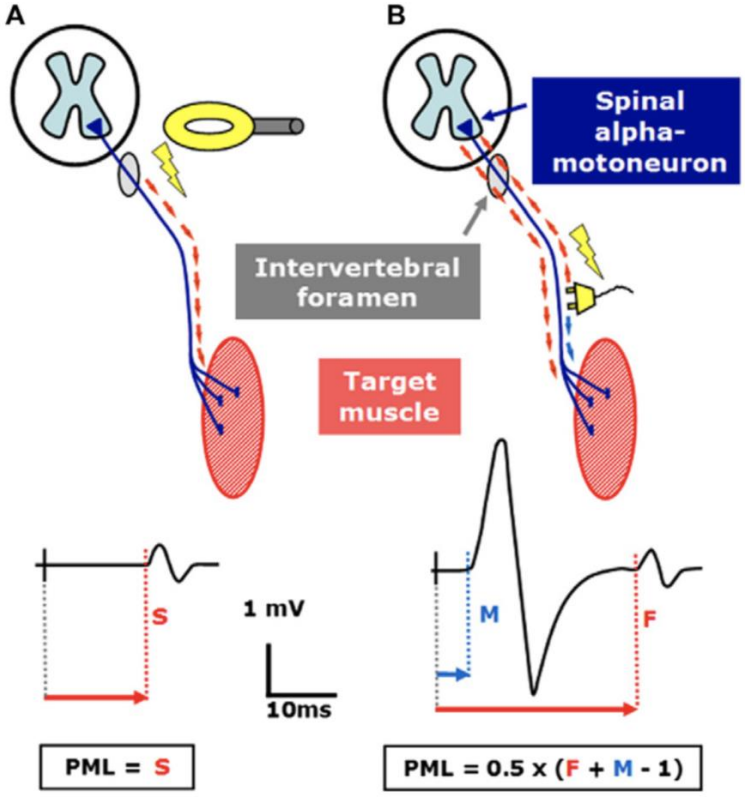


Groppa S, et al.

A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee.

Clin Neurophysiol. 2012 May;123(5):858-82. doi: 10.1016/j.clinph.2012.01.010.





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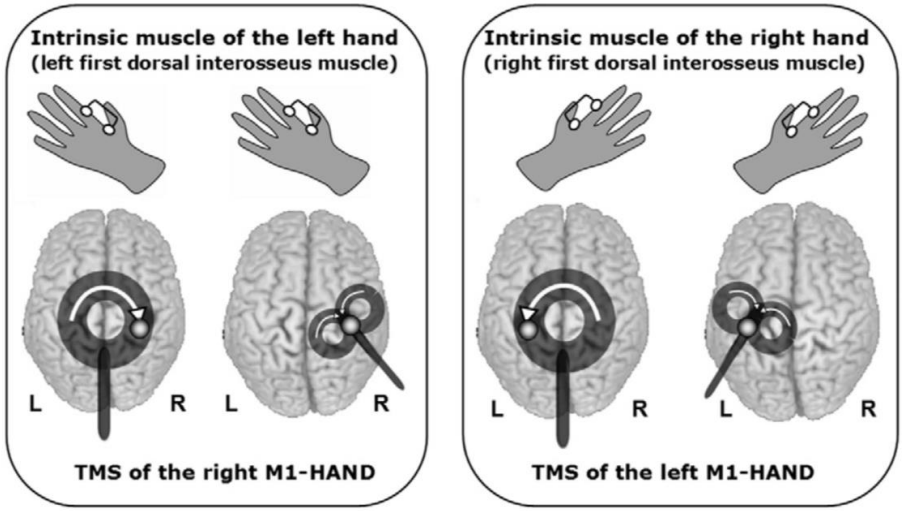
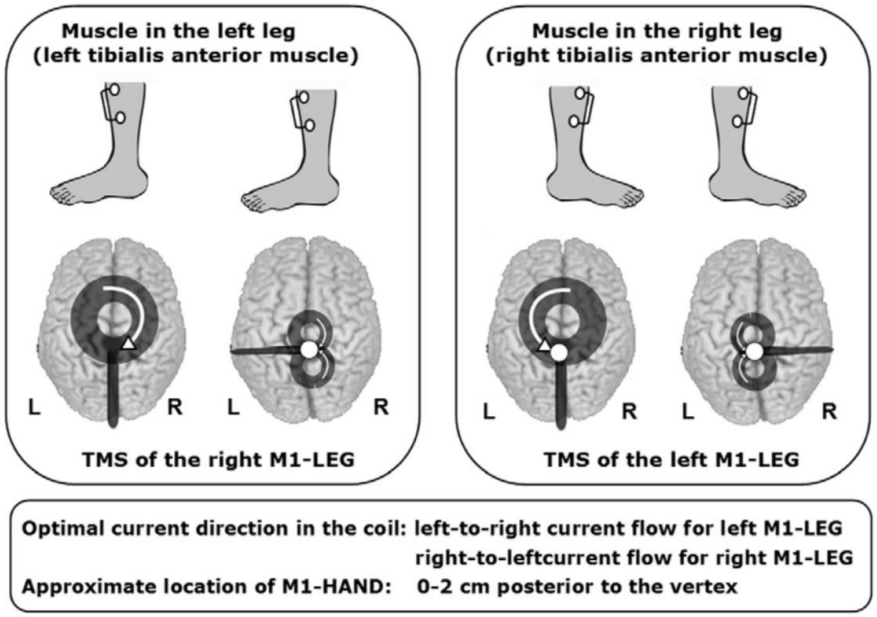




JANNATI A, ET AL.

BIOMARKERS OBTAINED BY TRANSCRANIAL MAGNETIC STIMULATION IN NEURODEVELOPMENTAL DISORDERS.

J CLIN NEUROPHYSIOL. 2021 AUG 3. DOI: 10.1097/WNP.0000000000000784.

TREMBLAY S, ET AL.

CLINICAL UTILITY AND PROSPECTIVE OF TMS-EEG.

CLIN NEUROPHYSIOL. 2019 MAY;130(5):802-844. DOI: 10.1016/J.CLINPH.2019.01.001.

EEG + TMS

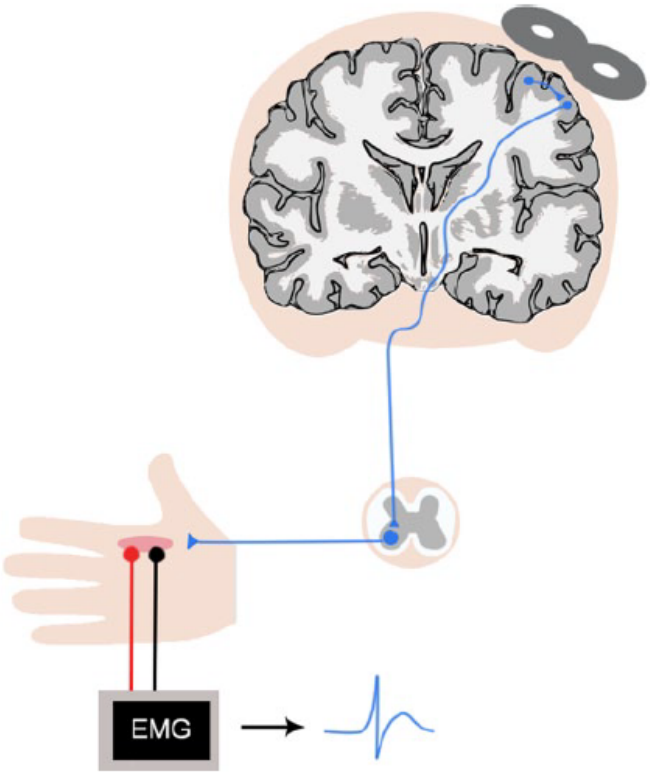
Jannati A, et al.

Biomarkers Obtained by Transcranial Magnetic Stimulation in Neurodevelopmental Disorders.

J Clin Neurophysiol. 2021 Aug 3. doi: 10.1097/WNP.0000000000000784.

1. Single-Pulse TMS
2. Paired-Pulse TMS
3. Repetitive TMS (several pulses at 1 to 20 Hz frequency over long periods of stimulation)
4. Paired Associative Stimulation (PAS) (involves repeated pairing of two stimuli, e.g., a peripheral electrical pulse delivered to a nerve of the hand, usually the median nerve, that activates the primary somatosensory cortex and a TMS pulse over the corresponding hand representation in the contralateral M1)

Box 2. Transcranial Magnetic Stimulation.



TMS is a noninvasive method of brain stimulation in which an electrical current is generated in a wire coil (TMS coil), producing a magnetic field. This magnetic field passes painlessly through the scalp and induces an electric field perpendicular to that of the magnetic field, activating cortical neurons beneath the TMS coil. When delivered to the motor cortex, it creates a descending volley in the corticospinal tract and leads to a response in the target muscle, known as a motor-evoked potential (MEP). The size of the MEP reflects the integrity of the corticospinal tract. In paired-pulse form, TMS can be used to assess inhibitory and excitatory intracortical and interhemispheric phenomena, which reflect receptor and transcallosal activity, respectively. The first stimulus, known as the conditioning stimulus, modulates the second stimulus, known as the test stimulus. Intracortical phenomena are assessed by delivering two TMS stimuli to the same hemisphere while interhemispheric phenomena are assessed by delivering a TMS pulse to each hemisphere. Below are parameters that are typically used in TMS studies.

Intracortical phenomena	Receptor activity	Common stimulation parameters
Short-interval intracortical inhibition	$GABA_A$	ISI: 2 ms, TS: 1 mV, CS: 80% or 90% AMT
Long-interval intracortical inhibition	$GABA_B$	ISI: 100 ms, TS: 1 mV, CS: 1 mV
Intracortical facilitation	NMDA	ISI: 10 ms, TS: 1 mV, CS: 80% or 90% AMT
Ipsilateral silent period	—	TMS pulse to the ipsilateral hemisphere during isometric contraction of muscle

Receptor activity: Ziemann and others 2014; ISI = interstimulus interval; TS = test stimulus; CS = conditioning stimulus; AMT = active motor threshold.

Jannati A, et al.
Biomarkers Obtained by Transcranial Magnetic Stimulation in Neurodevelopmental Disorders.
J Clin Neurophysiol. 2021 Aug 3. doi: 10.1097/WNP.0000000000000784.

TABLE 1. Neurophysiological Measures Derived From TMS-EMG

TMS-EMG Measure	Protocol	Likely Mechanism(s)
rMT	spTMS: measure of minimum stimulus intensity necessary for a motor response at rest (recorded either by visual inspection or EMG) on ≥ 5/10 trials	Cortical motor neuron voltage-gated sodium channel-mediated membrane excitability
aMT	spTMS: measure of minimum stimulus strength necessary for ≥ 200 μV MEP during isometric contraction on ≥ 5/10 trials	Cortical motor neuron voltage-gated sodium channel-mediated membrane excitability+spinal contributions
MEP amplitude	spTMS: average peak-to-peak amplitude of MEP over 15–30 single pulses at 5–8 seconds ITI	Cortical motor neuron voltage-gated sodium channel-mediated membrane excitability
cSP	spTMS: measure of EMG suppression after MEP during voluntary contraction of a contralateral muscle	$GABA_B$-mediated and $GABA_A$-mediated motor cortex inhibition
iSP	spTMS: measure of EMG suppression after MEP during voluntary contraction of an ipsilateral muscle	$GABA_B$-mediated and $GABA_A$-mediated motor cortex inhibition
I/O curve	spTMS: measure of slope and plateau of the sigmoid curve of MEP amplitudes obtained at a wide range of stimulus intensities	Cortical motor neuron sodium- and calcium channel-mediated membrane excitability and $GABA_A$-mediated motor cortex inhibition
SICI	ppTMS CS = 50%–90% rMT | < 100% aMT TS = 1 mV | 100%–120% rMT ISI = 1–6 ms	$GABA_A$-mediated regional cortical inhibition
LICI	ppTMS CS = 100%–130% rMT | TS 1 mV TS = 1 mV | 120% rMT ISI = 50–200+ ms	$GABA_B$-mediated inhibition and (likely) $GABA_A$-mediated network inhibition
ICF	ppTMS CS = 90+ % rMT | > 80% aMT TS = 0.5–1.5 mV ISI = 8–30 ms	Glutamate (NMDA and AMPA receptor types)-mediated excitation
SICF	ppTMS CS = 100%–130% RMT | TS 1 mV TS = < rMT | 90% rMT ISI = 1–5 ms	Glutamate (non-NMDA receptor type)-mediated excitation
iTBS	rTMS: 50 Hz bursts of three TMS pulses repeated every 200 ms in a 2-second on, 8-second off pattern for 190 seconds (a total of 600 pulses)	Glutamate- and GABA-mediated mechanisms
cTBS	rTMS: 50 Hz bursts of three TMS pulses repeated every 200 ms for 40 seconds (a total of 600 pulses)	Glutamate- and GABA-mediated mechanisms
PAS	spTMS + MNS: 90–200 + pairs of MNS at the wrist and spTMS to contralateral M1 at 7–10 second ITI ISI = 25 ms (PAS_{25}) | 10 ms (PAS_{10}) | N20 latency of MNS-evoked SSEP + 2 ms (PAS_{N20+2})	Glutamate (NMDA receptor type)-mediated excitation

TMS HAS ROBUST PROSPECTS IN THE DIAGNOSTIC AND BIOMARKER SPACE.

SPECIFICALLY, TMS-DERIVED BIOMARKERS HAVE BEEN OBTAINED FOR A RANGE OF DISEASE STATES THAT INCLUDE EPILEPSY, MIGRAINE, AND PAIN.

Tsuboyama M, Kaye HL, Rotenberg A. Biomarkers obtained by transcranial magnetic stimulation of the motor cortex in epilepsy. Front Integr Neurosci 2019;13:57.

Brighina F, Raieli V, Messina LM, et al. Non-invasive brain stimulation in pediatric migraine: a perspective from evidence in adult migraine. Front Neurol 2019;10:364.

Zaghi S, Thiele B, Pimentel D, Pimentel T, Fregni F. Assessment and treatment of pain with non-invasive cortical stimulation. Restor Neurol Neurosci 2011;29:439–451.

Lebedev MA, Nicolelis MA.
Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation.
Physiol Rev. 2017 Apr;97(2):767-837. doi: 10.1152/physrev.00027.2016.

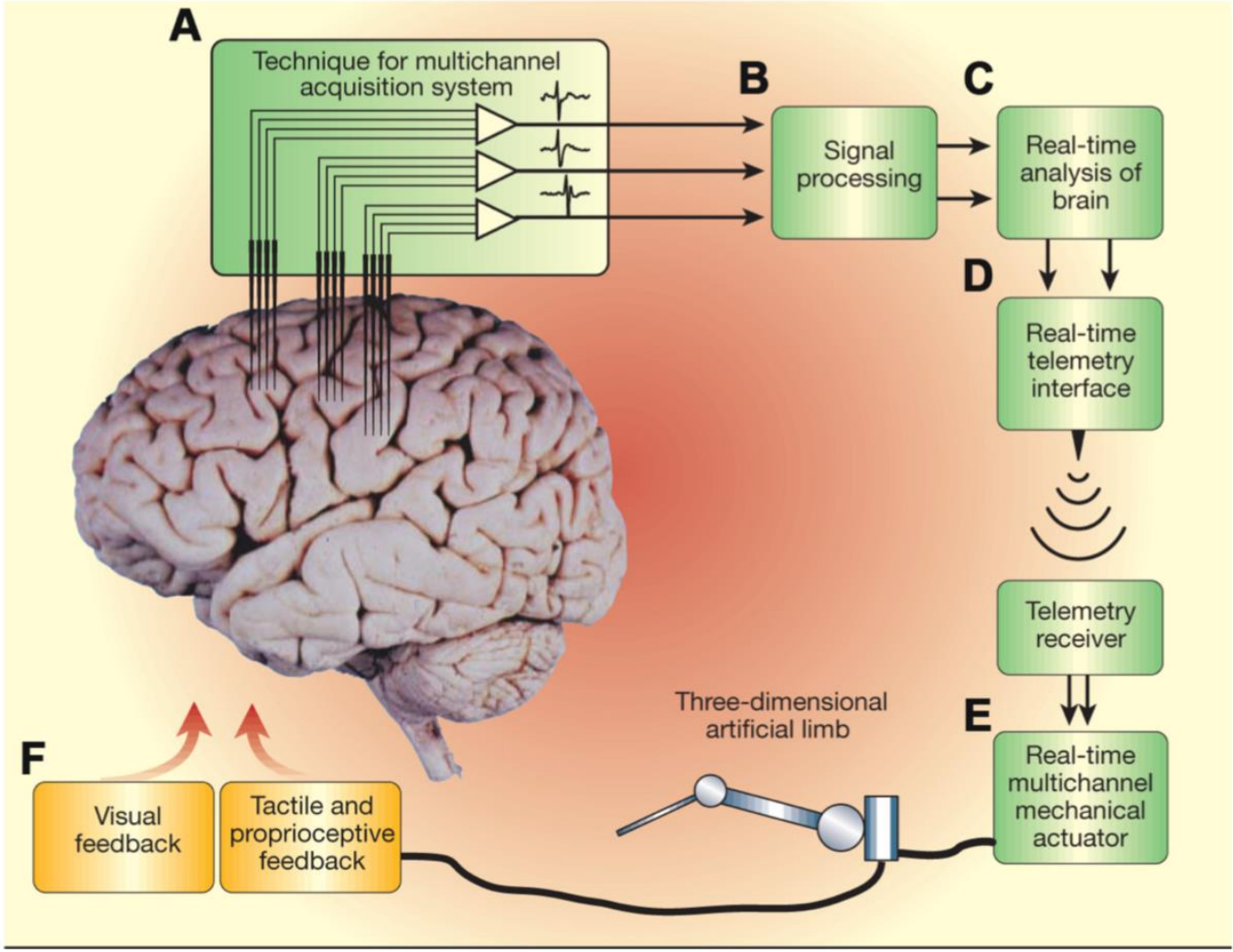
- However, with the publication of a series of original studies, conducted in rats and monkeys in the early 2000s, it soon became apparent that BMIs could also serve as the foundation of a new generation of neuroprosthetic devices aimed at restoring mobility to patients severely paralyzed due to trauma to the nervous systems, notably spinal cord injuries (SCIs) or neurodegenerative diseases.

Lebedev MA, Nicolelis MA.

Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation.

Physiol Rev. 2017 Apr;97(2):767-837. doi: 10.1152/physrev.00027.2016.

shows the original schematic description of this idea, proposed in the early 2000s, as an envisioned direct link between a human brain and a robotic arm



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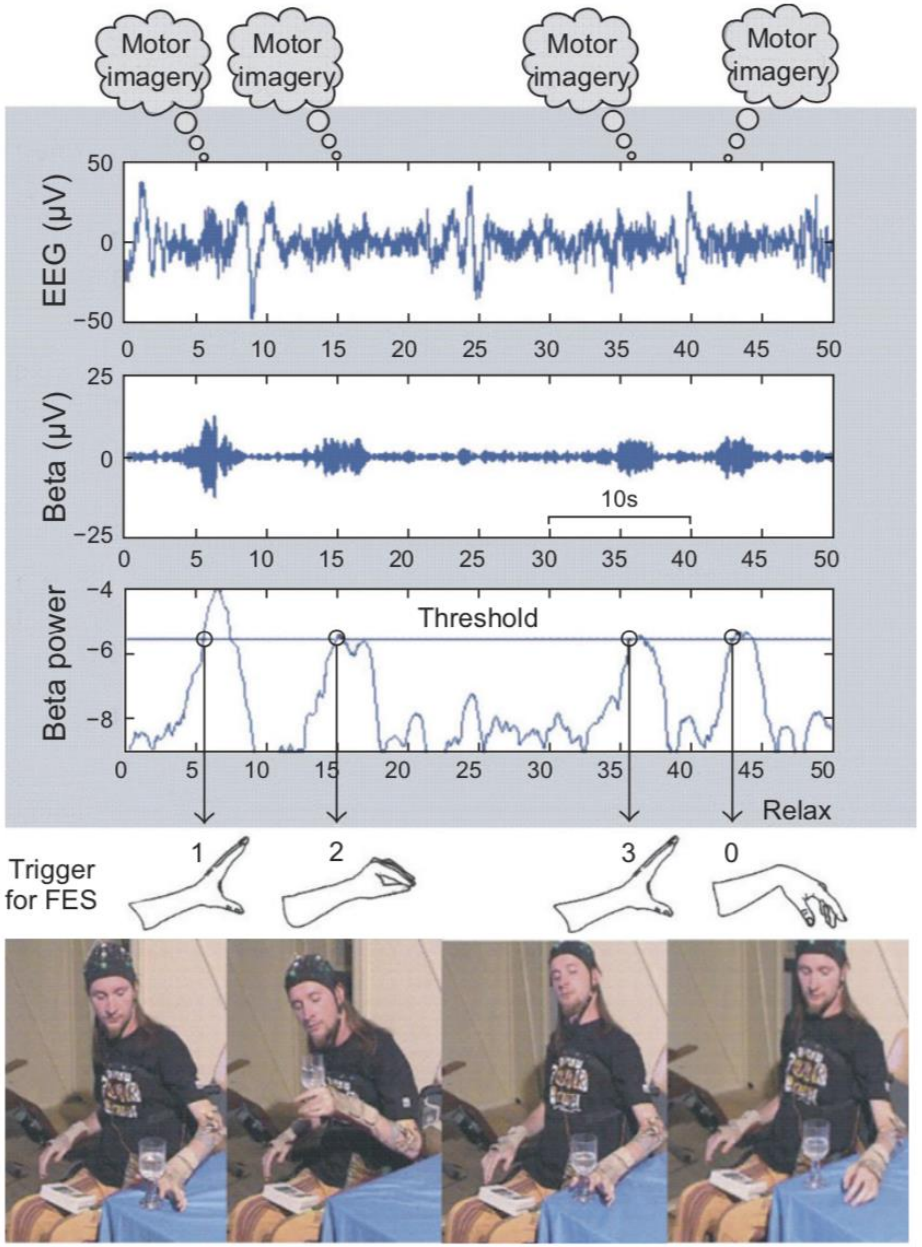
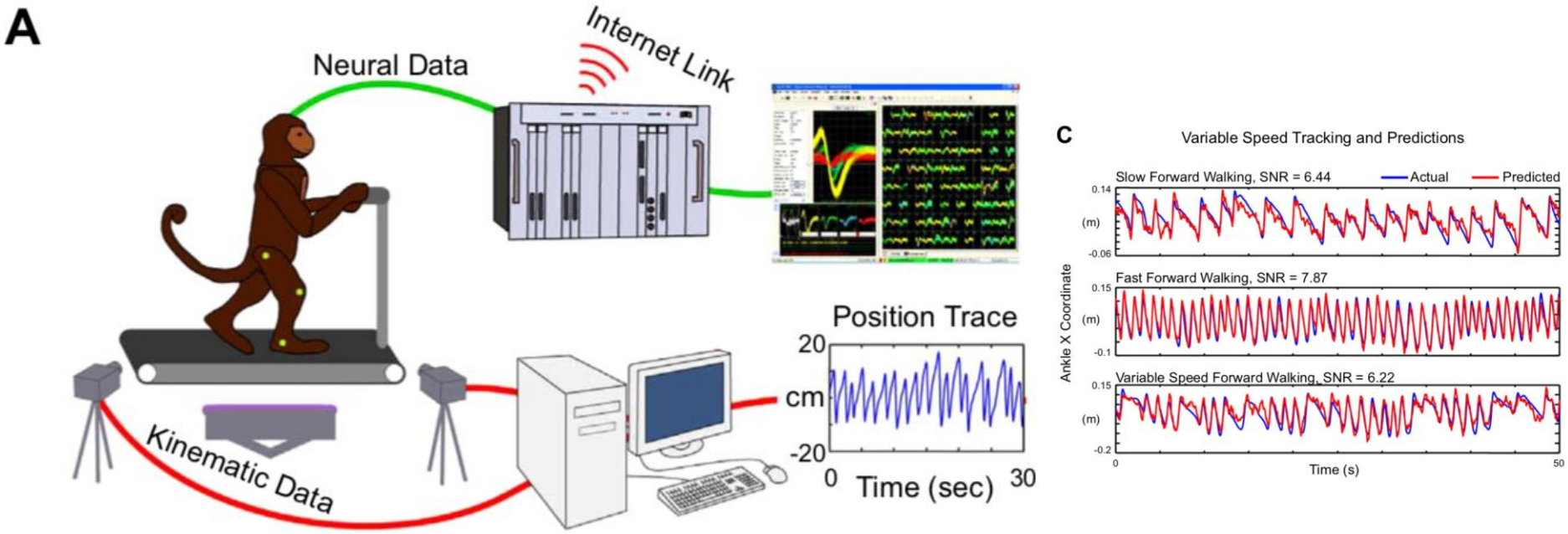
Physiol Rev. 2017 Apr;97(2):767-837.
doi: 10.1152/physrev.00027.2016.

recently a BMI core was used to allow patients to control stimulators that activate their own muscles through functional electrical stimulation (FES)



Lebedev MA, Nicolelis MA.
Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation.
Physiol Rev. 2017 Apr;97(2):767-837. doi: 10.1152/physrev.00027.2016.

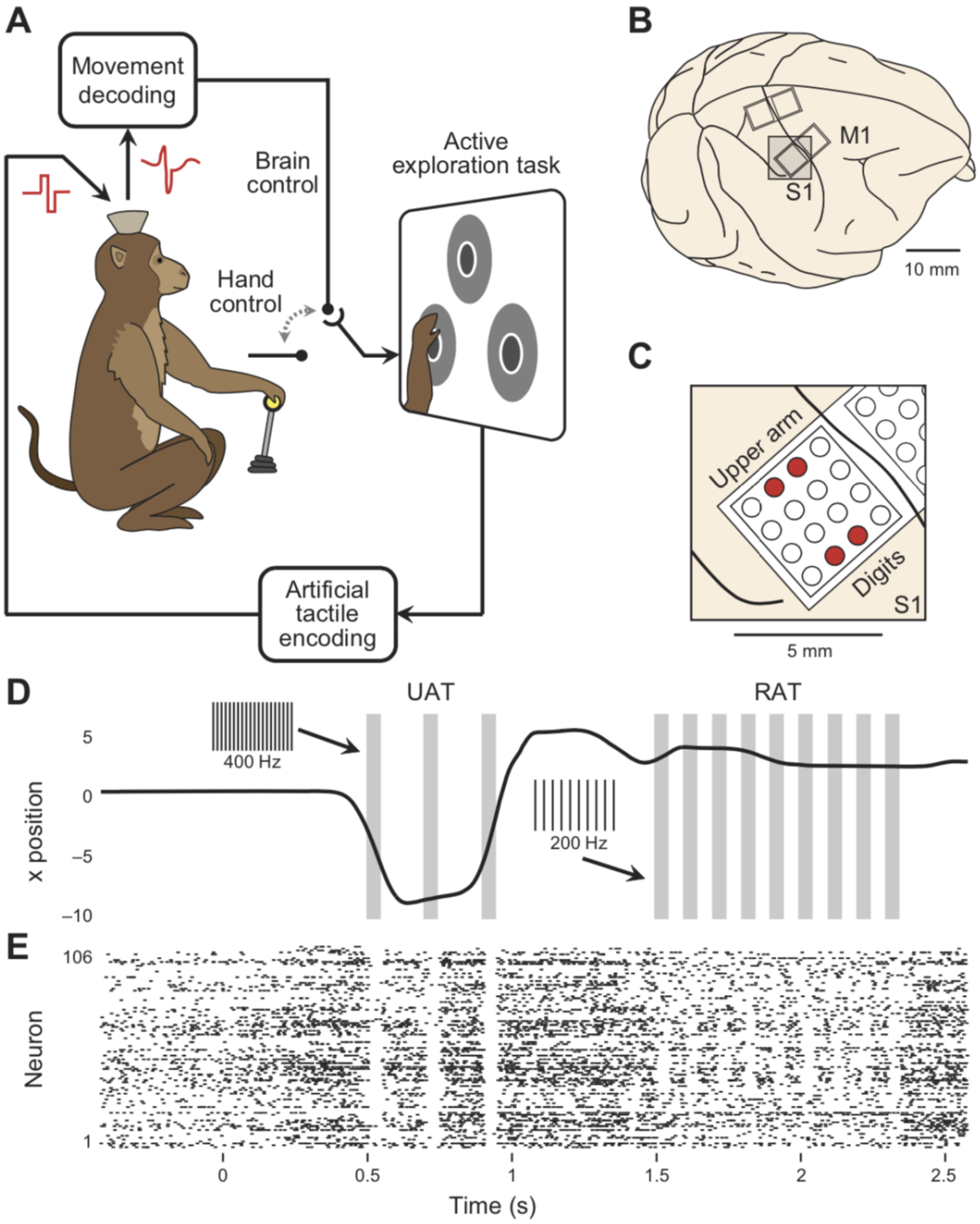


In 2009, the Nicolelis laboratory published the first BMI approach to decode kinematics of bipedal walk- ing in rhesus monkeys.

Two years later, in 2011, the same laboratory implemented, for the first time, a method for multi-channel ICMS as a tool to deliver direct tactile feedback to the subject's somatosen- sory cortex in a BMI setup = named a **brain-machine-brain interface (BMBI).**

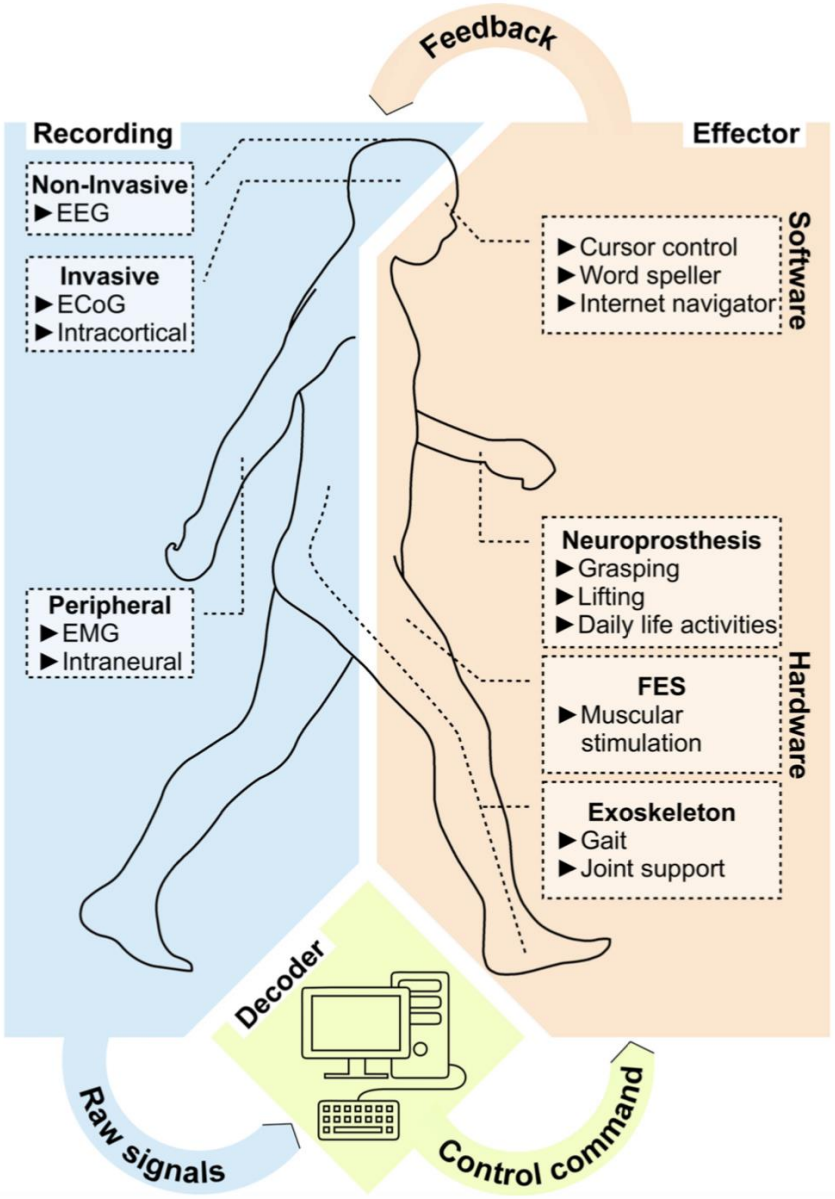
Lebedev MA, Nicolelis MA.
Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation.
Physiol Rev. 2017 Apr;97(2):767-837. doi: 10.1152/physrev.00027.2016.

- Brain-machine-brain interface. *A*: diagram of experimental setup. Monkey was seated in front of a computer screen showing an avatar arm an multiple targets. Motor commands were decoded from motor cortex activity. Artificial tactile feedback was produced by intracortical microstimulation ap- plied to primary somatosensory cortex. *B*: cortical location of microelectrode implants. *C*: microelec- trodes used for microstimulation (accented in red). *D*: avatar arm position for a representative trial. The monkey first placed the avatar hand over the unre- warded artificial texture (UAT), then ultimately se- lected rewarded artificial texture (RAT). Vertical gray bars correspond to the periods of microstimulation; *insets* indicate stimulation frequency. *E*: raster dis- play of motor cortex discharges for the same trial; spikes were not detected during microstimulation de- livery because of the stimulation-induced artifacts. Only the periods void of microstimulation were used for neural decoding. [Adapted from O'Doherty et al.



Lebedev MA, Nicolelis MA.
Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation.
Physiol Rev. 2017 Apr;97(2):767-837. doi: 10.1152/physrev.00027.2016.

- BMI systems are commonly categorized as follows:
- *1*) motor,
- *2*) sensory,
- *3*) sensorimotor (or bidirectional),
- *4*) cognitive.
- The recent introduction by our laboratory of BMIs that incorporate multiple brains of different subjects adds one more BMI class, which we named Brainet

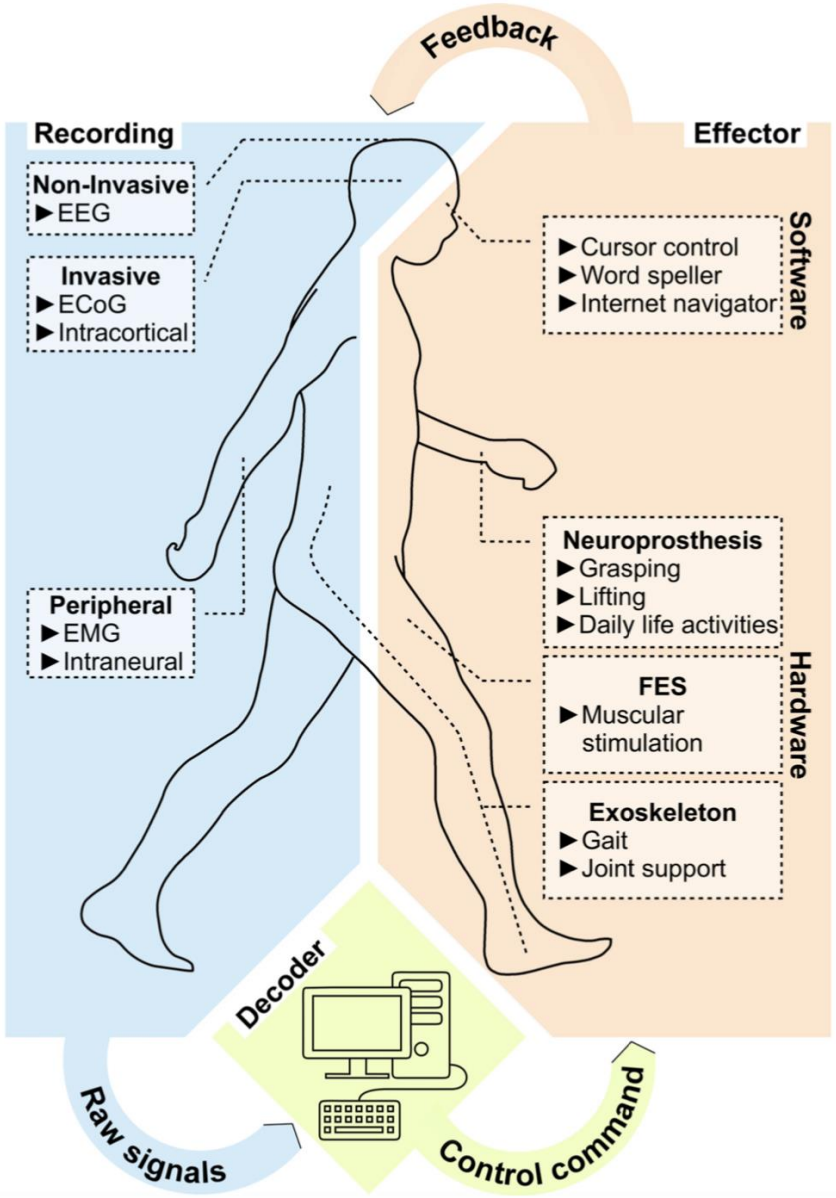


Pisotta I et al.
Hand-in-hand advances in biomedical engineering and sensorimotor restoration.
J Neurosci Methods. 2015 May 15;246:22-9. doi: 10.1016/j.jneumeth.2015.03.003.

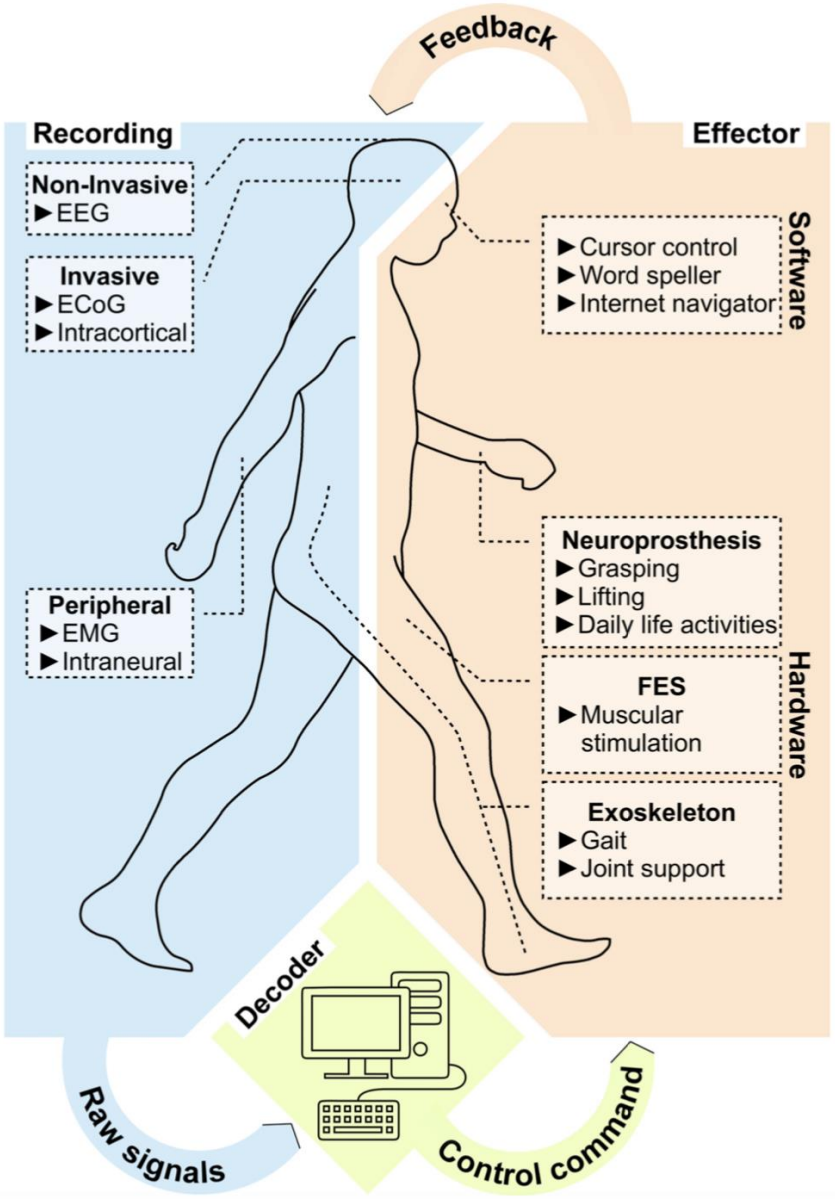
- "Brain–Machine Interfaces" (BMIs).

- Invasive and non-invasive BMIs
- the recording of the neural activity can assume two different forms: invasive or non-invasive.
- Neural activity can be recorded by means of electrodes implanted in the brain and translated in real-time into computational commands to control a robotic device.

- Beta 1, Beta 2, and Gamma rhythms are dominant in frontal areas associated with the regulation of motor commands, imagery, and plans



- Level of physical exertion affect cognitive neural dynamics, even if the brain reallocated resources to perform both tasks simultaneously



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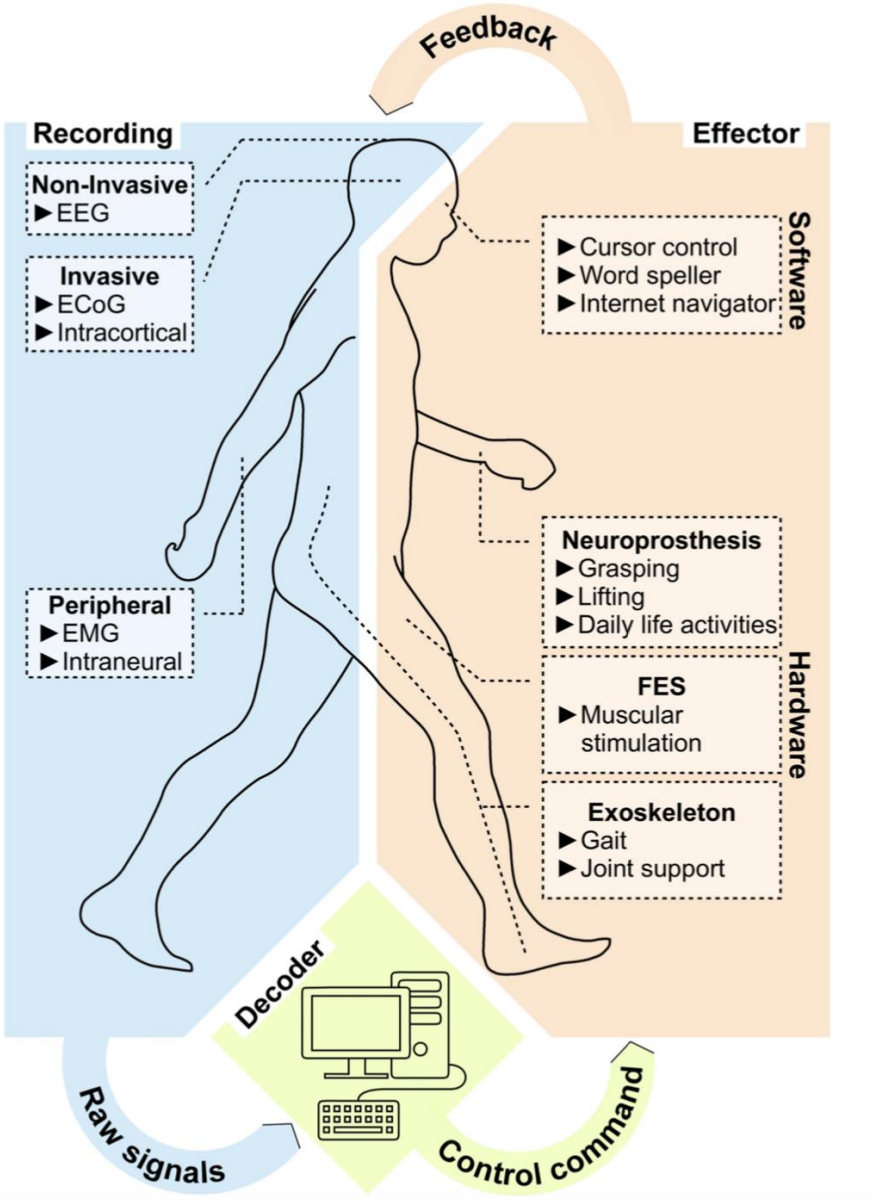
- non-invasive BMI for controlling external devices by means of non-invasively recorded neural activity using electroencephalography (EEG).
- With respect to invasive BMI, the signals have lower quality and the system requires longer training.
- However, the risks of non-invasive BMI are lower, the quality of the signal can be improved by using adaptive algorithms during the training (Wolpaw and McFarland, 2004), and its sensitivity renders it the best BMI candidate to differentially classify a broad panel of conditions, including cognitive states



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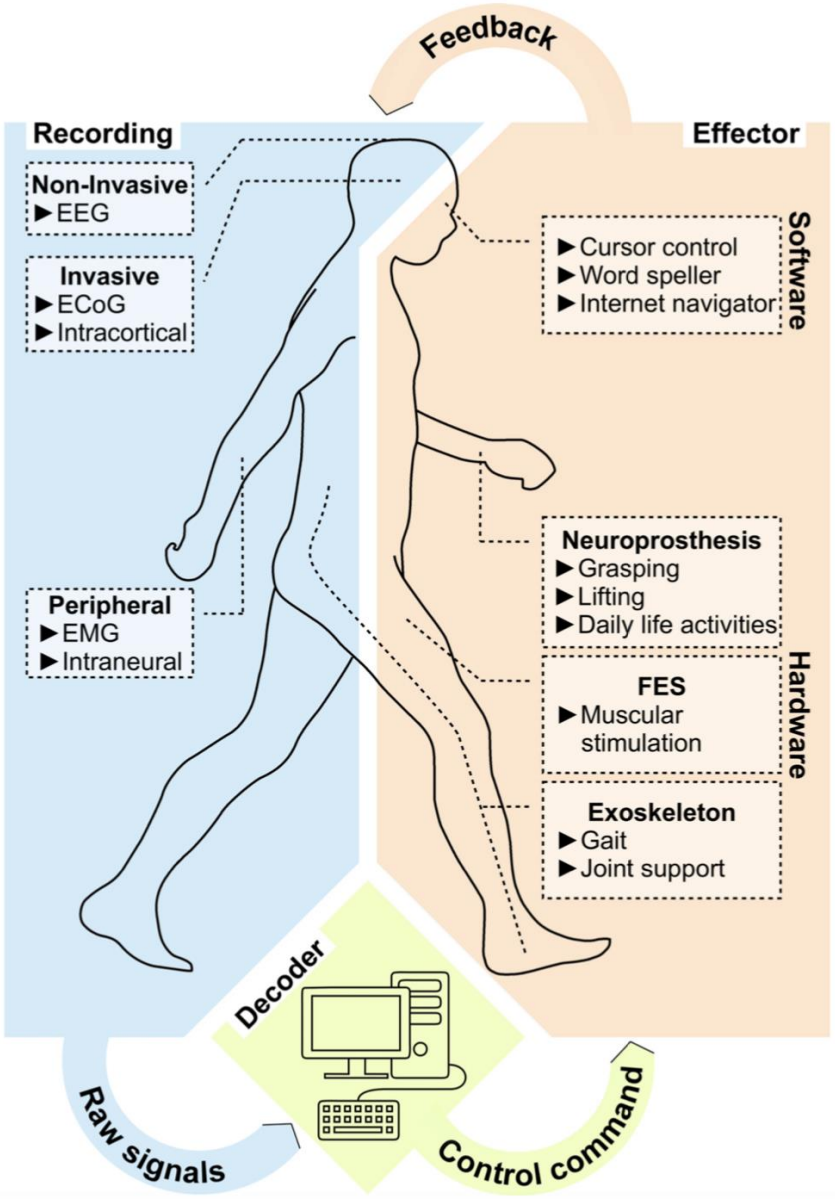
J Neurosci Methods. 2015 May 15;246:22-9. doi: 10.1016/j.jneumeth.2015.03.003.

- Being based on the recording and encoding of the residual muscular activity, EMG-based systems are particularly feasible for partially paralyzed patients
- the EMG-based BMI and can use it for controlling neuroprostheses and exoskeletons in daily life conditions more frequently with respect to EEG-based systems (Light et al., 2002; Zecca et al., 2002).
- The combination of EEG- and EMG-based BMIs to create a hybrid system, is the most recent advance in neuroprosthetics and the most promising future direction of BMI research.



Pisotta I et al.

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- One of the most challenging and at the same time necessary developments of contemporary research in neuroprosthetics is the effort to help users incorporate the prosthesis into the body schema, i.e. the online sum of all the somatosensory information related to the body including e.g. proprioception, pain, interocep- tion, etc. (Berlucchi and Aglioti, 2010).
- Recent evidence in cognitive neuroscience research showed the importance of the congruence between visual and tactile information for a proper functional representation of one's own limb with respect to the rest of the body (Ionta et al., 2013).

Sharifi S, et al.
Directionality of corticomuscular coupling in essential tremor and cortical myoclonic tremor.
Clin Neurophysiol. 2021 Aug;132(8):1878-1886. doi: 10.1016/j.clinph.2021.04.011.

- A common hypothesis regarding the origin of ET involves dysregulated neuronal signaling within the cerebello-thalamo-cortical network, or ‘‘tremor network”
- A prominent role of the central sensorimotor cortex was suggested following several EEG-EMG and MEG-EMG studies that demonstrated corticomuscular coupling at tremor frequency
- Each recording was segmented in L epochs (2 seconds). Subsequently, the spectra and coherence values were estimated for each epoch. Per participant per task, the EMG channel with the most distinct tremor peak on visual inspection and in power spectral density was chosen for further analyses. Also, we determined the ‘EEG hotspot’: the EEG electrode with the strongest corticomuscular coherence. we selected the electrode over the central (sensorimotor) cortical area contralateral to the tremor with strongest corticomuscular coherences (FC3 and C3) per participant to calculate directionality

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Directionality of corticomuscular coupling in essential tremor and cortical myoclonic tremor.

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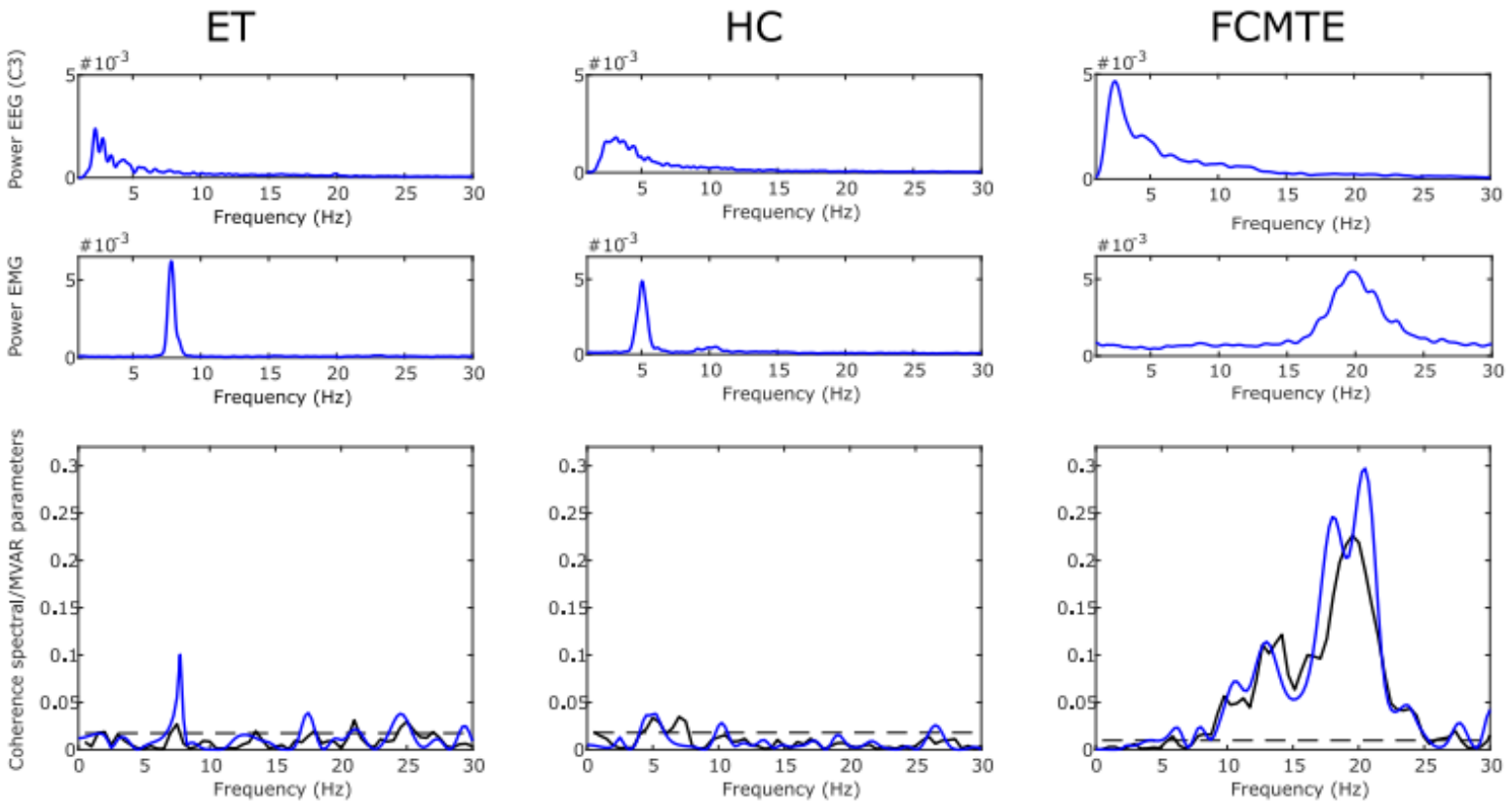


Sharifi S, et al.
Directionality of corticomuscular coupling in essential tremor and cortical myoclonic tremor.
Clin Neurophysiol. 2021 Aug;132(8):1878-1886. doi: 10.1016/j.clinph.2021.04.011.

- RPDC, which is based on Granger causality, is a robust technique to investigate directionality with statistical endorsement (Schelter et al., 2006, 2009).
- It starts from the premise that causes must precede their effects in time; thus, information in a cause's past must improve the prediction of the effect and crosscorrelation.
- With standard corticomuscular coherence analysis, a common (exogenous) cause may synchronize two signals revealing coherence, however, without having a directional causal relationship (Mullen, 2010).
- Also, the corticomuscular loop consists out of multiple relays including afferent and efferent pathways. Therefore, bidirectional coupling or a 'simultaneous' information flow in both directions is likely to exist.
- The coefficients of the coupling are calculated in two directions: the afferent information flow (EMG→EEG) and the efferent information flow (EEG → EMG).

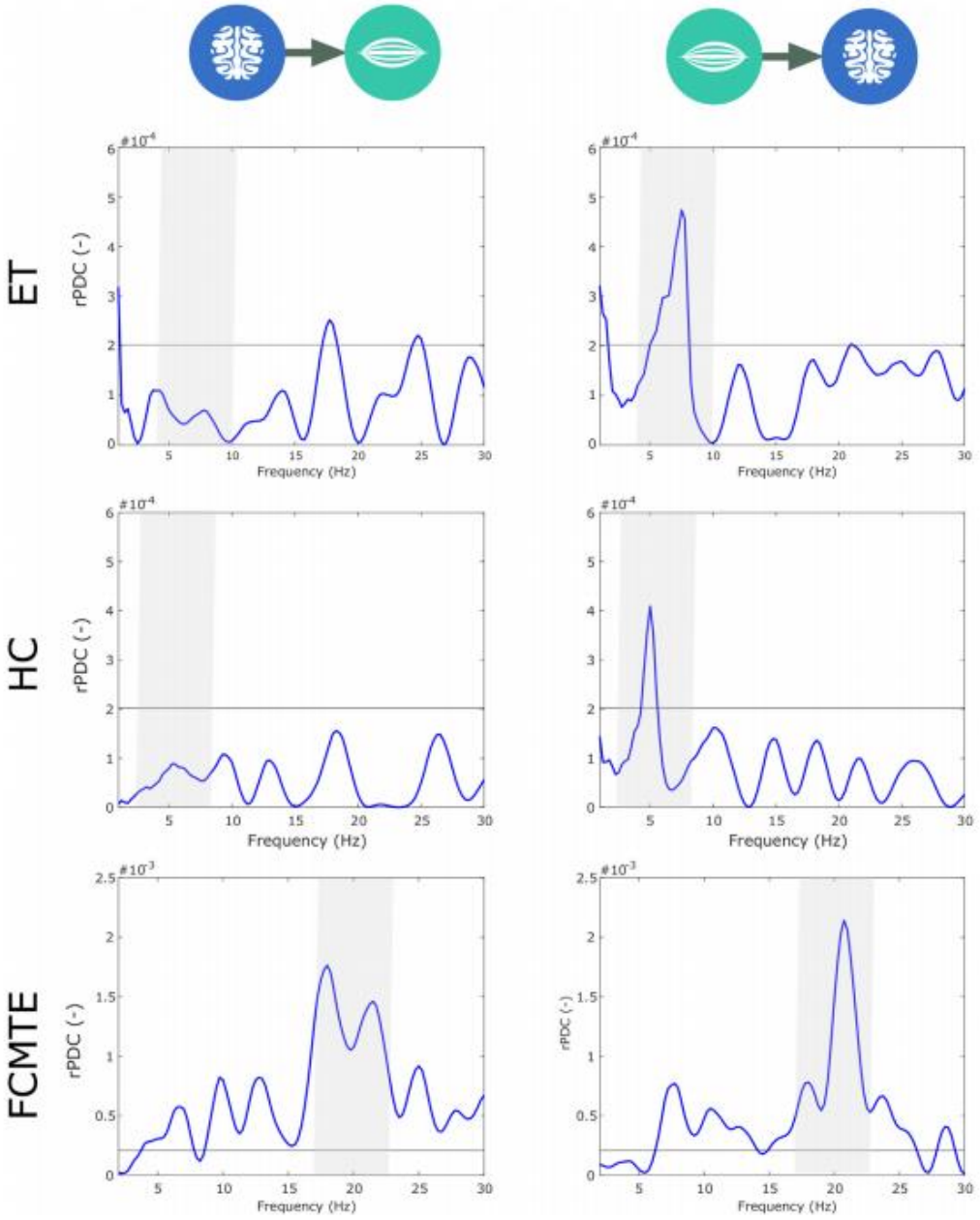
Sharifi S, et al.
Directionality of corticomuscular coupling in essential tremor and cortical myoclonic tremor.
Clin Neurophysiol. 2021 Aug;132(8):1878-1886. doi: 10.1016/j.clinph.2021.04.011.

Renormalized partial directed coherence is a suitable approach to investigate corticomuscular directionality in tremor.

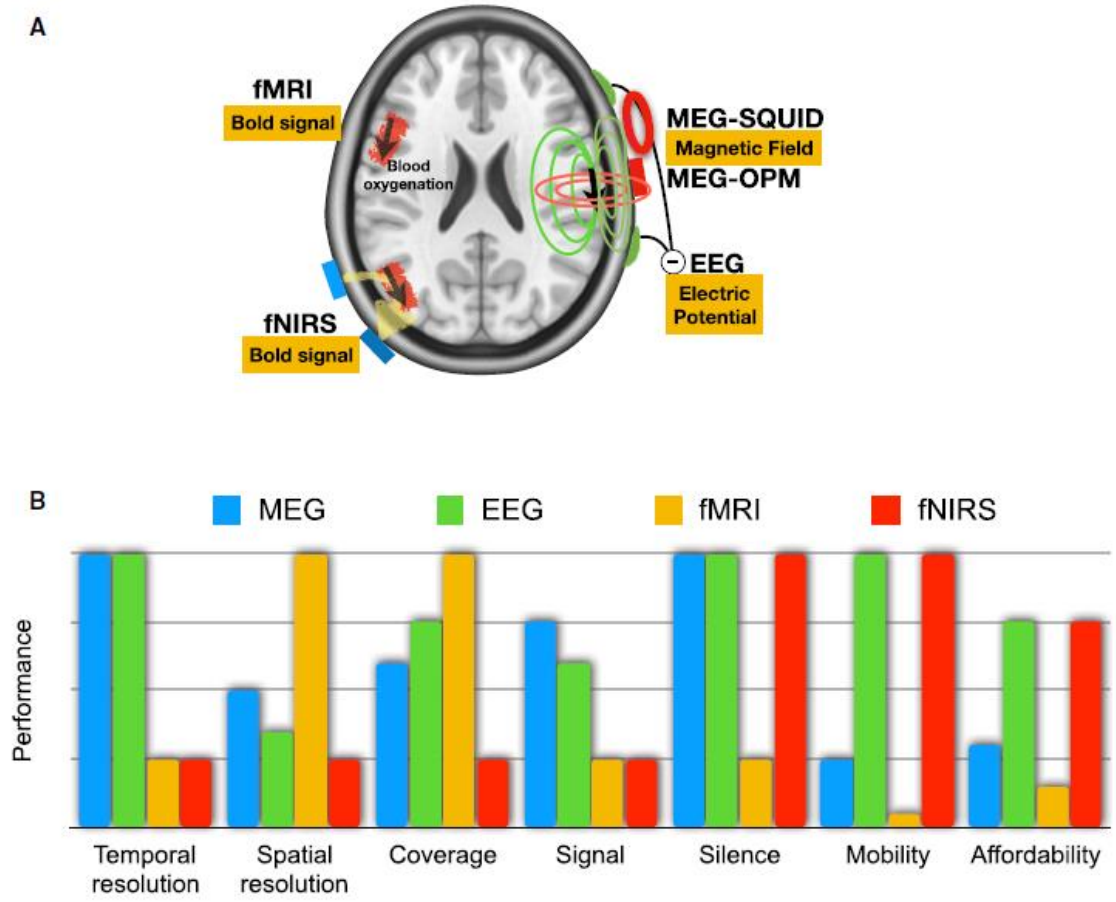
An efferent cortical drive is lacking in the majority of essential tremor (ET) patients; corticomuscular coupling in ET has predominantly an afferent direction.

ET might be associated with a non-linear (rate-dependent) cortical transmission.

A linear cortical drive is lacking in the majority of ET patients



MEG and Other Recording Techniques



Kim JA, Davis KD.
Magnetoencephalography: physics, techniques, and applications in the basic and clinical neurosciences.
J Neurophysiol. 2021 Mar 1;125(3):938-956. doi: 10.1152/jn.00530.2020.

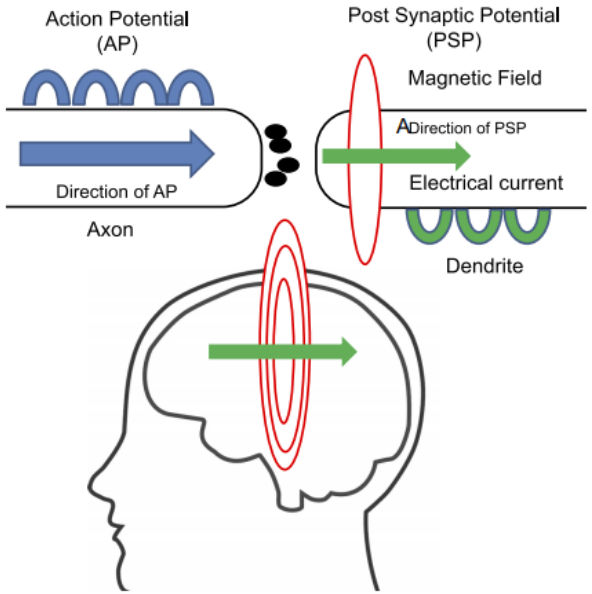
Clinical Neurophysiology 129 (2018) 1720–1747

Contents lists available at ScienceDirect

Clinical Neurophysiology

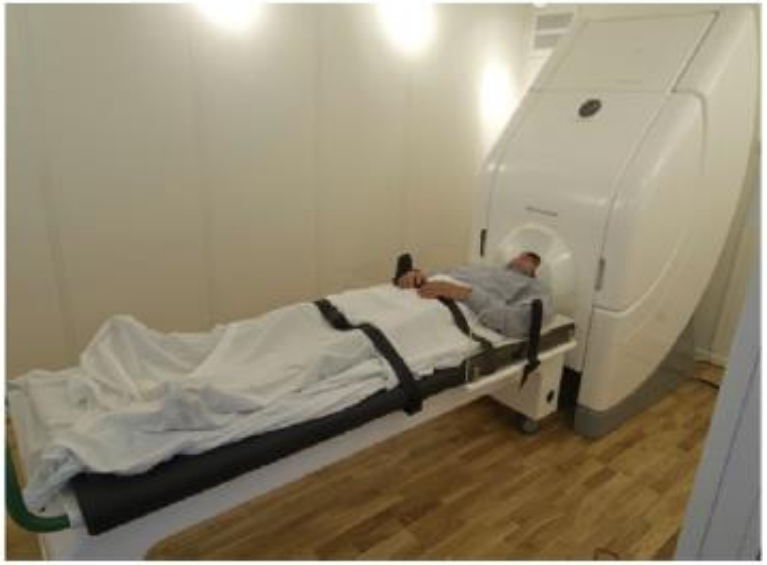
journal homepage: www.elsevier.com/locate/clinph

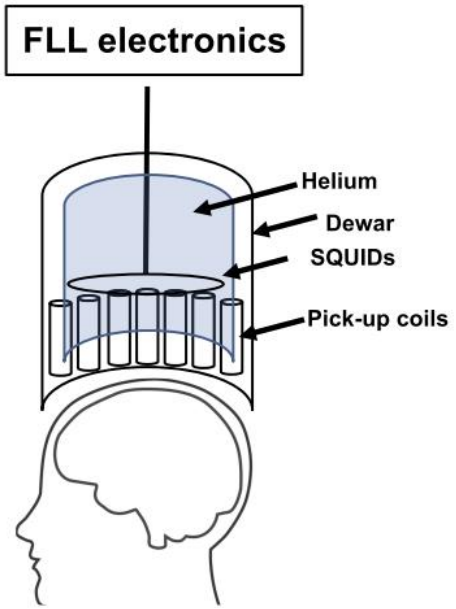
IFCN-endorsed practical guidelines for clinical magnetoencephalography (MEG)



MEG instrumentation

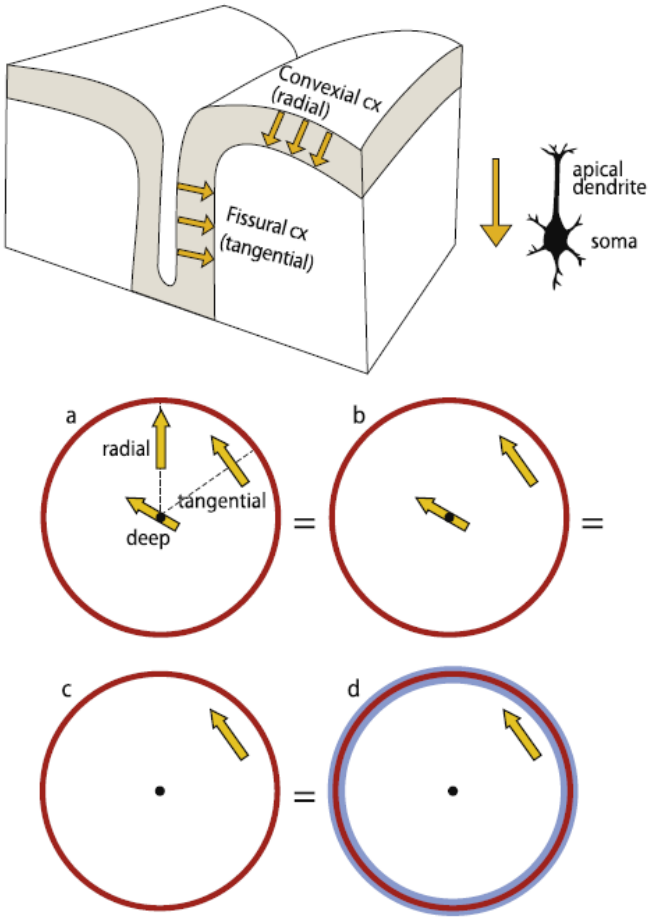
- SQUID
- Flux transformers
- Shielded room
- Head position indicator



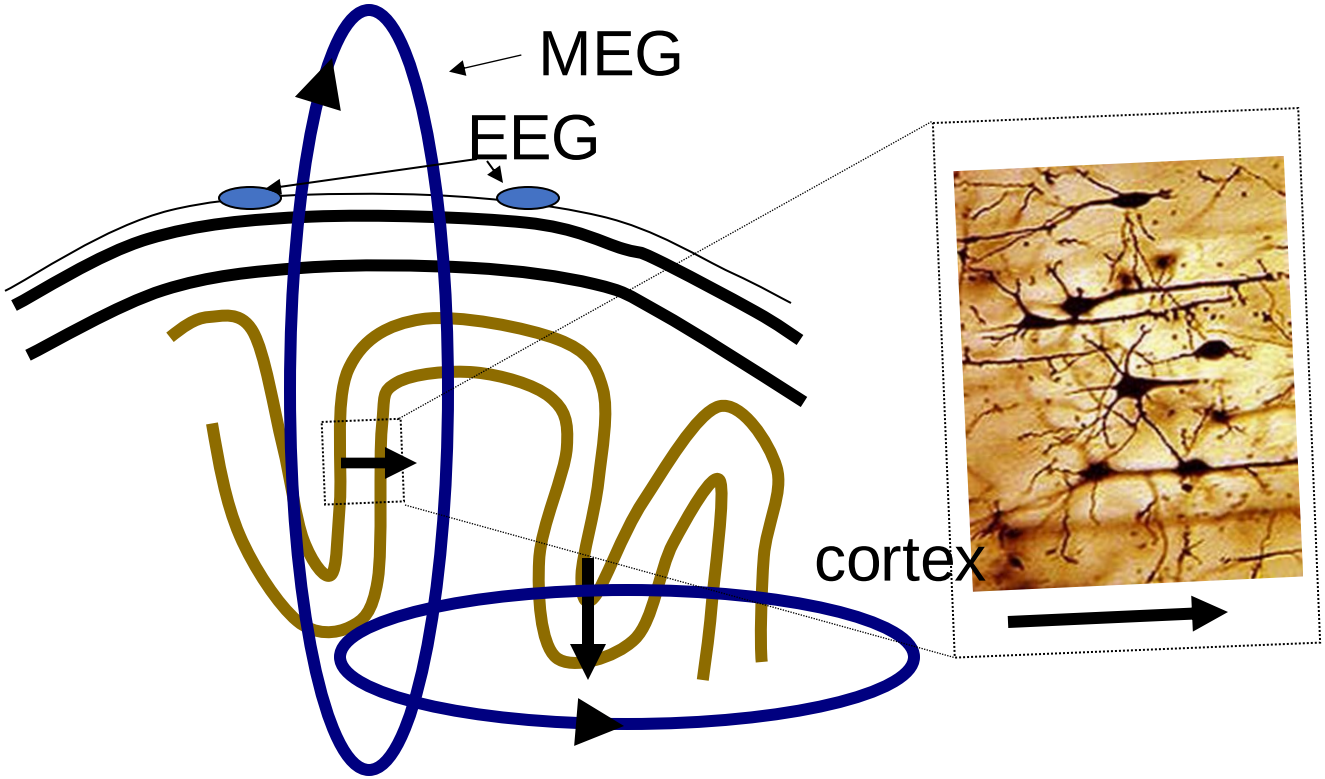


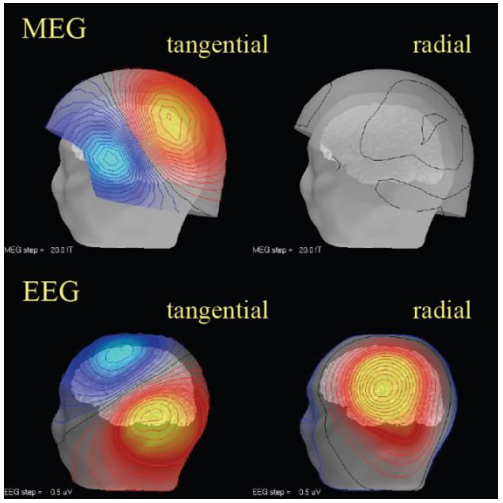
MEG VERSUS EEG

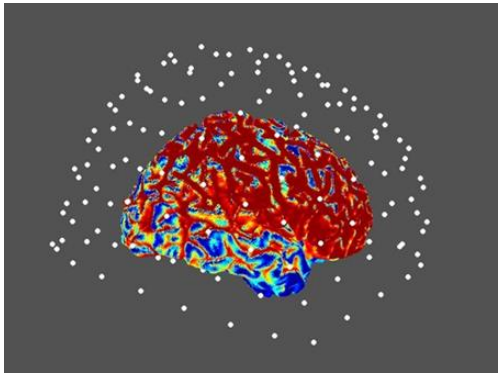
- As a non-invasive recording technique, MEG is most closely related to electroencephalography (EEG). Both techniques measure the consequences of transmembrane currents but in different ways.
- Whereas MEG measures the extracranial magnetic fields predominantly related to primary dendritic currents, EEG records potential differences that reflect volume currents across different locations on the scalp.
- Therefore, the distortive effect of especially skull and skin compartments is larger in EEG than in MEG. As a result, the spatial distribution of measurements across sensors, arising from a specific active neuronal population, is less distorted for MEG than it is for EEG.
- For the same reason, the localization of the activated neuronal populations in EEG is much more sensitive to errors in modeling the distribution of tissue conductivities in the head, compared to MEG.
- This problem is exacerbated by the fact that these tissue conductivities, which are required for accurate head models, are notoriously difficult to measure.
- MEG and EEG signals also differ in their sensitivity to the orientation of neuronal currents. In contrast to EEG, MEG is less sensitive to radial currents than to tangential currents. This complementarity means that researchers may opt to use simultaneous EEG and MEG recordings to localize the underlying generators.



Radial and tangential sources

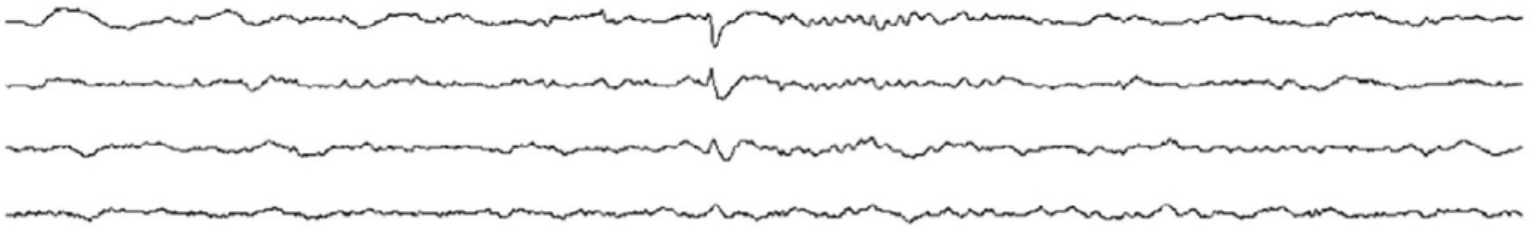






EEG and MEG waveforms

EEG



MEG

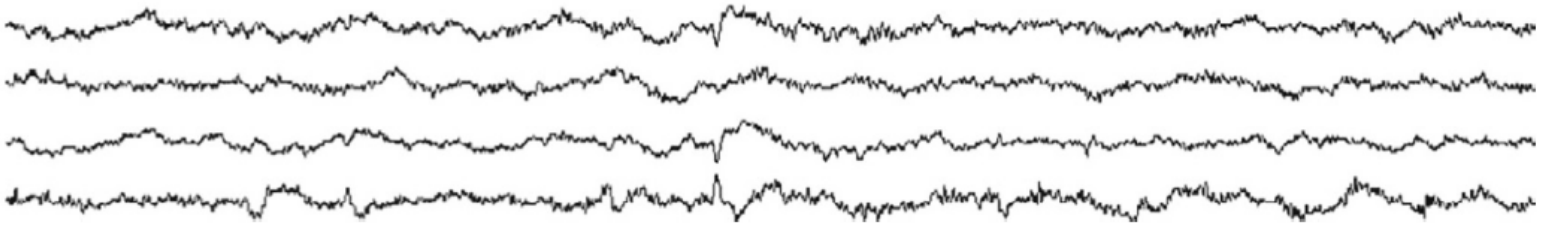
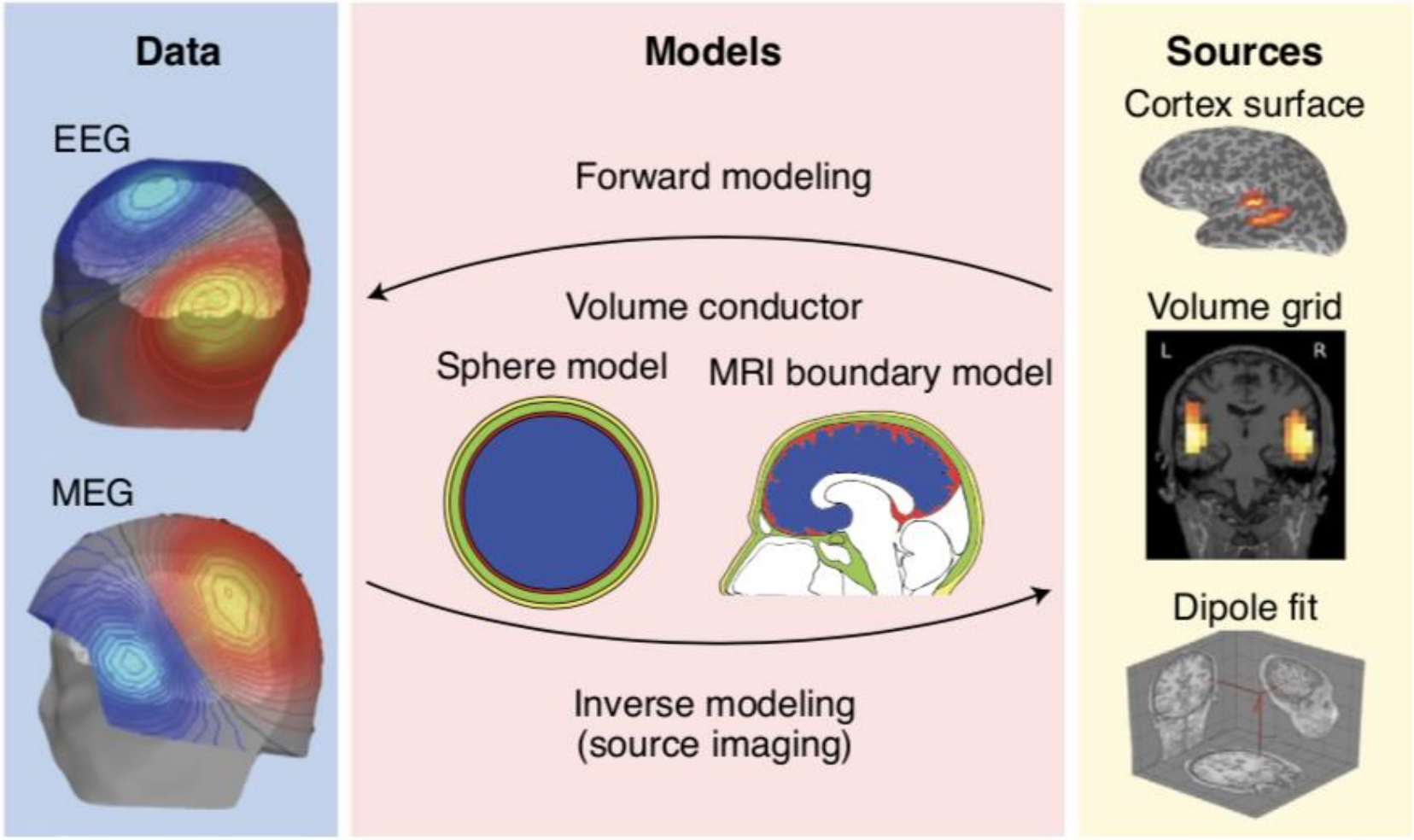


Fig. 2. Simultaneously recorded EEG and MEG, including an epileptic spike. The 8-s page demonstrates the similarity of the waveforms, which both derive from the same underlying neuronal currents.

Pernet C et al.

Issues and recommendations from the OHBM COBIDAS MEEG committee for reproducible EEG and MEG research.

Nat Neurosci. 2020 Dec;23(12):1473-1483.



Pernet C et al. Issues and recommendations from the OHBM COBIDAS MEEG committee for reproducible EEG and MEG research. Nat Neurosci. 2020 Dec;23(12):1473-1483.

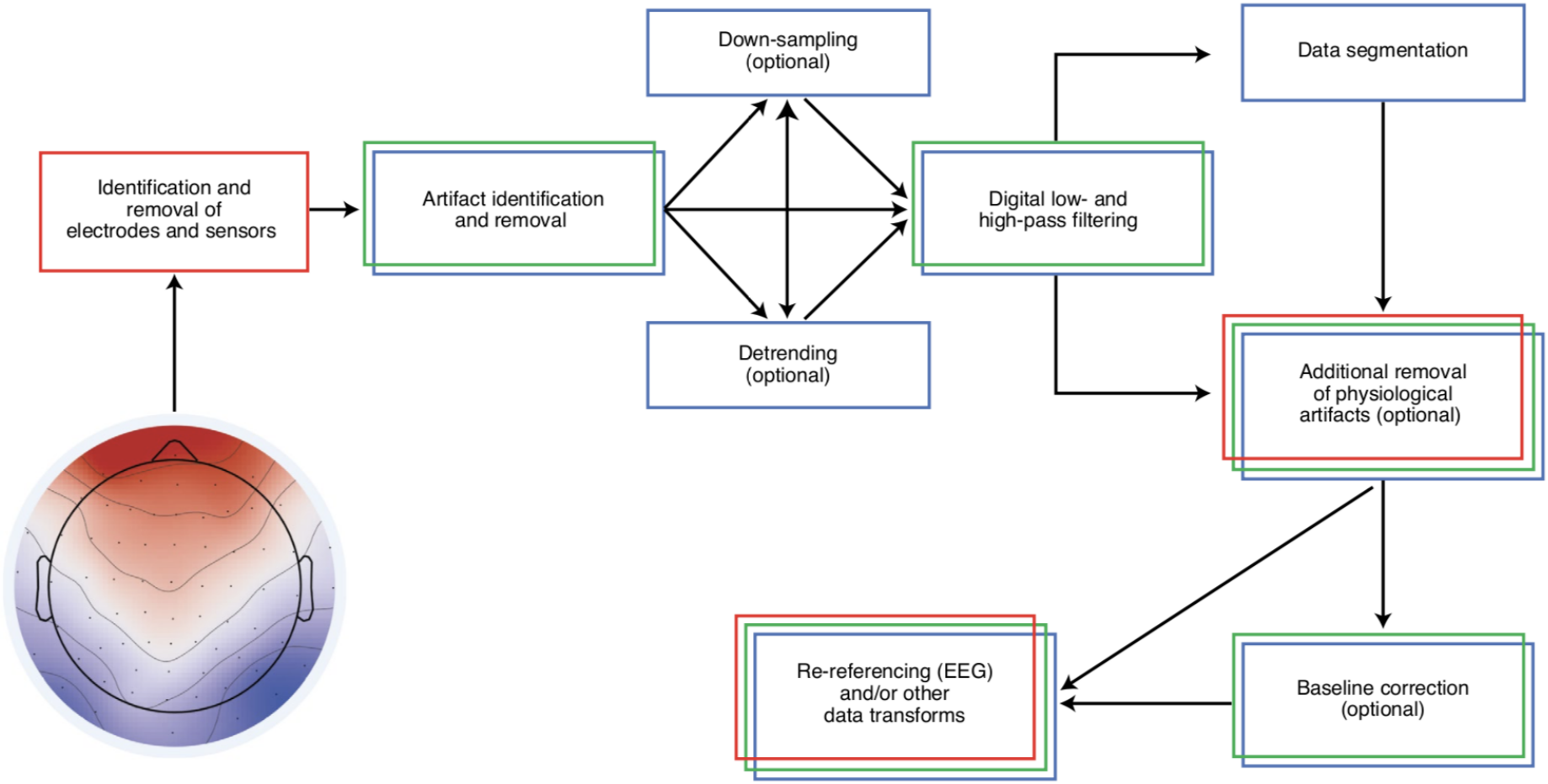
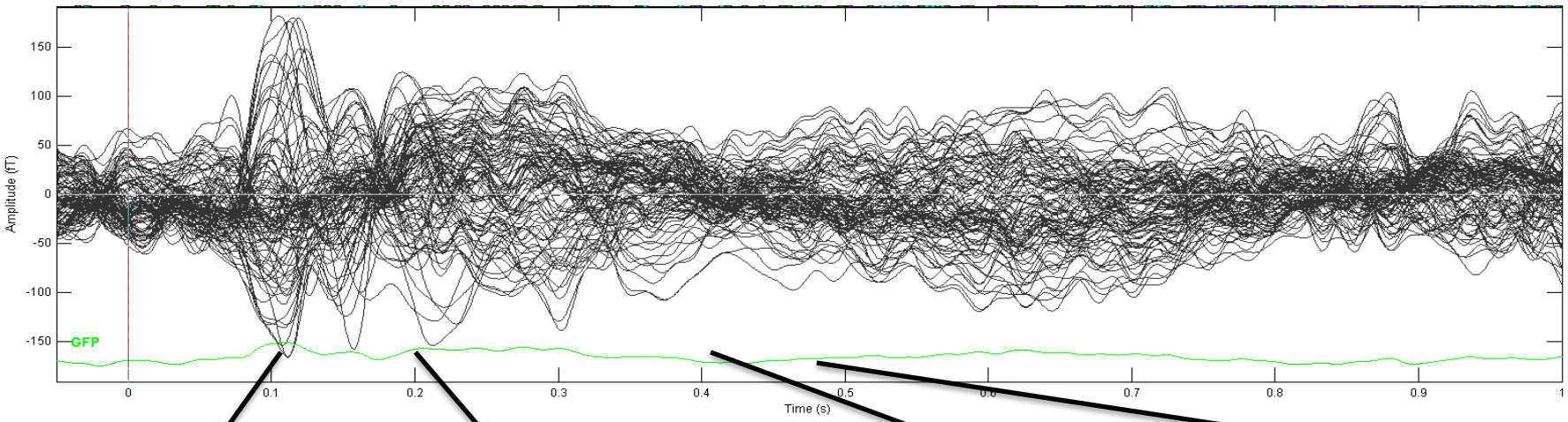


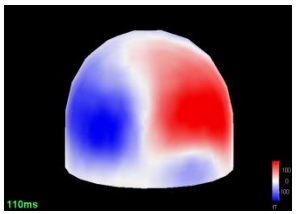
Fig. 2 | Standard MEEG preprocessing steps. Each step affects the data in the space (red boxes), time (blue boxes) and/or frequency (green boxes) domains. Deviations from the proposed order are possible, given the experimental set-up and/or MEEG feature(s) investigated, but should be justified.

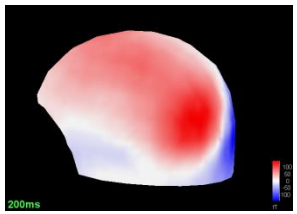
Spatio-temporal dinamic (Word recognition)

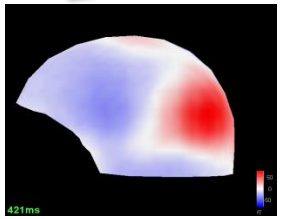
Early (Visual)

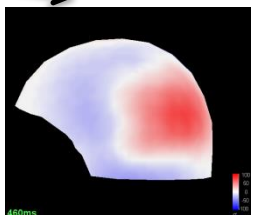
Late (Language specific)

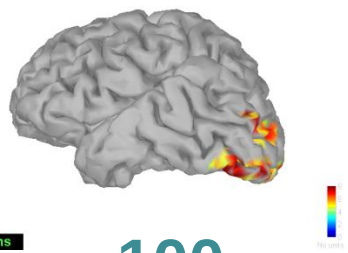












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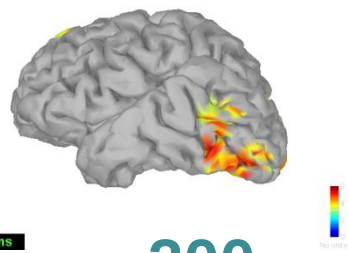

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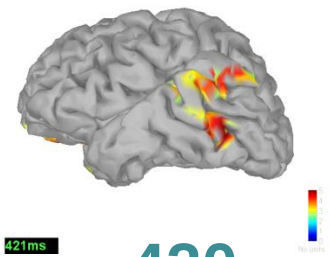

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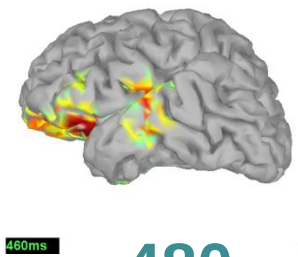

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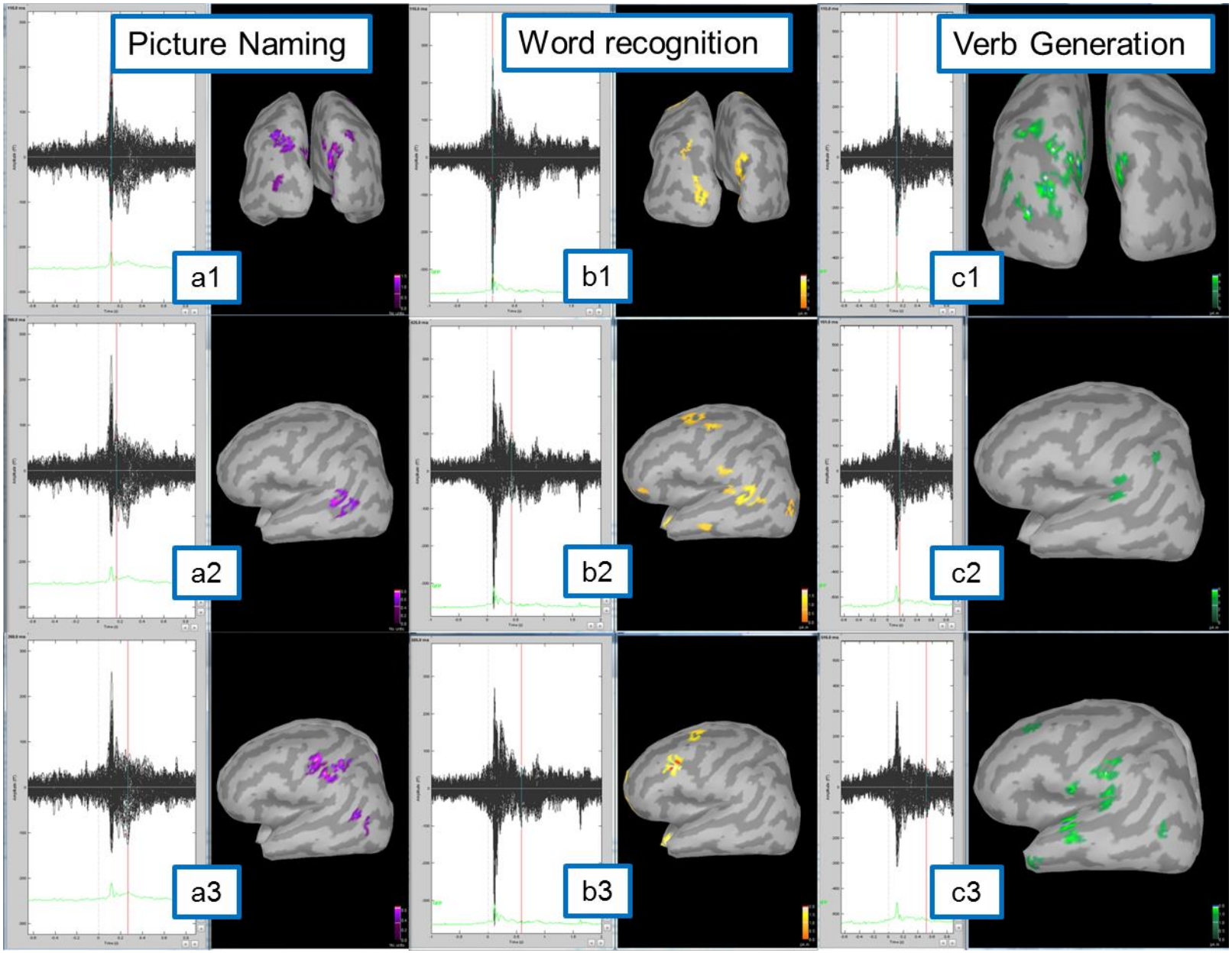
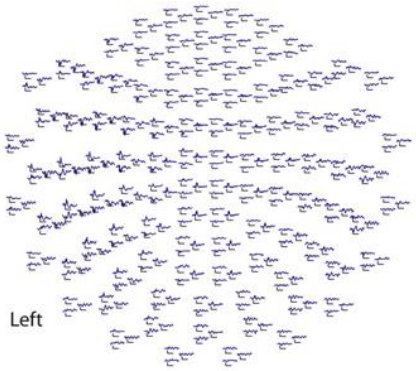
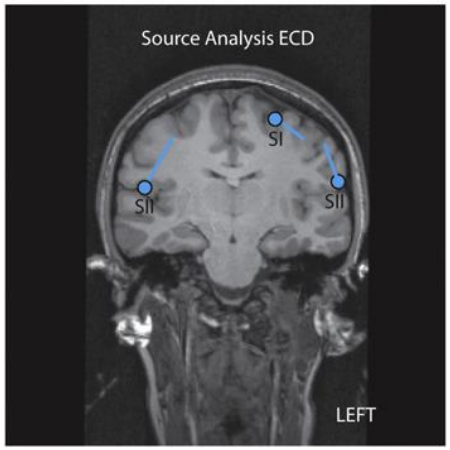
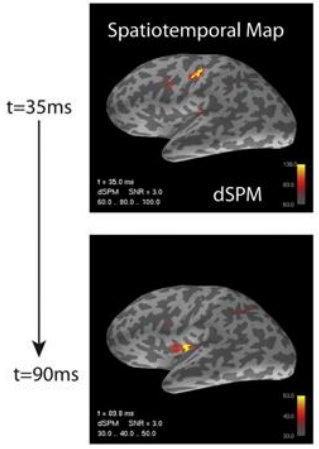

Picture Naming
Word recognition
Verb Generation
a1
b1
c1
a2
b2
c2
a3
b3
c3

Imaging neuromagnetic
From signal to sources





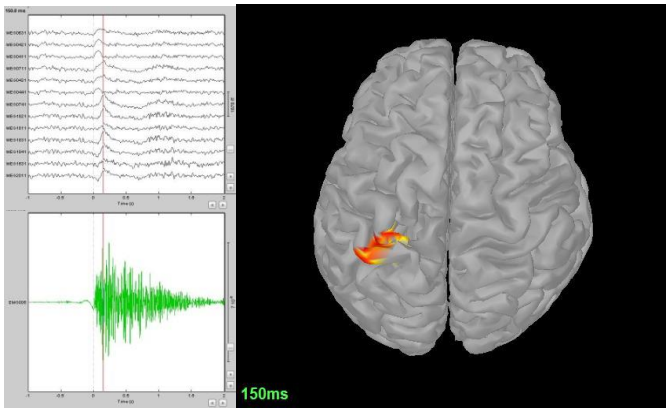


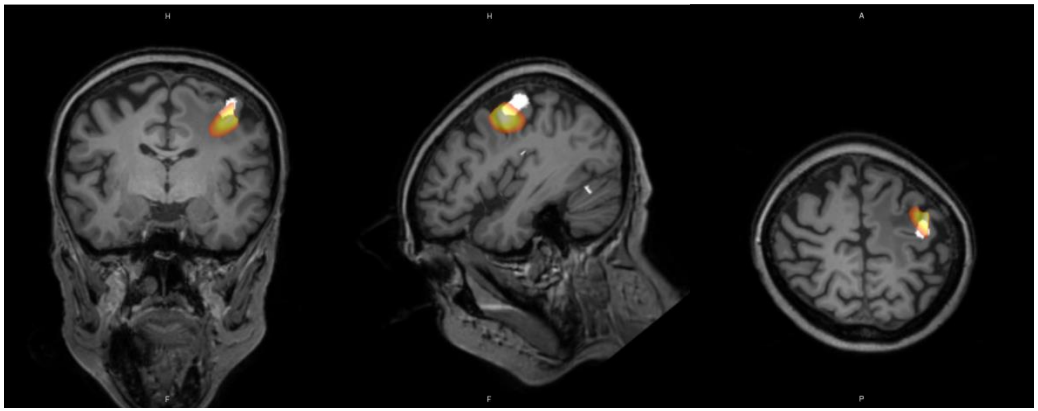
Mapping of motor area and integration with functional imaging

MEG

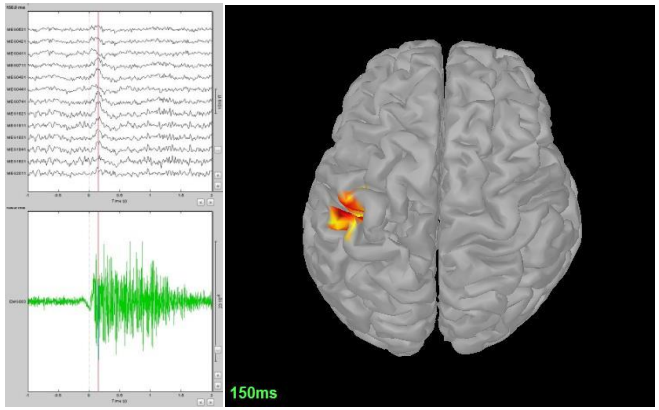
MEG fMRI

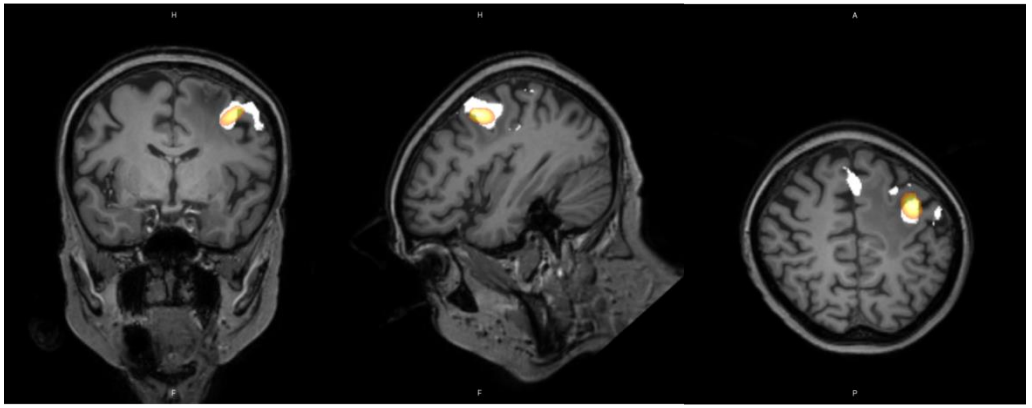
Right hand





Right index





Overview

Imaging and Target Volume Delineation in Glioma

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Received 2 April 2014; accepted 11 April 2014

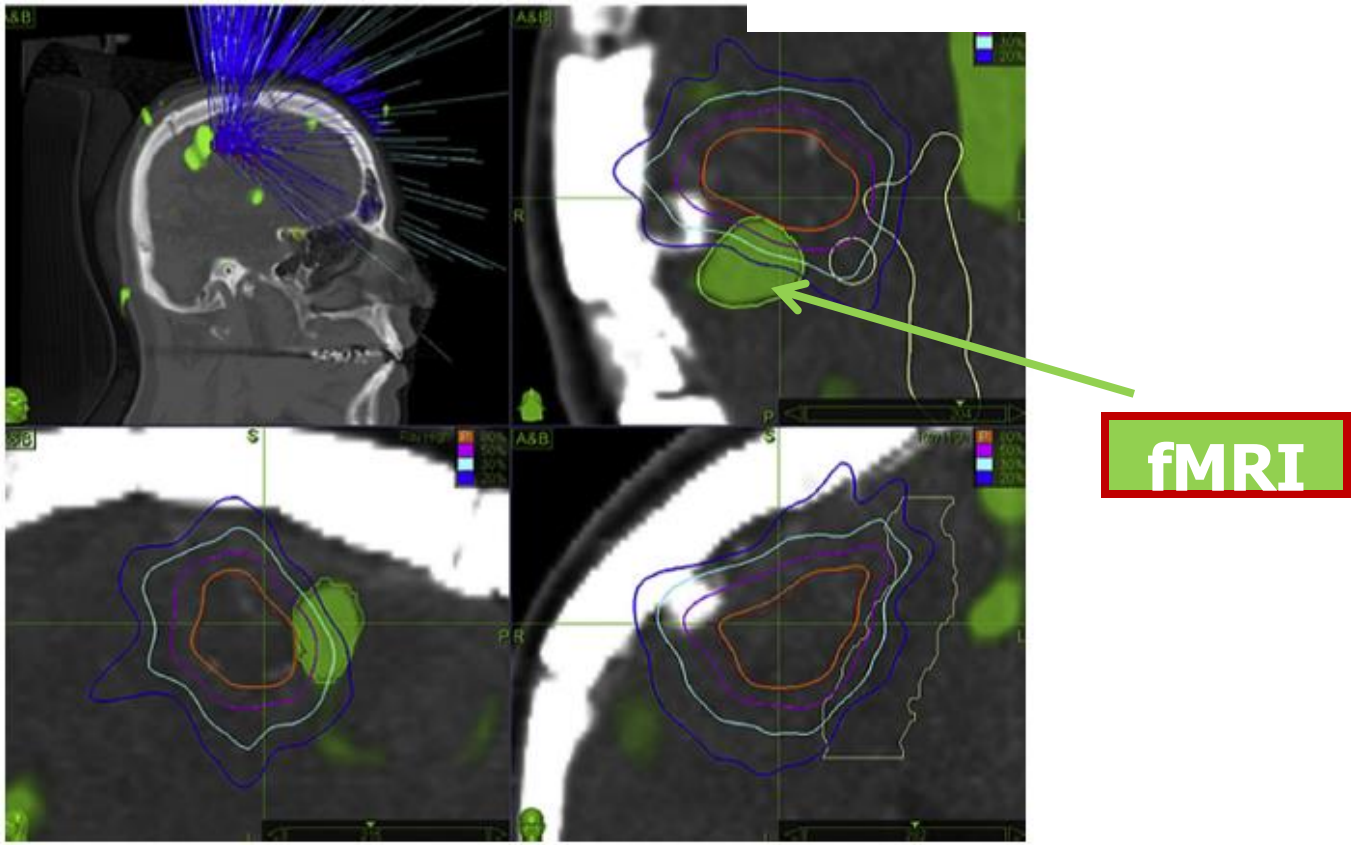

Fig 7. Stereotactic radiosurgery treatment plans developed without (top panels) and with (bottom panels) the functional structures and fibre pathways considered as organs at risk in the optimisation process, for a patient with World Health Organization grade II astrocytoma plotted in axial, coronal and sagittal planes. The configuration of the beams and the motor cortex (green) derived from functional magnetic resonance imaging are also depicted. In this unconventional case, because the glioma directly abutted the motor cortex, the authors felt the dose could only be modestly reduced from 2100 to 1900 cGy and therefore the biologically equivalent dose was calculated and delivered in three fractions. Reproduced with permission from [60].

Integration of Functional Magnetic Resonance Imaging and Magnetoencephalography Functional Maps Into a CyberKnife Planning System: Feasibility Study for Motor Activity Localization and Dose Planning

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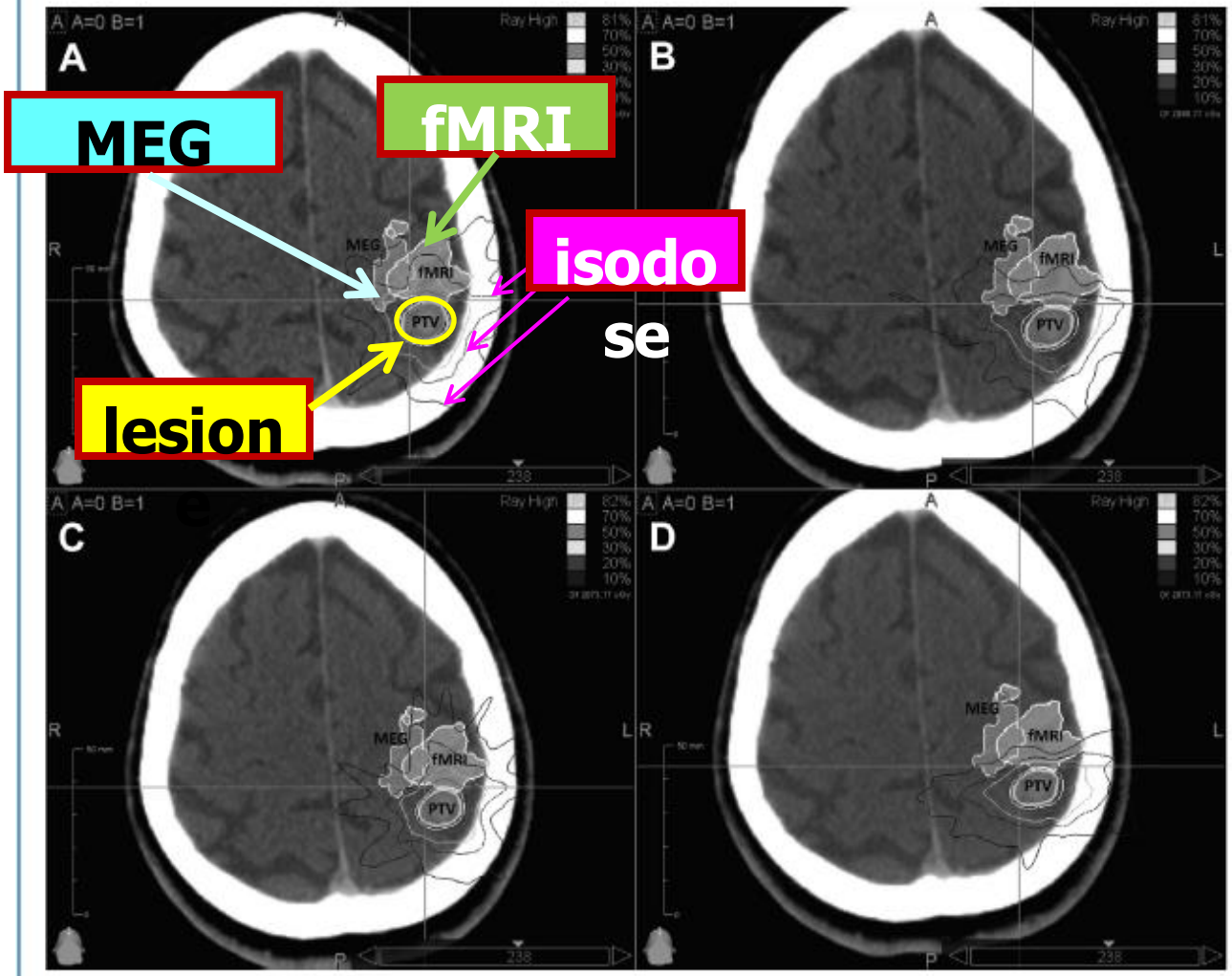

Figure 1. Isodose distributions for 1 of the patients using the 4 different optimization scenarios: (**A**) free optimization, (**B**) functional magnetic resonance imaging (fMRI) constrained-optimization, (**C**) magnetoencephalography (MEG) constrained-optimization, and (**D**) fMRI and MEG constrained-optimization.

A Optimization of "free" radiation

B Optimization of the radiation on the basis of the data

fMRI

C Optimization of the radiation on the basis of the data

MEG

D Optimization of the radiation on the basis of the data

MEG fMRI

Which is one of the the principal limit?

The need for a common neurophysiology format is fundamental to both clinical practice and research. Such a format should be efficient and portable, and should be readable and writeable by many different commercial and open-source software systems.

Neurophysiological data re often stored in various vendor specific formats and can only be assessed using the software provided by the device vendor or a third party vendor

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Standardization of neurophysiology signal data into the DICOM® standard.

Clin Neurophysiol. 2021 Apr;132(4):993-997. doi: 10.1016/j.clinph.2021.01.019.

- For the last 20 years, the International Federation of Clinical Neurophysiology (IFCN) recommends that all original equipment manufacturers (OEMs) make their digital data available in a file format that can be read by others who use systems produced by other OEMs (Nuwer et al., 1998).

- The de-facto common neurophysiology data format has been the European Data Format (EDF) and its successor EDF+ (Kemp and Olivan, 2003) due to its simplicity and the avail- ability of open-source review and analysis tools. However, there are several notable limitations to EDF and EDF + that make it unsuitable to fully handle many clinical and research applications.

European Data Format

- standard **file format** for exchange and storage of **medical time series**
- open and non-proprietary
- published in **1992**

  Electroencephalography and Clinical Neurophysiology (82: 391-393)
  Full specification: http://www.edfplus.info/specs/edf.html

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- Standardizing neurophysiology data in a format that can interface seamlessly with existing **Picture Archiving and Communication Systems PACS** systems would improve efficiency and organization in healthcare, and would leverage considerable infrastructure developed by radiology departments.

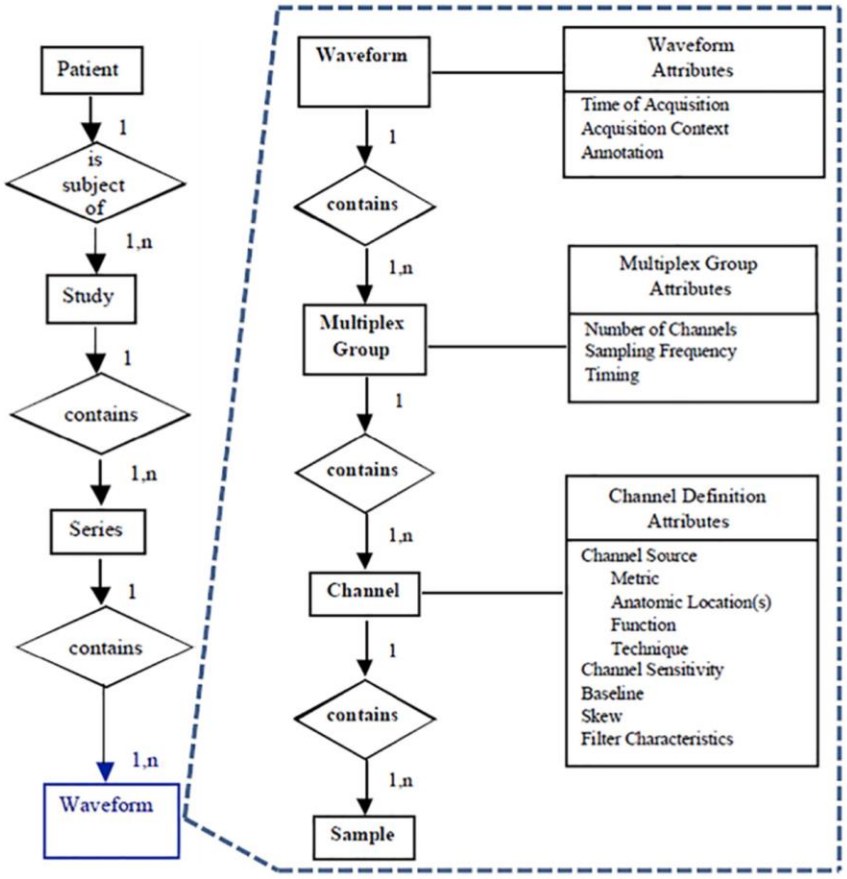

Fig. 1. DICOM Waveform Information Model (NEMA PS3.17).

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- **New DICOM neurophysiology information object definitions (IODs)**

- WG-32 created new IODs that were added to the DICOM Standard in Supplement in early 2020.
- IODs have been added for routine EEG, electromyography (EMG) and electro-oculography (EOG). Additional waveform IODs have been defined to allow for DICOM-compliant polysomnography (PSG).
- These neurophysiologic recording types were selected to be added to DICOM first because of their relevance in clinical practice and their relative simplicity.
- More complex IODs for long-term EEG monitoring, high density EEG, intracranial EEG monitoring, evoked potentials and magnetoencephalography are planned as later additions in future supplements. The DICOM Standard is available for free download at https://www.dicomstandard.org/current

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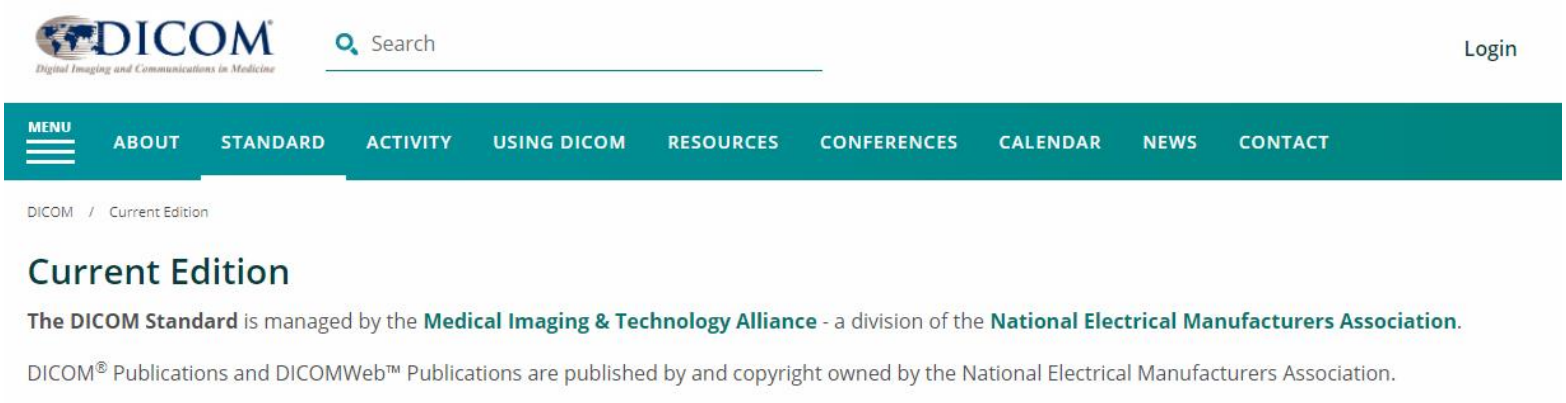
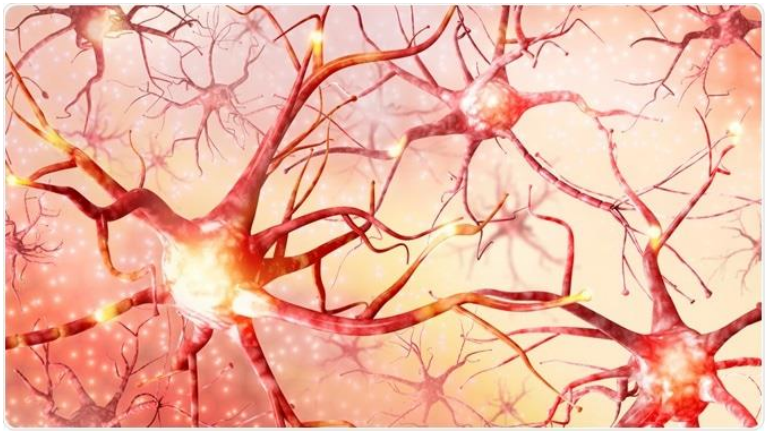
- **New DICOM neurophysiology information object definitions (IODs)**

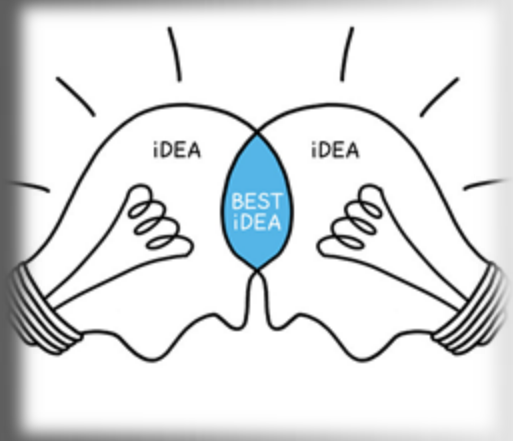
- With the support of the IFCN and partners in industry, DICOM WG-32 has created an initial set of standards for routine EEG, PSG, EMG and EOG.
- Longer and more complex neurophysiology data types such as high-definition EEG, long-term monitoring EEG, intracranial EEG, magnetoencephalography, advanced EMG, and evoked potentials will be added later.



We can use our neurophysiological techniques to build bridges to new and more meaningful end points that redefine disorders of the mind as disorders of the brain and thus drastically improve our ability to provide individualized, personalized, precise medical care to individuals with these disorders.

BIOMARKER





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THANK YOU
FOR
YOUR
ATTENTION
ANY QUESTIONS?

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