

Global Brain Consortium (GBC), Workgroup 6

“EEG/ERP Paradigms, Clinical Applications, and Validation”

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Varadero, Cuba, February 28th, 2020



Workgroup 6 “**EEG Paradigms, Clinical Appl., and Validation**”

GBC Committees (“EEG paradigms and more”, “Clinical applications”)



Vision and mission:

- Definition of standard operating procedures for the translation of experimental EEG/event-related potential (ERP) discoveries in patients with neurological and psychiatric disorders into candidate **EEG/ERP biomarkers** to prevent, screen, diagnose, and monitor diseases
- Special interest in prevention and triage role in early diagnosis
- Building pathways (**survey and consensus papers**) with clinical scientific societies and stakeholders (transnational regulatory agencies, etc.) for clinical care translation using qEEG
- Discuss innovative applications of EEG/ERP biomarkers based derived from telemedicine (i.e., recording of EEG/ERP activity at point-of-care such as pharmacy, audit of family doctor, resident patients’ home, etc.) and **multimodal approaches (neuroimaging) combined with genotypes**

**What EEG/ERP paradigms for Global
Brain Consortium (GBC) mission?**

What EEG/ERP paradigms for Global Brain Consortium (GBC) mission?

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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



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International Federation of Clinical Neurophysiology

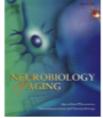
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Review

What electrophysiology tells us about Alzheimer's disease: a window into the synchronization and connectivity of brain neurons



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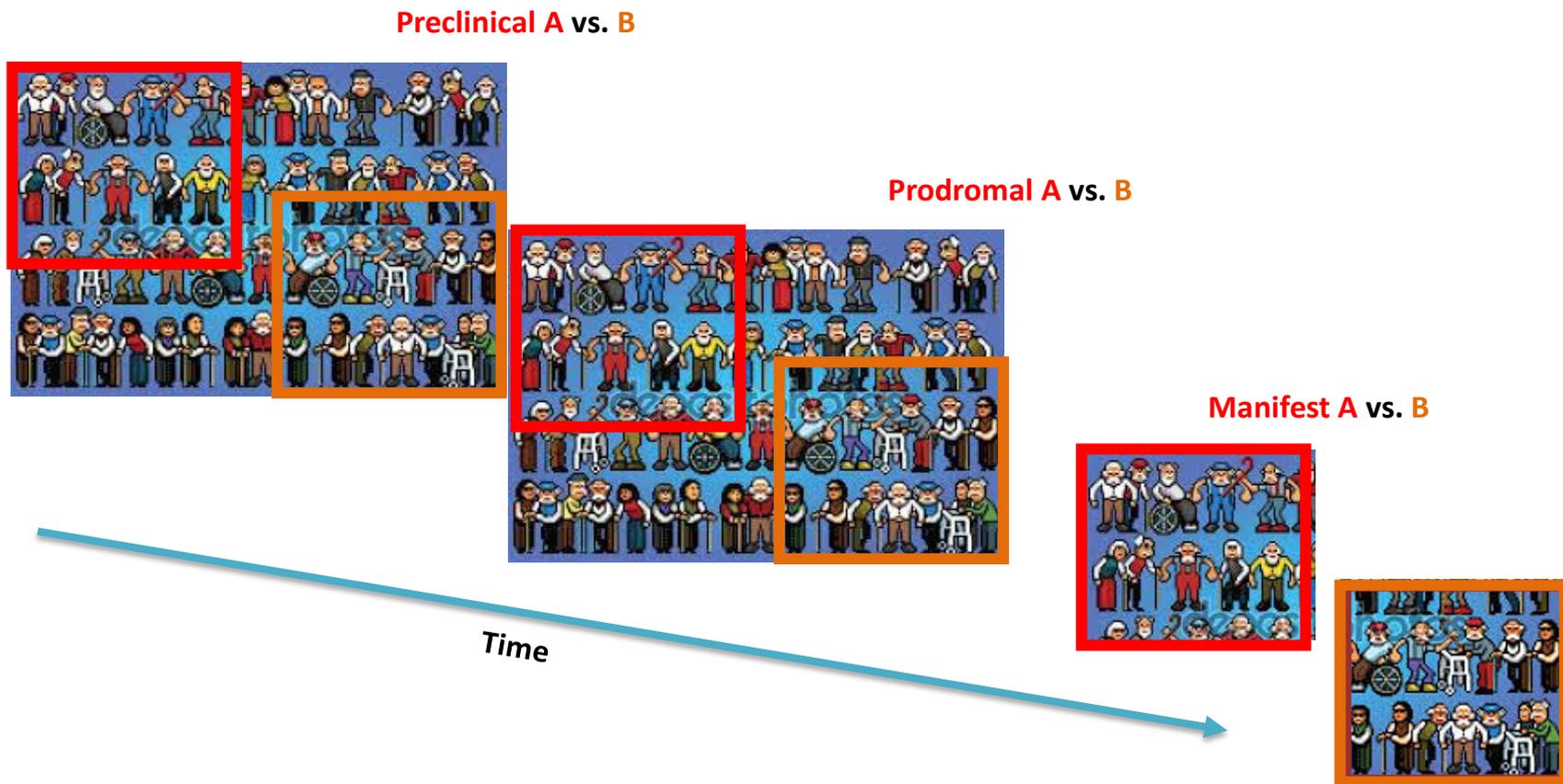
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ISTAART
alzheimer's association

INTERNATIONAL SOCIETY TO ADVANCE
ALZHEIMER'S RESEARCH AND TREATMENT

ELECTROPHYSIOLOGY PROFESSIONAL
INTEREST AREA (EPIA)

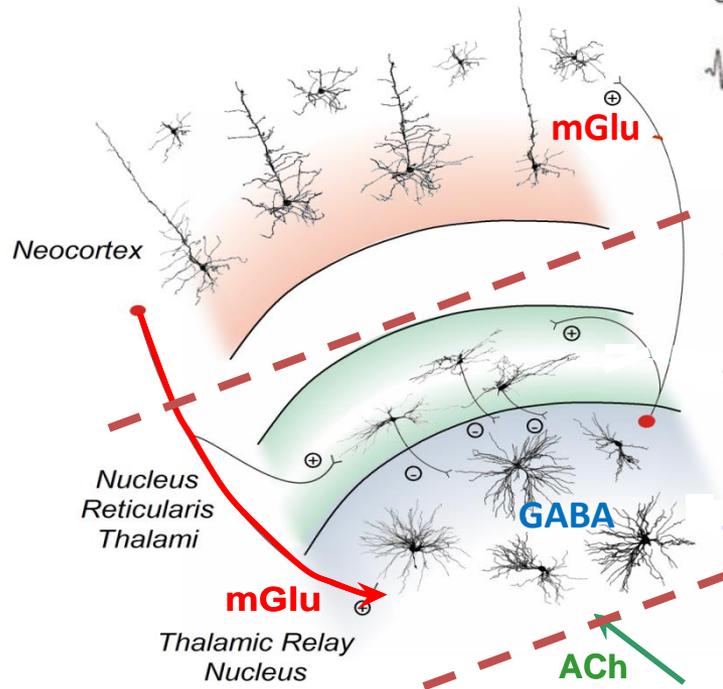
What EEG/ERP biomarkers for **monitoring** brain diseases (A and B)?



Neurophysiological underpinnings of rsEEG: **thalamus-cortical** synchronizing capacity



Alpha rhythms reflect **cortical inhibition**:
low brain arousal in quiet wakefulness



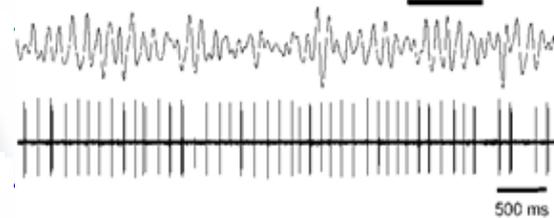
Visual cortex

α WAVES (relaxed wakefulness)



Thalamus (lateral geniculate nucleus)

α WAVES (150 μ M trans-ACPD)

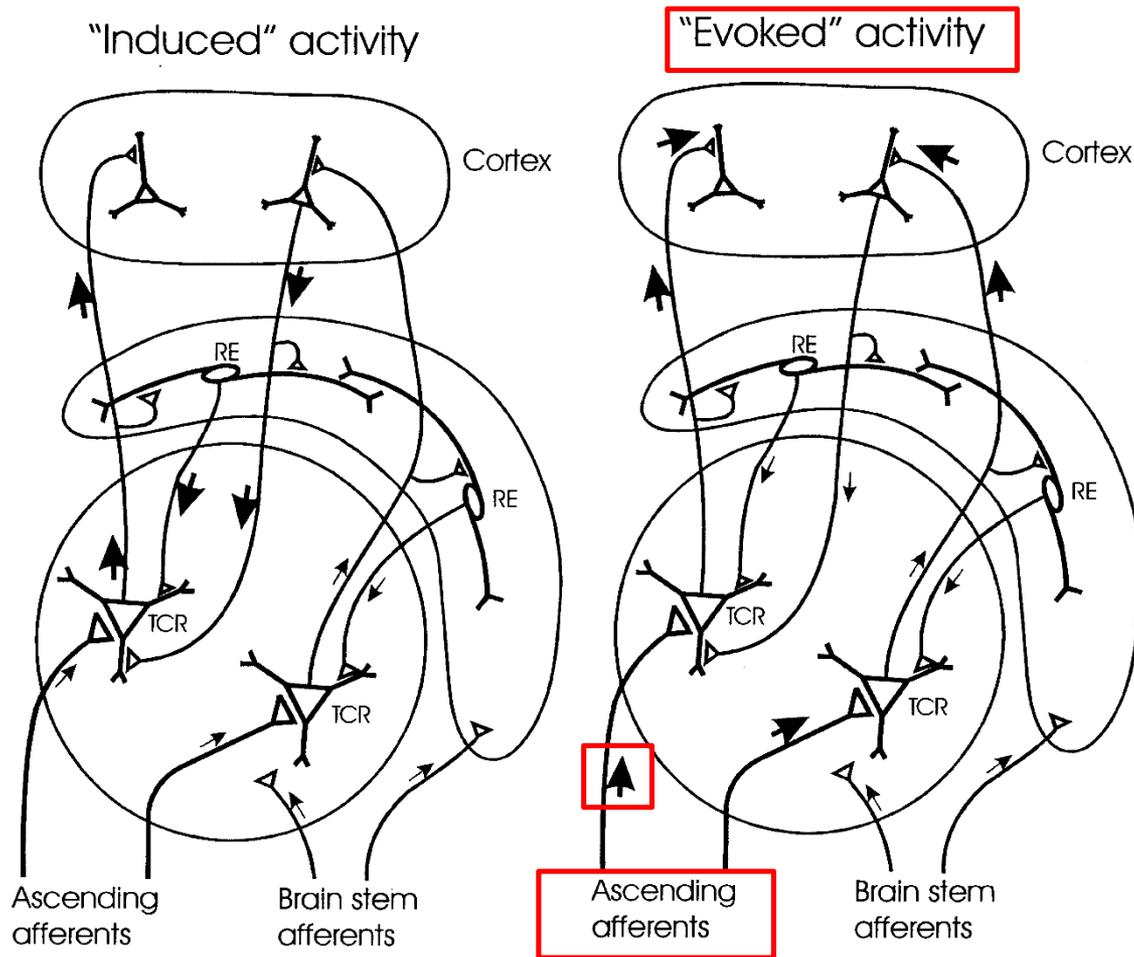


Ascending reticular activating systems

“Induced” and Evoked” brain activity in ERPs



Phase-locked “evoked” component of the EEG signals might be due to prominent inputs to thalamus and cerebral cortex.



Resting state conditions: vigilance processes



- Resting eyes closed (3-5 min) and eyes open (3-5 min) in sequence to explore ascending activating systems **maintaining vigilance** stable over time
- Resting eyes closed (30 s) and eyes open (30 s) in rapid sequence repeated 3-4 times to explore ascending activating systems **increasing/decreasing the vigilance** (“reactivity”)
- Resting eyes closed for a long period without any alert (> 30 minutes) to explore transition **from quiet vigilance to drowsiness and sleep onset**



Oddball without target detection (mismatch negativity, MMN): pre-attentive processes



- In the pre-attentive MMN paradigm, **frequent** (about 80%) and **rare** (20%) **sensory stimuli** (e.g., visual, auditory, etc.) to be ignored are delivered while the subject is focused on another task (e.g. reading or watching videos).
- EEG signals associated with any single stimulus are averaged to produce ERPs associated with frequent and rare stimuli, separately.
- **Time domain:** ERPs to frequent and rare stimuli averaged separately. Amplitude and latency of a frontal negative component peaking at about 200 ms post-rare stimulus, the MMN.
- **Frequency domain:** changes in magnitude from delta to gamma of ERPs (event-related oscillations) or single EEG epochs (event-related synchronization/desynchronization).

Oddball with target detection (P300 paradigm): attentive and short memory processes



- In the attentive P300 paradigm, **frequent** (about 80%) and **rare** (20%) **sensory stimuli** (e.g., visual, auditory, etc.) are delivered while the subject is asked to respond only to rare ones (e.g. counting them or pressing a button).
- EEG signals associated with any single stimulus are averaged to produce ERPs associated with frequent and rare stimuli, separately.
- **Time domain:** ERPs to frequent and rare stimuli averaged separately. Amplitude and latency of a parietal positive component peaking at about 300 ms post-rare stimulus, the P300 or P3b. When a rare distracter every changing (3rd stimulus) is included, a frontal P300 or P3a) is observed.
- **Frequency domain:** changes in magnitude from delta to gamma of ERPs (event-related oscillations) or single EEG epochs (event-related synchronization/desynchronization).

Semantic incongruence (N400 paradigm): semantic linguistic processes



- In the linguistic N400 paradigm, several **sequences of two words** are presented some of them with semantic incongruence while the subject is asked to pay attention to them but with no response
- EEG signals associated with any single stimulus are averaged to produce ERPs associated with congruent and incongruent pairs, separately.
- ***Time domain:*** ERPs to semantically congruent and incongruent stimuli averaged separately. Amplitude and latency of a temporoparietal negative component peaking at about 400 ms post-rare stimulus, the N400, sensitive to those incongruences. Amplitude of midfrontal N400 decreases with familiarity/repetitions.
- **Frequency domain:** changes in magnitude from delta to gamma of ERPs (event-related oscillations) or single EEG epochs (event-related synchronization/desynchronization).

Syntactic errors (P600 paradigm): grammar linguistic processes



- In the linguistic P600 paradigm, several **phrases** are presented some of them with syntactic errors while the subject is asked to pay attention to them but with no response
- EEG signals associated with any single stimulus are averaged to produce ERPs associated with correct and wrong phrases, separately.
- **Time domain:** ERPs to syntactic correct and incorrect phrases averaged separately. Amplitude and latency of a centroparietal positive component peaking at about 600 ms post-stimulus, the P600, sensitive to those errors.
- **Frequency domain:** changes in magnitude from delta to gamma of ERPs (event-related oscillations) or single EEG epochs (event-related synchronization/desynchronization).

Memory ERPs (retrieval info paradigm): episodic retrieval processes



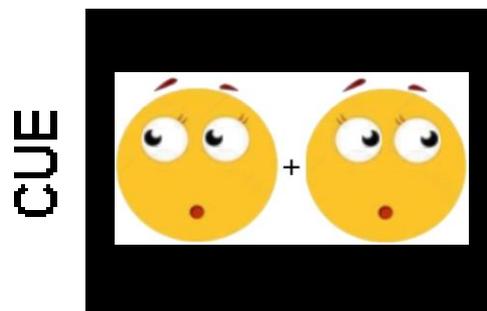
- In the memory P600 paradigm, several **words or objects** are presented in an encoding phase, the subject responds “living beings” or “nonliving ones”. In the retrieval phase (after minutes to hours), old and new words are presented and the subject responds “seen before” or “unseen before”.
- EEG signals associated with any single stimulus are averaged to produce ERPs associated with successful and unsuccessful recognitions, separately.
- ***Time domain:*** ERPs to correct and incorrect retrieval averaged separately. Amplitude and latency of a left parietal positive component peaking at about 600 ms post-stimulus, the P600, sensitive to successful “seen before”.
- ***Frequency domain:*** changes in magnitude from delta to gamma of ERPs (event-related oscillations) or single EEG epochs (event-related synchronization/desynchronization).

Primary consciousness paradigm: social cognition processes



- **Social cue stimuli** (two schematic faces with eyes gazing each other or not) are given at sensory threshold, so only 50% of them are consciously detectable. After masking stimuli, the same stimuli are given over-threshold (go). In the **social condition**, the subject reacts indicating (button press) if the two faces gaze each other or not.
- In the **non-social condition**, the go stimuli show both faces gazing upward or downward. The subject reacts indicating if the eyes gaze downward or upward (nonsocial condition).
- In both conditions, the subject responds again (button press) indicating if he/she perceived the cue stimulus (“seen” vs. “unseen”).
- **Time domain:** ERPs to “seen” and “unseen” **cue** stimuli averaged separately. Amplitude and latency of a temporoparietal negative component peaking at about 170 ms post-stimulus, the N170, and later positive peaks.
- **Frequency domain:** changes in magnitude from delta to gamma of ERPs (event-related oscillations) or single EEG epochs (event-related synchronization/desynchronization).

Primary consciousness and **social cognition**. Cue stimuli at **threshold** time (passive view)

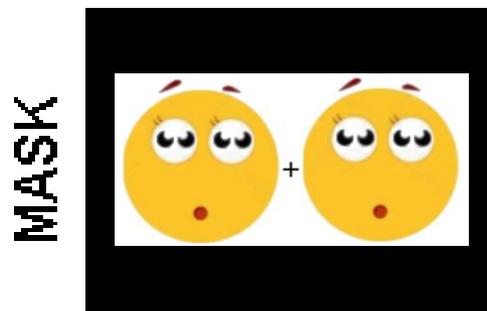


TRESHOLD

50% of the cue stimuli are **consciously detected** ("seen")

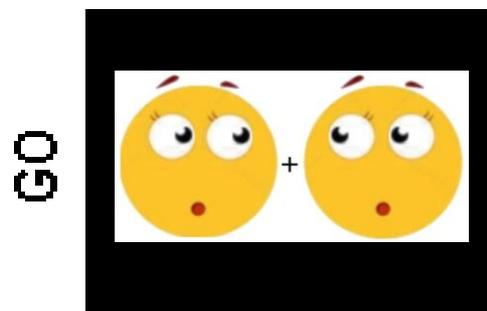
VS.

50% of the cue stimuli are **consciously missed** ("not seen")



2 s

Social cognition set



0,5 s

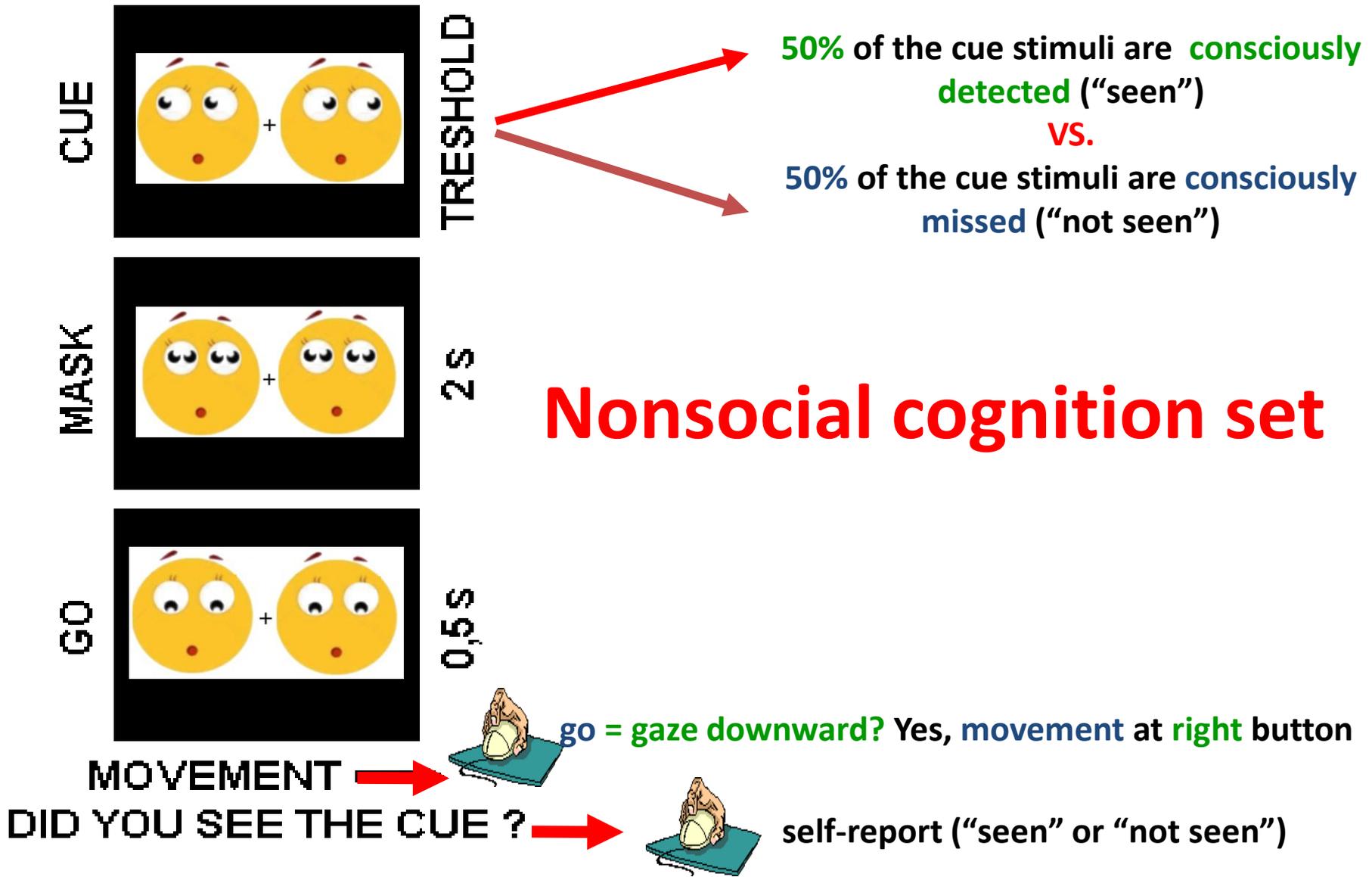
go = gaze each other? Yes, movement at **right** button

MOVEMENT → 

DID YOU SEE THE CUE ? → 

self-report ("seen" or "not seen")

Primary consciousness and nonsocial cognition. Cue stimuli at threshold time (passive view)



Expectancy ERPs (CNV paradigm): anticipation of “go” processes



- In the contingent negative variation (CNV) paradigm, a cue sensory stimulus precedes (few seconds) an imperative go stimulus eliciting a motor response. Increasing anticipatory and motor preparation processes are expected between these two stimuli.
- EEG signals show a posterior cue-evoked potentials followed by an increasing parietal and central negative shift (CNV) anticipating the imperative stimulus and motor response.
- **Time domain:** Averaging EEG epochs at cue stimulus onset shows the CNV. Amplitude and area of parietal midline CNV are typical measures.
- **Frequency domain:** changes in magnitude in alpha, beta, and gamma rhythms at single EEG epochs (event-related synchronization /desynchronization).

Motor ERPs (movement-related potentials, MRPs): somatomotor preparatory and executive processes



- In the MRP paradigm, subjects typically perform self-paced voluntary (hand-finger) movements. Increasing motor preparation and executive processes are expected before movement onset.
- EEG signals show parietal and central midline negative shifts (readiness potential, RP) anticipating movement onset and a sharp central negative motor potential (MP) during the motor response.
- **Time domain:** Averaging EEG epochs at movement (or EMG) onset shows the RP and MP. Amplitude and latency of these potentials are typically measured.
- **Frequency domain:** changes in magnitude in alpha-beta (μ) and gamma rhythms at single EEG epochs (event-related synchronization/desynchronization).

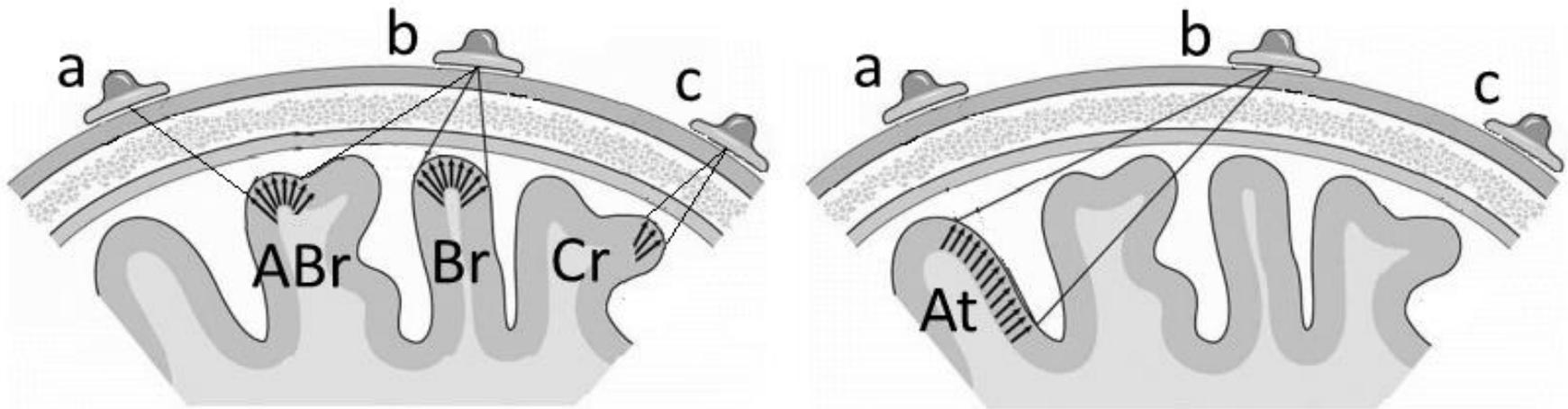


Frequency (Hz)	IFCN 1999 (I)	IFCN 1999 (II)	IPEG 2012	IFCN-2017 Glossary
Delta	0.5 - 4	0.5 - 4	1.5 - < 6	0.1 - < 4
Theta	4 - 8	5 - 7	6 - < 8.5	4 - < 8
Alpha	$\alpha 1$: 8 - 10 $\alpha 2$: 10 - 12/13	8 - 12	$\alpha 1$: 8.5 - < 10.5 $\alpha 2$: 10.5 - < 12.5	8 - 13
Beta	$\beta 1$: 12 - 16 $\beta 2$: 16 - 20 $\beta 3$: 20 - 24 $\beta 4$: 24 - 28 $\beta 5$: 28 - 32	$\beta 1$: 14 - 20 $\beta 2$: 21 - 30	$\beta 1$: 12.5 - < 18.5 $\beta 2$: 18.5 - < 21 $\beta 3$: 21.0 - < 30	14 - 30
Gamma	$\gamma 1$: 32 - 36 $\gamma 2$: 36 - 40 $\gamma 3$: 40 - 44 $\gamma 4$: 44 - 48 ...	$\gamma 1$: 30 - 40 $\gamma 2$: 40 - ...	30 - < 40 $\gamma 1$: 30 - < 65* $\gamma 2$: 65 - < 90* $\gamma 3$: 90 - < 135* *: empirical subdivision	> 30 - 80

Divergent Guidelines of International Federation of Clinical Neurophysiology (IFCN I and II; [Nuwer et al. 1999](#)), International Pharmacology-EEG Society (IPEG; [Jobert et al. 2012](#)), IFCN Glossary of terms most commonly used by clinical electroencephalographers ([Kane et al., 2017](#))

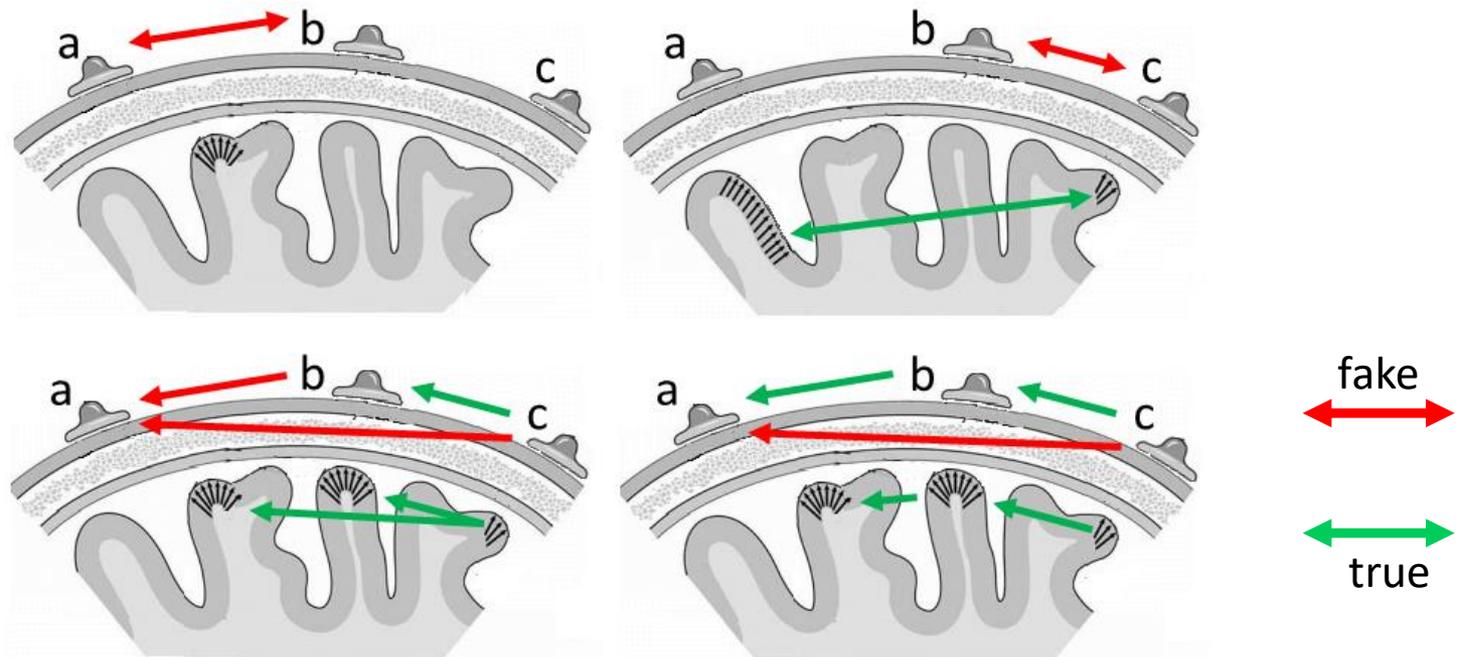
Recommendation for individual bands based on **individual alpha frequency peak** (Klimesch)

- **Head volume conduction effect** spreading electric fields generated by brain sources can inflate (especially bivariate) measures of interdependence of scalp rsEEG rhythms (Blinowska, 2011, Nunez and Srinivasan, 2006)



Legend. Three exploring scalp electrodes "a", "b", and "c" and four underlying cortical sources "At" (i.e., under the electrode "a" with a tangential orientation), "ABr" (i.e., halfway between the electrodes "a" and "b" with a radial orientation), "Br" (i.e., under the electrode "b" with a radial orientation), and "Cr" (i.e., under the electrode "c" with a radial orientation). In the model, the source "At" electric fields are volume conducted to the electrode "b". The source "ABr" electric fields are volume conducted to the electrodes "a" and "b". The source "Br" electric fields are volume conducted to the electrode "b". The source "Cr" electric fields are volume conducted to the electrode "c". In this model, the electrode "b" records electric fields generated by both the cortical tangential source "At" and the cortical radial sources "ABr" and "Br".

- “Common drive” and “cascade flow” effects depend on physiological conduction of action potentials through axons from a brain neural mass to two (or more) cortical neural masses as EEG-MEG sources (Blinowska, 2011, Nunez and Srinivasan, 2006)



Legend. Due to the effect of “common drive”, a coherent activation of the source “Cr” with the sources “Br” and “ABr” may induce an interdependence of the rsEEG rhythms recorded at the electrodes “a” and “c” and those recorded at the electrodes “b” and “a”. Such interdependence could be erroneously interpreted as a functional connectivity between the cortical sources “At” and “Cr” and between the cortical sources “Br” and “ABr”, underlying those electrodes. A directional connectivity from the source “Cr” to “Br” and from “Br” to “ABr” (see nomenclature in the previous slide) is illustrated to show the difference between “direct” and “indirect” connection pathways. The green arrows indicate the interdependence of scalp EEG activity (not shown) that would correspond to the functional source connectivity, while red arrows indicate the interdependence of scalp EEG activity (not shown) that would not.



- **Inverse estimates of EEG source activity** are quite consistent across the following conditions (Mahjoory et al., 2017):
 - two independent cohorts,
 - two anatomical head templates (i.e., Colin27 and ICBM152),
 - three electrical models (i.e., boundary element model, finite element model, and spherical harmonics expansions),
 - three inverse methods (eLORETA, weighted minimum norm estimation, and linearly constrained minimum-variance beamformer)
 - three software platforms (Brainstorm, Fieldtrip, and a home-made toolbox).
- **Inverse estimates of EEG source connectivity** show a considerable variability in relation to different procedures and cohorts (Mahjoory et al., 2017).
- **More basic research needed** on how to make reliable and sensitive rsEEG source connectivity measures, before clinical applications.



- EEG rhythms show prominent **linear features** (Lopes da Silva et al., 1994; Stam et al., 1999; Blinowska and Zygierevicz, 2012).
- Epilepsy (Pijn et al., 1997), schizophrenia (Kim et al., 2000), and neurodegenerative disorders may induce some **nonlinear EEG features** (Hernandez et al., 1996; Jeong et al., 2001; Stam, 2005).
- **Linear** and **nonlinear** regression, phase synchronization, and generalized synchronization methods were compared (Wendling et al., 2009):
 - some methods were **insensitive** to the imposed coupling parameter,
 - performance of those methods was dependent on the **extension of the frequency band**,
 - there was **no ideal method**, namely none of the methods performed better than the other ones in all tested situations and evaluation criteria.
- **More basic research needed** on how to make reliable and sensitive nonlinear measures, before clinical applications.

**What clinical applications for EEG
paradigms in GBC?**

Clinical Application of EEG Paradigms



Main examples of **Clinical applications of EEG biomarkers (resting state and sleep):**

- Diagnosis of Epilepsy
- Localization of epileptic onset zones by EEG source estimates in the presurgical workup in patients with Epilepsy resistant to drugs
- Diagnosis of NREM and REM sleep disorders
- Disturbances of consciousness (coma, persistent vegetative state, brain death)

Objectives:

- To expand the availability of the corresponding standard operating and quality control procedures in underserved populations in all countries, especially in low- and middle-income countries
- To identify optimal insertion in different types of public health systems

Clinical Application of EEG Paradigms



Novel use of EEG biomarkers (resting state and sleep):

- Identification of high risk for Alzheimer's disease (gatekeeper-**triage** role)
- Diagnosis of NREM and REM sleep disorders as biomarkers of dementia with Lewy bodies or Parkinson disease
- Identification of high risk of cognitive decline in patients with **complex chronic diseases such as HIV, chronic renal disease, diabetes, and blood hypertension**
- Treatment selection in patients with major depression
- Measurement of brain health/frailty as a risk factor of brain diseases

Objectives:

- To promote a **survey** and **consensus papers** about a roadmap for the introduction of new EEG biomarkers for use in public health systems with emphasis in underserved populations in all countries, especially in low- and middle-income countries

Clinical Applications of EEG Paradigms



Actions needed as a basis of clinical applications of EEG biomarkers:

- Training courses for personnel including technicians
- Agreement of stakeholders on recruitment of patient groups and procedures to collect data for development of novel EEG biomarkers
- ICT platform (telemedicine) for remote quality control of EEG data and derivation of biomarkers
- Artificial intelligence machines for tentative classification and predictions based on EEG biomarkers
- Make available less expensive equipment (i.e., less than 10,000 USD)
- Cuban Clinical Neuroscience Network as example of clinical applications in lower-middle income countries (“crash test”)

**What clinical validation for EEG
paradigms in GBC?**

Clinical Validation of EEG Paradigms



Actions needed for established and novel use of EEG biomarkers:

- Consult with a survey EEG Workgroups of experts in “Clinical Translation of EEG Biomarkers” operating in the main international societies of clinical neurosciences such as International Federation of Clinical Neurophysiology (IFCN; e.g., Special Interest Groups) and the following:
 - International Organization of Psychophysiology (IOP),
 - International League Against Epilepsy (ILAE),
 - International Society of Pharmaco-EEG,
 - Society of Basic, Clinical Multimodal Imaging (BaCI),
 - International Society for Neuroimaging in Psychiatry,
 - EEG & Clinical Neuroscience Society,
 - Organization of Human Brain Mapping (e.g., Best Practice in Data Analysis and Sharing,
 - The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment; and Electrophysiology Professional Interest Area
- Consult with a survey patients' advocates, international public health stakeholders. Pharma companies (e.g., WHO, UNESCO)

Survey developed by GBC Workgroup 6 on Clinical Applications of EEG and needs of the community:

- (See the Appendix A)

Clinical Validation of EEG Paradigms



Expected outcomes:

- Doodle a **survey** on “*Actual bioethical and clinical barriers to be overcome for the clinical translation of EEG biomarkers and neurological and psychiatric diseases of interest*” to be sent to all members of the scientific societies mentioned above, Patients’ advocates, Public Health organizations, Pharma companies, etc.
- **Clinical protocols** defining the **standard operating procedures** for data recording and analysis for the derivation of **EEG biomarkers** in patients with neurological and psychiatric disorders
- **Position paper** about the most promising EEG biomarkers and clinical areas for clinical care translation of EEG biomarkers
- Improvement in **good medical practice** and prevention/screening/intervention clinical trials using EEG biomarkers, making sustainable neurological and psychiatric care systems, with a special attention for applications for low to middle income countries

**Appendix A: Survey developed by GBC
Workgroup 6 on Clinical Applications
of EEG and needs of the community**

GBC Questionnaire



Background information about survey participants. Participants are asked to provide some general information about their institution (nation, research and/or medical service) and work (research and/or medical service)

How did you find out about this survey?

Testo risposta lunga

What is the nation of your institution/organization?

Testo risposta breve

What is your organization's mission?

Testo risposta lunga

What is your function in it?

Testo risposta lunga

Expertise



Participants are asked to indicate their most expertise in Neurology and Psychiatry (diagnosis, prognosis, monitoring, target diseases) and use of EEG techniques (resting state, evoked potentials, event-related potentials, qualitative-quantitative analysis) and clinical applications

Please indicate your field of experience with Clinical Research (e.g., observational or intervention clinical trials, exploratory proof-of-concept clinical studies), NeurologyPsychiatry

- Clinical: Neurology / Clinical neurophysiology
- Clinical: Psychiatry
- Clinical: Sleep
- Non-clinical (research): Neurological / clinical neurophysiology
- Non-clinical (research): Psychiatry
- Non-clinical (research): Sleep
- Non-clinical (research): Developmental neuroscience
- Altro...

Does part of your work involve resting-state EEG recordings?

- Yes
- No

Do you perform analyses on EEG resting-state recordings

- EEG signal cleaning
- Qualitative inspection
- Quantitative analyses: Power spectra or analyses of alpha, beta, theta bands
- Quantitative analyses: Non-linear spectral analysis (entropy, chaos, etc.)
- Quantitative analyses: Connectivity and network measures
- Quantitative analyses: EEG source estimation and mapping

Does part of your work involve evoked potentials or event-related responses in EEG?

- Yes
- No

Do you perform analyses on event-related recordings?

- EEG signal cleaning for ERP
- Peak latency and amplitude measures
- Frequency domain analysis

Areas to be enhanced by a world-wide online platform.



Participants are asked to indicate the areas to be enhanced to expand the use of quantitative EEG techniques for clinical use in Neurology and Psychiatry and for research purposes.

In what area do you think your current EEG application could be enhanced?

- New digital equipment
- More human resources for EEG recordings and analysis
- More documentation about standard operating procedures of EEG recording and analysis
- More international initiatives to standardize operating procedures of EEG recording and analysis
- A platform to make it accessible reference EEG databases
- A platform to make it accessible data analysis toolboxes and manuals for their use
- Altro...

Domanda

- Opzione 1

Needs, suggestions, and recommendations.

Participants are asked to indicate their specific needs, suggestions, and recommendations to enhance the use of EEG techniques in clinical research and routine in Neurology and Psychiatry.



How could help be established?

- Providing a training platform for the analyses of EEG traces (general)
- Training: videos for the use of EEG apparatus
- Training: videos for the extraction of EEG clinical markers
- Training: Standard Operating Procedures and quality control procedures for the extraction of EEG clinica...
- Providing EEG apparatus (general)
- Providing apparatus: Mobile devices
- Providing apparatus: Polysomnography
- Providing data management support
- Providing advanced analysis support (general)
- analysis support: Training
- analysis support: Web-based analysis tools
- Altro...

Research into novel EEG biomarkers



Participants are asked to indicate what fields of research into novel EEG biomarkers they would be interested in

What are the fields of research regarding novel EEG clinical markers that you would be most interested in?

- Epilepsy
- Developing novel biomarkers in your a specific clinical population (for example, a specific country)
- Defining novel epileptiform makers in general
- Advanced multivariable modeling in epilepsy
- Sleep disorders
- Developing novel biomarkers in a specific clinical population (for example, in a specific country)
- Tracking sleep disorders in neurology (Lewis Body, Parkinson's)
- Tracking development in children
- Tracing normative development in your specific clinical population
- Tracking cognitive decline
- In HIV
- In neurological disorders
- Brain frailty as risk factor and brain health as protective factor

- Stroke
- Triage of ischemic versus hemorrhagic stroke
- Tracking efficacy of interventions
- Altro...

Do you have an interest to integrate EEG signals with other imaging modalities or scientific fields?

- Integration with genetics
- For calculating genetic risk to be linked to EEG biomarkers
- For determining interactions of genetic risk with EEG biomarkers
- For (quantitative) determination of ancestry
- Integration with MRI (e.g. for source localization)
- Integration with DTI (e.g. for mapping connectivity)
- Integration with functional measures, e.g. fMRI
- Altro...