Measures of Resting State EEG Rhythms for Clinical Trials in Alzheimer's Disease

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Measures of Resting State EEG Rhythms for Clinical Trials in Alzheimer's Disease:
Recommendations of an Expert Panel

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Conflict of interests

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Running Title:
EEG measures for clinical trials in AD

Lists of abbreviations

AA- Alzheimer's Association
AChEIs-Acetylcholinesterase inhibitors
AD-Alzheimer's Disease
ADD-AD dementia
ADMCI-Alzheimer's disease mild cognitive impairment
ADms- AD, moderate/severe index
AEC-Amplitude Envelope Correlation
ANNs-Artificial neural networks
ATN-Amyloid, tau and neurodegeneration
bvFTD- Behavioral variant Frontotemporal dementia
CSF-Cerebrospinal
CU-Cognitively unimpaired
D2-Global correlation dimension
DAT-Dementia of Alzheimer's Type
DLB- Lewy Body
DSM-IV and DSM-V ---Diagnostic and Statistical Manual of Mental Disorders
DTF- Directed transfer function
ECOG- Electrocorticography
EEG-Electroencephalography
EMG-Electromyographic
EPIA-Electrophysiology Professional Interest Area
EOG-Electrooculographic
FDG-PET-Fluorodeoxyglucose PET
ff-DTF- Full frequency DTF
FFT-Fast Fourier Transform
fMRI-Functional magnetic resonance imaging
GDC-Global Dimensional Complexity
GFP-Global field power
GFS-Global field synchronization
ICD-10---10th revision of the International Classification of Diseases

IFAST- Implicit Function as Squashing Time (as an artificial neural network)
IFCN- International Federation of Clinical Neurophysiology
ISTAART-Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment
IWG-The International Working Group
K2-Kolmogorov entropy
LFP-Local field potential
LP-DLB/PDD index
LPS-Lagged phase synchronization
MCI-Mild Cognitive Impairment
MEA-Micro-electrode array MEG-Magnetoencephalography
MMSE-Mini mental state evaluation
MRI- Magnetic resonance imaging
NIA-AA Research Framework-US National Institute on Aging–Alzheimer's Association Research Framework
NINCDS-ADRDA- National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NIRS-Near-infrared spectroscopy
NRM-CU persons' index
P-physiologic
PET-Positron emission tomography
PET SUVR- positron emission tomography standardized uptake value ratio
PIA-Electrophysiology professional interest area
PLI-Phase Lag Index
RFMs-Random forest learning machine classifiers
ROC-Receiver operating characteristic
rsEEG-Resting-state electroencephalographic
SCC-Subjective Cognitive Complaint
SCD-Subjective cognitive decline
SES-Stochastic event synchrony
SL-Synchronization likelihood
SMC-Subjective memory Complaint
sMCI-Stable MCI
SVD-Subcortical vascular dementia
SVMs-Support vector machines
qEEG-Quantitative EEG
TVB-The Virtual Brain
VaD-Vascular dementia
WMH-White matter hyperintensities

HIGHLIGHTS

- Resting-state electroencephalographic (rsEEG) measures may reflect synchronization of cortical neurons in humans.
- Patients with Alzheimer's disease (AD) show consistent abnormalities in rsEEG measures at both the group and individual level.
- Linear EEG measures may be used as neurophysiological markers in AD clinical trials.

ABSTRACT

The Electrophysiology Professional Interest Area (EPIA) and Global Brain Consortium endorsed recommendations on candidate EEG measures for Alzheimer's disease (AD) clinical trials. The Panel reviewed the field literature. As most consistent findings**,** AD patients with mild cognitive impairment and dementia showed abnormalities in peak frequency, power, and "interrelatedness" at posterior alpha (8-12 Hz) and widespread delta (<4 Hz) and theta (4-8 Hz) rhythms in relation to disease progression and interventions. The following consensus statements were subscribed: (i) Standardization of instructions to patients, rsEEG recording methods, and selection of artifact-free rsEEG periods are needed; (ii) Power density and "interrelatedness" rsEEG measures (e.g., directed transfer function, phase lag index, linear lagged connectivity, etc.) at delta, theta, and alpha frequency bands may be use for stratification of AD patients and monitoring of disease progression and intervention; and (iii) International multisectoral initiatives are mandatory for regulatory purposes.

1. BACKGROUND

1.1. Qualified biomarkers for the diagnosis and monitoring of Alzheimer's disease (AD) patients in clinical trials

The International Working Group (IWG) and the US National Institute on Aging–Alzheimer's Association Research Framework (NIA-AA Research Framework) have recently proposed and refined recommendations and research criteria for the diagnosis and monitoring of Alzheimer's disease (AD) at the preclinical, prodromal (with objective mild cognitive impairment, ADMCI), and overt dementia (ADD) stages for clinical trials, based on in-vivo fluid and neuroimaging biomarkers [1; 2; 3; 4]. According to these diagnostic criteria, AD status is associated with (i) a reduction of cerebrospinal (CSF) Aβ42 and an increase in amyloid at the brain level as revealed by amyloid positron emission tomography (PET) mapping, and (ii) an increase of phospho-tau in CSF and of tau PET tracer retention. Neurodegeneration over the course of disease progression may be revealed by ^{18}Fluorodeoxyglucose PET (FDG-PET), total tau in CSF, and magnetic resonance imaging (MRI) of brain atrophy in temporoparietal cortex and the medial temporal lobes (including the hippocampi).

1.2. Measures of eyes-closed resting state electroencephalographic (rsEEG) rhythms

The use of the above neuroimaging techniques for serial recordings in longitudinal AD clinical trials may be limited due to their high costs and invasiveness, especially in lower- and middle-income countries. Apart from the indirect role played by FDG-PET as a marker of synaptic integrity, none of these biomarkers reflects effects of AD neuropathology on neurophysiology of brain neural signal transmission underpinning cognitive processes. It is the "gap" of physiology in the amyloidosis, tauopathy, and neurodegeneration framework of biomarkers in AD research [4].

To fill that gap, measures of ***eyes-closed resting state electroencephalographic (rsEEG)*** rhythms are quite promising as they are non-invasive, reproducible (without learning effects) until severe dementia, cost-effective, and based on recording techniques largely available worldwide including lower- and middle-income countries [5, 6;7]. These measures

may probe effects of AD on ascending activating systems and reciprocal thalamocortical circuits in which oscillatory (de)synchronizing signals dynamically underpin cortical arousal in the regulation of quiet vigilance [5, 6; 8;7]. This phase synchronization/desynchronization of cortical neural activity may occur in an interrelated way in multiple cortical areas, gating transmissions and communications of action potentials within both local and long-range neural networks [9; 10; 11; 12]. Animal studies elucidated the cellular and molecular basis of on-going EEG activity at cortical and subcortical level [13; 14; 15]. Furthermore, they demonstrated that AD neuropathology may cause disconnection among neural cells, damage to cortico-cortical and cortico-subcortical pathways, and loss of myelinated axons possibly associated with cortical neural hyperexcitability and hypersynchronization as well as reduced neurotransmission, neural signaling and synaptic activity [16; 17]

In clinical contexts, rsEEG activity is typically recorded from 19-25 to > 80 scalp electrodes placed according to 10-10 montage system [18; **Figure 1**] while patients are in quiet wakefulness with their eyes closed. They are instructed to stay psycho-physiologically relaxed with no cognitive demand and to allow their mind to wander freely (**Panel 1**).

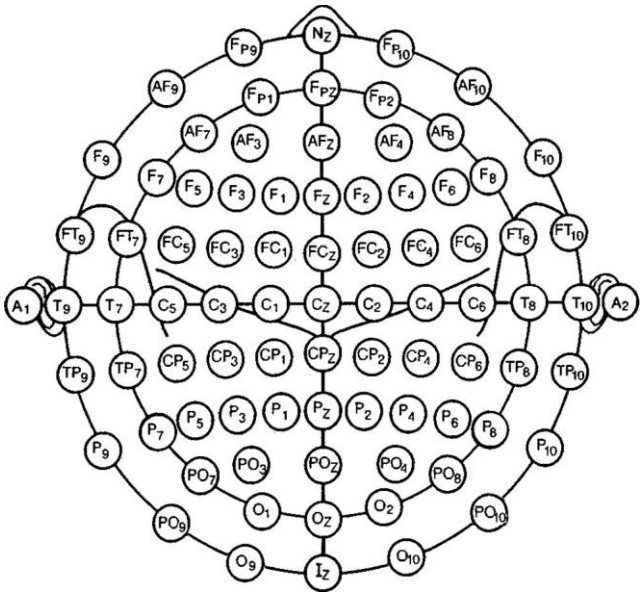

Figure.1: *Modified combinatorial nomenclature of the 10–10-system of scalp electrode montage for clinical electroencephalographic (EEG) recordings, extended with anterior and posterior electrodes in the inferior chain. Adapted from [18], (courtesy from the Publisher).*

Panel 1: *Experimental conditions of recordings of electroencephalographic (EEG) activity in quiet vigilance (resting state) in humans.*

Neurophysiological mechanisms, duration, and instructions

- Neurophysiological mechanisms keeping the state of low vigilance with eyes-closed for several minutes (i.e., 5-15 minutes or more). It also probes the transition to drowsiness and sleep, hence the experimenter (or trained technologist) should not alert the subject in case of sleep. The instructions invite the subject to sit quietly, stay relaxed in a state of mind wandering (i.e., no goal-oriented mental activity), and keep the eyes closed.
- Neurophysiological mechanisms regulating the increase and decrease in the vigilance level while opening and closing the eyes sequentially (i.e., 5-10 minutes). The periods of eyes-open and -closed in response to the experimenter's cue are short (i.e., 1 min), and the sequence of eyes-open and -closed is repeated (i.e., 2-4 times). The instructions to the subject are like those of the first condition. The experimenter will have to alert the subject in case of sleep to have enough EEG data related to the proper mental state.
- The third condition tests the neurophysiological mechanisms underlying the steady maintenance of low vigilance at eyes-closed (i.e., 3-5 min) and moderate vigilance at eyes-open (i.e., 3-5 min). The instructions to the subject are like those of the second condition.

Due to the resistive features of skull and scalp, rsEEG rhythms recorded at the scalp level is mainly represented by frequencies spanning about from 1 to 100 Hz, detectable by the high ***temporal resolution*** (< 1 ms) of EEG recording systems [19; 20, 21].

Spatial resolution of EEG techniques is low to moderate (i.e., few centimeters) as compared to the neuroimaging techniques mentioned above. Indeed, rsEEG activity measured at a scalp electrode may results from cortical sources located several centimeters apart or distributed into large regions due to head volume conduction effects [> 10 cm^2; 20]. This resolution depends on the number of scalp EEG electrodes and mathematical techniques for EEG source estimation (**Figure 2**).

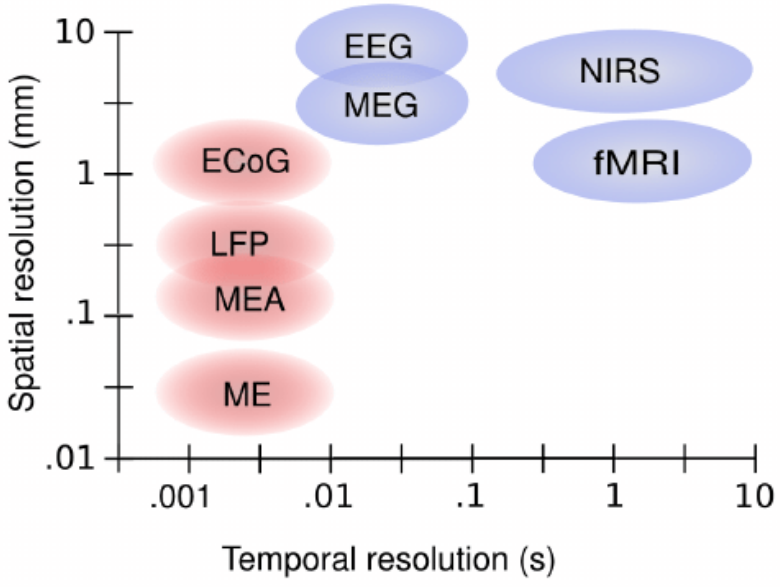

Figure 2: *Schematic overview of the scale of spatial and temporal resolution of measurement methods used for electrophysiology and functional neuroimaging. Measurement methods are EEG, magnetoencephalography (MEG), near-infrared spectroscopy (NIRS), functional magnetic resonance imaging (fMRI), electrocorticography (ECOG), local field potential (LFP) recordings, micro-electrode array (MEA) recordings, and microelectrode (ME) recordings. Non-invasive methods are shown in blue and invasive methods are shown in red. Adapted from [192] (courtesy from the Publisher).*

In artifact-free rsEEG activity, posterior ("dominant") ***alpha rhythms*** (about 8-12 Hz) are the dominant oscillations and reduce in amplitude in the transition from eyes closed to open condition, due to activation of visual-spatial cortical systems [5, 6; 22]. In quiet vigilance (no task demands), high amplitude of low-frequency alpha rhythms (about 8-10 Hz) may reflect low levels of general brain arousal, attention, and readiness [23; 24], while high amplitude of high-frequency alpha (about 10-13 Hz) and low-frequency ***beta*** (about 12-20 Hz) ***rhythms*** may reflect low levels of perceptual, somatomotor, and memory processes [23; 25].

During sensorimotor and cognitive events, alpha rhythms are replaced by faster cortical rsEEG oscillations, namely ***high-frequency beta*** (20-30 Hz) and ***gamma*** (30-70 Hz) ***rhythms***, mainly prompted by (i) forebrain cholinergic direct inputs to hippocampus and cerebral cortex and (ii) thalamocortical projections [15; 20].

In healthy adults, rsEEG activity at ***delta*** (1-4 Hz) and ***theta*** (4-7 Hz) ***rhythms*** may typically show small amplitude and exhibit complex patterns of changes during sensorimotor and cognitive events [26; 20]. Therefore, abnormally prominent theta or delta rhythms in the resting state condition are considered as signs of brain dysfunctions [5, 6].

Several methods can probe information embedded in artifact-free scalp rsEEG waveforms (see ***Supplementary materials: Main features of resting state EEG measures used in studies on Alzheimer's disease***). Fast Fourier Transform (FFT) assumes a linearity of rsEEG signals and returns "***local*** "power density of rsEEG voltage time series at each scalp electrode, frequency-bin-by-frequency bin (**Figure 3**). Other methods estimate ***"interrelatedness of rsEEG activity at scalp electrode pairs or EEG source connectivity,"*** based on an assumption of linearity or nonlinearity of rsEEG signals [5; 27, 28, 29] and ***graph theoretical indices*** represent general topological features of those estimates as network nodes connected (or not) by edges [30; 31; 32; 33; **Panel 2**].

The inclusion of rsEEG measures in AD clinical trials (e.g., patients' stratification, monitoring disease progression, efficacy of therapeutics, etc.) as enriching neurophysiological biomarkers has to steam on a preliminary demonstration that those measures are reliable,

consistent, and sensitive (e.g., test-retest reliability, effect and sample sizes, etc.). For example, the statistical power and the variability of effect-sample sizes of a given rsEEG measure are relevant parameters to evaluate if that candidate biomarker can be included in clinical trial protocols of phases > 1 designed for AD patients, namely protocols testing the neurobiological efficacy and therapeutic effects of new drugs against AD. It should be considered that clinical trials of phases 2 and 3 typically involve 100-300 and 300-3,000 patients for each patients' group, respectively [34]. Therefore, a suitable rsEEG biomarker is expected to be reliable, consistent, and have a sample size substantially lower than n=300 patients for group.

Concerning the issue of test-retest reliability, previous studies reported that the power density of artifact-free rsEEG rhythms is stable at 12-40 months retest performed in healthy adults [35; 36]. Namely, those studies showed high test-retest correlations (r = 0.92 at 5 min, 0.84 at 12–14 weeks, [37]; intra-class correlation coefficients = 0.8-0.9 at 4 weeks, [36]. Furthermore, the absolute and relative power densities of rsEEG activity, including dominant posterior alpha rhythms during the eyes-closed condition, were quite consistent when computed from artifact-free rsEEG data lasting 20 s, 40 s, 60 s to 4 minutes [36; 37; 38] which are the typical durations of rsEEG datasets used for the quantitative analysis performed in Clinical Neurophysiology [5].

In general, results of the previous test-retest studies showed that the rsEEG relative power density was slightly more repeatable than the absolute power density, probably for the general property of normalization procedures to reduce measure variabilities [e.g., 36]. Furthermore, the reproducibility of spectral rsEEG measures over sessions was higher in the eyes-closed than -open condition, possibly due to the effects of residual blinking and saccades in the data used for rsEEG spectral analyses [39; 36]. Moreover, the reproducibility of rsEEG measures was higher in rsEEG power density than interrelatedness (connectivity) estimates at both sensor and source levels [36]. Finally, such a reproducibility was slightly higher at sensor than source levels, but the findings encouraged the use of both levels of analysis for clinical applications [36; 40].

Keeping in mind the above data and considerations, the reliability and consistency of typical rsEEG measures derived from healthy adults seem to be generally suitable for applications in Clinical Neurophysiology [5]. However, those statistical features should be carefully taken into account to interpret the statistical effects reported in the studies using rsEEG measures to compare AD and control individuals and to investigate AD progression and therapy responses.

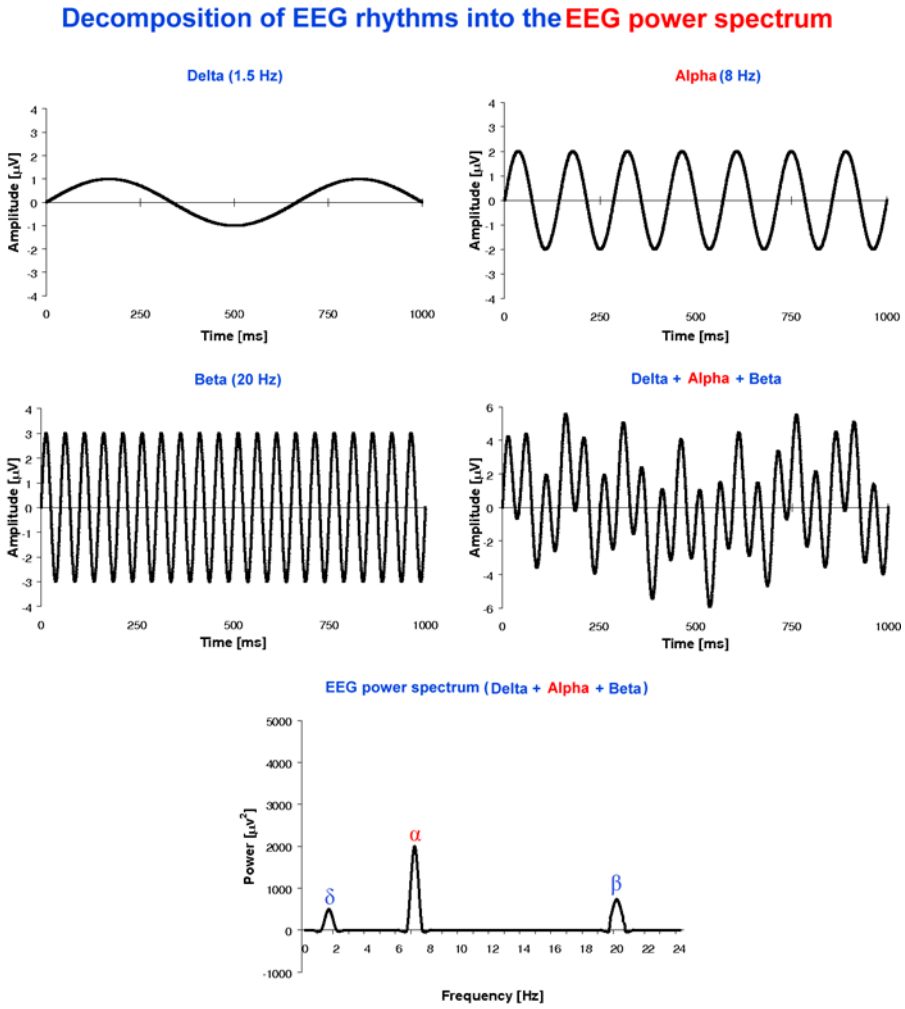

Figure 3: *Decomposition of EEG rhythms into an EEG power spectrum. A sketch illustrates example of sinusoidal EEG waveforms at frequency binds od delta, alpha and beta rhythms and how they can be represented (i) when summed each other at given phases or (ii) used as an input for the calculation of an EEG power density spectrum. Modified [193].*

Panel 2: *Graph theory modeling the topology of measures of rsEEG interrelatedness. Activity*

Gore graph indexes in rsEEG research

- ***"Clustering coefficient"*** as the degree to which nodes in a graph tend to cluster together.
- ***"Path length"*** as the mean number of edges any node needs to reach the others of the graph.
- ***"Betweenness centrality"*** as number of edges one node needs to reach all the other nodes of the graph (the lower the number, the higher the centrality).
- ***"Clustering coefficient"*** as the degree to which nodes in a graph tend to cluster together.
- ***"Local efficiency"*** is computed on node neighborhoods and is related to the clustering coefficient ("global efficiency") as a measure of how efficiently it exchanges information among nodes of the network.
- ***"Modularity"*** as the degree to which the network may be subdivided into delineated groups.
- ***"Small-worldness"*** is defined as a good balance between an intense local connectivity and effective "hubs" connecting far nodes.

- ***"Robustness and adaptation"*** are the ability of a network to maintain its connectivity when a fraction of nodes (links) is damaged.

1.3. Aims and methodology

Although international panels of experts have emphasized the merits of rsEEG measures in AD research [6;7], there are still uncertainties about the specific biomarker value (e.g., disease status, progression, etc.) of different rsEEG measures for their use in AD clinical trials, possibly due to the heterogeneity of methodological approaches that are available. To clarify these uncertainties, the Electrophysiology Professional Interest Area (EPIA) of Alzheimer's Association and Global Brain Consortium endorsed this article written by a multidisciplinary Expert Panel to provide ***recommendations*** about candidate rsEEG measures for AD clinical trials. The core question was ***"Are there rsEEG measures that reveal consistent effects across previous studies carried out in AD patients for use in future clinical trials for patients' stratification, monitoring of disease progression, and study of the efficacy of interventions?"*** Expertise in the Panel covers several relevant disciplines (i.e., Neurology, Psychiatry, Neuroimaging of Dementias; Clinical Neurophysiology; Quantitative Analysis of rsEEG rhythms in Dementias; Cognitive Neurosciences; Public Health) strictly related to the core question.

The Panel formulated the recommendations based on a comprehensive review of the field literature performed through Web of Science, Scopus, and MEDLINE, using several appropriate combinations of the following key words.

For the "***populations of interest***," the following key words were used: "Subjective memory Complaint" (SMC), "Subjective Cognitive Complaint" (SCC), "Mild Cognitive Impairment" (MCI), "Mild Neurocognitive Disorder", "Alzheimer's neuropathology", "Alzheimer's Disease" (AD), "Dementia of Alzheimer's Type" (DAT), "Major Cognitive Impairment", "Major Neurocognitive Disorder", and "Dementia."

For the "***EEG techniques of interest***," the following key words were used: "Electroencephalography (EEG)", "Resting State EEG", "Ongoing EEG", "Background EEG", "Quantitative EEG (qEEG)", "Brain rhythms", and "Brain Oscillations."

For the "***EEG measures of interest***," we used the following key words: "Waveforms (i.e., visual analysis and description of well-known graphoelements observed on ongoing rsEEG traces), "EEG Power Density," "Relative Power Density," "Alpha peak frequency,"

"Complexity and Irregularity (referring to the dynamics of temporal patterns at one scalp electrode or spatiotemporal patterns in many scalp electrodes) [40]," "Interrelatedness of EEG activity or EEG source connectivity," "Spectral Coherence, " "Partial Coherence, " "Entropy, " "Chaos, " "Information Theory, " "Granger Causality," "Directed Transfer Function," "Phase-Amplitude Coupling," "Synchronization likelihood (SL)," "Phase Lag Index (PLI)," "Phase Locking Value (PLV)," "Amplitude Envelope Correlation (AEC)," "Graph Theory," "Clustering coefficient," "Characteristic path length," "Modularity index," "Linear Source Estimation," "Nonlinear Source Estimation," "Functional Connectivity," and "Inverse problem."

For the "***Experimental design of interest***," the following key words were used: "Longitudinal studies" (cohorts of AD patients followed over time), "Cross-sectional studies" (samples of AD patients with different severity and disease duration), "Classification studies" (accuracy of EEG measures in the discrimination between controls, patients with AD and/or other types of cognitive impairment at individual level).

Only papers published in international journals with peer-review and impact factor were selected (-2020). Some papers could not be downloaded from available Internet resources and were not considered. All selected abstracts/papers were critically reviewed by selected members of the Expert Panel (i.e., C.B., L.B., C.D.P, B.G., R.L., F.T., S. L. G.N., and G.Y.) taking into account the criteria reported in Jelic and Kowalski [42] namely original article published in English with 10 or more persons per diagnostic group, diagnosed according to the established consensus clinical diagnostic criteria used as a "gold standard." The validity of the rsEEG measures was mainly based on the guidelines for rsEEG recordings and data analysis in Clinical Neurophysiology [5]. The selected rsEEG papers were distinguished in three arbitrary classes with increasing weight in the formulation of the recommendations. They were as follows:

1) ***Class A***. ADD or ADMCI patients mostly diagnosed using ***qualified*** CSF or PET ***diagnostic biomarkers*** of AD [1; 2; 3; 4, 43] and > 10 participants for each group. When the data were available in the Class-A paper, we reported the effect and sample sizes of the main rsEEG measures characterizing AD patients over controls (see Tables 1, 2, and 3).

2) ***Class B***. ADD or ADMCI patients enrolled using ***traditional criteria for the clinical diagnosis*** of AD as inclusion criteria [e.g., 44] and large ***populations (> 100 participants)*** of AD and control CU persons.

3) ***Class C***. As Class B but with smaller populations (< 100 participants). In the article, Class C papers were described without reporting the "Class C" label and without the specification of the number of persons for the sake of brevity.

The selected members of the Expert Panel (i.e., C.B., L.B., C.D.P, B.G., R.L., F.T., S. L. G.N., and G.Y.) produced a first draft of the article. This draft has been sent to the other co-Authors (January 6th, 2020) for further discussions looking towards a unanimous consensus about the recommendations to be released. It was finalized in March 2020.

Significant caveats and intrinsic limitations of this article include (i) the potentially restrictive criteria used for the literature revision and classification; (ii) the inclusion of studies that have applied the heterogeneous diagnostic criteria for AD used for decades, which may not exclude the presence of moderate cerebrovascular, non-AD hippocampal impairment (TDP-43), and Lewy body co-pathology, especially in older ages; (iii) the blurring effects of head as a volume conductor spreading scalp rsEEG activity (**Figure 4**), and (iv) heterogeneous procedures for the detection of artifacts in preliminary rsEEG data analysis. See more details in the ***Supplementary materials: Caveats and intrinsic limitations***.

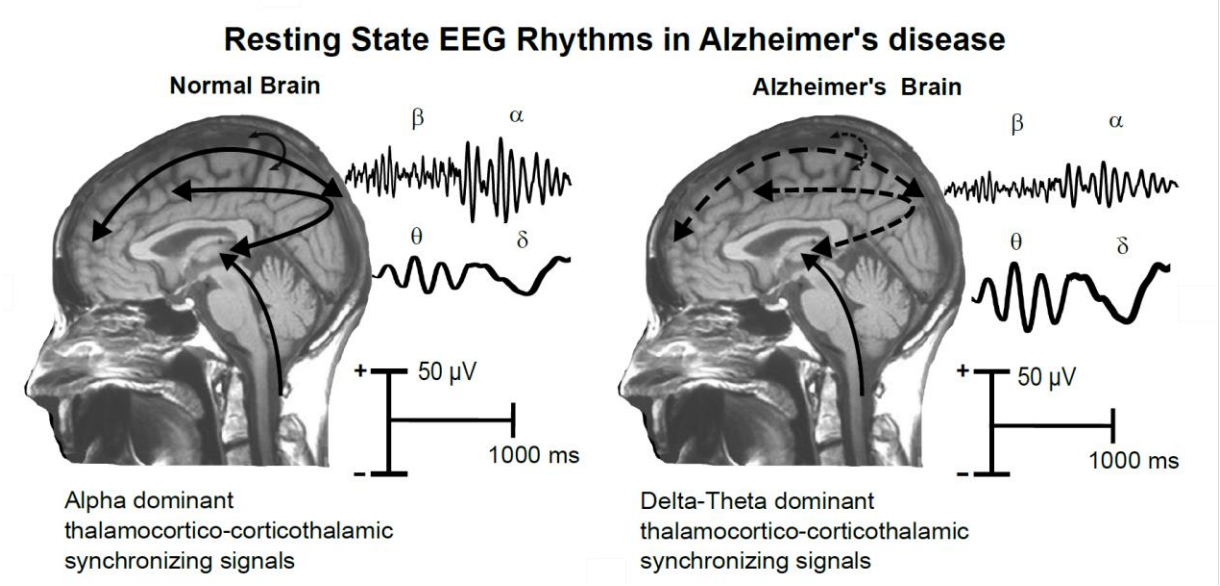

Figure 4. *Tentative physiological model of the generation of resting state eyes-closed EEG (rsEEG) rhythms in the brain of age-matched old cognitively unimpaired (CU) persons and Alzheimer's disease (AD) patients. In the normal brain, dominant EEG rhythms are observed at alpha frequencies (8-12 Hz), which would denote the background, spontaneous synchronization around 10 Hz of neural networks regulating the fluctuation of the subject's global arousal and consciousness states. These networks would span neural populations of cerebral cortex, thalamus, basal forebrain and brainstem, including glutamatergic, cholinergic, dopaminergic and serotoninergic parts of the reticular ascending systems. In the brain of AD patients, the amplitude of these rhythms is reduced (i.e., tonic background desynchronization) together with an amplitude increase of the pathological rsEEG slow frequencies*

spanning delta (< 4 Hz) and theta (4-7 Hz) rhythms. This "slowing" of rsEEG rhythms would mainly reflect a sort of thalamocortical "disconnection mode".

2. RsEEG MEASURES FOR AD PATIENTS' STRATIFICATION

2.1. "Local" measures of rsEEG rhythms in AD patients

ADD and ADMCI patients repeatedly showed marked changes in ***linear measures*** of rsEEG power density at delta, theta, and alpha bands in relation to ***CSF, neuroimaging, and clinical markers***. The main results are reported below.

In two experiments of the international multicentric North Baltic (NORDEEG) study (***Class A***), as compared to age-matched old cognitively unimpaired (CU) persons (n=138), ADD (n=117) and ADMCI (n=138) patients showed increased global theta power density and lower cognitive performance as well as a positive relationship between posterior alpha-beta power density and cognitive performance [45]. Furthermore, decreased CSF amyloid β42 significantly correlated with increased theta and delta power density averaged across all electrodes (global field power, GFP) in patients diagnosed with subjective cognitive decline (SCD, n = 210), MCI (n=230), and ADD (n=197). In contrast, increased p- and t-tau correlated with decreased alpha and beta GFP [46]. Moreover, decreased CSF amyloid β42 and increased p- and t-tau were significantly associated with decreased alpha and beta global field synchronization (GFS) at zero voltage across all alectrodes as a function of cognitive status [46].

European multicentric PHARMACOG study (***Class A***) compared rsEEG measures in amnesic MCI seniors with diagnostic CSF markers incompatible (noADMCI, n = 54) and compatible (ADMCI, n = 72) with AD diagnosis [47]. A statistical model incorporated rsEEG source estimates from recordings performed every 6 months for 2 years. Results displayed that as compared to noADMCI patients, ADMCI patients were characterized by greater global delta and theta source activity and greater ratio between posterior delta-theta and alpha source activity [47]. Furthermore, ADMCI patients who could be evaluated until the last follow-up (n=63) exhibited an association between occipital theta/alpha source activity and global cognitive status, as measured by ADAS-cog13 score, and reduced connectivity within the default mode network in resting state functional MRI markers [47].

In an ITALIAN-TURKEY rsEEG study (***Class A***), as compared to CU persons (n=60), ADMCI patients with high (n=35) and low (n=35) education attainments presented greater alpha source activations topographically widespread [48]. On the contrary, in relation to the ADMCI subgroup with the low education attainment, the ADMCI subgroup with the high education attainment displayed lower alpha source activations topographically widespread (notably, the two ADMCI subgroups had matched cerebrospinal AD diagnostic biomarkers, APOEε4 genotyping, brain gray-white matter measures, and neuropsychological scores).

Another study [41; ***Class A***] examined the association between CSF biomarkers and EEG parameters in AD patients (n=14). Those patients showed significant negative correlation between CSF beta-amyloid (Aβ)-42 concentration and the logarithms of CSD over the right temporal area in the theta band. Total tau concentration was negatively correlated with the lagged phase synchronization (LPS) between the left frontal eye field and the right auditory area in the alpha-2 band in patients with AD.

The effects of AD neuropathology on the amplitude of delta, theta, and alpha rhythms are corroborated by the following studies of independent worldwide consortia (***Class B***).

In a study based on the NEWYORK (n=264) and the STOCKHOLM (n=155) rsEEG databases, ADD and ADMCI patients were characterized by decreased alpha, beta, and gamma Global Field Synchronization (GFS), and increased delta GFS as compared to CU individuals with intact cognition [49]. In another STOCKHOLM rsEEG study, ADD (n=38) patients showed decreased alpha and beta GFP, and anteriorization of dipole source location fitting scalp alpha and beta rhythms as compared to ADMCI (n=31) and age-matched CU persons (n=24) [50].

In some experiments of the ITALIAN rsEEG study, as compared to CU persons (n=126), ADD (n=193) and ADMCI (n=155) patients presented a widespread increase of delta source activity and a decrease of posterior alpha source activity in relation to cognitive performance, as revealed by mini mental state evaluation (MMSE) score and other neuropsychological tests [51]. Furthermore, those abnormalities in rsEEG source activities were related to structural (e.g., hippocampal and cortical gray matter atrophy) [52, 53, 54] and functional (e.g., poor FDG-PET metabolism in posterior cortical regions) [55] neuroimaging markers. Findings at source level were cross validated by GFP markers at the scalp level. In fact, ADMCI patients (n=85) showed that the ratio between theta and gamma power density and the ratio between high- and low-frequency alpha power density were

related to gray matter atrophy in hippocampus, thalamus, and basal ganglia in relation to cognitive status [56, 57, 58, 59, 60].

In the European DESCRIPA rsEEG study, when compared to non-amnesic MCI (n=51), SMC (n=53) not tested for amyloid deposition in the brain, and age-matched CU (n=79) persons, ADMCI patients (n=92) exhibited increased occipital-frontal theta source activity and lower posterior alpha source activity [61].

In the study by Roh and colleagues, as compared to CU persons (n=39), ADD (n=41) and ADMCI (n=38) patients presented (1) higher temporal and parieto-occipital theta power density and a decrease of posterior alpha source activity and (2) lower parieto-occipital alpha and frontal and temporal beta 2 power density in relation with cognitive deficits [62].

Other rsEEG studies of Class C showed similar results about delta, theta, and alpha power density in relation to cognitive functions [56, 59; 63].

Furthermore, beta power density (13-25 Hz) was positively correlated with good cognitive functions in ADD patients [64].

Other studies of Class B and C explored the relationship between rsEEG power density and neuroimaging measures in ADD patients. As compared to age-matched CU persons, ADD patients showed abnormal resting state functional MRI connectivity and decreased regional cortical blood perfusion and or metabolism by ^{99m}Tc-HMPAO SPECT or FDG-PET and scans, respectively, in relation to spatially widespread delta power density or cortical source activity [65 Class C; 66 Class B; 67 Class B; 68Class C; 69 Class C; 70 Class C].

Age and genetic risk factors

The above effects were modulated by **age** and ***genetic risk factors***, as shown by the following rsEEG studies (***Class B***), while gender factor was matched or used as a covariate. In the rsEEG study of VU Amsterdam University Medical Center (AMSTERDAM study), abnormalities in delta and alpha power density were more pronounced in young (≤ 65 years) than old (> 65 years) seniors with ADD (n=320) and intact cognition (n=246) [71].

In the ITALIAN rsEEG study, posterior alpha source activity was lower in ADMCI patients (n=84) than in age-matched CU persons (n=89), especially in those patients carrying the haplotype B of cystatin C genotyping [72]. A similar effect on posterior alpha source activity was also observed in ADMCI (n=89) and ADD patients (n=103) with ApoEϵ4 genotyping over non-carriers [73]. This effect was replicated in ADD (n=125) and CU persons (n=60) in an independent study using a similar methodology [74]. However, it was not

replicated in the AMSTERDAM study carried out with ADD (n=320) and CU persons (n=246) using a methodological approach based on scalp rsEEG power density measures [75].

The above rsEEG measures (e.g., increased delta-theta power density and decreased posterior alpha power density) differed in ADD and ADMCI patients in other studies, as reported by the following studies (***Class B***). As compared to age-matched CU persons (n=35), ADD patients (n=61) were characterized by abnormalities in widespread scalp delta power density [76, 77].

A rsEEG study by the European Consortium of Lewy Body Dementia (E-DLB study) was performed in CU (n=42) and ADD (n=42) patients, Results displayed greater abnormalities in posterior alpha source activity and fewer abnormalities in delta source activity estimated in AD patients over controls [78].

In the ITALIAN study, there was greater delta and theta GFP and lower alpha GFP in ADD (n=60) than age-matched CU persons (n=30) [79], in line with previous relevant evidence [80; 81]. Furthermore, as compared to age-matched CU persons (n=38), ADD patients (n=48) showed reduction in posterior alpha source activities and increase in spatially widespread delta source activities [82].

In another rsEEG study [83], the ratio between alpha and delta+theta power density, and the global rsEEG mean frequency, were lower in ADD patients (n=62) than CU persons (n=14).

Preclinical AD

Previous rsEEG studies showed mixed results in ***SMC seniors with significant amyloid brain deposition (preclinical Alzheimer's neuropathology)***.

In the French INSIGHT-preAD study (***Class A***), SMC seniors (n=318) 70-85 years old were tested by ^{18}F-florbetapir PET SUVR as marker of amyloid deposition in the brain and received an extensive data collection including rsEEG recordings [84]. Three articles reported the rsEEG findings. In the first study [85], there was only a negative trend in the relationship between amyloid deposition and posterior alpha power density (no effect in beta power density). In the second study [86], results unveiled a nonlinear U-shaped relationship between Alzheimer's neuropathology and delta, beta, and gamma power density, while the relationship with alpha rhythms remained unclear.

In the third study [87], high values of Alzheimer neuropathology and education attainment were related to posterior alpha power density (no effect in the other standard

frequency bands). Taken together, those findings suggest that the preclinical Alzheimer's neuropathology may affect rsEEG rhythms in SMC seniors but with variable consequences on posterior alpha rhythms or other rsEEG measures.

Nonlinear rsEEG measures

Nonlinear rsEEG measures demonstrated an overall loss of EEG complexity in ADD patients [88;89; 90; 91; 41; 92, 93; 27; 94; see 95 for a review], especially at alpha rhythms [96] and even in patients with autopsy-confirmed neuropathology [97]. Furthermore, ADD and VaD patients showed different EEG complexity values [98], with the general limitation of a relatively low number of AD patients and the lack of control on the severity of cognitive dysfunctions in the patients' groups. Overall, the following considerations motivate further validation studies before the use of ***nonlinear complexity rsEEG measures*** in regular AD clinical trials: (i) the heterogeneity of the above reference theories and methodological procedures (i.e., information theory, entropy, chaos, etc.); (ii) experimental databases with relatively small groups of AD patients; (iii) variable findings at rsEEG frequency bands [99]; (iv) sensitivity of those measures to instrumental and biological noise; and (v) the lack of validations with neuroimaging and diagnostic biomarkers of AD.

2.2 RsEEG measures of "interrelatedness/source connectivity"

In the INSIGHT-PreAD project (***Class A***), as compared to SMC seniors (n=175) without significant amyloid accumulation in the brain, those with preclinical Alzheimer's neuropathology (n=25) showed that neurodegeneration, as revealed by FDG-PET hypometabolism, was associated with increased frontocentral beta and gamma power density, decreased delta power density, higher spectral entropy, higher complexity, and increased functional connectivity measured by weighted symbolic mutual information in theta rhythms Interestingly, if persons with neurodegeneration exceeded a certain threshold of amyloid load, the whole trend of rsEEG metrics reversed with increased delta power and the decrement of the following variables: beta and gamma power, median spectral frequency, spectral entropy, complexity and others typically characterizing ADMCI and ADD [86].

A bulk of previous studies have shown convergent evidence of differences between CU persons and ADD patients in measures of "interrelatedness" of rsEEG rhythms at electrode pairs or estimates of cortical source connectivity. Many of them were performed using "spectral coherence" at electrode pairs, a very popular linear rsEEG technique. As

compared with age-matched CU persons, ADD patients pointed to lower "spectral coherence" between electrode pairs at alpha (8-12 Hz) and beta (13-20 Hz) rhythms [41; 100; 101; 102; 103; 104; 105; 106,107; 108; 109, 110; 111; 112; 113]. However, these effects were topographically variable being observed in temporo-parieto-occipital electrode pairs in some investigations [100; 106; 111] and frontocentral [104] and fronto-parietooccipital electrode pairs in others [41, 109; 103].

In the AMSTERDAM study (***Class B***), global alpha and beta "synchronization likelihood" across all combinations of electrode pairs (sensitive to both linear and nonlinear "interrelatedness") was lower in ADD (n=109) and ADMCI (n=88) patients as compared to age-matched CU persons [29]. Furthermore, the ADD patients exhibited decreased global alpha "phase lag index" in relation to disease severity [114].

In the same line, the ITALIAN multicentric rsEEG study (***Class B***) reported a reduction of the global alpha "spectral coherence" in ADMCI patients (n=57) as a function of the cerebrovascular impairment in cholinergic tracts from basal forebrain to cerebral cortex as revealed by MRIs [115]. These effects were spatially specified in ADD (n=109), VaD (n=25), and ADMCI (n=88) patients as compared to CU (n=69) [116, 117]. In relation to the CU persons, the ADD and ADMCI patients showed a reduction in fronto-parietal alpha "synchronization likelihood" [116, 117]. Furthermore, "directed transfer function" (DTF; a multivariate measure of directional rsEEG "interrelatedness" derived from Granger causality) was lower from parietal to frontal electrodes in ADD and ADMCI patients as compared to age-matched CU persons [118, 119; 120]. This effect was confirmed in independent investigations [121, 122].

In a monocentric rsEEG study (***Class B***), another measure related to "spectral coherence" (namely, "phase synchronization") showed decreased alpha "interrelatedness" between temporal and parietal electrodes in ADD (n=125) patients compared with age-matched CU persons (n=60) [123].

In the European E-DLB study (***Class B***), another rsEEG measure called "linear lagged connectivity" (removing the zero-lag "interrelatedness" more sensitive to head volume conduction effects) exhibited widespread lowering of alpha inter-hemispherical alpha source connectivity in ADD (n=120) and ADMCI patients (n=70) as compared to age-matched CU persons (n=100) [124, 125, 126].

The effect of AD on the above rsEEG "interrelatedness" was less clear at delta (< 4 Hz) and theta (4-7 Hz) bands. Compared with age-matched CU persons, ADD patients showed decreased "spectral coherence" at low frequencies, especially at central theta rhythms

[100; 108]. In contrast, other rsEEG studies reported widespread increases of "spectral coherence" at delta rhythms [115] or quite complex topographical patterns showing increases and decreases of "spectral coherence" values at different electrode pairs [127].

Specifically, Sankari et al. [127] observed (i) an increase in left intrahemispheric frontal coherence in alpha, theta, and delta rhythms; (ii) an increase in left intrahemispheric temporo-parietal coherence in all bands; and (iii) a decrease in right intrahemispheric temporal-parietal-central coherence in all bands [127].

Other measures of rsEEG "interrelatedness" showed the following results.

In a large monocentric rsEEG study (***Class B***), global theta "phase synchronization" was higher in ADD patients (n=125) over CU (n=60) [74].

In the ITALIAN rsEEG study (***Class B***), "linear lagged connectivity" exhibited higher delta inter-hemispherical connectivity at occipital sources and higher theta intra-hemispherical connectivity at occipital-temporal sources in ADD patients (n=120) compared with age-matched CU persons (n=100) [124, 118], whereas "synchronization likelihood" showed widespread increased interrelatedness at delta rhythms in ADD (n=82) and ADMCI patients (n=88) over CU persons (n=69) [116, 117].

In contrast, a national monocentric rsEEG study displayed decreased "phase lag index" (removing the influence of zero-lag coherence) at the delta and theta rhythms within the frontal and between the frontal and temporal/parietal electrodes in ADMCI patients (n=9) as compared to age-matched CU persons (n=14) [128].

Some divergent results in the above studies may be due to different applied rsEEG measures of "interrelatedness" ("spectral coherence, synchronization likelihood, phase lag index, lagged connectivity, DTF") and their different sensitivity to head volume conduction and common drive effects (see ***Supplementary materials: Main features of rsEEG measures used in AD studies*** for more discussion).

2.3. "Local and interrelatedness" measures of rsEEG rhythms in the classification of AD individuals

RsEEG measures may be used to quantify brain neurophysiological dysfunctions in ADD and ADMCI individuals for their sub-group stratification in observational and intervention clinical trials. This use may imply a classification rate > 80% in the discrimination between AD and control individuals based on rsEEG measures.

In the NORDEEG study (***Class A***), temporal theta power density showed a classification rate of 73% in the discrimination between ADD (n=117) and CU persons (n=138) [45]. In the same study, combined alpha and theta GFP reached 84% in the discrimination between ADD (n=38) and CU (n=24) persons as well 78% between ADD and ADMCI patients [50]. Furthermore, alpha and theta relative power density combined with mean frequency from left temporo-occipital electrodes (T5-O1) correctly predicted ADMCI (n=27) patients progressing to dementia with an accuracy of 85% [106].

In the AMSTERDAM study (***Class A***), global rsEEG power density, pair-wise "interrelatedness" ("phase transfer entropy"), and minimum spanning tree graph indexes at several frequency bands were used to train random forest learning machines (i.e., highest degree, leaf number, and tree hierarchy) for classifications between ADD (n=66) and age-matched CU persons (n=66) individuals [129]. This approach reached 62% of classification accuracy in the discrimination between the CU persons and ADD individuals.

In the ITALIAN rsEEG study (***Class B***), the ratio between parieto-occipital delta and alpha cortical source activities reached discriminated ADD (n=127) and age-matched CU persons (n=121) individuals with 75% of ***area under the receiver operating characteristic (ROC) curve*** [130]. The clinical significance of those results was also tested by a correlation analysis between the activity of parieto-occipital cortical delta or alpha 1 sources and the MMSE score in all Nold and AD subjects as a whole group [130]. Results showed that the higher the activity of parieto-occipital delta sources, the lower the MMSE scores (i.e., global cognitive status). Furthermore, the higher the activity of dominant parieto-occipital alpha 1 sources, the higher the MMSE scores.

Furthermore, a first-order polynomial regression of graph small-worldness index reached an area under the ROC curve of 61% in discriminating between stable (n=74) and progressing (n=71) ADMCI patients, while considering ApoEϵ4 allele it reached 97% accuracy [131].

In the E-DLB rsEEG study (***Class B***), delta and alpha cortical source estimates reached 85-90% of the area under the ROC curve of in the discrimination between age-matched CU persons vs. ADD patients (n=42 each group) [78]. Such accuracy dropped under 80% in the classification of individuals with prodromal (i.e., MCI) stages of AD (n=75) [132].

These findings extended those of other smaller national rsEEG studies. Global delta and alpha "spectral coherence" between electrode pairs successfully classified ADD (n=64) compared with CU people (n=54) with a classification accuracy > 80% [133]. Furthermore, a stepwise logistic regression analyses reached a classification accuracy of 82% between ADD

(n=31) and CU persons (n=17) using left temporal alpha "spectral coherence" and global theta power density [100].

A seminal national study (***Class B***) was very important from a methodological point of view. Two rsEEG databases were used, one formed by ADMCI (n=25) and CU (n=56) persons [122] while the other was based on ADD (n=17) and CU (n=17) persons [134]. In the first experiment [122], mean-square and phase coherence, Granger causality principle (e.g., partial coherence, DTF, direct DTF, full-frequency DTF), phase synchrony indices, information-theoretic divergence, state space based indices, and stochastic event synchrony (SES)[1] were comparatively used to discriminate ADMCI and CU persons. Most synchrony measures indicated decreased EEG synchrony in MCI patients. However, this effect was statistically significant for only two measures (ffDTF and ρ of SES method). The SES reached 68% and 75% of classification accuracy as measured by linear and quadratic discriminant analyses, respectively. Instead, the ff-DTF reached 70% by both linear and quadratic discriminant analyses. Combined measures reached 83% of classification accuracy.

In the second experiment [134], ff-DTF and SES reached classification rates of 83% and 98% using ADMCI and ADD patients, respectively. These results were replicated by other national monocentric studies showing > 90% of accuracy in the discrimination between AD and control CU persons with a combination of those procedures on theta and alpha rhythms [135; 136].

In European DECIDE rsEEG study (***Class B***), non-normalized DTF and spectral coherences of rsEEG activity mainly combining delta, theta, and alpha rhythms reached an area under ROC curve of 86%-88% in the discrimination between ADD and control CU persons [120].

Bennys and colleagues [137] reported that the ratio between parieto-temporo occipital theta and alpha + beta calculated from absolute power EEG bands reached an area under the ROC curve of 86 % in the discrimination between ADD (n=35) and age-matched CU (n=35) persons with a significant decrease in fast activities in mildly impaired patients.

The above results were corroborated using more advanced mathematical classifiers based on ***learning classifiers*** (see caveats in the ***Supplementary materials***: ***The risk of***

[1] SES method relies on i) identification of so-called "bumps" in the time–frequency space and ii) aligning the bumps. The discrimination is based on parameters: ρ: fraction of non-coincident bumps, δ_t and δ_f : average time and frequency offsets respectively between coincident bumps. However the problem of aligning is ambiguous and depends on arbitrary choices.

"inflated" discrimination accuracy in classification studies) in the following large national monocentric rsEEG studies (***Class B***).

A classification rate of 90% was obtained through an ***artificial neural network*** as a classifier in the discrimination between patients with dementia (n=111) and age-matched CU persons (n=56) using the topographic distributions of absolute delta and theta power density as input rsEEG measures [138]. Furthermore, a similar discrimination accuracy between ADD patients and CU persons was reached giving rsEEG power density and measures of "interrelatedness" as inputs to several mathematical classifiers including principal component linear discriminant analysis, partial least squares linear discriminant analysis, principal component logistic regression, partial least squares logistic regression, bagging, random forest, support vector machines and feed-forward neural network (10-fold cross-validation runs) [139]. As best results, ***random forests*** reached 81.5% classification accuracy in the discrimination between mild ADD patients (n=116) and age-matched CU persons (n=45), while neural networks reached 88.5% classification accuracy between moderate ADD (n=81) and CU persons [139].

The ITALIAN rsEEG study (***Class B***) tested the discrimination among ADD (n=180), ADMCI (n=115), and CU individuals (n=171) using multichannel rsEEG voltage time series as inputs to advanced "***IFAST***" artificial neural networks [140,142;141]. This approach showed classification accuracies > 90% between ADD and CU persons as well as between ADD and ADMCI patients [140; 141]. Based on rsEEG rhythms (0-12 Hz) recorded at baseline and 1-year clinical follow up, the ADMCI patients were retrospectively classified with 86% accuracy in the discrimination between those progressing to ADD and those with a stable ADMCI condition [142]. Notably, the classification accuracy did not improve using the most discriminant cortical source activity such as posterior alpha in relation to delta/theta sources as an input to backpropagation artificial neural networks [77% accuracy; 143].

In other studies, high classification accuracies of 94-98% were obtained with novel rsEEG "interrelatedness" measures based on Sugihara causality analysis in CU (n=15), MCI (n=16), and ADD (n=17) persons [144; **Class C**] and based on inter-regional transfer entropy analysis in CU (n=15), MCI (n=16), and ADD (n=17) persons [145; **Class C**].

In the NORDEEG study (***Class A***), a stepwise classification procedure using ***support vector machines*** as a statistical pattern recognition (SPR) produced 5 values from 0 to 1 for each person, based on the analysis of 20 selected rsEEG measures (i.e., power density and "spectral coherence") extracted from the original EEG recording. These 5 values referred to the following diagnostic labels: "NRM" (CU persons index), "sMCI" (MCI index), "AD" (AD

index), “ADms” (AD, moderate/severe index), and “LP” (Lewy body/Parkinson’s disease index). A graph represented these values within their confidence intervals to support the diagnosis. A seminal experiment tested the diagnostic accuracy in the evaluation of clinicians based only on that EEG-based graph, using as a gold standard clinical diagnosis obtained by an experienced multidisciplinary team with the agreement of at least 2 experienced physicians (specialist level in dementia). The team gave the clinical diagnosis using all available examination results (e.g., clinical, neuropsychological, fluid biomarkers, neuroimaging markers), but independently (“blind”) of the EEG results [146]. Five clinical units using harmonized EEG procedures were involved. This procedure was followed in the diagnosis of ADD (n=32), MCI (n=56, 65% of them having CSF diagnostic biomarker values compatible with AD), and CU individuals (n=41) who had received the evaluation of CSF diagnostic biomarkers [146]. The diagnostic accuracy of the EEG-based graph was expressed as a percentage of correct diagnosis, using the mentioned clinical diagnosis as a gold standard. Results exhibited the following relatively low-moderate diagnostic accuracy based on the EEG-based graph: 60% for ADD vs. MCI, 66% for ADD vs. CU, and 56% for MCI vs. CU persons [146].

In precedence, the same Consortium had developed other experiments (***Class B***) in larger populations in which not all persons had received CSF diagnostic biomarker analysis. In an interesting experiment, accuracy in the correct classification of individuals between two groups, based on the mentioned SPR index from 0 to 1, was tested in CU individuals (n=146), ADD (n=135), and LP (n=15) seniors [147]. The SPR index was used as an input for the ROC curve analysis. Results displayed the following correct binary classifications: 90% for ADD (n=135) vs. CU (n=146) persons [147]. These findings outperformed the same classification exercise based on a standard visual assessment of neuroimaging [148] and agreed with previous evidence obtained by the same classification procedure applied in ADD (n=226), ADMCI (n=41), and CU persons (n=226) [149] from the same NORDEEG cohort. Similar results were obtained using an independent SPR procedure based on support vector machines carried out in small populations of CU individuals and patients with dementia [150].

Keeping in mind the above rsEEG results at the individual level, combined “synchronization” and “interrelatedness” measures across rsEEG frequency bands could repeatedly produce binary classifications of ADD and ADMCI over control CU persons with an accuracy ranging from 90% to 70%, thus potentially being useful for patient stratification purposes in AD clinical trials. Notably, the use of these binary classifications for mono-modal diagnostic purposes provided modest accuracy around 60%.

2.4. Topology of the "interrelatedness/functional connectivity" measures of rsEEG rhythms in ADD and ADMCI patients: the new wave of the graph theory indices

The popular Graph theory probed the topology of rsEEG "interrelatedness" at electrode or source pairs in the comparison between groups of ADD/ADMCI patients and CU individuals [9; 151; 32; 31; see also 152 for a review]. As compared to age-matched CU persons, ADD and ADMCI patients were characterized by a more random topology of rsEEG "interrelatedness" at electrode or source pairs, possibly due a reduction in "small worldness" properties of the underlying cortical neural networks [9; 10; 153; 154; 155, 156; 157]. However, it should be remarked that the rsEEG studies lending support to such an interpretation exhibited inconsistent findings about the single graph indices forming the "small world" construct (i.e., "clustering coefficient" and "path length") and unclear effects on delta, theta, alpha, beta, and gamma bands [32; 9; 154; 155,156]. This inconsistency can be explained at least in part by (i) different rsEEG measures of "interrelatedness" used in those studies; (ii) the application of bivariate measures of such "interrelatedness," which are more sensitive to volume conduction and common drive effects than multivariate measures are (see Supplement 2.2); (iii) the use of sensor vs. source level; and (iv) diverse statistical thresholds used 5).

Beyond small worldness, further graph measures were tested (see **Panel 2** for the definitions). In the NORTH-EAST ENGLAND study (***Class A***), minimum spanning trees (MSTs) of "phase lag index" of rsEEG rhythms at electrode pairs were used to model the hierarchical clustering organization of cortical networks as topology of rsEEG "interrelatedness" between CU individuals (n=17) and ADD (n=26) [158]. Compared to age-matched CU persons, the ADD patients showed lower alpha "phase lag index" and lower dominant frequency (maximum rsEEG power density at alpha range) [158].

In the AMSTERDAM study (***Class B***), MSTs of "phase lag index" of rsEEG rhythms at electrode pairs were also used to model the topology of rsEEG "interrelatedness" between ADD (n=133) and CU individuals (n=115) [114]. Compared to age-matched CU persons, ADD patients presented decreases of alpha "phase lag index" with increasing disease severity and a shift of the "betweenness centrality" center of mass from posterior to more anterior scalp regions ("nodes") with increasing disease severity [114]. Concerning the specificity of those results, frontal delta "phase lag index" was selectively affected in bvFTD patients

(n=48) against the background of preserved “global efficiency”, whereas parietal and occipital loss of network organization and “global efficiency” was observed in ADD patients (n=69) in relation to decreased alpha “phase lag index” [159].

Keeping in mind the above results, the graph topology of the “interrelatedness” of rsEEG rhythms may enrich our understanding of AD as a “disconnection” syndrome [6; 160; 11; 12]. However, the most consistent topographic patterns and rsEEG measures to model this abnormality for systematic applications in AD clinical trials has not yet been determined. More international research is needed to improve the promising techniques computing the “interrelatedness” of rsEEG activity based on multivariate models and source estimations [5].

2.5. Predictive value of baseline rsEEG measures in CU persons and AD seniors

Previous longitudinal studies in CU persons and AD patients tested the value of rsEEG measures derived from baseline datasets to predict their cognitive status at follow-ups.

In the AMSTERDAM rsEEG study (***Class A***), high delta-theta and lower alpha power density predicted clinical worsening over time in SCD (n=63) and MCI patients (n=142) with amyloid deposition in the brain [161].

In the STOCKHOLM rsEEG study (***Class A***), combined alpha and theta power density and mean frequency from left temporal-occipital regions predicted cognitive decline in ADMCI patients (n=27) at 1-year follow-up [106]. In a parallel rsEEG study, anterior localization of alpha sources predicted the cognitive decline in ADMCI patients (n=31) at about 2-year follow-up [50].

In another national rsEEG study (***Class B***), low posterior alpha power density predicted the cognitive decline in ADMCI (n=88) and ADD (n=42) patients at 1-year follow-up [162].

In the ITALIAN rsEEG study (***Class B***), ADMCI patients (n=74) with high alpha3/alpha2 frequency power density ratio at scalp electrodes presented greater cortical atrophy and lower perfusion rate in the temporo-parietal cortex as revealed by neuroimaging markers and conversion to ADD status at 3-year follow up [163]. Furthermore, high temporal delta source activity predicted marked cognitive decline in ADMCI patients (n=69) at an average of 14-month follow-up [164].

In the NEWYORK rsEEG study, high temporoparietal theta power density and slowing of mean rsEEG frequency predicted cognitive decline from SMC (n=44) to

significant cognitive deficits at 7-9-year follow-up with an overall predictive accuracy of 90%, thus extending previous evidence of the same Workgroup in CU persons, SMC, ADMCI, and ADD individuals [165,166,167].

In another national rsEEG study, baseline high theta power density and cognitive performance predicted cognitive decline at an average of 20-month follow-up with an overall predictive accuracy of 93% in CU persons ranging from intact cognition (n=24) to ADMCI (n=20) and ADD (n=14) status [63;168].

Tables 1 and 2 report the most consistent findings of the rsEEG studies of ***Class A*** reviewed in this chapter. They lead support to the value of rsEEG measures of "cortical neural synchronization" and "interrelatedness/connectivity" in the ***characterization of AD status*** and ***prediction of cognitive decline*** for ***patients' stratification purposes*** in clinical trials.

Purpose	Design	Patient samples	EEG biomarkers	Main findings	Selected References (Class A)
Disease Status	Cross-Sectional	SMC seniors (N= 318; age= 76)	Delta, theta, alpha and beta power density and sources	*The most prominent effects of neurodegeneration on EEG metrics were localized in frontocentral regions with an increase in high frequency oscillations (higher beta and gamma power) and a decrease in low frequency oscillations (lower delta power)*	Gaubert et al., 2019
Disease Status	Cross-sectional	ADD (N= 117; age= 70), ADMCI (N= 138; age= 75), CU persons (N= 138; age= 66)	Delta, theta, alpha and beta power density and sources	*Findings suggest that the increase in relative theta power may be the first change in patients with dementia due to AD.*	Musaeus et al., 2018
Disease Status	Cross-sectional	HC (N= 17; age= 76), AD (N= 26; age= 76),	Alpha and theta power density	*Compared to CU persons, the patients' groups showed lower alpha "phase lag index" and lower dominant frequency (that showing maximum rsEEG power density in alpha range). The effect size was 1.23 calculated by Cohen's method (Cohen's d) and the sample size per group was 10.*	Peraza et al., 2018
Disease Status	Cross-sectional	ADD (N= 197; age= 67), MCI (N= 230; age= 65), Significant cognitive deficit (SCD) (N= 210; age= 60)	Delta, theta, alpha and beta global field power (GFP) and global field synchronization (GFS)	*Decreased CSF amyloid b 42 significantly correlated with increased theta and delta GFP, whereas increased p- and t-tau with decreased alpha and beta GFP.*	Smailovic et al., 2018
Disease Status	Cross-Sectional	SMC seniors (N= 318; age=76)	Delta, theta, alpha and beta power density and sources	*Statistical trend in the relationship between amyloid deposition and posterior alpha power density.*	Teipel et al., 2018
Disease status	Cross-sectional	CU persons (N= 66; age= 70), ADD (N= 66; age= 70)	Beta power and global rsEEG power density	*rsEEG variables showed that the trained random forest learning machine reached 62% of classification accuracy in the discrimination between the CU persons and ADD individuals*	Dauwan et al., 2016
Disease status	Cross-sectional	CU persons (N= 60; age= 69) ADMCI (N= 70; age= 69)	Alpha power density	*As compared to ADMCI group, the CU group showed greater alpha sources activations. The ADMCI subgroup with high education attainment showed a lower alpha source activation topographically widespread as compared to the ADMCI subgroup with low education. The effect sizes were 0.49 for the global alpha 2 source activity and 0.65 for the global alpha 3 source activity. The sample sizes were 53 ADMCI patients (for each subgroup) for the global alpha 2 source activity and 30 ADMCI patients for the global alpha 3 source activity.*	Babiloni et al., 2020c
Disease status	Cross-sectional	ADD (N= 372; age= 71), CU persons (N= 146; age= 66)	Delta, theta, alpha and beta power density and sources	*In receiver operating characteristic curve analyses obtained using statistical pattern recognition (SPR) method, the EEGs separated AD patients from healthy elderly individuals with an area under the curve (AUC) of 0.90, representing a sensitivity of 84% and a specificity of 81%.*	Engedal et al., 2015
Disease status	Cross-sectional	ADD (N= 31; age= 60), CU persons (N= 17; age= 60)	Alpha "spectral coherence" and global theta power density	*In AD patients, global theta power was increased, left temporal alpha "spectral coherence" and interhemispheric theta coherence were decreased. The effect size (Cohen's d) was 0.88 for the theta power and the sample size was 22 for each group.*	Adler et al., 2003

Table 1. *Measures of eyes-closed resting state electroencephalographic (rsEEG) rhythms for **patients' stratification** in Alzheimer's disease (AD) clinical trials. These biomarkers refer to cross-sectional and longitudinal rsEEG studies of the so-called "Class A" in which AD patients with dementia (ADD), amnesic mild cognitive impairment (ADMCI) or subjective memory complaint (SMC) / subject cognitive impairment (SCI) were compared with old cognitively unimpaired (CU) persons with intact cognition (CU persons) resting in quiet wakefulness for a few minutes. In "Class A" studies, AD patients received a diagnosis based on qualified biomarkers of AD derived from cerebrospinal fluid (CSF) or amyloid positron emission tomography (PET) in line with recent international guidelines [1; 2; 3; 4]. Patients' stratification may be based on rsEEG measures showing either **differences** between AD patients and CU control persons at the group or individual level (i.e., classification studies including those calculating discriminant accuracy by area under the receiving operating characteristic -AUROC- curve) or significant accuracy in the statistical **prediction** of their cognitive decline at a follow-up of 12 months or later. Noteworthy, to test the generalizability of the findings of the articles with the symbol "*" [129; 147], the reported classification accuracy should be cross-validated using the same (trained) classifiers and rsEEG measures in fully independent individual rsEEG datasets obtained from clinical recording units not involved in the original experiments. Frequency bands of rsEEG rhythms were standard, namely delta, theta, alpha, beta, and gamma. More literature evidence and the meaning of rsEEG measures in the table (i.e., rsEEG power density, "spectral coherence", estimates of cortical source activity generating scalp rsEEG rhythms, etc.) are reported in the main text. When the data were available in the "Class-A" paper, the effect and sample sizes of the main rsEEG measures characterizing AD patients over controls are reported. Other explanations and considerations are reported in the "**Supplementary materials**".*

Purpose	Design	Patient samples	EEG biomarkers	Main findings	Selected References (Class A)
Prediction	Longitudinal	ADMCI (N= 72; age= 69), noADMCI (N= 54; age=68)	Delta, theta, and alpha source activities	*Compared to the noADMCI patients, the ADMCI patients were characterized by greater global delta and theta source activity and lower ratio between posterior delta-theta and alpha source activity. The output of the Linear Mixed Models was presented in terms of standardized coefficient, corresponding p-value and, for the interaction factor only, effect size (pseudo h2) calculated as the ratio of explained variability of interaction effect on the total variability of each model.*	Jovicich et al., 2019
Prediction	Longitudinal	SMC seniors (N= 318; age= 76)	Alpha and Delta power density and sources	*Brain β-amyloidosis had not affected behavior and cognition when measured at 30 months. β-amyloidosis alone is insufficient to identify patients at high risk of rapid progression to prodromal Alzheimer's disease. It was calculated the sample size for achieving sufficient confidence around a positive and a negative likelihood ratio. These likelihood ratios incorporated the sensitivity and specificity of the predictive model, providing a direct estimate of how much the combination of predictors would change the odds of a progression to prodromal Alzheimer's disease. Based on Rowe and colleagues reported variable progression of 14% over 3 years, and the use of 95% CIs, sample size was 82.*	Dubois et al., 2018
Prediction	Longitudinal	ADD (N= 32; age= 69), MCI (N= 56; age= 68), CU persons (N= 41; age= 65)	Delta, theta, alpha and beta power density and spectral coherence	*AUROC showed a low discriminative ability of SPR method: 60% for ADD vs. MCI, 66% for ADD vs. CU persons, and 56% for MCI vs. CU persons.*	Nielsen et al., 2018
Prediction	Longitudinal	SCD amypos (N= 25; age= 67) SCD amyneg (N= 38; age 67) MCI (N= 142; age 68)	Delta and theta power density and sources	*High delta-theta and lower alpha power density predicted clinical worsening over time in SCD seniors with amyloid deposition in the brain. The effect size (Cohen's d) was 0.78 for the theta power and the sample size was 27 for each group.*	Gouw et al., 2017
Prediction	Longitudinal	ADMCI (N= 27; age= 58)	Alpha and theta power density and sources	*Alpha and theta relative power density combined with mean frequency from left temporo-occipital derivation (T5-O1) correctly classified at 85% ADMCI using logistic regression model applied on baseline EEG variables by means of chunk test*	Jelic et al., 2000
Prediction	Longitudinal	AD (N= 38; age= 62), MCI (N= 31; age= 63), CU persons (N= 24; age= 61)	Delta, theta, alpha, EEG mean frequency, gamma coherence, network topology	*Predictors of conversion from MCI to AD:* • *alpha /theta power ratio* • *delta, theta and alpha power* • *more anterior alpha sources* • *midline gamma coherence* • *alpha 3/alpha 2 power ratio* *The effect size (Cohen's d) was 0.64 for the alpha power and the sample size was 40 for each group.*	Huang et al.,2000

Table 2. *Biomarkers of eyes-closed rsEEG rhythms for **patients' stratification** in AD clinical trials. These biomarkers refer to rsEEG measures showing significant accuracy in the statistical **prediction** of their cognitive decline at a follow-up of 12 months or later. Noteworthy, to test the generalizability of the findings of the articles with the symbol "*" [106], the reported classification accuracy should be cross-validated using the same (trained) classifiers and rsEEG measures in fully independent individual rsEEG datasets obtained from clinical recording units not involved in the original experiments. Frequency bands of*

*rsEEG rhythms were standard, namely delta, theta, alpha, beta, and gamma. More literature evidence and the meaning of rsEEG measures in the table (i.e., rsEEG power density, "spectral coherence", estimates of cortical source activity generating scalp rsEEG rhythms, etc.) are reported in the main text. When the data were available in the "Class-A" paper, the effect and sample sizes of the main rsEEG measures characterizing AD patients over controls are reported. Other explanations and considerations are reported in the "***Supplementary materials***".*

3. MEASURES OF rsEEG RHYTHMS REFLECTING AD PROGRESSION AND EFFECTS OF INTERVENTION

3.1. Value of rsEEG measures of disease progression in ADMCI and ADD patients

Several studies on AD and CU persons tested the value of rsEEG measures to monitor ***progression of brain dysfunctions*** comparing those measures derived from baseline and follow-up recordings. Core results are reported in the following.

In the STOCKHOLM rsEEG study (***Class A***), ADMCI (n=27) seniors showed increased temporal and occipital theta-delta power density and decreased beta power density at an averaged follow-up of 21 months [106].

In the international multicentric PHARMACOG rsEEG study (***Class A***), as compared to noADMCI patients (n=54), ADMCI patients (n=72) presented increased limbic theta source activity and greater cognitive decline at 24-month follow-up in relation to reduced functional connectivity within cortical default mode network as revealed by resting state fMRI [47].

In the ITALIAN rsEEG study (***Class B***), in relation to age-matched CU persons (n=35), ADD patients (n=88) showed increased delta and reduced parieto-occipital alpha and beta source activities at an averaged follow-up of 13 months [24]. In the same study, similar effects were observed at the prodromal stage of ADMCI [169]. Specifically, the ADMCI patients (n=55) displayed reduced alpha source activities in posterior regions at an averaged follow-up of 13 months.

Other national monocentric studies on AD and control CU persons tested the value of rsEEG measures to monitor progressive brain dysfunctions. ADD patients (n=40) presented increased parietal and occipital theta-delta power density and reduced alpha-beta power density at an averaged follow-up of 30 months [170]. In another study, half of ADD patients (n=40) were characterized by increased temporal and occipital delta-theta power density at an averaged follow-up of 12 months [171]. In another study, ADD patients showed increased delta-theta power density and decreased alpha power density at an averaged follow-up of 2 years while ***no changes*** were observed in VaD and functional psychiatric patients [80]. Finally, measures of "interrelatedness" of rsEEG rhythms revealed progressive brain dysfunctions in AD patients. Compared with age-matched CU persons (n=14), ADMCI

patients (n=9) exhibited decreased delta and theta "phase lag index" within frontal and between frontal and temporal/parietal areas at 1-year follow-up [128].

3.2. Value of rsEEG measures in monitoring disease progression and intervention in ADMCI and ADD patients

Several national studies presented ***effects of Acetylcholinesterase inhibitors*** (AChEIs), enhancing the cholinergic tone, on rsEEG measures obtained in ADD patients.

In the STOCKHOLM rsEEG study (***Class A***), as compared to untreated ADD patients, AD patients (n=15) receiving AChEIs (tacrine) had a reduction of theta GFP after 3 and 12 months of therapy, while both delta and theta GFP reduced after 6 months (n=10) [107]. These results extended previous evidence [172;173].

In the GERMAN study (***Class B***), rsEEG measures were sensitive to AChEIs in ADD patients. In a group of AD patients (n=15), alpha-theta power density ratio responded to a single dose of AChEIs (tetrahydroaminoacridine) predicting clinical effects of a chronic treatment of 7 weeks [174]. In other ADD patients (n=15), a significant reduction in spatially widespread delta and theta power density was observed after AChEI treatment (rivastigmine) of 5 days [175], while after treatment of 1-2 weeks (rivastigmine) only decreased theta power density (n=35) was observed [176]. In another group of ADD patients (n=20), decreased theta power density after 1 week and short-term memory performance did predict treatment response (rivastigmine) at 6-month follow-up [177].

In the ITALIAN rsEEG study (***Class B***), in relation to CU individuals (n=65), ADD patients (n=58) presented a reduction in posterior alpha source activity at 1-year follow-up, which was less marked in those patients (n=28) clinically responding to concomitant treatment with AChEIs (donepezil), as revealed by global cognitive status (i.e., MMSE score), when compared to those who did not respond (n=30) [178].

Other smaller national rsEEG studies reported similar effects in ADD patients. Specifically, AD patients (n=18) showed a significant reduction in temporal delta power density and an increase in power density at other frequency ranges including temporal and centroparietal theta after AChEIs (donepezil) administered for 6 months [179]. This effect was in line with other evidence [180,181]. Furthermore, another group of ADD patients (n=16) displayed a significant reduction in widespread delta and theta power density after AChEIs (rivastigmine) given for 3 months [182]. Cortical source estimation of those data pointed to

significant effects in a network that included left fronto-parietal regions, posterior cingulate cortex, bilateral parahippocampal regions, and the hippocampus [182].

Other pharmacological interventions presented significant effects on rsEEG measures in ADMCI and ADD patients. Core results are reported in the following.

In the PQ912 study (***Class A***), ADMCI and ADD patients formed an experimental group (n=60) receiving a 12-week treatment with an inhibitor of the glutaminyl cyclase enzyme (PQ912) that plays a central role in the formation of synaptotoxic pyroglutamate-A-beta oligomers while a placebo group (n=60) received a hypocaloric beverage for the same period. Results showed an improvement of memory and a reduction of theta GFP in the experimental group as compared with the increase of that rsEEG measure in the placebo group [183]. Of note, the PQ912 intervention did not affect the "phase lag index" as measure of rsEEG "interrelatedness" [183]. In a re-analysis of those rsEEG data, a new measure of rsEEG "interrelatedness" at electrode pairs comprising the amplitude envelope correlation with leakage correction (AEC-c) increased more in the alpha frequency band of the experimental group (n=47) compared to the placebo group (n=56) [184].

In the international SOUVENAID study II (***Class B***), ADD patients formed an experimental group receiving Souvenaid functional food for 24 weeks (n=86) while a placebo group received a hypocaloric beverage for the same period (n=93). Results displayed an improvement of memory and an increase in global delta "phase lag index" across all electrode pairs in the Souvenaid group as compared to the placebo group [185]. A re-analysis of "phase lag index" data presented a stable graph index at 24-month follow-up of local brain network connectivity at beta rhythms in a subsample of the experimental group (n=70-66) as compared to the placebo group (n=77-75) [186].

Table 3 reports the most consistent findings of the rsEEG studies of ***Class A*** reviewed in this chapter. They lend support to the value of rsEEG measures in the ***characterization of AD progression*** and ***pharmacological intervention*** in clinical trials.

Purpose	Design	Patient samples	EEG biomarkers	Main findings	Selected References (Class A)
Disease progression and monitoring	Longitudinal	ADMCI (N= 72; age= 69), noADMCI (N= 54; age= 68)	Delta, theta, and alpha source activities	*ADMCI patients showed increased limbic theta source activity and greater cognitive decline at a 24-month follow-up in relation to reduced functional connectivity. The output of the Linear Mixed Models was presented in terms of standardized coefficient, corresponding p-value and, for the interaction factor only, effect size (pseudo h2) calculated as ratio of explained variability of interaction effect on total variability of each model.*	Jovicich et al., 2019
Disease progression and monitoring	Longitudinal	ADMCI (N= 27; age= 58)	Alpha and theta power density and sources	*ADMCI showed increased temporal and occipital theta-delta power density and decreased beta power density at an averaged follow-up of 21 months*	Jelic et al., 2000
Assessment of treatment effects	Longitudinal	ADMCI (N= 47; age=70), ADD (N= 56; age= 72)	Delta, theta, alpha, dominant frequency, functional connectivity	*ADMCI receiving a glutaminyl cyclase inhibitor involved in the amyloid production (PQ912) showed enhanced interrelatedness of alpha rhythms as revealed by an improved phase lag index.*	Briels et al., 2020
Assessment of treatment effects	Longitudinal	ADMCI (N= 60; age= 72), ADD (N= 60; age= 71)	Delta, theta, and alpha source activities	*Results showed an improvement of memory and a reduction of global theta power density across all electrodes in the Souvenaid PQ912 as compared with the placebo group. The effect size was 0.37 for theta power, while the sample size was 116 for the protocol group (PP), 0.29 and 188 for the intent to treat (ITT) group, and 0.32 and 155 for the modified ITT group.* *PQ912 intervention did not affect the "phase lag index" as measure of rsEEG "interrelatedness"*	Scheltens et al., 2018
Assessment of treatment effects	Longitudinal	ADD (N= 15; age= 65), ADD placebo (N= 10; age= 61)	Delta and theta GFP	*AChEIs (tacrine) reduced theta GFP after 3 and 12 months, while both delta and theta GFP reduced after 6 months*	Jelic et al., 1998

Table 3. *Measures of rsEEG rhythms for **monitoring AD progression** and **response to interventions** in AD clinical trials. These biomarkers refer to longitudinal rsEEG studies of the so-called "Class A" (see Table 1 for definitions). The qualification of those measures was based on studies showing **differences** in rsEEG measures at baseline vs. follow-up recordings or before vs. after a pharmacological intervention in relation to placebo. For example, in the PQ912 study, ADMCI and ADD patients formed an experimental group (n=60) receiving an inhibitor of the glutaminyl cyclase enzyme (PQ912) that plays a central role in the formation of synaptotoxic pyroglutamate-A-beta oligomers for 12 weeks, while a placebo group (n=60) received hypocaloric beverage for the same period [181]. In other studies, ADD and ADMCI patients received Acetylcholinesterase inhibitors (AChEIs) for weeks/months. Frequency bands of rsEEG rhythms were standard, namely delta, theta, alpha, beta, and gamma. When the data were available in the "Class-A" paper, the effect and sample sizes of the main rsEEG measures characterizing AD patients over controls are reported. More literature evidence and the meaning of rsEEG measures in the table are reported in the main text.*

4. NEUROPATHOPHYSIOLOGICAL BASIS OF EEG MEASURES IN AD PATIENTS

In the review of the literature, AD patients showed the most consistent abnormalities in (eyes-closed) rsEEG rhythms featured as changes in delta-theta and alpha power density at scalp electrodes or estimates of cortical source activity. It can be speculated that these abnormalities may reflect, directly or indirectly, the effect of AD neuropathology on distributed brain neural networks involved in the generation of cortical rsEEG rhythms and the regulation of general brain arousal, balance of cortical inhibition/excitation, and vigilance [6; 11;7]. Those networks might be formed by subcortical and cortical neural circuits [187; 14; 188], with a special role of thalamocortical functional connectivity during active event-related information processing [25].

However, more literature relating AD neuropathology to beta and gamma rhythms is emerging. It was recently shown that once the amyloid load exceeds a certain level, the power spectrum level of beta and gamma decreased markedly [86]. Other bodies of evidence have demonstrated that gamma power as well as gamma coherence is markedly affected in human patients with AD [49; 29; 189].

More discussion about the neurophysiological underpinnings of the rsEEG findings reviewed in this article can be found in the ***Supplementary materials*** (***Physiological basis of abnormal rsEEG measures in AD patients***).

5. RECOMMENDATIONS

5.1. Diagnostic specificity of stand-alone rsEEG measures

Despite historical efforts at evidence-based reviews [6,7], the diagnostic usefulness of rsEEG measures is still controversial. Using an evidence-based technique, Jelic and Kowalski [42] performed a systematic review of the literature regarding the diagnostic accuracy of rsEEG in dementing disorders published from 1980 until 2009. They concluded that although the classification accuracy values were in general high (> 80%), the evidence for the diagnostic utility of rsEEG markers in AD was insufficient to suggest its use alone in memory clinics routines, also considering that they do not provide a direct measure of the underlying AD neuropathology. Along the same line, international guidelines on AD diagnosis did not recommend the use of rsEEG biomarkers for diagnostic purposes; rather, they target molecular

and structural measures of AD neuropathology [2; 3; 4]. Notably, the present review did not find consistent novel findings to change this position to date. However, novel techniques including rsEEG measures based on local, "interrelatedness/connectivity", and improved/standardized graph theory markers as inputs to machine learning algorithms may hold the promise in increasing the diagnostic utility of quantitative EEG in future, especially in lower- and middle-income countries [7].

5.2. Stratification of AD patients in clinical trials based on rsEEG measures

The present article reports that ADD and ADMCI patients may be characterized by consistent changes in rsEEG measures.

The most consistent findings were obtained using ***linear rsEEG measures*** pointing to reduced relative power density at scalp electrodes or estimates of source activity as well as reduced "interrelatedness" (e.g., "spectral coherence" and "phase lag index" at electrode pairs or linear lagged source connectivity) at ***dominant alpha rhythms*** in posterior regions in ADD and ADMCI patients as compared to age-matched CU persons and patients with matched cognitive deficits due to other neurodegenerative and cerebrovascular causes (Table 1). Furthermore, the same linear rsEEG measures of amplitude and "interrelatedness" of ***posterior theta rhythms*** were repeatedly associated with higher probability to develop a significant cognitive decline in CU persons and AD patients (Table 2). Also, rsEEG measures at delta frequencies were often reported as significant markers (Tables 1 and 2).

Those linear rsEEG measures are recommended for the stratification of ADD and ADMCI patients in a ***stepwise triage procedure*** for the enrollment of patients in clinical trials. In the ***first step***, probable ADD and ADMCI patients may be selected based on the traditional NINCDS-ADRDA criteria for the clinical diagnosis of AD [44; 2]. In the ***second step***, these patients may receive standard non-invasive and cost-effective rsEEG recordings and be sub-grouped in those with lowest vs. highest abnormalities in rsEEG measures (i.e., threshold based on median values). In the ***third step***, the ADD and ADMCI patients with the highest abnormalities of rsEEG measures may receive invasive and relatively expensive procedures to extract CSF and neuroimaging diagnostic biomarkers of AD [3; 4]. Only the ADD and ADMCI patients who are positive for those diagnostic biomarkers would then be used in the observational or intervention clinical trials. This procedure would confer some benefit to financial resources, reducing the number of patients "negative" to the CSF and neuroimaging diagnostic biomarkers of AD in the enrollment phase. Furthermore, the enrolled patients having highest abnormalities of rsEEG measures may be ideal to test new diagnostic procedures and therapeutic interventions in ADD and ADMCI patients.

Alternatively, should the above clinical trials aim to recruit prodromal AD people in the very early stages of disease, rsEEG recordings may be helpful to those with normal or minimally abnormal local or "interrelatedness" rsEEG measures.

Discussion about costs of rsEEG measures in AD clinical trials can be found in ***Supplementary materials*** (***Physiological basis of abnormal rsEEG measures in AD patients***).

5.3. RsEEG measures of AD progression and efficacy of interventions

Disease progression biomarkers are clearly important in both observational and intervention AD clinical trials. In the monitoring of AD progression and response to therapies, the most consistent findings were obtained using ***linear rsEEG measures*** pointing to reduced power density at scalp electrodes or estimates of source activity as well as reduced "interrelatedness" (e.g., "spectral coherence", DTF, and "phase lag index" at electrode pairs or linear lagged source connectivity) at ***delta, theta, alpha and gamma rhythms*** (Table 3).

In this respect, those rsEEG measures may be used as secondary endpoints of interventions and have a complementary value compared with neuroimaging biomarkers providing more direct measurements of progressive AD neuropathology and neurodegeneration [2; 3; 4].

5.4. International initiatives for research on rsEEG measures in AD

In general, the findings reviewed in the present article raise the need for international consensus initiatives to develop or refine a multi-center standardization of instructions to patients, rsEEG recordings, and selection of artifact-free rsEEG periods in line with the standards of clinical trials in AD. First attempts can be found in initiatives of International Federation of Clinical Neurophysiology [5;7]. Future double-blind, prospective, multicenter clinical trials may also carry out comparisons of different linear and non-linear rsEEG measures (e.g., "local", "interrelatedness/connectivity" and Graph theory) of disease monitoring, progression, and intervention to reach consensus about optimal standard operating computational procedures and their validity and reliability. Ideally, these procedures will be based on well-established open-access Internet-based software platforms to ensure future replicability [see two interesting examples in 190; 191].

We also recommend that all efforts should be made to make neurophysiological datasets (with accompanying anonymized data) open access. This open science approach would also ensure replicability of reported results, in addition to enabling datasets to be pulled

(allowing big data analytics), and algorithms/classification models to be developed/tested against one another, accelerating the data science in this field. For this purpose, repositories could be used such as OpenNEURO (https://openneuro.org/).

In those initiatives, an important role should be played by regulatory authorities (e.g. Food and Drug Administration, European Medicine Agency, etc.), international scientific Societies of Clinical Neurophysiology and Neurology, and Alzheimer's Association as validated rsEEG measures are expected to be used as biomarkers in clinical trials relevant for drug regulation and licensing in the future.

A summary of the recommendations of the present expert panel is reported in Panel 3.

Panel 3: *Recommendations*

Summary

- ***"Data acquisition"*** after careful multi-center standardization and harmonization of instructions to patients and rsEEG recordings.
- ***"Data analysis"*** based on standardized selection of artifact-free rsEEG periods and extraction of linear "local" (e.g., rsEEG power spectral density) and "interrelatedness/connectivity" rsEEG measures by open-access Internet-based software platforms for replicability.
- ***"Use"*** for stratification of AD patients and monitoring of disease progression and intervention.
- ***"Endorsement"*** for multi-sectoral international initiatives for further validation of rsEEG measures in AD

6. CONCLUSIONS

What can be the added value of rsEEG measures for the instrumental assessment and monitoring of disease status and progression in ADD and ADMCI patients?

In precedence, IWG-2 suggested two classes of biomarkers for the assessment of ADD, namely the ***"diagnostic"*** biomarkers (i.e., those measuring the pathophysiological hallmarks of the disease such as the cerebral amyloidosis and the amount of total or phospho-tau in the cerebrospinal fluid or directly within the brain by PET), and the ***"progression or topographical"*** biomarkers (i.e., those measuring progression of region-specific neurodegeneration with characteristic "AD-signatures", such as FDG-PET and structural MRI). More recently, NIA-AA Research Framework [4] suggested three classes of biomarkers for the assessment of AD. They named ***"diagnostic disease"*** biomarkers as those measuring cerebral amyloidosis (i.e., "A" biomarkers) and phospho-tau (i.e., "T" biomarkers) by CSF or PET techniques. They also named ***"neurodegenerative/progression"*** biomarkers (i.e., "N"

biomarkers) those measuring total tau by CSF sampling, FDG-PET hypometabolism, and structural MRI markers of brain atrophy.

Keeping in mind the ***"physiologic"*** meaning of rsEEG measures reviewed in the present article, we posit that the term ***"physiologic (P) biomarker"***. In this line, the AD biomarker framework [4] may become "A", "T", "***P***", and "N." This "P" biomarker (e.g., + or -) may possibly reflect vulnerability or resilience of subcortical and thalamocortical loops and the ascending activating systems as additional and supplementary relevant information concerning the AD status and progression.

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