

# Technical and statistical milestones and standards for construction, validation and/or comparison of Quantitative Electroencephalogram (QEEG) normative databases

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## Abstract

Quantitative electroencephalogram (QEEG) and the QEEG normative database help in characterization of normal versus neurocognitive diseases, in diagnosis and prognosis and in treatment tailoring. Constructing QEEG normative databases and standardization of QEEG protocols for use in both research and clinical settings has proven challenging over the last 61 years. The present paper focuses on a) historical and technical milestones the field had to overcome, b) standards to be followed when constructing and validating a normative databases, c) commonly used normative databases, and d) provides an illustrated step-by-step guide to QEEG normative database validation and comparison.

## Introduction

While clinical evaluation and correlation is key to diagnosis of mental and neurocognitive disorders, it is subjective. Among objective markers (biochemical, imaging and genetic tests) the electroencephalography (EEG) and in particular the digital EEG (dEEG) has evolved as a sensitive diagnostic and prognostic tool meeting the American Academy of Neurology (AAN) standards (Class III evidence, Type C recommendation) [1,2]. Nuwer defined dEEG as “... the paperless acquisition and recording of the EEG via computer-based instrumentation, with waveform storage in a digital format on electronic media, and waveform display on an electronic monitor or other computer output device” [2]. The advent of the dEEG paved the way for quantitative electroencephalography (QEEG) with both serving complementary to each other. The dEEG captures an individual’s brain wave patterns, frequency, resting-state, and event- or evoke-related responses to visual, auditory, tactile, error, Go/No GO etc stimuli in healthy and disease states.

American Academy of Neurology defined qEEG as ...., “the mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison” [2], QEEG requires an individual patient’s numerical EEG results to be transformed from the time domain into the frequency domain and Gaussian approximation and cross-validation be carried out. Following this Z-scores are computed with relation to an appropriate normative database followed by construction of a topographic/brain map to be used either for diagnosis, prognosis or treatment tailoring [1,2]. The assessment of changes in QEEG brain maps is especially suited for differential diagnosis in cross-border diseases / diseases with symptom overlap for example in differentiating between delirium, dementia and depression [3-7].

Other areas where QEEG has made unique contributions include; epilepsy screening and in drug-resistant epilepsy, in court sentencing, pharmaco-QEEG, neurocognitive issues, traumatic brain injury (TBI) severity, post-concussion syndrome, mood disorders, exo- or endogenously induced behavioral disorders, attention deficit disorder (ADD/ADHD), schizophrenia, depression, tinnitus, encephalopathies and alcohol and/or substance abuse [3-7]. On the issue of differential diagnosis of cross-border diseases another parallel development which has bearing on QEEG’s usefulness as a diagnostic and prognostic tool is the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Figure 1) [8]. Changes in disease definitions and classification as per the DSM influence cross-study comparability, QEEG derived biomarker reliability and validity. However, DSM-5, released in 2013 keeping in mind neurocognitive developments in the field has helped lay to rest many of the issues pertinent to disease classification [8].

The backbone of the QEEG is the normative database (a term coined by Graham and Dietlien in 1965) used in drawing comparisons [9]. In the hands of the untrained (operators, data analyzers and interpreters), the QEEG can yield results that are not of clinical relevance [10]. Therefore, over the last 61 years several QEEG standards have been developed to ensure.

- The validity and reliability of QEEG for research and clinical use in diagnosis, prognosis and pharmaco-QEEG,
- That a balance between “standardized medicine” and “precision medicine” is struck so as to meet the World Health Organization

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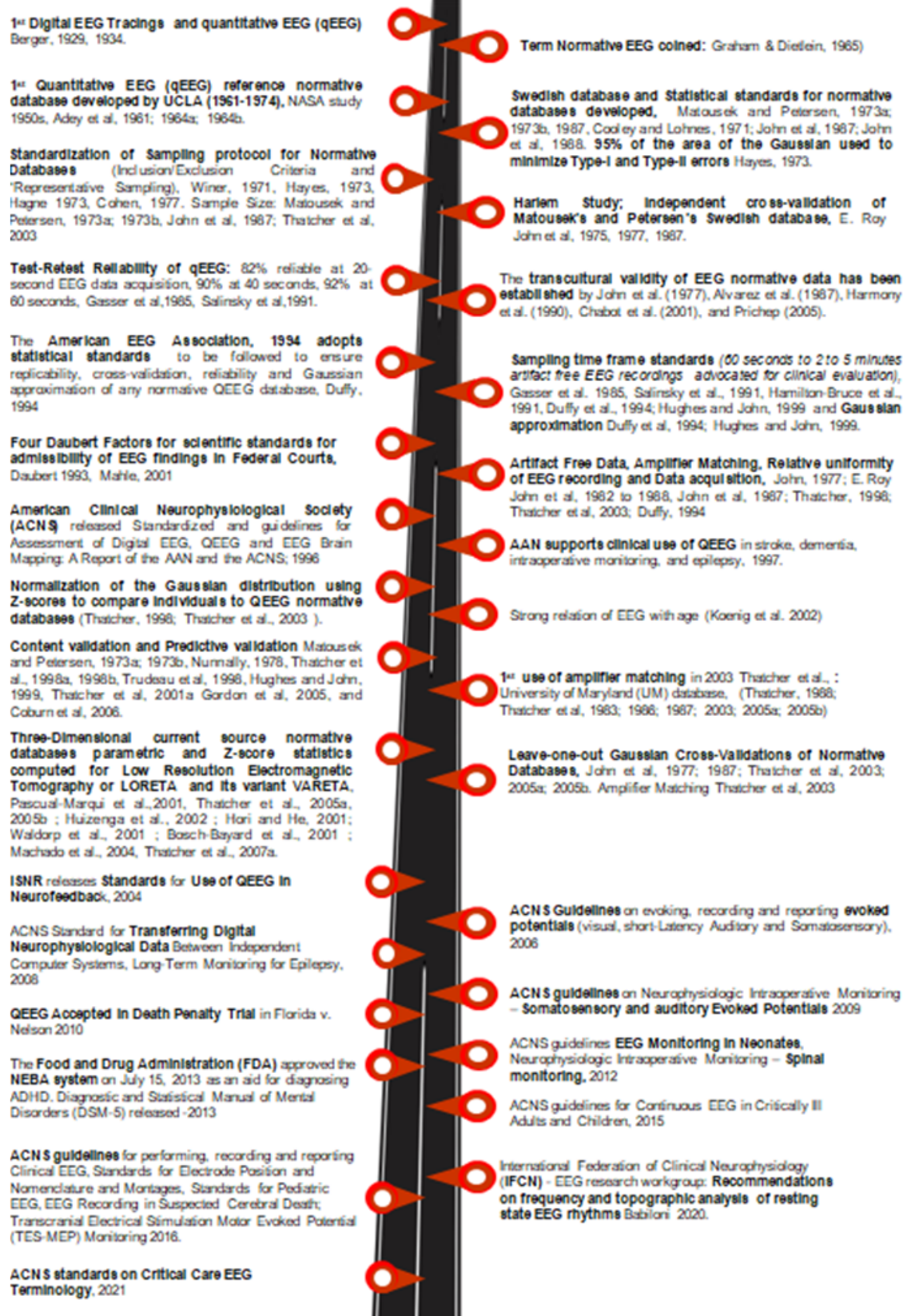


Figure 1. History of the scientific, technical and statistical improvements in constructing QEEG normative databases

(WHO) “High 5s Project” goals to ensure patient safety and finally [11].

- To meet health insurance requirements [11-17].
- Standard methods of EEG data acquisition, visualization (synchronization, connectivity and topographic features), processing (de-artifacting, extraction and classification), storage and statistical comparisons have been and are in continuous development (Figure 1) [9-17].
- Standard methods of normative databases construction, guidelines on the same and FDA registered normative databases.
- World-wide efforts are on to generate long-tailed data and merge them to generate big data that will allow for both cross-study and cross-cultural comparisons [16-18].

The goal of this paper is to present; i) a brief historical review of technical and statistical milestones and standards that apply to QEEG and QEEG normative databases over the last 61 years (Figures 1 and 2) (Table 1), ii) protocols involved in normative database evaluation and comparison (Figure 3), iii) common normative QEEG databases in use and iv) to provide a step-by-step guide to normative database evaluation and comparison from EEG recording to Z-score computing, followed by construction of topographic maps using EEG machines like BrainView by Medeia (Figures 4a, 4b).

## Methodology

The online search engines used were Google, Google Scholar, PubMed, MEDLINE. In keeping with the goal of this paper the keywords and phrases used to conduct the literature search were “EEG”, “electroencephalogram”, “quantitative electroencephalogram”, “QEEG”, “history of EEG/QEEG”, “guidelines”, “standards”, “normative database”, “technical standards EEG/QEEG”, “protocols for normative database construction EEG/QEEG”, “normative database comparison EEG/QEEG”, “FDA registered normative EEG/QEEG database”, “Z-score computing EEG/QEEG”.

First the titles and then abstracts that met the study goals were shortlisted from each of the above keyword-based searches: The preference was for articles whose full text was available in English and free. If any article was extremely important for the study but was not available for free, we obtained the article. Text books, book chapters, published original and review articles, standards and guidelines American Clinical Neurophysiology Society (ACNS), American Electroencephalographic Society (American EEG Society, AEEG), American Academy of Neurology (AAN), white and grey papers, focusing on QEEG normative databases, their construction, comparison, FDA registered normative databases (e.g. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf4/K041263.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf4/K041263.pdf)) and the historical developments in the field of QEEG were included in the study. The BrainView in-house manual by Medeia on the historical developments in the field of QEEG, normative database construction and comparison was also used. Articles beyond the scope of interest were excluded from the study.

## Results and discussion

The results and discussion is presented in four parts; the first part deals with the history of the scientific standards followed in constructing QEEG normative databases. The second part deals with QEEG normative databases validation and comparison and the third presents a list of commonly used normative databases. The fourth

and final section deals with a step-by-step guide to evaluation and comparison of QEEG normative databases.

## History of the scientific standards followed in constructing QEEG normative databases

In 1929 the human EEG was first measured and the first QEEG study was carried out by Hans Berger (Figure 1) (Table 1) using the Fourier transform to spectrally analyze EEG data and to compare different EEG measures to a normative database [9,19-21]. The first quantitative EEG (QEEG) reference normative database was developed in the 1950s at the UCLA Brain Research Institute by Ross Adey between 1961-1974. Its drawback was it was intended for selection of astronauts for NASA space travel and not clinical use (Figure 1) [22-24]. The statistical tests run on the database included calculation of means and standard deviations, measures to determine if the data followed the normal/Gaussian distribution, complex demodulation, Fourier spectral analysis and basic statistical parameters necessary for any reference normative database.

The first known statistical standards for normative databases and the first peer reviewed publication of a normative database was by two Swedish Neurologists Dr. Milos Matousek and Dr. Ingemar Petersen in 1973 [25,26]. They measured QEEG in n=401 subjects (Female%: 54.4%) aged between 2 months to 22 years with a sample size of n=18 to 49 per one year age grouping, all subjects lived in Stockholm, had no clinical histories and performed at grade level [25,26]. The sample sizes varied from 18 to 49 per one year age groupings. The Swedish pair set the standards for clinical inclusion/exclusion criteria, parametric statistical tests and peer reviewed publications.

The Swedish database was independent culturally cross-validated and deemed reliable by E. Roy John and colleagues in 1975 using EEG from 9- to 11-year-old Harlem black children, also performing at grade level with no history of neurological disorders (Figure 1) [27-29]. E. Roy John and colleagues formed a consortium of universities (1982 to 1988) to address the “need for standardization” [27-31]. In 1994 the American EEG Association, 1994 adopted the statistical standards mentioned below to ensure replicability, cross-validation, reliability and Gaussian approximation of any normative QEEG database [31]. Between 1993 and 2001 the four Daubert factors (Figure 2) for scientific standards for admissibility of EEG findings in federal Courts were derived [32-35]. The standards mentioned below set the stage for the evolution of QEEG and EEG standards currently advocated by the International Federation of Clinical Neurophysiology (IFCN) [15].

- In term of sampling time frames and intra and inter test-retest reliability, QEEG has proved to be highly reliable and reproducible [10-22]. Sampling/acquisition time frames were 82% reliable at 20-second EEG data acquisition, 90% reliable at 40 seconds, and 92% reliable at 60 seconds [13,21]. Current standards recommend at least 60 seconds to- preferably 2 to 5 minutes of artifact free EEG recordings for clinical evaluation [30,31]. Predictive accuracy and error rates depend on the data that make up a given EEG database as well as the statistical methods used to produce and compare QEEG normative databases. Split-half reliability and test re-test reliability measures (>0.9) are also important to demonstrate the internal consistency and reliability of the normative database [28,29,31,36-40].
- QEEG-database sample size is dictated by “effect size” and “power” i.e. the sample size required to detect a particular effect, the sample size required to achieve Gaussian distribution and cross-validation,



**Table 1.** Findings for QEEG studies on selected Neurocognitive Disorders

Neurocognitive Disorders		QEEG Findings	References
Epilepsy	Differential Diagnosis	<ul style="list-style-type: none"> <li>• QEEG spectrograms to seizure sensitivity: 43% to 72%</li> <li>• QEEG asymmetry to focal seizures (n=117/125) a sensitivity: 94%</li> </ul>	[95-102]
	Antiepileptic Therapy	<ul style="list-style-type: none"> <li>• spectral power in repeated EEG records for 16 months associated with plasma dosages of ethosuximide, diphenylhydantoin, valproic acid, and phenobarbital EEG slowing, increase in delta (<math>\delta</math>), and theta (<math>\theta</math>) activity and decrease in the high-frequency bands, a slowdown in the dominant rhythm being specific</li> </ul>	
	Cognitive Impairment (CI)	<ul style="list-style-type: none"> <li>• Seen in 70-80% of patients with epilepsy over 18 years. Absolute power was increased and intra- and intra-hemispheric coherence (<math>\theta</math> band) was higher in epilepsy v/s healthy subjects</li> </ul>	
	Pediatric Epilepsy	<ul style="list-style-type: none"> <li>• QEEG is increasingly being used for non-convulsive seizures (NCS) detection in critically ill children (sensitivity 65 to 83% and specificity 65–92%) that follow pediatric convulsive status epilepticus (CSE).</li> </ul>	
Traumatic Brain Injury (TBI)		<ul style="list-style-type: none"> <li>• No specific EEG or QEEG patterns in TBI</li> <li>• Prospective study (n=162) one-year post-TBI (severe, moderate, or minor TBI): phase and coherence found best predictors of prognosis</li> <li>• QEEG changes may develop early in TBI and remain detectable for a long time- TBI severity index with 96% accuracy, 95% sensitivity, and 97% specificity</li> <li>• In 2018 a new index developed Brain Function Index (BFI) it indicates severity of the lesion and prognosis</li> </ul>	[103-106]
	Acute	<ul style="list-style-type: none"> <li>• Epileptic activity followed by diffuse attenuation (2-minute) of cortical activity returning to normal in 10 minutes- 1 hour.</li> <li>• Reduction in mean <math>\alpha</math> frequency, increase in <math>\theta</math>, <math>\delta</math> and <math>\theta/\alpha</math> ratio</li> </ul>	[107-115]
	Subacute	Increase in 1-2 Hz posterior $\alpha$ rhythm	[116,117]
	Chronic changes	Epileptiform changes 16%, Slow-wave changes in 63%, Increase/Reduction in $\delta$ power in patients with post-concussion syndrome	[107,118]
QEEG in Intensive Care Units (ICU)		<ul style="list-style-type: none"> <li>• In pathological conditions like carotid endarterectomy, cerebrovascular interventions, when cerebral blood flow is compromised in comatose patients.</li> <li>• AAN recommends QEEG in patients at high risk of ischemic stroke, acute intracranial hemorrhage, vasospasm or severe intracranial hypertension; diagnosis and management of epilepsy; titration of barbiturates; antiepileptic drugs; mannitol and to determine the appropriate time to turn off life support</li> </ul>	[2,119-121]
Learning and Attention Disorders		<ul style="list-style-type: none"> <li>• Diagnosis in learning disorders using spectral power and coherence: an accuracy 46-98%</li> <li>• Children and adults diagnosed with ADHD show increased power in bands <math>\theta</math> and <math>\delta</math>; meanwhile, adolescents with ADHD have reduced <math>\beta</math> power compared to a control group [56–58].</li> <li>• Bresnahan and Barry suggest a pattern of ADHD on the Cz electrode (open eye, fixed sight): the <math>\theta/\beta</math> ratio increased compared to the control group with a sensitivity of 86-90% and a specificity of 94-98% [59].</li> <li>• audio-visual and cognitive tests, QEEG can be used to track therapeutic response and concentration performance in patients with ADHD [60]</li> <li>• Neuropsychiatric EEG-Based Assessment Aid (NEBA) System measures the resting theta/beta ratio of the EEG with an electrode located at the central midline position (referred to as position CZ in the international 10-20 EEG system). The Food and Drug Administration (FDA) approved the NEBA system on July 15, 2013 as an aid for diagnosing ADHD in patients aged 6 to 17 years in conjunction with evaluation by a qualified clinician.</li> </ul>	[119,122-129]
Depression		Coherence in monitoring depression was generally measured by the method described by Thatcher in 1986 for TBI: in $\alpha$ and $\theta$ bands, the interhemispheric coherence (F3-F4, C3-C4, P3-P4, T7-T8), left interhemispheric coherence (F3-C3, F3-P3, F3-T5, C3-P3, C3-T5, P3-T5) and right interhemispheric coherence ( F4-C4, F4-P4, F4-T6, C4-P4, C4-T6, P4-T6) [76].	[130]
		Unipolar: $\alpha$ frontal asymmetry, $\alpha$ frontal interhemispheric asymmetry and Increased left frontal $\alpha$ power Bipolar: Reduced left $\alpha$ and increased $\beta$ power. $\alpha$ increase in right temporal inferior and superior region, left occipital lobe and in the right precentral gyrus. Reduction in $\alpha$ coherence in right frontal and central regions and increase in $\alpha$ coherence in right parietal and temporal lobes	[131-142]
Anxiety, social phobia and panic attacks		<ul style="list-style-type: none"> <li>• Higher right frontal <math>\alpha</math> activity</li> <li>• Parietotemporal asymmetry</li> <li>• QEEG captures anxiety, insecurity, fear, panic and phobia at levels of total Beta &gt;17% and High-Beta waves &gt;10% at T3 and T4. Potential for diagnosis and treatment.</li> <li>• Increase in delta power in the central region and left P3 negatively correlated with decline in executive function. In terms of anxiety and executive function absolute delta power plays a possible yet specific role in task-negative default mode network.</li> </ul>	[143-148]
Dementia		<ul style="list-style-type: none"> <li>• Alterations of the <math>\delta</math> and <math>\theta</math> waves in the background activity and the reduction of the <math>\alpha</math>-central frequency</li> <li>• Reduction in the <math>\alpha</math>-frequency band</li> <li>• Reverse correlation between the stage of ci and power in low-frequency bands</li> <li>• Coherence captures hemispherical connectivity via corpus callosum during waking and sleeping in AD and senile dementia</li> <li>• Decreased coherence in the <math>\theta</math>, <math>\alpha</math>, and <math>\beta</math> bands in the frontal and central areas</li> </ul>	[149-155]
Parkinson's disease (PD)		<ul style="list-style-type: none"> <li>• Reduction of relative power <math>\delta</math>, <math>\theta</math>, <math>\alpha</math>, <math>\beta</math> and absolute power <math>\theta</math>, <math>\alpha</math>, <math>\beta</math> in the anterior regions and interhemispheric asymmetry in <math>\theta</math>, <math>\alpha</math>, <math>\beta</math> bands with a right hemispheric activation</li> <li>• 24 studies on QEEG and PD showed spectral and connectivity markers discriminate between PD patients with different level of cognitive decline. QEEG variables correlate with cognitive assessment to predict PD-related dementia</li> </ul>	[156,157]
Delirium		Autoregression/Auto-regressive (AR) spectral estimation for quantification of EEG power and renormalized partial directed coherence (rPDC) for analysis of directed functional connectivity demonstrate significant potential for QEEG based detection of delirium. Delirious subjects exhibited pronounced EEG slowing as well as severe general loss of directed functional connectivity	[158]

- Four Daubert Factors/Criteria**

  - Hypothesis testing
  - Error estimates of reliability and validity
  - Peer reviewed publications and
  - General acceptance

**Other factors:**

  - Subject selection:
    - Clearly and carefully defined inclusion/exclusion criteria
    - Demographic representativeness (e.g., balanced gender, ethnicity, socioeconomic status, etc.),
    - adequate sample sizes per age groups
  - Methods to remove artifact
  - Approximation to Gaussian distribution with means and standard deviations being normally distributed
  - Leave one out Gaussian Cross-Validation and
  - Content validity and predictive validity by correlations with Neuropsychological test scores and IQ achievement scores, etc.
  - FDA registered

Figure 2. Scientific standards for admissibility of EEG normative databases in federal courts

- I) Standard protocol followed in data acquisition and editing:**

**Data acquisition**

  - Resting State EEG
    - Eyes-Closed (EC)
    - Eyes-Open (EO)
  - Task
    - Evoked Potentials (EP)
    - Event Related Potential (ERP)

**De-Artifaction: Removal of non-neural EEG signatures**

  - Manual
  - Semiautomatic
  - Fully Automatic eg. “Blind Source Separation” (BSS)

**Re-Montage**

  - Linked Ears (LE)
  - Average Reference Method (Ave-Ref)
  - Laplacian or Current Source Density (CSD)”

**EEG analysis: Feature Extraction and Classification (Semi- Automatic/Automatic)**

  - Frequency Domain Methods (*Fast Fourier Transform - FFT*)
  - Time Domain Methods (*Linear Prediction and Component Analysis - CA*)
  - Time-frequency Domain Methods (*Wavelet, and Hilbert-Huang Transform,*)
  - Nonlinear Methods (*Lyapunov Exponent, Correlation Dimension, and Entropies (Approximate Entropy and Sample Entropy)*)
  - Artificial Neural Networks (ANN), Recurrent neural networks (RNN) and CNN (Convolution Neural Networks) Methods
  - Deep Neural Networks (DNNs).

**II) Database construction and validation:**

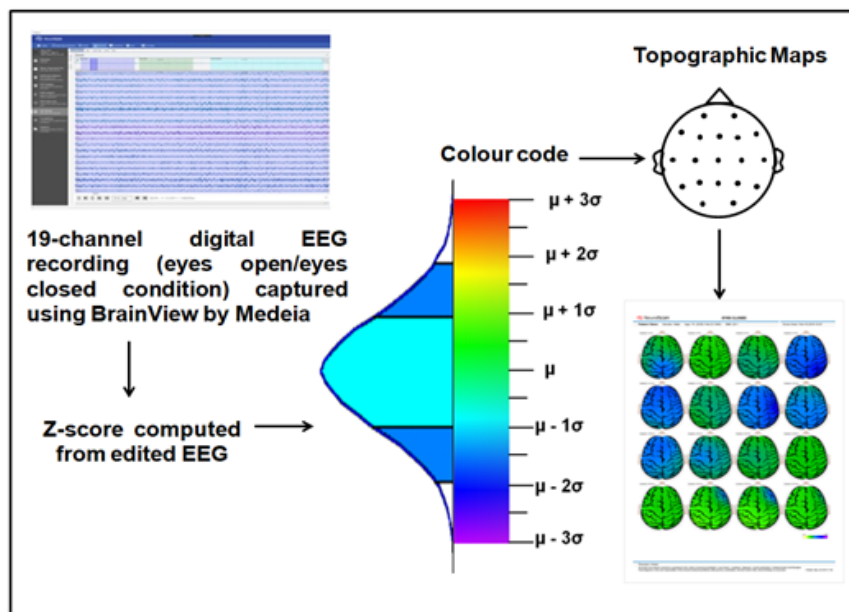
  - Client-based QEEG normative database construction: *as absolutely ‘healthy’ subjects is unrealistic, removing the variance from the EEG of ‘healthy’ subjects that can be explained by the variance in the questionnaire*
  - Amplifier equilibration: Equilibration of EEG amplifiers to the normative EEG amplifiers thus allowing for
    - Computing of Absolute power and enabling cross-comparisons with other Z-scores from other normative databases
    - Equilibration of a normative QEEG database to a different EEG machine
    - Diagnosing and treating brain function through the use of
  - Statistical cross-validation of the edited EEG data as obtained from all leads for each subject to compute
    - i) Mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix, ii) Cross-Spectral Power, iii) Auto-Spectral Power, iv) Amplitude asymmetry of auto-spectral power, v) Coherence, vi) Phase, vii) Real coefficients
    - Gaussian Validation: Approximation to Gaussian distribution with means and standard deviations being normally distributed
    - Leave one out Gaussian Cross-Validation
  - Determining the Content and Predictive Validity of the Normative Database

Figure 3. Standard protocol followed in database construction and validation

cost and duration available for sample collection (Figures 1 and 3) [19,29,40-42]. Careful screening of the subjects that comprise a representative normative database is critical to prevent bias and prevent miss-classification of healthy versus disease individuals. (Figures 1 and 3). “Representative sampling” means obtaining a demographically balanced sample in terms of gender, ethnic-background, socio-economic status and age. However, ensuring hyper-healthy normals or controls is unrealistic and instead “street normal” subjects that meet the exclusion criteria are more the norm. Another key issue pertinent to sample size is encountered with pediatric databases due to growth spurts in mental development. Thus, in pediatric databases sample size may at times differ by months instead of years as dramatic developmental changes occur

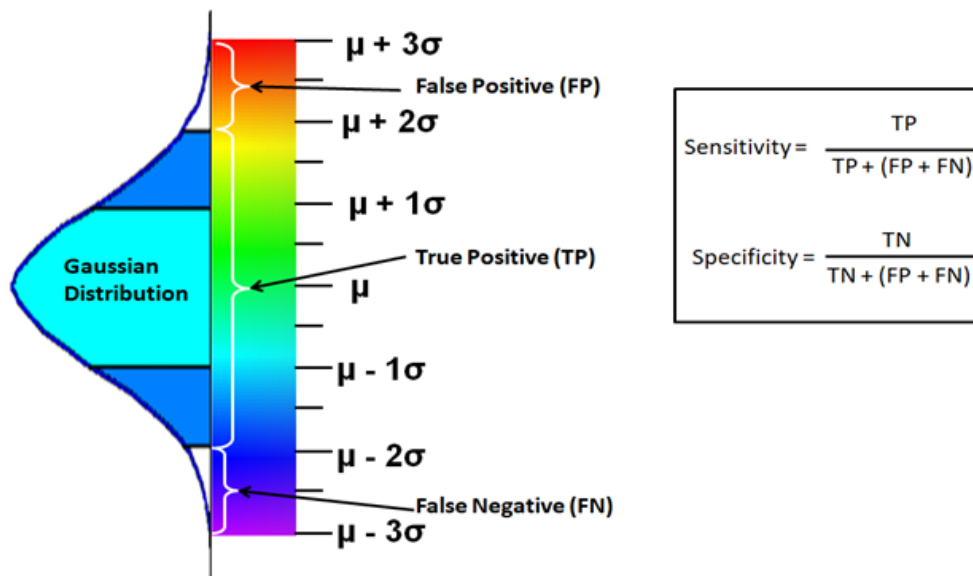
over relatively short time intervals while in adult databases even 2-year differences in age-grouping are valid [25,26,36,40,43,44]. “Age Regression” is another method used to adjust for age related variations in QEEG [27-29].

- Manual de-artifacting is subjective, involving marking segments containing artifacts; the drawback is it can result in suboptimal inter- and intra-rater reliability. Automated de-artifacting methods can be either “semiautomatic” or “fully automatic” involving artifact “correction” or artifact “rejection” methods (Figures 1 and 3). Artifact rejection methods remove segments of EEG that are identified as being contaminated by artifacts, while artifact correction methods apply techniques that remove artifacts without



- ❑ Following Amplifier matching; digital EEG recordings from the 19 channels (eyes open and eyes closed condition) are captured for each individual belonging to the study population. Example of a 19-channel digital EEG recording (eyes open/eyes closed condition) captured using BrainView by Medeia at a frequency range of 1-40 Hz (in 2 Hz increments).
- ❑ De-artifacting, re-montage and feature extraction of each 19-channel EEG (eyes open and eyes closed condition) is carried out.
- ❑ Age-wise Z-scores computed for “each individual” in the study population for each “QEEG variable” (mentioned below) using FDA registered QEEG databases like NeuroGuide (Applied Neuroscience, Inc), or qEEG-Pro database (qEEG-Pro B.V.), or HBI database (HBImed AG).
  - Absolute Power
  - Relative Power
  - Total Power
  - Delta, Theta, Alpha, Beta, and High Beta
    - Amplitude Asymmetry
    - Coherence
    - Phase
- ❑ Z-scores are also computed using three different montages (Linked ears, Average Reference and Current Source Density–CSD).
- ❑ Topographic Maps constructed using BrainView by Medeia capturing in colour the deviation from the mean ( $\mu$ ) at 1 - 30 Hz (in 1 Hz or 2 Hz increments) are drawn.
  - <4 Hz: Delta waves
  - 5 - 8 Hz: Theta waves
  - 9 - 12 Hz: Alpha waves
  - 13 - 25 Hz: Beta waves
  - 26 - 30 Hz: High Beta waves

Figure 4a. Step-by- step guide to construction of QEEG topographical maps.



- Age-wise approximation to the Gaussian distribution of “the study population” is carried out for each of the “QEEG variables” (mentioned above). Gaussian cross-validation is carried out to determine if 2.3% of the study population is at + 2 S.D., 2.3% at -2 S.D., 0.13% at + 3 S.D. and 0.13 % at -3 S.D. and 95% is within +2SD and -2SD (True Positive, TP).
- “Age-wise” Z-scores Sensitivity and Specificity computed using formulae shown above.
- “Age-wise” Z-scores are computed for “the study population” for the normative databases being compared from 1 to 30 Hz for the “QEEG variables” (mentioned in Figure 4a). Z scores are also computed using three different montages (Linked ears, Average Reference and Current Source Density –CSD) to confirm reliability and repeatability.
- “Age-wise” Z-scores comparisons are drawn between Z-scores computed for the normative database/s being compared and the FDA registered QEEG databases (mentioned in Figure 4a).
- Predictive validity or clinical usefulness is determined by determining the classification accuracy of the normative database in terms of i) health/normal and disease /injury, ii) cognitive ability/function and iii) correlation between cognitive scores/scales and QEEG variables.
- Both parametric and non-parametric content validity of the “new/candidate” normative is determined by evaluating its appropriateness for a domain being assessed. For example; Will the QEEG findings reflect/capture cognitive decline following traumatic brain injury (TBI) in terms of memory capacity, attention, executive function, default mode network etc.

Figure 4b. Step-by- step guide to construction/comparison/validation of two or more normative database

removing the underlying EEG signal. One example of an artifact correction method is the use of “blind source separation” (BSS) that identifies different independent sources of variance in the EEG. The benefit of fully automatic de-artifacting methods is that they eliminate inter- and intra-rater variability thus and guarantee that each EEG will be de-artifacted using the exact same set of criteria.

- In the 1980s primitive analytic software hindered EEG comparability resulting in QEEG users using relative power versus absolute power. It was not until the mid-1990s that computer speed and software development made amplifier matching and normative database amplifier equilibration a possibility (Figures 1 and 3). Each channel has three electrical contacts: a ground contact and two other contacts that go directly into the differential pre-amplifier [45,46]. Different frequency response curves exist for different amplifiers and there is no one “gold standard” for EEG amplifiers. To circumvent this issue a universal equilibration process was developed so that micro-volts in a given amplifier could be converted/ equilibrated to microvolts

in all other amplifiers and more importantly to normative database amplifiers. Calibrated sine waves are injected into the input of the EEG amplifiers to be compared to the normative database ensuring that amplifiers frequency range matches the normative database amplifiers. Then take the ratio of the micro-volt values at each frequency are obtained and the ratios is used as gain or amplitude scalars in the FFT to exactly equate the spectral output values to the normative database amplifiers. Following equilibration amplifiers used for recording a subject’s EEG can be directly compared with the normative database means and standard deviations.

- The combination of electrode inputs, summed to show the whole set of electrodes being studied, is called the “montage”. A montage is selected to most clearly demonstrate the EEG pattern being monitored. One example is the Laplacian/Hjorth montage [47]. In a set of differential amplifiers, one is the “active” electrode and the other the “reference” electrode. “References” electrodes include linked ear, ipsilateral and contralateral ear, the Cz or “vertex” reference, and

the sequential or “bipolar” references, common average or global average and the weighted average reference montages and montages on the tip of nose, the mastoid process [46]. As each montage has its own strengths and weakness it has to be tailored to suit the need however the montage selected has to match the montage of the normative EEG database to which the data is being compared. Proper montage selection will allow a good EEG recording.

- Depending on the mental or neurocognitive disorder being studied data acquisition can either be resting EEGs with eyes-closed or eyes-open conditions or active Tasks i.e. Go-NoGO (inhibition), visual or auditory tasks, or cognitive task, evoked potentials (EPs) and event related potential (ERP) and Go-No while a subject performs a task (Figure 1, 2 and 3).
- Many a times QEEG analysis is used as evidence in court. In 1993 the Supreme Court in Daubert, stipulated the statistical foundations regarding admissibility of scientific evidence in court. The Four Daubert Factors for scientific standards of admissibility in Federal Courts are presented in Figure 2 [32-35]. In 2010 QEEG was accepted in the Grady Nelson death penalty trial in Florida and its findings led to change in sentencing from “death penalty” to “lifetime sentencing without parole” [6,7].
- From 1996 till date the American Clinical Neurophysiological Society (ACNS), American Academy of Neurology (AAN) and International Federation of Clinical Neurophysiology (IFCN) have released several guidelines and standards (Figure 1) (Table 1) to ensure both standardized and personalized healthcare is achieved in the area of QEEG and diagnosis, management and monitoring of neurocognitive disorders [48]. This has in turn allowed for cross-study comparability of QEEG findings in various neurocognitive disorders (Figure 1) (Table 1). Among them worth mentioning is the Food and Drug Administration (FDA) approval of the NEBA system on July 15, 2013 for diagnosis of ADHD in conjunction with clinical tests and the FDA approval of two commonly used normative databases qEEG
- the “qEEG-Pro” database (qEEG-Pro B.V.) and the “Lifespan” database (Applied Neuroscience, Inc) [49-51].

### QEEG normative databases validation and comparison

Matousek and Petersen in their Swedish study were the first to compute means, standard deviations and Z-scores in one-year age-groups and use t-tests to compare an individual to a normative database (Figures 3, 4a and 4b) [25,26]. E. Roy John and collaborators from 1974 to 1977 carried out the independent cross-validation of normative QEEG databases when they compared data from their Harlem study with the Swedish database [27-29,52]. Following this in 1994 the American EEG Association and the IFCN reiterated these methods as acceptable basic standards to be met by any normative QEEG database [15,27-29,31,52-81]. Data normalization to the Gaussian distribution using Z-scores helps in comparing individuals to a QEEG normative database. The values of Z within  $\pm 2SD$  i.e. 95% of the area of the Gaussian aids in minimizing Type-I and Type-II errors and in determining the sensitivity, false positives and false negatives of a normative database (Figure 1, 4a and 4b) [39,40,42,53]. Due to the expense to acquire independent data, most cross-validations are computed using a leave-one-out cross-validation procedure following equilibration using amplifier matching [13,27-29,43,44,56-81]. Figure 3 presents and overview of protocols followed in normative database construction and evaluation, Figures 4a, 4b provide a step-by-step

guide from EEG data acquisition to construction normative data to construction of topographic maps and normative database validation using EEG machines like Brain View.

In brief, following visual analysis of the dEEG, manual or automated deartifactation and feature extraction and data and statistical processing spectral analysis is carried out. Following this univariate or multivariate comparisons to a normative database is carried out. More advanced comparisons include cluster analysis where individuals are grouped by EEG features. Cluster analysis often aids in distinguishing between subtypes. For example, it helps differentiate between individuals with the same disorder (eg, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD)) one group of whom responded to medication and the other was drug-resistant [82-85]. In the area of mental and neurocognitive health; omission errors in the GO/NOGO test discriminated between subjects with Attention Deficit/Hyperactivity Disorder (ADHD) and controls [3,86,87]. The NEBA® system (received FDA approval on 2013) wherein resting theta/beta ratio (TBR) recorded at Cz (international 10-20 EEG system) is ratified by Blue Cross Blue Shield Association to clinically diagnose/indicate if further tests are required in children and adolescents with ADHD [49,88,89]. Amplitude, power and synchronization can be used to differentiate mild (sensitivity 85% and specificity 78%) and moderate Alzheimer’s disease (AD) (sensitivity 89% and specificity 88%), from healthy controls [90]. Another study carried out by Stylianou *et al.* illustrated QEEGs ability to differentiate between AD, dementia with Lewy bodies (DLB), Parkinson’s disease dementia (PDD) patients and healthy controls and identify QEEG signatures of cognitive fluctuations (CFs) in DLB with a diagnostic accuracy of 94%, sensitivity of 92.26% and specificity of 83.3% [91]. Yet another study showed that spectral analysis (spectA) was more sensitive than coherence (Coh) in differentiating 40 subjects with mild to moderate AD from 40 healthy elderly controls (91). A unique retrospective study on AD (n=169, female%:65.1%) carried out by Houmani *et al.* used neuropsychological tests, brain imaging and blood sampling to first diagnose AD following which retrospective normative EEG data was acquired between 2009 and 2013. Epoch-based entropy and bump modeling (automatic discrimination) exhibited a classification accuracy of 91.6% (specificity = 100%, sensitivity = 87.8%) when discriminating subjective cognitive impairment (SCI) from possible AD patients [92]. In terms of clinical usefulness of QEEG and normative databases Figure 1 and Table 1 presents a snapshot of key milestones crossed and key QEEG findings in selected neurocognitive disorders [2,20-27,32-35,36-40,48,52-77,93-159].

### Common normative databases

Normative reference databases form the veritable backbone of QEEG analysis increasingly used in diagnosis or prognosis or Neurofeedback or Pharmacoo-QEEG. Listed below are a few of the commonly used normative databases:

- UCLA Brain Research Institute database was the first of its kind developed by Ross Adey between 1961-1974 it was used to select astronauts for NASA space travel [22-24].
- The Swedish database was developed by Dr. Milos Matousek and Dr. Ingemar Petersen in 1973 [25,26]. It measured QEEG in n=401 subjects (Female%: 54.4%) aged between 2 months to 22 years.
- The BrainDX (BrainDX, L.L.C.) database, formerly the NXLink – NYU database was developed between 1970’s-1980’s, it has a total of 464 subjects and manual deartifacting was carried out.



- The Neurometrics database measured delta, theta, alpha, and low frequency beta bands, absolute power, relative power, coherence, mean frequency within band, and symmetry (left-right and front-back) extracted from approximately two minutes of data in n=782 “normal” individuals with n=356 aged between 6-16 years and n=426 aged from 16 to 90 [29]. It has received a 510(k) clearance by the FDA (July 1998, #K974748), indicating that construction of the database has been scrutinized for good manufacturing practices (GMPs). However, only information about delta, theta, alpha, and low frequency beta bands are available.
- Thatcher Lifespan Normative EEG Database (LSNDB/NeuroGuide), a.k.a NeuroGuide, Applied Neuroscience, Inc; the University of Maryland (UM) database was developed by Robert W. Thatcher (Thatcher, 1998). Eyes closed (EC) and eyes open (EO) resting-state recordings acquired from 1979 to 1987 and in 2000 include n=625 individuals (2 months to 82 years of age). In 2008 an additional 53 adult subjects aged between 18.3 years to 72.6 years were added to the database bringing the numbers up to 678 subjects [37,40,159-162]. NeuroGuide has FDA 510 (k) clearance.
- The Serman-Kaiser (SKIL) Database: includes 135 adults (18 to 55 years of age) and is comprised of students and laboratory personnel (50%), volunteers recruited from the community (25%), and U.S. Air Force personnel (25%) [163].
- The International Brain Database: is being developed (n=1000 controls and n=1000 normals) by a consortium of leading neuroscientists from 50 laboratories across U.S.A, United Kingdom, Holland, South Africa, Israel and Australia. The database will include EEG (EO and EC), ERP and autonomic activity data and data on 50 ADHD subjects. Psychophysiology Paradigms that will be used include Startle paradigm (fight and flight reflex) – Go-NoGO (inhibition) – Resting EEG (cortical stability) – Visual tracking task (automatic tracking) – Habituation paradigm (novelty learning) – Auditory oddball (efficiency of target processing) – Visual oddball (visual novelty target processing) – Conscious and subconscious processing of facial emotions – Visual working memory task (memory and sustained attention) – Executive maze task (planning and error correction) [164,165].
- qEEG-Pro by qEEG-Pro B.V. uses automatic deartifacting and client-based. It includes resting-state recordings acquired between 2004-2013, EC: n=1482 and EO: n=1232 and the age range is 6-82 years.
- HBI by HBImed AG, data was collected in the 1990’s and automatic deartifacting was carried out. 5 active tasks (two GO/NOGO tasks, arithmetic and reading tasks, auditory recognition and auditory oddball tasks) and EC and EO resting-state recordings were carried out on n=1000, children and adolescents (age 7-17): n=300, adults (18-60): n=500, and seniors (61+):n=200 [10,166]
- Cuban Human Brain Mapping Project (CHBMP): EEGs of 30 minutes duration including the following conditions: eyes closed, eyes open, hyperventilation and subsequent recovery. 56 participants, reaction times were recorded using a go-no- go paradigm which consisted in a visual attention task. High-density (64-120 channels) resting state electroencephalograms (EEG), magnetic resonance images (MRI), psychological tests (MMSE, Wechsler Adult Intelligence Scale -WAIS III, computerized reaction time tests using a go nogo paradigm) were carried out in 282 healthy participants (age range 18–68 years) acquired from 2004 to 2008 [167].
- EEG tomographic analysis called “LORETA” (low resolution EEG tomography analysis). The NovaTechEEG database has n=84 cases.
- Hudspeth offers the “Neurorep AQR” (Adult QEEG Reference Database, see: www.neurorep.com). The database measured absolute and relative power for 19 scalp electrodes, n=171 [168].
- BrainView QEEG normative database: It is a client-based QEEG database. EC (n=1965) and EO (n=2303) resting-state recordings were acquired between 2018 and 2020 (age range: 4 to 80 years; male %:48.5%) and delta, theta, alpha, and low frequency beta bands were measured. Spectral analysis was between 1 to 40 Hz. Age regression method was by age bins. Deartifactation was both by manual and automatic methods.

### A step-by-step guide to evaluation and comparison of QEEG normative databases

Figures 4a, 4b i-iii present a step-by-step guide to construction, evaluation and comparison of QEEG normative databases (15,52-81). Following data acquisition using EEG machines like BrainView, artifact cleaning, and reliable dEEG data conversion to time series after which it may be re-referenced or re-montaged, it is then analyzed in either the time domain or the frequency domain. The selected normal subjects are grouped by age. The means and standard deviations of the EEG time series and/or frequency domain analyses are computed for each age group. Transforms are applied to approximate a Gaussian distribution of the EEG measures that comprise the means. Once approximation to Gaussian is completed, Z-scores are computed for each subject in the database and leave one out Gaussian cross-validation is computed in order to arrive at optimum Gaussian cross-validation sensitivity (Figures 4a, 4b). Finally, the Gaussian validated norms are subjected to content and predictive validation procedures such as correlation with neuropsychological test scores and intelligence, etc. and also discriminant analyses, neural networks and outcome statistics, etc., [61]. Content validation is carried out with respect to clinical measures such as intelligence, neuropsychological test scores, school achievement etc., (Figures 1, 3, 4a and 4b) [57]. Predictive validation is carried out with respect to discriminative, statistical or neural network clinical classification accuracy (Figures 1, 3, 4a and 4b). Both parametric and non-parametric statistics are used to determine the content and predictive validity of a normative EEG database (Figures 1, 3, 4a and 4b).

### Conclusion

QEEG today provides information about the underlying neurophysiological correlates of psychological disorders. The development and integration of standardized protocols for EEG and QEEG: processing, analysis and interpretation and for normative database: construction, comparison and evaluation over the last 61 years have contributed to the current validity, reliability, and usability of QEEG. Technical and statistical improvements in the field since the inception of QEEG have greatly contributed to it fast becoming a personalized and precise medicine tool with enormous clinical and research potential.

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