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Validation of Quantitative Electrœncephalogram (qEEG) Normative Databases

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Abstract

Quantitative electroencephalogram (qEEG) helps a) characterize normal versus disease, developmental and neurocognitive states as well as b) in diagnosis and prognosis enabling a clinician to determine via statistics if a client/subject is, i) within a reference normal population, ii) how best to customize treatment based on the client's/subject's qEEG results and iii) if a client/subject is responding positively to treatment. However constructing of qEEG normative databases for use in both research and clinical settings has proved challenging over the last 61 years due to methodological issues such as, i) determining who makes up the "normal" study population and ii) lack of standardized procedures when acquiring, measuring, analyzing, and interpreting resting state or active task EEG data. This review focuses on a) the many challenges/milestones the field had to overcome, b) standards to be followed when constructing and validating a normative databases c) commonly used peer-reviewed normative databases, and d) 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 et al. 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) wherein numerical EEG results are transformed from the time domain into the frequency domain, Gaussian approximation and cross-validation carried out and Z-scores computed with relation to an appropriate normative database to be used either for diagnosis, prognosis or treatment tailoring [1, 2].

In terms of clinical usefulness of qEEG 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 [3-5]. The NEBA® system 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 further tests are required in children and adolescents with ADHD [6]. 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 [7]. 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% [8]. 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 [9]. 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 [10].

The backbone of qEEG is normative databases a term coined by Graham and Dietlien back in 1965 [11]. In the hands of untrained operators, data analyzers and interpreters, qEEG can yield results that are not of clinical relevance [12]. With a view of striking a balance between a) ensuring the validity and reliability of qEEG for research and clinical use in diagnosis, prognosis and pharmaco-EEG, as well as b) "standardized medicine", "precision medicine" and the World Health Organization (WHO) "High 5s Project" to ensure patient safety and finally c) to meet health insurance requirements; over the years several qEEG standards have been developed [12-18]. Standard methods of data acquisition, visualization (synchronization, connectivity and topographic features), processing (de-artifaction, extraction and classification), storage and statistical comparisons have been and are in continuous development [12-17]. Another parallel development which influenced qEEG's usefulness as a diagnostic and prognostic tool was the 2013 release of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [18].

The focus of this review paper is to present:

i) A brief historical review of technical and statistical milestones and standards that apply to qEEG in particular qEEG normative databases (Figure-1 and Figure-2),
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 (Figure-4a-c).

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) using the Fourier transform to spectrally analyze EEG data and to compare different EEG measures to a normative database [11, 19-21]. The first quantitative EEG (QEEG) reference normative database was developed in the 1950s at the UCLA Brain Research Institute by Ross Adey between1961-1974. 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.

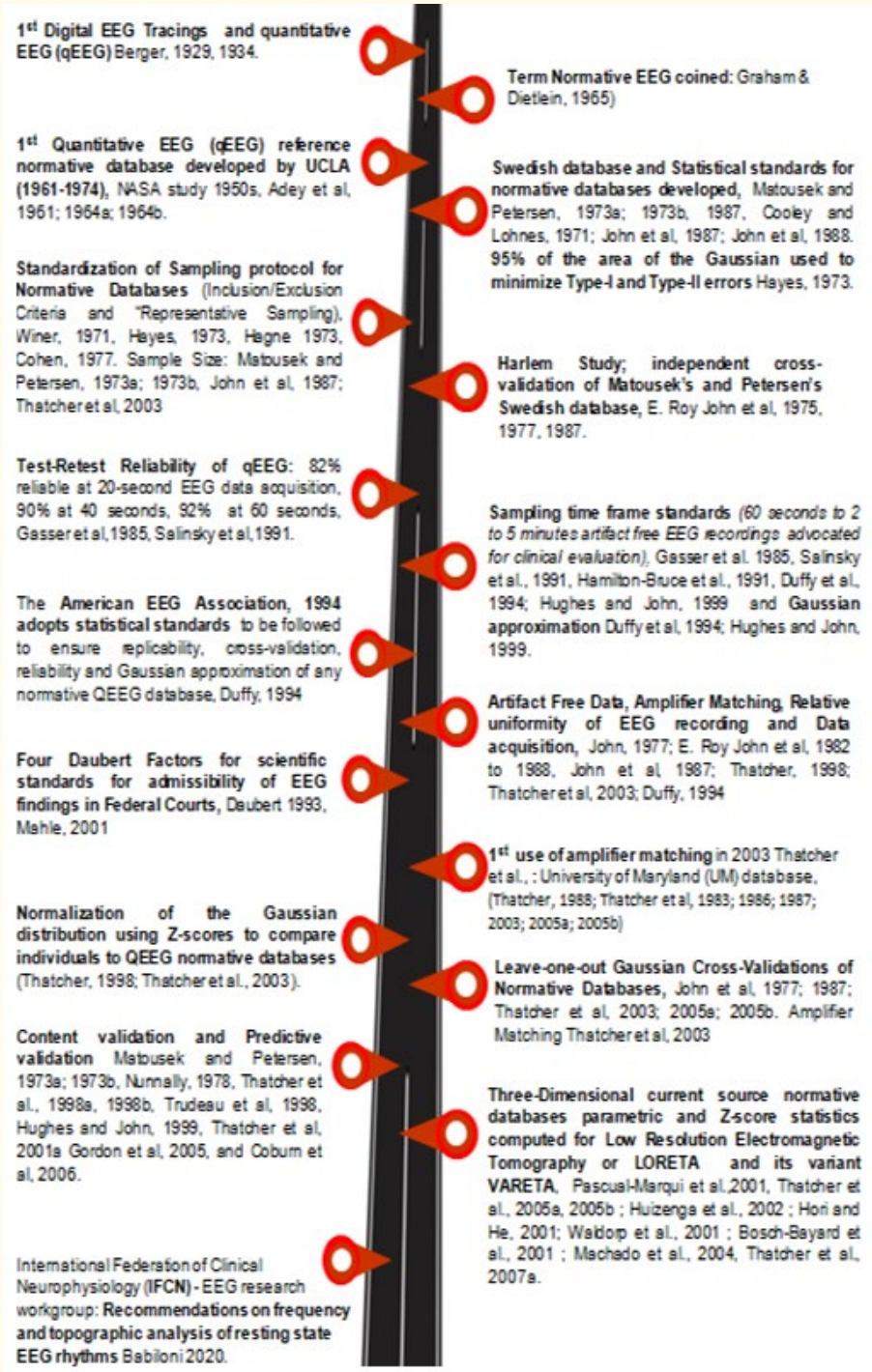

Figure 1: History of the Scientific, Technical and Statistical improvements in constructing qEEG Normative Databases.

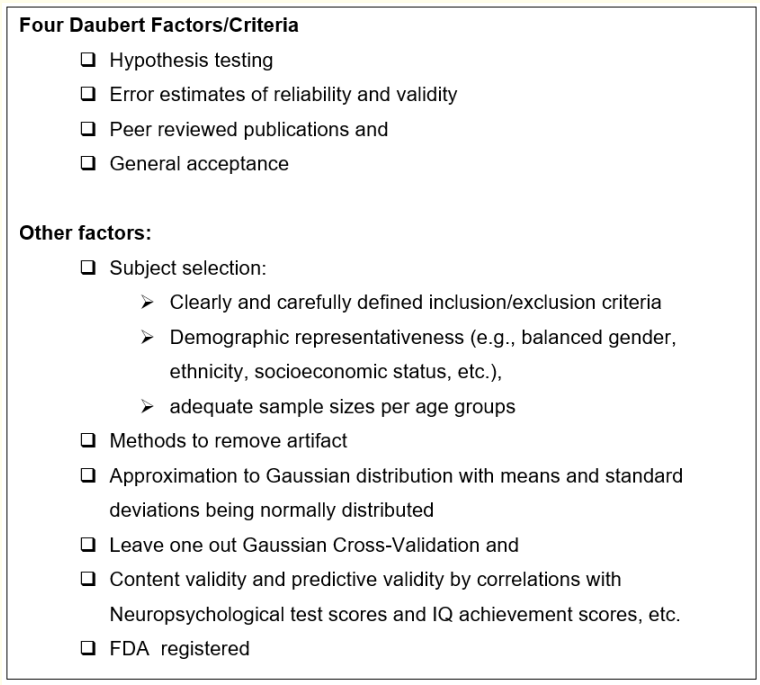

Figure 2: Scientific Standards for admissibility of EEG normative databases in Federal Courts.

The first known statistical standards for normative databases and the first peer reviewed publication of a normative database was by two Swedish Neurologists Matousek and 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) [17].

- In term of sampling time frames and intra and inter test-retest reliability, qEEG has proved to be highly reliable and reproducible [12-22]. Sampling/acquisition time frames were 82% reliable at 20-second EEG data acquisition, 90% reliable at 40 seconds, and 92% reliable at 60 seconds [15, 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, cost and duration available for sample collection (Figure 1 and Figure 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. (Figure 1 and Figure 3). "Representative sampling" means obtaining a demographically balanced sample in terms of gender, ethnic-background, socio-economic status and age. 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-artifaction 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 (Figure 1 and Figure 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 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 (Figure 1 and Figure 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, Figure 2 and Figure 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].

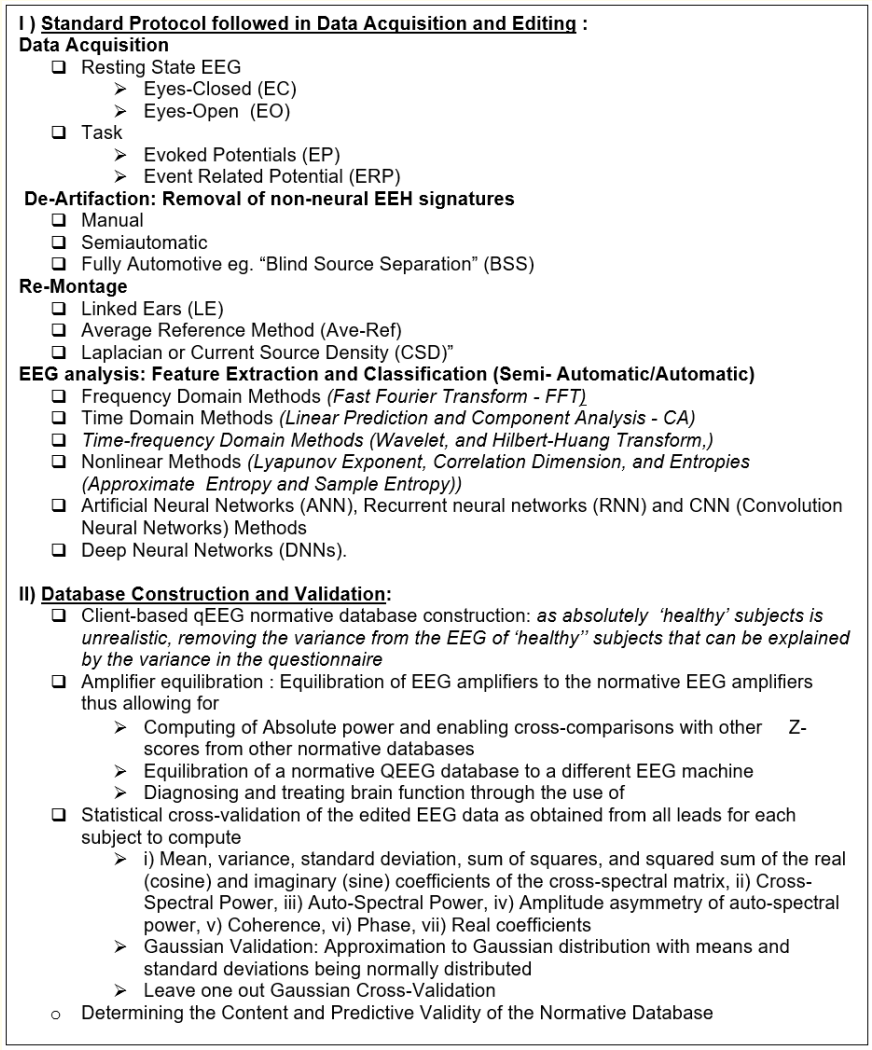

Figure 3: Standard Protocol followed in Database Construction and Validation.

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 (Figure 3, Figure 4a and Figure 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, 48]. 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 [17, 27-29, 31, 48-77]. Data normalization to the Gaussian distribution using Z-scores helps in comparing individuals to a qEEG normative database. The values of Z within ±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, Figure 4a and Figure 4b) [33, 34, 39, 40, 42, 48, 49]. 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 [15, 27-29, 43, 44, 52-77]. Figure 3 presents and overview of protocols followed in normative database construction and evaluation, Figure 4a, Figure 4b and Figure 4ci-iii 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 BrainView.

Common Normative Databases

Normative reference databases form the veritable backbone of qEEG analysis increasingly used in diagnosis or prognosis or Neurofeedback or Pharmaco-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 Matousek and 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 between1970'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, Appli ed Neuroscience, Inc; the University of Maryland (UM) database (Thatcher et al., 2003) was developed by Robert W. Thatcher (Thatcher, 1998). Eyes closed (EC) and eyes open (EO) resting-state recordings acquired from 1979 to1987 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, 78-81]. NeuroGuide has FDA 510 (k) clearance.
- The Sterman-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%) [82].
- 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) [83, 84].
- qEEG-Pro byqEEG-Pro B.V. uses automatic deartifacting and client-based qEEG. 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 deartifaction 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 [14, 85].
- 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 [86].

- 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 [87].

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

a, b and ci-iii present a step-by-step guide to construction, evaluation and comparison of qEEG normative databases [17, 48-77]. 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 (Figure 4a, Figure 4b and Figure 4ci-iii). 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., [57]. Content validation is carried out with respect to clinical measures such as intelligence, neuropsychological test scores, school achievement etc., (Figure 1, Figure 3, Figure 4a, Figure 4b and Figure 4ci-iii) [53]. Predictive validation is carried out with respect to discriminative, statistical or neural network clinical classification accuracy (Figure 1, Figure 3 Figure 4a, Figure 4b and Figure 4ci-iii). Both parametric and non-parametric statistics are used to determine the content and predictive validity of a normative EEG database (Figure 1, Figure 3 Figure 4a, Figure 4b and Figure 4ci-iii).

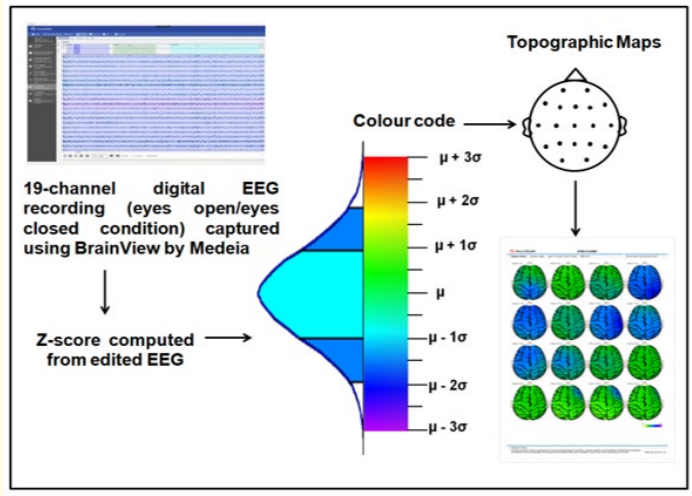

Figure 4a: Step-by- step guide to Construction of qEEG Topographical Maps.

- 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.

- ❑ De-artifaction, 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 (μ) 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.

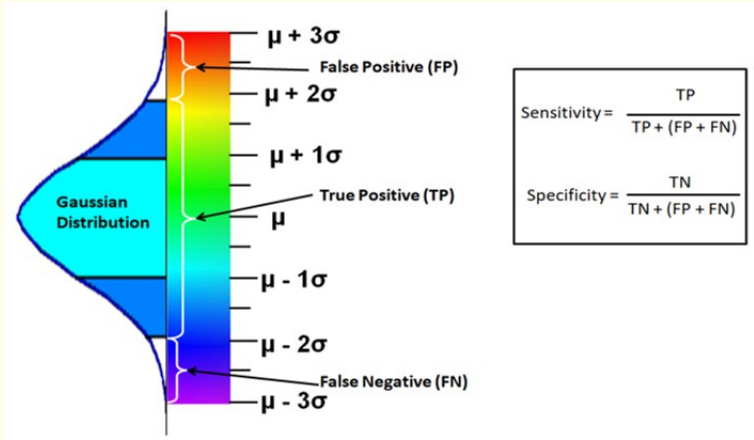

Figure 4b: Step-by-step guide to Construction/Comparison/Validation of two or more Normative database.

- ❑ 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. 4c i-iii: Example of Comparisons of Z-scores from Four Normative Databases.

Modified from (Source): http://brainmaster.com/wp-content/uploads/2017/08/DatabaseComparisons_for_website-1.pdf.

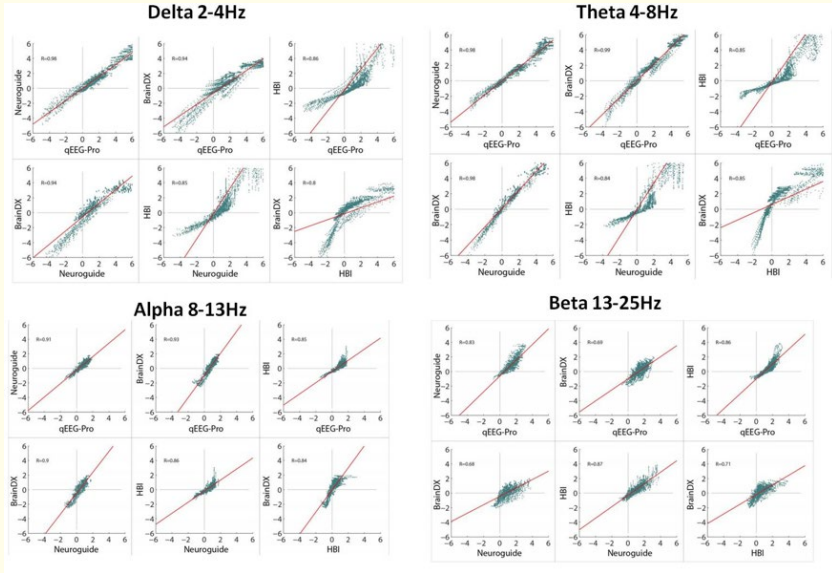

Figure 4c.i: Z-score Comparisons of Four Database: NeuroGuide (NG), qEEG-Pro (QP), BrainDX (BDX), and HBI.

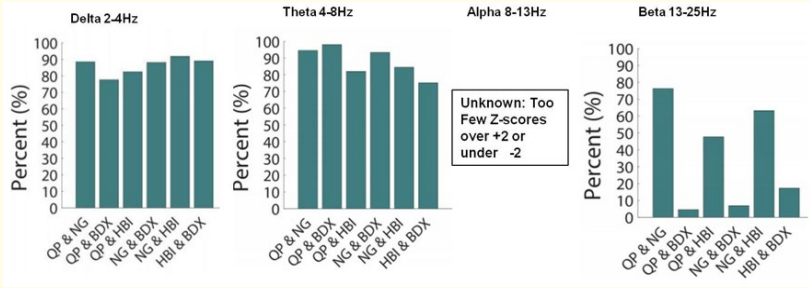

Figure 4c.ii: Database Correspondence.

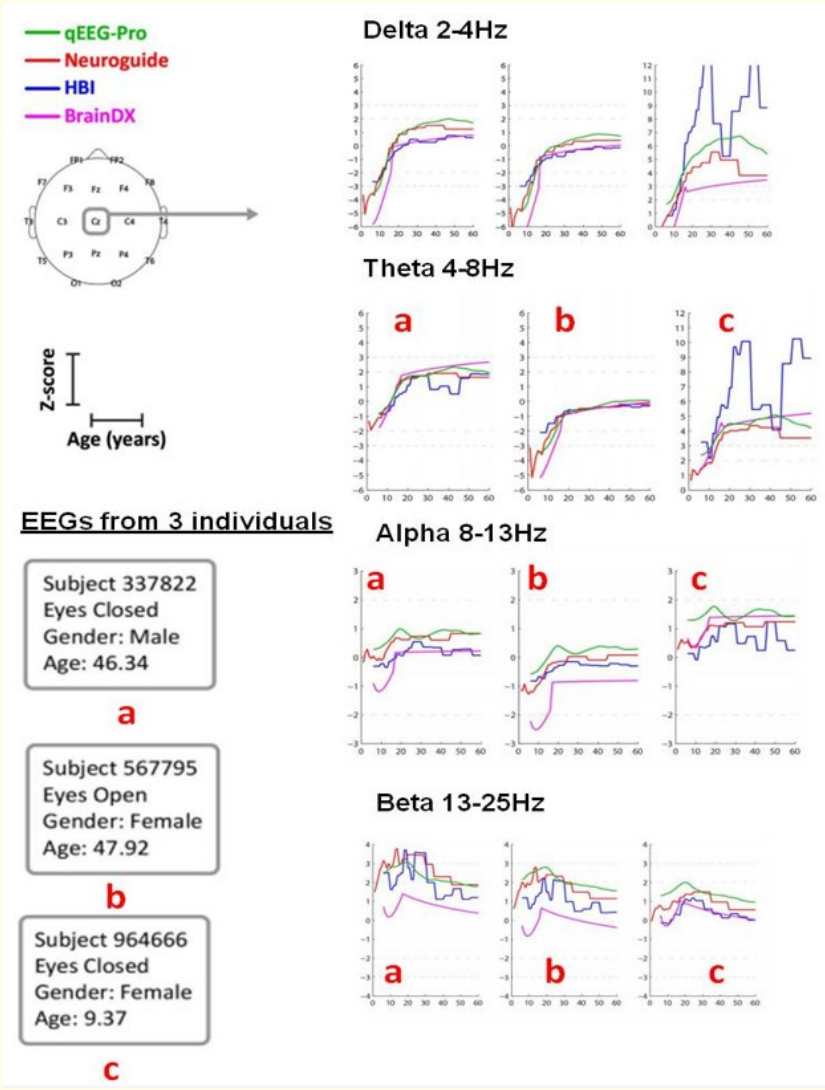

Figure 4c.iii: Comparisons of EEGs recorded from 3 individuals with Z-scores computed using the Four Database: NeuroGuide (NG), qEEG-Pro (QP), BrainDX (BDX), and HBI.

Conclusion and Future Directions

The use of qEEG in clinical practice shows great potential as a tool that provides information about the underlying neurophysiological correlates of psychological disorders. qEEG can combine a high level of standardization with a personalized medicine approach to mental health care. However, the validity, reliability, and usability of qEEG in clinical practice depend on the development of automated and standardized processing methodologies. Technical and statistical improvements in the field since the inception of qEEG have greatly contributed to its clinical potential. The integration of standardized de-artifacting techniques, qEEG databases, and qEEG interpretation methods is necessary for qEEG to reach its full potential in clinical practice.

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