After 25 Years the NeuroGuide Normative Databases are Accepted Science

In 1979, Robert W. Thatcher, Ph.D. was a professor at the University of Maryland and he was the principal investigator of a project to correlate nutrition and environmental toxins and human brain development from which over 1,350 EEG recordings were obtained. From this total population approx. 620 healthy normal control subjects were identified based on neuropsychological and neurological questionairs and interviews. This is the same reference normal database used inside of Neuroguide. In the last five years more adult carefully screened normal subjects were added to the reference database so that total sample size N = 727 and spans the age range from 2 months to 82 years. The database was fit to a Gaussian distribution and cross-validated and the results published in various journals. Because of the 25 year history and the number of replications and cross-validations the Univ. of Maryland normative database is considered as accepted science used repeatedly in hundreds of studies over this 25 year period of time, including the National Institutes of Health, the Department of Defense and VA medical centers and universities throughout the world. It has been used in many studies that are independent of Robert Thatcher, Ph.D. (the PI responsible for the database) and there has not been a single study that has refuted the findings in the normative database. This is important because after 25 years of published science that has been tested and independently evaluated and, importantly, without a single study that has refuted the database by comparisons to a different database. No database is perfect, they all are simply statistical references but adherence to scientific standards and mathematical standards is essential for all clinical databases and qEEG is no different. (see Thatcher and Lubar, 2008).

As explained in Thatcher and Lubar (2008) there are two primary methods of reference database construction: 1- Stratification of means & standard deviations by age groups and, 2- Polynomial regression fits across age. The regression fit has the drawback of accounting for a small percentage of the variance across age and a failure to quantify growth spurts (e.g., age 5-7 language development, or age 9-11 of formal operations or 11-14 for puberty, etc.). The age stratification requires a larger population than the regression method and overlapping of age groups in order to minimize jumps between age groups. The University of Maryland reference normative database has a large number of younger age individuals, especially age 3 to 15 which allowed for one year overlapping and smooth developmental trajectories. The adult age range had a lower sample size, e.g., about 150 subjects and requires creating 10 year age groups with five year overlaps resulting in small (e.g., about 0.5 st. dev.) jumps between these larger age ranges. Recently, the addition of about 180 new subjects giving rise to a total population size of over 900 subjects has provided for greater age overlap of groups and further reduction of jumps as one advances age.

In 2007 an independent cross-validation of the New York University and the University of Maryland FFT age based normative databases were conducted. The

study was conducted because a company had collected raw digital EEG from several hundred clinical patients and had computed Z scores using the New York University (NYU) normative database (John, 1977; John et al, 1977; 1987; 1988). The question was: does the University of Maryland (UM) normative database produce similar of comparable Z scores as the NYU database using the same exact raw digital data? The correlation coefficients from the independent cross-validation between the NYU and UM normative databases is shown in the figure below The analysis included 332 psychiatric patients and an age range from 6.2 years to 84.9 years.

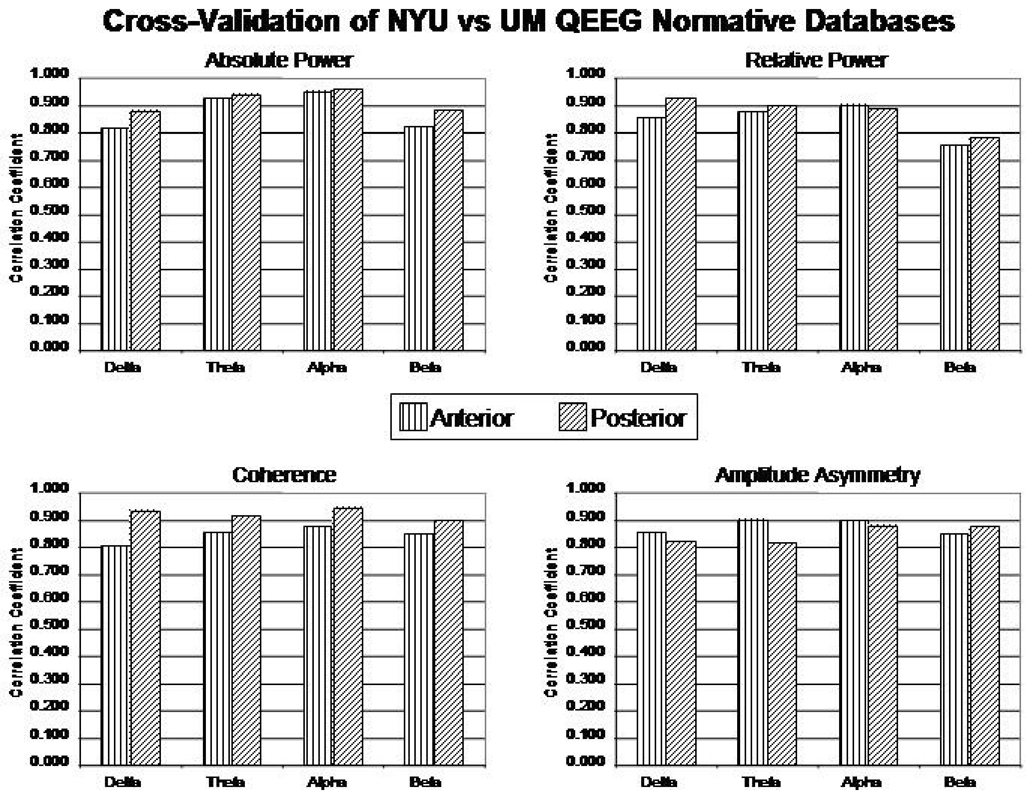

Fig. 1 – Results of an independent cross-validation comparison of Z scores from 332 psychiatric patients ranging in age from 6.2 years to 84.9 years using the NYU and UM normative databases. Anterior and posterior refers to the anterior and posterior location of electrodes. Highly significant independent cross-validation was observed which shows the high degree of consistency between two peer reviewed and clinically validated QEEG normative databases. (Reprinted with permission from Brian McDonald, CNS Response, Inc.

In 2004, a Joint-Time-Frequency-Analysis (JTFA) Hilbert transform was used to compute "Instantaneous" power, coherence and phase values in which auto and cross-spectra are computed at each time sample in about one microsecond, hence the term "Instantaneous". The same subjects as used in the FFT norms in which means are computed across age groups was used for the Instantaneous means

and standard deviations. The instantaneous means and standard deviations involved summing the auto and cross spectral values at each instant of time over the entire EEG recording for all subjects within a given age group and then dividing by the total number of samples which was many thousands of values. The JTFA values are different than FFT values and the method of computing the means and standard deviations for the JTFA norms are different than the method of computing the FFT norms and the means and standard deviation of the FFT norms can not be used to compute Z scores based on instantaneous values or vice versa. To do so introduces error because of the fundamentals of statistical sampling theory. Analyses show a range of error from 8% to 14% if the mean of a FFT with windowing is used to compute a Z score based on a JTFA calculation of instantaneous frequency. The FFT and JTFA are mathematically different which is one source of the error. The method used by the Neuroguide database is JTFA means and standard deviations to compute JTFA instantaneous Z scores. This method has zero digital signal processing difference and therefore it is more accurate.

The list below includes some replication studies by Thatcher et al and other scientists as collaborators. These are primarily department of defense funded medical doctors and scientists to evaluate the database for evaluation and treatment of brain injured individuals. The studies by van Baal, and van Beijsterveldt et al are genetic studies that replicated the normative database growth spurts and showed that both environmental and genetic factors are operating in the development of the human brain as measured in the normative database. Below is a partial list of national and international universities and medical centers that are using the Univ. of Maryland normative database each day of the week in the evaluation of patients with neurological and psychiatric problems.

Cross-Validation and Reliability Tests of the Normative Database

Thatcher, R.W., McAlaster, R., Lester, M.L., Horst, R.L. and Cantor, D.S. Hemispheric EEG Asymmetries Related to Cognitive Functioning in Children. In: Cognitive Processing in the Right Hemisphere, A. Perecuman (Ed.), New York: Academic Press, (1983).

Thatcher, R.W., Walker, R.A. and Guidice, S. Human cerebral hemispheres develop at different rates and ages. Science, 236: 1110-1113, 1987.

Thatcher, R.W., Walker, R.A., Gerson, I. and Geisler, F. EEG discriminant analyses of mild head trauma. EEG and Clin. Neurophysiol., 73: 93-106, 1989.

Wolff, T. and Thatcher, R.W., Cortical reorganization in deaf children. J. of

Clinical and Experimental Neuropsychology, 12: 209-221, 1990.

Thatcher, R.W., Cantor, D.S., McAlaster, R., Geisler, F. and Krause, P. Comprehensive predictions of outcome in closed head injury: The development of prognostic equations. Annals New York Academy of Sciences, 620: 82-104, 1991.

Thatcher, R.W. Maturation of the human frontal lobes: Physiological evidence for staging. Developmental Neuropsychology, 7(3): 370-394, 1991.

Thatcher, R.W. EEG normative databases and EEG biofeedback. Journal of Neurotherapy, 2(4): 8-39, 1998.

Thatcher, R.W., Walker, R.A., Biver, C., North, D., Curtin, R., Quantitative EEG Normative databases: Validation and Clinical Correlation, J. Neurotherapy, 7 (No. ¾): 87 – 122, 2003.

Thatcher, R.W., North, D., and Biver, C. EEG inverse solutions and parametric vs. non-parametric statistics of Low Resolution Electromagnetic Tomography (LORETA). Clin. EEG and Neuroscience, 36(1), 1 – 9, 2005.

Thatcher, R.W., North, D., and Biver, C. Evaluation and Validity of a LORETA normative EEG database. Clin. EEG and Neuroscience, 2005, 36(2): 116-122.

Thatcher, R.W., North, D., and Biver, C. EEG and Intelligence: Univariate and Multivariate Comparisons Between EEG Coherence, EEG Phase Delay and Power. Clinical Neurophysiology, 2005, 116(9):2129-2141.

Thatcher, R.W., Biver, C. J., and North, D. Spatial-Temporal Current Source Correlations and Cortical Connectivity, Clin. EEG and Neuroscience, 38(1): 35 – 48, 2007.

Thatcher, R.W., Biver, C. J., and North, D. Intelligence and EEG current density using Low Resolution Electromagnetic Tomography, Human Brain Mapping, 2007, 28(2): 118 – 133.

Thatcher, R.W., North, D., and Biver, C. Development of cortical connectivity as measured by EEG coherence and phase. Human Brain Mapp., 2008, 12:1400-1415.

Thatcher, R.W. and Lubar, J.F. History of the scientific standards of QEEG normative databases. In: Introduction to QEEG and Neurofeedback: Advanced Theory and Applications, T. Budzinsky, H. Budzinsky, J. Evans and A. Abarbanel (eds)., Academic Press, San Diego, CA, 2008.

Thatcher, R.W. Reliability and validity of quantitative electroencephalography (qEEG). J. of Neurotherapy, 14:122-152, 2010.

Thatcher, R.W., North, D.M., and Biver, C.J. 2011. Diffusion Tensor Imaging 'Modules' Correlated with LORETA Electrical NeuroImaging 'Modules'. Human Brain Mapping (EPub, Jan. 2011).

Partial list of independent evaluations of the normative database with no studies that have refuted the database in the last 25 years

Bell, M.A and Fox, N.A. (1992), The relations between frontal brain electrical activity and cognitive development during infancy. Child Dev. 63(5): 1142-63.

Boldyreva GN, Zhavoronkova LA. (1991). Interhemispheric asymmetry of EEG coherence as a reflection of different functional states of the human brain. Biomed Sci.; 2(3): 266-70.

Béla Clemensa,∗, Pálma Piros a, Mónika Bessenyeia, Edit Vargab, Szilvia Puskásc, István Feketec (2009). The electrophysiological ''delayed effect'' of focal interictal epileptiform discharges. A low resolution electromagnetic tomography (LORETA) study. Epilepsy Research (2009) 85, 270—278

M. Besenyeia, E. Vargab, I. Feketec,∗, S. Puskásc, K. Hollódyd, A. Fogarasi e, M. Emrif, G. Oppositsf, S.A. Kis f, B. Clemens. (2012). EEG background activity is abnormal in the temporal and inferior parietal cortex in benign rolandic epilepsy of childhood: A LORETA study. Epilepsy Research (2012) 98, 44—49

B. Clemens, M. Bessenyei a, I. Fekete b, S. Puskás b, I. Kondákor c, M. Tóth d, K. Hollódy (2010). Theta EEG source localization using LORETA in partial epilepsy patients with and without medication. Clinical Neurophysiology 121 (2010) 848–858.

B. Clemensa,∗, S.Puskásb, M.Bessenyeia, M.Emric, T.Spisákc, M.Koselákc, K. Hollódyd, A.Fogarasi e, I.Kondákorf, K.Fülef, K.Benseg, I.Fekete (2011). EEG functional connectivity of the intrahemispheric cortico-cortical network of idiopathic generalized epilepsy. Epilepsy Res. (2011), doi:10.1016/j.eplepsyres.2011.04.011

B. Clemensa, S. Puskásb, M. Besenyeia, M. Emric, G. Oppositsc, S.A. Kis c, K. Hollódyd, A. Fogarasi e, I. Kondákorf, K. Fülef, K. Benseg, I. Fekete. (2012). EEG-LORETA endophenotypes of the common idiopathic generalized epilepsy syndromes. Epilepsy Res. (2012), doi:10.1016/j.eplepsyres.2011.12.008

Clemens, B., et al., Remission of benign epilepsy with rolandic spikes: An EEG-based connectivity study at the onset of the disease and at remission. Epilepsy Res. (2013), http://dx.doi.org/10.1016/j.eplepsyres.2013.04.006

Clemens, B., et al., Neurophysiology of juvenile myoclonic epilepsy: EEG-based network and graph analysis of the interictal and immediate preictal states. Epilepsy Res. (2013), http://dx.doi.org/10.1016/j.eplepsyres.2013.06.017

Dawson G, Panagiotides H, Klinger LG, Hill D. (1992). The role of frontal lobe functioning in the development of infant self-regulatory behavior. Brain Cogn. 20(1): 152-75.

Fisher, K.W. (1987), Relations between brain and cognitive development. Child Dev. 58(3): 623-32.

Hammer, B.U., Colbert, A.P., Brown, K.A. and Ilioi, E. C. (2011). Neurofeedback for Insomnia: A Pilot Study of Z-Score SMR and Individualized Protocols. Appl Psychophysiol Biofeedback, DOI 10.1007/s10484-011-9165-y

Hanlon, H. W. (1996). Topographically different regional networks impose structural limitations on both sexes in early postnatal development. In: K. Pribram & J. King (Eds.), *Learning as self-organization* (pp. 311-376). Mahwah, NJ: Lawrence Erlbaum Assoc., Inc.

Huang-Storms, Lark , Bodenhamer-Davis, Eugenia , Davis, Richard and Dunn, Janice(2007) 'QEEG Guided Neurofeedback for Children with Histories of Abuse and Neglect: Neurodevelopmental Rationale and Pilot Study', Journal of Neurotherapy, 10: 4, 3 — 16

Ito Y, Teicher MH, Glod CA, Ackerman E. (1998). Preliminary evidence for aberrant cortical development in abused children: a quantitative EEG study. J Neuropsychiatry Clin Neurosci. 10(3): 298-307.

John, E. R., Prichep, L. S. & Easton, P. (1987). Normative data banks and neurometrics: Basic concepts, methods and results of norm construction. In A. Remond (Ed.), *Handbook of electroencephalography and clinical neurophysiology: Vol. III. Computer analysis of the EEG and other neurophysiological signals* (pp. 449-495). Amsterdam: Elsevier.

Kaiser J, Gruzelier JH. (1996). Timing of puberty and EEG coherence during photic stimulation. Int J Psychophysiol. 21(2-3): 135-49.

McAlaster, R. (1992). Postnatal cerebral maturation in Down's syndrome children: a developmental EEG coherence study. Int J. Neurosci. 65(1-4): 221-37.

McCormick, L.M., Yamada, T., Yeh,M., Brumm, M.C. and Thatcher, R.W. Antipsychotic Effect of Electroconvulsive Therapy is Related to Normalization of Subgenual Cingulate Theta Activity in Psychotic Depression. J. of Psychiatric Res., 43(5): 553-560, 2009.

Paquette V, Beauregard M, Beaulieu-Prévost D. (2009). Effect of a psychoneurotherapy on brain electromagnetic tomography in individuals with major depressive disorder.Psychiatry Res. 2009 Dec 30;174(3):231-9. Epub 2009 Nov 13.

S. Puskása, M. Bessenyeib, I. Feketea,∗, K. Hollódyc, B. Clemensb (2010). Quantitative EEG abnormalities in persons with ''pure'' epileptic predisposition without epilepsy: A low resolution electromagnetic tomography (LORETA) study. Epilepsy Research (2010) 91, 94—100

Narushima K., McCormick, L.M., Yamada, T., Thatcher, R.W. and Robinson, R.G. Subgenual cingulate theta activity predicts treatment response of repetitive transcranial magnetic stimulation in participants with vascular depression. J. Neuropsychiatry and Clinical Neuroscience, 22(1):75-84, 2010.

Doran Todder1, Joseph Levine1, Ahmad Abujumah1, Michael Mater1, Hagit Cohen1, and Zeev Kaplan (2012). The Quantitative Electroencephalogram and the Low-Resolution Electrical Tomographic Analysis in Posttraumatic Stress Disorder Clinical EEG and Neuroscience 43(1) 48-53

van Baal, G. C. (1997). A genetic perspective on the developing brain: EEG indices of neural functioning in five to seven year old twins. *Organization for scientific research (NWO*). The Netherlands: Vrije University Press.

van Baal, G. C., de Geus, E. J., & Boomsma, D.I. (1998). Genetic influences on EEG coherence in 5-year-old twins. *Behavioral Genet*ics, *28* (1), 9-19.

van Beijsterveldt, C. E., Molenaar, P. C., de Geus, E. J., & Boomsma, D. I. (1996). Heritability of human brain functioning as assessed by electroencephalography. *American Journal of Human Genet*ics, *58* (3), 562-573.

van Beijsterveldt, C. E., Molenaar, P. C., de Geus, E. J., & Boomsma, D. I. (1998). Genetic and environmental influences on EEG coherence. *Behavioral Genetics, 28* (6), 443-453.

Some of the Universities and Institutions that use the normative database:

Departments of Psychiatry and Neurology, University of Iowa School of Medicine, Iowa City, IA

Department of Psychiatry, Wayne State Medical Center, Detroit, MI

Departments of Psychiatry and Behavioral Science, Konkuk University School of Medicine, Seoul, Korea

Department of Neuropsychiatry, Konkuk University Hospital, 4-12 Hwayang-dong Gwangjin-gu, Seoul Korea

Dept. of Psychology, School of Human Sciences, University of Wales, Swansea, UK

Dept. of Psychology, Brown University, Providence, RI

Dept. of Epidemiology, Stanford University, Palo Alto, CA

Dept. of Cognitive & Biological Psychology, Vrije Universiteit Brussel, Pleinlaan 2, Brussels, Belgium

Department of Psychology, Drexel University, Philadelphia, PA

University of North Texas, Denton, Texas

Fort Carson US Army Military Base, Colorado Springs, CO

McGuire Research Institute, Research Service, Richmond VA Medical Center, Richmond, VA

Behavior Medicine, Marion VA Medical Center, Marion, IL

Henry Jackson Foundation, Washington , D.C.

VA Medical Center , Richmond , VA

Camp Lejeune, USMC and Landsdorf Army Hospital, Germany

Department of Business Education, Arizona State University, Phoenix, AZ

Beer Sheva Mental Health Center, Hazadik Miroshalim, Beer Sheva, Israel

Sociedad de Neurofisiologia Clinica, Hospital Espanol de Mexico, Mexico City, Mexico

Division of Biological Neurosciences, Hines VA Medical Center, Hines, Il

Research and Development, VA Medical Center, Marion, IL

Malcolm Grow Medical Clinic, Andrews Air Force Base, MD

Department of Psychology, Drexel University, Philadelphia, PA

Department of Psychiatry, Korea University Ansan Hospital, South Korea

Biological Sciences Department, Michigan Tech University, Houghton, MI

Department of Psychology, Univ. of Tennessee, Nashville, TN

Department of Rehabilitative Medicine, University of Utah School of Medicine, Salt Lake City, UT

Département de Psychologie Université de Montréal, Montreal, Quebec, Canada

Fundacja Wspierania Rozwoju Kliniki Psychiatrycznej, Akademii Medycznej, Warszawie, Poland

Institute for Basic Research in Developmental Disabilities, Staten Island, New York

Department of Psychology, University of Alberta, Edmonton, Canada

Department of Psychology, Kettering University, Flint, MI

The Hong Kong Polytechnic University, Hong Kong, China

Department of Psychology, University of Central Missouri, Warrensburg, MO

Neuroscience Department, Columbia University , New York

Translational Neuroscience MIND Research Network, Albuquerque , NM

Army Brain Injury Center, Fort Campbell, Kentucky

UNIVERSITÉ DU QUÉBEC, C.P. 500, Trois–Rivières (Québec)

Ammar ebn Yasser, Military Academy , Heliopoles, Cairo EGYPT

Ross Hyslop, Wuttke, Institute, Scotland

Warszawski Uniwersytet Medyczyny ul. Zwirki I Wigury, Warszawa

UNAM -JURIQUILLA, JURIQUILLA, QRO. MEXICO

Department of Veterans Affairs, Austin , Texas

University Putra , Malaysia Timbalan Pengarah Institut Teknologi Maju (ITMA) Serdang Selangor 43400 MALAYSIA

Center for the Army Profession and Ethics, U.S. Army Training and Doctrine Command, West Point, New York