

Draft of paper accepted for publication by Neuropsychiatry (May 2011)

Neuropsychiatry and Quantitative Electroencephalography (qEEG) in the 21st Century

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Abstract

The human brain weighs about 3 pounds and consumes 40% to 60% of blood glucose. This disproportionate amount of energy is used to create electricity in about 100 billion interconnected neurons. Quantitative electroencephalography (qEEG) is a real-time movie of the electrical activity of the preconscious and conscious mind at frequencies from about 1 Hz to 300 Hz. Numerous studies have cross-validated Electrical Neuroimaging by structural MRI, fMRI and Diffusion Spectral Imaging (DSI) and thereby demonstrated how qEEG can aid in linking patient's symptoms and complaints to functional specialization in the brain. Electrical neuroimaging provides an inexpensive millisecond measure of functional modules including the animation of structures through phase shift and phase lock. Twenty first century Neuropsychiatrists use these methods to link patient's symptoms and complaints to functional specialization in the brain and use this information to implement treatment via Brain-Computer-Interface and neurofeedback technology.

Key words: EEG, qEEG, Electrical Neuroimaging

Introduction

Electroencephalography (EEG) is the measurement of the brain generated electrical potential between locations on the scalp and/or with respect to a reference. Quantitative electroencephalography (qEEG) is the use of computers to precisely quantify the electrical potentials from about 1 Hz to 300 Hz representing sub-second measures of summated local field potentials (LFPs) generated in groups of cortical pyramidal neurons (45). In the last 40 years over 90,000 qEEG studies are listed in the National Library of Medicine's database that can be accessed at: <https://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed>. To review this vast literature it is best to use the search terms "EEG and x" where x = a topic such as schizophrenia, dyslexia, attention deficit, reliability, validity, obsessive compulsive disorders, evidenced based medicine, anxiety, phobia, etc. A reading of the studies and abstracts shows that the vast majority of these studies are qEEG studies involving computer analyses (e.g., spectral analyses, ratios of power, coherence, phase, etc). The search term "EEG" and not "qEEG" is necessary because the National Library of Medicine searches article titles/abstracts and rarely if ever use the term "qEEG" in the title (e.g., this author has published six books and over 200 total publications and never used the term "qEEG or QEEG" in the title or abstract). This is why a small 'q' is used in this paper to emphasize that the summation of electrical potentials generated by pyramidal neuron synapses are the sources of the EEG and the 'q' designates quantification as opposed to 'eye-ball' or visual examination of the EEG traces or squiggles without quantification as used in clinical routine. This paper is written with a special emphasis on the use of qEEG after visual examination by psychiatrists, neuropsychiatrists, clinical psychologists, psychologists, neuropsychologists and neuroscientists who are the primary users and publishers of psychiatric related articles using quantitative EEG.

Historically, visually recognized EEG patterns and other electrophysiological measures (EPs & ERPs) were used to discern etiological aspects of brain dysfunction related to psychiatric disorders with reasonable success, but not at the level that qEEG can be used as a stand alone diagnostic method for psychiatric disorders (1). Instead, qEEG was used as an indicator of organicity or a physiological etiology of unknown origin similar to how a clinical blood test is used as well as an objective evaluation of treatment efficacy upon follow-up. In the 1960s and 70's prior to the advent of MRI or PET scans or modern knowledge of brain function it was speculated that the development of large qEEG databases of patients with different clinical disorders will result in the development of qEEG diagnostic measures that provide indications of psychiatric disorders (2). However, it was quickly shown that only a statistical approach is feasible due to the number of measures and the fact that the EEG changes with age. As a consequence age regression and stratified reference normative databases were developed by Matousek and Petersen in 1973 (3,4) and later by John (2, 5 - 7), Duffy (8), Thatcher (9) and Congrego and Lubar (10) and others (see 11 - 13, 29, 88, 89). The Stockholm, Sweden norms of Matousek and Petersen were independently replicated by John and collaborators in New York (2, 5). Subsequent replications of different qEEG normative databases demonstrated the statistical stability and value of using reference normative databases to aid in identifying deviant EEG features and in linking the location of deviant features to symptoms and complaints (1 - 8, 11, 88, 89). The reference data base provides a statistical match to reliable quantitative features available in the 1970s and 80s. However, the spectral methods in the 1970s relied upon the Fourier transform that did not have sufficient temporal resolution to measure high speed

dynamics such as rapid shifts in phase differences and phase lock. This problem was solved in the late 1980s with the application of Joint-Time-Frequency-Analysis (JTFA) where a time series of real-time measures of phase differences are produced. JTFA analyses provided precise measures of phase shift and lock duration across the human lifespan for all combinations of the 10/20 electrode system and normative JTFA databases soon developed (11, 144).

Efforts are still being undertaken in a few laboratories to record and classify qEEG from thousands of patients with the belief that a stand alone diagnosis can be developed for different psychiatric disorders. However, as explained by John (1, 2) and Duffy (8) it is unlikely that qEEG can serve as a stand alone diagnostic measure no matter how large the databases. For example, meta analyses of evidenced based medicine (EBM) criteria only shows moderate to strong effect sizes for particular EEG features in schizophrenia (3) and obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder (PD), generalized anxiety disorder (GAD) and phobias (1, 14, 15). This scientific literature shows that there are a wide variety of different changes in the amplitude and frequency of the EEG at the scalp surface and effect sizes are too small to allow qEEG limited to the scalp surface to serve as a stand alone diagnostic test and this is why qEEG is best used as one test along with other clinical measures to aid a clinician to derive a diagnosis. In other words, evidenced based medicine (EBM) studies and other meta analyses of 40 years of qEEG publications indicate that reliance solely on the surface qEEG is unlikely of providing a stand alone diagnostic measure for a specific psychiatric disorder. In the realm of clinical science this statement also holds true for the majority of clinical tests used by clinicians throughout the world, for example, blood test norms, bone density norms, sonograms, functional MRI (fMRI), positron emission tomography (PET) and SPECT, etc. are rarely if ever used as a stand alone diagnostic test.

In spite of the fact that the surface qEEG is not a stand alone diagnostic test, nonetheless, recent advances in EEG tomography have harkened in a new era for qEEG with increased value going beyond a general measure of “organicity” to providing important information linking symptoms and complaints to functional systems in the brain and thereby enhancing qEEG’s clinical value. It is these new advances in qEEG that are the subject of this review and the goal of this paper is to note that in the decades to come continued improvement and applications of EEG tomographic technology will change the face of neuropsychiatry by providing inexpensive clinical evaluation and treatment for psychiatric disorders. The reasons for this conclusion are two-fold: one is because the spatial resolution of qEEG source analyses will be comparable to that of fMRI and PET scans but provide sub-second resolution available at a fraction of the cost of other imaging methods and, second is the fact that the brain is plastic and can be modified by biofeedback using 21st century technology guided by the qEEG and the neuroscience of operant conditioning.

History of EEG Tomography (tEEG)

Tomography means imaging by sections or sectioning. The word was derived from the Greek word *tomos* which means "part" or "section" and represents the idea of a "slice". EEG tomography (also called tEEG and qEEGt) is based on the ability to measure the location of 3-Dimensional sources of the scalp surface EEG in the interior of the brain and then register the sources to MRI tomographic slices (139). It is the co-

registration of the EEG sources to the MRI that is essential in the use of EEG tomography referred to as tEEG. Others refer to EEG tomography (tEEG) as "Electrical Neuroimaging" (17) or "Brain Electromagnetic Tomography" (BET) (18). The history of inverse methods is accurately described by Malmivuo and Plonsey "Bioelectromagnetism" (19) including the history of these methods in the field of cardiology in the 1800s. Helmholtz in the 19th century mathematically proved that without constraints then the inverse problem has no unique solution. Subsequently, there is a long history of physiological constraints to aid in solving the inverse solution in physics and engineering using discrete and distributed source methods. Distributed source methods provide a smoother match to the tomographic MRI and are the dominant EEG tomographic method in use today (see Table I). Distributed methods often use the mathematical statistics of the minimum norm as a standard mathematical method in matrix algebra discovered by Banach in 1922 – 1929 (e.g., L^p spaces and norms in the mathematics of linear functional analysis, i.e., Riesz's 1910 inverse solutions (166, p. 1085). The minimum norm is special because it provides a unique solution to certain linear and nonlinear inverse solutions and has been applied to cardiology for decades before its application to EEG. For example, 1984 is the date that is most commonly attributed to the first application of a distributed linear solution to the electromagnetic sources of the EEG (20).

Efforts were made at NIH in the 1980s and in 1990-1994 to co-register all imaging modalities to a common anatomical atlas (i.e., Talaraich atlas and later the Montreal Neurological atlas) including EEG as part of the Human Brain Mapping project (21, 22; 139). In the late 1980s, Michael Scherg developed discrete EEG/MEG source solutions but only a distributed method like used in cardiology is acceptable for EEG Tomography or BET (e.g., 23, 24, see 19 for a review). The discrete source solutions are primarily to localize epileptic events and not for tomographic representations. Distributed source solutions uses thousands of dipoles where as discrete source solutions use only one or a few dipoles and consequently the discrete solution can not be used for tomographic localization. In the late 1980s and early 1990s many individuals worked on the application of distributed inverse solutions and in 1992 Wang and collaborators (25) were the first to apply the minimum norm to the inverse problem to the tomographic EEG based on the mathematics of linear algebra and the science of electrical fields. It was quickly found that a problem with the non-smoothed minimum norm is excessive weighting of sources near to the surface of the cortex. Around 1994 Roberto Pascual-Marqui solved the problem of the surface bias by using a maximum smoothing constraint (spatial Laplacian) of the minimum norm (26). The Laplacian operator pushed sources away from boundaries and regularized the matrix resulting in unique solutions with sufficient spatial resolution to measure synchronous clusters of neurons in 7mm^3 volumes of current sources which is the electroencephalogram. This method is called Low Resolution Electromagnetic Tomography (LORETA) in which the term "low resolution" does not mean low accuracy of the maximum current density voxel but rather a smearing around the maximum current density voxel (27). The importance of statistical solutions of the inverse problem was introduced by Pedro Valdez in 1994 (28) resulting in a method called variable resolution electromagnetic tomography (VARETA) (29) and later a statistical normalization applied to LORETA called sLORETA (30). The first tEEG normative databases using Z scores and Gaussian distributions similar to what is used in

fMRI (31) and referred to as “statistical parametric mapping” (SPM) was introduced by Valdez and colleagues in 2001 (29) followed by Thatcher and colleagues in 2005 (32, 33).

Subcategories and Validation of EEG Tomography

Today there are many different BET or tEEG methods using apriori assumptions imposed on the solutions (see reference 34 for a review). The two sub-categories of inverse solution are described in Table I (adapted from ref. 34). The matrix norm and the two categories: non-smooth and smooth include swLORETA (35) as a standardized version of the depth-weighted minimum norm and LAURA ("Local Auto Regressive Average") (36).

Table I.

Norm	Non-smooth	Smooth
L0	Dipole (37) MUSIC (38, 39)	
L1	Minimum Current Estimates (40)	VARETA (29) FOCUSS (41)
L2	Minimum Norm (20)	LORETA (26) LAURA (36) sloreata (30) swLORETA (35)
Combination of L1 and L2	Combined Minimum Norm/Minimum Current (42)	Combined LORETA/VARETA (42)

There are hundreds of accuracy validation studies in the scientific literature of tEEG showing spatial resolutions on the same order as fMRI and sufficiently accurate to measure Brodmann areas. For example, for LORETA alone there are 795 publications listed on the internet in 2009 and the National Library of Medicine cites 373 citations of LORETA in 2010 and 2011. The internet citation of a listing of 795 LORETA publications is at:

<http://www.uzh.ch/keyinst/NewLORETA/QuoteLORETA/PapersThatQuoteLORETA05.htm>

It is easy to demonstrate that different samples of EEG yield the same localization and/or that a particular local event in the EEG corresponds to an expected source of that event, for example, alpha spindles maximum the occipital cortex Brodmann areas 17 and 18 by LORETA and not some where unexpected or right hemisphere hematoma localized to the right parietal lobe Brodmann area , or hemiretinal stimulations shifts current sources based on the connections between the retina and cortex, etc. This is an example of content validity. The reliability and validity of LORETA source localization has been further demonstrated using mathematical simulations, stimulating from implanted

electrodes in epileptic patients and standard tests as well as by determining that the distribution of current sources is represented by a Gaussian distribution (29, 32 - 34).

The advent of EEG Tomography is important because it provides for co-registration of an imaging modality to regions of the brain similar to those imaged by fMRI and PET that measure blood flow. tEEG is similar in spatial resolution to fMRI but adds high temporal resolution of the electrical sources in the brain that give rise to changes in blood flow. EEG tomography also provides for 3-dimensional network analysis including source coherence and phase differences and source phase reset at high temporal resolutions using Joint-Time-Frequency-Analysis (JTFA).

The spatial cross-validation studies of distributed inverse solutions like LORETA/VARETA and other inverse solutions are both mathematical and empirical. Pascual-Marqui et al (26) and Pascual-Marqui (27) provide mathematical cross-validation accuracies for LORETA, sLORETA and eLORETA. Frequency and time mathematical cross-validation by Gomez and Thatcher (43) demonstrated equivalence in the time and frequency domain which is important when using Joint-Time-Frequency-Analysis. Empirical cross-validation studies used simulation from implanted electrodes in epileptic patients, phantom head models, physiological experiments using different stimulus modalities, using diffusion weighted spectroscopy of connection density and cross-validation in, TBI, stroke and tumor patients confirmed by MRI T2 relaxation time (44, 162 - 164). Cross-validation studies of LORETA have also been published with respect to normative Z scores in stroke patients, tumor patients, epileptic patients as well in combined fMRI and/or SPECT studies in depression, traumatic brain injury and other neuropsychiatric disorders (see 44, 33).

An important fact that will influence the future of neuropsychiatry is that EEG tomography (tEEG) provides a portable sub-second measure of 3-dimensional functional coupling between brain regions. With JTFA computation times are in microseconds and time resolution is the sampling rate where 1 to 8 msec resolution at 128 – 1,000 Hz are common in the science of qEEG. This includes phenomena that are invisible to the human eye such as sub-second animation of Brodmann area phase shift and phase lock that is known to be fundamental to brain function (45, 144). Psychiatrists, neuropsychologists and neurologist are currently using these methods to link patient's symptoms and complaints to functional systems in the brain to implement treatment via Brain-Computer-Interface and neurofeedback technology. The paragraphs to follow are a brief review of modern knowledge about the electroencephalogram and some of the growing applications of high speed computers and biofeedback to improve mental health.

The large expansion of knowledge about the functions of the brain prompted by the Decade of the Brain in the 1990s and continuing into the 21st century is now prompting a widespread use of qEEG for clinical evaluation, treatment decisions and monitoring treatment efficacy. For example, the last forty years of neuroscience has shown that specialized groups of neurons mediate specific functions that operate in parallel and are integrated into large dynamical systems that are briefly phased locked in an integrated and coordinated manner to mediate adaptive functions (45, 46, 57 – 68, 144).

Neurological and neuropsychological studies have shown that integrated function is global and not located in any one part of the brain (48, 49). Instead the brain is made up of complex and interconnected groupings of neurons that constitute “functional

systems”, like the “digestive system” or the “respiratory system” in which cooperative sequencing and interactions give rise to an overall function at each moment of time (48). This widely accepted view of brain function became dominant in the 1960s and 1970s and is still the accepted view today. For example, since the 1980s new technologies such as functional MRI (fMRI), PET, SPECT and qEEG/MEG have provided numerous examples of psychiatric symptoms linked to instabilities and deregulation of specialized brain systems (12, 21, 22,).

Modern PET, qEEG, MEG and fMRI studies are consistent with the historical view of coordinated “functional sub-systems” and show that the brain is organized by a relatively small subset of “Modules” and “Hubs” which represent clusters of neurons with high within cluster connectivity and sparse long distance connectivity (50 – 52, 167). Modular organization is a common property of complex systems and ‘Small-World’ models fit best because maximum efficiency is achieved when local clusters of neurons rely on a small set of long distance connections in order to minimize the “expense” of communication. This is an explanation of why long distance connections appear to be vulnerable to aging in general and why the loss of distant connections is a predictor of early stages Alzheimer’s disorder (53 - 56).

qEEG Normative Databases

The first normative qEEG reference databases were developed in the 1960s to 1980s provide comparisons of individuals to groups of age matched healthy individuals and clinically used similar to the way that blood analyses are used to compare an individual to a group of healthy individuals (1). During the 1990s and 2000 normative qEEG databases were extended to 3-dimensional source localization registered to the Talariach atlas (26, 27, 29, 33, 34). These databases provide a simple and easy to use statistical Z score as a metric by which estimates of the location and extent of deregulation with respect to a group of age matched and healthy individuals can be measured off-line or in real-time. Electrical Neuroimaging normative databases of Brodmann areas and Hub and Modules when linked to the patient’s symptoms and complaints aids a clinician along with other measures to derive a diagnosis. In addition, qEEG normative database Z scores help evaluate the course of treatment such as medications, rTMS or biofeedback and thereby help evaluate the comparative efficacy of treatment (1 – 13, 28, 29, 33, 34).

Normative reference databases spanning the age from birth to senescence are used to compare a patient’s EEG current sources to an age matched group of normal subjects (1 – 13, 29, 32 - 34). Another confirmation of the content and construct validity of a LORETA normative database involves testing the accuracy of a normative database using patients with confirmed pathologies where the location of the pathology is known by other imaging methods, e.g., CT-scan or MRI or PET, etc. Validity is estimated by the extent that there is a high correspondence between the location of the confirmed pathology and the location of the 3-dimensional sources of the EEG that correspond to the location of the pathology. Here is a partial list of studies showing concordance validity with fMRI and LORETA (90 - 97) and between PET and LORETA (98 - 101) and between SPECT and LORETA (103).

Coherence is a measure of coupling between groups of neurons and phase differences are a measure of time delays due to conduction velocity, synaptic delays and

synaptic rise times in neural networks. Hypercoherence is related to reduced functional differentiation and hypocoherence is related to reduced functional connectivity (1, 2, 6, 7 9). Phase shift and phase lock duration are correlated with coherence and are measured in milliseconds and reflect fundamental processes involved in the coordination of neural activity located in spatially distributed “modules” at each moment of time at all levels of the nervous system (45, 57 – 68, 144). Importantly, only EEG/MEG has sufficient spatial and temporal resolution to measure the millisecond dynamics of modules and hubs and use Z scores to estimate deregulation in brain regions that can be linked to the patient’s symptoms and complaints. In comparison to MEG, qEEG can better detect deeper cortical sources and is not limited to only tangential dipoles. Also, MEG is expensive on the order of hundreds of thousands of dollars and high monthly maintenance costs whereas qEEG is less than ten thousand dollars no monthly maintenance and portable. The use of modern qEEG methods provide accurate evaluation of deregulated brain regions linked to symptoms in the anatomical, PET, fMRI and EEG/MEG literature and can lead to better treatment decision and improved monitoring of the efficacy of treatment (this knowledge is so widespread that today Google searches of symptoms and brain systems provide the anatomical linkages).

The clinical treatment aspect of qEEG is represented by the science of Brain-Computer-Interface (BCI) and EEG Biofeedback also called Neurofeedback (NF). EEG BCI and NF clinical treatment is based on the use of a reinforcement and operant conditioning to train patients to modify specific EEG frequencies and phases at particular scalp locations, including the use of 3-dimensional source analysis to modify the EEG generated in specific brain regions such as the anterior cingulate gyrus or lateral pre-frontal lobes, etc. (69 - 76). Operant conditioning of specific brain regions has also been used with fMRI but this method is very expensive with low temporal resolution and long delays between brain changes and reinforcement (77). Another clinical treatment is the application of magnetic pulses referred to as repetitive transcranial magnetic stimulation or rTMS that momentarily disrupts the ongoing electrical network dynamics acting like a perturbation after which the cortex converges to a new stable state. Even low levels of magnetic pulses can effect the phase coupling in the EEG and similarly can temporarily disrupt the normal and ongoing activity followed by a new and different stable state. Combining qEEG and rTMS allows clinicians to refine the duration and location of magnetic stimulation and more accurately target deregulated brain regions linked to the patient’s symptoms and complaints. Clinical qEEG treatment can include a two stage procedure of rTMS that briefly resets neural dynamics followed by EEG biofeedback to train the brain dynamics toward the mean of a reference group of age matched normal subjects.

Clinical Applications of Electrical Neuroimaging

Figure one provides a comparative perspective of the temporal and spatial resolution of different neuroimaging modalities. As discussed below Electrical Neuroimaging using the discrete inverse solution has a maximum spatial resolution of about 1 cubic centimeter with one or two dipoles and the highly accurate multidipole method called Low Resolution Electromagnetic Tomography (LORETA) has maximum resolutions of about 1 cm to 3 cm.

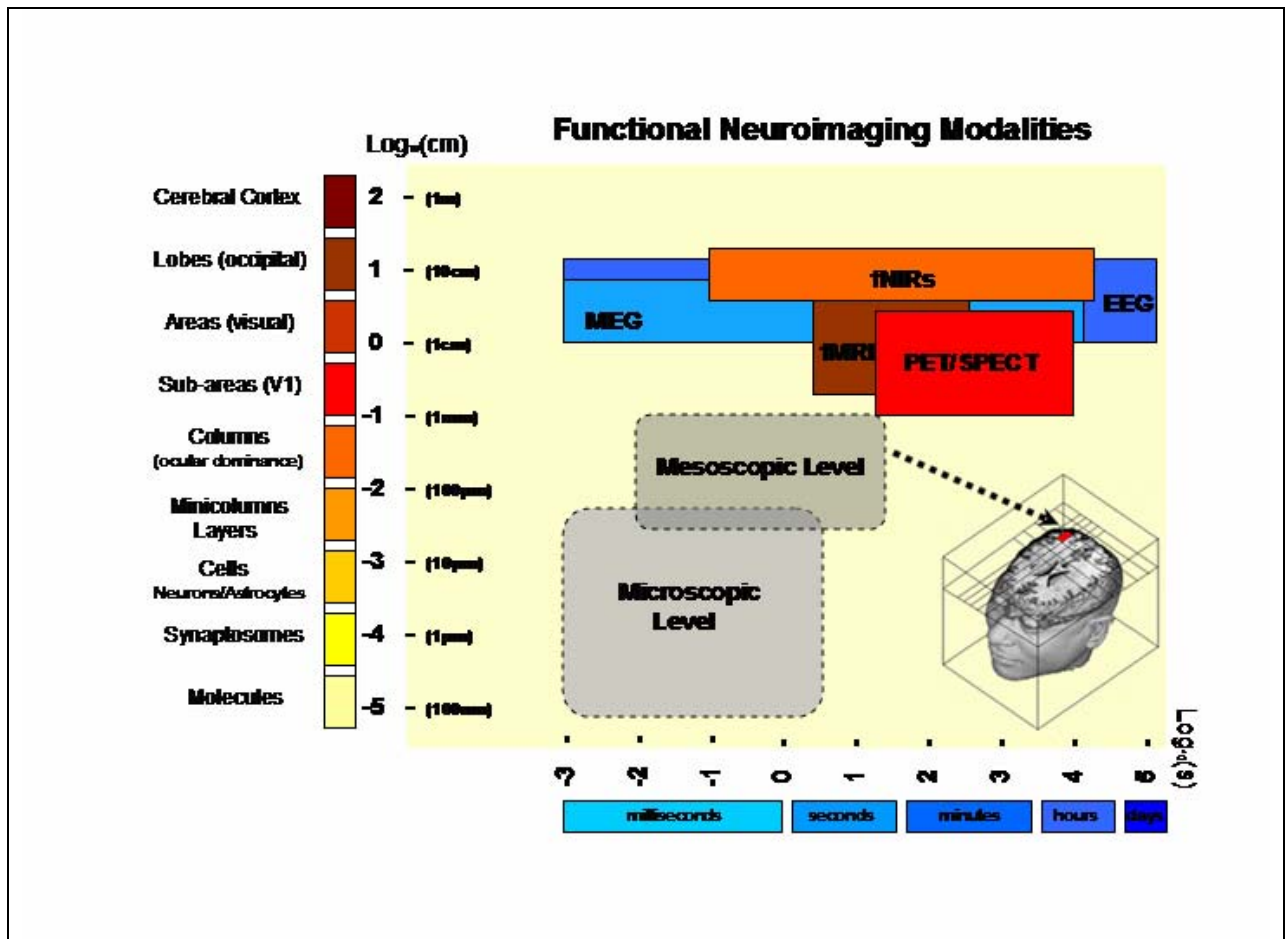


Fig. 1- Comparative spatial and temporal resolution of different neuroimaging methods. The y-axis is the \log_{10} of space and the x-axis is the \log_{10} of time. The nested dynamics of the microscopic and mesoscopic levels being within the macroscopic level is illustrated in figure one. qEEG spatial resolution ranges from about 7 mm^3 to 6 cm^3 and temporal resolution less than 1 millisecond with the ability to measure events over a 24 hour period of time.

Deregulation of specialized parts of an integrated system can be identified as well as compensatory processes and thereby provide a more comprehensive understanding of the patient's symptoms and complaints and also aid in the evaluation of treatment. Some are hesitant to use qEEG for the purposes of Electrical Neuroimaging in the same manner as fMRI or PET is used because of the mistaken belief that qEEG has low spatial resolution. However, as reviewed in the sections below there are more than 700 peer reviewed publications listed at:

<http://www.uzh.ch/keyinst/NewLORETA/QuoteLORETA/PapersThatQuoteLORETA05.htm> (44) that use the same voxel sizes for EEG distributed inverse solutions at 7 mm^3 and with spatial resolution of approximately 1 cm^3 to about 3 cm^3 (26, 27, 29). In contrast, the best spatial resolution of fMRI is about 4 mm^3 under the most ideal circumstances but often several centimeters which is a similar spatial resolution as for tEEG (74, 75). The advantage of Electrical Neuroimaging over fMRI and PET is the reduced cost and the marked improvement in temporal resolution. Comparative studies of the respective spatial resolution of qEEG and MEG show that although the high resistivity of the skull decreases the spatial resolution of the qEEG, it does not make it worse than that of MEG. In fact, if special care is taken to address the considerable

influence of the shape and conductivity of the volume conductor, the localization accuracy of qEEG could be equivalent or even superior to that of MEG (84 - 86).

Spatial and Temporal Scaling

Neurons rapidly synchronize and the spatial extent of global or macro function is about 1 cm to 6 cm if fMRI or PET or any other imaging modality is used. This indicates that synchronization of large groups of pyramidal neurons is itself a fundamental property of information processing in the human brain. Another important fact is that the axonal connections of the human cortex are arranged in six basic clusters referred to as ‘Modules’ as measured by Diffusion Imaging Spectroscopy (50). The synaptic density of connections is spatially heterogeneous and clustered with phase shift and phase lock between clusters or Modules providing the ‘vitality’ or temporal dynamics of the qEEG as mediated by stable loops in thalamo-cortical, cortico-thalamic and cortico-cortical connections. Pacemakers and natural resonance of pyramidal neurons and loops give rise to stable rhythms that operate like a “carrier wave” in which phase shift of neurons with respect to the local field potential to “In-Phase” where they are excited to “Anti-Phase” where they are suppressed is orchestrated by phase shift and phase lock mechanisms that are easily measurable in real-time by standard qEEG methods (45, 111, 147 - 152).

Figure two illustrates the relationship between the micro, meso and macro levels of spatial and temporal scaling and emphasizes the role of phase shift and phase lock as basic causal mechanisms that link all levels and are reflected in the qEEG, especially with respect to functional modules in the brain.

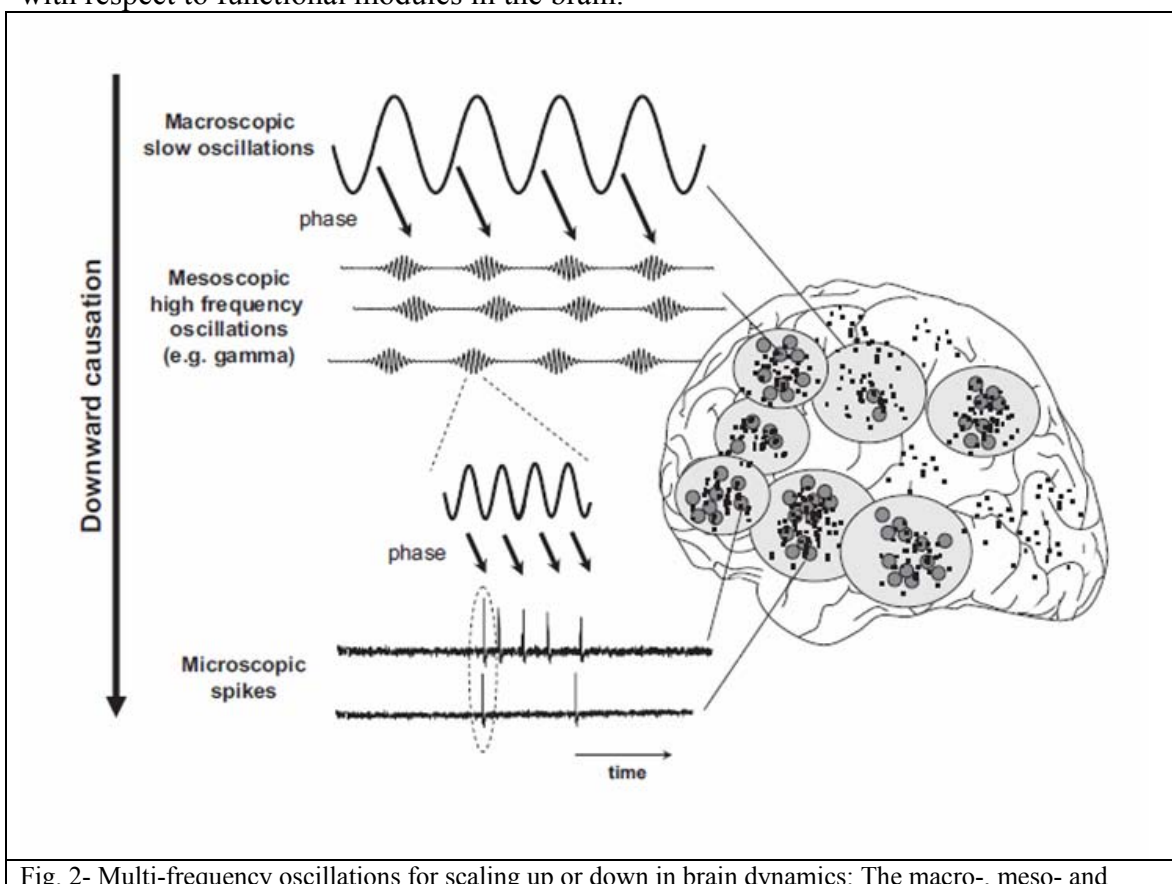


Fig. 2- Multi-frequency oscillations for scaling up or down in brain dynamics: The macro-, meso- and

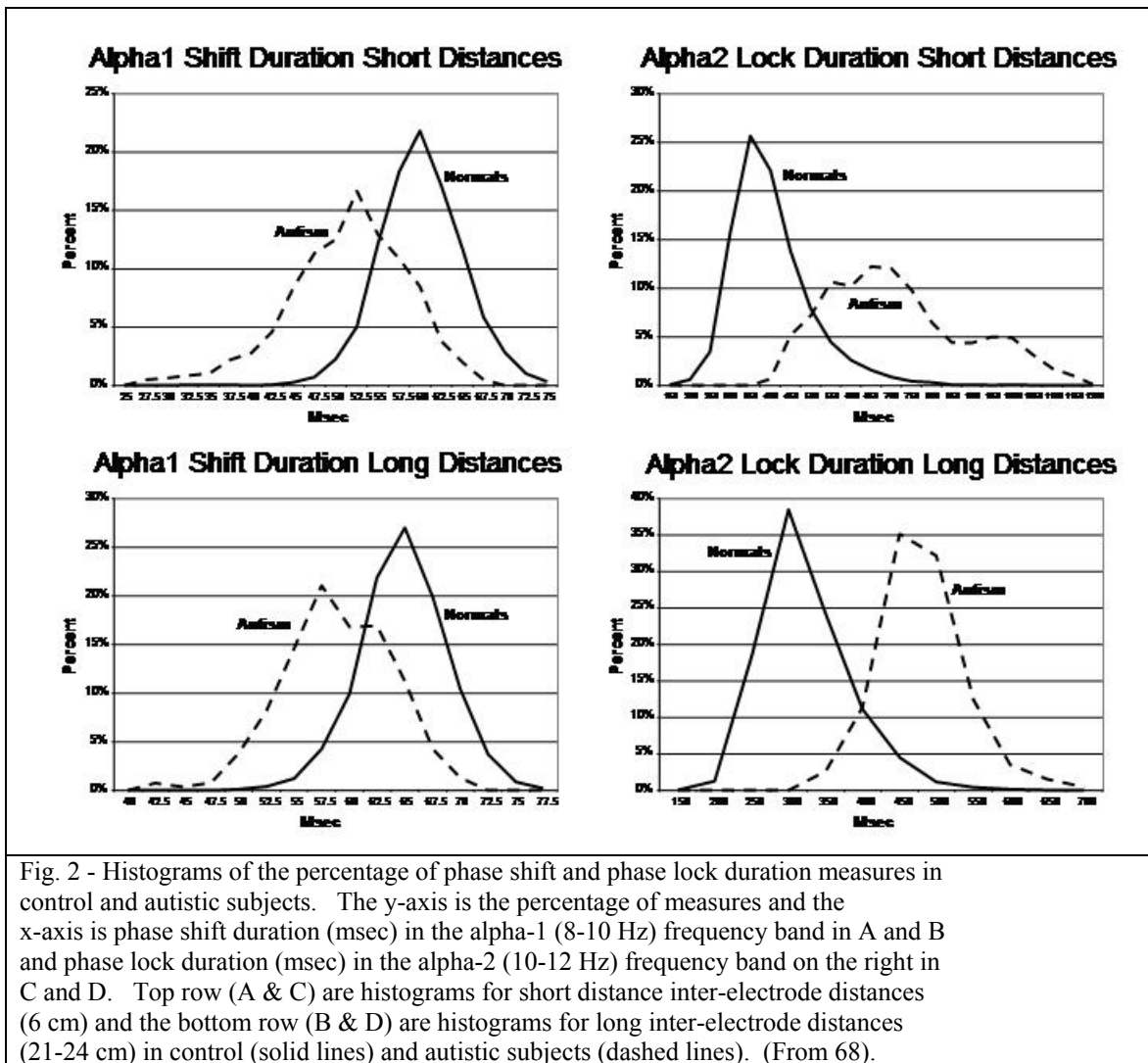
micro-scopic processes are braided together by coordinated oscillations at successively faster frequencies that modulate each other by variations of the underlying neuronal excitability. In particular, through their phases, global brain oscillations in the low-frequency range (<4 Hz) may constrain local oscillations in the high-frequency range (40–200 Hz, e.g. gamma oscillations). In turn, these high-frequency oscillations determine, in the millisecond range, the probability of occurrence of spikes and of their temporal coincidences between different brain regions. (From 105).

Quantitative EEG measures such as directed short and long distance coherence, phase delays, phase locking and phase shifting of different frequencies at millisecond time resolution is essential in understanding how specialized neurons at the microscopic, mesoscopic and macro levels are spatially and temporally scaled with lower frequencies (delta 0-4 Hz & theta 4 to 8 Hz) phase synchronized to higher frequencies (e.g., alpha 8-12 Hz, beta 12 – 20 Hz & gamma 20-50 Hz) (29, 45, 106, 107, 130, 162). The qEEG reflects top down causality at the macro level by coordinating the meso and micro levels of neural organization by scaled temporal and spatial frequencies and time constants. It is the low spatial and temporal frequencies of the macro level that are the order parameters to coordinate and synchronize the micro and mesoscopic levels and this is another reason why the macrodynamic EEG is so important in clinical evaluation and treatment. The deregulation of specialized groups of neurons at micro and meso levels that simultaneously mediate specialized functions can be measured at the macro level using quantitative EEG.

Quantitative EEG and Phase Lock and Phase Shift of Neural Modules

The rapid creation and destruction of multistable spatial-temporal patterns have been evaluated in evoked, transient and spontaneous qEEG studies (133 - 135). As described previously, modern neuroscience shows that the patterns of spontaneously occurring synchronous activity involve the creation of differentiated and coherent neural assemblies at micro, meso and macro scales. The dynamic balance between synchronization and desynchronization is essential for normal brain function and abnormal balance is often associated with pathological conditions such as epilepsy (54, 112, 113, 153); dementia (114, 115); traumatic brain injury (116), cognitive function (117 - 119), working memory (120 - 123), sensory-motor interactions (124 - 125), hippocampal long-term potentiation (126), Intelligence (57), Autism (68) and consciousness (127 – 129, 154).

Phase shift and phase lock can also be measured in real-time which means that these measures can be used for BCI and qEEG biofeedback (NF) purposes as discussed in a later section. Figure three provides an example of the effect size and fundamental importance of phase reset in a study of Autism. One of the advantages of phase shift and lock duration is that they are measured in the time domain and are correlated with IPSP and EPSP synaptic durations (147 - 151). Figure three (left column) are histograms of phase shift duration in short and long inter-electrode distances in the alpha-1 frequency band (8 – 10 Hz) in a group of autistic spectrum disorder children (dashed lines) and an age matched control group (solid lines). Figure 3C & 3D (right column) are histograms of phase lock duration in short and long inter-electrode distances in the alpha-2 frequency band (10 - 12 Hz) in autistic vs controls. This figure shows that phase shift duration is shorter in autistic subjects than control subjects in the alpha-1 frequency band (8 – 10 Hz) and that phase lock duration is longer in autistic subjects in the alpha-2 frequency band (10 – 12 Hz) independent of inter-electrode distance (68).



EEG Tomography and Diffusion Spectral Imaging ‘Modules’

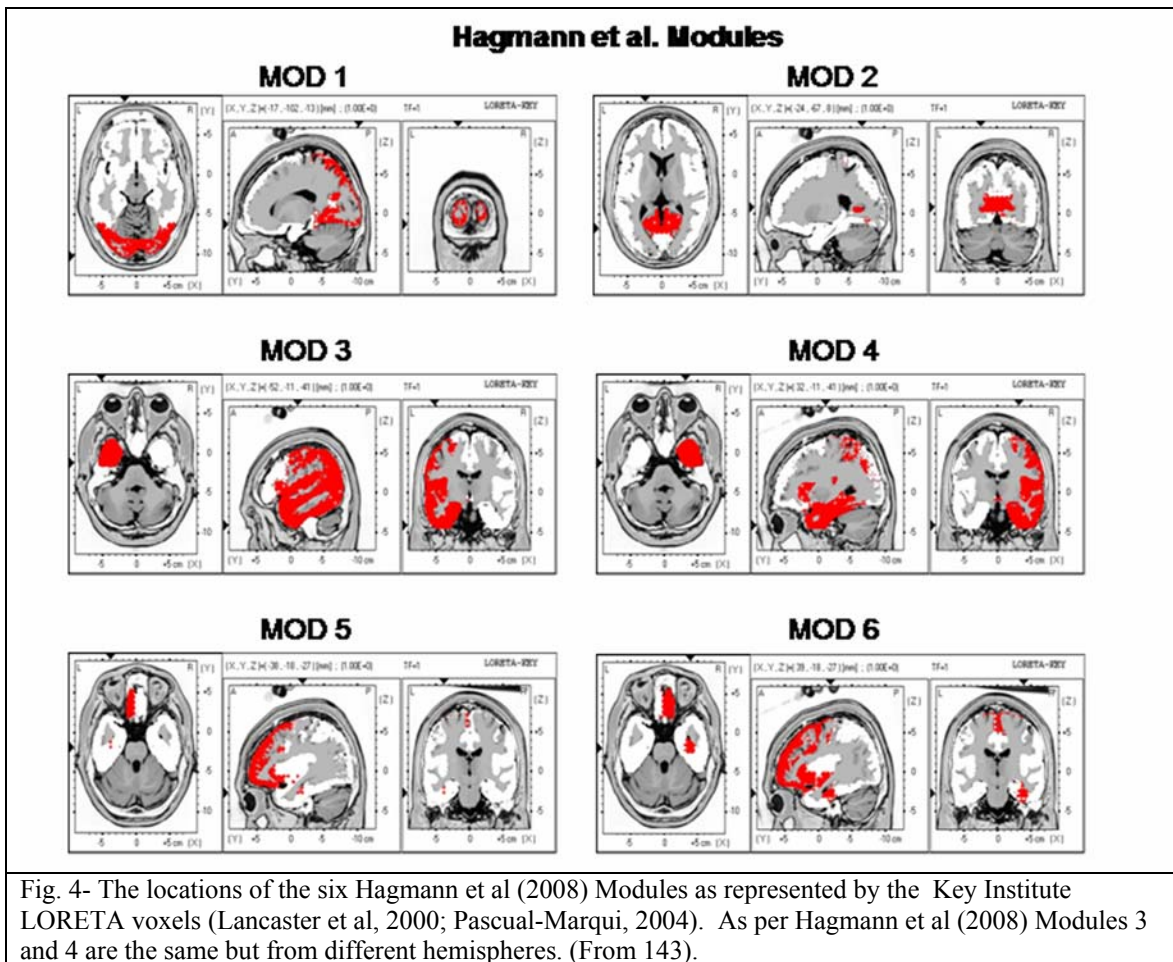
As mentioned previously, convergent evidence from different imaging modalities has demonstrated that the human brain is a network organized by ‘Nodes’ with linkages and clustering of connections defined as ‘Modules’ based on the density of synaptic connections and constituting ‘Functional Modules’. Graph theory is commonly used to quantify the structural topology of the human brain using different imaging methods and achieving similar results from Diffusion Spectral Imaging (DSI), functional MRI (fMRI) and quantitative EEG/MEG (50, 98 – 100, 115). Recently, Hagmann et al (50) used DSI and tractography to trace the cortical white matter connections of the human cerebral cortex between 66 cortical regions with clear anatomical landmarks, using the same gyri and sulci as used by von Brodmann (137) and is still used in all of the Neuroimaging technologies today. Network spectral analyses of nodes and edges of the regions of interest were grouped into six anatomical Modules with maximum centrality defined as high within density anatomical connectivity (50). The six main anatomical connection density Modules included but are not exclusive of : the posterior cingulate, the bilateral precuneus, the bilateral paracentral lobule, the unilateral cuneus, the bilateral isthmus of the cingulate gyrus and the bilateral superior temporal sulcus.

Quantitative electroencephalography using Electrical Neuroimaging methods such as LORETA share the ability to link synchronous neural activity registered to a common and standardized anatomical Talairach atlas (138 – 139, 141) as well as to an age match normative database with Z scores in real-time. Because local synchrony of neurons is necessary to produce a recordable scalp EEG, another constraint is that the density of synapses in clusters of pyramidal neurons is positively related to current source density in a given volume of the brain. Spatial correlation of LORETA spectral amplitudes is a measure of the spatial-temporal synchrony of neurons located in different regions of interest (ROIs) and in different Brodmann areas (80, 124, 134 - 137).

Several studies have used Electrical Neuroimaging coherence and correlation to investigate electrical coupling in different Brodmann areas (140 – 143, 167). Lehman et al (155) computed coherence and phase lock between regions of interest in resting vs meditating subjects. Thatcher et al (87) used LORETA spatial correlations and demonstrated spatial undulations and regular spacing of correlations as a function of distance. All of these qEEG studies revealed interesting and reproducible relations between current sources and network connectivity that is independent of volume conduction and provide a deeper understanding of the surface EEG dynamics. For example, in the Thatcher et al (87) study regions that had the highest neuron packing density exhibited the highest nearest neighbor source correlations and a model of a ‘U’ shaped cortico-cortical fiber system fit the spatial patterns of source correlations (156, 157) (see figure 5).

Given the large scientific literature in support of accurate qEEG source localization, it is reasonable to hypothesize that there is a linkage between structural MRI and LORETA because diffusion weighted images reflect anatomical connectivity (axons) and anatomical connectivity is the basis for effective connectivity, (one region influencing another), therefore, it follows that the MRI should predict synchrony between distant brain regions as measured by LORETA and all distributed inverse solutions. Thatcher et al (143) tested the null-hypothesis that LORETA current sources exhibit a random clustering and random ranking of correlations that are not like the anatomical clusters or modules measured by DSI in the Hagmann et al (50) study. This hypothesis was rejected because the results demonstrated statistically significant spatial correspondence between electroencephalographic source analysis and the anatomical density of connectivity as measured by MRI. The spatial “clustering” of qEEG source correlations were not random and instead were the same as observed with MRI. A simple explanation of why qEEG source correlations are spatially “clustered” in the same manner as MRI is because synaptic densities are measured by both MRI and EEG source analyses. qEEG differs from MRI by higher temporal resolution of phase shift and phase lock or synchrony between time series of sources, however, the basic six anatomical “clusters” are present in the two different measurement domains and thereby demonstrating a linkage between structural MRI and dynamical EEG. This is important because it provides another cross-modality validation of Electrical Neuroimaging as a neurophysiologically useful measure of the preconscious and conscious mind. The Hagmann et al (50) ‘Modules’ are also functional modules in that each involves different specialized brain regions clustered in functional groups. By co-registration of qEEG sources to the Hagmann et al (50) anatomical clusters allows for a spatial reference by which phase dynamics and fine temporal coherence within and between ‘Modules’ can be analyzed.

Figure four shows an example of the replication of the Hagmann et al (50) DSI modules using quantitative EEG (Thatcher et al, 143).



Quantitative EEG and Cortico-Cortical Connections

Volume conduction occurs because synchronous electrical sources produce an electrical field with zero phase lag that falls off smoothly and rapidly with distance. It is also known that the greater the connectivity between neurons then the higher the amplitude of qEEG because connectivity is necessary for synchrony. Anatomical studies also demonstrate a smooth decrease in synaptic density as a function of distance from any collection of neurons (156 - 159). Thus, electrical volume conduction and connection density are confounded to some extent, especially in the short distance domain. Schulz and Braitenberg (160) showed that there are three categories of cortico-cortical connections in the human brain: 1- intra-cortical connections which represent the majority of cortical connections and are on the order of 1 millimeter to approximately 5 millimeters and involve collateral axonal connections that do not enter the cerebral white matter; 2- 'U' shaped myelinated fibers representing the majority of the cerebral white matter that connect cortical gyri and sulci and are on the order of 3 millimeters to 3 centimeters and, 3- deeply located long distance fiber systems referred to as fasciculi with connections from approximately 3 to 15 centimeters that represent approximately 4% of the cerebral white matter. The intra-cortical fiber system is too short at 1 to 3 millimeters for 19 lead or even 512 lead EEG to resolve connectivity differences at the scalp surface (71). Nonetheless, the effects of the intra-cortical system on the amplitude of the EEG are strong

because fiber bundles carry action potentials that produce somadendritic excitatory post synaptic potentials and thereby synchronize large groups of neurons (81, 161).

LORETA source correlation studies have demonstrated spatial heterogeneity consistent with the studies by Schulz and Braitenberg (160), especially in the longer distances and these studies can not be explained by volume conduction. For example, figure five is an example of increases and decreases in source correlations as a function of distance in a subject in this study with a pattern consistent with the Schulz and Braitenberg (160) cortico-cortical connection model which can not be explained by volume conduction.

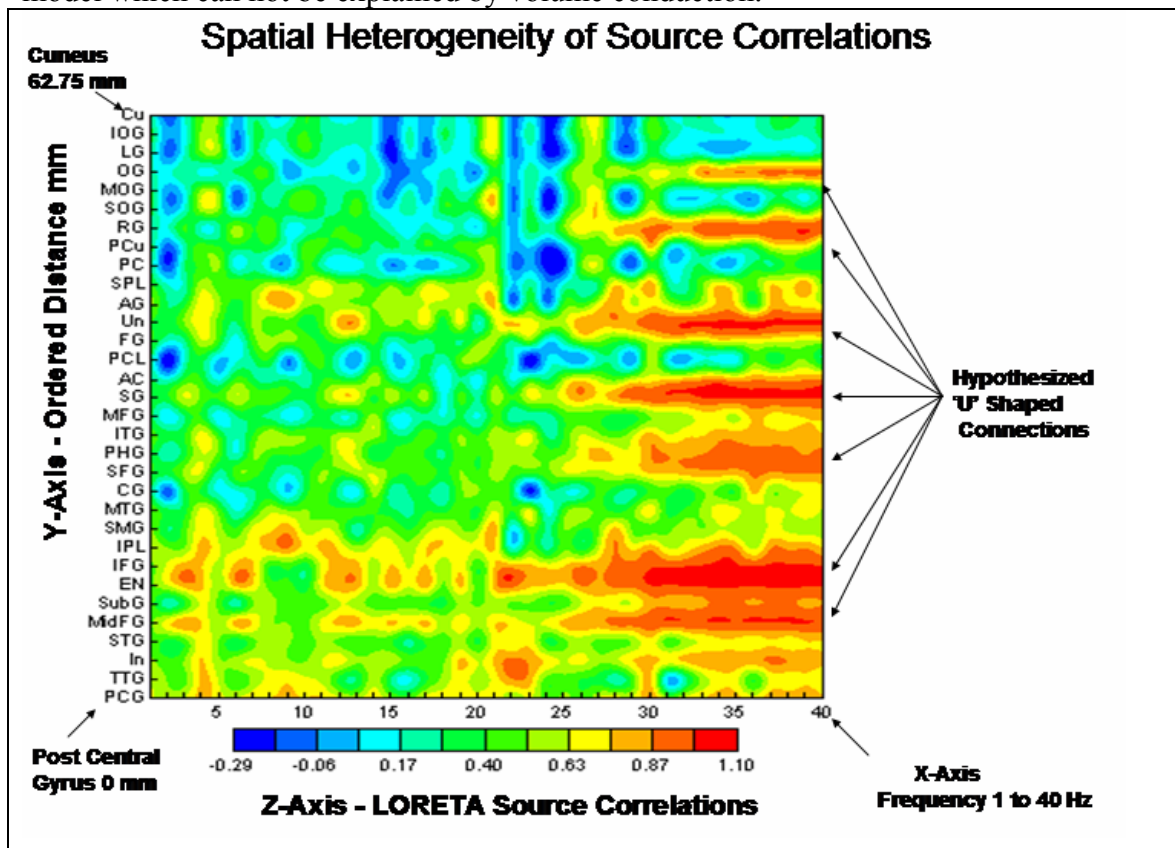


Fig. 5 - From Thatcher et al (79) and an exemplar of one of the subjects demonstrating spatial heterogeneity of LORETA source correlations which can not be explained by volume conduction. The regions of interest (ROIs) are ordered as a function of distance from the reference Brodmann area 1 or left post central gyrus to the left cuneus (Brodmann area 17 that is 62.75 mm distant). The x-axis is frequency (1 to 40 Hz), the y-axis are regions of interest (ROIs) and the regions of interest are ordered as a function of distance from the post central gyrus. The z-axis is the magnitude of the LORETA source correlation as represented by the color bar of the contour map. The alternating horizontal red and blue lines represent a regular spacing of increases and decreases in coupling with a spacing consistent with the 'U' shaped fiber system of the human cortex. The 'U' shaped fibers are strongly coupled at 20 Hz to 40 Hz. The alternating vertical red and blue represent a regular spacing of frequency in which a specific Brodmann area is coupled to many other Brodmann areas but only within a particular frequency band, for example, theta and beta and alpha and gamma. The cortico-cortical fiber system is highly coupled in gamma band frequencies at 20 to 40 Hz and less in the lower frequency ranges. PCA = Posterior Precentral gyrus, TTG = Transverse Temporal gyrus, In = Insula, STG = Superior Temporal gyrus, MdFG = Middle Frontal gyrus, Sub G = Sub Gyral region, EN = Extra-Nuclear frontal gyrus, IFG = Inferior Frontal gyrus, IPL = Inferior Parietal lobule, SMG = Supramarginal gyrus, MTG = Middle Temporal gyrus, CG = Cingulate gyrus, SFG = Superior Frontal gyrus, PHG = Parahippocampal gyrus, ITG = Inferior Temporal gyrus, MFG = Medial Frontal gyrus, SG = Subcallosal gyrus, AC = Anterior Cingulate, PCL = Paracentral lobule, FG = Fusiform gyrus, UN = Uncus, AG = Angular gyrus, PC = Posterior Cingulate, PCu = Precuneus, RG = Rectal gyrus, SOG = Superior

Occipital gyrus, MOG = Middle Occipital gyus, OG = Orbital gyrus, LG = Lingual gyrus, IOG = Inferior Occipital gyrus, Cu = Cuneus (From 143).

Z Score Biofeedback

Operant conditioning of specific EEG frequencies has been published in over 690 EEG biofeedback studies since the 1960s (search the National Library of Medicine with the search terms ‘EEG biofeedback’ for a listing of studies) and 2,348 Brain-Computer-Interface studies. Evidenced based medicine designs and meta-analyses show the relative efficacy of EEG biofeedback (168, 169). Often more than 40 sessions of EEG biofeedback are required to achieve improved clinical outcome. Although it is beyond the scope of this paper to review the EEG biofeedback literature, suffice it to say that the goal of future clinical applications of EEG biofeedback is to obtain better clinical outcomes in fewer sessions. One approach to achieve improved clinical outcome in fewer sessions is to target the ‘weak’ systems of the brain that are linked to the patient’s symptoms and to avoid modifying compensatory networks. A recent method to improve the clinical efficacy of EEG biofeedback is the use of real-time age matched normative database comparisons to scalp locations and Brodmann areas using Z scores. The Z scores or standard deviations with respect to an age matched reference population provides a real-time guide to train patients toward $Z = 0$ in brain regions associated with particular disorders (145, 146, 165). The clinical use of qEEG in Neuropsychiatry involves three distinct steps: 1- A clinical interview and evaluation of the patient’s symptoms and complaints, 2- Linking the patient’s symptoms to functional specialization in the brain based on the scientific literature (qEEG/MEG; fMRI; PET; SPECT, etc) and, 3- Real-time Z score biofeedback to modify deviant or deregulated brain regions associated with the patient’s symptoms and complaints.

Figure six is an example of various functions associated with particular Brodmann areas based on fMRI, PET, EEG/MEG and lesion/tumor studies (48, 49). Convergence of classical and well established studies that link

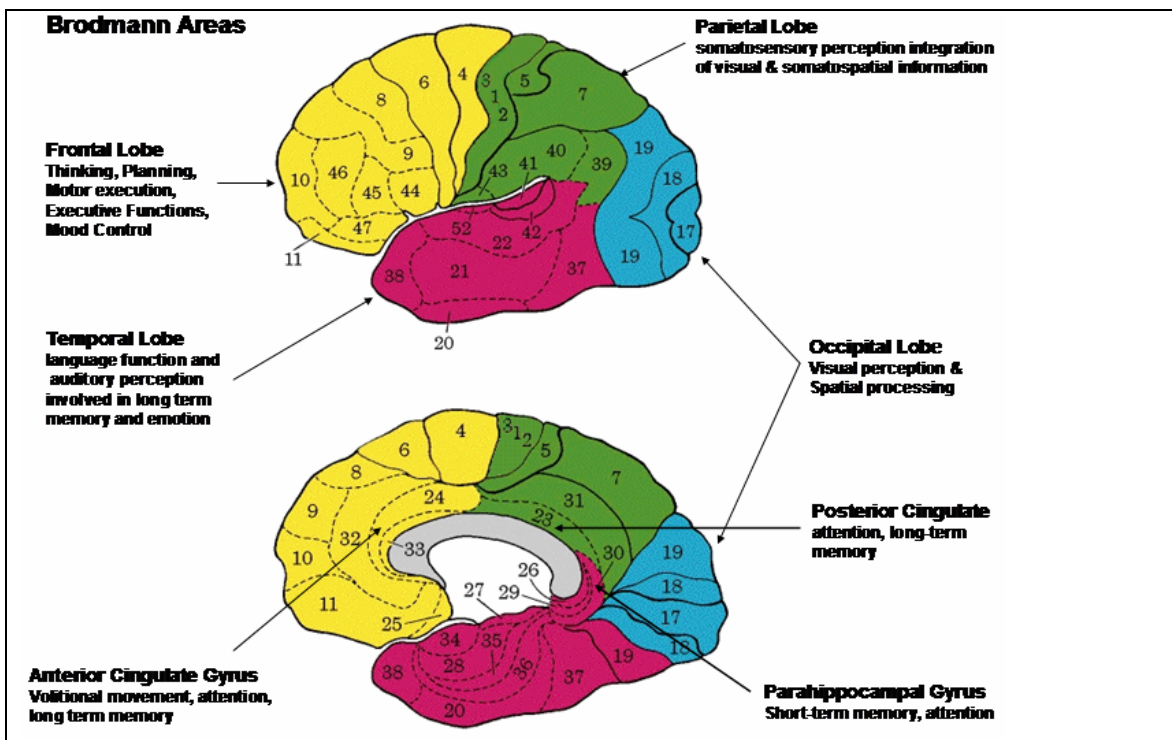


Fig. 6- Illustration of Brodmann areas (Brodmann, 1909) linked to particular functions. Brodmann areas operate at the macroscopic level as measured by the qEEG with spatial areas of common functional cytoarchitecture that range in size from about 1 cm^3 to 6 cm^3 . The goal is to link a patient's symptoms and complaints to deregulation or deviation from normal in brain regions known to be related to specific functions. qEEG also provides high temporal resolution so that measures of dynamic connectivity and phase reset can also be evaluated with respect to an age match normative database. Treatment follows assessment in order to 'move' deregulated sub-systems and global linkages toward the normal range of function. This approach is similar to the use of a blood test to identify deviant constituents of the blood, e.g., elevated liver enzymes or white blood cell count, that can be linked to the patient's symptoms and aid in the decision for treatment and in monitoring the efficacy of treatment.

clinical disorders to functional specialization help clinicians to target variables for EEG biofeedback and the use of real-time Z scores aids in reinforcing regulation of unstable brain systems linked to the patient's symptoms. Figure seven shows an example of LORETA Z score biofeedback selections using a symptom check list and/or a neuropsychological assessment check list to target deregulated brain regions and reinforce EEG variables toward $Z = 0$ which is the center of the healthy normative database values.

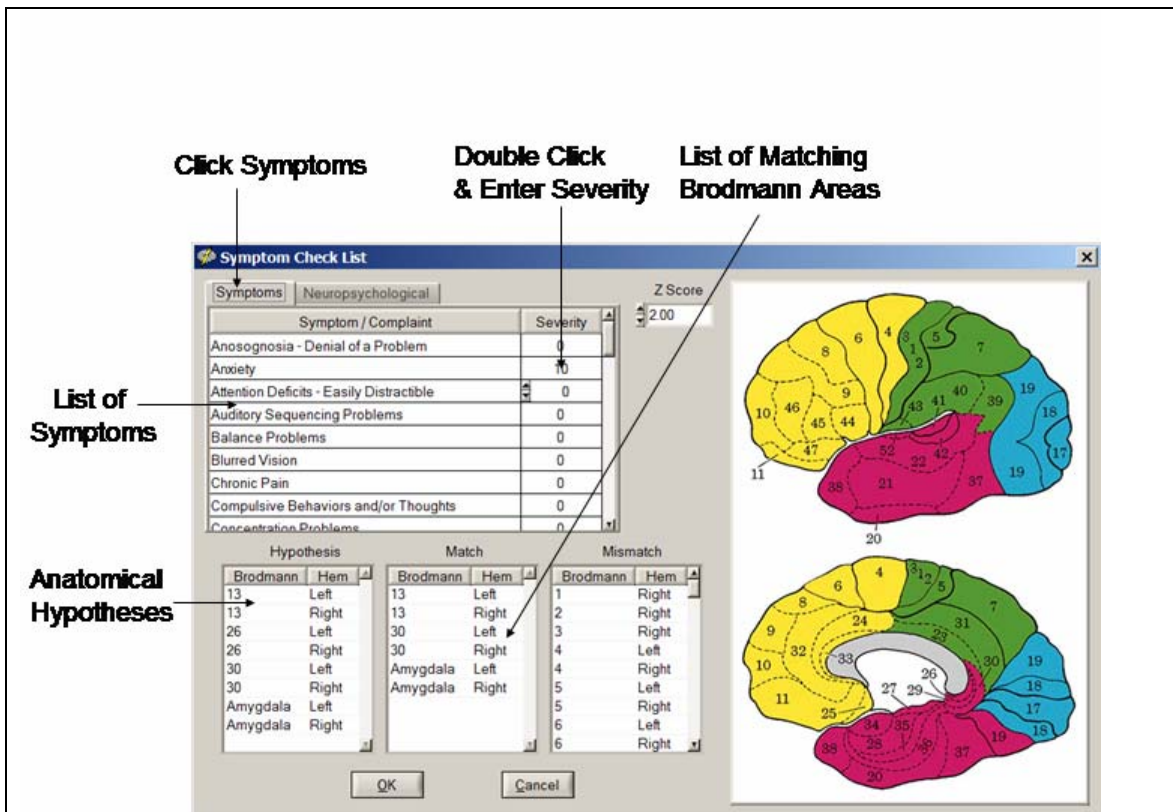


Fig. 7- EEG biofeedback of LORETA Z score that are linked to the patient's symptoms and complaints. The upper left panel is a symptom check list, the right are Brodmann areas and the lower left panel are hypothesized Brodmann areas known to be related to a given symptom or neuropsychological assessment based on the scientific literature. The lower middle panel are the matches of deviant qEEG Z LORETA Z scores to the hypothesized Brodmann areas linked to the patient's symptoms. The lower right are the mismatches of deviant LORETA qEEG Z scores that are likely related to compensatory processes. The goal of this procedure is to separate the 'weak' systems from the 'compensatory' systems and to target the 'weak' systems for EEG biofeedback training and reinforce movement of the weak system toward $Z = 0$ which is the center of an age match normal population. Specific Brodmann areas can be trained such as the anterior cingulate gyrus in depression or attention deficit or the parahippocampus in attention deficit or the left angular gyurs in dyslexia, etc.

Clinical Practice Points

The application of qEEG to determine "organicity", to link to symptoms and to evaluate treatment efficacy has been its mainstay the last 40 years. Treatment using qEEG biofeedback is growing and is being applied in clinics throughout the world. The practical steps involved in the clinical application of qEEG for both assessment of organicity and biofeedback include:

- 1- Measure eyes open and eyes closed artifact free qEEG
- 2- Use auto and cross-spectra to identify scalp locations and network deviations from normal
- 3- Use EEG Tomography (tEEG) to identify deregulation in brain systems linked to the patient's symptoms and complaints.
- 4- Separate the 'weak' systems from the possible compensatory systems

- 5- Use the qEEG to decide treatment modalities and then follow-up evaluations to determine treatment efficacy (medications, rTMS, ECT, BCI, Biofeedback, etc).
- 6- If surface qEEG and tomographic Z score biofeedback is used then target the deregulated brain subsystems to reinforce optimal and homeostatic states of function while the clinician monitors the patient's symptom reduction. Use the patient's feedback to change protocols.

A growing number of clinicians are adding qEEG assessment to link patient's symptoms and complaints to deregulation of functional systems in the brain followed by one or more treatments followed by follow-up evaluation to assess treatment efficacy.

Conclusion and Future Perspectives

Reliance solely on surface EEG patterns without linking a patient's symptoms and complaints to locations and systems in the brain has resulted in only moderate clinical utility of the qEEG. A new era of tomographic EEG has arisen that is inexpensive and portable that will affect the convergence of Neurology, Neuropsychology and Neuropsychiatry in the decades to come. The ability to link patient's symptoms and complaints to functional specialization in the brain is essential to understanding a patient's disorder. Location is most important because it provides a link to two centuries of neurology and to blood flow measures such as PET, fMRI, SPECT and structure by MRI and DTI with the advantage of millisecond time resolution. In the 21st century, the Talariach Atlas coordinates linked to the patient's symptoms provides a type of cross-validation so that the clinician can use a simple Google search or search of the National Library of Medicine of the scientific literature to confirm the anatomical linkage to the patient's complaints. In addition to location, Electrical Neuroimaging provides accurate measures of phase shift and phase lock within and between Brodmann areas which are sufficiently large to be accurately measured using LORETA and other distributed inverse solutions. In the 21st century a growing number of Neuropsychiatrists will use Electrical Neuroimaging to help link the patient's symptoms to the time frames of local and distant couplings between Brodmann areas and modules.

In the future a growing number of pharmaceutical companies will use neuroimaging tools, including qEEG imaging to develop new medications to better understand the millisecond time domain of the brain (neuromodulators, neurotransmitters, etc.). Quantification of medication effects on the brain and the use of EEG biofeedback to modify deregulated neural networks can be synergistic with medication and result in fewer sessions, lower dosages and improved clinical outcome. Neuropsychiatry faces a bright future and will continue to grow by the benefit of new discoveries in neuroscience and neuroimaging.

Acknowledgments

I want to acknowledge the inspiration and vision that my friend and colleague E. Roy John provided over the years. Dr. John passed away on February 28, 2009 but his many contributions are enduring.

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Figure Legends

Figure One- Comparative spatial and temporal resolution of different neuroimaging methods. The y-axis is the \log_{10} of space and the x-axis is the \log_{10} of time. The nested dynamics of the microscopic and mesoscopic levels being within the macroscopic level is illustrated in figure one. qEEG spatial resolution ranges from about 7 mm^3 to 6 cm^3 and temporal resolution less than 1 millisecond with the ability to measure events over a 24 hour period of time.

Figure Two - Multi-frequency oscillations for scaling up or down in brain dynamics: The macro-, meso- and micro-scopic processes are braided together by cooccurring oscillations at successively faster frequencies that modulate each other by variations of the underlying neuronal excitability. In particular, through their phases, global brain oscillations in the low-frequency range ($<4 \text{ Hz}$) may constrain local oscillations in the high-frequency range ($40\text{--}200 \text{ Hz}$, e.g. gamma oscillations). In turn, these high-frequency oscillations determine, in the millisecond range, the probability of occurrence of spikes and of their temporal coincidences between different brain regions. (From 105).

Figure Three - Histograms of the percentage of phase shift and phase lock duration measures in control and autistic subjects. The y-axis is the percentage of measures and the x-axis is phase shift duration (msec) in the alpha-1 (8-10 Hz) frequency band in A and B and phase lock duration (msec) in the alpha-2 (10-12 Hz) frequency band on the right in C and D. Top row (A & C) are histograms for short distance inter-electrode distances (6 cm) and the bottom row (B & D) are histograms for long inter-electrode distances (21-24 cm) in control (solid lines) and autistic subjects (dashed lines). (From 68).

Figure Three- Comparative spatial and temporal resolution of different neuroimaging methods. The y-axis is the \log_{10} of space and the x-axis is the \log_{10} of time. The nested dynamics of the microscopic and mesoscopic levels being within the macroscopic level is illustrated in figure one. qEEG spatial resolution ranges from about 7 mm^3 to 6 cm^3 and temporal resolution less than 1 millisecond with the ability to measure events over a 24 hour period of time.

Figure Four - The locations of the six Hagmann et al (2008) Modules as represented by the Key Institute LORETA voxels (Lancaster et al, 2000; Pascual-Marqui, 2004). As per Hagmann et al (2008) Modules 3 and 4 are the same but from different hemispheres.(From 143).

Figure Five – From Thatcher et al (87) and an exemplar of one of the subjects demonstrating spatial heterogeneity of LORETA source correlations which can not be explained by volume conduction. The regions of interest (ROIs) are ordered as a function of distance from the reference Brodmann area 1 or left post central gyrus to the left cuneus (Brodmann area 17 that is 62.75 mm distant). The x-axis is frequency (1 to 40 Hz), the y-axis are regions of interest (ROIs) and the regions of interest are ordered as a function of distance from the post central

gyrus. The z-axis is the magnitude of the LORETA source correlation as represented by the color bar of the contour map. The alternating horizontal red and blue lines represent a regular spacing of increases and decreases in coupling with a spacing consistent with the 'U' shaped fiber system of the human cortex. The 'U' shaped fibers are strongly coupled at 20 Hz to 40 Hz. The alternating vertical red and blue represent a regular spacing of frequency in which a specific Brodmann area is coupled to many other Brodmann areas but only within a particular frequency band, for example, theta and beta and alpha and gamma. The cortico-cortical fiber system is highly coupled at 20 to 40 Hz and less in the lower frequency ranges. PCA = Posterior Pentral gyrus, TTG = Transverse Temporal gyrus, In = Insula, STG = Superior Temporal gyrus, MdFG = Middle Frontal gyrus, Sub G = Sub Gyral region, EN = Extra-Nuclear frontal gyrus, IFG = Inferior Frontal gyrus, IPL = Inferior Parietal lobule, SMG = Supramaginal gyrus, MTG = Middle Temporal gyrus, CG = Cingulate gyrus, SFG = Superior Frontal gyrus, PHG = Parahippocampal gyrus, ITG = Inferior Temporal gyrus, MFG = Medial Frontal gyrus, SG = Subcallosal gyrus, AC = Anterior Cingulate, PCL = Paracentral lobule, FG = Fusiform gyrus, UN = Uncus, AG = Angular gyrus, PC = Posterior Cingulate, PCu = Precuneus, RG = Rectal gyrus, SOG = Superior Occipital gyrus, MOG = Middle Occipital gyus, OG = Orbital gyrus, LG = Lingual gyrus, IOG = Inferior Occipital gyrus, Cu = Cuneus (From 143).

Figure Six – Illustration of Brodmann areas (Brodmann, 1909) linked to particular functions. Brodmann areas operate at the macroscopic level as measured by the qEEG with spatial areas of common functional cytoarchitecture that range in size from about 1 cm^3 to 6 cm^3 . The goal is to link a patient's symptoms and complaints to deregulation or deviation from normal in brain regions known to be related to specific functions. qEEG also provides high temporal resolution so that measures of dynamic connectivity and phase reset can also be evaluated with respect to an age match normative database. Treatment follows assessment in order to 'move' deregulated sub-systems and global linkages toward the normal range of function. This approach is similar to the use of a blood test to identify deviant constituents of the blood, e.g., elevated liver enzymes or white blood cell count, that can be linked to the patient's symptoms and aid in the decision for treatment and in monitoring the efficacy of treatment.

Figure Seven – EEG biofeedback of LORETA Z score that are linked to the patient's symptoms and complaints. The upper left panel is a symptom check list, the right are Brodmann areas and the lower left panel are hypothesized Brodmann areas known to be related to a given symptom or neuropsychological assessment based on the scientific literature. The lower middle panel are the matches of deviant qEEG Z LORETA Z scores to the hypothesized Brodmann areas linked to the patient's symptoms. The lower right are the mismatches of deviant LORETA qEEG Z scores that are likely related to compensatory processes. The goal of this procedure is to separate the 'weak' systems from the 'compensatory' systems and to target the 'weak' systems for EEG biofeedback training and reinforce movement of the weak system toward $Z = 0$ which is the center of an age match normal population. Specific Brodmann areas can be trained such as the anterior cingulate gyrus in depression or attention deficit or the parahippocampus in attention deficit or the left angular gyurs in dyslexia, etc.