Quantitative EEG and Neurofeedback in Children and Adolescents

Anxiety Disorders, Depressive Disorders, Comorbid Addiction and Attention-deficit/Hyperactivity Disorder, and Brain Injury

Deborah R. Simkin, MD[a,b,*], Robert W. Thatcher, PhD[c], Joel Lubar, PhD[d,e,f]

KEYWORDS

• Quantitative EEG • Neurofeedback • LORETA • Anxiety disorders • Depression • Addiction • ADHD • Brain injury in children and adolescents

KEY POINTS

- The waveforms on an electroencephalogram (EEG) result directly from synaptic activity in brain networks, and neurofeedback offers the opportunity for patients to use operant conditioning to alter their waveforms and brain functioning.
- Quantitative EEGs (qEEGs) represent a patient's waveforms compared with normative EEG databases and may be corepresented with functional magnetic resonance imaging (fMRI), single-photon emission computed tomography, positron emission tomography (PET), and magnetic resonance imaging.
- qEEG, modern PET, magnetoencephalography, and fMRI studies concur in showing that the brain is organized by a small set of modules or hubs that represent clusters of neurons characterized by high within-cluster connectivity and sparse long-distance connectivity.
- During child development, functional brain connectivity is substantially reorganized, but several large-scale network properties seem to be preserved over time, suggesting that functional brain networks in children are organized like other complex systems in adults.

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[a] Committee on Integrative Medicine, American Academy of Child and Adolescent Psychiatry, Attention, Memory and Cognition Center, 4641 Gulfstarr Drive, Suite 106, Destin, FL 32541, USA; [b] Department of Psychiatry, Emory University Medical School, Atlanta, Georgia; [c] Neuroimaging Laboratory, Applied Neuroscience Research Institute, 7985 113th Street, Suite 210, Seminole, FL 33772, USA; [d] University of Tennessee, Knoxville, TN, USA; [e] Southeastern Neurofeedback Institute, Inc, 111 North Pompano Beach Boulevard, Suite 1214, Pompano Beach, FL 33062, USA; [f] International Society for Neurofeedback and Research
* Corresponding author. 4641 Gulfstarr Drive, Suite 106, Destin, FL 32541.
E-mail address: deb62288@aol.com

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Key Points (*Continued*)

- Circuitry dysconnections (in and between these hubs or networks) have been associated with symptoms of psychiatric illness, and these dysconnections can be targeted using neurofeedback.
- Quantitative EEG provides an opportunity for new evaluation techniques permitting more efficient treatment matching, such as determining which patients will be responsive to certain medications or which areas of the brain should be targeted during neurofeedback treatment.
- Clinicians must be intensively trained in appropriate protocols and technologies in order to provide appropriate clinical neurofeedback treatment and to develop sound research.
- Although little research has been done using neurofeedback in children and adolescents with anxiety disorders, mood disorders, comorbid addiction and attention-deficit/hyperactivity disorder, and brain injury, the adult literature and more recent advances in neurofeedback interventions (eg, low-resolution electromagnetic tomography) hold particular promise for future research using fewer sessions.

Abbreviations: Quantitative EEG and Neurofeedback

ADHD	Attention-deficit/hyperactivity disorder
ApoE	Apolipoprotein E
BET	Brain electromagnetic tomography
BRIEF-R	Behavior Rating Inventory of Executive Function-R
DRD2	Dopamine D2 receptor
DSI	Diffuse spectral imaging
EEG	Electroencephalogram
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
GABA	Glutamate and gamma-aminobutyric acid
HD	High dysregulation
IVA-Plus	Integrated Visual and Auditory Continuous Performance Test
JTFA	Joint time-frequency analysis
LD	Low dysregulation
LFP	Local field potentials
LORETA	Low-resolution electromagnetic tomography
LPFC	Lateral prefrontal cortex
LTP	Long-term potentiation
MEG	Magnetoencephalography
NF	Neurofeedback
NIMH	National Institute of Mental Health
PET	Positron emission tomography
PFC	Prefrontal cortex
PTSD	Posttraumatic stress disorder
qEEG	Quantitative electroencephalogram
RDoC	Research domain criteria
rIFG	Right inferior frontal gyrus
ROIs	Subregions of interest
SMR	Sensory motor rhythms
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric mapping
TOVA	Test of variable assessment
USPSTF	United States Preventive Services Task Force
vmPFC	Ventromedial prefrontal cortex
WISC-R	Weschler Intelligence Scale for Children-Revised

INTRODUCTION

Neurofeedback (NF) is a treatment method for altering brain functioning by the use of signals provided to a patient that reflect the moment-to-moment changes in the patient's electroencephalogram (EEG). The method typically uses advanced statistical analysis of quantitative data from the EEG (quantitative EEG [qEEG]) to provide biofeedback to the patient in real time. This approach allows the operant conditioning of the patient's EEG, which, perhaps surprisingly, can have the effect of therapeutically altering cognition, emotions, and behavior.

This article explores the science surrounding NF and reviews the early research on the use of NF technology for treating psychiatric disorders in children and adolescents. Although surface NF (using 2–4 electrodes, which did not use qEEG initially) has long been used, several new NF interventions have been developed. Many of these new interventions, along with surface NF, can now incorporate the use of quantitative electroencephalography to enhance their clinical value.

Three major NF methodologies are real-time z-score surface NF, low-resolution electromagnetic tomography (LORETA), and functional magnetic resonance imaging (fMRI) NF.

Real-time z-score surface NF (EEG biofeedback) uses 2 to 4 or more scalp electrodes to monitor the brain's electrical activity in a particular anatomic location. It uses continuous real-time computerized calculations based on qEEG data comparing the way that the patient's brain is functioning on different variables with an age-matched normative database, using z scores to measure differences from normal EEG activity. The z score is the number of standard deviations of an observation (data on EEG waveform) more than (positive) or less than (negative) the mean. The z scores or standard deviations relative to an age-matched reference population provide a real-time indication of abnormal instabilities in brain networks. These z scores provide a guide to train patients toward quantitatively normal waveforms ($z = 0$) in brain regions associated with particular disorders.

If the surface NF involves the use of 2 or more electrodes, coherence (the measure of the number of connections and communications between groups of neurons) can also be trained during NF training. However, if only 1 electrode is used during NF training, no coherence training can occur. In addition, surface NF involves measuring the amplitude of neurons directly beneath the electrode where 95% of the neurons arise from a distance of 6 cm and all frequencies are mixed together at each electrode. However, LORETA uses three-dimensional source localization applied to human qEEG in which the mixture of frequencies under each scalp electrode are unscrambled and linked to three-dimensional sources in the interior of the brain with accuracies of approximately 1 cm in many situations.

LORETA NF uses a different kind of qEEG NF analysis that provides an estimation of the location of the deep underlying brain generators, called modules or hubs (eg, the anterior cingulate, insula, fusiform gyrus) and networks of the patient's EEG activity within a frequency band. It allows the clinician to translate qEEG data into a three-dimensional figure that corresponds with and looks like the images in fMRI that are associated with disease states. It requires more labor-intensive preparation, because an electrode cap with 19 electrodes must be applied in every session, but it can shorten the length of treatment. Coherence training can include multiple areas.

fMRI NF's advantage is that it can examine functioning at deep subcortical areas of the brain. However, the practical disadvantage of fMRI NF is that it is expensive, with equipment that costs $1 million or more and is not portable.

NF research has been limited in children and adolescents, especially with regard to anxiety, mood, addiction, and traumatic brain injury (TBI). Research has shown that functional hub architecture matures in late childhood and remains stable from adolescence to early adulthood. Thus, LORETA NF, which targets modules and connections between modules, is expected to work the same in patients from 10 years of age to adulthood.

New transdiagnostic approaches, proposed by the National Institute on Mental Health, to defining psychiatric disorders based on dysfunctional connectivity are particularly significant because NF targets dysfunctional connectivity. Clinicians want to familiarize themselves with possible new treatment interventions that target these transdiagnostic symptoms. Other uses of qEEG include determining whether patients will be responsive to medications. In addition, the initial findings on NF research for treating psychiatric symptoms in youth will be covered.

NEUROFEEDBACK BASICS

NF is based on operant conditioning. NF is based on measurements of evoked potentials as measured in electroencephalography. An evoked potential can be negative or positive relative to the average baseline potential. An N100 is a negative evoked potential that is generated by a network of neurons, usually provoked by an unexpected stimulus, in a brain location depending on the sensory modality. P100 is a positive evoked potential in the same region.

Suppose an electrode is recording a P100 evoked potential in a particular area of the brain, and the goal of the NF intervention (to treat a symptom) is to change the P100 positive evoked potential to an N100 negative evoked potential. Following the methods used in operant conditioning, every time an N100 evoked potential begins to occur by chance, a positive reinforcement is provided. The positive reinforcement could be milk delivered into a bowl for a cat. In NF, the patient is provided with a positive reinforcement through the biofeedback presentation of a signal that is linked to the desired alteration in brain wave pattern. The brain would eventually learn to search for this N100 evoked potential in order to receive the positive reinforcement associated with this evoked potential. This example shows how, through operant conditioning, NF can provide a reward for the appearance of a particular electrical event in the brain. The electrical pattern soon begins to appear before the reward, leading to increased frequency of appearance of that electrical pattern. In a similar way in humans, if a dot appears on the screen during an NF session with each occurrence of a particular targeted EEG pattern or rhythm (eg, delta 0–4 Hz, theta 4–8 Hz, alpha 8–12 Hz, beta 12–20 Hz, gamma 20–300 Hz), the rhythm eventually continue to occur in anticipation of the dot appearing.

By knowing the anatomic location of a particular electrical pattern associated with a targeted brain function, NF can be used to change a wide variety of brain functions, including depressed states, anxiety, addiction, injury-induced abnormalities, and attention-deficit/hyperactivity disorder (ADHD). Thus, a precise system for mapping locations in the brain is essential to NF.

To detect specific electrical patterns in the brain, EEG electrodes are placed on the scalp corresponding with anatomic areas associated with particular Brodmann areas, with the aim of targeting certain functions associated with these areas. A targeted rhythm can be pinpointed by an electrode placed on the scalp (for example, corresponding with T3, using the International 10–20 System illustrated in **Fig. 1**, which corresponds with a particular area of the brain). For example, T3 is associated with Brodmann areas 22/42 on the superior temporal gyrus. Affective prosody is

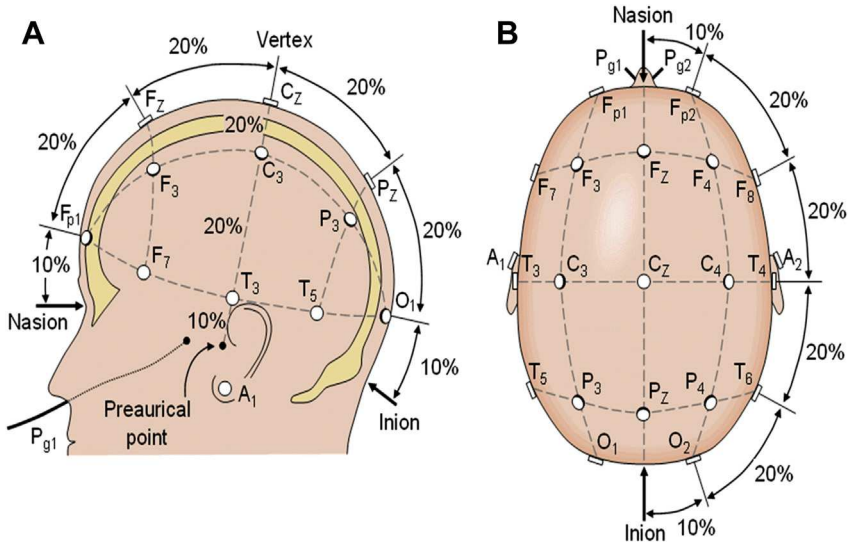

Fig. 1. The International 10–20 System seen from (*A*) the left and (*B*) above the head. A, ear lobe; C, central; F, frontal; F_p, frontal polar; O, occipital; P, parietal; P_g, nasopharyngeal. (*From* Ferreira A, Celeste WC, Cheein FA, et al. Human-machine interfaces based on EMG and EEG applied to robotic systems. J Neuroeng Rehabil 2008;5:10.)

associated with this Brodmann area on the right and language processing on the left. Abnormal evoked potentials (representing abnormal brain wavelengths) in this region may be identified on an EEG. Using NF to target specific Brodmann areas that have abnormal evoked potentials that are found in an individual to be associated with symptoms or specific disorders may change that area of the brain back to a normal pattern and, it is hoped, decrease the symptoms of the disorder.[1]

NF is based on the clinician's ability to link a patient's symptoms and complaints to dysregulation or deviation from normal in EEG patterns in particular brain regions known to be related to specific functions. **Fig. 2** shows the various anatomic regions of the brain, originally delineated by Brodmann[2] in 1909 based on their microarchitecture and their links to particular functions, as based on the findings of various techniques across many patients. Brodmann areas are macroscopic brain regions of common functional cytoarchitecture ranging in size from about 1 cm to 6 cm, and a qEEG can give a precise delineation of these Brodmann areas for each individual. Following qEEG assessment of abnormal brain rhythms in precisely defined brain regions in an individual, NF treatment aims to modify dysregulated subsystems and global linkages toward the normal range of function. Periodic qEEG assessments during treatment can be used to monitor treatment efficacy. The assessment is similar to the use of a blood test to identify deviant constituents of the blood (eg, increased liver enzymes) that can be linked to the patient's symptoms and aid in making treatment decisions and monitoring treatment efficacy.[3]

HOW NEUROFEEDBACK CHANGES ACTION POTENTIALS

The science and techniques involved in NF are described in more detail in the *Handbook on Quantitative Electroencephalography and EEG Biofeedback* by Thatcher.[1]

The registration of wavelengths on a raw EEG results directly from synaptic electrical action potentials produced by chemical synapses in neuronal networks. There are

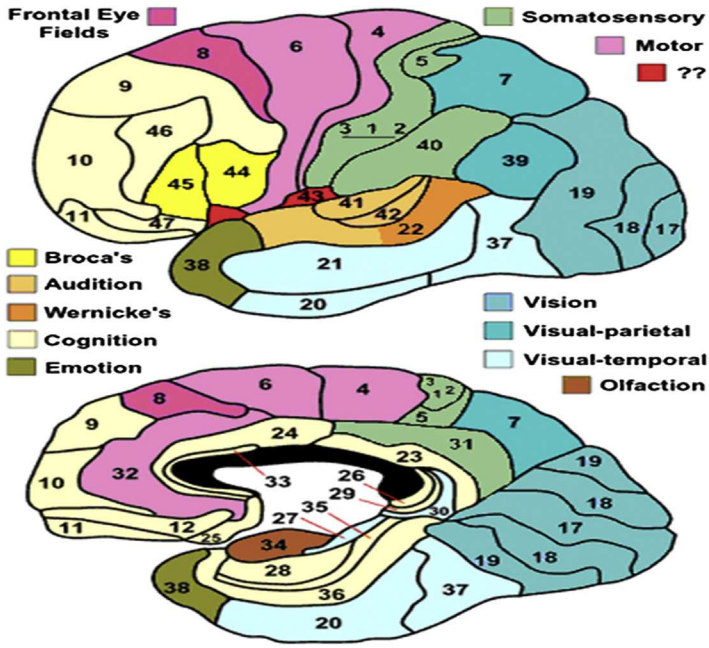

Fig. 2. Various functions associated with particular Brodmann areas based on fMRI, PET, EEG/magnetoencephalography (MEG), and lesion/tumor studies. (*Data from* Refs.[1–5]; and *Courtesy of* M. Dubin, PhD, Boulder, CO.)

2 types of chemical synapses that produce the EEG wavelengths. First, fast synapses involve the neurotransmitters glutamate and gamma-aminobutyric acid (GABA), which are associated with fast gated ion channels (which occur from 0–80 milliseconds). Second, slow synapses involve dopamine, serotonin, acetycholine, and norepinephrine, which are associated with slow voltage gated ion channels (which occur from 100 milliseconds to 1 second). These excitatory and inhibitory postsynaptic potentials give rise to local field potentials (LFPs). LFPs influence the firing of action potentials in pyramidal neurons near the surface of the brain.[1,6] These wavelengths can be changed by operant conditioning that targets these networks. Operant conditioning of the EEG involves changes in synapses caused by what is referred to as a phase reset. Operant conditioning begins by reinforcing a frequency (eg, 5 Hz) associated with a particular wavelength (eg, theta) detected by EEG electrodes near the surface of the brain. When a desired wavelength occurs, there is a burst of action potentials that impinges on the dendrites and cell bodies of pyramidal neurons. The time it takes for this wavelength shift to occur is referred to as phase shift duration and it can be seen on an EEG when the same wavelengths are not in sync (**Fig. 3**). When a phase lock occurs, the desired wavelengths will be synchronized (see **Fig. 3**).

To describe a phase shift or wavelength shift, Thatcher[1] gave the following example. Imagine a family is at a Thanksgiving dinner, and an unexpected relative suddenly arrives whom no one has seen in years. The family shifts from focusing on the dinner to focusing on the relative at the door. Over time, as more and more of the family members recognize the unexpected relative, more family members shift their attention and move toward the door. If more time is given (phase shift duration), more family members move to the door. This analogy also applies for phase shifts in the brain. The

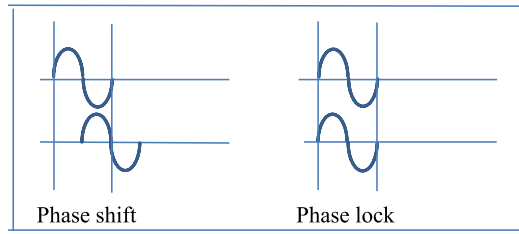

Fig. 3. Phase lock.

longer the duration of the phase shift, the greater the number of neurons that are recruited.[1] When this burst of neuronal activity synchronously occurs in millions of neurons, then a detectable change in the EEG frequencies occurs, (eg, from theta 4–8 Hz to alpha 8–12 Hz).[7]

When all the family members arrive at the door, a phase lock occurs (when all of the EEG frequencies are the same for a particular rhythm). During operant conditioning, a wavelength rhythm is reinforced when the duration of phase lock is increased and the frequency of phase shift is decreased. Likewise, a rhythm is inhibited when the duration of phase lock is decreased and the frequency of phase shift is increased.[1] During NF, a change in an individual's EEG activity can be reinforced by a visual and/or auditory stimulus. As NF continues, the reinforcement is more difficult to obtain because the length of time the individual has to sustain the preferred wavelength is increased. As the individual masters the level of difficulty in sustaining the preferred wavelength, the clinician increases the level of difficulty in order to continually challenge the brain by increasing the length of time the individual must hold the preferred wavelength.

Fast excitatory chemical synapses dominate long-distance corticocortical loops and fast inhibitory synapses dominate short-distance loops. However, long-duration neurotransmitters shape and mold the mechanisms of long-term potentiation (LTP).[1,8] Synapse modifications occur during the phase lock. Neurotransmitters, such as dopamine, are released in anticipation of these rewarding experiences that occur when particular wavelength patterns are elicited during phase lock. Neurotransmitters released during phase lock can influence structural plasticity within the brain. Phase lock produces a long-lasting enhancement in signal transmission between 2 neurons that results from their synchronous firing, which is associated with increased dendrite formation and increase neurotransmitter delivery into the cleft. This process of synapse modification is called LTP, and it requires synapse growth and the development of new synapses during learning. Kandel[9] received the Nobel Prize in 2000 for his work linking LTP to DNA, RNA, and protein production associated with learning and memory formation. Phase lock results in LTP or neuronal learning at the molecular level that moves the patient having NF treatment toward normal functioning.

In effect, EEG NF uses operant conditioning to (1) reinforce particular brain rhythms by reinforcing phase lock and decreasing phase shift, or (2) inhibiting rhythms by decreasing the frequency of phase lock and increasing the frequency of phase. The phase shifts and phase locks reinforced by NF are associated with long-term synaptic modifications characterized by changes in neurotransmitter release and neuronal functioning. For example, if the symptoms of ADHD are known to be associated with an abnormal wavelength in a particular area of the brain, then NF can change the wavelength to those found in normal individuals. By using NF, clinicians may be able to effectively treat the symptoms of ADHD by selectively enhancing dopamine transmission in the relevant parts of the brain.

In addition to frequency changes and phase shifts, NF can be used to modify synaptic and network functioning by operating on EEG data reflecting brain coherence. Coherence is a measure of coupling between groups of neurons, or more precisely a measure of the number of connections and communications (or frequency of activity) between groups of neurons with a constant phase relationship. Coherence is proportional to phase lock and inversely proportional to phase shift; when coherence is working well in desired networks, several areas of the brain are in phase lock.

IS ALL BRAIN BIOFEEDBACK ALIKE?

NF is a subtype of EEG biofeedback in which EEG data, or signals based on EEG data, are used as the feedback to the patient. Other types of biofeedback include electromyography (EMG) biofeedback and thermal (or temperature) biofeedback. EMG biofeedback measures electrical activity associated with muscle contractions, and it is often used for relaxation training, stress management, peak performance training, and pain management. Thermal biofeedback uses a temperature sensor (electronic, computerized, liquid crystal, or a glass thermometer) to detect temperature changes in the extremities (usually fingertips or toes). Stress and nervous system excitation/arousal causes blood vessels in the extremities to constrict, and the reduced blood flow leads to cooling. Thermal biofeedback is used to train people to quiet the nervous system arousal mechanisms that produce hand or foot cooling, and this is often used for relaxation training, stress management, and pain management.[10]

In contrast, NF specifically uses data based on brain functioning, specifically EEG data. Surface NF, involving 2 to 4 electrodes, started before the advent of qEEG, but modern surface NF often uses qEEG data for assessment before NF treatment is begun. LORETA, which involves many more electrodes and can capture EEG data from deeper structures, is a newer approach that makes integral use of qEEG data. Other forms of NF are discussed by Hurt and colleagues elsewhere in this issue.

QUANTITATIVE ELECTROENCEPHALOGRAPHY AND ITS ROLE IN NEUROFEEDBACK

Quantitative electroencephalography involves computerized data analysis to precisely quantify the electrical potentials or frequency bands from 0 Hz to transform the EEG to a format that elucidates relevant information, such as highlighting specific waveforms components.[11] The mathematical technique used to decompose and transform the mixture of waves in the human EEG is Fourier transform or, given the periodic nature of EEG data, the Fourier series coefficients. Joint time-frequency analysis (JTFA) is another mathematical procedure developed in the late 1980s that gave rise to precise time-frequency measures and quantification of phase locks and phase shifts.[12]

For technically informed readers, some features of qEEG that can be used as the basis for NF include absolute power (the average amount of power uV2 in each frequency band or wavelength and in the total frequency spectrum recorded from each electrode site), relative power (the percentage of total power contributed by each frequency band or wavelength in the spectrum from each electrode site), coherence (the amount of synchronization of electrical events in corresponding brain regions, separately for each frequency band and for the entire frequency spectrum), and symmetry (the ratio of power in each band between a symmetric pair of electrodes).

A qEEG can only be validly interpreted after artifacts are removed from the digital record. If a clinician does not have the training to interpret EEGs, then a skilled and trained professional consultant should be involved. The artifact-free information is then compared with normative databases to identify brain regions whose EEG data

are deviant by 2 or more standard deviations more than or less than the mean. These brain regions are targeted for NF training if the z scores (the number of standard deviations off the mean) are thought to be relevant to the patient's symptoms and if these symptoms are associated with the area of the brain that is typically responsible for the patient's malfunctioning.

The uses of normative databases have been validated in the scientific literature. The normative databases contain the raw EEG records and features derived from analysis of data from individuals aged 6 months to about 90 years. The number of subjects required for reliability at each age point were statistically determined and increased until consistent split-half replications were obtained. The sampling requirement was interesting because each age required different numbers of participants. For example, in the ages from 6 months to 13 years, when brain maturation changes are rapid, higher numbers of subjects were needed. This use of age-regression normative equations and z scores, good test-retest reliability, and lack of ethnic bias allows the use of qEEG that is not only noninvasive but highly sensitive to abnormalities in brain function found in psychiatric populations.[13–15] Replications of normative databases have been extended to cover the range from 1 to 95 years of age for each of the electrode positions in the standardized International 10–20 System, and they have been broadened to include measures of absolute power, relative power, mean frequency, coherence, and symmetry.[14–20]

Distinctive patterns of qEEG abnormalities have been described in diverse psychiatric disorders in adults and youth. These distinctive diagnostic patterns allow differentiation of these disorders from normal and from each other.[8,13] A large body of peer-reviewed published data from independent laboratories reports the sensitivity of neurometrics in varied clinical populations, including head injury,[13,14,21] schizophrenia,[22] depression,[23] marijuana abuse,[24] and ADHD.[25,26]

VALIDATION OF QUANTITATIVE ELECTROENCEPHALOGRAPHY BY USE OF NEUROIMAGING AND OTHER TECHNIQUES

In the early 1990s, efforts were made to identify the three-dimensional location of deep sources in the interior of the brain of the surface (scalp) EEG data, and then to correlate these deep sources with MRI tomographic data.[27] This coregistration of deep EEG sources to MRI slices is known as EEG tomography (tEEG), electrical neuroimaging,[28] or brain electromagnetic tomography.[15] These efforts were expanded to coregister all imaging modalities, including, positron emission tomography (PET), single-photon emission computed tomography (SPECT), and fMRI, and to create a common anatomic atlas. Based on neurosurgical identification of areas pertinent to function, the Talaraich atlas and later the Montreal Neurological Atlas were subsequently used to incorporate EEG data into the Human Brain Mapping Project.[27,29–32] It was used to visualize Brodmann areas as they were defined for the Talairach brain[33] and to compare Brodmann areas across subjects.

tEEG is based on the ability to measure the location of three-dimensional sources of the scalp surface EEG in the interior of the brain and then register the sources to MRI tomographic slices. The advent of tEEG is important because it provides coregistration of 2 imaging modalities that have similar spatial localization characteristics, in which fMRI measures blood flow and the qEEG adds a high temporal resolution of changes in the electrical sources in the brain that are associated with changes in blood flow.[1]

In 1994, Robert Marqui-Pascual[4] devised accurate estimates of the deep (lower) brain sources of the EEG patterns in small regional voxels (approximately 4 mm to

1 cm cubic voxels) coregistered to MRI slices. He transformed these raw EEG signals into three-dimensional images that were then coregistered on the Talairach MRI atlas. This new method was called LORETA. The Web site to obtain additional information on LORETA is http://uzh.ch/keyinst/loreta.htm. LORETA provides better temporal resolution than can be achieved with either PET or fMRI. This high temporal resolution is important for studies using event potentials (ie, time-locked events) and also for investigating brain changes proposed to be associated with psychological states, such as depression.[34] Using LORETA allows a clinician to translate qEEG data into a three-dimensional figure that corresponds with and looks like the images in fMRI that are associated with the same disease state. Furthermore, during NF treatment, as waveforms are adjusted toward normal, the three-dimensional images generated by LORETA also become more consistent with a normal fMRI.

A statistical normalization was later applied to LORETA and was called sLORETA.[35,36] The first normative tEEG databases, using z scores and Gaussian or normal distributions similar to fMRI, are referred to as statistical parametric mapping (SPM) and were introduced by Valdez in 2001[32] and followed by Thatcher and colleagues[37,38] in 2005.

Modern PET, qEEG, magnetoencephalography (MEG), and fMRI studies all agree that electrical activity in the brain is organized by a small set of modules or hubs that represent clusters of neurons with high within-cluster connectivity and sparse long-distance connectivity (**Fig. 4**).[29,39–41]

Quantitative electroencephalography and MEG are the only 2 imaging methods that have sufficient spatial and temporal resolution to measure the millisecond dynamics of

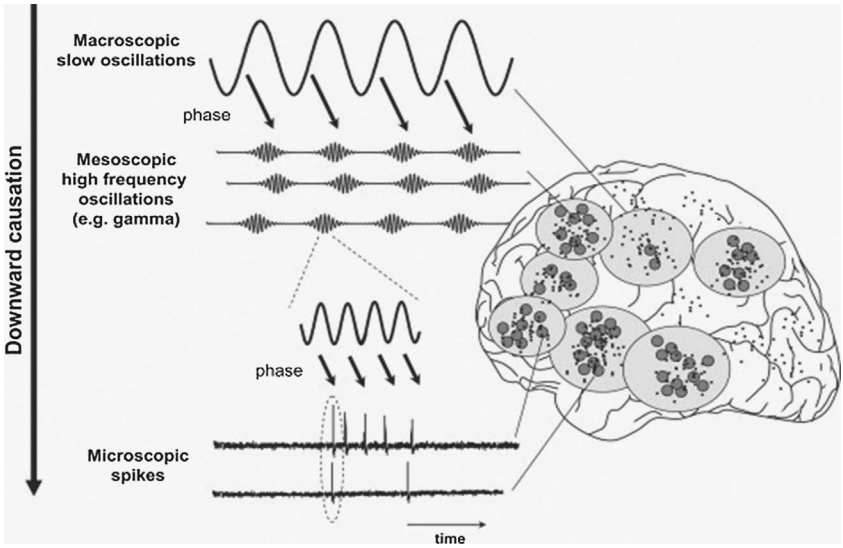

Fig. 4. Quantitative EEG measures short-distance and long-distance coherence, phase delays, phase locking, and phase shifting of different frequencies. The qEEG reflects top-down causality at the macro level (scalp surface EEG) coordinating the meso and micro levels of neural organization. The dysregulation of groups of neurons at the micro and meso levels, which simultaneously mediate specialized functions, can be measured at the macro level using quantitative EEG. (*From* Le Van Quyen M. The brainweb of cross-scale interactions. New Ideas Psychol 2010;29:57–63; with permission.)

hubs and modules. Both use z scores to estimate dysregulation in these brain areas, and these z scores can be linked to a patient's symptoms. However, quantitative electroencephalography can better detect deeper cortical sources and is much less expensive than MEG. For that matter, a qEEG is less expensive than fMRI and PET scans.[29]

COREGISTRATION OF QUANTITATIVE ELECTROENCEPHALOGRAPHY WITH DIFFUSE SPECTRAL IMAGING AND OTHER NEUROIMAGING METHODS

The human cortex has been arranged in 6 basic cluster modules that have been measured using diffuse spectral imaging (DSI) (**Fig. 5**). Coregistration of quantitative electroencephalography to these 6 modules based on DSI can be used to determine phase dynamics and fine temporal coherence within and between these modules.[38]

Hagmann and colleagues[39] developed these 6 modules. They used DSI to trace cortical white matter connections of the human cerebral cortex between 66 cortical regions, using clear anatomic landmarks, based on Brodmann areas.[42] From the 66 cortical regions, 998 subregions of interest (ROIs) were calculated using a connection matrix of inter-regional cortical connectivity. Network spectral analyses of nodes and edges of the 998 ROIs were grouped into 6 anatomic modules.[38] These 6 anatomic modules include, but are not exclusive to, the posterior cingulate, the bilateral precuneus, the bilateral paracentral lobule, the unilateral cuneus,

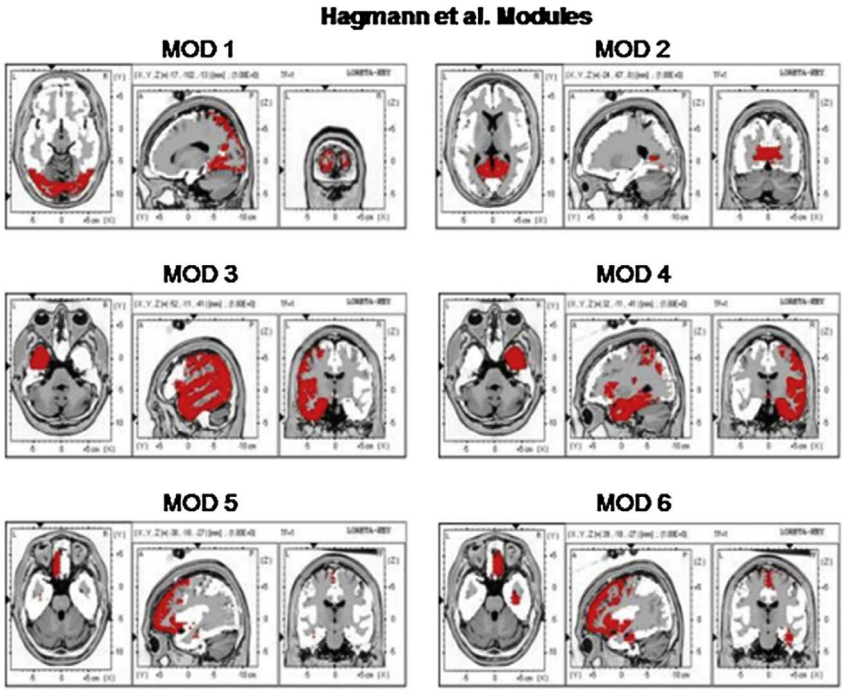

Fig. 5. The locations of the 6 Hagmann modules (MOD1–6). These modules represent the Hagmann DSI-based modules coregistered to quantitative electroencephalography. (*From* Thatcher W, North DM, Biver CJ. Diffusion spectral imaging modules correlate with EEG LORETA neuroimaging modules. Hum Brain Mapp 2011;33:1062–75; with permission.)

the bilateral isthmus of the cingulate gyrus, and the bilateral superior temporal sulcus. A replication of the 6 modules described by Hagmann and colleagues[39,43] using DSI and coregistered to quantitative electroencephalography is shown in Fig. 5.

In summary, z scores (based on qEEGs) allow clinicians to determine the location and extent of dysregulation with respect to a group of age-matched controls. A tEEG normative database of Brodmann areas and hub and modules when linked to a patient's symptoms aids a clinician in making a diagnosis. The goal is to target weak systems and avoid compensatory systems. 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.[1,44–46] The clinical use of qEEG in neuropsychiatry involves 3 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, and so forth) and, (3) real-time z-score surface or LORETA to modify deviant or deregulated brain regions associated with the patient's symptoms and complaints.[1,29]

Z scores derived from a normative qEEG database can be used as an aid to diagnosis, but they cannot be used as a stand-alone approach to diagnosis (just as PET scans can help but not make a diagnosis). However, qEEG normative database z scores, like PET scans or fMRI, can be used to monitor the course of treatment (eg, of transcranial magnetic stimulation, NF training, or psychopharmacologic interventions) or evaluate the comparative efficacy of treatments.

QUANTITATIVE ELECTROENCEPHALOGRAPHY AND NF FOR PSYCHIATRIC CONDITIONS

Role of the EEG Power Spectrum, Neuromodulators, and Psychiatric Disorders

As discussed earlier, the changes in wavelengths produced during phase lock can cause the release of neuromodulators, which in turn can cause synaptic modifications. However, these neuromodulators also have a role in specific systems or circuits in the brain that influence the expression of clinical psychiatric symptoms.

How Complex Homeostatic Systems Regulate the EEG Power Spectrum

Hughes and John[47] provide a more detailed explanation of the brief summary given here. Large neuronal populations in the brainstem, thalamus, and the cortical areas mediate EEG power spectrums.[47] The thalamus is part of the brainstem through which all sensory information (except olfactory information) flows. This sensory-driven information is sent to the cortex, and the cortex relays information back to the thalamus (the thalamic-cortical-thalamic pathway); the thalamus then sends the information to the other parts of the brain.

Changes in the EEG frequency in the thalamus can increase or decrease the flow of information by way of large pacemaker neurons that are distributed throughout the thalamus. Inhibition of information flow in the thalamic-cortical-thalamic pathway occurs when the rhythm increases from a theta (4–8 Hz) and low alpha (8–10 Hz) range to the faster rhythms in the high alpha (11–12 Hz) range and still faster beta (12.5–2.0 Hz) range. These faster activity ranges are thought to be involved in corticocortical and corticothalamic interactions during information processing.[47] When phase shift and phase lock are functioning efficiently (eg, in a patient without ADHD), neuromodulators influence rhythms that are responsible for selectively inhibiting cortical regions during cognitive processing. Deficiencies or excesses of neurotransmitters or modulators can therefore affect the efficiency of the relay of information, and thereby the

homeostasis of the brain (and potentially play a role in psychiatric disorders). Thus, NF, by changing theta waves to high alpha and beta waves, may correct these deficiencies and bring the brain back to a more normative and efficient way of processing.

Comparison with normative databases shows that raw EEG power spectrums (conventional EEG) of alpha, beta, theta, and delta frequency bands for each electrode in the standardized International 10–20 System have links to psychiatric disorders. Normal distributions of power in these frequency bands in normal, healthy individuals also show high test-retest reliability. However, although the conventional EEG can be used in the diagnostic work-up of such things as acute confusional states; first presentation of schizophrenia; major mood or mania; and refractory behavioral problems such as obsessions, panic, or violence, qEEG is particularly well suited to identify subtle changes in the topographic distributions of background activity. qEEG may aid in identifying difficult differential diagnosis, such as: distinguishing between mood disorders and schizophrenia; assessing cognitive, attentional, or developmental disorders; distinguishing between environmentally induced and endogenously induced mediated behavioral disorders; evaluating alcohol and substance abuse; and evaluating postconcussion syndrome.[47] More research using NF in children and adolescents is needed to determine whether NF may be able to change these disease states as well.

How May This Occur in the Case of ADHD?

ADHD provides an example of how changes in the flow between these pathways can influence psychiatric symptoms. The major qEEG frequency abnormalities seen in ADHD involve an excess of theta and, in some cases, low alpha.[48–50] Furthermore, an excess of theta and low alpha waves might result from low dopamine levels that may be caused by a hypofunctioning prefrontal cortex (PFC) and/or the nigrostriatal system, via low dopaminergic firing. These qEEG findings are in agreement with the dopaminergic theory of ADHD expressed by Levy,[51] which conceptualizes ADHD of the polysynaptic dopaminergic circuits between prefrontal and striatal centers of activity. These findings are also compatible with the neurophysiologic model of ADHD proposed by Niedermeyer and Naidu,[52] which emphasizes prefrontal, frontal and striatal, and thalamic interconnections. The Levy[51] model is also supported by MRI and PET imaging studies and by behavioral, pharmacologic, and neuroanatomic studies on the nature of cortical and subcortical disturbances in function that characterizes children with attention and learning problems.[16]

In summary, the dysregulation of the thalamic-cortical-striatal system in ADHD is still not completely understood. However, the high levels of theta and low alpha wavelengths registered on qEEG, which are associated with ADHD in specific regions of the brain, are thought to be changed by NF through operational conditioning, changing the theta waves (inattentive state) to high alpha and beta waves (attentive state). However, the effects of NF training are not limited to ADHD alone.

Psychiatry as Related to Circuitry: Moving from Categorical Disorders to Transdiagnostic Symptoms

As psychiatry prepares to better understand psychiatric disorders from a neurobiological perspective, clinicians are developing a new way of describing psychiatric symptoms. Core connectivity circuits may be disrupted in the brain, which leads to the expression of these symptoms. Buckholtz and Myer-Lindenberg[53] expanded on this idea. Populations of neurons are segregated to perform specialized functions (ie, language processing in the left inferior frontal gyrus). Simple execution of these functions requires that specialized output of each of these segregated neuron populations be integrated or connected. The notion that schizophrenia is a disorder of

dysconnectivity has a long history. Connectivity analysis (using fMRI research) in healthy individuals has uncovered specific networks associated with cognition, affect, motivation, and social function.

These networks have been identified as part of an initiative at the National Institute of Mental Health (NIMH). The Research Domain Criteria (RDoC) at NIMH[54] have organized symptom domains that correspond with neuropsychological junctions based on connectivity between specialized neuronal populations. There are 4 domains: the corticolimbic, the corticocortical, the frontoparietal, and the default mode network (**Fig. 6**). These circuits underpin core executive, affective, motivational, and social domains. Heritable variation in the function of these circuits produces deficits in circuit-specific cognitive domains that manifest as psychiatric symptoms. Using these domains, these symptoms are seen to be common to multiple disorders rather than specific to unique categorical disorders.

Buckholtz and Meyer-Lindenberg[53] summarized these circuits and their function as follows (see **Fig. 6**):

1. The amygdala, medial prefrontal cortex (ventromedial and medial orbital aspects along with the perigenual cingulated cortex), and lateral prefrontal cortex (LPFC)

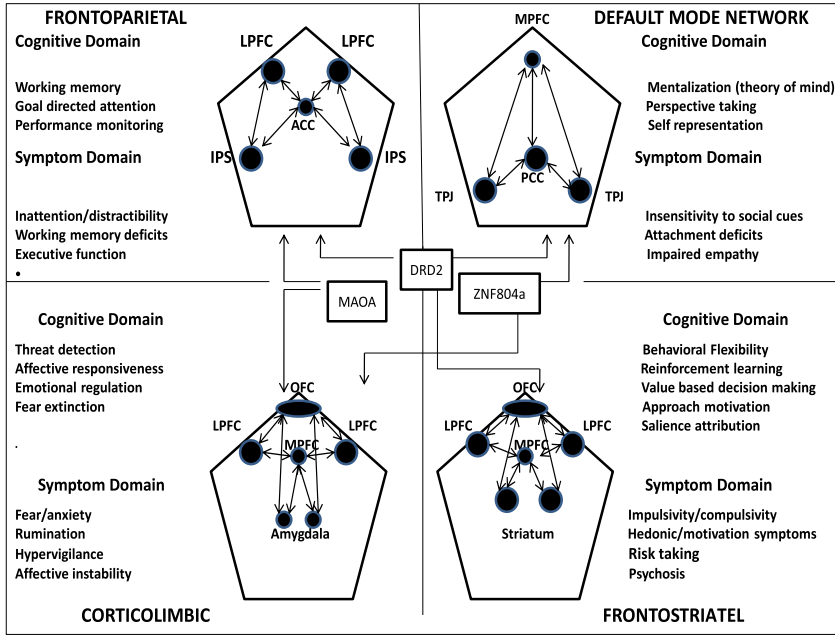

Fig. 6. Genetic variation affects risk for mental disorder by disrupting cognition-specific brain circuits. dACC, dorsal anterior cingulate; DRD2, dopamine D2 receptor (associated with substance abuse, ADHD, schizophrenia, and antisocial personality disorder); LPFC, lateral prefrontal cortex; MAOA, monoamine oxidase A (associated with serotonin and mood disorder and antisocial personality disorder); MPFC, ventromedial prefrontal cortex (ventromedial and medial orbital cortex, and perigenual cingulate cortex); OFC, orbital frontal cortex; PCC, posterior cingulate cortex; TPJ, temporal parietal junction; ZNF804a, a series of genome-wide association with schizotypal and decreased social cognition. (*Adapted from* Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the human connection: toward a transdiagnostic model of risk for mental illness. Neuron 2012;74(6):990–1004. http://dx.doi.org/10.1016/j.neuron.2012:06.002; with permission.)

make up the corticolimbic circuit and is associated with affective symptoms, such as anger, anxiety, rumination, and hypervigilance. This circuitry in healthy individuals is engaged during negative emotional arousal and requires regulation of these negative emotions. The dysregulation of these affective symptoms is associated with mood, anxiety, schizophrenia, conduct, substance abuse, and personality disorders.

2. The default mode network is thought to be more commonly engaged when people think about the thoughts, beliefs, emotions, and intentions of others. It involves the temporoparietal junction, posterior cingulate, and ventromedial prefrontal cortex (vmPFC). Dysfunction of this circuitry is associated with poor social cognition and is associated with psychosis, personality disorders, mood disorders, and ADHD.
3. The frontostriatal network is made up of the vmPFC, LPFC, orbital frontal cortex, and the striatum. Dysconnectivity can lead to impairment of motivational and hedonic responses, cognitive flexibility, value-based learning, and decision making. Such impairments cut across many mental disorders, including anhedonia in schizophrenia and mood disorders; impulsivity in ADHD, substance abuse, schizophrenia, and personality disorders; and compulsivity in obsessive-compulsive disorder and substance abuse.
4. In addition, the frontoparietal network involves the dorsal LPFC, dorsal cingulate, and parietal cortex, which are critical to executive function. Executive function involves tasks that use working memory, goal-directed attention, conflict detection, and performance monitoring. Deficits in executive function span several disorders, including schizophrenia, ADHD, major depression, and substance abuse.

These pathways are influenced by multiple small effect risk alleles, like the DRD2 allele, which can affect different circuitry in these 4 networks as shown in **Fig. 6**. Therefore, a genetic variant of DRD2 affecting, for instance, the frontoparietal network can cause a deficit in executive function. This deficit increases susceptibility to multiple disorders because the resulting deficits are not disorder specific. For instance, the dopamine DRD2 receptor shows significant effects associated with schizophrenia, ADHD, substance abuse, and antisocial behavior. The reader is referred to the article by Buckholtz and Meyer-Lindenberg[53] for further explanation of how genetic variations of particular genes in **Fig. 6**, as well as other variants of genes, can disrupt circuitry in these networks.

Hence, certain genes can influence connectivity in networks linked to symptom domains, which implies that connectivity changes seen in mental illness reflect the cause of the illness and are not consequences of the illness.

These pathways can also be influenced by environmental risk factors, as well as epigenetics. Nonetheless, this hypothesis could lead to a new way to organize psychiatric disorders. Instead of discrete categorical disorders, the influence of genes and environment can disrupt system-level circuits for several dimensions of cognition, producing instead transdiagnostic symptoms or symptoms that overlap several disorders, which may why comorbidity among diagnoses is so frequently observed. Correcting dysfunction in circuits in these 4 networks can explain how interventions using transmagnetic stimulation, qEEG, and (for deeper structures) LORETA NF may work to relieve symptoms associated with broad domains of mental disorder. For instance, LORETA can target every brain area listed in all 4 networks with the exception of the striatum.

Research that gives credibility to targeting these circuits has already begun. For instance, the Longitudinal Assessment of Mania Study[55] was designed to identify

distinct developmental trajectories of behavioral and emotional dysregulation in youth with bipolar disorder and high dysregulation (HD) and youth without bipolar who had low dysregulation (LD). Youth with LD had greater activity in the dorsolateral prefrontal cortex and greater functional connectivity among the amygdala, dorsolateral and ventrolateral prefrontal cortex, and anterior cingulate. Therefore, a possible use of LORETA NF in youth with HD with bipolar disorder is to target the dorsolateral prefrontal cortex and, perhaps, improve coherence in the less functional circuits (ventral LPFC to amygdala).

Targeting specific networks in youths who are already ill is not the only way LORETA NF may be used. Research using MRI is now beginning to identify dysfunctional areas of the brain that may predict the risk of developing a particular disease. For instance, in a study by Hajek,[56] youths who had a risk of developing bipolar disorder (identified by having 1 or 2 parents with a diagnosis of bipolar disorder) were compared with unaffected youths who did not have one or more parents with a diagnosis for bipolar disorder. Of those who were unaffected (and who had a risk of developing bipolar disorder), 8 of 21 had an abnormally large right inferior frontal gyrus (rIFG) compared with controls. The individuals were followed 4.5 years after the scanning. Of the 8 who had a larger rIFG, 4 converted to a psychiatric disease, 3 developed a major depression, 1 an anxiety disorder, and 1 a personality disorder (all requiring medication). Of the unaffected with a risk for developing a bipolar disorder who had rIFGs that were comparable with controls, only 2 converted to an axis I disorder (1 who developed an adjustment disorder following a motor vehicle accident and 1 who had a milder depressive disorder). Therefore, it can be postulated from this study that the development of more severe forms of psychiatric disorders can be better associated with certain abnormal circuits before the diseases develop. Also, the identified circuits at risk can develop into a variety of disorders, congruent with the idea behind transdiagnostic symptoms. Therefore, future studies of these networks may help to predict who may be at risk and interventions to correct these abnormalities may help prevent the development of psychiatric disorders. More research is needed.

In summary, targeting networks in individuals with known symptoms associated with one or several psychiatric diseases and cross-correlating the research with qEEG may provide an avenue to target these areas using LORETA NF. It is speculated that, by using LORETA NF, the symptoms of these diseases may be relieved or decreased in severity. The new trend to consider psychiatric illnesses as transdiagnostic entities may be an avenue for many new interventions, not limited to LORETA NF, such as repetitive Transcranial Magnetic Stimulation (rTMS) or cognitive training programs.

NEUROFEEDBACK TREATMENT IN CHILDREN AND ADOLESCENTS

Two types of NF have been described in case reports in adults and youth. Z-score surface NF training, using 2 to 4 or more scalp electrodes, uses continuous real-time computerized calculations comparing the way that the patient's brain is functioning with a normative database on different variables (eg, power, asymmetries, phase-lag, and coherence). LORETA uses a different kind of qEEG NF analysis that provides an estimation of the location of the underlying brain generators (eg, the anterior cingulate, insula, fusiform gyrus) and networks of the patient's EEG activity within a frequency band. There is no current published research on the use of LORETA NF in youths. It requires more labor-intensive preparation, because an entire electrode cap with 19 electrodes must be applied in every session, but it can shorten the length of treatment. fMRI NF's advantage is that it can examine functioning at deep

subcortical areas of the brain. However, the practical disadvantage of fMRI NF is that it is very expensive, with equipment that costs $1 million or more and is not portable.

Unless specifically stated, the following research has been done in adults.

Neurofeedback Treatment of Depression

qEEG research in adults with depression has focused on the structures involved in processing emotions, which are found in the left and right hemispheres, including the amygdala, orbitofrontal cortex, basal ganglia, and the hippocampus. Most of the research has been done in adults and involves surface NF. The left hemisphere is involved in processing positive emotions and the right is involved in processing negative emotions.[57] Depression is associated with hypometabolism in the cingulate and occasionally in the orbitofrontal cortex, insula, anterior temporal cortices, amygdala, basal ganglia, and thalamus.

The details of the associations between brain wavelength rhythms and behavioral states are complex and do not need to be understood in order to understand NF; however, some of these details are mentioned here. Delta (0–4 Hz) and theta (4–8 Hz) rhythms are associated with hypoactive states, and alpha (8–12 Hz) is associated with activated states. However, higher alpha in the right frontal cortex and lower alpha in the left frontal cortex are associated with positive mood. Beta rhythms (12–30 Hz) are usually associated with activated states, but can be subdivided: beta 1 (12–15 Hz) on the right is associated with a calm and observant state, beta 2 (15–18 Hz) on the left is associated with a fully attentive and less depressed state, and beta 3 (19–30 Hz) on the left and right is associated with the anxious and irritable state. These known associations between behavioral states and wavelengths can provide targets for NF treatment of depression.[58–62]

Quantitative EEG has been used to distinguish between unipolar depression and bipolar disorder in adults.[59] Increases in alpha power in the left hemisphere and decreases in left parietal-occipital beta and hypercoherence in the right anterior region were found in adults with unipolar depression, whereas decreased alpha on the left and increased left parietal-occipital beta were found in adults with bipolar disorder.[16,59–61]

The hypercoherence in depression can be related to networks being oversaturated in order to attempt to overcompensate for the inefficiency in the networks and therefore being unable to process emotional information appropriately. Higher theta and alpha coherence is found primarily in longer-distance connections between the frontopolar prefrontal cortex (Brodmann area 10, **Fig. 2**) and the temporal or parieto-occipital regions. Higher beta coherence is primarily found in connections within and between electrodes overlying the dorsolateral prefrontal cortex or the temporal regions.[60,61]

Adults with depression show alpha asymmetry on qEEG, and this alpha asymmetry has been used as a primary target in the treatment of depression in adults and also as a target in some reports in youth: in alpha asymmetry, the frontal lobes show higher alpha on the left and lower alpha on the right; in contrast, posterior (parietal-temporal) regions show lower alpha on the left and higher alpha on the right.[59,60] Individuals showing the frontal alpha asymmetry mentioned earlier typically are prone to experiencing negative withdrawal states. Those who experience increased alpha activity on the right relative to the left tend to experience more positive affective states.[61]

In female adolescents with depression, one study showed that the right posterior lobe had findings typically found in adult depression.[62] However, the same study showed that, in those female adolescents with depression and anxiety disorders, the posterior asymmetry was reduced. These findings highlight the importance of

looking for comorbid conditions that may offset the effects of depression and account for inconsistencies found in posterior asymmetry in adolescents with depression. In the same study, female adolescents with depression alone did not show the same anterior alpha asymmetry found in adults with depression. These findings may be caused by adolescent frontal regions developing later in life and the findings therefore not correlating with findings is seen in adults with depression. These facts may indicate that, in female adolescents, posterior alpha asymmetry may be a more predictive way of detecting depression than anterior asymmetry. This study highlights the importance of using qEEG findings that match the symptoms of individual patients based on their developmental age, especially when attempting to use alpha asymmetry as a target of NF treatment in adolescents.

qEEG may also be used to estimate the risk for developing a mood disorder.[63] Baseline electroencephalographic activity was recorded from adolescents from 12 to 14 years old whose mothers had a history of depression (high-risk group) and whose mothers were lifetime free of axis I mental disorder (low-risk group). High-risk adolescents showed the hypothesized pattern of relative left frontal hypoactivity on alpha-band measures. These findings may indicate that individuals with left frontal hypoactivation should be followed closely for the development of depression.

Another potentially useful qEEG parameter is cordance, which combines absolute power (the amount of power in a frequency band or wavelength at a given electrode) and relative power (the percentage of power contained in a frequency band relative to the total spectrum) normalized across electrode sites and frequency bands. Cordance has a stronger association with regional cerebral blood flow than other EEG measures. Hunter and colleagues[64] showed that cordance can be used to predict antidepressant treatment response or remission with 70% or greater accuracy. Changes in prefrontal theta-band cordance within the first week of medication treatment predicted 8-week treatment outcome in 27 adult subjects. Early change in theta-band cordance in those treated with either serotonin selective reuptake inhibitors or mixed serotonin-norepinephrine agents predicted a good response to medication.[64] Similar findings have been reported for the treatment of bipolar depression in adults.[65] There are no qEEG studies predicting antidepressant treatment effectiveness in children or adolescents.

Although many studies in adults have effectively treated depression in adults by targeting alpha asymmetry, only 1 published study has been conducted using the alpha asymmetry model in a depressed adolescent. The adolescent had nonbipolar major depression and had not responded to psychotherapy. Surface EEG biofeedback was used until the alpha asymmetry changes occurred, which appeared normal for a nondepressed individual. This treatment required 67 sessions and the patient did not require medication.[66] More research is needed.

This is the first and, at present, only reported case of NF treatment of depression in an adolescent, and there are no reported cases in children. There are no case reports in youth regarding the qEEG prediction of response to treatment with psychiatric medications. However, based on findings on the treatment of adults with depression and of adults with bipolar disorder, this area needs further development in youth.

Neurofeedback Treatment of Anxiety Disorders

Available qEEG studies suggest a high incidence of abnormalities in adults with anxiety, panic, and obsessive-compulsive disorder (OCD).[16,67–70]

Two subtypes of (OCD) in adults have been described. One subgroup had excess alpha throughout most of the brain along with excess beta in the frontal, central,

and midtemporal regions. The other group had a theta excess mostly in the frontal areas and at posterior temporal electrodes.[71]

Youth (aged 10–14 years) with anxiety who responded to 19 channel surface NF based on EEG characteristics had significant increases in the ratio of amplitudes of alpha and theta rhythms, sensorimotor and theta rhythms, as well as the modal frequency of alpha rhythm.[72] The study was small (n = 7 in experimental group and n = 10 in control group). The groups were divided into those with high levels of anxiety versus low levels of anxiety based on the Prikhojan questionnaire, the Spielberger-Khanin test, and the House-Tree-Person projective test. Between 10 and 12 NF sessions were performed. Feedback was used with acoustic sounds when eyes were closed and with visual stimuli when eyes were opened. Different feedback protocols were used. When patients tried to control the loudness of white noise (with eyes closed) or the intensity of colors in pictures (with eyes opened), the NF sessions were more effective. In the experimental group, estimates of the level of anxiety decreased in all scales of the psychological tests but were not significant. Significant decreases in the experimental group were observed in the scales of feelings of inferiority and frustration. In both groups, before and after reports by parents indicated decreases in emotional instability. Also, in the control group, significant decreases on the scale of feelings of inferiority were observed. The study is small and more research is needed.

In OCD, adults whose qEEG showed increased alpha relative power responded positively to serotonergic antidepressants (82% response rate), whereas 80% of adults with increased theta relative power (especially in the frontal area) failed to improve. Responders to placebo showed increased prefrontal cordance and medication responders showed decreased cordance within 48 hours of treatment.[73,74] No studies of response to antidepressant medication using qEEG have been done on children and adolescents with OCD or depression.

In summary, qEEGs may help to predict response to medication treatment in depression and OCD, but none of these studies have been done in children and adolescents. One study using NF in adolescents with anxiety has been published with fair to good results. Quantitative EEG in adolescents with depression and anxiety may indicate that those with anxiety may be protective against developing more severe symptoms of depression.

Neurofeedback Treatment of Substance Abuse

The effects of drug abuse on a qEEG vary depending on the substance and the duration, acute versus chronic, use or abuse. There seems to be a consensus that chronic cannabis and cocaine use are associated with an increase in alpha brainwave activity[75] and that chronic alcohol abuse is associated with an increase in beta brainwave activity.[76] In addition, several research studies show that, in both alcoholics and cocaine addicts, the best predictor of relapse is the excessive amount of fast beta brainwave activity.[75,76] EEG investigations of the children of alcoholics have documented that they also have an excess of fast beta activity, and this predicts a risk of developing alcohol abuse in adulthood. Alcoholics and their children frequently have lower levels of alpha and theta brainwaves, which similarly predict a risk for developing alcohol abuse. Following the intake of alcohol, alcoholics and/or their children feel more relaxed and show an increase in the levels of alpha and theta brainwaves, suggesting self-medication of symptoms.[10,75,76]

NF has been used to train adult alcoholics to promote stress reduction and achieve profoundly relaxed states by increasing alpha and theta brainwaves and decreasing fast beta brainwaves[77] when the patients' eyes were closed. Increasing theta

brainwaves with eyes closed was felt to produce a relaxed state, which is not to be confused with theta brainwaves that are produced in the eyes-opened state (indicating the inattention state) as is seen in ADHD. This same study showed promising potential as an adjunct to alcoholism treatment. In a 4-year follow-up in which only 20% of the traditionally treated group of alcoholics remained sober, 80% of the subjects who had received NF training showed sustained reductions in alcohol use. Furthermore, these subjects showed improvement in psychological adjustment on 13 scales of the Millon Clinical Multiaxial Inventory, compared with the traditionally treated alcoholics who improved on only 2 scales and became worse on 1 scale.[10,77] This single study suggests that NF may have some potential to improve treatment effectiveness in adults with chronic alcohol use. There have been no studies using alpha/theta training in adolescents with a history of substance abuse, but, speculatively, NF might in the future have a role in preventing or treating alcohol abuse in youth.

Neurofeedback Treatment of Substance Use Disorders in the Context of Comorbid ADHD

Although there have not been any studies using NF for the treatment of substance abuse disorders in adolescents, qEEG research has discovered a difference in individuals who started using cocaine chronically before age 20 years as opposed to those who became chronic users after age 20 years.[78] For example, there was significantly more theta excess in adolescents who began abusing cocaine before age 20 years compared with those whose abuse began after age 20 years. A significantly larger proportion of early cocaine users had ADHD. It has been known for some time that many youth with ADHD have increased theta.[79,80] Therefore, ADHD may be a risk factor for the development of cocaine abuse during adolescents and using NF to suppress theta in these youth may decrease the risk of developing chronic cocaine abuse.

This example shows how treating ADHD by suppressing theta may be helpful in reducing the risk of developing cocaine abuse in youth. However, some protocols used to treat ADHD and a comorbid substance abuse may increase the risk of using specific substances of abuse. To understand why the risk may be increased, a brief summary of surface NF protocols is needed. Lubar and colleagues[79,80] were the first to introduce these protocols. In individuals with combined type ADHD, either increasing sensory motor rhythms (SMR) and suppressing theta (at electrodes C3 and C4 and linked earlobes) or increasing SMR and suppressing beta 2 (C4 and linked earlobes followed by the first protocol) has led to positive results. SMR involves strengthening sensory motor inhibition in the cortex. For the inattentive type of ADHD, Clarke and colleagues[81] described a protocol involving theta suppression and beta 1 enhancement, which was done at electrode Cz with linked ears, at FCz-PCz with single ear reference or at Cz-Pz with single ear reference.[82]

If an adolescent has alcohol abuse (decreased theta and alpha and increased beta) and ADHD combined type, increasing theta (although helpful in some alcoholics) may cause the ADHD to worsen. In this case, if the adolescent has increased beta at baseline, the first half of the Lubar protocol (suppressing theta and increasing SMR) may be of more benefit because decreasing beta may help reduce alcohol abuse and the symptoms of ADHD. Suppressing theta and increasing SMR may also be advantageous in ADHD youth who are abusing cocaine because both of these conditions increase theta.

It has also been shown that individuals who abuse both cocaine and marijuana have excess alpha activity.[75,83] In this case, any protocol in youth with comorbid ADHD and marijuana and cocaine abuse that increases alpha activity may not be preferred. Instead, decreasing theta, which reduces ADHD symptoms and decreases the abuse of cocaine, may be preferred.

Because increases in beta activity seem to predict the risk of developing alcohol abuse in children of alcoholics[75,76] and can increase the risk of relapse in cocaine and alcohol abusers, any protocol used in youth engaged in alcohol and cocaine abuse with comorbid ADHD that increases beta activity (as suggested in Clarke and colleagues[81] NF protocol) should be used with caution. The previously mentioned limitations to surface NF in youth with comorbid substance abuse and ADHD are speculative and baseline and subsequent qEEGs performed during NF along with correlation to clinical symptoms and outcomes should guide the clinician in treatment protocols used in youth with comorbid ADHD and substance abuse. These suggested protocols are summarized in **Table 1**.

Table 1
Proposed surface NF treatment of comorbid ADHD and substance abuse using qEEG findings

Findings in Chosen Substance of Abuse	ADHD Protocol	ADD Protocol
Alcoholics: decreased theta and alpha and increased beta	Decrease beta 2 and increase SMR and increase alpha	Decrease beta 1 and increase alpha
Cocaine users in whom increased theta is found and the predictor of cocaine relapse may be caused by increased beta and increased theta in those who started using before age 20 y	Decrease beta 2, increase SMR and decrease theta, or increase SMR	Decrease beta 1 and decrease theta
Cocaine and marijuana users with increased alpha	Avoid increasing alpha and decrease beta 2	Avoid increasing alpha and decrease beta 1
Children of alcoholics with increased beta and decreased theta and alpha	Decrease beta 2 and increase SMR	Decrease beta 1 and increase SMR

Abbreviation: ADD, attention deficit disorder.

Surface Neurofeedback Treatment of Posttraumatic Stress Disorder

The first study of posttraumatic stress disorder (PTSD) in adults examined surface NF as an adjunct to conventional treatment of Vietnam combat veterans in a Veterans Administration hospital.[84] To target PTSD symptoms, a sequence of thirty 30-minute sessions of alpha-theta NF training was provided to 15 veterans, and a contrast group of 14 veterans received treatment as usual. No attempt was made to provide a sham or alternative adjunctive treatment of the contrast group. At the end of the study, among the patients receiving traditional treatment and medication (n = 14), only 1 patient decreased medication needs, 2 reported no change, and 10 required an increase in psychiatric medications. On the Minnesota Multiphasic Personality Inventory, patients receiving NF training improved significantly on all 10 clinical scales, whereas the traditionally treated patients showed no significant improvements on any of the scales. At follow-up 30 months after treatment, all 14 patients in traditional treatment had relapsed and were rehospitalized, whereas only 3 of 15 patients having NF treatment had relapsed. All 14 of the patients having NF treatment receiving medication were able to be managed on less psychiatric medication at follow-up.

The only surface NF study of PTSD symptoms in youth examined 26 adopted children, aged 6 to 15 years, with histories of abuse and/or neglect.[85] Most of the subjects showed symptoms of reactive attachment disorder and were taking a variety of psychiatric medications before and during the NF trial. All of the children had increased theta waves in at least one frontal site, and most had decreased delta waves in frontal regions. NF training consisted of thirty 30-minute sessions involving auditory and

visual feedback, with feedback initially contingent on reduction of delta/theta activity. Before-and-after Child Behavior Checklists were completed by the adoptive parents. Before-and-after Test of Variable Assessment (TOVA) evaluation was also done. All but 3 subjects completed a posttreatment TOVA evaluation. Total syndrome scale scores decreased an average of 23.05 points (standard deviation = 21.44) with a 95% CI of 12.73 to 33.39, and were significant at $t(18) = 4.69$, $P<.001$. Six of the 8 CBCL syndrome scale scores significantly improved (medium effect sizes [ESs] $d>0.55$), although only nonsignificant improvements were observed in somatic complaints and withdrawn scale scores. The TOVA scores showed significant improvements on omission errors, commission errors, and total variability ($d>0.60$). Limitations of the study include the small and nonrandomized sample, lack of control group, and failure to control for potential effects of medications and other concurrent therapies. This single study provides encouragement for further NF studies in abused or neglected children with PTSD.

NEUROFEEDBACK TREATMENT OF INTRAUTERINE BRAIN DAMAGE, MILD HEAD INJURY, CONCUSSION, AND TBI

Numerous qEEG studies of severe (Glasgow Coma Scale 4–8) and moderate head injury (Glasgow Coma Scale 9–12) on patients aged 14 years and older have shown that such injuries produce persistent qEEG abnormalities. These qEEG abnormalities may include increased theta and decreased alpha power, decreased coherence, and increased asymmetry.[16,86]

Regarding treatment of TBI, a recent research review by Thornton and Carmody[87] suggests that qEEG-guided NF is superior to both neurocognitive rehabilitation strategies and medication treatment in the rehabilitation of TBI in adults, especially for auditory memory. There have been no studies of this type published with regard to children and adolescents.

Only 1 study in children was conducted that examined EEG NF versus physical/occupational therapy in 12 children (aged 7 months to 14 years) who had had a stroke before birth. The mothers had no history of drug use, hypertension, or viral infection. All children were evaluated for baseline range of motion, and the older children provided self-descriptions of mood and completed a short-term memory test (how these tests were administered was not available for this publication). Six children were selected randomly for EEG NF, for 30 minutes a week, whereas 6 children received physical or occupational therapy once a week. The EEG NF targeted brain regions T4, C4, T3, and C3 to inhibit theta waves (4–7 Hz) and reduce their voltage, and to produce beta waves (15–18 Hz) for 0.5 seconds at 1 μV. After 3 months of treatment, children receiving EEG NF had improved range of motion, improvement in concentration (or, in young children, eye tracking), improved short-term memory, and fewer mood swings. The control group showed only improved range of motion, but no improvement in cognitive or emotional status.[88] This lone report suggests that NF might be useful for treating a variety of effects of intrauterine stroke, although further studies are needed.

With regard to EEG indicators of postconcussion syndrome in adults, there is also a broad consensus that common EEG indicators include increased focal or diffuse theta, decreased alpha, decreased coherence, and increased asymmetry, similar to the changes observed in TBIs in general. Multiple reports suggest that these qEEG variables also successfully separate patients with a history of mild to moderate head injury, even years after apparent clinical recovery, from normal individuals.[21] Compared with postconcussion syndrome, TBI seems to show increases in slow

frequencies (delta, theta, slow alpha 8–10 Hz), and decreases in fast frequency alpha (10.5–13.5 Hz), and increases in beta levels.[89]

A study of patients (aged 18–65 years) with TBI (and who had a Glasgow Coma Scale of 9 or higher) examined qEEG 1 to 3 days after the TBI. Subjects were screened to determine whether they were carriers of the apolipoprotein E (ApoE), whose E4 allele is thought to decrease blood cerebral blood flow. ApoE4 carriers had fewer alpha and beta waves and more delta and theta waves compared with noncarriers and controls. This finding suggests that ApoE carriers may show more abnormal qEEG effects in the early stages of TBI, which supports the Buckholtz and Meyer-Lindenberg[53] theories that different alleles of certain genes are more likely to be associated with connectivity dysfunction.[90] These findings may open opportunities for research to determine whether using NF to target these abnormalities (in ApoE carriers after TBI) would be a complementary treatment of those who regain consciousness.

Many cognitive functions are affected by TBI, and studies indicate that some of these same cognitive functions are impaired in ADHD.[91] MRI and qEEG studies suggest that the same brain regions are dysfunctional in both conditions.[92] Gerring and colleagues[93] found that children who had thalamic injuries had a 3.6 times higher risk for developing ADHD. The same logistic regression models used in Gerring and colleagues'[93] analysis also showed a 3.15 times higher risk for developing ADHD if injuries occurred in the basal ganglia. Using variable-resolution electromagnetic tomography qEEG data of children with ADHD, the same study found that excess theta seemed to be generated from the septal-hippocampal pathway of the basal ganglia, whereas excess alpha derived from the thalamus.[94] These studies emphasized the possible correlation between TBI-acquired ADHD and the underlying mechanisms found in ADHD. It may be that some of the NF protocols used in the treatment of ADHD are similar to protocols used to improve cognitive function in children with TBI.

Although Down syndrome is not classified as a brain injury disorder, some of the cognitive functions found in TBI and ADHD are also found in these children. In a study of 8 medication-free children (aged 6–14 years) with Down syndrome, qEEGs generally showed excess delta and theta EEG patterns. All children displayed limited vocabulary (5–10 words), poor attention and concentration, weak memory, impulsivity, and behavior problems. All 7 children who completed 60 sessions of surface NF training showed significant ($P<.02$) improvement in all areas, as evaluated by questionnaire and parent interviewing, and beneficial changes were found in qEEGs.[95]

The overlap of qEEG findings in ADHD, TBI, and mental retardation was further explored in 23 subjects (7–16 years old) with mild to moderate mental retardation. Most subjects showed increased theta, increased alpha, and coherence abnormalities, and a few showed increased delta over the cortex. Of 23 patients who received NF training, 22 showed clinical improvement according to the Developmental Behavior Checklist-Parent scores, and patients showed significant improvement on the Weschler Intelligence Scale for Children-Revised (WISC-R) and the TOVA. The WISCV-R was repeated at 6 months' follow-up after the completion of NF treatment. The mean verbal intelligence quotient (IQ) score was 49.6 before treatment and 53.05 after treatment ($P<.0295$). Performance IQ scores were 55.45 before treatment and 63.20 after treatment ($P<.0007$). Full scale mean was 49.0 before treatment and 54.6 after treatment ($P<.0003$). The mean and standard deviation of the number of sessions were 134.78 and 7.874 respectively. The range of the sessions was from 80 to 200. There were significant TOVA improvements and significant decreases in impulsivity, temper tantrums, problems with sleep, telling lies, attention, and distractibility. All improvements in behavior and attention that had been observed during the

treatment remained stable in the 2 years of follow-up according to parents' reports.[96] This study indicates that the use of qEEG may have some indication for increasing IQ and targeting disruptive behaviors.

These studies suggest that there are similarities in some clinical features and qEEG findings in TBI, postconcussive symptoms, ADHD, Down syndrome, and other forms of mental retardation. There is some promising evidence that NF may be helpful in treating these various conditions using generally similar NF protocols. However, the research is limited, the qEEG for each individual needs to be carefully evaluated for potential NF targets, and treatment needs to be matched with the symptoms in order to develop appropriate qEEG protocols.[96]

Looking to the future, the United States Army is implementing LORETA z-score biofeedback as a clinical treatment of active duty military personnel involved in an extensive rehabilitation program for treating PTSD/TBI at the Fort Campbell Warrior Resiliency and Recovery Center, headed by Dr Marc Zola in collaboration with Drs Joel Lubar and Robert Thatcher. The areas targeted include symptoms associated with concussion, posttraumatic stress, depression, chronic pain, headache and substance abuse disorder. A qEEG assessment is used to rank order the most deviant nodes and hubs of the networks most commonly associated with these symptoms and periodic follow-up qEEG analyses are used to assess the progress of treatment. The US Army program is just getting started and is scheduled to continue for the next 5 years, during which extensive pretreatment versus posttreatment assessments and statistical analyses will be conducted. Most of the patients will be between 18 and 25 years of age, and preliminary findings suggest promising results in as little as 12 sessions.

Neurofeedback in Reducing Performance Anxiety

Alpha/theta NF training was used in 2 studies involving musical performance. The effects of alpha/theta training were the same in both studies. In both studies, NF training occurred over 10 sessions and involved alpha/theta training with eyes closed and auditory feedback intended to increase theta more than alpha waves. In a replication study, students were randomized to one of 6 interventions, including 3 different NF techniques and 3 other techniques: alpha/theta NF training, beta training (intended to reduce fast waves at the beta frequencies), or SMR NF (which involved strengthening sensorimotor inhibition in the cortex and inhibiting alpha frequencies), and mental skills performance, aerobic fitness, and the Alexander technique (postural retraining and somatic stress reduction). The results provided confirmation of the beneficial effects of alpha/theta NF, which was the only intervention that improved music performance (overall quality, musical understanding, stylistic quality, and interpretive imagination). All 6 interventions were successful in reducing preperformance anxiety, so the performance enhancement by alpha-theta training could not be attributed to anxiety reduction alone.[97]

Alpha/theta training has been used with university dancers who compete in ballroom dancing. Twenty-four male/female pairs were randomly assigned to either alpha/theta training, heart rate coherence (HRC) training (involving heart rate variability training), or a nonintervention control group before and after performance was judged by 2 dance experts who were blinded to which groups got the intervention. Both the HRC and alpha/theta training groups improved on the overall rating of execution more than the control group. Subscale ratings revealed that HRC improved technique, but alpha/theta training improved timing.

As noted by the investigators, theta oscillations are speculated to affect meditative concentration, and reduce anxiety and sympathetic autonomic activation. Theta

oscillations may also affect virtual spatial navigation, focused and sustained attention, and working and recognition memory.

In summary, it is thought that alpha-theta training targets optimal performance and enhancement of technical, communication, and artistic domains of performance in the arts.

Does Neurofeedback Technique Have to be Modified for Developmental Age?

Recent research[98,99] has shown that the major brain networks develop early in life and are essentially the same in adolescents and adults. One study[99] used measures of network topology to investigate the development of functional hubs in 99 normal subjects, aged 10 to 20 years. Hub architecture was evident in late childhood (age 10 years) and was stable from adolescence to early adulthood, but the strength of connectivity changed with development. From childhood to adolescence, the strength of connections increased between frontal hubs and frontal, parietal, temporal, and cerebellar spoke regions, whereas connections decreased in the posterior part of the brain. It was hypothesized that this pattern reflects the gradual maturation of the ability of the frontal lobe to coordinate distributed cortical functions for goal-directed behaviors. The subsequent developmental increases in hub-spoke connectivity between adolescence and adulthood were fewer and tended to be more posterior, involving connections between subcortical hubs (the putamen and cerebellum) and frontal, occipital, and temporal spoke regions. These findings suggest that developmentally stable functional hub architecture provides the foundation of information flow in the brain, whereas connections between hubs and spokes continue to develop, presumably supporting the maturation of cognitive functions. Based on these findings, it is expected that NF would work in a manner that is identical from age 10 years to adulthood.

Controversies

Although there is extensive scientific evidence to validate the use of qEEG, there has been limited acceptance in the United States. There are several reasons for this. First, psychiatrists do not often follow the EEG literature and are unaware of developments in the field. Second, because of the evolving understanding about technology and appropriate protocols, some falsely negative findings have been reported[16,100,101] and adopted by some expert panels[102] but rejected by others.[103] More recent studies provide substantial additional support for the validity and clinical use of qEEG in several areas of psychiatry.[16,104] The American Academy of Pediatrics has recently listed EEG biofeedback as a level 1, best-support (a valid first-line) intervention for ADHD (www.aap.org/en-us/advocacy.../aap.../CRPsychosocialInterventions.pdf).

Questions continue to be raised concerning the available normative databases, but current methodological adjustments and mathematical techniques allow cross-validation among different normative databases that have high intradatabase similarity.[12] Confidence in normative databases is based on widespread independent replications,[16] test-retest reliability confirmed in short-term and long-term follow-up large samples,[105,106] and small gender differences.

Some critics have argued that NF should not be an accepted intervention until double-blind placebo-controlled studies using sham controls have been conducted. There has been considerable debate and controversy in the NF literature about the pitfalls of attempted sham-NF controls, what technical innovations can be introduced to provide better controls, the validity of proceeding with randomized controls in the absence of an acceptable sham procedure, and the use of altered qEEG patterns in an individual as corroboration of the validity of the intervention (eg, as is often used with other interventions).

This issue of whether a sham is as effective, more effective, or less effective than contingent reinforcement may involve a serious misconception. Both experimental and sham groups are operating under the contingencies of classical and operant conditioning. Imagine a child with ADHD who already spends a lot of time playing computer games and is now placed in front of a display that purportedly is going to help but he is in the sham group. The child becomes engaged by the display, tries to make it occur more frequently, and in the process is releasing dopamine in both the dorsal and ventral attention networks and from dopamine-producing regions within the brain such as the nucleus accumbens and related areas. The display elicits an unconditioned response of increasing EEG activation in many areas including the one in which the sensor has been placed, such as FZ or CZ, resulting in more beta and less theta. Sometimes when a burst of beta activity associated with decreased theta activity occurs at the location where the sensor is placed, reinforcement is delivered. Now the child is experiencing partial noncontingent reinforcement on a variable ratio schedule. This same type of reinforcement, used in the gambling industry, is the most powerful reason why casinos make billions of dollars. As a result, the child in the sham conditioning group often has an activated EEG, tries hard to get the noncontingent reinforcement, which is sometimes contingent, and shows improvements in several ADHD indices such as rating scales and perhaps even academic performance.

So what is the answer? It has been repeatedly stated that, because an operant conditioning of a particular EEG pattern reinforcement is usually delivered after 0.5 to 1 second of the production of that pattern, the EEG recording can be marked every time reinforcement is delivered in both the experimental and sham control group. In the sham group, a simple correlation can be run between the percentage time that the reinforcement was contingent and the degree to which the measured EEG parameters changed in the desired direction along with all of the appropriate before and after measures. It would not be surprising that, even if there was a 20% contingency in the sham group, powerful learning effects might occur. As a result it is impossible to develop a sham in which reinforcement never coincides with the EEG pattern that is being trained in the experimental group.

Until a generally agreed on placebo can be developed, continuing active randomized controlled studies should be encouraged.

Furthermore, the lack of understanding of NF has led to several other problems regarding research. For instance, some studies that have questioned the effectiveness of NF have been poorly done for many reasons.

First, some studies have been done that have little to support the role of a feasible sham. One reason has to do with the use of different NF protocols that are not recognized as proven and the use of technology that has little proven effectiveness. In a study that was done to show the effectiveness of a double-blind, sham-controlled, randomized pilot feasibility trial in patients with ADHD, there were no significant differences between the NF group and the sham group. However, the investigators appropriately admitted that they did not use NF technology that is considered effective.[107] The equipment used was Smart Brain by Cybert Learning Technology (www.smarttech.com). This technology allows altering the reinforcement threshold from minute to minute, adopting the threshold to just completed performance, and not requiring focus on the NF training. This technique is referred to as autothresholding. If a patient is not paying attention, the thresholding may be adjusted to a nonlearning event and the reinforcement may not produce the desired effect.

Second, some studies were done without evaluating pre-qEEG data. When participants are selected based on their pre-qEEG data, the protocol used would be better

matched to the participant and the use of this protocol would more likely produce a larger ES (an ES is considered large when it is 0.8 or greater). An ES of 0.8 means that the mean of the treated group is at the 79th percentile of the untreated group. As noted in an article by Sherlin and colleagues,[108] when pre-qEEG data are evaluated in, for instance, a study involving preselection of participants based on abnormal theta/beta ratios for ADHD, the ES for inattention was 2.22 and for hyperactivity was 1.2.[109] These ESs are substantially larger than the ES calculated from a meta-analysis of NF by Arns and colleagues,[110] in which the ES was 0.81 for inattention and 0.4/0.69 for impulsivity/hyperactivity. This later meta-analysis had similar ES discussed in an article by Faraone and Buitelaar,[111] which was comparable with medication for inattention (0.84) but not for the ES for medication for impulsivity/hyperactivity (1.01). Therefore, NF must be based on pre-qEEG data and, in this case, may improve therapeutic outcomes. If children are very hyperactive and unable to be still during NF and a pre-qEEG analysis has occurred, it is suggested that they may require medication (if they are good responders to stimulant medication) initially in order to have good control of their disorder. This can be gradually tapered as the NF proceeds. If the hyperactivity does not subside, but the attention improves, they may still require medication. More research is needed.

Third, meta-analysis of NF studies have concluded that the ES of NF was small because studies were included that did not included standard NF protocols, which again points to the lack of knowledge surrounding NF. In a meta-analysis of nonpharmacologic interventions for ADHD by Sonuga-Barker and colleagues[112] Arns and Strehl[113] pointed out that, when statistics were recalculated using only studies with standard NF protocols, parent ratings obtained a significant standardized difference of 0.58 (95% CI = 0.12–0.94; z = 3.52; P = .0004) and for teacher ratings a significant standardized mean difference was found of 0.39 (95% CI = 0.07; z = 2.39; P = .02). The inclusion of nonstandardized protocols in a meta-analysis points to a problem in NF: the lack of the standardized protocols that are critical to future research. In addition, for every disorder, best-practice approaches should be individualized and the same before and after instruments should be uniformly used. These instruments should not be limited to rating scales from multiple sources and may include neuropsychological instruments, such as the TOVA (http://www.tovatest.com/), Integrated Visual and Auditory Continuous Performance Test (IVA-Plus) (http://www.braintrain.com/ivaplus/), and the Behavior Rating Inventory of Executive Function-R (BRIEF-R) (http://www4.parinc.com/Products/Product.aspx?ProductID=BRIEF#).

Fourth, with regard to lack of knowledge about standardized protocols, some studies, although well intentioned, do not use well-known facts about learning curves and operant conditioning. For instance, in randomized placebo-controlled trial of NF for children with ADHD done by van Dongen-Boomsma and colleagues,[114] the percentage of reward used was too high (80%) for operant conditioning to occur. If the reward is too easy (rewards are delivered every time) no learning occurs.

However, some users of NF are not trained professionals. Given the evolution of NF, only clinicians who are well trained in neurophysiology, neuroanatomy, and neuroendocrine and metabolic processes should be allowed to do NF. Given the need to remove artifact appropriately in order to use qEEG, only clinicians who are trained to do so should be allowed to extract the artifacts, or a requirement that an untrained clinician must be supervised by someone who is proficient in reading EEGs may be necessary. NF is most appropriately used as an adjunct to a multimodal biological, psychological, and social treatment approach. These

points may indicate that the accreditation used in NF may need to be reconsidered.

New mathematical techniques for qEEG analysis are developing rapidly, and new technology will promote this development. The advent of LORETA and z-score NF allows clinicians to selectively target data that are substantial deviations above or below the normative population means, enabling more accurate matching of those deviations to symptoms and to the relevant brain regions. LORETA (19 electrodes) allows targeting of deeper structures than can be reached with surface NF (2–4 electrodes), will likely reduce the number of sessions and costs required to get effective results, and seems to have long-lasting effects after treatment is stopped.

Summary of Tables

In evaluating this limited literature on NF treatment in children and adolescents, the system developed by United States Preventive Services Task Force (USPSTF) can be used.

Table 2 provides a summary of the quality of evidence that is currently available in the published literature as well as a summary of the strength of recommendations that can be offered to clinicians concerning the value of the treatment. **Table 3** is similar, except that the right-hand column provides the authors' clinical expert opinions rather than being based purely on publications.

Table 2
Evaluation of surface NF in youth: the evidence base

Indications	NF Method	Quality of Research	Strength of Recommendation	Evidence Base
Depression	Alpha asymmetry	Fair	Recommend	1 case study[66]
Anxiety	Increase alpha/theta ratio or SMR/theta ratio	Fair	Recommend	1 RCT[72]
Performance anxiety	Alpha/theta training	Good	Recommend	1 RCT and 1 open trial[97,115]
Mental retardation	NF based on individual qEEG	Good	Recommend	2 clinical trials
TBI	Decrease theta/increase beta	Fair	Recommend	1 RCT comparing physical therapy with NF
PTSD	Decrease delta/theta activity	Fair	Recommend	Non–randomized controlled study
Alcohol abuse	Alpha/theta training	ND	ND	ND
Substance abuse	Alpha/theta training	ND	ND	ND

USPSTF quality of evidence grade is a qualitative ranking of the strength of the published evidence in the medical literature. Limited, indirect evidence; good, consistent benefit in well-conducted studies in different populations; fair, data show positive effects, but weak, limited, or indirect evidence; poor, cannot show benefit because of data weakness.

USPSTF strength of recommendations: A, recommend strongly (good evidence of benefit and safety); B, recommend (fair evidence of benefit and of safety); C, neutral (fair evidence for, but seems risky); D, recommend against (fair evidence of ineffectiveness or harm); I, insufficient data.

Abbreviations: ND, no data on youth; RCT, randomized controlled trial.

Table 3
Evaluation of surface NF in youth: authors' recommendations and personal comments

Indications	Strength of Recommendations Based on Published Data	Authors' Clinical Recommendations	Authors' Other Comments
Depression	Recommend	Possible benefit	Requires further study given the variance between findings in frontal lobes in alpha asymmetry adolescents vs adults. qEEG should always be used before and during treatment with regard to clinical symptoms. Studies needed using LORETA NF
Anxiety	Recommend	Shows promise and improvement trends	May have greater effect if based on qEEG. Studies needed using LORETA NF
Performance anxiety	Recommend	Shows promise and improvement trends	Promising for decreasing performance anxiety and performance skill. Studies needed using LORETA NF
Mental retardation	Recommend	Shows promise and possible benefit based on pretreatment and ongoing treatment on qEEGs	Promising for possible increase in IQ and decreasing disruptive behaviors and improving attention. May help to reduce medications used to treat these behaviors. Studies needed using LORETA NF
TBI	Recommend	Shows promise	May help to increase range of motion and memory in persons who have had a stroke. Need to use qEEG and watch to see whether increasing beta will make symptoms worse. Studies needed using LORETA NF
PTSD	Recommend	Recommend	Helpful in decreasing PTSD symptoms and improving attention in abused children. Studies needed using LORETA NF
Alcohol and substance abuse	Neutral with comorbid ADHD	See Table 1 for recommendations	Studies needed using LORETA NF

USPSTF strength of recommendations: A, recommend strongly (good evidence of benefit and safety); B, recommend (fair evidence of benefit and of safety); C, neutral (fair evidence for, but seems risky); D, recommend against (fair evidence of ineffectiveness or harm); I, insufficient data.

SUMMARY

Although most NF research has targeted ADHD, there are some limited studies in children and adolescents suggesting possible applications for treatment of anxiety, depressive disorder, addiction (with or without ADHD), brain injury (including TBI, mild head injury, concussion, and intrauterine brain damage), Down syndrome, and perhaps some other forms of mental retardation in children and adolescents. There are additional data suggesting that NF might also be useful for treating certain intractable seizure disorders in youth,[47,116,117] but a neurologist should be involved in managing those cases. Although some of the data remain controversial, the American Academy of Pediatrics has recently endorsed NF as a valid and possibly first-line treatment of ADHD in youth, and the United States Army is implementing an innovative program to examine the role of NF in treating TBI in veterans. As the technology and statistical analytical methods advance, many of the remaining uncertainties can be expected to be addressed.

Research has documented that many of the same areas targeted in the NF treatment of ADHD (right ventrolateral prefrontal cortex, right dorsal anterior cingulate, left thalamus, left caudate nucleus, and left substantia nigra) are involved in mediating selective attention and response inhibition in children with ADHD, and similar NF treatment is helpful for improving attention in a variety of other psychiatric disorders.[118] The targeting of such transdiagnostic symptoms holds particular promise for the future of NF treatment.

A small study has suggested that NF and methylphenidate similarly improve several behavioral and cognitive functions in children with ADHD.[119] This raises the question of whether nondrug treatment might be able to eventually augment or, conceivably, supplant some of the established current psychopharmacologic interventions. For many families, NF might be a more acceptable option than psychostimulants for treating ADHD. Furthermore, NF might be a particularly valid option for treating ADHD with comorbid substance abuse, especially because NF may be beneficial for both conditions, without the risks associated with using abusable medications in this population.

The use of qEEG to characterize and localize brain dysfunction creates new opportunities. Current data suggest that qEEG might eventually be useful for predicting medication responders and nonresponders,[120] for identifying patients at risk for developing antidepressant-induced treatment-emergent suicidal ideation,[121] and for identifying patients at particularly high risk for relapse (depression, cocaine addiction, nicotine craving).[122] In addition to identifying patients at risk by qEEG monitoring, NF can be used to target the dysfunctional circuitry in relevant brain regions and could conceivably act proactively to reduce the risks.

The newer technologies may eventually be found to be particularly suitable for providing a more penetrating picture of dysfunctional circuitry and for yielding more effective treatments with fewer NF sessions and lower costs. There was a recent presentation of a patient with multiple diagnosis starting in adolescence (including major depression, ADHDF, bipolar I, social phobia, TBI, OCD, and PTSD), and multiple medications (including sertraline, dextroamphetamine mixed salts, Synthroid, lithium carbonate, hydroxyzine, alprazolam, and lorazepam), who had not adequately responded to surface NF and therapy over a 2-year period. He had made 3 previous suicide attempts. Once LORETA NF was used (for 33 sessions over a 6-month period), the patient was off all medications and functioning well.[123] His Global Assessment of Functioning (GAF) score improved from 15 to 90. A single case cannot be the guide for clinicians to use LORETA NF in every person with multiple disorders, but this case

presentation highlights the need to do more research using this intervention, especially in patients who are not responding to conventional interventions and therapy.

Although LORETA seems to offer some promise for advances compared with the older surface NF methods, the two approaches can currently be viewed as complementary. Some children are not able to tolerate the many electrodes required for LORETA and may be better candidates for the more user-friendly surface NF methods using 2 to 4 electrodes.

At present, NF can be considered when patients or parents prefer not to use psychopharmacologic treatments or when medication treatments are not well tolerated or adequately effective.

Child and adolescent psychiatrists are well aware of the importance of well-trained clinicians who are skilled in doing biopsychosocial evaluation and treatment. NF should never be used as a single intervention in child and adolescent psychiatry, just as medications should never be the only intervention for depression. NF is properly used when integrated into a multimodal series of interventions for the child and family that precedes and continues after the time period of active NF treatment. Although this may be obvious to child psychiatrists, clinicians should be advised that an increasing number of lay persons are inappropriately obtaining NF equipment and offering to put electrodes on someone's head and to alter the brain functioning of individuals with serious medical and psychological conditions. In less drastic cases, some inadequately trained clinicians have assumed that a patient with ADHD can benefit from a predetermined protocol to increase alpha or beta activity, without having conducted proper individualized assessments. The risk, for example, in a patient who already has excess beta and cortical irritability is the induction of tics, anxiety, or seizure activity.[124]

Psychiatrists who are collaborating with NF specialists are strongly encouraged to use licensed clinicians with certification in NF (eg, from the Biofeedback Certification Institute of America) and or clinicians supervised by clinicians with certification and/or certification in qEEG (eg, from the EEG and Clinical Neuroscience Society, the Quantitative Electroencephalography Certification Board, or the Society for the Advancement of Brain Analysis).

In regards to the effectiveness of neurofeedback, the reader is referred to a recent review by Arns and colleagues[125] which addresses this issue with a concise summary of previous studies. Although double blind placebo controlled studies are clearly the preferred type of research in regards to proving the effectiveness of treatment regimens, until a convincing sham is found, randomized controlled studies based on appropriate protocols and methods should continue. Meanwhile, a collaborative group has been formed to address the issue of a credible sham.[126]

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