Emerging brain-based interventions for children and adolescents: overview and clinical perspective

Laurence M. Hirshberg, PhD[a,b],*, Sufen Chiu, MD, PhD[c],
Jean A. Frazier, MD[d]

[a]The NeuroDevelopment Center, 260 West Exchange Street, Suite 302, Providence, RI 02903, USA
[b]Department of Psychiatry and Human Behavior, Brown Medical School, Providence, RI, USA
[c]Department of Psychiatry and Behavioral Sciences, University of California–Davis,
Sacramento, CA, USA
[d]Department of Psychiatry, Harvard Medical School, Cambridge Hospital, Macht Building,
Third Floor, 1493 Cambridge Street, Cambridge, MA 02193, USA

Technology and psychiatry

The use of sophisticated technology to intervene and improve brain function is just beginning. It promises a transformation in practice in many fields: rehabilitation, neurology, psychiatry, and psychology. The science fiction fantasy of brain chip implants is getting ever closer to realization. Neuroscientists in several university centers recently demonstrated the viability of brain-computer interfaces and the capacity, with relative ease, to control external devices by the brain through volition and practice. Human beings and animals are able to exercise volitional control of brain function through practice accompanied by immediate feedback regarding that practice so that they can manipulate an external device with their brain.

Until recently, the enormous technologic sophistication that has enabled the rapid advances in neuroscience in the past 15 years primarily has benefited psychiatry research, not practice. Neuroimaging is finally allowing us to study brain function directly. Although there is no question that the field is in the early

* Corresponding author. The NeuroDevelopment Center, 260 West Exchange Street, Suite 302, Providence, RI 02903.
E-mail addresses: lhirshberg@neurodevelopmentcenter.com, lhirshberg@cox.net (L.M. Hirshberg).

stages of its understanding of the complex interplay of brain, behavior, and experience, the temptation to make use of this same technology to intervene to improve in brain function is strong but largely unsatisfied.

This state of affairs is beginning to change, however. Serendipitously, it was discovered that exposure to echo-planar magnetic resonance spectroscopic imaging occasioned significant mood improvement in adults with bipolar disorder immediately after a research scanning procedure [1]. A systematic study was then designed to further assess this effect. Results showed that adults with bipolar disorder who received echo-planar magnetic resonance spectroscopic imaging showed significant improvement on the Brief Affect Scale compared with the sham and healthy control groups.

In a recently published study, DeCharms et al [2] showed that participants were able to learn enhanced voluntary control over task-specific activation in the somatomotor cortex when provided with feedback derived from real-time functional MRI (fMRI). The enhancement took place when real-time fMRI-based training was provided but not in a control group that received similar training without real-time fMRI information, which showed that the effect was not caused by conventional, practice-based neural plasticity alone. Similarly, Charnowsky et al [3] recently reported successful self-regulation of the blood oxygen level–dependent signal of supplementary motor area and parahippocampal place area using real-time fMRI neurofeedback. Blecker et al [4] reported that participants exercised control over activation at Broca's area using real-time fMRI feedback.

This phenomenon represents an important convergence in findings and interest among disparate groups of scientists, researchers, and practitioners. Academic neuroscientists are discovering with the advanced technology of the fMRI what has been known and practiced for more than 30 years using the ''poor man's'' form of neuroimaging: the electroencephalograph (EEG). As this issue of *Child and Adolescent Psychiatric Clinics of North America* makes clear, there is an ample body of extant research on EEG biofeedback (EBF). Although there are significant methodologic weaknesses in some of these studies and much fundamental research remains to be conducted, virtually all the EBF research has demonstrated what these three most recent fMRI studies have replicated using a more complex and sophisticated imaging technology: we are able to use real-time information about brain function to alter and enhance that function.

As the three real-time fMRI studies show, this effect can be demonstrated in several areas of the brain, which suggests that neurofeedback, whether using EEG or real-time fMRI, is applicable to functional brain disorders that arise out of various different patterns of functional disturbance or dysregulation. This also has been recognized in the field of EBF for some time, after the initial application to epilepsy led to the extension of this technique to related disorders (attention deficit hyperactivity disorder [ADHD], traumatic brain injury [TBI], depression).

An important convergence also occurs between academic psychiatry and EBF through the interest of both groups in event-related potentials (ERPs). ERPs are brain-generated electrical responses to specific stimuli. A subset of ERPs known

as auditory-evoked potentials has entered mainstream medical practice as a screening instrument for newborn hearing impairment [5]. Researchers have renewed interest in using ERPs to study the pathophysiology of psychiatric disorders, such as adult schizophrenia [2,6] and posttraumatic stress disorder [3,7]. ERP research in children primarily has centered on autism [4,8] and ADHD [5,9]. Researchers have investigated differences in ERPs and event-related desynchronization in ADHD and normal children [10,11]. Work has been underway for several years on the development of a quantitative ERP database, similar to quantitative EEG (qEEG) databases for assessment purposes. EBF studies are increasingly using ERPs as an index of changes in information processing in the brain and as a physiologic outcome measure in EBF efficacy and validation studies [12,13], as is described in the article by Gruzelier and Egner elsewhere in this issue.

Multiple pathways for intervention in psychiatry

Not too long ago, clinical bias toward treating psychiatric disorders was based on the assertion that interventions required direct effects on the brain through medications that modulate neurotransmitters at the receptor or transporter level because this was the only scientifically measurable change in the brain in response to treatment. New research and treatment options challenge those assumptions and present new alternatives to traditional medications. For example, the US Food and Drug Administration (FDA) has approved devices such as vagal nerve stimulation (VNS), a wrist electrical stimulator, and a cranial electric stimulator for treating brain-based disorders.

Altering inputs to the brain by auditory, olfactory, visual, tactile, and even motor stimulation modulates neuronal processing in ways that may improve psychiatric symptoms. Auditory visual stimulation or entrainment devices, which use rhythmic photic and auditory stimulation to "entrain" the brain to known EEG rhythms, have shown promise in preliminary studies for intervention for attention, mood, and anxiety. Similarly, a simple, repetitive motor timing intervention has shown benefits for attention and aggressiveness among children in early research. Even acupuncture may be a form of treatment that alters the brain via peripheral stimulation of the brain via sensory inputs.

In general, there seem to be two forms for these newer approaches: feedback or brain-based self-regulation techniques and stimulation strategies. EEG and other forms of neuroimaging biofeedback should be understood as a form of self-regulation. Given the robust effect size of EBF, which repeatedly has been shown to be equivalent to that of stimulant medication, it is easy to forget that the technique simply involves showing the trainee what his or her brain is doing. Although research in nonlinear dynamic or chaotic systems consistently has revealed the regulating power of feedback in complex systems, individuals accustomed to more traditional, linear-based thinking in western medicine and

psychology may find it hard to believe that merely showing the brain to itself has the same strength of effect as a carefully controlled psychoactive medication.

The second group of new strategies—brain stimulation methods—involves the more traditional process of new inputs being provided or of something being imposed on the brain or nervous system from without. These strategies include VNS, transcranial magnetic stimulation (TMS) (both of which are presented in detail in this issue), and cranial electric stimulation, audiovisual stimulation, and wrist electrical stimulation, which have interesting, although perhaps less central applications.

Finally, several emerging approaches in the EBF field combine and integrate feedback and stimulation strategies. For example, several EBF systems use visual, auditory, or magnetic stimulation that is provided based on the real-time emergent pattern of the EEG to assist in entraining (eg, stimulating to enhance rhythmic activity) or dis-entraining (eg, using stimulation to inhibit rhythmic activity) during the process of EBF training. Stimulation inputs are used to assist the self-regulation through feedback. Although comparative research has not yet been completed, widespread clinical experience indicates that these combined stimulation and feedback approaches may be more effective than either alone.

Overview of three emerging approaches: electroencephalographic biofeedback, repetitive transcranial magnetic stimulation, and vagal nerve stimulation

Each of the articles that follows in this issue reviews in detail the research and clinical experience to date with these three new approaches, including critical review of the extant research, case presentations, and discussion of limitations and future directions. In some instances, there is little experience to date with child and adolescent populations, requiring inferences about application to this group. What follows herein is a summary of the most salient and interesting findings for child and adolescent psychiatry from these articles, omitting most aspects of the critical discussion of methodologic detail.

Research using qEEG, in which the EEG signal is quantified and statistically analyzed in comparison to a normative database, has provided substantial evidence of a significant relationship between EEG abnormalities and various disorders of behavior, emotion, thinking, learning, and development. This research into the electrophysiology of psychiatric disorders is reviewed by Chabot et al. Simply put, their article reveals that the EEG signal is a good indicator of patterns of cortical activation that play a role in many forms of psychiatric disorder. Much of this research has been amply cross-validated using other neuroimaging techniques.

One intriguing finding is the presence of different patterns of EEG abnormality within diagnostic groups. These patterns have been measured reliably in different laboratories and may reflect neurophysiologically distinct subtypes of

dysfunction within groups that are phenomenologically similar. It is widely assumed that many, if not most, forms of psychopathology, as designated by symptom-based nosologies, are etiologically heterogenous. There seems little question that this heterogeneity has hindered research and treatment in psychiatry. Both are likely to be more effective when based on participant and patient selection that shows greater homogeneity.

Electrophysiologic subtyping based on qEEG may provide such a means in the future, because qEEG research is providing evidence of physiologically specifiable subtypes within these heterogeneous groups. This is described for various disorders, including schizophrenia, substance abuse, mood disorder, anxiety disorders, ADHD, and learning disabilities. Some promising research suggests that these electrophysiologic subtypes may have practical significance for psychopharmacologic and other forms of treatment. For example, one qEEG subtype observed among cocaine abusers accurately predicted rapid relapse after treatment. Another qEEG measure accurately predicts positive response to selective serotonin reuptake inhibitors among persons hospitalized for major depression within 48 hours of treatment initiation.

Several areas of qEEG research into developmental psychopathology are of interest. Replicated qEEG studies have revealed what may be a neurophysiologic substrate of reactive or anxious temperament among infants. This pattern of frontal activation asymmetry such that there is greater activation in the right compared with the left frontal cortex is similar to that observed in some adults with depression. Infants of depressed mothers also display this same frontal EEG activation asymmetry, even as young as 3 to 6 months and 1 month of age.

The bulk of qEEG research into child and adolescent psychiatric disorders has been conducted with ADHD. Multiple qEEG studies have demonstrated a pattern of electrophysiologic abnormality among individuals with this disorder. Discriminant function analysis using qEEG variables has shown high levels of sensitivity and specificity in identifying ADHD participants in several studies. In two studies, a single ratio of theta-beta power recorded from a single site resulted in sensitivity levels of 86% and 90% and specificity levels of 94% and 98%. Some experts have recommended that neuroimaging studies be included in the routine assessment of ADHD. This research suggests that qEEG should be the preferred means, because validity and reliability are high and cost is relatively low.

Summary of articles on feedback strategies

If the domain of brain electrophysiology, as revealed in the EEG, is meaningfully associated with psychiatric dysfunction, then this domain seems to be a fertile ground for intervention, such that EEG change would map onto functional change in behavior. This is the avenue of entry of EBF into psychiatry. The capacity of individuals to use real-time feedback of the EEG to alter it through

operant conditioning or learning has been established for many years. Numerous studies have shown that EBF, also called neurofeedback or neurotherapy, results in measurable and replicable improvements in attention, impulsivity, mood, anxiety, memory, and learning and clinically significant improvements in addictive disorders and epilepsy in children and adults.

As with qEEG, the bulk of research on EBF has been with ADHD. This work is reviewed by Monastra and by Gruzelier and Egner elsewhere in this issue. Five controlled studies have been published, including one randomized, controlled trial (RCT). A double-blind, randomized, sham treatment study has just been completed but is not yet published. Many open or clinical trials, with hundreds of participants, also have been published. These studies uniformly show significant benefit for 70% to 80% of participants, with an effect size for EBF equivalent to that of stimulants, as measured by computerized continuous performance tests and standardized rating scales. Several of the studies also have documented neurophysiologic changes, including improvements in EEG and in ERPs. A recently completed RCT showed normalization of activation as measured by fMRI in the prefrontal cortex bilaterally and in the anterior cingulated gyrus after 40 sessions of EBF in a sample of ADHD patients. Although much more follow-up research needs to be conducted, several studies show the maintenance of gains years after the EBF training ended. There also is growing evidence of the specificity of effect in EBF, such that the effect (eg, behavioral and physiologic) varies by specific location and frequencies trained.

Substantial validation research also has been completed on EBF for epilepsy. Several controlled studies have been completed, including three ABA condition reversal studies. Several other open trials or case series also have been reported. A recent meta-analysis indicated that 82% of patients demonstrated more than 30% reduction in seizures, with an average more than 50% reduction. This outcome is all the more significant because most of the participants included in these studies were refractory to medical treatment; for many, EBF was the only alternative to surgery. Recent clinical experience has shown significantly improved outcomes using EBF individually targeted at deviations in the degree of co-activation of different cortical sites, as guided by coherence findings in the qEEG. The efficacy research and a case series using the newer qEEG guided approach is reviewed by Walker and Kozlowski elsewhere in this issue.

Hammond reviews the scientific literature on EBF for anxiety and depression. Research on EBF for anxiety is less well developed than for ADHD and epilepsy. Multiple small studies on generalized anxiety disorder (GAD), obsessive-compulsive disorder, phobic anxiety, and posttraumatic stress disorder have been published, with several controlled trials. Overall results show significant reduction in anxiety with EBF, although several of the studies involved many fewer sessions than is used in clinical settings. Clinical trials presented by the author using qEEG-guided EBF seem to show stronger benefit. With depression, several case studies have been published providing preliminary evidence of efficacy with major depression. An open case series presented by the author also suggests that qEEG-guided EBF training may have a larger effect size.

Trudeau reviews the literature on the use of EBF in adolescent psychoactive substance use disorder. In research with adults with psychoactive substance use disorder, multiple RCTs and uncontrolled studies have shown protocol-specific EEG changes and improvements on measures of depression (self-rating), attention (continuous performance test [CPT]) and stress (physiologic). Several long-term follow-ups showed a significant reduction in the 1-year abstinence/recidivism rate for the EBF group compared with controls. No formal research has been published on the use of EBF with adolescent populations, although clinical reports are encouraging and suggest that adolescents should benefit from this treatment. Given that EBF is medication free and has been shown to be effective with ADHD, a frequent comorbid condition with psychoactive substance use disorder, EBF seems to have particular value for these patients (ie, individuals with psychoactive substance use disorder with ADHD), in whom the risk of medication abuse is high. Currently, family therapy is the primary intervention for adolescent substance abuse [14]. Because few safe, patient-centered treatment options exist for children and adolescents with substance abuse, neurofeedback warrants further investigation and consideration in treatment planning.

Reviews of the literature on treatment for TBI and reading disabilities indicate that few of the commonly used interventions have shown efficacy in formal research and that the effect size of these techniques is usually small. Thornton and Carmody provide an overview of the research and clinical experience with the use of EBF with TBI and reading disabilities. Several open case series and controlled studies (including one RCT) have shown significant benefits for EBF with TBI, primarily in adults, with improvements on measures of attention, executive function, cognitive flexibility, problem solving, information processing, verbal fluency, and depression and in the EEG. Cessation and reduction of medication also have been reported, as has return to productive work. For reading disabilities, no formal studies have been published to date, although several studies of the effect of EBF on ADHD have provided suggestive preliminary evidence of improved cognitive function. An open case series of patients with TBI and reading disabilities is described using EBF guided by qEEG based on a cognitive task activation database. Significant improvements are shown as measured by various neuropsychological measures.

Summary of articles on stimulation strategies

VNS, reviewed by Martinez et al, represents a novel but invasive method for controlling epilepsy. Case and controlled trial studies demonstrate efficacy with adults with treatment refractory epilepsy. Studies of VNS with adolescents show seizure reduction of 23%, 32%, 37%, and 44% at 3, 6, 12, and 18 months, respectively. Similar benefit is seen in a case series of patients younger than age 12.

Consideration of the mechanism of action of VNS and reports of mood improvement when used for epilepsy suggest that VNS may have antidepressant effects. Two studies of VNS for treatment-resistant depression have been conducted with adults. In an open label trial, response and remission rates were 30.5% and 15.3%, and 46% and 29% at 10 weeks and 1 year, respectively, with no negative effects on neuropsychological testing. A subsequent RCT showed a 15% response rate for the VNS group and a 10% response rate among sham controls. No research or case reports exist on the use of VNS for depression in children and adolescents.

Significant risks associated with surgical implant and general anesthesia must be weighed when considering this intervention. Patients who suffer from chronic refractory epilepsy may choose the possible clinical benefit over the risk. Adult patients who suffer from chronic refractory depression face similar risk-benefit considerations, although the single RCT completed to date shows limited benefit. It is rare that safer alternative interventions are exhausted in childhood and adolescent depression, however. VNS shows promise as an intervention for depression in this population. Further research is warranted.

Research and clinical experience with repetitive TMS (rTMS) is reviewed by Morales et al in the final article of this issue. Although not currently approved by the US FDA for the treatment of any disorder at any age, this noninvasive form of brain stimulation is under active study in adults as a form of intervention for major depression, schizophrenia, anxiety disorders, and some neurologic conditions. Although no controlled trials have been conducted on the efficacy of rTMS for treatment of any disorder in children and adolescents, case studies are reported with nine children. Based on informal case reports, five of seven children in a heterogenous group diagnosed with bipolar disorder, unipolar depression, and schizophrenia were judged to be improved. In a separate published case report, one of two children with epilepsia partialis continua showed a cessation of seizures within 24 hours; the other showed no change. Single and paired pulse TMS seems to carry minimal risk to children. Because rTMS carries greater risk and no safety studies have been completed to date, however, research to investigate the safety of rTMS with child and adolescent populations is needed.

Recent work with rTMS has renewed interest in an established form of brain stimulation: electroconvulsive therapy. With empirically established efficacy with major depression in adults, electroconvulsive therapy is generally used as a second-line treatment with treatment-resistant adult patients. It is rarely used with children and adolescents, however, and efficacy data are limited. No controlled trials have been published. In a review of published case studies, it seems that response is consistent with that with adults and better with affective than psychotic illnesses. Although some significant adverse effects were reported in earlier case studies, improvements in anesthetic techniques and management of comorbid conditions have improved significantly the side effect and adverse events profile in adult and adolescent populations. Recent reports suggest that children and adolescents seem to have transient cognitive side effects that resolve completely. Further safety and tolerability research is needed.

Clinical considerations in evaluating new treatments modalities

The articles in this issue describe new treatment modalities outside of the conventional psychiatric practices of medication management and psychotherapy. With increasing emphasis on evidence-based practice and the empirical validation of clinical methods, it is widely accepted that all such new approaches should be evaluated carefully as to the level of evidence base or degree of formal, controlled empirical support available. The highest standard of such empirical support is that from RCTs.

Simultaneously, the complex realities of clinical practice usually require that the results of formal empirical research (controlled trials) be reconsidered or moderated in the light of these realities [15,16]. For example, many, if not most, controlled trials exclude participants with comorbid conditions. Research has shown that "the majority of patients were excluded from participating in the average study" because of the presence of comorbid conditions [17]. The clinical reality faced by practitioners is that few patients have only one clearly definable Axis I diagnosis, however.

The use of strictly manualized approaches or treatment protocols, as in controlled research, is often impossible or contraindicated in clinical practice because of various factors that may be controlled in research but cannot be controlled in everyday practice without negatively impacting rapport and the therapeutic relationship. Research has shown that specific practices account for no more than 15% of variance in therapeutic outcome, whereas the therapeutic relationship accounted for 30%, patient characteristics and extra therapeutic change accounted for 40%, and expectancy and placebo accounted for 15% [18]. For these reasons, it is clear that real-world conditions may limit the implementation of research-based treatments [19] and that research-based dictates that interfere with the therapeutic relationship should be adjusted in clinical practice.

For these and other reasons, Seligman and others have argued that controlled (RCT) trial research, although high in internal validity, is weak on external or ecologic validity. To provide empirical support more aligned with the complex realities of clinical practice, these authors favor "effectiveness research"—formal measurement of outcomes from treatment as administered in everyday clinical practice. Although debate continues on the relative value of these different forms of evidence, most of the emphasis in the evidence-based treatment movement remains on the central importance of RCTs.

For the purposes of summarizing in this article the degree of empirical support for each of these three new interventions in child and adolescent psychiatry, three dimensions are discussed [20]: (1) efficacy, or evidence of benefit in controlled research, especially RCT, (2) effectiveness, or evidence of usefulness in clinical settings, and (3) efficiency, or evidence of cost effectiveness relative to other treatments.

Several professional associations have promulgated standards for evaluating the degree of empirical support or the evidence base for interventions or practices in their fields. Several of the articles in this issue have referred to guidelines

issued by the two professional organizations for EBF providers [21], which are substantially similar to those that have been offered by the American Psychological Association [22]. This format specifies four levels of empirical support or evidence base: efficacious and specific, efficacious, probably efficacious, and possibly efficacious.

The American Academy of Child and Adolescent Psychiatry (AACAP) has outlined a set of guidelines to evaluate clinical practices, for example, as in the Academy's practice parameters for the use of stimulant medication [23]. They are considerably less stringent than parameters adopted by the American Psychological Association and the EBF professional associations. Unlike the latter, which do not give any weight to clinical experience, they give considerable weight to the informal knowledge base that emerges from shared clinical experience.

This is fitting for several reasons. First, patients who suffer from child and adolescent psychiatric disorders and their families have few therapies from which to choose that are conclusively proven through empirical research or are approved by the US FDA. Should child and adolescent psychiatrists limit themselves to treatments that have been fully validated through empirical research with their population, they would have too few tools available. This state of affairs requires the practitioner to employ scientifically informed clinical judgment when using treatment approaches that have not been fully evaluated in a given age range. Here the clinician applies the basic clinical method of careful observation of the specific effects of a treatment approach on a single patient and then adjusts treatment according to these observed effects and side effects. Simply put, the current state of the field requires the frequent use of clinical judgment in practice, and the AACAP guidelines recognize this fact in evaluating practices. Second, because research to validate new treatments is slow to progress and is limited in scope, this situation is not likely to change rapidly. Third, many advances in psychiatry over the last decade have been caused by changes in the way medications are use in clinical practice rather than based on methods first validated in research. Experiences shared among informal networks that operate among clinicians lead to the spread of new approaches, with continual clinical "testing" with individual patients in practice. At some point in this process, controlled research may be done to provide a more formal test of these clinically derived practices. Simply put, much discovery occurs through the clinical use of interventions before formal empirical study; and the AACAP guidelines recognize this fact. This process of clinical discovery followed by empirical testing is seen in most other areas of mental health. Finally, recent studies suggest that an overly strong emphasis on the need for RCTs to demonstrate efficacy may be mistaken [24–26], because results from nonrandomized observational studies generally have been similar to RCTs.

In this article, the AACAP's practice parameter for the use of stimulant medication is used to assess the dimension of the evidence of efficacy and effectiveness of the new approaches described in this issue. The dimension of efficiency also is discussed for each new intervention.

The AACAP classification [23] uses a hierarchal system with four levels: "Minimal Standard" (MS), "Clinical Guidelines", "Options", and "Not Endorsed" (NE). "Minimal Standards" are expected to apply to cases in clinical practice at least 95% of the time and meet that standard due to "substantial empirical evidence (such as well controlled, double blind trials) or overwhelming clinical consensus." "Clinical Guidelines" are expected to apply to cases in clinical practice approximately 75% of the time. "These practices should always be considered by the clinician, but there are exceptions to their application." Treatments that meet this standard show limited empirical evidence (such as open trials, case studies) or strong clinical consensus. "Options" are practices that are acceptable but lack sufficient empirical evidence to support their recommendation: "In some cases, they may be appropriate, but in other cases, they should be

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Box 1. American Academy of Child and Adolescent Psychiatry guidelines for recommending evidence-based treatments

"Minimal Standards" [MS] are recommendations that are based on substantial empirical evidence (such as well-controlled, double-blind trials) or overwhelming clinical consensus. Minimal standards are expected to apply more than 95% of the time. i.e., in almost all cases. When the practitioner does not follow this standard in a particular case, the medical record should indicate the reason.

"Clinical Guidelines" [CG] are recommendations that are based on limited empirical evidence (such as open trials, case studies) and/or strong clinical consensus. Clinical guidelines apply approximately 75% of the time. These practices should always be considered by the clinician, but there are exceptions to their applications.

"Options" [OP] are practices that are acceptable but not required. There may be insufficient empirical evidence to support recommending these practices as minimal standards or clinical guidelines. In some cases they may be appropriate, but in other causes they should be avoided. If possible, the practice parameter will explain the pros and cons of these options.

"Not Endorsed" [NE] refers to practices that are known to be ineffective or contraindicated.

Data from Greenhill LL, Pliszka D, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 2002;41(2 Suppl):26S–49S.

Table 1
Interpretation of effect size

General interpretation of the strength of a relationship	The *d* family	The *r* family	2 × 2 Associations		
	d	*r*	AUC (%)	RD (%)	NNT
Much larger than typical	≥1.00	≥0.70	≥76	≥52	≤1.9
Large or larger than typical	0.80	0.50	71	43	2.3
Medium or typical	0.50	0.30	64	28	3.6
Small or smaller than typical	0.20	0.10	56	11	8.9

We interpret the numbers in this table as a range of values. For example, a *d* more than 0.90 (or less than −0.90) would be described as much "larger than typical" in the applied behavioral sciences, a *d* between 0.70 and 0.90 would be called "larger than typical," and a *d* between 0.60 and 0.70 would be "typical to larger than typical". We interpret the other columns similarly.
Abbreviations: AUC, area under the receiver operating characteristic curve; NNT, number needed to treat; RD, risk difference.
Data from Kraemer HC, Morgan GA, Leech NL, et al. Measures of clinical significance. J Am Acad Child Adolesc Psychiatry 2003;42:1524–9.

avoided." "Not Endorsed" are used for practices known to be ineffective or contraindicated (Box 1).

As an example of the AACAP practice standards, stimulant medications are "Options" in the treatment of apathy caused by a general medical condition and in adjuvant medical uses, such as for psychomotor retardation and treatment-refractory depression. Stimulant medications for ADHD meet the criteria for "Clinical Guidelines" not "Minimal Standard".

These standards may be confusing to patients and parents when discussing treatment alternatives. Discussion of treatments using an evidence-based approach is possible in the clinical setting, however [27]. The clinician must use his or her professional training to critically assess the data and present it to the patient and family in everyday language. An important concept to share with families is "how big of a change" results from a treatment, otherwise known as effect size. The clinician assesses effect size based on three possibilities: (1) strength of association, (2) magnitude of difference, and (3) measures of risk potency [28]. Interpretation of effect size is given in Table 1 but must be balanced by clinical assessment of severity of disorder versus side effect or risks of treatment. For example, "smaller than typical strengths of relationship" may be relevant in the case of terminal cancers but not in the treatment of ADHD.

American Academy of Child and Adolescent Psychiatry guideline ratings for feedback strategies

EBF meets the AACAP criteria for "Clinical Guidelines" for treatment of ADHD, seizure disorders, anxiety (eg, obsessive-compulsive disorder, GAD, posttraumatic stress disorder, phobias), depression, reading disabilities, and addictive disorders. This finding suggests that EBF always should be considered as an intervention for these disorders by the clinician. Clearly there is stronger

evidence of efficacy—the strongest among the three new approaches being considered in this issue—for the use of EBF for ADHD in children and adolescents. Because of this high level of empirical support, the use of EBF for ADHD will (with the publication of the second RCT) meet the most stringent American Psychological Association criterion of efficacious and specific, which requires two independent RCTs, among other factors.

It is not entirely clear what would be required to meet the AACAP "Minimal Standard" guideline, which requires "substantial empirical evidence (such as well controlled double blind trials)." Although the research base for most interventions in psychopharmacology that would meet the "Minimal Standards" clinical guideline includes many more than two RCTs, this is a (financial and practical) burden considerably more easily borne when testing a medication than testing an intervention that requires between 20 and 40 treatment sessions. EBF for ADHD arguably can be considered to meet this standard once the additional RCT is published.

EBF has been widely used clinically by practitioners from a range of disciplines, including psychiatry, psychology, social work, counseling, nursing, and education. The dimension of clinical effectiveness represents the peculiar strength of EBF as its application has become widely disseminated in many areas well before the base of research support was established. There is strong clinical consensus among practitioners that it is useful in clinical practice with each of these disorders. The strongest evidence of clinical effectiveness is in the area of ADHD. Several of the larger case trials summarized by Monastra in his article in this issue were effectiveness studies completed in outpatient practices. EBF also is widely used with children and adolescents with anxiety, depression, and disruptive or explosive behavior.

Specific recommendations based on the body of empirical evidence currently available suggest that EBF be considered by clinicians and parents as a first-line treatment for ADHD when parents or patients prefer not to use medication and as an empirically supported treatment choice when significant side effects or insufficient improvement occurs with medication. EBF should be considered an empirically supported treatment choice for epilepsy, anxiety and depression, addictive disorders, and TBI when patients or parents prefer not to use medication, when medications are not well tolerated or are not fully effective, or when proven psychotherapeutic approaches are ineffective or contraindicated. EBF also may be used in combination with psychopharmacology or psychotherapy. EBF for reading disabilities may be recommended as an option when more conventional methods fail.

Emerging areas of application of EBF are with migraines, reactive attachment disorder, and autistic spectrum disorder (ASD). There are widespread and consistent clinical reports of efficacy with migraines and reactive attachment disorder. For migraines, in addition to EBF, a newer form of EBF called passive infrared hemoencephalography has shown considerable promise in clinical trials [29]. Passive infrared hemoencephalography uses an infrared lens mounted on the forehead to measure long-range infrared temperature. Increases in the passive

infrared hemoencephalography signal are believed to reflect a composite of thermal energy generated by brain cells, vascular supply, and vascular return [30–32]. Training migraineurs to increase the passive infrared hemoencephalography readings through feedback has led consistently to significant reduction in the frequency and intensity of the migraine attacks. A clinic based pilot study of 100 migraine sufferers was conducted using 30-minute passive infrared hemoencephalography sessions. More than 90% of the participants, most of whom had not responded to medication, reported significant improvements in migraine pain and frequency of migraine attacks.

Based largely on word of mouth communication among parents of children with autistic spectrum disorder, there is rapidly growing clinical experience with EBF. In one published controlled group study of EBF for autism [33], 24 autistic participants were randomly assigned either to the EBF treatment or to a waitlist control group. Twenty or more sessions (average, 36) of EBF using a standard protocol were given. EBF participants showed significant improvements on measures of sociability, communication, health, and sensory awareness compared with controls.

There is a strong consensus among EBF clinicians who work with the ASD population that EBF offers substantial benefit to a significant percentage of this population. It seems to be helpful to more severe autistic individuals and individuals with high functioning autism and Asperger's disorder. Approximately 70% to 80% of patients with ASD benefit from the treatment. The degree of benefit ranges from mild to profound. For example, one 4-year-old boy recently was diagnosed with pervasive developmental disorder-not otherwise specified (NOS). He had severe behavioral and emotional self-regulation problems, with episodes of extreme aggression toward his brother and parents and self-injurious behavior, such as biting and head banging many times daily. He spoke in two- to three-word phrases, primarily echolalic, engaged in considerable repetitive behavior, and showed little social engagement, even with his mother. After 3 months of twice weekly EBF sessions, aggressive behavior and tantrums had largely subsided, language had improved markedly, he began to engage in parallel and some joint pretend play with peers, and his relatedness with his parents and brother had improved markedly. Generally, improvements are seen in attention and other aspects of executive function, in anxiety and emotional self-regulation, and in the degree to which a child is tuned in to or engaged with the world around him rather than being ''in his own world.'' It seems to be the case that EBF treatment in ASD requires many more sessions than for other disorders; therefore, home training under the supervision of the clinician is often used.

The rationale for use of neurofeedback for ASD is similar to that for psychopharmacology for this population. Virtually all children with ASD have significant attention deficits and often impulsivity. Although this fact is widely ignored in practice, the *Diagnostic and Statistical Manual IV* recognizes this when it dictates that ADHD should not be diagnosed in the context of a pervasive developmental disorder. Virtually all children with ASD also suffer from anxiety, obsessive-compulsive symptoms, and mood disturbances. EBF, like psychophar-

macology for ASD, is targeted at these specific domains of dysfunction—attention and executive function deficits in general, anxiety and obsessive symptoms, and mood.

There are few risks or contraindications for EBF. In the ABA condition reversal studies with epilepsy described in the article by Walker and Koslowski in this volume, participants were first trained with a protocol designed to decrease slow EEG activity (theta 4–7 Hz) and increase faster activity (sensory-motor rhythm [SMR] 12–16 Hz). The methodologically dictated treatment reversal condition entailed using the opposite protocol, training to increase slow activity and decrease fast activity. The third condition was to restore the first protocol to decrease slow EEG activity and increase faster activity. In this study, seizure incidence did increase under the reversal condition. This reversal condition, which surely would no longer be permitted under institutional review board review, was not used to treat seizures but to demonstrate the specificity of the seizure-inhibiting effect of theta reduction/SMR enhancement EBF. Proper use of EBF has been shown to reduce seizure frequency; there are no documented reports of adverse effects when appropriately used with this disorder or with any other disorder. Temporary negative effects, such as sleep-onset insomnia or increased irritability, anxiety, or emotional lability, can occur. These effects are self-limiting or can be ameliorated by adjusting the training protocol. There are no published reports of permanent negative effects from EBF training.

Finally, regarding the cost-benefit ratio with EBF, which must be evaluated in comparison to other approaches, the issue is complex. Like psychotherapy, a course of EBF almost certainly is more costly than use of medication during the same period of time. If the benefits of EBF endure long after the treatment ends, while medication use is ongoing, however, EBF may have a cost advantage in the long run. Much more research into the longevity of benefits from EBF is needed to clarify this question. Because many insurance companies do not cover EBF, however, the initial cost is too high to sustain for many families.

Another practical difficulty is that it may be difficult to find an EBF provider and even more difficult to ascertain his or her competence. A professional certification organization (Biofeedback Certification Association of America) certifies basic competence in EBF. In EBF practice, as in other areas of clinical practice, however, clinical skill level varies by individual clinician. Because most practicing child psychiatrists are unlikely to have established familiarity with EBF providers through previous referrals, this difficulty is all the more significant.

American Academy of Child and Adolescent Psychiatry guidelines ratings for stimulation strategies

Turning to neurostimulation strategies covered in this issue, VNS meets the AACAP standards for "Clinical Guidelines" as an intervention for treatment refractory epilepsy because a significant number of published open trials and case studies exist that show efficacy. This suggests that VNS should be considered in

the treatment of epilepsy. Until further improvements in VNS safety and efficacy occur and research is published on efficacy for specific psychiatric disorders with child and adolescent populations, however, AACAP guidelines indicate that VNS meets criteria for "Options" for treatment refractory psychiatric disorders.

rTMS is not a US FDA-approved treatment intervention but is being actively investigated in adults for the treatment of depression, schizophrenia, anxiety disorders, and some neurologic conditions. rTMS meets the standard for "Clinical Guidelines" as a treatment for bipolar disorder, unipolar disorder, and schizophrenia, based on seven case reports that showed benefit. This number of cases is small and suggests that rTMS may be considered as a treatment option for these disorders in adolescents by the clinician but should be reserved for individuals who have had multiple medication trials with limited efficacy or intolerable side effects until further data appear in the literature. rTMS also has been used in the treatment of seizure disorders in children and adolescents, and there are a few case reports of its clinical application for that indication.

The risk of rTMS is considerably greater than the risk of single or paired pulse TMS based on adult studies, in which headache, scalp pain, affected hearing, and increased risk for seizures were described. No safety studies of rTMS have included children and adolescents; particular caution is warranted with respect to dosing of rTMs in children because of their lower seizure thresholds.

Future directions

Much additional research is needed for all of the strategies reviewed in this issue. Work is in the early stages with VNS and rTMS for child and adolescent psychiatric disorders, and further investigation is needed at every level.

EBF has a greater body of empirical support, but for several types of disorders, this work is also at early stages. Unlike VNS and rTMS, little research on EBF has been conducted to date in major medical centers, and none has been conducted in psychiatry settings. Major research support has been lacking, which seems unfortunate given the promise shown by EBF in the body of empirical study completed to date. Further research into the efficacy of EBF for each of the psychiatric disorders discussed in this issue is warranted. In particular, research into the mechanism of effect and the specificity of effect using different training protocols would be useful. Further study also is needed to compare fixed protocol training to training that is individualized based on qEEG assessment.

Better understanding of the neurophysiologic basis of EBF may facilitate wider acceptance by the general medical community and help dispel longstanding negative biases, according to which EBF is often viewed as "quack science." For example, in the article on EBF for epilepsy, Walker and Kozlowski describe an alternative theory of seizure generation—that seizures result from overactivation of the "anti-binding" mechanism to prevent synchrony of brain electrical activity that would interfere with temporal coding of memory, in contrast to the traditional

theories regarding spatial organization of memory that are disrupted by sei-zure foci and local injury. This view focuses attention on the organization of brain electrical activity on the dimension of time, which is critical to proper brain function. (Neurofeedback may be the only treatment that reorganizes brain activity in the space of time otherwise known as temporal coding.)

Further research into the efficacy of rTMS, VNS, and EBF for psychiatric disorders in children and adolescents is needed using large, randomized, double-blind, placebo-controlled trials. The use of placebo may involve increased risk in some instances, however, which was documented in the ABA condition reversal studies described previously, in which seizure frequency increased during the treatment reversal condition. Sham surgery for VNS implants would carry all the risks of surgery and general anesthesia without any possible benefit to the patient.

It also should be recognized that it is difficult to provide a genuine placebo in EBF research. EBF trainees quickly recognize that the display reflects their own activity. They clearly see in the visual display when artifact is produced by movement, eye blinks, sneezes, or clenching of the jaw. Placebo conditions in which the control participant is shown a noncontingent display (either random "feedback" or, in yoked control studies, the display contingent on another trainee's EEG) are unlikely to evoke the same experience of "that's me" that virtually all trainees notice and comment on. In this sense, it is unlikely to serve as a genuine placebo. The trainees are then also unlikely to be genuinely blind, even when formally "blinded."

For these reasons, it may be inappropriate to insist on the application of the methodology widely used in RCTs to each of these interventions. New research models beyond the traditional, randomized, placebo-controlled trials must be developed to validate these emerging interventions.

Given the early success of real-time feedback with fMRI, it seems likely that much more work will be done in this area. fMRI is much more expensive and less widely available than EEG equipment, however. Particularly as real-time fMRI biofeedback training advances, it will be crucial to conduct comparative studies of real-time fMRI and EEG in their application to neurofeedback training.

Real-time fMRI has a significant advantage over EEG because it allows for imaging of subcortical structures, which then can be impacted by feedback-based training. EEG source localization techniques have been developed that allow for EEG surface recordings to image accurately three dimensionality using high-time resolution statistical parametric mapping for tomographic images of electric neuronal activity. This method, called Low Resolution Electromagnetic Tomography (LORETA), applies to the EEG the methods of statistical inference for the localization of brain function as used in PET and fMRI studies, and results in a low spatial resolution estimate of the electric neuronal activity [34]. Most recently, quantitative neuroanatomy was added to the methodology, based on the digitized Talairach atlas provided by the Brain Imaging Centre, Montreal Neurological Institute. The combination of these methodologic developments has placed LORETA at a level that compares to the more classic functional imaging

methods, such as positron emission tomography and fMRI. Initial validation studies of LORETA have been positive.

Pilot clinical investigations of real-time feedback using LORETA are currently underway. There are many technical hurdles, because artifact much more significantly impacts this feedback modality than it does EBF. Considerable research is needed in this area to validate further the neuroimaging function of LORETA and investigate the efficacy of LORETA feedback.

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