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Introduction: 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 have 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 technological sophistication that has enabled the rapid advances in neuroscience in the past decade and a half has primarily benefited psychiatry research, not practice. Neuroimaging is finally allowing us to directly study brain function. Although there is no question that the field is in the very early 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.

However, this state of affairs is beginning to change. Serendipitously, it was discovered that exposure to EP-MRSI (echo-planar magnetic resonance spectroscopic imaging) occasioned significant mood improvement in adults with bipolar disorder (BPD) immediately following a research scanning procedure . A systematic study was then designed to further assess this effect. Results showed that BPD adults receiving EP-MRSI showed significant improvement on the Brief Affect Scale compared to the sham and healthy control groups.

In a recently published study, DeCharms et al 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 magnetic resonance imaging (rtfMRI) . The enhancement took place when rtfMRI-based training was provided, but not in a control group that received similar training without rtfMRI information, showing that the effect was not due to conventional, practice-based neural plasticity alone. Similarly, Birbaumer et al have recently reported successful self-regulation of the BOLD signal of supplementary motor area (SMA) and parahippocampal place area (PPA) using rtfMRI neurofeedback and Blecker et al 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 now discovering with the advanced technology of the fMRI what has been known and practiced for over thirty years using the "poor man's" form of neuroimaging – the EEG. As this volume makes clear, there is an ample body of extant research on EEG biofeedback. Although there are significant methodological weaknesses in some of these studies, and much fundamental research

remains to be done, still virtually all the EEG biofeedback 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 rtfMRI studies noted above show, this effect can be demonstrated in several areas of the brain, suggesting that neurofeedback, whether using EEG or rtfMRI, is applicable to functional brain disorders arising out of various different patterns of functional disturbance or dysregulation. This has also been recognized in the field of EEG biofeedback for some time, after the initial application to epilepsy led to the extension of this technique to related disorders (ADHD, TBI, depression).

There is also an important convergence occurring between academic psychiatry and EEG biofeedback through the interest of both groups in event related potentials. Event-related potentials (ERPs) are brain generated electrical responses to specific stimuli. A subset of ERPs known as auditory evoked potentials (AEPs) has entered mainstream medical practice as a screening instrument for newborn hearing impairment . Researchers have renewed interest in using ERPs to study the pathophysiology of psychiatric disorders such as adult schizophrenia [and post-traumatic stress disorder . ERP research in children has primarily centered on autism [and ADHD . Researchers have investigated differences in ERP's and ERD's (event related desynchronization) in ADHD and normal children . Work has been underway for several years on the development of a quantitative ERP database similar to qEEG databases for assessment purposes, with ERP's and ERD's measured under several task conditions. Initial clinical work with this database suggests that ERP's and ERD's reveal dysfunction that is independent of abnormalities shown through spectral analysis in QEEG. EEG biofeedback studies are increasingly using ERP's as an index of changes in information processing in the brain, and hence as a physiological outcome measure in EEG biofeedback efficacy and validation studies , as was described above in the chapter by Gruzelier.and Egner.

Multiple pathways for intervention in psychiatry

Not too long ago, clinical bias towards 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 Food and Drug Adminstration (FDA) has approved devices such as VNS, a wrist electrical stimulator, and a cranial electric stimulator for treating brain based disorders.

Altering inputs to the brain either 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 EEG biofeedback, which has repeatedly 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 non-linear dynamic or chaotic systems have consistently revealed the regulating power of feedback in complex systems, those 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 - involve 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 vagal nerve stimulation, transcranial magnetic stimulation (both presented in detail in this volume) as well as cranial electric stimulation, audio-visual stimulation, and wrist electrical stimulation, which have interesting, though perhaps less central applications.

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

Overview of three emerging approaches – EEG biofeedback, rTMS, VNS

Each of the chapters that follow in this volume reviews in detail the research and clinical experience to date with these three new approaches. This includes 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 here is a summary of the most salient and interesting findings for child and adolescent psychiatry from these chapters, omitting most aspects of the critical discussion of methodological detail.

Research using quantitative 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 a variety of disorders of behavior, emotion, thinking, learning, and development. This research into the electrophysiology of psychiatric disorders is reviewed in chapter 2 by Chabot, DiMichele, and Prichep. Simply put,

their review 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 reliably measured in different laboratories, and may reflect neurophysiologically distinct subtypes of dysfunction within groups that are phenomenologically similar. It is now 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 both research and treatment in psychiatry. Both are likely to be more effective when based on participant/patient selection that shows greater homogeneity.

Electrophysiological subtyping based on the QEEG may provide such a means in the future, as QEEG research is providing evidence of physiologically specifiable subtypes within these heterogeneous groups. This is described for a variety of disorders, including schizophrenia, substance abuse, mood disorder, anxiety disorders, attention-deficit hyperactivity disorder (ADHD), and learning disabilities. Some promising research is presented that suggests that these electrophysiological subtypes make have practical significance for psychopharmacology and for 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 SSRI's among those 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 neurophysiological substrate of reactive/anxious temperament among infants. This pattern, of frontal activation asymmetry such that there is greater activation in the right compared to the left frontal cortex, is similar to that observed with some adults with depression. In addition, the infants of depressed mothers display this same frontal EEG activation asymmetry, even as young as at 3-6 months and at 1 month of age.

The bulk of QEEG research into child and adolescent psychiatric disorders has been done with ADHD. Multiple QEEG studies have demonstrated a pattern of electrophysiological abnormality among individuals with this disorder. Discriminant function analysis using QEEG variables has shown very high levels of sensitivity and specificity in identifying ADHD participants in several studies. In fact, 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 would suggest that QEEG should be the preferred means, since validity and reliability are high and cost is relatively low.

Summary of chapters on feedback strategies

If the domain of brain electrophysiology, as revealed in the EEG, is meaningfully associated with psychiatric dysfunction, then this domain would appear 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 EEG biofeedback into psychiatry. The capacity of individuals to use real time feedback of the

EEG in order to alter it through operant conditioning or learning has been established for many years. Numerous studies have shown that EEG biofeedback (EBF), also called neurofeedback or neurotherapy, result in measureable and replicable improvements in attention, impulsivity, mood, anxiety, memory, and learning, as well as clinically significant improvements in addictive disorders and epilepsy, in children and adults.

As with QEEG, the bulk of research into EBF has been with ADHD. This work is reviewed by Monastra in chapters 3, and by Gruzelier and Egner in chapter 4. Five controlled studies have been published, including one 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, have been published as well. 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 have also documented neurophysiological changes as well, including improvements in EEG and in ERPs. Although much more follow up research needs to be done, several studies show the maintenance of gains years after the EBF training ended. There is also growing evidence of the specificity of effect in EBF, such that the effect (behavioral and physiological) varies by specific location and frequencies trained.

Substantial validation research has also 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 have also been reported. A recent meta-analysis indicated that 82% of patients demonstrated greater than 30% reduction in seizures, with an average greater than 50% reduction. This outcome is all the more significant in that 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 as well as a case series using the newer QEEG guided approach, is reviewed by Walker and Kozlowski in chapter 8.

In chapter 5, 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 GAD, OCD, phobic anxiety, and PTSD 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 appear to have 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 EEG biofeedback in adolescent psychoactive substance use disorder (PSUD) in chapter 6. In research with adults with PSUD, multiple RCT's as well as uncontrolled studies have shown protocol specific EEG changes, and improvements on measures of depression (self-rating), attention (CPT) and stress (physiological). Several long term follow-ups showed a significant reduction in the one year abstinence/recidivism rate for the EBF group compared to 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 also benefit from this treatment. Given that EBF is medication free and has been shown to be effective with ADHD, a frequent co-morbid condition with PSUD, EBF appears to have particular value for these (PSUD with ADHD) patients where the risk of medication abuse is high. Family therapy, currently, is the primary intervention for adolescent substance abuse Given that few safe, patient centered treatment options exist for children and adolescents with substance abuse, neurofeedback warrants further investigation as well as consideration in treatment planning.

Reviews of the literature on treatment for traumatic brain injury (TBI) and reading disabilities (RD) indicate that very few of the commonly used interventions have shown efficacy in formal research, and that the effect size of these techniques is usually quite small. In chapter 7, Thornton and Carmody provide an overview of the research and clinical experience with the use of EBF with TBI and RD. 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, as well as in the EEG. Cessation and reduction of medication has also been reported as well as return to productive work. For RD, 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 RD is described using EBF guided by QEEG based on a cognitive task activation database. Significant improvements are shown as measured by a variety of neuropsychological measures.

Summary of chapters on stimulation strategies

Vagal Nerve Stimulation (VNS), reviewed by Martinez, Marangell, and Hollrah in chapter 9, 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 12.

Consideration of the mechanism of action of VNS as well as reports of mood improvement when used for epilepsy suggest that VNS may have anti-depressant effect. 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 one 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 as well general anesthesia need to be weighed when considering this intervention. For patients suffering from chronic refractory epilepsy, they may choose the possible clinical benefit over the risk. Adult patients suffering from chronic refractory depression face similar-risk benefit considerations, although the single RCT completed to date shows limited benefit. However, it is rare that safer alternative interventions

are exhausted in childhood and adolescent depression. Nevertheless, VNS shows promise as an intervention for depression in this population. Further research is warranted.

Research and clinical experience with repetitive transcranial magnetic stimulation (rTMS) is reviewed by Morales, Henry, Nobler, Wasserman, Sackheim, and Lisanby in the final chapter of this volume. Although not currently approved by the FDA for the treatment of any disorder at any age, this non-invasive form of brain stimulation is under active study in adults as a form of intervention for major depression, schizophrenia, anxiety disorders, and some neurological conditions. Although there have been no controlled trials on the efficacy of rTMS for treatment of any disorder in children and adolescents, case studies are reported with nine children. Based on an 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 appears to carry minimal risk to children. However, given that repetitive TMS carries greater risk, and that no safety studies have been completed to date, research investigating 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, ECT is generally used as a second line treatment with treatment resistant adult patients. However, it is rarely used with children and adolescents, and efficacy data are quite limited. No controlled trials have been published. In a review of published case studies, it appears 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 co-morbid conditions have significantly improved the side effect/adverse events profile in both adult and adolescent populations. Recent reports suggest that children and adolescents appear to have transient cognitive side effects that resolve completely. Further safety and tolerability research is needed.

Clinical considerations in evaluating new treatments modalities

The chapters in this volume 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 carefully evaluated 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 randomized controlled trials (RCT's).
At the same time, 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 . For example, many if not most controlled trials exclude participants with co-morbid conditions. Research has shown that "the majority of patients were excluded from participating in the average study" due to the presence of co-morbid conditions . However, the clinical reality faced by practitioners is that few patients have only one clearly definable Axis I diagnosis.

In addition, the use of strictly manualized approaches or treatment protocols, as in controlled research, is often impossible or contraindicated in clinical practice due to a variety of factors which may be controlled in research but cannot 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, while the therapeutic relationship accounted for 30%, patient characteristics and extra therapeutic change for 40%, and expectancy and placebo for 15%. For these reasons, it is clear that real world conditions may limit the implementation of research based treatments , and that research based dictates which interfere with the therapeutic relationship should be adjusted in clinical practice
For these and other reason, it has been argued by Seligman and others that controlled (RCT) trial research, while high in internal validity, is weak on external or ecological validity. In order 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 RCT's.

For the purposes of summarizing in this chapter the degree of empirical support for each of these three new interventions in child and adolescent psychiatry, three dimensions will be discussed : (1.) efficacy – or evidence of benefit in controlled research, especially randomized controlled trials (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 chapters in this volume have referred to guidelines issued by the two professional organizations for EEG biofeedback providers. , which are substantially similar to those that have been offered by The American Psychological Association (APA) 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 has outlined a set of guidelines to evaluate clinical practices, as for example in the Academy's practice parameter for the use of stimulant medication. They are considerably less stringent than those adopted by the APA and the EEG biofeedback 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 a number of reasons. First, patients suffering from child and adolescent psychiatric disorders and their families have very few therapies to choose from that are conclusively proven through empirical research or are Food and Drug Administration (FDA) approved. 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 to utilize treatment approaches that have not been fully evaluated in this age range, and then use the basic clinical method of careful observation of the effects on a single

participant of that treatment approach, adjusting treatment according to the response and side effect profile shown. 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 limited in scope, this situation is not likely to change rapidly. Third, many advances in psychiatry over the last decade have been due to changes in the way medications are use in clinical practice, rather than based on methods first validated in research. Experiences shared among informal networks operating 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 prior to 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 are suggesting that an overly strong emphasis on the need for RCT's to demonstrate efficacy may be mistaken, since results from non-randomized observational studies have generally been quite similar to randomized controlled trials.

In this chapter, the Academy's practice parameter for the use of stimulant medication will be used to assess the dimension of the evidence of efficacy and effectiveness of the new approaches described in this volume. The dimension of efficiency will also be discussed for each new intervention.

The AACAP classification uses a hierarchal system with four levels: minimal standard (MS), clinical guidelines (CG), options (OP), 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) and/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 avoided." Not endorsed are used for practices known to be ineffective or contraindicated.

As an example of the AACAP practice standards, stimulant medications are options (OP) in the treatment of apathy due to a general medical condition, adjuvant medical uses such as for psychomotor retardation, and treatment-refractory depression. Stimulant medications for ADHD meet the criteria for clinical guidelines (CG) not minimal standard (MS). The conservative recommendation is most likely due to the lack of overwhelming clinical consensus and somewhat limited number of published double-blind trials.

These standards may be confusing to patients and parents when discussing treatment alternatives. However, discussion of treatments using an evidence-based approach is possible in the clinical setting . The clinician needs to use his/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, other wise known as effect size. The clinician assesses effect size based on three possibilities: 1) strength of association 2) magnitude of difference, and/or 3) measures of risk potency . Interpretation of effect size is given in Table 2 but needs to be balanced by clinical assessment of severity of disorder versus side effect and/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.

AACAP guideline ratings for feedback strategies

EEG biofeedback meets the AACAP criteria for clinical guideline (CG) for treatment of ADHD, seizure disorders, anxiety (OCD, GAD, PTSD, phobias), depression, reading disabilities, and addictive disorders. This suggests that EEG biofeedback should always be considered as an intervention for these disorders by the clinician. Clearly there is stronger evidence of efficacy, indeed the strongest among the three new approaches being considered in this volume, for the use of EEG biofeedback for ADHD in children and adolescents. Due to this high level of empirical support, the use of EEG biofeedback for ADHD will (with the publication of the second RCT) meet the most stringent APA criterion of efficacious and specific, which requires two independent RCT’s among other factors.

It is not entirely clear what would be required to meet the AACAP minimal standard guideline requiring “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 (MS) 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. EEG biofeedback for ADHD can arguably be considered to meet this standard once the additional RCT is published.

EEG biofeedback has been widely utilized clinically by practitioners from a range of disciplines – psychiatry, psychology, social work, counseling, nursing, and education, among others. Indeed, the dimension of clinical effectiveness represents the peculiar strength of EEG biofeedback, as its application has become widely disseminated, in many areas well before the base of research support had been established. There is strong clinical consensus among practitioners that it is useful in clinical practice with each of these disorders. Again here, the strongest evidence of clinical effectiveness is in the area of ADHD. Several of the larger case trials summarized by Monastra in his chapter in the volume were, in essence, effectiveness studies completed in outpatient practices. In addition, EEG biofeedback is widely used with children and adolescents with anxiety, depression, and disruptive or explosive behavior.

Specific recommendations, based on the body of empirical evidence available at present, 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 option in cases when significant side effects or insufficient improvement occurs with medication. EBF should be considered an option for epilepsy, anxiety and depression, addictive disorders, and TBI when patients and/or parents prefer not to use medication, when medications aren’t well tolerated or are not fully effective, and/or when proven psychotherapeutic approaches are ineffective or contraindicated. EBF may

also be used in combination with psychopharmacology and/or psychotherapy. EBF for reading disabilities may be recommended as an option when more conventional methods fail.

Emerging areas of application of EEG biofeedback are with migraines, reactive attachment disorder (RAD), and autistic spectrum disorder (ASD). There are widespread and consistent clinical reports of efficacy with migraines and with RAD. For migraines, in addition to EEG biofeedback, a newer form of EEG biofeedback called passive infrared hemoencephalography (pirHEG) has shown considerable promise in clinical trials. pirHEG uses an infrared lens mounted on the forehead to measure long range infrared temperature. Increases in the pirHEG signal are believed to reflect a composite of thermal energy generated by brain cells, vascular supply, and vascular return. Training migraineurs to increase the pirHEG readings through feedback has consistently led 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 pirHEG sessions. Over 90% of the participants, most of whom had not responded to medication, reported significant improvements in migraine pain and frequency of migraine attacks.

With autistic spectrum disorder, based largely on word of mouth communication among parents, there is rapidly growing clinical experience with EBF. There is one published controlled group study of EBF for autism . In that study, 24 autistic participants were randomly assigned either to the EBF treatment or to a waitlist control group. Twenty or more sessions (average = 36) of EEG biofeedback using a standard protocol were given. EBF participants showed significant improvements on measures of sociability, communication, health, and sensory awareness compared to 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 appears to be helpful both to more severe autistic individuals and to individuals with high functioning autism and Asperger's disorder. Approximately 70 to 80% of patients with ASD benefit. The degree of benefit ranges from mild to quite profound. For example, one 4 year old boy had recently been diagnosed with PDD-NOS. He had extremely severe behavioral and emotional self-regulation problems, with episodes of extreme aggression toward his brother and parent 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 very little social engagement, even with his mother. After three months of twice weekly EEG biofeedback 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 the child is tuned in to or engaged with the world around him rather than being "in his own world". It appears to be the case the EEG biofeedback treatment in ASD requires many more sessions than for other disorders; for this reason, home training under the supervision of the clinician is often employed.

The rationale for use of neruofeedback 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 DSM 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. EEG biofeedback, like psychopharmacology 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 EEG biofeedback. In the ABA condition reversal studies with epilepsy described in chapter 8, participants were first trained with a protocol designed to decrease slow EEG activity (theta - 4 to 7 HZ) and increase faster activity (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. However, this reversal condition, which surely would no longer be permitted under IRB review, was not employed 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 employed 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 are self-limiting or can be ameliorated by adjusting the training protocol. There are no published reports of permanent negative effects from EEG biofeedback training.

Finally, regarding the cost benefit ratio with EEG biofeedback, which must be evaluated in comparison to other approaches, the issue is complex. On the one hand, like psychotherapy, a course of EBF will almost certainly be more costly than use of medication during the same period of time. However, if the benefits of EEG biofeedback endure long after the treatment ends, while medication use is ongoing, EEG biofeedback may have a cost advantage in the long run. Much more research into the longevity of benefits form EEG biofeedback is needed. to clarify this question. However, since many insurance companies do not cover EEG biofeedback, 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 their competence. There is a professional certification organization (BCIA – Biofeedback Certification Association of America) that certifies basic competence in EEG biofeedback. However, in EEG biofeedback practice, as in other areas of clinical practice, clinical skill level varies by individual clinician. Because most practicing child psychiatrists are unlikely to have established familiarity with EEG biofeedback providers through previous referrals, this difficulty is the more significant.

AACAP guidelines ratings for stimulation strategies

Turning now to neuro-stimulation strategies covered in the volume, vagal nerve stimulation (VNS) meets the AACAP standards for clinical guidelines (CG) as an intervention for treatment refractory epilepsy because a significant number of published open trials and case studies exist showing efficacy. This suggests that VNS should be considered in the treatment of epilepsy.

However, until further improvements in VNS safety and efficacy occur and research is published on efficacy for specific psychiatric disorders with child and adolescent populations, AACAP guidelines indicate that VNS should be considered an option (OP) in treatment refractory psychiatric disorders.
rTMS is not an FDA approved treatment intervention, but is being actively investigated in adults for the treatment of depression, schizophrenia, anxiety disorders, and some neurological conditions. rTMS meets the standard for clinical guidelines (CG) as a treatment for bipolar disorder, unipolar disorder, and schizophrenia, based on seven case reports showing benefit. This number of cases is very 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 those who have had multiple medication trials with limited efficacy or intolerable side effects, until further data appears in the literature. rTMS has also 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 for rTMS is considerably greater than the risk of single or paired pulse TMS, based upon adult studies, in which headache, scalp pain, affected hearing and increased risk for seizures have been described. There have been no safety studies of rTMS that included children and adolescents; particular caution is warranted with respect to dosing of rTMs in children due to their lower seizure thresholds.

Future directions

A great deal of additional research is needed for all of the strategies reviewed in this volume. Clearly, work is in the very early stages with VNS and rTMS for child and adolescent psychiatric disorders, and further investigation is needed at every level.

EEG biofeedback has a greater body of empirical support, but for several types of disorder, this work is also at early stages. Unlike VNS and rTMS, little research on EBF has been done to date in major medical centers, and none in psychiatry settings. Major research support has been lacking. This seems unfortunate given the promise shown by EBF in the body of empirical study completed to date. Further research is clearly warranted into the efficacy of EBF for each of the psychiatric disorders discussed in this volume. In particular, research into the mechanism of effect and into the specificity of effect using different training protocols would be useful. In addition, further study is needed comparing fixed protocol training to training which 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 chapter on EBF for epilepsy, Walker and Kozlowski describe an alternative theory of seizure generation, that seizures result from over activation 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 seizure 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. However, the use of placebo may involve increased risk in some instances. This was documented in the ABA condition reversal studies described above, 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.

In addition, it should be recognized that it is quite 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 non-contingent 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 need to be developed to validate these emerging interventions.

Given the early success of real time feedback with fMRI (rtfMRI), it appears likely that much more work will be done in this area. However, fMRI is much more expensive and less widely available than EEG equipment; therefore, particularly as rtFMRI biofeedback training advances, it will be crucial to conduct comparative studies of rtfMRI and EEG in their application to neurofeedback training.

rtfMRI has a significant advantage over EEG in that this technique allows for imaging of subcortical structures, which can then be impacted by feedback based training. EEG source localization techniques have been developed which allow for EEG surface recordings to accurately image three dimensionality using high time resolution statistical parametric mapping for tomographic images of electric neuronal activity. This method, called Low Resolution Electromagnetic Tomography (LORETA), employs the methods of statistical inference for the localization of brain function as used in PET and fMRI studies to the EEG, and results in a low spatial resolution estimate of the electric neuronal activity . 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 methodological developments has placed LORETA at a level that compares to the more classical functional imaging methods, such as PET 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, as artifact much more significantly impacts this feedback modality

than it does EBF. Considerable research is needed in this area in order to further validate the neuroimaging function of LORETA and investigate the efficacy of LORETA feedback.

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