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Neurofeedback for Autistic Spectrum Disorder: A Review of the Literature

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Abstract There is a need for effective interventions to address the core symptoms and problems associated with autistic spectrum disorder (ASD). Behavior therapy improves communication and behavioral functioning. Additional treatment options include psychopharmacological and biomedical interventions. Although these approaches help children with autistic problems, they may be associated with side effects, risks or require ongoing or long-term treatment. Neurofeedback is a noninvasive approach shown to enhance neuroregulation and metabolic function in ASD. We present a review of the literature on the application of Neurofeedback to the multiple problems associated with ASD. Directions for future research are discussed.

Keywords Autistic spectrum disorder · Treatment · Neurofeedback

Introduction

Autistic spectrum disorders (ASD) are a heterogeneous group of pervasive developmental disorders including Autistic disorder, Rett disorder, Childhood disintegrative disorder, Pervasive developmental disorder-not otherwise specified (PDD-NOS), and Asperger disorder. Children with ASD demonstrate impairment in the following functions: (1) social interaction, (2) verbal and nonverbal communication, and (3) behaviors or interests (DSM-IV-TR; APA 2000). ASD may be comorbid with sensory integration difficulties, mental retardation or seizure disorders. Children with ASD may have severe sensitivity to sounds, textures, tastes, and smells. Cognitive deficits are often associated with impaired communication skills (National Institute of Mental Health; NIMH 2006). Repetitive stereotyped behaviors, perseveration, and obsessionality, common in ASD, are associated with executive deficits. Executive dysfunction in inhibitory control, set shifting, and mediating frontostriatal neural pathways have been attributed to ASD (Schmitz et al. 2006). Seizure disorders may occur in one out of four children with ASD; frequently beginning in early childhood or adolescence (National Institute of Mental Health; NIMH 2006).

Autistic disorder includes the following triad of symptoms: (1) impaired social interaction, failure to develop peer relationships, or lack of initiating spontaneous activities; (2) deficits in communication including delay in or lack of spoken language, inability to initiate or sustain conversation with others, stereotyped repetitive use of language or idiosyncratic language; and (3) restricted repetitive and stereotyped behavior, interests, inflexible adherence to routines or rituals, and repetitive motor patterns (e.g., hand or finger flapping or twisting) (DSM-IV-TR; APA 2000).

Individuals with Asperger disorder frequently have high cognitive function, engage in literal pedantic speech, experience difficulty comprehending implied meaning, exhibit problems with fluid movement, and manifest inappropriate social interactions. Pervasive developmental

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disorder-not otherwise specified (PDD-NOS) reflects deficits in language and social skills, which do not meet the criteria of other disorders. In contrast, childhood disintegrative disorder and Rett's disorder both have normal periods of early development followed by loss of previously acquired skills. Common features among these conditions include communication and social skill deficits. There is considerable variability in terms of onset and severity of symptomatology within the autistic spectrum of disorders (Attwood 1998; Hamilton 2000; McCandless 2005; Sicile-Kira 2004; Siegel 1996).

Research reviewing the epidemiology of autism (Center for Disease Control and Prevention; CDC 2006) reported between 1 in 500 to 1 in 166 children in the United States diagnosed with the disorder. In fact, their most recent report (CDC 2007) suggests a prevalence of 1 in 150 and as high as 1 in 92 boys. According to Blaxill (2004), the rates of ASD were reported to be <3 per 10,000 children in the 1970s and rose to >30 per 10,000 in the 1990s. This rise in the rate of ASD constituted a ten-fold increase over a 20 year interval in the United States. With increased prevalence comes a need to design and empirically validate effective treatments for those impacted by autistic disorders.

A review of multiple studies reported the rate of abnormal EEGs in autism ranged from 10 to 83%, while the mean incidence was 50%. Atypical EEGs often predict poor outcomes for intelligence, speech, and educational achievement (Hughes and John 1999). In a more recent review of research, Rippon et al. (2007) proposed a model of reduced connectivity between specialized local neural networks and overconnectivity within isolated neural assemblies in autism. Disordered connectivity may be associated with an increased ratio of excitation/inhibition in key neural systems. Anomalies in connectivity may be linked to abnormalities in information integration. A common deficit characterizing children with autism is executive dysfunction. Executive deficits of planning, flexibility, and inhibition are associated with dysfunctional integration of the frontal lobes with other brain regions. Therefore, executive dysfunction impacts upon social, behavioral, and cognitive function (Hill 2004). In SPECT (single photon emission computed tomography) scans of children with autism, abnormal regional cerebral blood flow in the medial prefrontal cortex and anterior cingulate gyrus was related to impaired communication and social interaction. Altered perfusion in the right medial temporal lobe was associated with the obsessive desire for sameness (Ohnishi et al. 2000). Functional neuroimaging studies have linked social cognition dysfunction and language deficits in autism to neural substrates (Pelphrey et al. 2004; Welchew et al. 2005). During a sentence comprehension test, individuals with autism showed less functional connectivity between Broca's area and Wernicke's area, suggesting a lower degree of information organization and neural synchronization relative to a control group during language tasks (Just et al. 2004). A review of neuroimaging studies has found key brain structures including the amygdala, superior temporal sulcus region, and fusiform gyrus to function differently in individuals with autism than in controls (McAlonan et al. 2004). The aforementioned research provides evidence for a neuropathological basis of ASD.

Treatments for ASD

Green et al. (2006), who surveyed parents on the therapies they most frequently selected for their children with ASD, found as many as seven different therapies were utilized. Speech therapy was the most common treatment, being selected by 70% of parents. Psychopharmacological treatment was utilized by 52% of parents. Other treatments included: visual schedules (43%), sensory integration (38%), and applied behavior analysis (36%). Special diets were implemented by 27% of parents and 43% utilized vitamin supplements.

Behavioral Interventions

The method of treatment with the most empirical support is applied behavior analysis (ABA), a form of behavior modification. The goal of this therapy is to improve social interaction, behavior and communication (Bassett et al. 2000). ABA is firmly based on the principles of operant conditioning and measures small units of behavior to build more complex and adaptive behaviors through reinforcement. Typically, imitation, attention, motivation, and compliance are targeted early (Couper 2004). The first program, developed in 1970 by Lovaas et al. (1973), which utilized this technique was the Young Autism Project (YAP). This full time program uses an intensive, highly structured behavioral program which is delivered on a one-to-one basis requiring several hours a day. An evaluation of the program for children diagnosed with autism receiving 40 or more hours per week for two or more years included: increased cognitive and academic function (47% of the treatment group versus 2% of controls) (Lovaas 1987); and follow-up research of children into late childhood and adolescence reported improved cognitive function and education in regular classrooms (47% of the treatment group versus 0% of controls) (McEachin et al. 1993). However, these studies have been criticized based on the use of their outcome measures (Schopler et al. 1989), which included IQ scores and school placement. Subjects in the study were not randomly assigned, which is believed to have contributed to the

observed outcome differences. It is also believed that the individuals used in the study were high functioning autistics, which may account for the high IQ scores (Mundy 1993).

Other studies that measured outcomes of ABA treatment in autism found less promising results than those of Lovaas (1987). In an attempt to replicate Lovaas' study, Birnbrauer and Leach (1993) designed the Murdoch Early Intervention Program for 24–48 month old children with autism. After 24 months of their program, they reported four of the nine children in the experimental group showed signs of approaching normal levels of functioning, compared to only one of five children in the control group. However, none of the children achieved completely normal functioning and improvements in other symptoms were minimal to moderate. In a retrospective study of a home-based ABA program of shorter duration than the Lovaas study, Sheinkopf and Siegel (1998) compared 11 children who received ABA to a control group receiving an unspecified school based treatment. Children in the experimental group had significantly higher posttreatment IQ scores. Smaller differences in symptom severity were found between the groups, but the experimental group still met diagnostic criteria for either autism or PDD. Anderson et al. (1987) conducted home-based ABA on 14 children for between 15 and 25 h per week. While modest gains were made in mental ages scores and communication skills, the most impaired children failed to make progress, and none of the children were able to be integrated into regular classrooms following treatment.

Fenske et al. (1985) examined the influence of age at intervention on treatment outcome using an ABA protocol. They compared nine children who began treatment before 60 months of age to those who started treatment after 60 months. While four of nine children in the younger group were able to be enrolled in a regular classroom after 2 years of treatment, only one of the nine children in the older group was. Although it appears that age at program entry was an important variable in treatment outcome, enrollment in a regular classroom was their main outcome measure and so this conclusion requires further research support. Harris et al. (1991) compared preschool children who were autistic to those who were not, both before and after a behavioral intervention during the school year. The children with autism showed a 19 point average IQ gain and an 8 point average gain in their language quotient. The more typically developing children showed no significant change in such measures over the same time period.

Project TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children), developed by Eric Schopler and colleagues (Schopler and Reichler 1971) at the University of North Carolina at Chapel Hill, differs from ABA, but utilizes behavioral principles to maximize the skills of children who are autistic (Herbert et al. 2002). Structured settings are provided and teachers use individual workstations where children can practice their skills. For example, because they process visual information more efficiently than verbal information, visual cues may be provided to compensate for auditory processing deficits. Ozonoff and Cathcart (1998) investigated the effectiveness of a home-based TEACCH treatment program for children with autism. Parents were taught to work on cognitive, academic, and prevocational skills, which they provided for 4 months. The treatment group was compared to a control group who underwent testing with the psychoeducation profile-revised (PEP-R; Shopler et al. 1990), but did not receive any treatment. Children who received the TEACCH treatment from their parents showed significant improvement over the control group on tests of imitation, fine and gross motor, nonverbal conceptual skills, and overall PEP-R scores. Progress was three to four times greater on all outcome tests in the treatment group as compared to the control group.

Smith et al. (2000) conducted research on behavior therapy that utilized a matched-pair random assignment procedure. One group received intensive behavioral treatment, while the other received parent training. Participants, who ranged in age from 18 to 42 months at the start of treatment, were reassessed at follow-up at ages 7–8 years. Significant differences were noted for the intensive treatment group (30 h of training per week over 2–3 years) in contrast to the parent training group (5 h per week of training for 3–9 months) for IQ and language function.

Other longitudinal research has also been conducted utilizing intensive behavioral therapy for children with autism. Sallows and Graupner (2005) randomly assigned 24 children with autism (aged 3 years) to a clinic-directed group replicating the behavioral program implemented by Lovaas (1987) and McEachin et al. (1993), or a parent-directed group. Both clinic and parent-directed groups received approximately the same treatment of nearly equal intensity, however. After combining both treatment groups at the end of the first year of treatment, 11 of 23 (48%) children showed rapid learning (determined by change in IQ scores), and achieved average scores on cognitive, language, daily living, and socialization skills measures at post-treatment. Children in the parent-directed condition did about as well as the children in the clinic directed group. Following 4 years of therapy, rapid learners (those with a 49 point increase in Full Scale IQ) were successfully attending regular classrooms. Moderate learners (2.5 point increase in Full Scale IQ) also showed increases in cognitive, adaptive, language, and social skills but continued to require support services, modified curriculums, or special education. The children who had the capacity for imitation, social responsiveness, and language attained the

best treatment outcomes (Sallows and Graupner 2005). These authors found an extremely large change in IQ for the rapid learners. Almost half of the 23 subjects in this study fell into this group. Some possible confounds include the fact that some children were originally assessed with the Bayley Scales of Infant Development (Bayley 1993) and then assessed using the Wechsler (1989) scales at follow up. However, the authors found no significant differences between those assessed with the Bayley scales twice, and those assessed with the two different measures. Furthermore, although the two groups were matched on IQ, other variables were not adequately controlled for, such as imitation.

Eikeseth et al. (2002) compared children between 4 and 7 years of age receiving 28 h per week of behavioral treatment to a comparison group receiving 29 h of eclectic special education treatment per week. At a 1 year follow up evaluation, children in the behavioral treatment group gained 17 average IQ points, 13 points on a standardized measure of language comprehension, 27 points on a measure of expressive language, and 11 points on a measure of adaptive behavior. In contrast, the group receiving the eclectic treatment gained 4 IQ points, 1 point on the language measures, and zero points on adaptive behavior. A follow up study of both groups of children who continued to receive their respective treatments (i.e., behavioral and eclectic) 3 years later was recently conducted by Eikeseth et al. (2007). The behavioral treatment group again showed greater gains from pretreatment to follow up, though gains between the first treatment study and this follow up were only significant on the Vineland Adaptive Behavior Composite and Vineland Socialization scales. Although most gains in IQ score were obtained between pretreatment and the 1 year follow-up from their first study, the Vineland Composite score increased throughout all years of treatment, and significant changes in the Vineland Socialization and Daily Living scores occurred only after the first year. Thus, it may be important to continue ABA treatment beyond 1 year to obtain the greatest benefit to the child.

Butter et al. (2006) recently described eight case reports of children with ASD and mental retardation who received early intensive behavioral intervention (EIBI), a behavioral treatment designed to address the core symptoms of autism. In EIBI, reinforced practice as well as functional analysis is utilized in a comprehensive and individualized format. This treatment is most frequently conducted for 30–40 h per week, and involves one-on-one instruction along with small group activities. Following treatment, none of the children met criteria for either mental retardation or any PDD. There were large improvements in IQ (34.6 point increase) and adaptive behavior (increased 43 standard score points), with both Nonverbal IQ and achievement scores ending in the average range, although language abilities remained impaired for seven of the eight children.

Ben-Itzchak and Zachor (2007) investigated the effects of intellectual functioning and severity of autistic symptoms on outcome following intensive behavioral intervention. Groups were formed based on IQ scores (high >70 vs. low <70), level of social interaction (high versus low), and communication deficits (high versus low) using the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 1999), which were assessed prior to treatment. After 1 year of intervention provided one-on-one by a behavioral therapist for at least 35 h per week, significant improvements were noted in all domains measured by the ADOS, which include imitation, receptive and expressive language, nonverbal communication skills, play skills, and stereotyped behaviors. The authors found that children with higher cognitive levels and those with fewer social interaction deficits were more apt to acquire developmental skills post-treatment, particularly in the areas of receptive and expressive language, and play skills. Progress in expressive language abilities was more related to good social abilities, while play skills progress was more related to the child's cognitive level.

In addition to ABA, a new behavioral treatment utilized with ASD patients is errorless compliance training, developed by Joseph Ducharme (2005). It is a non-coercive, parent-mediated approach, which involves teaching a child to comply with requests from their parents in a systematic and gradual manner. During an initial observation period, a hierarchy of compliance probabilities (Levels 1–4) is developed based on a wide range of parental requests. Level 1 indicates a high level of child compliance and level 4 indicates low probability of child compliance. Several level 1 requests are delivered to the child while providing extensive praise and reinforcement, while higher level requests are slowly faded in to prevent noncompliance. Ducharme et al. (2007) applied errorless compliance training to three boys with characteristics of Asperger syndrome. Observational data from the parents indicated great improvement in the children's' compliance following treatment, with generalized and durable effects at 2 months post treatment. Furthermore, parents reported being satisfied with the intervention.

In their clinical practice guidelines report, the New York State Department of Health Early Intervention Program recommended that ABA and other behavioral interventions be included in the treatment of autism. They specify that intensive behavioral programs should include a minimum of 20 h of intervention with a therapist per week. Furthermore, the guidelines state that parents should be included in the intervention, and that they be trained in the use of behavioral techniques to provide additional instruction at home, with regular therapist consultation.

Although promising, intensive behavioral programs are costly and require extensive time on the part of the therapist as well as the family, and debates are ongoing about who should pay for such services (Couper 2004). The Human Services Department of Victoria, British Columbia found that 63% of 262 families with autistic children spend between $1,000 and $10,000 a year on treatment, while the median annual income was only $40,000.

Although behavior therapy improves social, cognitive and language skills, a year or more of intensive training has been used in most research studies that have demonstrated improvement. A strong commitment by parents to complete therapeutic programs is necessary to achieve positive outcomes. Although behavioral treatment methods show the most empirical support, there is still a need for additional therapies, which may be more easily administered and used in conjunction with the behavioral methods described. On the whole, research into this area is promising. However, there has been great variability between studies in their results, outcome measures have often been questionable (e.g., IQ scores, returning to regular classrooms), and this approach appears to be more effective with those who are higher functioning (i.e., higher IQ), thus leaving out the lower functioning individuals who are perhaps in greatest need of treatment.

Pharmacological Treatments

Pharmacological and biomedical interventions have also been utilized to treat individuals with ASD. A study conducted at the Yale Child Study Center found that 55% of a group of 109 individuals with a PDD were taking psychotropic medication, with 29.3% taking more than one medication (Martin et al. 1999). The most common medications were antidepressants (32.1%), followed by stimulants (20.2%) and neuroleptics (16.5%). The objectives of psychopharmacological treatment for autism include: decreasing the core symptoms of autism; decreasing anxiety and overfocus, improving social skills, reducing aggressive self-injurious behavior; increasing the effects of other interventions, and improving the quality of life for the child and their family. There is no single medication known to be beneficial to all children with ASD, nor that has specifically been developed for individuals with autistic spectrum disorder. Neuroleptics such as haloperidol and thioridazine have been utilized to reduce dysfunctional behaviors associated with ASD. The adverse side effects of sedation, irritability, and extrapyramidal dyskinesias limit the use of these medications, however.

A newer class of neuroleptic, referred to as atypical antipsychotics, improves social interaction and decreases aggression, irritability, agitation, and hyperactivity (Barnard et al. 2002). They have fewer extrapyramidal adverse side effects than haloperidol and thioridazine. However, most children experience a substantial weight gain within the first months of treatment (Committee on Children with Disabilities 2001). Risperidone is the only drug that has been approved by the FDA to treat the symptoms (irritability) of autism. A review published in the Cochrane Library examined three randomized controlled trials (Jesner et al. 2007). Meta-analysis indicated the drug was effective in treating the symptoms of irritability and aggression. The authors concluded that although risperidone may be beneficial, its use must be weighed against its adverse effects, most notably weight gain, and that long-term follow up is needed prior to determining its efficacy in clinical practice. However, researchers have provided some evidence of the drug's long term effects. A study conducted by the RUPPS Autism Network (Research Units on Pediatric Psychopharmacology; RUPP Autism Network 2005a) investigated the long-term benefit of risperidone in a two part study. Part one was a 4 month, open label trial, which was followed by an 8 week randomized, double-blind, placebo substitution study of risperidone withdrawal in those who were considered "responders". Participants whose medication levels were gradually reduced showed a greater return of aggression, temper outbursts, and self-injurious behaviors than those who continued the medication, for whom over 80% maintained their improvements and showed "very good tolerability". Although not an RCT, there is evidence to suggest that risperidone may be effective for time periods of up to 1 year (Zuddas et al. 2000). The relapse rate for those maintained on this medication has ranged from 12.5 to 25% (RUPP-AN, 2005a; Troost et al. 2005).

Recently a similar atypical anti-psychotic medication, Abilify (Aripiprazole), has been used with patients who are autistic. Stigler et al. (2004) administered the drug to 5 boys between the ages of 5–18 in a naturalistic, open-label trial over the course of about 20 weeks. Based on ratings from the Clinical Global Impressions-Improvement scale, they reported all children responded (CGI-I ratings of "much improved" or "very much improved") with minimal side effects including mild somnolence, and weight gain in one patient and weight loss in two others. They also reported significant improvement in aggression, agitation, and self-injurious behavior. This study, however, was obviously limited by its small sample size, lack of blinding, absence of a control group, and a failure to use randomization. Santangelo and Tsatsanis (2005) reported that there are currently no drugs that produce major improvement in the core social or pragmatic language deficits in autism, although several have limited effects on the behavioral features of the disorder.

Psychostimulant medications are often used with children who are autistic due to its success in the treatment of

ADHD (Jensen et al. 2007). Despite this, stimulant use in children who are autistic remains controversial and largely unproven in terms of efficacy. In the RUPP Autism Network Methylphenidate study (2005b), 49% of the sample was considered positive responders, leaving a significant percentage as non-responders and an 18% side effect rate overall.

Repetitive stereotypical and perseverative behaviors have been shown to be characteristic of both obsessive compulsive disorder (OCD) and autism (McDougle et al. 1995). The overlap between these disorders and the success of selective serotonin reuptake inhibitors (SSRIs) in treating OCD (Geller et al. 2001) has led to the use of SSRIs in treating symptoms of autism. One of the first trials of the SSRI, Prozac (Fluoxetine), found that doses ranging from 20 to 80 mg per day were effective based on Clinical Global Impressions in 15 of 23 individuals with autism (Cook et al. 1992). However, 6 out of the 23 experienced significant side effects such as restlessness, hyperactivity, agitation, increased appetite, and insomnia. A more rigorous 20 week placebo controlled crossover study found that fluoxetine significantly reduced repetitive behaviors compared to placebo (Hollander et al. 2005). Although there were no significant side effects, there also were no significant improvements in measures of speech or social interaction. Delong et al. (2002) reported a 69% positive response rate for fluoxetine in children, aged 2–8, who were autistic. Treatment parameters were quite variable with treatment duration ranging from 5 to 76 months and doses ranging from 4 to 40 mg/day.

A 12 week, double blind, placebo controlled study of fluoxetine reported this drug to be efficacious (McDougle et al. 1996). Eight out of fifteen adult subjects were rated as "responders", with improvements occurring for repetitive thoughts and behaviors, maladaptive behaviors, and repetitive language use. Side effects were noted to be mild and included sedation and nausea. However, a more recent study by McDougle et al. (2000) with children and adolescents found only 1 of 18 responded to the drug, with common side effects including insomnia, hyperactivity, agitation, and aggression. Martin et al. (2003) found similar results in children, reporting only 3 out of 18 subjects to be responsive to fluvoxamine.

At least four other SSRIs have been reported to have at least some beneficial effect, although none have demonstrated efficacy through placebo controlled studies. McDougle et al. (1998) found Zoloft (sertraline) to be effective for aggression and repetitive behavior in 42 adults with PDD, including adults with autism, Asperger's, and PDD-NOS, though 3 of the subjects dropped out of the study due to either agitation or anxiety. They found sertraline to be more effective for those with autism and PDD-NOS than for those with Asperger's disorder. Social relatedness did not appear to improve. Hellings et al. (1996) administered sertraline to adults with mental retardation, which included adults with autism. Aggression and self-injurious behavior were decreased in 8 out of 9 subjects. Other evidence of sertaline's effectiveness comes from case studies published by Steingard et al. (1997) who found improvement in anxiety, irritability, and behavioral problems associated with change in routine. Very limited support has been reported for the SSRI Paxil (paroxetine). Case studies have reported reductions in self-injurious behavior in a 15 year old male with high functioning autism (Snead et al. 1994), and improvement in irritability, temper tantrums, and interfering preoccupations in a 7 year old boy with autism (Posey et al. 1999).

Two retrospective studies of Celexa (citalopram), another SSRI, have reported improvement in some of the symptoms of autism. Couturier and Nicolson (2002) found improvement in 10 out of 17 children in aggression, anxiety, stereotypies, and preoccupations, though not in social interactions and communication. In addition, four children developed adverse side effects such as increased agitation and insomnia causing their treatment to be stopped. Namerow et al. (2003) found similar improvements in children and adolescents in repetitive behavior, mood, and anxiety. Mild side effects were reported in one-third of their sample, two of whom discontinued treatment due to side effects. The fourth SSRI that has been studied to treat the symptoms of PDD is Lexapro (escitalopram). In an open label design of children and adolescents with autism, Asperger's, or PDD-NOS, Owley et al. (2005) found significant improvement in 17 of 28 patients based on ratings from the Aberrant Behavior Checklist Irritability subscale (Aman et al. 1985). There was wide variability in dose response, which could not be accounted for by weight or age. Due to the limited research on this drug, more rigorously controlled trials are suggested.

Based on the research cited, the limited benefits of psychopharmacology come at the cost of side effects and rebound of aggressive behavior when medication is discontinued. Furthermore, these drugs appear to only be treating certain symptoms, though typically not the core symptoms of ASD. Many children require multiple medications to improve their symptoms, and often the benefits do not outweigh the side effects. In addition to patients responding to highly variable doses, the majority of studies reviewed indicate that not all children with ASD respond to these various medications, and there is no good explanation for why some are considered responders and some are not. However, risperidone has been approved by the FDA, and although more studies are needed, this and other medications appear to be beneficial at managing some of the behavioral disturbances seen in autism.

Diet Treatments

Research has suggested that individuals with autism may not properly metabolize the proteins in casein (dairy) and gluten (wheat and related grains) resulting in an opioid effect on the brain as they enter the bloodstream (Reichelt 2001). Autism may be comorbid with metabolic anomalies including: (1) failure of the digestive tract to fully metabolize casein and gluten into amino acids; and (2) leaky gut syndrome which allows undigested peptides to pass into the bloodstream (Reichelt 2001). Cade et al. (1999) reported that following a gluten-casein free diet, children with autism experienced an 81% improvement in symptoms within 3 months based on parent and physician ratings of severity on a Likert scale. It was also noted, qualitatively, that the mothers of four of the children in this study reported seizure frequency had significantly decreased in three children and had ceased completely in the fourth. Reichelt and Knivsberg (2003) conducted a longitudinal single blind controlled pair-wise study of children with autism over 4 years to investigate the effects of a gluten-free/casein-free (GFCF) diet. Following the dietary intervention, there was significant improvement on outcome measures of cognitive function, language, and social skills. Knivsberg et al. (2002) conducted a randomized single blind controlled study of ten children with autism on the GFCF diet. At 1 year follow up, the experimental group had showed significantly greater improvement in autistic behavior, nonverbal cognitive ability, and motor problems. More recently, Elder et al. (2006) conducted a rigorous double blinded controlled trial of the GFCF diet in autism. Fifteen (12 boys, 3 girls) children with ASD between the ages of 2–16 were studied over the course of 12 weeks. The authors reported no significant differences between groups on their primary measure, the Childhood Autism Rating Scale, while parents reported improvement in their children. The authors noted that the children were quite heterogeneous, which may have masked any group differences, in addition to the relatively small sample size.

An obvious limitation to this type of treatment is the lack of strict control over the diet of these children. When immunoglobulin A antigliadin and antiendomysium antibodies are measured to assess compliance, some studies indicate that roughly only half strictly follow dietetic prescriptions (Paolo et al. 1998). It may be difficult for parents to know which foods should be restricted, and children may respond more slowly than others, requiring greater effects to be noticed. One of the major problems with the GFCF diet, however, is that it may lead to reduced bone cortical thickness (Hediger et al. 2008). Boys, between the ages of four and eight, who were autistic showed a 18.9% deviation in metacarpal bone cortical thickness, which was nearly twice that of boys on minimally restricted or non-restricted diets. Furthermore, the GFCF diet may induce nutritional imbalances by limiting the foods that may be eaten. It has also been shown to increase the risk of becoming overweight/obese (Paolo et al. 1998).

Vitamin Supplements and Enzymes

An interest in the use of secretin, a gastrointestinal hormone, as a treatment for autism began with a report by Horvath et al. (1998) on three children with ASD. After receiving intravenous administration of secretin for upper gastrointestinal endoscopy, there was improvement in the children's gastrointestinal symptoms. In addition, within 5 weeks of the secretin administration the children's parents noticed behavioral improvements as evidenced by improved eye contact, alertness, and increased expressive language. The authors suggested that these clinical observations may indicate an association between GI functioning and brain functioning in autism. However, these behavioral observations were incidental and not an expected outcome in the procedure. As a result, there was no control group utilized and the non-experimental nature of the procedure precludes drawing any firm conclusions about its use in treating autistic behaviors. However, in October 1998, Horvath et al.'s (1998) results were reported on national television on NBC's *Dateline*, which likely sparked the demand and sharp increase in price that followed (NIH News Alert 1999). Anecdotal reports followed, with some parents reporting dramatic improvements in their children, and others reporting no change (NIH News Alert 1999). The National Institutes of Child Health and Human Development (NICHD) soon funded a study to investigate the use of secretin in the treatment of autism (Sandler et al. 1999). In the double blind, placebo controlled study the researchers found no difference on any of the standardized behavioral measures utilized between the secretin and placebo groups. Commenting on the results of this study, the director of the NICHD, Duane Alexander stated, "These findings strongly suggest that secretin should not be recommended to treat autism until the results of our other ongoing studies are known." (NIH News Alert 1999). Similarly, the American Academy of Child and Adolescent Psychiatry released a policy statement on the use of secretin in treating autism: "…the available evidence does not suggest that secretin is a useful treatment for children with autism" (American Academy of Child and Adolescent Psychiatry Policy Statement 1999).

Roberts et al. (2001) investigated the effects of repeated doses of intravenous secretin on 64 children diagnosed with autism in a randomized, placebo controlled study. Outcome measures included assessment of cognitive, social, language, and gastrointestinal (GI) function. Following treatment, receptive and expressive language skill improvement

occurred to the same extent in the secretin and placebo groups. However, parents anecdotally reported sleep improvement, toilet training success shortly after the injection, and more connectedness. Untoward side effects of secretin were evident for some of the children; 21% had generalized flushing in the neck, face, or chest following injection; 6.25% experienced irritability and hyperactivity; and 4.68% had an increase in aggression. Although no significant effects were reported for secretin, parent reports of improvement suggest there is a small subgroup of Autistic children with GI symptoms who may benefit from treatment with secretin (Roberts et al. 2001). However, it is important to note that repeated use has not been approved by the FDA, and there is the possibility of an allergic reaction with multiple doses of secretin (Hirsch 1999), so extreme caution must be taken when using secretin in this manner.

A comprehensive review of research studies utilizing secretin to treat autism was conducted by Esch and Carr (2004). Seventeen quantitative studies were reviewed, encompassing approximately 600 children, ages 2–15, and twelve adults with ASD. Only one of the studies reviewed found a causal relationship between secretin administration and amelioration of autistic symptoms across various treatment variables (type of secretin, dosage potency, frequency), observation times, and participant characteristics (e.g., GI status, severity of ASD, age, history of medication use). Twelve of the thirteen placebo controlled studies reviewed obtained negative results. Despite the lack of empirical support for secretin, parents of autistic children continue to seek out secretin treatment from their physicians (Esch and Carr 2004). The reviewers attempted to explain this by the media attention that secretin received early on, coupled with the fact that parents of these children are often desperate to find a treatment for this debilitating condition.

In addition to secretin, it has been suggested that the consumption of omega-3 fatty acids may have a positive effect on the symptoms of autism (Amminger et al. 2007). These highly unsaturated fatty acids are essential for normal brain development and functioning (Wainright 2002), and some studies have found fatty acid deficiencies in children who are autistic (Bell et al. 2000; Vancassel et al. 2001). Amminger and colleagues (2007) recently completed a double-blind, RCT of omega-3 fatty acid supplementation in children who were autistic. They found that with administration of 1.5 g/day, the treatment group showed no significant change in hyperactive behaviors including disobedience, distractibility, and impulsivity, relative to the control group. However, this study was conducted with only 12 subjects, and pre-selection of these subjects was based on high irritability scores based on the Aberrant Behavior Checklist (Aman et al. 1985).

Anecdotal reports that Methyl-B12 (Methylcobalamin) injections may improve the symptoms of autism have been plentiful; however, there have been very few controlled research studies to support the efficacy of this treatment. The effects of this coenzyme were reportedly discovered, accidentally, by Dr. James Neubrander, in May of 2002. He reported that following injections of Methyl-B12 in a child with autism he had been treating, the child's mother reported dramatic improvements in behavior (Neubrander 2005). He then began using the treatment on his other patients, again, anecdotally reporting dramatic improvements by the parents. He has reported that in his practice, "94% of children have been found to respond to methyl-B12 therapy". He has reported that executive functioning improved in 90% of children, speech and language improved in 80% of children, and socialization/emotion improved in 70% of children (Neubrander 2005). Richard Deth (2004) reported his results on the administration of 75 mcg/kg of methyl-B12, given every 3 days, in 85 children, between the ages of three and eleven, who were autistic. A "parental questionnaire" demonstrated improvements in speech and language in 71%, cognitive function in 52%, and socialization/emotional stability in 35%. He also reported that stopping treatment resulted in a worsening of symptoms, which reversed upon reinstatement of the injections.

The only published study we were able to find was an open trial of Methyl-B12 conducted in Japan with 13 children with autism, ranging from 2 to 18 years of age (Nakano et al. 2005). Dosages of 25–30 g/kg/day were administered for between 6 and 25 months. The authors found a significant increase in the intelligence and developmental quotients, as well as improvement on the childhood autism rating scale (Schopler et al. 1980). Even after the children were divided into subgroups based on age and intelligence, these effects did not diminish. However, this was not a controlled study. In contrast, a preliminary report of a double-blind crossover study presented at the American Academy of Child and Adolescent Psychiatry conference revealed no significant benefits in the 14 patients in their study after 3 months (Deprey et al. 2006). Specifically, there were no differences between the methyl B12 injections and the placebo on the Clinical Global Impression Scale Improvement, Peabody Picture Vocabulary Test, or Social Communication Questionnaire verbal results.

Chelation

Although still controversial, studies suggest there has been an increase in the incidence of ASDs over the past 30 years (Blaxill 2004). Even more controversial, however, are theories that the possible increase in autism may be related to environmental factors such as exposure to heavy metals

(Bradstreet et al. 2003), mercury (Hg) in particular. The medical literature indicates that autism and Hg poisoning have numerous similarities in their symptom profiles, including psychiatric disturbances, speech, language, and hearing difficulties, sensory impairment, and cognitive difficulties (Bernard et al. 2000). As a result, some health care providers are performing chelation therapy, which utilizes Di-mercaptosuccinic-Acid (DMSA) to clear the body of mercury and other toxic metals. One research study indicated that children with ASD have significantly higher concentrations of urinary mercury following oral chelation with DMSA as compared to normal controls (Bradstreet et al. 2003). One study has documented the progress of children with autism ($n = 85$; aged 1–5 years; 6–12 years; 13–17 years; and >18 years.) treated with chelation (DSMA and lipoic acid) for at least 4 months. In children aged 1–5 marked improvement was noted in behavior, language, and social interaction for 35%, with 39% revealing moderate improvement. In contrast, 52% of children aged 6–12 and 68% of children aged 13–17 made only slight improvement, while 75% of individuals over 18 made no improvement (Holmes 2001). The findings of Holmes suggest that chelation therapy may be effective only for young children with autism (under age six), with minimal benefit for older children and adolescents (Kirby 2005). Holmes (2001) noted that younger patients excreted larger quantities of mercury than did older patients, which may help explain this discrepancy in outcomes.

Recently, Adams et al. (2008) reported the results of a 2 phase study intended to determine the efficacy of DMSA/glutathione in treating children with autism. In phase I, children ($n = 82$) received nine doses of DMSA over 3 days; levels of metal excretion were measured at baseline and following the first and ninth dose. Those with "high" levels of toxic metal excretion ($n = 49$) continued to phase II of the study, a 3 month, double-blind, controlled treatment study, in which children were given DMSA for 3 days, followed by 11 days off, repeated six times. Most of the children (19 of the 26 in the treatment group) continued excreting lead at a high level following DMSA administration. Comparisons were made between groups receiving seven rounds of DMSA with another group receiving one round of DMSA. On the ATEC, both groups improved significantly, even though no significant differences were evident between the groups with one or seven rounds of treatment. Across all five measures (ATEC, ADOS, Pervasive Developmental Disorders Behavior Inventory, Severity of Autism Scale, Parent Global Impression), 77% reported improvement, 12% reported no change, and 11% reported worsening (in both seven-round and one-round groups combined). A regression analysis revealed that scores on the ATEC, SAS, PDD-BI, and ADOS could be partially explained by heavy metal excretion "with a very high statistical significance". Furthermore, the authors suggested that 22–49% of the severity of autistic symptoms appeared to be due to toxic metals, particularly lead, antimony, and mercury. However, in contrast to Holmes (2001), Adams et al. reported a slight negative correlation between age and test ratings, suggesting that older children tended to improve slightly more than younger children.

When thimerosal was removed from childhood vaccines in Denmark in 1992, Madsen et al. (2003) were unable to demonstrate any change in the trajectory of diagnoses of autism, nor have others who have since examined this relationship (Verstraeten et al. 2004). Based on available evidence, the Institute of Medicine has not endorsed any such association between thimerosal and autism (Stratton et al. 2001). Furthermore, even when lead is removed from the bloodstream, improvement in neurodevelopmental functioning has not been demonstrated (Dietrich et al. 2004). There have even been reports of death following chelation therapy in autism (Sinha et al. 2006), making it one of the more risky forms of intervention.

Hyperbaric Oxygen Therapy (HBOT)

Among other brain abnormalities that have been identified, numerous studies using PET and SPECT have shown cerebral hypoperfusion in autism (George et al. 1992; Mountz et al. 1995; Ohnishi et al. 2000; Starkstein et al. 2000; Zilbovicius et al. 2000), leading to the hypothesis that hyperbaric oxygen therapy (HBOT) may be beneficial in the treatment of autism (Rossignol and Rossignol 2006). HBOT involves the inhalation of 100% oxygen in a pressurized chamber, usually above one atmosphere absolute (ATA). It has been shown that HBOT can lead to improved functioning in various neurological populations that show cerebral hypoperfusion including stroke (Nighoghossian et al. 1995), cerebral palsy (Montgomery et al. 1999), chronically brain injured (Golden et al. 2002), and even a teenage male with Fetal Alcohol Syndrome (Stoller 2005).

Rossignol and Rossignol (2006) have suggested that the increased oxygen delivered by HBOT could counteract the hypoxia caused by hypoperfusion, and lead to a reduction in symptoms of autism. These researchers retrospectively reviewed cases of six children with autism children who had undergone low-pressure HBOT at 1.3 ATA and 28–30% oxygen over the course of 3 months. Based on ratings from the ATEC, they found an average improvement of 22.1%, though improvement was greater in younger (31.6% in children under age 5) than in older (8.8% in children over age 5) children. An average improvement of 12.1% was reported based on the CARS, and a 22.1% improvement on the SRS, again with greater improvement in younger (28.9%) than in older (13%) children. All children in this

study, however, continued all other therapies they were previously receiving, and were also able to initiate new therapies during the study. Furthermore, the study was retrospective, parents were not blinded to the treatment, and there was no control group.

Rossignol et al. (2007) treated eighteen children with autism with 40 sessions of HBOT at either 1.5 atm at 100% oxygen, or at 1.3 atm and 24% oxygen. They reported a trend toward improvement in C-reactive protein measurements (a marker of inflammation) and no significant increase in oxidative stress. Parental reports revealed statistically significant improvements in irritability, social withdrawal, hyperactivity, motivation, speech, and sensory/cognitive awareness. However, parents were not blinded as to the type of therapy their children were receiving and there was no placebo or control group. These results remain preliminary and further studies are needed with more rigorous experimental designs (blinded, placebo controlled, randomized). This study does suggest that it is a relatively safe treatment, as no adverse events were reported and all children were able to complete the 40 treatment sessions.

This review of the autism treatment literature reveals there are few treatments, except possibly behavior therapy, that have been well validated or that have exhibited favorable long term results. In addition, many forms of intervention include the possibility of adverse effects, require long-term use, or were not developed specifically for autistic spectrum disorder. Neurofeedback represents an alternative that may have the potential to help on a long term basis with little risk of harm.

Neurofeedback for ASD

Neurofeedback is designed to train individuals to enhance poorly regulated brainwave patterns by using sophisticated computer technology. While there are different forms of neurofeedback, the most traditional form is known as EEG Biofeedback. In EEG Biofeedback, information on brainwave activity is fed to a computer that converts this information into game-like displays that can be auditory, visual, or both. During a typical session, EEG electrodes are placed on the scalp and/or ear lobe(s). These sensors only measure a person's brainwaves; no electrical current enters the brain. Individuals utilize their brainwaves to learn to control the feedback they instantly receive about the amplitude and synchronization of their brain activity. An example of a typical set-up is displayed below in Fig. 1.

As a child learns to control and improve brainwave patterns, the game scores increase and progress occurs. The only way to succeed at the games is for children to improve their brainwave function (following an operant conditioning paradigm). In research and clinical treatment for children with ADHD, this conditioning process has resulted in improvements that have persisted for up to 5–10 years (Lubar 1995).

Fig. 1 Sample of neurofeedback set-up

Laibow (1999) described EEG biofeedback as a discipline based in neurophysiology, which draws from the multidisciplinary fields of neuroanatomy, pathophysiology, and behavioral medicine. Individuals learn to inhibit brainwave frequencies that are excessively generated (produce negative symptoms); and augment or enhance specific frequencies that are deficient (produce positive results). Table 1 displays the typical EEG brain wave frequency bands and lists their normal occurrences and respective significance. The information contained in this table was adapted from resources contained in Demos (2005) and Thompson and Thompson (2003a). Figure 2 shows examples of each of these brain wave frequencies shown across a 1 s epoch. Within these general frequency bands there may also be more detailed breakdowns of EEG activity. For example, the sensory-motor rhythm (SMR) is often thought to occur between 12 and 15 hz, but only over the sensorimotor cortex of the brain (Egner and Sterman 2006). Both alpha and beta frequency bands have been subdivided into more specific ranges as well. The alpha band has been divided into low alpha (8–10 hz) and high alpha (11–13 hz) (Thompson and Thompson 2003b). Mu rhythm abnormalities are associated with excesses in these frequency bands and have a characteristic morphologic and topographic distribution (Coben and Hudspeth 2006). Subdivisions of beta power have also been presented and related to clinical characteristics (Rangaswamy et al. 2002).

Individuals with poorly regulated cortical activity can learn to develop a fluid shift in brainwaves to meet task demands utilizing neurofeedback. This treatment modality can result in improvement of brainwave patterns as well as behavior, through the process of operant conditioning as described above. These changes in EEG patterns have been shown to be associated with regulation of cerebral blood flow, metabolism, and neurotransmitter function (Lubar 1997).

Table 1 EEG frequency bands

Name	Frequency	Normal occurrence	Significance
Delta	0.5–3.5 Hz	Deep sleep and infants	Sign of significant brain dysfunction, lethargy/drowsiness or cognitive impairment
Theta	4–7.5 Hz	Young children, drowsiness, some aspects of learning	Slowing often related to attention/cognitive impairments, internal focus
Alpha	8–13 Hz	Eyes closed, relaxation, self awareness	Excessive alpha during demand states can be a sign of difficulties with learning, emotional stability, relating to the environment or others
Beta	13–30 Hz	Fast activity associated with alertness and activity	Excessive beta is often associated with anxiety, irritability and poor integration
Gamma	Greater than 30 Hz	May be associates with problem solving and memory consolidation	Unknown

Adapted from Demos (2005) and Thompson and Thompson (2003a)

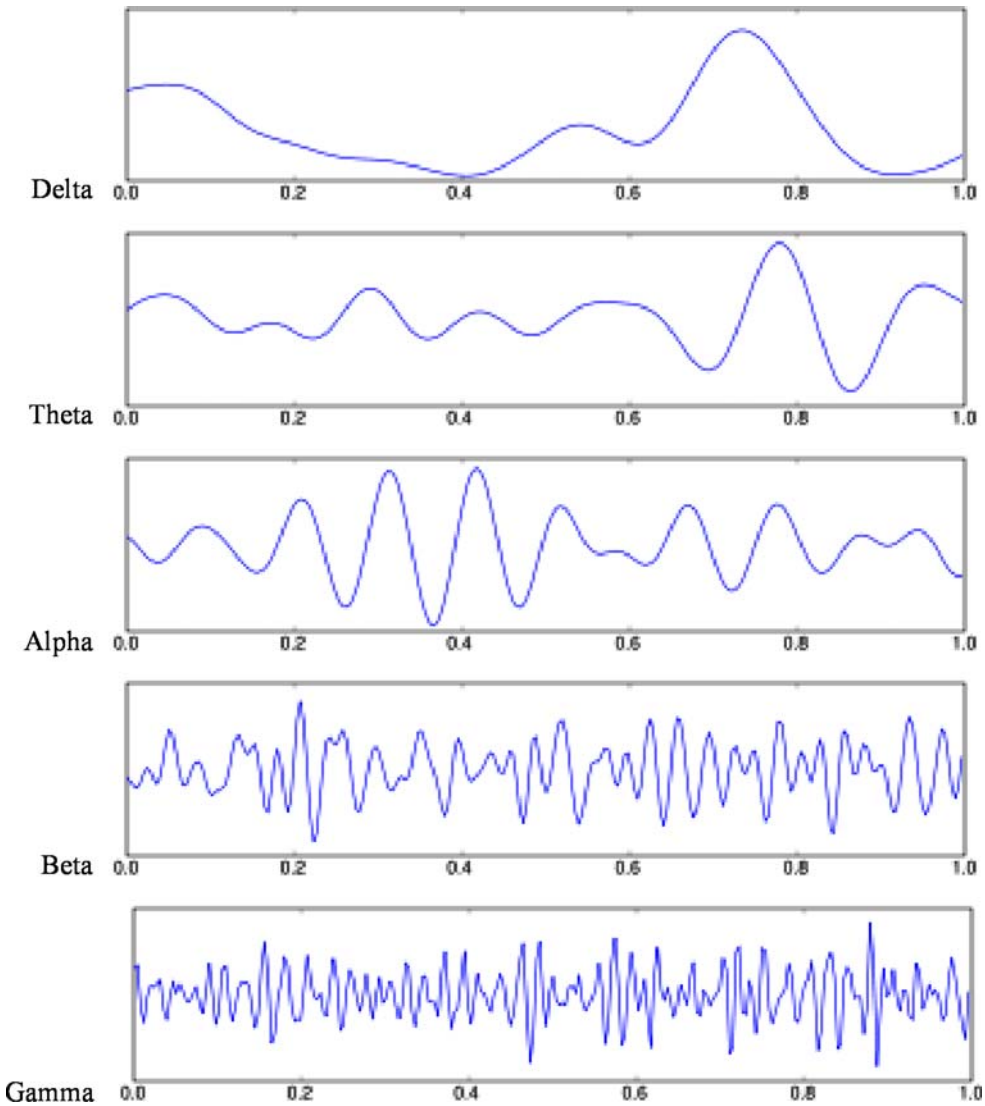

Fig. 2 Sample of EEG brain wave frequencies. Reprinted with permission from Wikipedia

Neurofeedback is a noninvasive approach that has been shown to enhance neuroregulation and metabolic function in ASD (Coben and Padolsky 2007). Neurofeedback has no known adverse side effects while psychopharmacological interventions, secretin and other interventions may be associated with side effects. As a noninvasive treatment,

there are no external substances introduced internally as part of neurofeedback interventions. The therapeutic treatment outcomes of neurofeedback training with individuals with ADHD (increased attention, reduced impulsivity and hyperactivity) have been reported to be maintained over time and not reverse after treatment is withdrawn (Linden et al. 1996; Lubar et al. 1995; Monastra et al. 2005; Tansey 1993) as in drug therapy and diet therapy. In contrast to behavior therapy, positive treatment outcomes that result from neurofeedback training are often achieved over the course of several months rather than a year or more of intensive training.

EEG biofeedback, as a form of internvetion, began with Barry Sterman PhD (Sterman and Friar 1972) at UCLA, who trained individuals to control their seizures by increasing their sensorimotor rhythm (SMR) brainwaves. In 1976, Joel Lubar published his first of numerous research studies using neurofeedback with students diagnosed with ADHD (Lubar and Bahler 1976). Studies indicated that by increasing Beta and decreasing Theta brainwaves at central scalp locations, improvements in attention, impulsivity and hyperactivity often occurred (Linden et al. 1996). Lubar's research in the 1980's and 1990's indicated that IQ increases also resulted from Neurofeedback (Lubar et al. 1995). Lubar (1995) published a longitudinal study, indicating that the positive results from neurofeedback were still significant in 15/16 behaviors after 10 years.

Linden et al. (1996) published the first controlled, randomized study of neurofeedback with students with ADHD. Their results supported Lubar's previous research, and indicated significant improvements in attention and intelligence compared to a wait list control group. Other researchers found that the effects of neurofeedback on ADHD were similar to the results of stimulant medication during treatment, but remained after treatment discontinued. For example, Monastra et al. (2002) compared a stimulant medication regime to neurofeedback, while providing parenting training to all parents of the 100 children with ADHD included in the study. Their results supported previous findings of neurofeedback's significant positive effects with ADHD children and showed that the effects were long-lasting, while those of stimulant medication were temporary. Fuchs et al. (2003) conducted a similar comparison of neurofeedback and stimulant medication. They used QEEG pattern analysis to emphasize more specific NF protocols, including inhibiting high Beta (18–30) activity. Their neurofeedback approach was shown to rival the effects of methylphenidate, with similar significant effects on multiple measures.

Neurofeedback, over a 30 year history of research with ADHD, has consistently resulted in improvements in attention, impulsivity, hyperactivity, and IQ (see Monastra et al. 2005, for a review and analysis). This successful background of literature has been the foundation for the emergence of using neurofeedback with ASD.

QEEG Evaluation and Autistic Spectrum Disorder

Quantitative electroencephalographic (QEEG) evaluation or mapping is an assessment instrument designed to pinpoint anomalies in brain function (Hammond 2005). QEEG Maps, collected using 19 electrodes based on the International 10–20 system (Jasper 1958), are quantitative analyses of EEG characteristics of frequency, amplitude and coherence during various conditions or tasks. These data can be statistically compared to an age-matched normative database to reveal a profile of abnormalities. Such regions and aspects of dysfunctional neurophysiology may then be targeted specifically through individualized neurofeedback protocols. QEEG analyses measure abnormalities, instabilities, or lack of proper communications pathways (connectivity) necessary for optimal brain functioning.

QEEG analyses are conducted to assess underlying neurophysiological patterns related to the symptoms and challenges of children with ASD. In addition, assessment of the raw EEG can be used to evaluate neurological abnormalities such as seizure disorders, which are common in children with autism. QEEG data are important for developing the most individualized, specific and successful neurofeedback protocols for patients with ASD (Coben and Padolsky 2007; Linden 2004). Figure 3 shows an example of a QEEG analysis conducted on a teenage female diagnosed with Asperger's disorder. This analysis is clearly focused on the lowest frequency bands from 1 to 4 hz. The analysis performed prior to neurofeedback (top line) indicated prominent right frontotemporal slow frequency excesses. Following neurofeedback (bottom line), there were significant reductions in these problems with this QEEG analysis revealing mainly normal findings. These neurophysiological changes were associated with clinical improvements in the patient including enhanced attention, emotional regulation and social skills.

Ross and Caunt (2003) presented a series of seven children with Asperger's syndrome (6 males/1 female; aged 5–15 years). The QEEG findings indicated several patterns, including elevated 4–7 Hz activity in posterior regions, slowing at the vertex (central), and regulatory dissociation (disconnection) between anterior and posterior regions of the cortex. This was the first reported case study of QEEG patterns of a student with Asperger's.

Linden (2004) identified four QEEG patterns of autism and two of Aspergers based on 19 channel EEG recordings and analysis of raw EEG, absolute power, relative power and multivariate connectivity. The four Autism

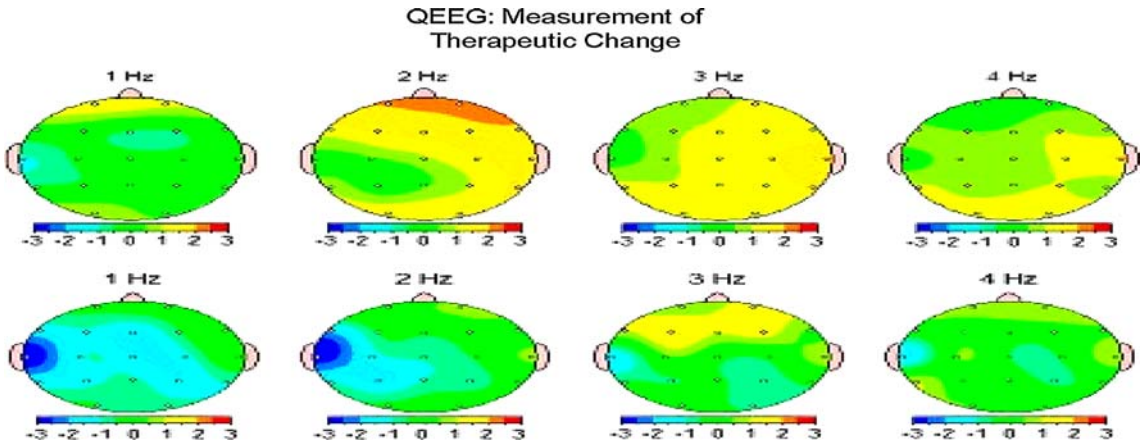

Fig. 3 Case example of QEEG analyses for a teenage female with Asperger's disorder. The *top line* is a measurement taken at *baseline* and the *bottom line* after neurofeedback

QEEG subtype patterns are: (1) high beta activity which corresponds to obsessing, overfocusing and anxiety, (2) high delta/theta activity which corresponds to cortical slowing and inattention, impulsivity and hyperactivity, (3) abnormal EEG/seizure activity, and (4) metabolic/toxic pattern of lower overall EEG activity (voltage). The high beta subtype was the most common subtype, occurring in approximately 50–60% of the students with ASD. The delta/theta subtype occurred in 30–40%, the Abnormal EEG subtype in 33% and the metabolic/toxic subtype in 10%. In addition, coherence abnormalities were usually present in the QEEG profiles.

The QEEG patterns with students with Asperger's primarily occurred in the right temporal and parietal regions, sites involved in social and emotional recognition mechanisms. The QEEG patterns of those with Aspergers' are: (1) high theta/alpha slowing in the right temporal/parietal areas and (2) low coherence between right temporal/parietal brain regions and other regions. More than one QEEG subtype pattern was frequently present in the students with ASD.

Coben et al. (under review) studied 91 individuals with autism and compared them to 310 normal controls. QEEG analysis revealed five relative power subtypes. Pure excesses of beta were observed in 26.5%, of alpha in almost 25.3%, and of theta in approximately 4.1%. Specific frontal dysfunction, including excesses of theta and alpha, was evident in 10.9%. However, many types of dysfunction overlap in people with autism and most reveal a combination of findings. In over 83% of the individuals with autism connectivity anomalies could be identified when compared to the normal control group. Coben and Myers (2008) have been able to utilize QEEG multivariate connectivity data to develop a typology of autism connectivity patterns. Patterns of hyperconnectivity were identified across bilateral frontotemporal regions and between left hemisphere locations, while hypoconnectivity may involve orbitofrontal, frontal to posterior, right posterior or left hemisphere sites. Additionally, a pattern of hypoconnectivity that underlies a mu rhythm complex was identified as well.

Neurofeedback: Case Studies and Case Series

Case studies of neurofeedback trials with clients diagnosed with autistic disorders have been reported since 1994 (See Table 1). The following section summarizes these case studies and series (Table 2).

In 1994, Cowan and Markham presented the first case study of neurofeedback with autism. EEG analysis, during eyes open and resting conditions, was performed on an 8 year old girl who was diagnosed with high functioning autism. The findings indicated an abnormally high amount of alpha (8–10 Hz) and theta (4–8 Hz) activity predominately in the parietal and occipital lobes. Based on these results, the neurofeedback protocol was designed to suppress the ratio of "thalpha" (4–10 Hz) to beta (16–20 Hz) EEG activity at central and parietal sites using a bipolar montage (two scalp electrodes and one ear ground electrode). After 21 neurofeedback sessions, the girl exhibited increased sustained attention, decreased autistic behaviors (inappropriate giggling and spinning), and improved socialization based on parent and teacher reports. There was also substantial improvement on the Test of Variables of Attention (TOVA) measures of inattention (omission), impulsivity (commission) and variability. A follow-up TOVA was administered 2 years later and all scores were within normal limits.

This was followed by several case studies reported by different authors (Ibric and Hudspeth 2003; Sichel et al. 1995; Thompson and Thompson 1995). Sichel et al. (1995)

Table 2 ASD neurofeedback case studies

Author	QEEG pattern	NF protocol	Improvements
Cowan and Markham (1994)	High alpha and theta	Suppress 4–10, enhance 16–20	Attention, motor behaviors, impulsivity, socialization, TOVA
Sichel et al. (1995)	High theta, low Beta	Suppress theta, enhance SMR	Socialization, self-stim behaviors, speech
Thompson and Thompson (1995)	High theta, low SMR	Suppress theta, enhance SMR P4-T4	Behaviors, social, academic
Ibric and Hudspeth (2003)	High beta, hypocoherence	QEEG based	Behavior, sleep, movements
Thompson and Thompson (2003a)	High theta, low beta/SMR	QEEG based; suppress theta, enhance 13–15 C4	EEG patterns, IQ, social interactions, alertness
Limsila et al. (2004)	Not measured	HEG frontally	Grades
Linden (2004)	High beta, high delta, low voltage, abnormal EEG, hypocoherence	QEEG based	Attention, impulsivity, hyperactivity, EEG patterns, communication, socialization
Scolnick (2005)	Abnormal patterns	EEG based	Behaviors

presented a case of an 8 year old boy with mild autism who was treated with SMR (12–15 Hz) enhancement and theta (4–8 Hz) suppression on the sensory-motor strip and parietal lobe, based on QEEG findings. Following 31 sessions of monopolar neurofeedback training, positive changes were reported across multiple domains related to his symptoms. Ibric and Hudspeth (2003) presented another case of an 8 year old boy with autism who was treated with success using Roshi-assisted neurofeedback. Forty sessions of training were conducted, based on QEEG data, which included theta suppression and alpha enhancement. This led to improvements in sleep, aggressive behavior, obsessions and involuntary movements.

Multiple cases and case series have been presented by Thompson and Thompson (1995, 2003a). Initially, Thompson and Thompson (1995) presented three cases of children with autism and Aspergers disorder whose neurofeedback protocols were primarily SMR enhancement and theta suppression at parietal and temporal scalp locations (P4-T4). Following neurofeedback, there were improvements in behavior and socialization skills. While these cases were clearly not controlled trials in any way, they did point to the possible benefits of this technique and encouraged further study.

Thompson and Thompson (2003b) presented a case series review of neurofeedback in 60 individuals with high functioning ASD ranging in age from 5 to 51 years old. The dependent measures of post-treatment improvement were EEG assessments (central scalp locations with eyes open), parent and teacher rating scales, IQ testing, academic measures and continuous performance tests (CPT). Neurofeedback training parameters were based on the EEG assessment and the patients' clinical symptoms. The most common neurofeedback protocol was suppression of dominant slow wave activity while enhancing 13–15 Hz activity with scalp placement at Cz or C4 (central brain sites) referenced to the right or left ear, respectively. The number of neurofeedback sessions ranged from approximately 40–100. Their results indicated improved EEG patterns, with decreased theta/beta ratios and increases in SMR amplitudes. IQ increases of 10 points were reported for the Neurofeedback group. The results of the TOVA CPT were inconclusive, because many of the patients with autism were unable to complete the tests. Significant improvement in social interaction was reported by parents. The most significant improvements were in those individuals who received greater than 80 sessions. Thompson and Thompson continue to collect case series data to date on hundreds of ASD patients and continue to report successful treatment outcomes (Thompson and Thompson 2007).

Limsila et al. (2004) conducted the largest case series study of 180 children (aged 3–18) with autism in Thailand. This included a form of neurofeedback called Hemoencephalography (HEG) or cerebral blood flow biofeedback. Following 40 sessions of near infrared (nir) HEG training over frontal sites (Fp1 and Fp2), HEG readings reflecting brain oxygenation increased by 53%. Eighty-six percent of the 81 children with the capacity to learn in public school increased their grade point average (GPA) more than 0.5 points, while only 4% decreased their GPA by more than 0.5 points. However, there was no control or non-treatment group and the study did not assess or control for IQ or the influence of other treatment interventions. These findings were suggestive of positive therapeutic outcomes for HEG neurofeedback as a treatment for children with autism, but must be viewed cautiously due to the lack of controls as would be true of any case series.

Linden (2004) presented a series of case studies with 15 students (14 males/1 female), aged 5–15 years old, diagnosed with autism or Aspergers. All subjects received

pre- and post- neurofeedback QEEG evaluations, parent and teacher ADD and ASD rating scales, and IVA and TOVA Continuous Performance Tests (CPT). IQ was not measured, however, and there was no control group. All of the neurofeedback protocols used with the ASD subjects were QEEG Guided (selected based on the QEEG analysis) and were selected with the goal of normalizing the QEEG patterns and improving the clinical symptoms. The subjects received between 20 and 60 (average was 50–60), 45 min sessions (30 min of actual neurofeedback training time) of neurofeedback between 2 and 5 times per week. The results indicated improved CPT scores and deceased inattention and hyperactivity on Parent and Teacher ADHD behavior rating scales. In addition, most of the abnormal QEEG patterns (there were several abnormal EEG patterns for some students) were improved in all students, including several students whose abnormal raw EEG patterns "normalized". Moreover, many of the students were able to reduce or eliminate their medications. Improvement was also reported on Parent and Teacher Autism (CARS) and Asperger (OASIS) behavior rating scales for communication and socialization in all cases. Several of the students with ASD were mainstreamed into regular classes without their classroom aides.

A pilot study of the effects of neurofeedback with Asperger's syndrome was completed by Scolnick (2005). Five adolescent males who attended a therapeutic day school completed 24 sessions of neurofeedback. The results indicated a trend to normalize their EEGs, but was not statistically significant. All subjects showed improved focusing, anxiety and disruptive behavior as rated by parent and teacher rating scales. Again, IQ was not measured and there was no control group.

In summary, several case studies and case series using QEEG and neurofeedback with individuals diagnosed with ASD have been reviewed. Although these studies utilized different instruments and neurofeedback protocols, and had a varied number of neurofeedback sessions, all reported significant improvement either on measures of QEEG, IVA/TOVA CPT tests, or Parent/Teacher behavior rating scales. In addition, significant clinical symptomatic improvements were reported for communication, socialization, anxiety, attention, stereotypic behaviors, and even medication reduction/elimination. As noted, however, these studies must be viewed cautiously, as they are uncontrolled and cannot demonstrate if the changes observed are due only to the neurofeedback treatment or other factors. As many of these referenced case/case series presentations have not been the subject of extensive peer review, additional cautions should be exercised in making generalizable conclusions. Additional controlled studies with larger sample sizes would be helpful in order to support the results of these case studies.

Group Pilot Studies of Neurofeedback for ASD

Two pilot group studies of neurofeedback for ASD have been conducted. In the first (Jarusiewicz 2002), twelve children each were assigned to an experimental or a control group. The experimental group received a mean of 36 treatment sessions (range = 20–69). Treatment protocols were based on the Othmer Assessment (1997) to determine over-, under-, and unstable arousal. The Autism Treatment Evaluation Checklist (ATEC; Rimland and Edelson 2000) was used to assess outcome. Children who completed neurofeedback training attained an average 26% reduction in the total ATEC rated autism symptoms in contrast to 3% for the control group. Parents reported improvement in socialization, vocalization, anxiety, schoolwork, tantrums, and sleep while the control group had minimal changes in these domains. However, the outcome measure used is based on only parent report with no other objective measures utilized.

The second pilot study of the effects of neurofeedback was conducted by Kouijzer et al. (2009). Fourteen children with ASD, 7 in the treatment and 7 in the waitlist (no treatment) control group, were matched for age, gender and intelligence, but were not randomly assigned. The treatment group received 40 sessions of neurofeedback treatment at scalp location C4. Theta activity (4–7 Hz) was inhibited while SMR activity (12–15 Hz) was rewarded. Pre and post assessment consisted of EEG learning curves, QEEG analysis, tests of executive functioning and behavior rating scales (CCC-2, Dutch Autism Scale). The findings showed that the neurofeedback trained group demonstrated significant improvement in attentional control, cognitive flexibility and goal setting compared to the control group. Results of parent rating scales also showed improvements in social interaction and communication skills. These changes were associated with improvements in EEG learning curves.

Interestingly, this same research group performed a 12-month follow-up of the treated patients with ASD (Kouijzer et al. 2009b). Both changes in executive functioning and behavior were maintained suggesting that neurofeedback may have long-lasting effects for children with autism. These pilot studies have shown positive results, but caution should be exercized as their sample sizes were quite small. Nevertheless, the optimism regarding their findings has led to more controlled research with larger sample sizes.

Controlled Group Studies of Neurofeedback for ASD

In the largest published, controlled study to date of neurofeedback for autistic disorders, Coben and Padolsky

(2007) studied 49 children on the autistic spectrum. The experimental group included 37 children that received QEEG connectivity guided neurofeedback (20 sessions performed twice per week) and the wait-list control group included 12 children that were matched for age, gender, race, handedness, other treatments, and severity of ASD. A broad range of assessments were utilized including: parental judgment of outcome, neuropsychological tests, behavior rating scales, QEEG analysis and infrared imaging. Treatment protocols were assessment-based (including QEEG power and coherence) and individualized for each child receiving neurofeedback training with a specific focus on the remediation of connectivity anomalies. Based on parental judgment of outcome, there was an 89% success rate for neurofeedback. There was an average 40% reduction in core ASD symptomatology based on parent ratings scales. There were also significant improvements, as compared to the control group, on neuropsychological measures of attention, executive functioning, visual-perceptual processes and language functions. Reduced cerebral hyperconnectivity was associated with positive clinical outcomes in this population. In all cases of reported improvement in ASD symptomatology, positive outcomes were confirmed by neuropsychological and neurophysiological assessment.

Another, as yet unpublished, controlled group study was conducted by Coben (2006). Forty patients with autism were non-randomly assigned to one of three groups: (1) a near infrared hemoencephalography (HEG) trained group ($n = 10$), (2) a passive infrared HEG trained group ($n = 18$), or (3) a wait-list control group ($n = 12$). Near infrared HEG (Toomim et al. 2004) measures changes in cerebral oxygenation at levels below one micron. Optical diodes detect changes in oxygenated and deoxygenated blood reflecting changes in regional cerebral blood flow. The specificity of its measurement is theorized to lead to highly localized changes. Passive infrared HEG (Carmen 2004) measures thermoregulatory output in the frequency range of 7–14 microns. Its surface areas of measurement and frequency range are quite larger than nirHEG and its effects may be more global as a result. The wait list control group ($n = 12$) was matched for gender, age, race, handedness, and other treatments. All patients had previously completed 20 sessions of EEG Biofeedback (see Coben and Padolsky 2007). The next phase of training was assessment-guided HEG, which identified frontal system dysfunction in all patients based on neurobehavioral, neuropsychological testing, infrared imaging, and QEEG data. Findings indicated an average success rate of 90% based on parental judgment. Parental ratings showed an average 42% reduction in overall autistic symptoms. Social interaction deficits decreased by 55%. Communication and social communication deficits decreased by 55 and 52%, respectively. In addition, there were statistically significant improvements in neurobehavioral and neuropsychological functioning. These improvements were associated with enhancement of brain thermal regulation and reduction in abnormal QEEG findings. Interestingly, there were differences in the effects of each type of HEG with nirHEG impacting attention more and pirHEG leading to better emotional control and social skills. There were also differential effects on the EEG based on which approach was employed.

Two studies have focused on abnormal Mu rhythms (a sign of mirror neuron dysfunction) (Oberman et al. 2005) in children with autism and if neurofeedback could lessen these anomalies. In a series of two experiments, Pineda et al. (2008) studied 27 children with high functioning autism. In study 1, 8 high functioning males were randomly assigned to an experimental ($n = 5$) or placebo group ($n = 3$). One subject dropped out of the experimental group midway through the training. Neurofeedback training included 30, 30 min sessions with rewards for mu-like activity (8–13 hz) and inhibits for EMG (30–60 hz). Parent ratings scale data (Autism Treatment Evaluation Checklist (ATEC); Rimland and Edelson 2000) showed small changes (9–13%) in two of the four experimental participants. These data should be considered in line with a pilot study considering the very small sample size. In Study 2, 19 children with high functioning ASD were randomly assigned to an experimental ($n = 9$) or placebo ($n = 10$) group. One very positive addition to this study was the verification of their diagnoses by administering the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 1999) and the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al. 2003). Neurofeedback training was similar to study one except the reward band was now 10–13 hz. Parent ratings showed a small, but significant reduction in symptoms (ATEC Total score). However, of concern was an increase in ratings of Sensory/Cognitive Awareness in excess of 40% that did not occur in the placebo control group. This suggests that, according to their parents, participants improved in some areas and worsened in others.

In another study related to mu-rhythms, Coben and Hudspeth (2006) studied fourteen children with ASD who were identified as having significantly high levels of Mu rhythm (distorted alpha-like) activity and a failure to suppress mu during observational activity. They all received assessment guided neurofeedback, with a strong focus on aspects of mu power and connectivity. The participants were non-randomly assigned to an interhemispheric bipolar training ($n = 7$) or a coherence training ($n = 7$) group designed to increase connectivity between central regions and the peripheral frontal cortex. All patients were given neurobehavioral, neuropsychological testing, and QEEG assessment. Both groups of patients improved significantly

on neurobehavioral and neuropsychological measures. However, only in the coherence training treatment group was Mu activity significantly reduced. Increased coherence was associated with diminished mu and improved levels of social functioning.

Lastly, Coben (2007) conducted a controlled neurofeedback study focused on intervention for prominent social skill deficits based on a facial/emotional processing model. Fifty individuals with autism were included in these analyses and all had previously had some neurofeedback. All patients underwent pre- and post neuropsychological, QEEG and parent rating scale assessments. Twenty-five individuals were each assigned to an active neurofeedback and wait list control group, respectively, in a non-randomized fashion. The two groups were matched for age, gender, race, handedness, medication usage, autistic symptom severity, social skill ratings, and visual-perceptual impairment levels. Neurofeedback training was QEEG connectivity guided and included coherence training (along with amplitude inhibits) between maximal sights of hypocoherence over the right posterior hemisphere. The group that received the coherence training showed significant changes in symptoms of autism, social skills and visual-perceptual abilities such that all improved. Regression analyses showed that changes in visual-perceptual abilities significantly predicted improvements in social skills. EEG analyses were also significant, showing improvements in connectivity and source localization of brain regions (fusiform gyrus, superior temporal sulcus) associated with enhanced visual/facial/emotional processing.

In the five controlled group studies that have been completed, a total of 180 individuals with autism have been studied with positive results reported in each study. These findings have included positive changes as evidenced by parental report, neuropsychological findings and changes in the EEG (Coben 2007). Both Coben and Padolsky (2007) and Yucha and Montgomery (2008) have viewed these data as demonstrating a level of efficacy of possibly efficacious based on the standards put forth by the Association for Applied Psychophysiology and Biofeedback (AAPB 2006). Added to these initial findings of efficacy is preliminary evidence that the effects of neurofeedback on the symptoms of autism are long-lasting (1–2 years) (Coben 2009; Kouijzer et al. 2009a). While these findings are initially encouraging, there are many limitations that prevent firm conclusions to be drawn from the data collected thus far.

First, these studies have largely included non-randomized samples. It is possible that an unknown selection bias exists which could have impacted the findings. Second, none of these studies have included participants or therapists/experimenters who were blind to the condition. Knowledge of group placement could have impacted the findings such that those in treatment (and their parents) would be prone to report significant changes. Third, there has been no attempt to control for placebo effects, attention from a caring professional or expectations of treatment benefit. A randomized, double-blinded, placebo-controlled study is clearly needed to further demonstrate efficacy.

In terms of generalization of these findings to the larger population of individuals who are autistic, very young children and adults have not been well represented in these group studies. Lastly, there is the question of whether neurofeedback may be applicable to persons who are lower functioning or whom have more severe symptoms associated with autism. These populations should be the focus of future investigations.

Discussion

With the possible exception of behavior modification interventions, there are few interventions for children with autism with proven efficacy. Pharmacologic interventions, hyperbaric oxygen and vitamin supplementation have shown some promise. However, further research is necessary to demonstrate their efficacy. Based on the above review, we consider neurofeedback to be in a similar position with respect to efficacy for ASD. While the recent research in this application is encouraging, further advancements are necessary in this ongoing research track to demonstrate efficacy according to current research standards.

The five levels of treatment efficacy that provide guidance for applied psychophysiologic research have been outlined (LaVaque et al. 2002; Yucha and Montgomery 2008) as follows. Level 1 is labeled "not empirically supported" and is assigned to treatments supported by evidence from only case studies in non-peer-reviewed journals and anecdotal reports. Level 2 is entitled "possibly efficacious" and is given to treatments investigated in at least one study, where statistical power is sufficient, outcome measures are well-identified, but random assignment to a control condition is lacking. Level 3, called "probably efficacious," is assigned to treatments that demonstrate beneficial effects in multiple observational studies, clinical studies, wait list controlled studies, or within-subject and intra-subject replication studies. Level 4, termed "efficacious," is reserved for treatments shown to be statistically superior (with sufficient power) to a control condition or equivalent to an established treatment, in designs that utilize random assignment and clearly identify the population of interest and the procedures employed, sufficient to permit replication by others. Additionally, positive treatment outcomes need to be confirmed in at least two independent research settings. Level 5, labeled "efficacious and specific," is assigned to treatments that demonstrate statistically superior results compared to a credible placebo,

medication, or another established treatment, again replicated in at least two independent research settings.

The group studies reviewed above are judged to support a Level 2 determination, possibly efficacious, for the application of neurofeedback for autistic disorders (Coben and Padolsky 2007; Yucha and Montgomery 2008). Further research is necessary utilizing random assignment, blinding of participants, procedures to control for placebo effects and replicated in at least two independent settings to establish neurofeedback as an efficacious treatment for ASD. We would add that such studies should also seek to document brain-related changes in the participants to further document the effects and mechanism of this treatment modality.

In addition to questions about the general efficacy of neurofeedback for ASD, there are additional questions about the relative efficacy of different types of neurofeedback. For example, while we have shown that connectivity (QEEG) guided neurofeedback may be effective (Coben and Padolsky 2007), there is also evidence that symptom based approaches are helpful as well (Jarusiewicz 2002). In the only study to compare these approaches, Coben and Myers (2009) have shown that connectivity guided neurofeedback has demonstrated enhanced efficacy, but that both approaches can be helpful. More studies of this type are warranted. Other types of neurofeedback, including power training, coherence training, hemoencephalography, and training of specific QEEG abnormalities (e.g., mu rhythm/mirror neuron dysfunction), may also prove to have differential efficacy for autism in general and particular symptoms specifically.

Future clinical work and research might also focus on possible synergistic effects between neurofeedback and other interventions (i.e., HBOT, behavior therapy, etc.) commonly used for this population. It also may turn out that such treatments could be used in combination, but in a sequential fashion. For example, ABA may be indicated with very young children to be followed by neurofeedback to "fine tune" treatment effects and address other cognitive and social aspects.

In sum, we view neurofeedback as an intervention that may prove to be efficacious in the treatment of symptoms of autism. Presently, it should be viewed as possibly efficacious with potential and would then be in the same category as most interventions used with this challenging population. There is a great need for carefully and well designed studies to address the issues discussed above (randomization, blinding, placebo controls, multiple measures, etc.). Measuring brain-related changes that may occur as a result of neurofeedback is one way of demonstrating its efficacy and mechanism of action. Additionally, longer follow-up periods should be included in such studies to measure the durability of effects.

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