EEG ASSESSMENT & TREATMENT FOR AUTISM SPECTRUM DISORDERS

By Robert Coben PhD and Kevin McKeon, MA

Robert Coben received his PhD in 1991 and has been a licensed psychologist in the state of New York since 1994. He is the director and chief neuropsychologist of NeuroRehabilitation & Neuropsychological Services. His post-doctoral training in clinical and rehabilitation neuropsychology was done at the UCLA Medical Center and Cedars-Sinai Medical Center in California. He is also the attending neuropsychologist in the Institute for Neurosciences at Winthrop University Hospital.

Dr. Coben is a Diplomate of the QEEG Certification board and is an Associate Fellow, board certified in EEG biofeedback. He is a fellow of the International Society for Neurofeedback and Research and an award-winning researcher in the fields of EEG assessment and biofeedback for autistic disorders.

Kevin McKeon earned his bachelor's degree in psychology from St. Johns University in 2005 and his master's in psychology from Queens College in 2007. In 2008 he came to work at NeuroRehabilitation & Neuropsychological Services, PC, under the clinic's director Dr. Robert Coben. Kevin currently resides in Mineola, NY.

Introduction

Autism is a neurodevelopmental disorder with possible genetic and environmental influences. The Centers for Disease Control and Prevention indicates that the current prevalence of autism spectrum disorder (ASD) is 1 in 150. Furthermore, the U.S. Department of Education reported that from the 1992-1993 to 2001-2002 school years the rate of autism increased 528%. Monetarily, in the United States approximately $3.2 million is spent to care for a single individual with autism over the course of his or her lifetime, which in turn equates to a total cost of $35 billion annually. Beyond the monetary costs, countless other collateral effects are felt by family members and caregivers of those with ASD. Parents with a son or daughter with autism have been found to have increased complaints of anxiety disorders, higher instances of obsessive-compulsive illness, and poorer sleep quality as well as quantity. Children with a sibling with ASD have been found to have more behavior disturbances, increased reports of loneliness, and suffer more peer-related problems. These detrimental ancillary effects compounded with the financial burdens associated with this disorder serve to provide clear evidence that ASD is a problem in society warranting increased treatment efficacy research.

Autism as a Disorder of Neural Connectivity

Recent research points to a theory of faulty neural connectivity as a mechanism underlying the symptoms of ASD. "Connectivity" can be defined as any number of means of measuring the communication between two or more neural locations within the brain. It has been suggested that autistic symptoms are associated with information integration deficits resulting from reduced or under-connectivity between specialized areas of the brain and increased or over-connectivity within other neural areas, particularly the frontal lobes. Etiologically, it has been theorized that early childhood neuroinflammation occurring between the ages of 0 and 2 years old sets off a series of events leading to these connectivity problems. Neurophysiologically, neuroinflammation causes a packing of neurons into abnormally close proximities which results in hyperconnectivity in that there is a structural and electrochemical tendency of neurons close to each other to "fire" or communicate together. Under-connectivity of neural regions is thought to be due to the hyperconnected brain's inability to form sufficient communications with other areas. Recent neuroimaging research has supported this connectivity theory.

Pathologically, over-connectivity of neural assemblies within and between the frontal lobes has been found to be associated with autistic symptoms related to integration of information from the emotional, language, behavioral, sensory, and automatic systems (Courchesne, Redkay, & Kennedy, 2004). Hypocoherence between frontal and posterior and across other posterior to temporal brain regions are associated with regional brain abnormalities. These have included region or network specific impairments in eye gaze (Senju et al., 2005), facial processing (Critchley et al., 2000), social cognition (Pelphrey et al., 2004), and language skills such as sentence comprehension (Just, Cherkassky, Keller, & Minshew, 2004). Furthermore, reducing these connectivity abnormalities is associated with

symptoms' resolution and improvements in the realms of attention, self-regulatory functions, social behavior, and communication skills in autistic persons (Coben & Myers, 2008).

Autism and Seizure Disorders

Multiple neuroimaging studies have demonstrated brain anomalies in autistics compared to healthy controls (McAlonan et al., 2004; Page et al., 2006). Consistent with this, seizures and epilepsy have been commonly observed in autistic samples. Recent analyses have estimated the prevalence of seizure disorders in autistic series at anywhere from 20% to 46%. Based on recent analyses, the prevalence of seizure disorders in autistic series is estimated at about 36% (Danielsson, Gillberg, Billstedt, Gillberg, & Olsson, 2005; Hara, 2007; Hughes & Melyn, 2005; Parmeggiani et al., 2007). In fact it has been reported that the autistic population has about a 3-to-22-fold increased risk of developing seizure disorders when compared to the normal population (Volkmar & Nelson, 1989). Increasing cognitive/ intellectual disability appears to be associated with seizure disorders in autism. Paroxysmal discharges occur in an even higher proportion of autistics, but the significance of these remains uncertain (Hughes & Melyn, 2005; Parmeggiani et al., 2007). Ray, Tao, Hawes-Ebersole, and Ebersole (2007) have suggested that the initial phase of cortical spikes may relate to underlying intracranial foci. Other work has suggested that EEG spikes may reflect underlying morphological brain abnormalities (Shelley, Trimble, & Boutros, 2008) and/ or metabolic disturbances (Kobayashi, Bagshaw, Grova, Dubeau, & Gotman, 2006).

Recent estimates suggest that approximately one-third of all children with autism experience a regression in speech or behavior early in life (Canitano, 2007). Tuchman and Rapin (1997) were unable to relate early regression to seizure disorders, but suggested that the EEG is abnormal in a greater proportion of children with autism who regress than those who do not. Abnormal EEGs are also present in the majority of autistic children with seizure disorders (Hughes & Melyn, 2005). For these reasons, experts in the field have recommended using routine and sleep EEGs when evaluating autistic disorders, especially when there is regression or there are signs of possible seizures.

The Importance of EEG Assessment

The electroencephalogram (EEG) is a premiere tool to assess dysfunctions related to neural connectivity due to its non-invasive nature, availability, and utility in detailing these types of difficulties. Moreover, when an EEG assessment is processed and analyzed with the most advanced techniques, it can be invaluable in evaluating autistic disorders, screening for possible seizures, and assessing the neurophysiological challenges of children with ASD. Assessment of regional brain dysfunction usually requires functional brain imaging techniques, as static measures tend to find few abnormalities in autistic disorders. This would include techniques such as functional MRI, PET, single photon emission computed tomography, EEG, or magnoencephalography (MEG). Some of these techniques require sedation or injection of radioactive material, which makes participation difficult for a typical child with autism. EEG appears to be the most clinically available and, again, least invasive of these techniques. There is emerging evidence that EEG data can be used to assess regions of neural dysfunction in children with autism. Recently, it has been demonstrated that children with autism can be distinguished from typically developing children by their EEGs alone at a rate in excess of 90%. Further, it has been found that unique patterns of regional dysfunction can be discerned through the quantitative analysis of the EEG.

Detection of Seizure Activity

EEG data has been found to be useful in the assessment of epileptiform and/or paroxysmal activity. Screening for seizure activity has been the primary role of the EEG for decades. The following case presentation is used to highlight the information that might be gleaned from such data. This patient was a 7-year-old boy referred to our clinic in 2006. A pediatric neurologist diagnosed him with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) at the age of 3. He was delivered at 36 weeks gestation due to gestational diabetes and had high liver enzymes. There was no history of regression, but a developmental delay in speech/language abilities and a complete inability to identify letters or read words. At the time of his assessment he was taking no medication, was receiving speech, occupational, and physical therapies at school, and his intelligence was considered low average.

Figure 1 shows 8 epochs (seconds) of data during which the patient clearly shows evidence of paroxysmal activity consistent with a focal spike and wave pattern. On the right side of this figure is a voltage topographic map suggestive of a left occipital-parietal-temporal localization.

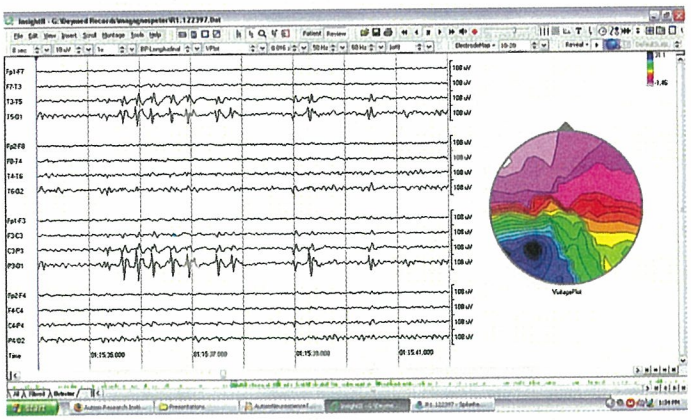

Figure 1. Spike and wave pattern detected by the Persyst/ reveal–spike and seizure detection system (longitudinal montage) with voltage mapping.

Figure 2 is the spike review of all detected events seen during a single EEG recording. There were a significant 165 events detected over the 20 minute recording time. Analysis of individual components of such activity showed five separate patterns with similar areas of morphological disturbance. All

involved the left posterior region, likely including regions near the left occipital and left temporoparietal junction. The spike review propagation maps (right side of Figure 2) show a deactivation followed by a hyperactivation of this region, which is often associated with seizure activity. Interestingly, these regions of the brain are responsible for some of his difficulties including poor comprehension and reading.

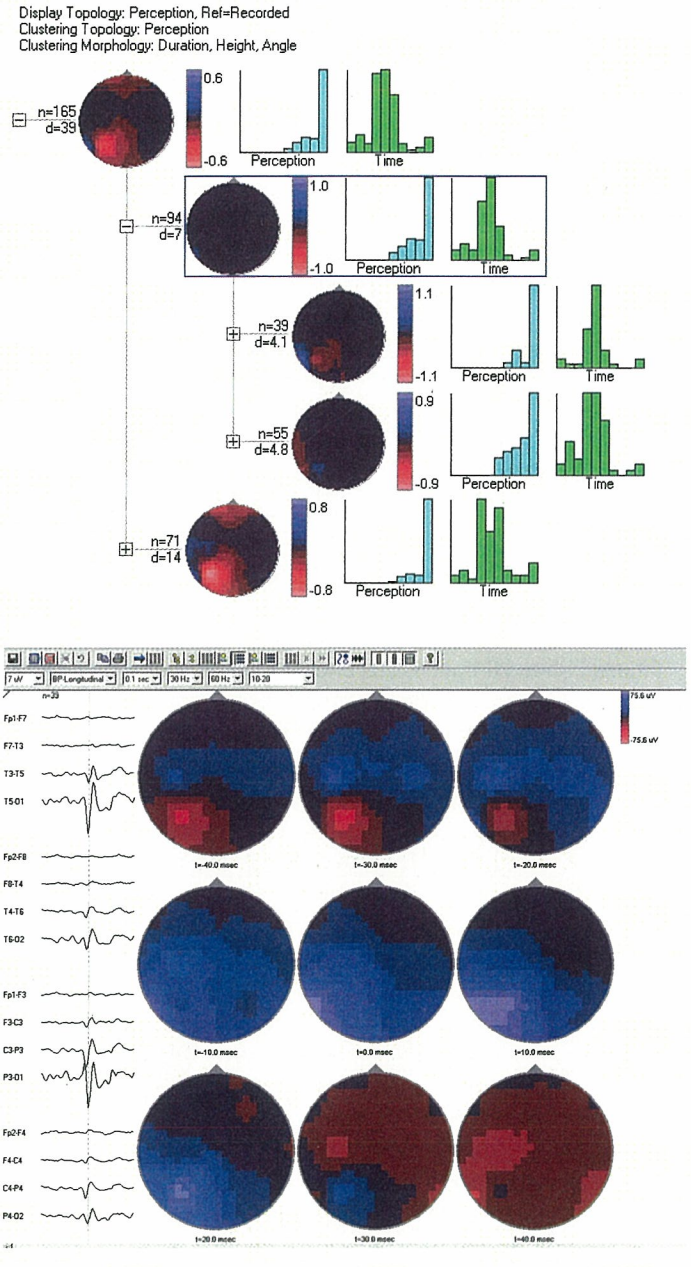

Figure 2. Summary of spike review/reveal with component mapping, time, and perception (left side of figure). Spike review propagation mapping (right side of figure).

Assessment of Regional Brain Dysfunction

In addition to paroxysmal disturbances, there is significant evidence of morphological and functional disturbances in brain functioning in individuals on the autistic spectrum. As reviewed above, assessment of regional brain dysfunction requires functional brain imaging techniques. The EEG appears to be the most clinically available and least invasive of these techniques. There is emerging evidence that EEG data can be used to assess regions of neural dysfunction in children with autism (Chan, Sze, & Cheung, 2007; Coben, Clarke, Hudspeth & Barry, 2008). Recently, Coben, Chabot, and Hirshberg (2008) have demonstrated that children with autism can be distinguished from typically developing children by their EEGs alone at a rate in excess of 90%. They were also able to show that unique patterns of regional dysfunction could be discerned through the quantitative analysis of the EEG. In the following example, we will illustrate how these techniques may be utilized in the assessment of brain functioning.

The EEG data and analyses presented below were gathered from a 19-year-old male diagnosed with Asperger's Disorder and nonverbal learning disability who was referred to our clinic in 2005. He had started college at a university specializing in young adults with learning challenges but dropped out as a result of his difficulties with aspects of independent living and socialization. Presenting symptoms included difficulties with organization, motivation, social skills, and pragmatics.

Figure 3 below shows 8 epochs (seconds) of EEG data referenced in a laplacian montage. These data exemplify an oscillatory pattern localized over C3 and C4 in the alpha band. This pattern has a wicket-like appearance and is referred to as a mu rhythm. Research has shown that poor mu rhythm suppression is present in some children with autism. This finding is related to the concept of mirror neuron dysfunction, which leads to deficits in their observation-execution system, initiation/motivation, imitation, and social skills. Beyond looking at segments of EEG data, there are more advanced statistical and quantitative analyses that can be helpful in understanding brain functioning.

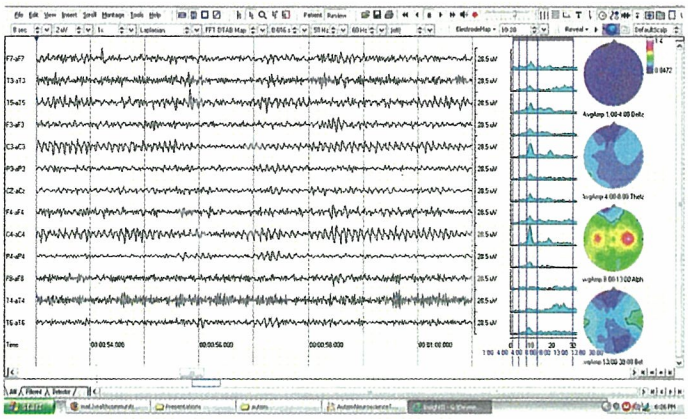

Figure 3. Mu oscillation with EEG, spectral display and topographical mapping (laplacian montage).

EEG data can be acquired, averaged, and compared to a normative database in a technique referred to as Quantitative EEG (QEEG). QEEG technology has been shown to be helpful in the diagnosis and treatment of various conditions including ADHD, learning disabilities, traumatic brain injury, epilepsy, and

more recently autistic disorders. Cross-spectral analysis of EEG data involves multiple steps of artifacting, data conversion, and topographical mapping (John, 1977). The case presented includes findings from resting eyes-open EEG data. These data were artifacted so that muscle, eye, and other artifacts (see Sethi, Sethi, Torgovnick, & Arsura, 2007, for a discussion of such artifacts) are removed from the data set. Once this data is relatively artifact free, a conversion of the data is performed with digital filtering/complex demodulation or a fast fourier transform function (Bendat & Piersol, 1971), following which frequency analyses may be performed. Specific analyses may then be performed and converted into topographical maps for visual display purposes with interpolation of data between electrode sites used to fill in missing data points. Our current case study involved an active mu rhythm as shown in Figure 3 above. Figure 4 shows his EEG eyes-open data averaged over the entire recording (following removal of artifacts) and compared to a normative database for absolute power. There were obvious excesses (significantly above the norm) from 8 to 10 Hz (alpha) and from 15 to 20 (greatest from 18 – 20) Hz. These data show that the mu rhythm observed previously was present beyond what is expected in the normal population. This also shows the location and frequency within which these anomalies occur, which may be used for treatment planning.

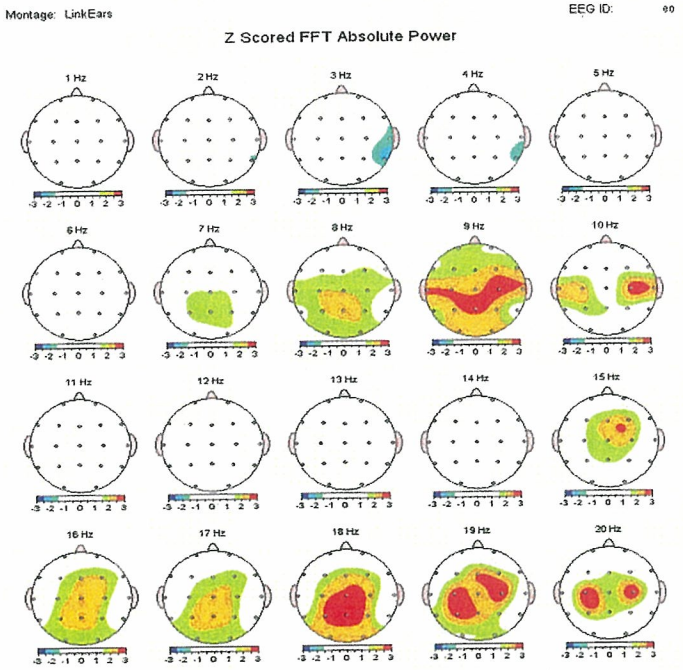

Figure 4. QEEG analysis of eyes-open absolute power processed in the Neuroguide normative database program.

In addition, there are more statistically sophisticated techniques that can help to fine tune such EEG analyses and provide specificity regarding source localization and coherence or connectivity relationships. Figure 5 displays findings from an independent components analysis (ICA) performed with the runica function of EEGLAB (Delorme & Makeig, 2004). ICA blindly decomposes multi-channel EEG data into maximally independent component processes that express brain-generated EEG activities once artifacts are removed. ICA reduces redundancy and reveals unique EEG components. This was performed on the logged power of the EEG data for this same case for the eyes-open condition, focusing on 10 Hz activity, which was the peak frequency of his mu rhythm. These multiple components suggest bilateral and distributed dysfunction including frontal, temporal, and central neural systems. This is additional information compared to figures 3 and 4, which mainly show anomalies over central regions. Components 1, 2, 4, and 6 all show frontal anomalies in addition to the central findings that were previously emphasized.

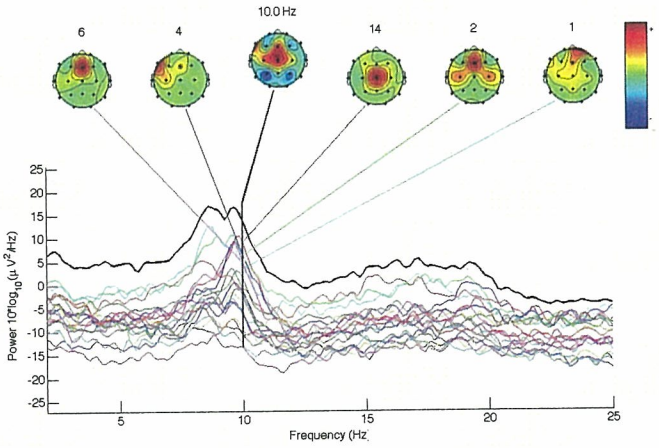

Figure 5. Independent Component Analysis (ICA) of an individuals EEG data.

Source localization of the EEG signal takes this analysis another step further. That is, what regions in the brain (underneath the surface) are responsible for the EEG measured at the scalp? Figure 6 displays the results of a standardized low-resolution brain electromagnetic tomography (sLoreta) analysis. This is an advanced inverse mathematical solution that localizes the sources of the EEG signal of interest. The interested reader should consult Pascual-Marqui (1999) for a discussion of these formulae and solution. These same EEG data (eyes open) were processed for the source localization of relative power anomalies. This resulted in significant findings for source localization of this mu rhythm problem to include the following brain regions: frontal pars opercularis (Brodmann 44), precentral gyrus, middle, and superior temporal gyri, fusiform gyrus, and insula. Interestingly, Dapretto et al. (2006) have shown that high functioning children with autism showed diminished activity in the pars opercularis while imitating and observing emotional expressions, and this was significantly correlated with their ratings of social skill impairments. These data extend our findings further in suggesting that this mu rhythm/mirror neuron dysfunction is a problem involving multiple brain regions including frontal, temporal, and limbic structures. This raises the possibility of a neural connectivity problem that may underlie these difficulties.

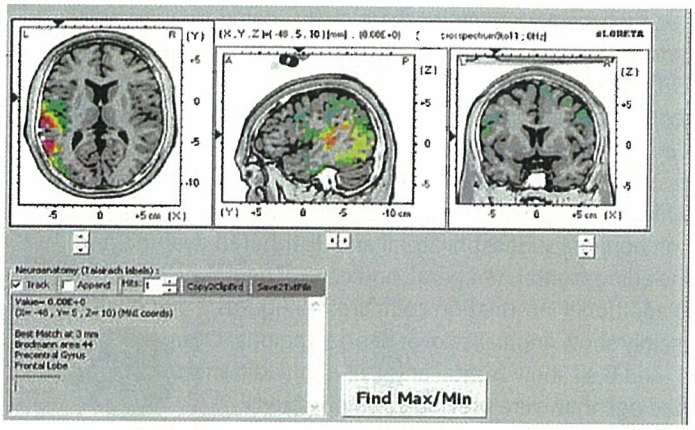

Figure 6. Source localization of mu pattern performed and displayed with sLoreta slice viewer. Maximal localization shown in white, red, yellow, and green.

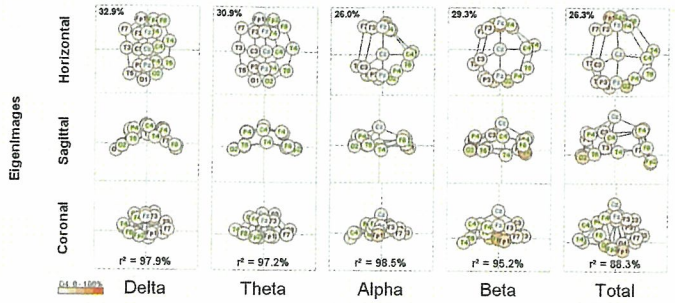

Figure 7. Multivariate connectivity (coherence) analysis in the horizontal, sagittal, and coronal views showing findings for mu activity.

As reviewed above, difficulties associated with ASD may be viewed as stemming from neural connectivity abnormalities. This same EEG data can be analyzed to determine coherence/connectivity relationships and their similarities or differences from those of typically developing children. Figure 7 shows a multivariate connectivity analysis (Hudspeth, 2009) for the eyes-open EEG from this same case, based on coherence data. These analyses are based on principal components analysis, which reduces redundancy and displays unique data. In this particular case, the greatest divergence from typical is seen in the horizontal eigenimage within the alpha band and, to a lesser extent, the beta band. In these images, elongated lines indicate underconnectivity (low coherence) and electrode sites near or on top of each other suggest overconnectivity (high coherence). There is clear evidence in this example of underconnectivity between temporal/central and frontal sites, which is more prominent on the left side. This is consistent with the source localization (sLoreta) analysis shown in Figure 6 and ICA components 1, 2 and especially 4 shown in Figure 5. This completes the picture of a neural system connectivity disturbance underlying the mu rhythm/mirror neuron dysfunction. These data can then be utilized to formulate effective treatments for children with ASD. We have shown how connectivity guided neurofeedback (EEG biofeedback) can effectively be used to reduce autistic symptoms, enhance cognitive, behavioral, and social outcomes in such children (Coben & Padolsky, 2007) and how this may be more effective than doing standard or symptom-based neurofeedback alone (Coben & Myers, in press).

EEG Biofeedback

Research suggests that EEG biofeedback may be an effective form of therapy for reducing autistic symptoms in children. It is a form of therapy that can be individualized for each child's unique needs based on complex analyses of EEG/QEEG data. During the therapeutic process, a client learns to train his or her brain to work in a new, more efficient way through the use of underlying operant conditioning paradigms. This form of therapy is not invasive, free of lasting side effects, effective, and may have long-lasting therapeutic effects.

The application of connectivity-guided neurofeedback begins with a complex analysis of EEG data as reviewed above. Based on these findings, training sets out to reduce abnormalities of connectivity and/or power between and within specific regions of an individual's brain. Clients then undergo neurofeedback in which a computer-analyzed signal of neural activity is fed back to the subject along with a more easily understood signal on a computer monitor, which can be reinforced. More simply, a game scenario is created using the client's actual neural activity translated by a computer in which they are encouraged to emit increasingly more functional neural activity that is targeted for training (see Figure 8 below). For example, a car racing game scenario can be setup where, when the client produces neural activity that is more functional (i.e., better connectivity or reduced power abnormalities), their race car on the screen will take the lead. If, during this training, their neural functioning begins to slow or move towards a more dysfunctional state their car will begin to slow and fall behind other cars. During this operant conditioning process, the client trains his or her brain to function in improved ways with reductions in symptoms and improvements in communication, cognition, behavior, and social skills occurring as a result. The greater the number of therapy sessions, the greater the likelihood for therapeutic change and persistence of these effects.

Efficacy of Neurofeedback

Research into the efficacy of neurofeedback for ASD has increased in recent years. The first published group study to assess the therapeutic nature of this intervention was done by Jarusiewicz (2002). This investigation found this therapy able to produce an average 26% reduction in autistic symptoms. More recently Coben & Padolsky (2007) assessed the efficacy of connectivity guided EEG biofeedback and found an 89% success rate with a 40% reduction in autistic symptoms with just 10 weeks of treatment.

More recently, Coben (2009) studied the largest series of cases yet of children with autism receiving neurofeedback. A total of 110 children were studied, 85 of whom received the active therapeutic intervention (connectivity-guided neurofeedback). The major finding of this study was that

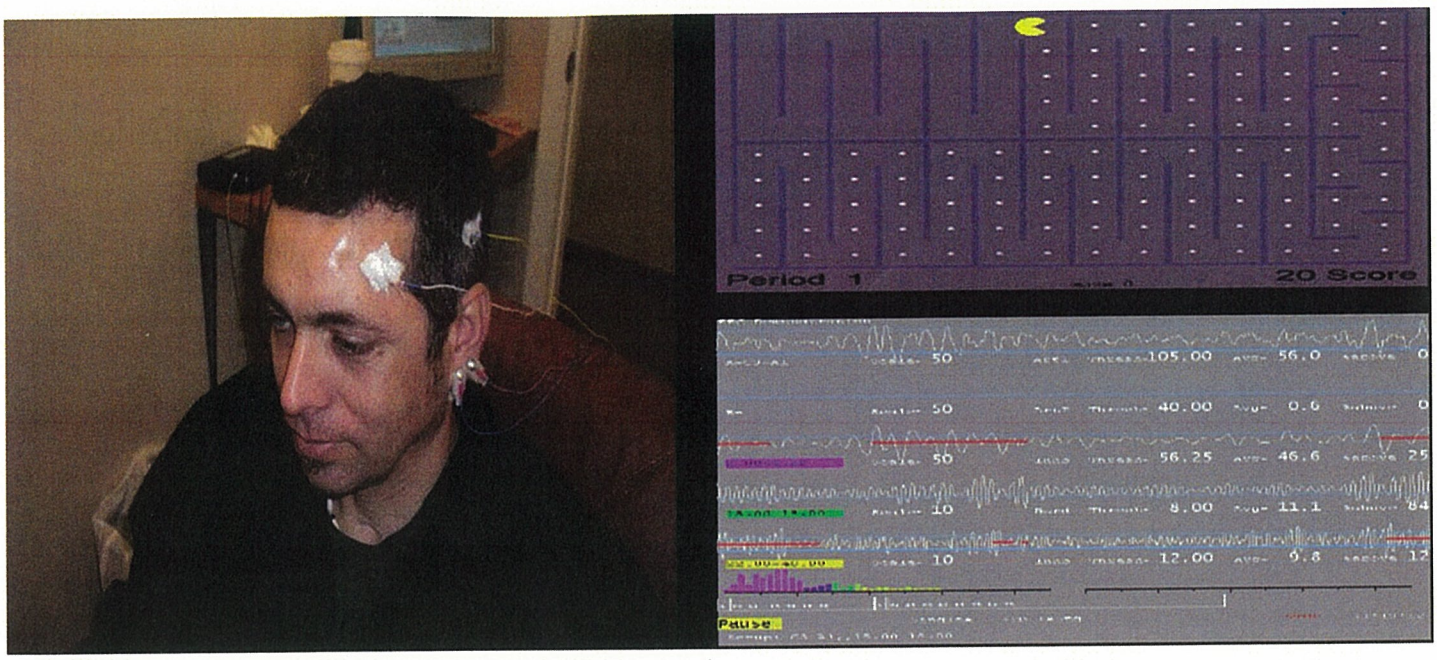

Figure 8. An example of a patient undergoing EEG biofeedback

children with ASD who received the active treatment improved significantly and experienced a reduction in autistic symptoms of close to 60% over an average treatment period of about 6 – 7 months. Figure 9 shows the results for pre- and post-neurofeedback training scores on the Autism Treatment Evaluation Checklist completed by their parents for both the experimental and control groups. The group that received the connectivity-guided neurofeedback training showed significant reductions in symptoms when compared to the control group.

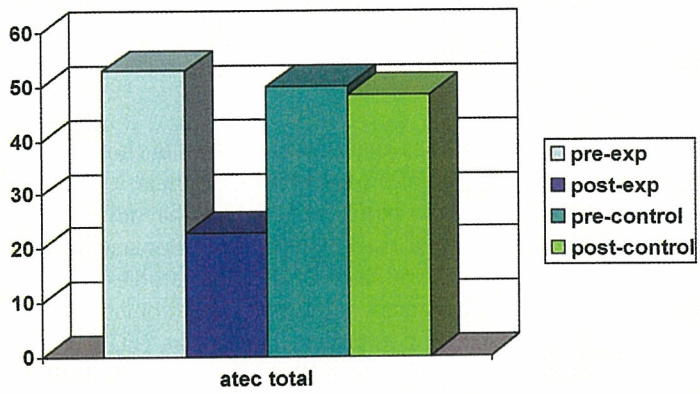

Figure 9. Autistic symptoms as assessed from pre- to post-treatment conditions on the Autism Treatment Evaluation Checklist (ATEC). Subjects receiving EEG biofeedback achieved an overall 57% reduction in rated symptoms, while the group receiving no treatment accomplished little reductions in symptoms.

These reductions in symptoms covered multiple domains of functioning, including improved behavioral and emotional control, social skills, communication abilities, and reductions in repetitive behaviors. In addition to changes in parents' ratings of symptoms, there were also significant reductions in levels of impairment on objective measures of neuropsychological functioning inclusive of attention, executive functioning, language, and visual-perceptual abilities. Any treatment must demonstrate both efficacy and safety. Figure 10 shows the proportion of parents who rated their children as improved (98%) and those who thought their children had not improved (2%). No parents rated their children as worse than when they began treatment. A sizeable proportion (94%) of parents rated their children as having improved significantly (reduction in autistic symptoms of at least 40%). Interestingly, level of functioning (based on IQ) and severity of autistic symptoms did not impact therapeutic outcome.

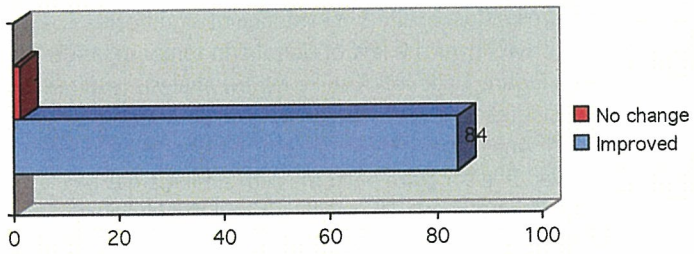

Figure 10. Parents rating of improvement in the experimental group receiving connectivity-guided neurofeedback

Lastly, the question is how does neurofeedback actually work? It is considered an operant conditioning procedure, but one that changes brain functioning instead of behavior. We have recently demonstrated (Coben, Sherlin, Hudspeth, & McKeon, 2009) that connectivity-guided neurofeedback designed to decrease bilateral frontotemporal hyperconnectivity leads to important clinical gains that are associated with therapeutic changes in brain functions. Figure 11 shows source localization changes

in brain activity associated with this treatment. This, to our knowledge, is one of the first demonstrations of a treatment for ASD with documented brain-related changes/improvements.

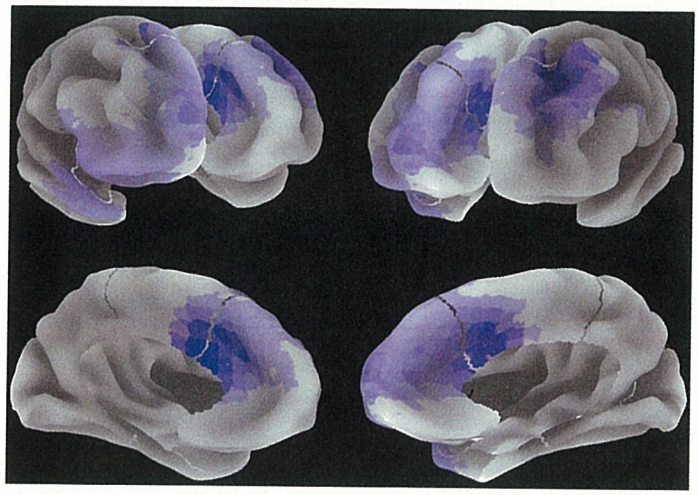

Figure 11. eLORETA changes in source localized relative power as a result of EEG neurofeedback.

Case Presentation

The following case presentation will illustrate the potential benefits of neurofeedback for a child diagnosed with ASD and a seizure disorder. This is the same child discussed above in the Detection of Seizure Activity section. At the time of referral, he was a 7-year-old boy diagnosed with PDD-NOS, with a low average IQ (FSIQ = 80), and impairments in the realms of repetitive language, reading, motor sequencing, visual-perceptual analysis, and social skills.

A clinical EEG conducted in our clinic at intake was analyzed with complex EEG/QEEG software algorithms. One component of this was the use of the Persyst/Reveal–spike and seizure detection system. This resulted in evidence of significant paroxysmal activity over the left occipital and temporoparietal junction (see Figure 1 above). A spike review analysis resulted in 165 events detected over the 20-minute recording time (see Figure 2). Analysis of individual components of such activity showed five separate patterns with similar areas of morphological disturbance. These all involved the left posterior region likely including regions near the left occipital and left temporoparietal junction. The spike review propagation maps (right side of Figure 2) show a deactivation followed by a hyperactivation of this region, which is often associated with seizure activity. Interestingly, these regions of the brain are responsible for some of his difficulties, including poor comprehension and reading.

The patient underwent connectivity guided neurofeedback training with a special emphasis on training regions involved in his apparent epileptiform activity. During this training, he was receiving no other medical or biomedical interventions. Figure 12 shows improvements in both spike events and parents' ratings of autistic symptoms.

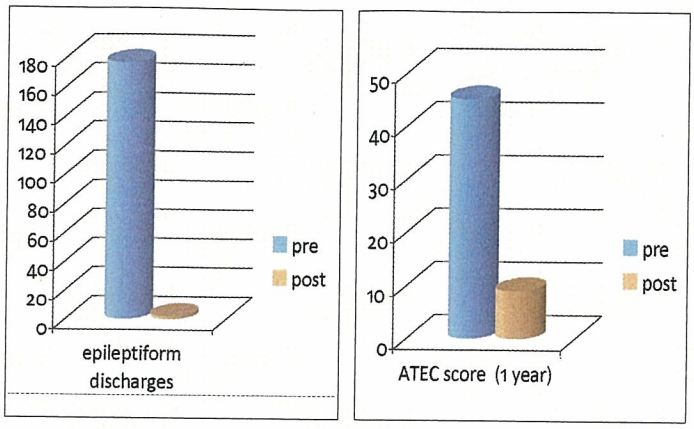

Figure 12. Improvement over the course of connectivity-guided neurofeedback training. Decreases in epileptiform discharges (left side) and parent rating of autistic symptoms (right side) are displayed for before treatment and after training was completed.

Over the course of one year of therapy sessions, his seizure events went from 165 during a 20-minute recording to being virtually non-existent. His parents' rating of his autistic symptoms diminished by 80% during this same time frame. By the completion of his training, all objective neuropsychological measures were within normal limits except for receptive language/auditory comprehension that was rated as mildly impaired compared to his age-matched peers. His inability to identify letters and words improved to the point where he could read words, sentences and was rated as being only one grade level behind in reading fluency abilities. Quantitative analysis of his post-treatment EEG showed no elevations above 2 standard deviations and one isolated difficulty over his left posterior temporal region.

Summary

Autism is a disorder that not only affects the lives of those afflicted but also the lives of those who care for them. It has been theorized and, at least partially confirmed, that autistic symptoms may be related to early neuroinflammation and neural connectivity disturbances. In fact, recent genetic studies have suggested anomalies among autistic samples on chromosomes related to the formation of neural connectivity. The EEG is useful in the assessment of such children as an evaluation tool for seizure detection, to assess for regions of brain dysfunction, and can provide useful information regarding neural connectivity or coherence. Advanced EEG/QEEG techniques may be employed to localize the source of such activity and to determine deviations as compared to a normative database. While the EEG may be useful as an assessment device alone, it may be most helpful in assisting with the design of a therapy regimen that can modify brain activity and lead to significant therapeutic gains. Connectivity-guided neurofeedback may be effective for ASD in general and for seizures specifically. This is a safe treatment that is non-invasive, tolerated well by most children with autism, and its positive effects may be long-lasting.

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