Chapter 12
EEG Analyses in the Assessment of Autistic Disorders

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12.1 Introduction

Autistic spectrum disorders (ASD) are a heterogeneous group of pervasive developmental disorders including autistic disorder, Rett's disorder, childhood disintegrative disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), and Asperger's disorder. Children with ASD demonstrate impairment in social interaction, verbal and nonverbal communication, and 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. Repetitive stereotyped behaviors, perseveration, and obsessionality, common in ASD, are associated with executive deficits. Executive dysfunction in inhibitory control and set shifting 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.

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

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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's disorder frequently have high levels of cognitive functioning, engage in literal pedantic speech, experience difficulty comprehending implied meaning, exhibit problems with fluid movement, and manifest inappropriate social interactions. Pervasive developmental disorder-not otherwise specified (PDD-NOS) reflects deficits in language and social skills, which do not meet the criteria of other disorders. In contrast, persons with childhood disintegrative disorder and Rett's disorder both have normal periods of early development followed by loss of previously acquired skills. Common features among all 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).

Research reviewing the epidemiology of autism (Center for Disease Control and Prevention; CDC 2009) reported between 1 in 80 and 1 in 240 children in the United States diagnosed with the disorder. A report of just 3 years ago (Center for Disease Control and Prevention 2009) suggested a prevalence of 1 in 110 and as high as 1 in 70 boys. In their most recent report, the CDC (2012) suggests that the rate has risen to 1 in 88. ASDs are five times more likely in boys for which it is seen in 1 out of 54 male children. 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 tenfold increase over a 20-year interval in the United States. These findings make accurate assessment of autistic individuals and their underlying neurophysiology a priority.

12.2 EEG Assessment in Autism

Multiple neuroimaging studies have demonstrated brain anomalies in autistics compared to healthy controls (McAlonan et al. 2004; Page et al. 2006). The electroencephalography (EEG) was one of the earliest techniques used to investigate the neurobiology of autism (Minshew 1991). The recognition of a high instance of EEG abnormalities and of seizure disorders in the autistic population was among the earliest evidence of a biologic basis for disorder (Minshew 1991). Moreover, the EEG is a premiere tool to assess neural dysfunctions related to autism and seizures due to its' noninvasive nature, availability, and utility in detailing these types of difficulties.

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 et al. 2005; Hara 2007; Hughes and Melyn 2005; Parmeggiani et al. 2007). In fact, it has been reported that the autistic population has about 3–22-fold increased risk

of developing seizure disorders as compared to the normal population (Volkmar and Nelson 1989). Increasing cognitive/intellectual disability appears to be associated with seizure disorders in Autism. Subclinical seizure activity or paroxysmal discharges occur in an even higher proportion of autistics, but the significance of these remains uncertain (Hughes and Melyn 2005; Parmeggiani et al. 2007). Ray et al. (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 et al. 2008) and/or metabolic disturbances (Kobayashi et al. 2006).

Recent estimates suggest that approximately one-third of all autistic children 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 autistic children that regress than those that do not. Abnormal electroencephalogram (EEG) recordings are also present in the majority of autistic children with seizure disorders (Hughes and Melyn 2005). In a more recent study, Parmeggiani et al. (2010) demonstrated that in a large inpatient sample, 58 % of adults with autism aged 20 or older had experienced epilepsy or a seizure during their lifetime.

For these reasons, experts in the field have recommended the use of routine and sleep EEGs in the evaluation of autistic disorders, especially when there has been regression or there are signs of possible seizures. In fact, seizure detection has been the primary role of the EEG for decades. Neurologists and epileptologists routinely use visual inspection of data as a basis for diagnosing seizure-related disorders.

When EEG assessment is processed and analyzed with the most advanced techniques, it can be invaluable for screening for possible seizures, evaluation of autistic disorders, and assessing the neurophysiological challenges of children with ASD. Presently, 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, magnetoencephalography (MEG), and even EEG. Some of these techniques require sedation or injection of radioactive material so as to make participation difficult for a typical autistic child. EEG however appears to be the most clinically available and again least invasive of these techniques. Further, it has been found that unique patterns of regional dysfunction could be discerned through the quantitative analysis of the EEG.

12.3 Quantitative EEG Findings and ASD

A review of the existing literature identified 14 studies that used quantitative techniques to analyze differences in EEG (QEEG) activity between children with autistic spectrum disorder (ASD) and normal controls with conflicting results. Two studies showed decreased delta frontally (Coben et al. 2008; Dawson et al. 1982), while one found increased activity in the delta frequency range (Murias et al. 2007).

Two studies reported increased generalized delta or described "slowing" (Cantor et al. 1986; Stroganova et al. 2007). Two studies showed theta increases (Coben et al. 2008; Small et al. 1975), while one study reported reduced theta (Dawson et al. 1982). By contrast, findings have been quite consistent within the alpha through gamma frequency range. All studies reported reduced alpha power (Dawson et al. 1982; Cantor et al. 1986) and increased beta (Coben et al. 2008; Chan and Leung 2006; Rossi et al. 1995) and gamma power (Orekhova et al. 2006). Multiple studies report a lack of hemispheric differences in QEEG spectral power in autistic samples compared to findings of hemispheric differences in normal controls. Autistic children showed decreased power asymmetry when compared to normal or mentally handicapped controls (Dawson et al. 1982; Ogawa et al. 1982). Three studies investigated cortical connectivity in ASD samples using QEEG coherence measures, with all reporting reduced connectivity, especially over longer distances (Cantor et al. 1986; Coben et al. 2008; Lazarev et al. 2004).

Sample sizes by and large have not been large enough to allow for investigation of the observed inconsistencies in findings reported above. One possibility is that the specific QEEG abnormalities found may be associated with differences in functioning and are characteristic of the phenotypic heterogeneity of autism spectrum disorder. Such an analysis has been useful in QEEG research in attention deficit disorder (Chabot et al. 1999, 2005; Clarke et al. 2003a, b). The present study was designed to document QEEG differences between a large sample of children diagnosed with autistic spectrum disorder and a matched sample of children with no known neurological or psychiatric disorders. The goal was to document the specific types of QEEG profiles found within this population, to develop a QEEG feature-based discriminant function (possible biomarker) to distinguish children with autistic spectrum disorder from the normal population of children, and to use the QEEG source localization technique VARETA to delineate the neuroanatomical structures that are dysfunctional in ASD.

12.3.1 Methods and Material

Clinical Population: All children were referred to the Neurorehabilitation and Neuropsychological Center in Massapequa, New York. A sample of 91 children was entered into this study (mean age = 9.9 years; sd = 3.4). None of the children were receiving psychotropic medication at the time of testing. Children with histories of drug abuse, head injury, or other neurological disorders were excluded. IRB approval was obtained for this study and all data were de-identified prior to processing. All participants in this study met diagnostic criteria for either autistic disorder, Asperger's disorder, childhood disintegrative disorder, or pervasive developmental disorder-not otherwise specified as described by the DSM-IV. All diagnoses were made by the first author, a licensed clinical psychologist and practicing neuropsychologist, and were based upon patient and parent interviews supplemented by

scores on the Gilliam Asperger's Disorder Scale and the Gilliam Autism Rating Scale (Gilliam 1995, 2001).

Normal Population: The normal controls included 91 children between the ages of 6 and 17 matched to the ASD population based upon age and gender. All normal subjects were free of neurological or medical disease; had no history of head injury, drug, or alcohol abuse; were of normal IQ; showed evidence of adequate functioning at home/school for the past 2 years; and had not taken any prescription medication for at least 90 days prior to evaluation.

Quantitative EEG Methodology: The Neurometric method of EEG data collection and analysis was utilized (John et al. 1977, 1988). Patients were seated comfortably in a sound and light attenuated room during the evaluation. Recording electrodes were placed over the 19 standard regions defined by the International 10/20 system referenced to linked ears. All electrode impedance levels were kept below 5,000 Ω. A differential recording channel above and below the right eye was used to monitor eye movement artifact. Twenty to thirty minutes of continuous eyes-closed resting EEG was recorded from all children. An experienced EEG technician selected the first 1–2 min of artifact-free EEG from this record for analysis. Particular care was taken to prevent EEG contamination due to drowsiness and to exclude EEG segments contaminated by artifact.

The artifact-free EEG from each channel was converted from the time to the frequency domain via fast Fourier transform (FFT). Two QEEG measures related to the frequency distribution of the EEG were calculated: absolute power defined as the amount of energy in the delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), and beta (12.5–25.0 Hz) frequency bands as well as the total power across all frequency bands (1.5–25.0 Hz); relative power in each frequency band defined as the amount of energy in each band divided by total power. Two QEEG measures were calculated that measured EEG connectivity across cortical regions including power asymmetry in each frequency band between the left and right hemispheres and waveform coherence or the correlation of EEG across selected cortical regions. Each measure was mathematically transformed to conform to a normal distribution and age-regressed and compared to the mean and standard deviation of that measure obtained from a previously published normal database of 310 children using a z or standard score. Conversion to z-scores allows each QEEG measure to be described using a common metric related to the probability of coming from the normal population, and as such, these features can be used together in subsequent discriminant analyses.

Variable resolution electromagnetic tomography (VARETA) is a three-dimensional source localization method that uses surface-recorded EEG to identify the most probable neuroanatomical generators of each EEG frequency band and maps these results onto a probabilistic brain atlas resembling slices obtained from an MRI (Bosch-Bayard et al. 2001). When z-score transformed relative to a normal population, these VARETA brain images can be used to depict the cortical and subcortical structures involved in the pathophysiology of various neurocognitive disorders (di Michele et al. 2005).

12.3.2 Results

12.3.2.1 QEEG Absolute Power Findings

Separate multivariate analyses of variance were calculated comparing the normal children and those with ASD for the delta, theta, alpha, and beta frequency bands across the 19 recording regions. For delta absolute power, all 19 univariate *F*-ratios reached the $p < 0.0001$ level of significance (d$f = 1,180$) with the overall multivariate *F*-ratio = 23.6 ($p < 0.0001$, d$f = 19,162$). ASD children showed a generalized deficit of delta absolute power that was greater in frontal and central than in more lateral and posterior regions. Theta absolute power was increased in the ASD population with univariate *F*-ratios significant at $p < 0.001$ in frontal, central, and left parietal and posterior/temporal regions (Multi $F = 10.9$, $p < 0.0001$). While the overall multivariate *F*-ratios for alpha and beta absolute power were significant ($F = 8.6$, $p < 0.001$; and $F = 7.1$, $p < 0.0001$), none of the univariate *F* values reached the $p < 0.001$ level of significance.

12.3.2.2 QEEG Relative Power Findings

For delta relative power, all 19 univariate *F*-ratios reached the $p < 0.0001$ level of significance with the overall multivariate *F*-ratio =16.6 ($p < 0.0001$). ASD children showed a generalized deficit of delta relative power that was greater in frontal and central than in more lateral and posterior regions. Theta relative power was increased in the ASD population with the univariate *F*-ratios significant at $p < 0.001$ for frontal and anterior and posterior/temporal regions (Multivariate $F = 4.4$, $p < 0.0001$). Alpha relative power was increased in the ASD population in all regions ($p < 0.001$) except for posterior/temporal and occipital recordings (Multivariate $F = 7.6$, $p < 0.0001$). Beta relative power was increased in ASD for all regions ($p < 0.001$) except for the anterior temporal and occipital regions (Multivariate $F = 6.3$, $p < 0.0001$).

12.3.2.3 QEEG Power Asymmetry Findings

Multivariate *F* values reached significance for each frequency band (*F* between 3.3 and 5.9 with *p* between 0.002 and 0.0001; d$f = 8,173$). Univariate *F*-ratios reached the $p < 0.001$ level of significance for frontal/lateral and parietal delta and theta, for frontal/lateral alpha, and for parietal beta. In frontal/lateral and parietal comparisons, ASD children had increased right hemisphere delta and theta and decreased alpha power relative to left hemisphere power values when compared to the normal population. In parietal comparisons, ASD children had increased left hemisphere beta power relative to right hemisphere power values when compared to the normal population.

12.3.2.4 QEEG Coherence Findings

Multivariate F values reached significance for each frequency band (F between 2.9 and 4.8 with p between 0.004 and 0.0001). Univariate F-ratios reached the $p < 0.001$ levels for frontal/lateral theta, alpha, and beta; for anterior and posterior/temporal alpha; and for posterior/temporal beta coherence. Frontal/lateral coherence values were increased (hypercoherent) in ASD in comparison with the normal population. Anterior and posterior/temporal coherence was decreased (incoherent) in ASD in comparison with the normal population.

12.3.2.5 QEEG Heterogeneity in ASD

A combination of factor and cluster analysis procedures was utilized to determine whether or not the relative power QEEG frequency distribution could be used to delineate subtypes of ASD. Factor analysis was used to reduce the number of relative power variables (19 regions by four frequency bands) that could be entered into cluster analysis in keeping with maintaining a minimum of 10/1 subject to variable ratio. Factor analysis with varimax rotation was performed for each frequency band across 19 monopolar regions. For each analysis, three factors were obtained. These factors accounted for 81.9 % of the variance for delta, 85.5 % for theta, 89.8 % for alpha, and 85.2 % for beta relative power. An examination of the rotated factor loadings revealed factors which corresponded to frontal plus anterior temporal, parietal/occipital plus posterior/temporal, and central regions for delta, theta, and alpha relative power. For beta relative power, there were frontal/central, parietal/occipital plus posterior/temporal, and anterior temporal factors. None of the factors was related to left versus right hemispheric differences.

Cluster analysis was then performed using mean relative power values that were averaged across the three regions identified by the factor results just described. Thus, there were 12 QEEG measures (four frequency levels by three average factor regions) entered into the cluster analysis of the 91 ASD children. Four, five, and six cluster solutions were examined. For all solutions, each cluster had a deficit of delta relative power. For the four cluster solution, there were a theta excess, alpha excess, theta and alpha excess, and beta excess cluster. With five clusters, the beta cluster was divided into two clusters, one with slight theta excess and the other with slight alpha excess. With six clusters an additional small theta excess cluster with elevated alpha and beta was seen. Figure 12.1 presents the relative power average z-score head maps for the individuals within each of the clusters in the five cluster solution.

12.3.2.6 QEEG Discriminant Analysis Findings

A step-wise discriminant analysis was calculated comparing the normal children with the children with autistic spectrum disorder. QEEG variables entered were selected using analysis of variance comparisons between the two groups with those

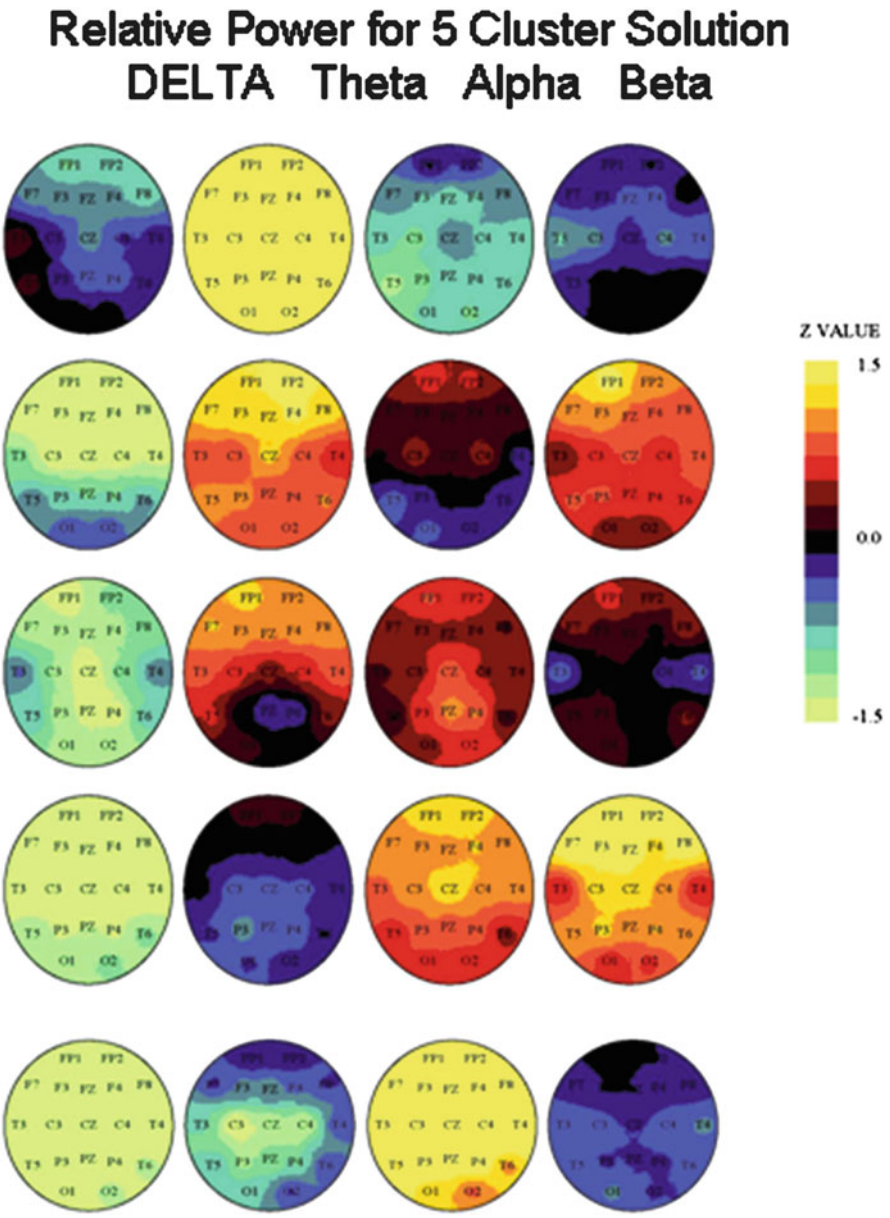

Fig. 12.1 Group average QEEG Z images for five QEEG subtypes of ASD. Images shown are oriented with nose up, left on left, and are color coded in standard deviation units (*z*-scores), with excesses in *red/yellow* and deficits in *blue/green*. In group average images, the significance of the *z*-score is estimated multiplying the square root of the group size by the *z*-value; thus, in these images, the extremes of the scale are $p < 0.001$

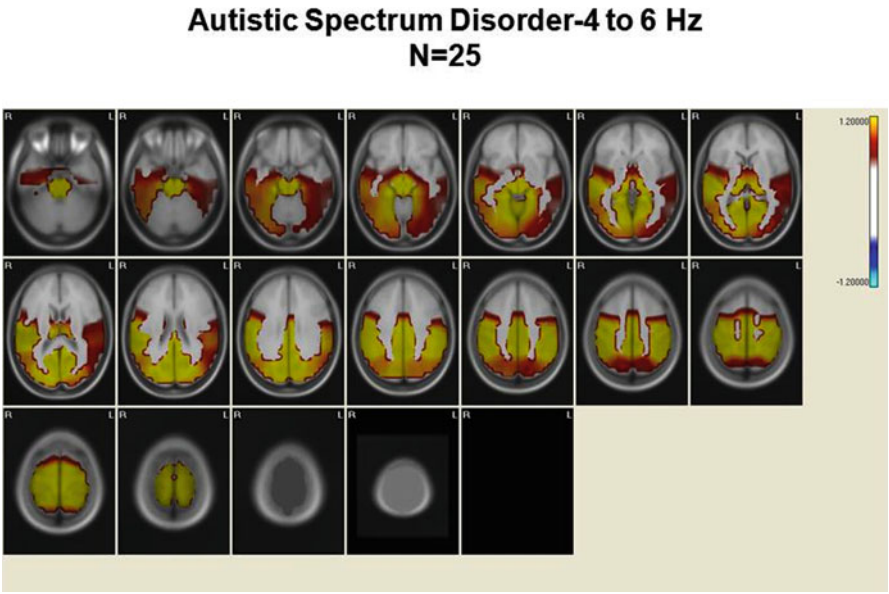

Fig. 12.2 The *panels* depict trans-axial images of the sources identified using VARETA, showing the mathematically most probable generators of the most abnormal QEEG activity for the group, and represent the mean *z*-values of each voxel computed across the group of ASD children and color-coded for significance. These images follow the radiological convention, with the right side of the head depicted on the left side of the slice

variables with the highest *F*-ratios and lowest intercorrelations chosen. A total of five variables were utilized resulting in 92.3 % (sensitivity) correct identification of normal children and 95.6 % (specificity) correct identification of ASD children. A jack-knife replication resulted in 92.3 % correct identification of normal and 95.6 % correct identification of ASD children. The positive predictive value was 95.5 % and the negative predictive value was 92.6 %. QEEG variables utilized included central delta mean frequency, central theta coherence, central delta relative power, right frontal/temporal alpha asymmetry, and right frontal/temporal theta relative power.

12.3.2.7 VARETA EEG Source Localization Findings

Group average VARETA images were constructed for each of the five above defined subtypes separately for the ASD children. An examination of these images revealed consistent findings across QEEG subtypes. Figure 12.2 presents a group average VARETA image in the axial plane for the theta excess subtype. The VARETA image uses threshold scaling such that colors shown represent statistically significant deviations from the normal population. ASD children were characterized by increased theta activity in the cerebellum, thalamus, hippocampus, parahippocampal, cuneus,

cingulate, and lingual gyrus and in temporal, precentral, postcentral, parietal, and occipital cortical regions. Note that the anatomical location of abnormal neurophysiological activity was very consistent across ASD subtypes and is illustrated in Fig. 12.2. Consistent differences were seen between the ASD subtypes and normal children at each frequency, and these differences showed virtually the same pattern of anatomical abnormality across subtypes. In other words, despite the different frequency distributions noted between ASD subtypes, the neuroanatomical structures identified by VARETA as showing abnormal activity are consistent and may represent the neuroanatomical structures which show dysfunction in ASD.

12.4 Discussion

In the largest study of its kind, differences between the ASD and normal populations were seen in both absolute and relative power for the delta, theta, alpha, and beta frequency bands. One of the more intriguing findings is that of a prominent delta absolute and relative power deficit in the autistic children. While this delta deficit was generalized, it was most prominent in frontal and central regions. Coutin-Churchman et al. have shown delta deficits to be associated with cerebral atrophy (Coutin-Churchman et al. 2003). Frontal white matter volume has also been negatively correlated with frontal delta power (Babiloni et al. 2006). Delta activity is believed to originate in deep cortical neurons and in the thalamus (John and Prichep 2006). Evans (2003) postulated a thalamocortical network responsible for the integration of brain electrical activity and that deficient delta activity may signify a weakness in this system. Consistent with this model have been the animal studies demonstrating associations between deficient slow-wave activity and functioning of the striatal dopaminergic system (Kitaoka et al. 2007; Alper 1999; Binienda et al. 2002). This theory is interesting as it relates to autistics given the pervasiveness of their neural connectivity impairments (Coben and Myers 2008b; Minshew and Williams 2007).

Excess relative and absolute theta power were more localized occurring mainly in frontal, central, and temporal regions. This finding is supported in the literature where three (Coben et al. 2008; Small et al. 1975; Chan and Leung 2006) of four previous studies have reported theta excesses in ASD, while only one (Dawson et al. 1982) has shown a theta deficit. Our finding of an alpha excess in all but posterior cortical regions differs from that reported in the literature (Dawson et al. 1982; Cantor et al. 1986), although the finding of increased beta especially in frontal and central regions is consistent with the previous literature (Coben et al. 2008; Chan and Leung 2006; Rossi et al. 1995). This inconsistent finding for relative and absolute alpha power may be explained by examining the cluster analysis results that show the heterogeneity of ASD relative power findings. Note that four of five clusters are characterized by some degree of alpha excess, although cluster 1 is characterized by an alpha deficit. An examination of the cluster analysis findings also reveals that 5/5 clusters showed some degree of delta deficit, three of five showed theta excess and 1/5 theta deficit, and 2/5 some degree of beta excess.

Differences between the normal and ASD populations were found in the power relationships between the two hemispheres (power asymmetry). The children with ASD showed increased right hemisphere delta and theta and decreased alpha power relative to their left hemisphere when compared to normal children's power relationships with this difference present in lateral frontal and parietal regions. On the other hand, ASD children had increased left hemisphere beta power relative to their right hemisphere when compared to normal children's hemispheric power relationships. Further, our findings indicate that ASD is characterized by increased frontal coherence and decreased anterior and posterior/temporal coherence between the two cerebral hemispheres. These findings suggest that the brain dysfunction in autistic disorders is often bilateral and impacts both anterior and posterior axes. Alternatively, one could view the brain dysfunction in autism as an abnormality in connectivity that disrupts function in multiple regions (Minshew and Williams 2007). This would suggest that such connectivity impairments are prevalent in autistic children. This is consistent with the findings of Coben et al. (2008). Such an interpretation is also supported by the literature suggesting that autism is primarily a disorder of neural connectivity.

12.4.1 Autism as a Disorder of Neural Connectivity

There is increasing evidence that the cardinal disruptions in autism are represented by disruptions in brain connectivity (Courchesne and Pierce 2005; Mak-Fan et al. 2012; Minshew and Williams 2007). There is mounting evidence of head enlargement as a result of brain overgrowth early in life (first 1–2 years) (Courchesne et al. 2001, 2003) as a result of enhancements in frontal white matter and minicolumn pathology (Carper and Courchesne 2005; Casanova et al. 2002; Herbert et al. 2004; Vargas et al. 2005). This overgrowth, then, leads frontal over-connectivity (Coben and Myers, 2008b; Courchesne and Pierce 2005; Rinaldi et al. 2008) which interferes with the normal developmental trajectory. This disruption, theoretically, then halts the natural developmental progression in which anterior to posterior brain regions would enhance their synchronization and specialization of functions (DaMasio 1989; Supekar et al. 2009). This pattern, in fact, was observed in our data above showing frontal hypercoherence and bilateral temporal hypocoherences.

Other data support this hypothesis as well. For example, Mak-Fan et al. (2012) examined changes in diffusivity with age within frontal, long-distance, longitudinal, and interhemispheric tracts across ages 6–14. Their findings showed that while typically developing controls change and evolve on such measures, children with autism did not. This suggests that such connectivity difficulty exists and persists in such children. More specifically, frontal and local (short neuronal paths) hyperconnectivity has been shown to be present in autistic samples (Li et al. 2012; Wass 2011). In addition, there is other recent data showing hypoconnectivity in long-distance and posterior to anterior or temporal regions in autistics. Isler et al. (2010) have shown low interhemispheric coherence in visual evoked potentials in such children.

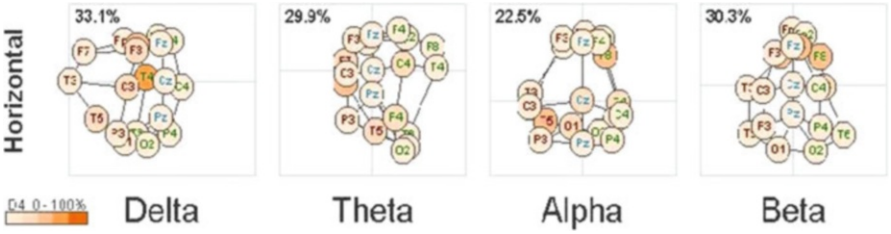

Fig. 12.3 NeuroRep multivariate connectivity analyses showing eigen images in the horizontal place across delta, theta, alpha, and beta frequencies. Observable features include (1) frontal hyperconnectivity in the alpha and beta frequency bands, (2) left anterior temporal/posterior frontal to posterior/temporal–parietal hypocoherence in the delta band, (3) right medial temporal to occipital–parietal–posterior/temporal hypocoherence in the theta band, and (4) bilateral frontal/temporal hypocoherences in the alpha band

Studies of functional connectivity related to visuospatial processing and the social-emotional processing networks have also shown reduced connectivity compared to healthy controls (Ameis et al. 2011; McGrath et al. 2012; vondem Hagen et al. 2012). Similarly, low functional connectivity has been shown to be related to poor language processing in autistic children (Kana et al. 2006). Many of these studies used three-dimensional imaging techniques such as MRI, fMRI, or DTI (diffusion tensor imaging).

Interestingly, EEG/QEEG studies of coherence have shown similar findings. In our study reviewed above, frontal hypercoherence and bilateral posterior-temporal hypocoherences were found. Similarly, high frontal coherence has been observed in other studies (Coben and Padolsky 2007; Murias et al. 2007). In addition, EEG technology has been able to demonstrate long-range, anterior to posterior and temporal hypocoherences (Coben et al. 2008; Murias et al. 2007). It has further been observed that multivariate strategies to assess coherence metrics are more accurate and effective than their pairwise counterparts (Barry et al. 2005; Kus et al. 2004; Pollonini et al. 2010). A clinical example is presented below in Fig. 12.3. This is taken from the first author's clinical practice and represents the EEG multivariate coherence analysis on a child with autism. This system of coherence assessment was created by Hudspeth (Multivariate connectivity within a spherical brain space. Unpublished manuscript, 2009) and is contained within the NeuroRep QEEG Software system. This system uses pairwise coherence data and through a principal components, statistical analysis converts the data into three-dimensional multivariate coherence eigen images. These eigen images can be viewed as an image in three-dimensional space representing the functional proximity or coherence among the various electrodes based on the 10/20 International EEG recording system (Niedermeyer and Lopes da Silva 2004). As such, electrode positions that are closer in proximity reflect greater hypercoherence, and electrodes that are further apparent are indicative of greater hypocoherences. In this case example, it is clear that this patient manifests simultaneous overlapping neurophysiological disruptions (as is observed in all autistic children). These include (1) frontal hyperconnectivity in the alpha and beta frequency bands, (2) left anterior

temporal/posterior frontal to posterior/temporal–parietal hypocoherence in the delta band, (3) right medial temporal to occipital–parietal–posterior/temporal hypocoherence in the theta band, and (4) bilateral frontal/temporal hypocoherences in the alpha band. These data can then be used for assessment purposes and treatment planning. The use of neurofeedback with these metrics as a basis has been shown to be more effective than other types of neurofeedback for children on the autistic spectrum (Coben and Myers 2008a).

12.4.2 EEG as a Discriminant in Autism

There has been great interest in techniques that can diagnose autism and younger and younger ages. For decades, ASD has been considered a disorder diagnosed based on behavioral principles or a symptom-based diagnosis (APA 2000). More recently, specific behavioral and interview procedures have created to lend objectivity to the diagnosis. These have included the Autism Diagnostic Observation Schedule (Lord et al. 2001) and Autism Diagnostic Interview—Revised (Le Couteur et al. 2003), which have demonstrated predictive diagnostic classifications in the 83–92 % ranges depending on the age of the child. These are largely considered the "gold standard" in the diagnosis of autism or autism spectrum cases.

Recently, there have been attempts to use EEG data to discriminate between autistics and healthy controls. Catarino et al. (2011) examined the role of EEG complexity in 15 autistics and 15 controls. There were significant differences between the groups with the autistic spectrum children showing less complexity. Duffy and Als (2012) recently studied a large cohort of children in which they compared EEG data between ASD and healthy controls. Looking at multivariate, principal components analysis coherence data, they were able to discriminate the groups. They demonstrated and confirmed short-distance hypercoherence and long-distance hypocoherences in the ASD sample. Overall, their classification success rate was between 86 and 88 %. Lastly, Ahmadlou et al. (2012) used a method called fuzzy synchronization to examine connectivity differences between autistics and controls. There was a 95 % discrimination rate but their sample size was quite small. Nevertheless, these studies have begun to show that EEG coherence data may be used as a neurophysiological basis to discriminate ASD from controls and this may help in the identification of these children. The rates at which these markers can predict group membership rival the "gold standards" in the field.

In our study reviewed above, we have shown that EEG variables can be used to discriminate between children on the autistic spectrum and normal controls. The sensitivity of this measure was 95.6 %, the specificity 92.3 % and the positive predictive value 95.5 %, and negative predictive value 92.6 %. These diagnostic accuracy rates compare quite favorably to the current "gold standards." Along with Duffy and Als (2012) study above, this is the first time that a physiological measure has been demonstrated to show such accuracy for autistic disorders. Because the measures used in this study to substantiate the ASD diagnosis fall

short of the highest degree of completeness, these results are best understood as preliminary and in need of replication.

Both the ability to discriminate autistic from normal children and the delineation of EEG subtypes of autistic disorder support the utility of the EEG in this condition. Such an analysis of differences in the type and pattern of power abnormalities has been useful in quantitative EEG research in ADHD (Chabot et al. 2005) and obsessive–compulsive disorder (Prichep et al. 1993). It has also been shown that the use of EEG power and connectivity data enhances the efficacy of EEG biofeedback for autistic children (Coben and Padolsky 2007; Coben and Myers, 2008a). The current study is, by far, the largest EEG study of autistic children. There were clear power and connectivity anomalies, discriminative power that rivals the "gold standards" in the field, and electrophysiological subtyping that may prove useful for future research and treatment planning. Future work is clearly needed to replicate these findings, test the power of the discriminant function to classify independent samples of normal and ASD children, and detail the source localization of these dysfunctions and enhance the regional resolution of connectivity findings.

The results of the VARETA analyses suggest that despite different patterns of EEG frequency abnormality across ASD subtypes, a single underlying neurophysiological pathway or network can be identified that shows dysfunction in ASD. When processed using the VARETA software, all five QEEG subtypes showed similar patterns of subcortical and cortical abnormality. VARETA images of ASD children revealed functional abnormality within the thalamus, hippocampus, and caudate nucleus that spread to and included the posterior cingulate, supramarginal gyrus, lateral and medial occipital/temporal, superior parietal, and occipital cortical regions bilaterally. The subcortical and cortical regions showing abnormal neurophysiological function in ASD children identified using QEEG-based VARETA imaging agree with the findings based upon other neuroimaging techniques such as MRI, fMRI, and PET.

Neuroimaging studies of ASD suggest abnormal function between frontal/striatal systems and more posterior cortical regions. This involves the disruption of the frontal/striatal and parietal networks important in the social brain system (McAlonan et al. 2005) and disruption of communication between the frontal/striatal, cerebellum, basal ganglia, thalamus, and ventral striatum important in mental-state attribution and the superior temporal region important in perception and eye gaze (Waiter et al. 2004), and decreased gray matter in frontal/temporal and somatosensory regions involved in social cognition (Rowe et al. 2007). Further studies in ASD note disruption of the connections between the posterior cingulate region and the inferior and ventral temporal regions involved with the integration of visual and affective information (Barnea-Goraly et al. 2004), decreased activity in the superior temporal region and the cerebellum involved in the integration of sensory and limbic information and social perceptual skills (Boddaert et al. 2004), and decreased caudate nucleus volume and repetitive behavior (Hollander et al. 2005).

QEEG and VARETA can play an important role in identifying the underlying neurophysiological abnormality present in ASD. Individual patterns of findings may have implications for diagnostic purposes as well as for treatment selection and

implementation. For example, individual QEEG frequency profiles and analysis of coherence patterns can be used to guide neurofeedback to reduce the salient QEEG abnormality, a treatment recently shown to have promise in ADHD and ASD (Monastra et al. 2005; Coben and Padolsky 2007). Neuropharmacotherapy can also use various pharmacological agents guided and assayed by their ability to normalize the QEEG which, from other pharmacokinetic studies, will predict favorable clinical responses (Saletu et al. 2006). Clearly, the findings reviewed in this chapter have implications for the diagnosis, assessment, and treatment of children on the autistic spectrum. We hope that future work in all of these areas progresses at a rapid pace.

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Biography

Robert Coben, Ph.D., received his doctoral degree 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 and 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. His experience in rehabilitation neuropsychology includes directing two separate inpatient neurorehabilitation programs. He is former director of inpatient and outpatient brain rehabilitation at Staten Island University Hospital. He is an affiliate of Winthrop University Hospital and an affiliated researcher of NYU Medical Center.

Dr. Coben is a member in good standing of the American Psychological Association, International Neuropsychological Society, International Society for Neurofeedback and Research, and the American Association of Psychophysiology and Biofeedback. He is an associate editor for the Journal of Neurotherapy and Frontiers in Child Health and Human Development. He is also a editorial reviewer for the following journals: Journal of Neurotherapy, Journal of Autism and Developmental Disorders, Frontiers in Child Health and Human Development, Clinical Neurophysiology, Neuroimage, and Journal of Psychophysiology. He has edited special issues of journals on EEG Connectivity and more recently an upcoming issue on Applied Neuroscience, Neuromodulation and Neurofeedback. He has also edited a book entitled Neurofeedback and Neuromodulation Techniques and Applications. His research interests include the study of Neuropsychology and Neurophysiology in the understanding of childhood neurodevelopmental disorders, especially autism, and treatment applications for the same.

Robert J. Chabot, Ph.D., (research associate professor), has been a member of the research staff at the Brain Research Laboratories, New York University School of Medicine for the past 25 years. He has been involved in research designed to document the clinical utility of Quantitative EEG in neurological and psychiatric patient populations. Recently, he has been involved in the development of QEEG as a clinical tool for aiding in the diagnosis and treatment of children with attention deficit disorder, learning disorders, and those with autistic spectrum disorder. This research has been published in Biological Psychiatry, Journal of Child Neurology, and the Journal of Neuropsychiatry and Clinical Neurosciences with a comprehensive review paper in Adolescent Psychiatric Clinics of North America. Currently, he is involved with the development of a QEEG-based index that is sensitive to the detection of concussion and traumatic brain injury in emergency department patients.

Laurence Hirshberg, Ph.D., is a licensed clinical psychologist and serves on the faculty of the Department of Psychiatry and Human Behavior of the Brown University Medical School as clinical assistant professor. Dr. Hirshberg recently served as guest editor and contributor to a special issue of Child and Adolescent Psychiatric Clinics of North America devoted to emerging interventions in applied neuroscience, including neurofeedback and other brain-based interventions.

Dr. Hirshberg is conducting research on genetic, neurophysiological, and cognitive factors that predict drug treatment response and non response in individuals with major depression. The NeuroDevelopment Center is one of 20 neuroscience research sites in the USA, Canada, UK, South Africa, New Zealand, The Netherlands, and Australia selected to participate in this study. This study is the largest study of neurophysiological markers for depression that has ever been conducted. Dr. Hirshberg has been specializing in work with neurodevelopmental disorders for over 15 years and consults and trains educators and clinicians across New England. Dr. Hirshberg has published and presented in many areas of clinical psychology and child development.