

Review Article

QEEG and VARETA based Neurophysiological Indices of Brain Dysfunction in Attention Deficit and Autistic Spectrum Disorder

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Quantitative Electroencephalogram (QEEG) and EEG source localization were used to describe the patho-physiological nature of brain dysfunction in children with Attention Deficit Hyperactivity Disorder (ADHD) or Autism Spectrum Disorder (ASD). QEEG frequency analyses revealed 4 subtypes that differed both in severity of abnormality and relative frequency of occurrence in both disorders but do not clarify distinctive neural networks associated within each of the disorders. Multivariate discriminant analyses proved to be effective in discriminating clinical groups from normal and from each other with high levels of sensitivity and specificity. EEG source localization indicated that ADHD was characterized by functional abnormality within the thalamus, hippocampus, caudate nucleus, and anterior cingulate, frontal/striatal, temporal, and parietal regions bilaterally and ASD by functional abnormality within the thalamus, hippocampus, caudate nucleus, and posterior cingulate, supramarginal gyrus, lateral and medial occipital/temporal, superior parietal, and occipital cortical regions bilaterally.

Keywords: Autism; ADHD; QEEG; VARETA; LORETA; Neurophysiology**Background**

Attention Deficit Hyperactivity Disorder (ADHD) and Autistic Spectrum Disorder (ASD) are two neurodevelopmental disorders which at various times in the past 40 years have been described as being epidemic in their scale amongst childhood psychiatric disorders. Both disorders occur early in childhood and can have extreme effects on the lives of these children. ADHD is characterized by symptoms of inattention, impulsive behavior, and varying degrees of hyperactivity which often result in problems in learning, cognition, and social interactions. Autistic spectrum disorder is characterized by deficits in social interaction and communication often accompanied by repetitive behavior and dysfunction in executive function, language, and emotional behavior. ASD individuals can also exhibit impaired attention regulation processes such as distractibility or at other times significant problems with hyper-focusing and difficulty in shifting their attention as needed. While several recent studies have documented the neuro-physiological and neuro-anatomical nature of these disorders [1,2], there are no published studies that examine the similarities and differences between the brain structures and neurological functions compromised within each if these disorders and a set of heuristics that can help provide the discriminability of these disorders

Quantitative EEG (QEEG) is a valuable technique used in the diagnosis and treatment of children and adults with psychiatric and neurological disorders [3,4]. The clinical utility of QEEG in child and adolescent psychiatric disorders including autism, specific developmental disorders, and attention deficit disorder has been documented [5]. QEEG is useful for aiding in the differential

diagnosis of children with learning disorders and those with various subtypes of attention deficit disorder [1].

Variable Resolution Electromagnetic Tomography (VARETA) is a 3 dimensional source localization method that uses surface recorded EEG to analyze current density and to identify the most probable neuro-anatomical generators of each EEG frequency band. The results of these analyses can be used to generate maps based upon a probabilistic brain atlas resembling slices obtained from a Magnetic Resonance Image (MRI) [6]. When z-score transformed relative to a normal population these VARETA brain images can be used to depict the cortical and sub-cortical structures involved in the pathophysiology of various neuro-cognitive disorders. The VARETA technique has been shown to be useful in the identification of the neuro-anatomical structures involved in; (1) epileptic activity generation [7,8], (2) hypoperfused regions due to neurocysticercosis, reversible ischemic attacks, and cerebral artery disease [6,9,10], (3) space occupying lesions [11,12], (4) the localization of cognitive processes [13], obsessive-compulsive disorder [14], and attention deficit disorder [15].

The present study was designed to document QEEG differences between large samples of children diagnosed with ASD, ADHD, 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 these populations and to develop QEEG feature based discriminant functions (possible biomarkers) to distinguish children with ASD and those with ADHD from the normal population of children as well as from each other. VARETA was utilized to identify the neuro-anatomical structures that underlie the pathophysiology of the childhood syndromes of ASD and ADHD

Table 1: Table showing findings for matching samples on age, sex and IQ.

Normal Kids	ASD			ADHD			F value	P value
	Mean	(SD)	Range	Mean	(SD)	Range		
Age: 9.98 (2.98) 6-17	10.01	3.3	6-17	10.03	3.1	6-17	0.1	<.99
VIQ: WNL	97.0	9.4	73-118	90.9	18.0	44-136	3.5	<.06
PIQ: WNL	97.8	9.5	74-126	92.7	17.0	46-136	16.2	<.0001
IQ: WNL	99.2	9.7	85-127	89.8	15.6	53-130	14.4	<.0002
Sex	92 males; 13 females			92 males; 13 females			92 males; 13 females	

and to identify any neurophysiological subtypes that exist within each disorder. We also identify the cortical and subcortical regions that generate abnormal activity within each disorder and then localize the anatomical differences between the two disorders. Collaborative evidence supporting our findings will be provided by reviewing the findings from brain structural imaging studies (MRI, fMRI, PET) of these two disorders.

Method

Normal population

A sample of 92 normal children from the NYU database of normal children was selected to match the age and sex distributions of our sample of ASD and ADHD children. 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 two years, and had not taken any prescription medication for at least 90 days prior to evaluation. Specific details of the procedures used to establish the normal data base have been previously published [16]. The reliability of this normal data base has been validated using independent samples of normal individuals [17-22]. This replication of the age-regression equations developed on the above data base justifies their generalized application [23].

Clinical populations

All Autistic Spectrum Disordered (ASD) children used in this study were referred to the Neurodevelopment Center in Providence Rhode Island or the Neurorehabilitation and Neuropsychological Center in Massapequa, New York. All ADHD children were referred to the Developmental Pediatrics and Learning Disorders Clinic in Sydney, Australia. Samples of 92 children were entered into this study from each of these clinical groups. All children were examined by a neuropsychologist and had a neuropsychological and QEEG evaluation. Children with histories of epilepsy, drug abuse, head injury, or psychotic disorders were excluded. The clinical and neuropsychological evaluations obtained on each child were those tests routinely administered at each outpatient clinic. None of children used in this sample, were on any medications.

The demographic information from these samples is shown in Table 1 indicating no significant differences between groups in terms of age or sex. None of the children used in this sample were on medication at the time of QEEG testing. An additional 14 ASD children had QEEG evaluations while on medication and these children were used to test for general medication effects on the QEEG.

Quantitative EEG (QEEG) methodology

The neurometric method of QEEG data collection and analysis

was utilized. The EEG power at each frequency, recorded from 19 electrodes located on the scalp in compliance with internationally standardized procedures, is subjected to visual editing to remove artifactual contamination by non-cerebral sources such as movements and then subjected to computer analysis to extract a wide variety of descriptive measures. The measures are grouped by broad frequency bands, into which the EEG is conventionally divided: delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), and beta (12.5-25 Hz). For each broad band frequency band, univariate measures were derived for: 1) absolute power; 2) relative power; 3) interhemispheric and intrahemispheric power asymmetry; and 4) interhemispheric and intrahemispheric coherence. Additionally, measures for various multivariate regional absolute power, relative power, power asymmetry, and coherence measures across the frequency spectrum; and multivariate measures collapsed across all frequency ranges were derived. The interested reader is referred to several published papers for a detailed description of this technique and the development of the normal EEG database [22,24,25].

All ADHD and ASD children were seated comfortably in a sound and light attenuated room during the evaluation. Electrode caps were used to place recording electrodes over the 19 standard regions defined by the International 10/20 system referenced to linked ears. All electrode impedance levels were kept below 5000 ohms. Twenty to thirty minutes of continuous eyes closed resting EEG was recorded using a Spectrum 32 (ADHD) or Deymed (ASD) EEG system. An experienced EEG technician observed the continuous EEG being recorded and selected from 1 to 2 minutes of artifact-free EEG for further analysis. All EEG was digitized and placed onto CDs for entry into a computer for subsequent quantification. Prior to EEG quantification, all EEG was examined by one of the authors who removed artifact contaminated epochs missed by the first technician. Particular care was taken to prevent EEG contamination due to drowsiness, and to exclude EEG segments contaminated by horizontal and lateral eye-movement, muscle activity, ECG artifact, or by EEG transients due to sharp waves or paroxysmal activity. EEG quantification was restricted to those children from whom a minimum of one minute of artifact-free EEG (24 epochs) could be obtained. Prior research has shown that this is the minimum amount of EEG required to obtain reliable quantitative EEG measures [26]. The artifact free EEG segments were read into the Nxlink software for quantification. This software converts the Deymed and Spectrum 32 EEG segments to meet the amplifier and frequency characteristics under which the normal database was collected and to equivocate digitized information collected from the different amplifier systems. The artifact-free EEG from each channel was then converted from the time to the frequency domain via Fast Fourier Transform (FFT). Each

Table 2: Table showing a summary of the qEEG cluster types, their representation in the clinical groups, and the relative trends in Z-scores in these clusters for each clinical group.

Cluster Subtypes of significant ($p < .10$) QEEG variable deviations*				
Clinical Group	Cluster 1	Cluster 2	Cluster 3	Cluster 4
ADHD	↓ Generalized Delta ↑ Generalized Theta ↑ Central & Temporal Beta	↓ Generalized Delta ↑ Generalized Theta (esp Frontal) ↑ Generalized Alpha (esp Central) ↓ Posterior relative pwr Beta	↓ Generalized Delta ↑ Frontal Theta ↑ Generalized Alpha ↓ Posterior Beta	↓ Frontal and Central Delta ↑ Frontal Theta ↑ Frontal and Central Beta
Representative %	17.5%	25.5%	24.1%	13.9%
ASD	↓ Generalized Delta ↑ Generalized Theta ↓ Posterior Alpha ↑ Frontal Beta	↓ Generalized Delta ↑ Generalized Theta ↑ Generalized Alpha (esp Frontal and Central) ↓ Posterior Beta	↓ Generalized Delta ↓ Central and Posterior Theta ↑ Generalized Alpha	↓ General Delta ↑ Frontal and Central Alpha ↑ Generalized Beta
Representative %	15.3%	17.5%	23.4%	24.1%

*All measures were of absolute power unless otherwise specified

Note that a common subtype characteristic across all clusters for both clinical populations is the presence of Delta deficits.

QEEG measure was compared to the mean and standard deviation of that measure obtained from the age-regressed normal database using a Z or standard score.

The VARETA technique

In the last few years a new method for localizing electrical activity in the brain, called Variable Resolution Electromagnetic Tomography (VARETA), has been developed. This imaging technique allows an estimation of the distribution of the electrical generators for each frequency band within the brain, by applying a mathematical inverse solution to the EEG data. The anatomical definitions of regional probability for source localization used in VARETA are derived from a Probabilistic Brain Atlas (PBA) developed at the Montreal Neurological Institute [27]. Use of the PBA obviates the need for individual MRI scans, in exchange for sacrificing precise anatomical localization. Three-dimensional coordinates for the position of each scalp electrode position, defined by the proportional 10/20 International Electrode Placement System, have been published [28]. These coordinates were used to project each electrode position onto the average surface of the mean dimensions of an age appropriate head, thus placing the proportional EEG electrode set into spatial registration with the proportional PBA. Based on this EEG-MRI head model, the problem of the 3-D sources of EEG may be specified in the frequency domain [6,29,30]. Resting, eyes closed EEGs from the normal population, constituted a normative database for VARETA using narrow band spectral analysis between 0.39 Hz to 19 Hz in increments of 0.39 Hz [31]. Using the resulting set of normal values for narrow band spectral power at each scalp electrode [29,32], the sources of power at each frequency were localized. Three-dimensional color-coded tomographic images were then generated, with source generator distributions superimposed upon the transaxial, coronal, and sagittal slices color-coded as z-score deviations from the normal population. The VARETA method is a useful adjunct to QEEG analysis. It provides additional information about the localization of the abnormal sources of surface electrical activity. Nevertheless, VARETA, like other inverse methods, presents some limitations: it represents an approximate solution for the most probable neuroanatomical generators. However studies have demonstrated the spatial resolution of such imaging techniques is with 5 mm consistent with MRI imaging for specific locations.

Results

QEEG discriminant analysis findings

A series of step-wise discriminant analyses were calculated comparing the normal children with ASD children, the normal children with the children with ADHD, and the ASD and ADHD children with each other. QEEG variables entered were selected using analysis of variance comparisons between the two groups with those variables with the highest F-ratios and lowest inter-correlations chosen. A total of 5 variables were used to discriminate the normal from the ADHD children with a sensitivity of 93.3%. A specificity of 88.6% with Positive Predictive Validity (PPV) of 89.1% and Negative Predictive Validity (NPV) of 93.0%. Variables utilized included delta and theta relative power and frontal coherence measures. A total of 5 variables were utilized to discriminate the normal from the ASD children with 92.3% sensitivity and 95.6% specificity. The positive predictive value was 95.5% and the negative predictive value was 92.6%. QEEG variables utilized included delta mean frequency, theta coherence, delta relative power, frontal/temporal alpha asymmetry, and frontal/temporal theta relative power. A total of 4 variables were used to discriminate the ASD from the ADHD children with 82.9% sensitivity, 79.0% specificity and PPV of 82.0% and NPV of 79.0%. Variables utilized included measures of delta absolute power, frontal theta coherence, and alpha temporal asymmetry and frontal/posterior theta asymmetry.

QEEG subtypes

In processing the ADHD and ASD data, we examined the narrow band spectral analyses from .39 to 19 Hz for each child across all 19 electrode placements and identified the frequency at which the maximum deviation from normal occurred. We then used these narrow band spectral results to place the ASD and ADHD children separately into 4 sub-types or phenotypes to include those with maximal narrow band spectral deviations from normal that fell between; (1) 3.9-6.63 Hz, (2) 7.02-8.58 Hz, (3) 8.97-10.53 Hz, and (4) 10.92-14.04 Hz. Results from these analyses are listed in Table 2.

For ADHD, these subtypes included 17.5%, 25.5%, 24.1%, and 13.9% of these children respectively. For ASD, these subtypes included 15.3%, 17.5%, 23.4%, and 24.1% of these children respectively. While the distributions of these EEG frequency based subtypes were similar for both developmental disorders, more ADHD children showed abnormality between 7 and 9 Hz (high theta and low alpha) and more ASD children had abnormal findings between 11 to 14 Hz activities (beta). In addition, 19.0% of the ADHD and 19.7% of the ASD children

QEEG Relative Power Subtypes

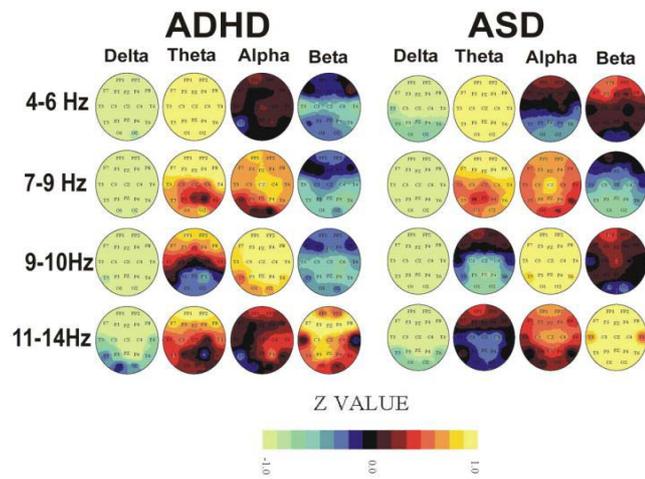


Figure 1: Figure showing univariate Z-score brain maps for a variety of broad bands of the qEEG.

had narrow band spectral analysis which failed to show a clear cut maximum peak deviation from normal and these children were not included within the present analyses. Group average VARETA images were then constructed for each of the 4 above defined subtypes separately for the ADHD and ASD children. Analysis of variance 'F' ratios were calculated comparing the VARETA images of the ADHD and ASD children at each of the 4 narrow band frequency groupings.

QEEG subtype differences

In order to document the QEEG differences between each of the ADHD and ASD subtypes defined in this study on the basis of the narrow spectral band findings described above, we calculated group average head maps of z-score relative power across the traditional delta, theta, alpha, and beta frequency bands. This makes the present work more amenable for comparison with other published studies which utilize these frequency bands. Figure 1 presents these head maps separately for the ADHD and ASD children with each grouping representing a neurophysiological subtype of each disorder based upon frequency distribution differences. Table 2 summarizes these general subtypes for power measures exceeding $p < .10$ in tabular form.

It was found that the EEGs of an independent sample of 14 medicated ASD children were distributed across all subtypes. ANOVAs computed comparing relative power findings between the medicated and non-medicated children indicated that medication resulted in less of a delta relative power deficit ($p < .01$), especially in frontal and central regions, and an increase in frontal alpha ($p < .01$) and beta ($p < .03$) relative power.

VARETA subtypes

Figures 2,3,4, and 5 present the group average VARETA images in the axial plane for each narrow frequency band grouped separately for the ADHD and ASD children as well as the analysis of variance F-values for the significance of the difference between the ADHD and ASD groups. All VARETA images use threshold scaling such that colors shown represent statistically significant deviations from the

QEEG VARETA Group Averages (4-6Hz)

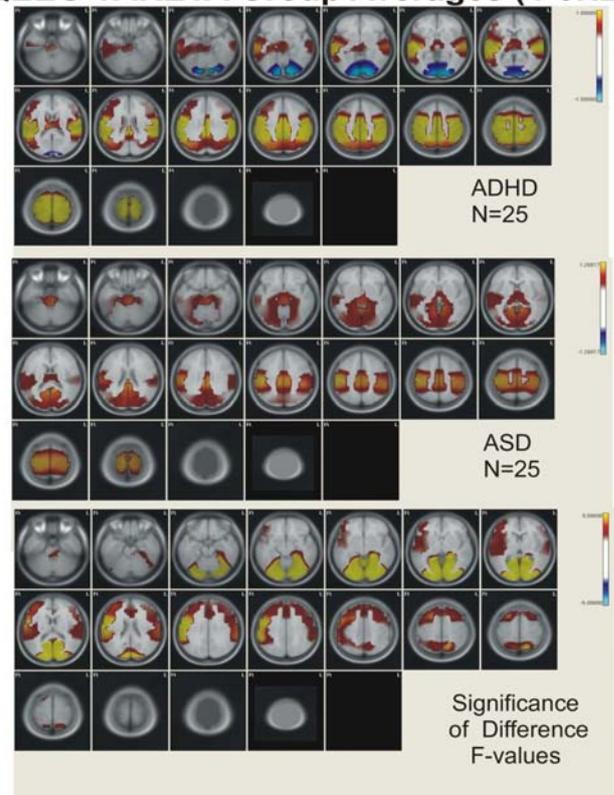


Figure 2: Figure showing VARETA structures and corresponding Z-scores in current density for the broad band 4-6 Hz activity.

normal population (upper two panels of each figure) or significant ANOVA differences between the ADHD and ASD children (bottom panel each figure). Note that the anatomical location of abnormal neurophysiological activity is very consistent across the ADHD and ASD subtypes with greater differences seen when comparing each ADHD and ASD subtype against each other. Consistent differences were seen between the ADHD and ASD subtypes 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 ADHD and ASD subtypes (as demonstrated in Figure 1; Table 2), the neuroanatomical structures identified by VARETA as showing abnormal activity are consistent within both the ADHD and ASD populations which differ significantly from one another.

Table 3 presents a comparison of the anatomical regions showing abnormal neurophysiological activity for the ADHD and ASD children. In general, ADHD is characterized by abnormal increased neurophysiological activity in the thalamus, caudate nucleus, cingulate, and in frontal, temporal, precentral, postcentral, parietal, and occipital cortical regions with decreased activity in the cerebellum. ASD children were characterized by increased activity in the cerebellum, thalamus, hippocampus, in parahippocampal, cuneus, cingulate, and lingual gyri, and in temporal, precentral, postcentral, parietal, and occipital cortical regions. In ADHD, abnormal activity was greater in inferior and superior frontal regions, in precentral and postcentral cortical regions, and in anterior cingulate cortex

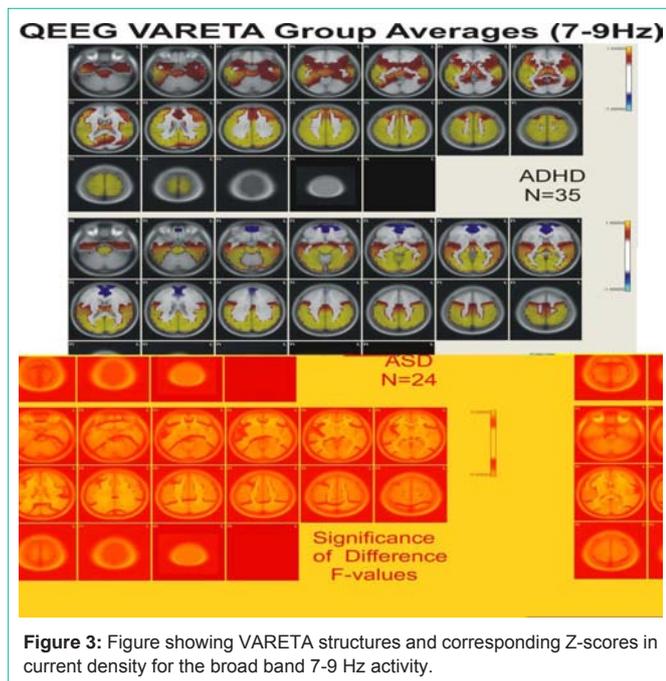


Figure 3: Figure showing VARETA structures and corresponding Z-scores in current density for the broad band 7-9 Hz activity.

and frontal/striatal regions than in ASD. In ASD, abnormal activity was greater than in ADHD in cerebellum, parahippocampus, lingual and parahippocampal gyri, and in occipital/temporal and posterior cingulate cortical regions.

Discussion

The majority of children with attention deficit disorder and those with ASD show QEEG abnormality indicative of functional impairment at sub-cortical and cortical regions. When very narrow band z-scored spectral components are examined within these two populations of children, 4 major subtypes or phenotypes of QEEG abnormality are identified and these were illustrated using the traditional broad band spectral components of z-relative power in Figure 1 and Table 2. When examining these findings, the commonalities of the QEEG features found in both the ADHD and ASD subgroups include generalized decreased delta activity and increased generalized theta activity. While some children from both the ADHD and ASD population fall into each of the four subtypes; theta excess, theta and alpha excess, alpha excess, and beta excess, the percentages of children within each subtype and the overall nature of each subtype varies across diagnostic category. A greater percentage of the ADHD children fell within the theta and alpha excess subtype (25.5% vs. 17.5%) while more ASD children showed a beta excess (24.1% vs. 13.8%). The ADHD children within all subtypes showed increased frontal theta not seen in the ASD children, and the degree of delta deficit present within each subtype was greater for the ASD population which also showed a greater degree of beta excess across subtypes than did the ADHD children. This beta excess is partially due to medication effects although the finding of a greater beta excess in ASD holds true when the medicated children were removed from all analyses. The beta excess present is noteworthy and was present with or without the presence of medication. The increased frontal abnormality in ADHD may reflect frontal/striatal dysfunction and the disruption of executive function often associated with problems of attention [33]. The deficit of delta common in ASD may reflect the

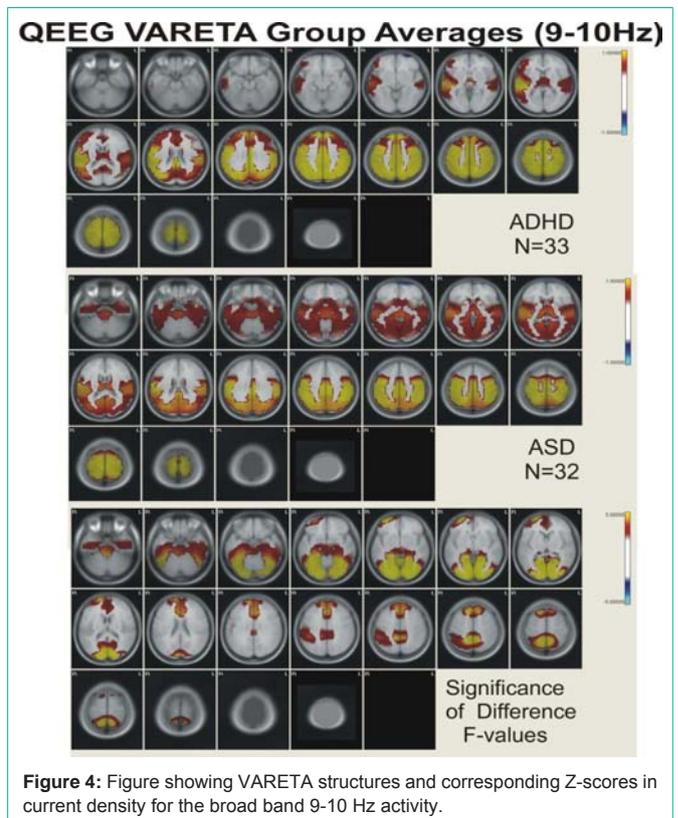


Figure 4: Figure showing VARETA structures and corresponding Z-scores in current density for the broad band 9-10 Hz activity.

cortical and subcortical connectivity issues often described in ASD [34]. The delta EEG rhythm has been hypothesized to play a role as an integrative mechanism across brain regions with two thalamo/cortical networks active. The first network involves the thalamus and its' connections to specific cortical regions and the second, involving delta, as a global integrative network [35]. In fact, Alper [36] suggests that delta power is modulated by dopamine and acts by facilitating the transition between local and global brain states.

Clarke [37] used cluster analysis of QEEG to document the existence of three ADHD subtypes in a sample of 184 ADHD boys and 40 age and gender-matched controls. Subtype 1 showed increased total power, increased relative theta and decreased relative delta and beta waves, and type 2 showed increased relative theta and decreased relative alpha and increased central/posterior relative delta. The third subtype showed increased relative beta and decreased relative alpha activity. These findings are similar to those reported in the present paper for our ADHD population. These findings are also in agreement with previous studies of eyes-closed resting QEEG in 407 children with ADHD or ADD. In these studies, QEEG frequency abnormality occurred in over 80% of these children with theta and alpha excess the most prevalent abnormal finding. Frontal and central regions were most likely to be involved, and if generalized, the magnitude of the frequency abnormality was greatest in these regions [38-40].

Studies of EEG frequency abnormality in children with ASD have provided less consistent results over those seen in ADHD. For example, two studies showed decreased delta frontally [2,41], while one found increased activity in the delta range [42]. Two studies reported increased generalized delta or described "slowing" [43,44]. Three studies showed theta increases [2,42,45], while one

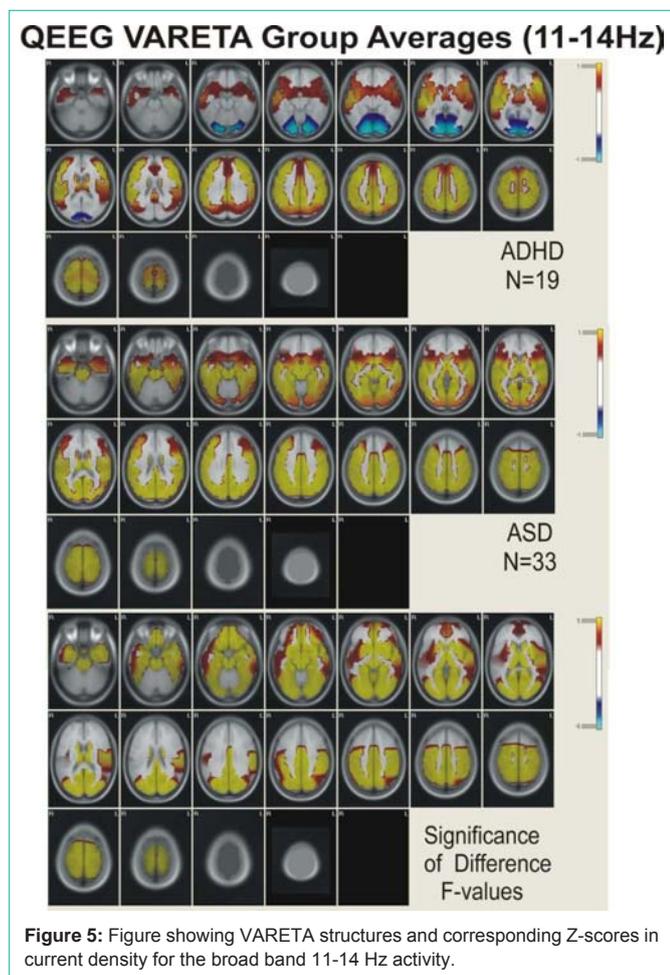


Figure 5: Figure showing VARETA structures and corresponding Z-scores in current density for the broad band 11-14 Hz activity.

study reported reduced theta [41]. These inconsistencies do not appear to be accounted for by considering whether the study was done with the subjects in a resting state or under task conditions. By contrast, findings have been quite consistent with spectral power analyses of faster frequencies, alpha through gamma. All studies that completed spectral power analyses reported reduced alpha power [41,43] and increased beta [2,42,46,47] and gamma power [48]. These inconsistent results are possibly due to effects of early use of psychotropic medications on brain-behavior development [5] even when the subjects at the time of study were off medication and/or due to the limited sample sizes utilized and may also reflect the heterogeneity found in this population of children. In the present study with substantially larger samples of ASD children this heterogeneity is substantiated by the existence of at least 4 subtypes of QEEG frequency abnormality which encompass most of the findings described above.

The results of the VARETA analyses suggests that despite different patterns of EEG frequency abnormality across ADHD and ASD children, abnormalities occur in specific regions of interest between ADHD and ASD children which are noteworthy. More specifically, abnormalities are noted in the Thalamus, Caudate, Hippocampus, Post-Central Gyrus, Angular Gyrus, Cuneus, and Lingual Gyrus. The co-occurring abnormalities in these common structures likely accounts for many of the commonalities found in

these two clinical populations. There appears to be a single underlying neurophysiological pathway or network that can be identified within each disorder. When processed using the VARETA software all four QEEG subtypes within a diagnostic category showed similar patterns of sub-cortical and cortical abnormality with consistent differences between the ADHD and ASD children present for each subtype. VARETA images of ADHD children revealed functional abnormality within the thalamus, hippocampus, and caudate nucleus that spread to and included the anterior cingulate, frontal/striatal, temporal, and parietal regions bilaterally. 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 sub-cortical and cortical regions showing abnormal neurophysiological function in ADHD and ASD children identified using QEEG based VARETA imaging agrees with the findings based upon other neuroimaging techniques such as MRI, fMRI, and PET.

Neuroimaging studies of ADHD indicate decreased regulation of the cerebellum and the frontal/striatal system [49] and decreased activation of frontal regions and connections between bilateral prefrontal regions and the temporal and parietal cortices, regions important for cognitive flexibility and executive function [33,50,51]. Disruptions in function of the frontal\striatal system and its connections with the caudate nucleus have also been reported [52]. Decreased activation of bilateral parietal regions, the precuneus region and the thalamus may indicate disturbances in salient feature detection and the ability to shift attention deficits often characteristic of ADHD [53]. Significant disturbances in the connections between the anterior cingulate cortex, the precuneus region and prefrontal cortex and with the posterior cingulate cortex have been reported

Table 3: Brain Structures Showing Abnormal Function using VARETA in Children with Attention Deficit Disorder and Autistic Spectrum Disorder.

Sub Cortical & Cortical Structures showing VARETA Abnormality	Attention Deficit Disorder	Autistic Spectrum Disorder	Significant Differences
Cerebellum	X	X	ADHD less
Thalamus	X	X	None
Caudate	X	X	None
Hippocampus	X	X	None
Inf. Mid. Sup. Temporal	ALL	Mid & Sup	ASD less
Inf. Mid. Sup. Frontal	ALL	Mid	ASD less
Precentral Gyrus	X		ASD less
Postcentral Gyrus	X	X	None
Inf. Mid. Sup. Occipital	X	Superior	ADHD less
Lat Mid Occipital/ Temporal		X	ADHD less
Sup. Parietal	X	X	ADHD less
Angular Gyrus	X	X	None
Supramarginal Gyrus		X	ADHD less
Cuneus	X	X	None
Lingual Gyrus	X	N	None
Cingulate	Anterior & Posterior	Posterior	None

in ADHD [54]. In fact, anterior cingulate cortex function has been shown to play a role in the executive control of attention another area of attention processing in which those with ADHD often have problems [55].

In contrast, 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 [56], 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 [57], and decreased grey matter in frontal/temporal and somatosensory regions involved in social cognition [58]. 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 [59], decreased activity in the superior temporal region and the cerebellum involved in the integration of sensory and limbic information and social perceptual skills [60], and decreased caudate nucleus volume and repetitive behavior [61].

The sub-cortical and cortical regions showing abnormal neurophysiological function in ADHD and ASD children identified using QEEG based VARETA imaging is supported by the findings described above which were based upon other neuroimaging techniques such as MRI, fMRI, and PET. Clearly, both QEEG and VARETA can play an important role in identifying the underlying physiological abnormality present in both ADHD and 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 can be used to guide Neurofeedback to reduce the salient QEEG/VARETA abnormalities. Such training protocols have recently shown to have promise in ADHD and ASD [62,63]. With the identification of more specific network involvement in each of these populations, neurofeedback targeting structures using VARETA or LORETA (Low Resolution Electromagnetic Tomographic Analyses) may have promise for more potent means of achieving clinical improvement [64]. 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 [65].

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Chapter 6

Neurofeedback for Autistic Disorders: Emerging Empirical Evidence

Robert Coben

6.1 Introduction

Autistic spectrum disorders 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's disorder. Children with ASD demonstrate impairment in social interaction, verbal and nonverbal communication, and behaviors or interests (American Psychiatric Association 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 obsessiveness, 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 (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) (American Psychiatric Association 2000).

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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 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 (Siegel 1996; Attwood 1998; Hamilton 2000; Sicile-Kira 2004; McCandless 2005).

Research reviewing the epidemiology of autism (Centers for Disease Control and Prevention 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 (Centers 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. With increased prevalence comes a need to design and empirically validate effective treatments for those impacted by autistic disorders.

Research studies utilizing electroencephalogram (EEG) and single photon emission computed tomography (SPECT) have provided evidence for a neuropathological basis of ASD. A review of numerous EEG 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. In SPECT 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, while altered perfusion in the right medial temporal lobe was associated with the obsessive desire for sameness (Ohnishi et al. 2000). Children with autism commonly display executive functioning deficits in planning, cognitive flexibility, and inhibition. These executive deficits are associated with dysfunctional integration of the frontal lobes with other brain regions and thus also impact upon social, behavioral, and cognitive function (Hill 2004).

Functional neuroimaging studies have also 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 and Wernicke's areas relative to a

control group, suggesting a lower degree of information organization and neural synchronization 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. 2005).

Parents of children with ASD select many different methods of treatment, with an average of seven different therapies being utilized (Green, Pituch, Itchon, Choi, O'Reilly, and Sigafos, 2006). Speech therapy (70 % of parents) was the most commonly selected treatment, followed by psychopharmacological treatment (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. While there may be some benefit to these treatments, many do not lead to long-lasting changes and/or have risks associated with their implementation. The potential benefits and risks of the major treatments for ASD are summarized below.

6.2 Treatments Often Used for ASDs

Other than neurofeedback, the most common treatments used for these children include applied behavior analysis (ABA), pharmacotherapy, special diets, vitamin supplements and enzymes, chelation, and hyperbaric oxygen therapy. Applied behavior analysis (ABA), a form of behavior modification, is the method of treatment with the most empirical support for treating ASD. 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). Efficacy has been demonstrated across multiple studies with variations on the technique (Schopler and Reichler 1971; Lovaas et al. 1973; Ozonoff and Cathcart 1998; Herbert et al. 2002; Ben-Itzhak and Zachor 2007) with follow-up studies showing ongoing improvements as a result (McEachin et al. 1993). Unfortunately, not all ABA studies have had such positive outcomes (Anderson, Avery, DiPietro, Edwards, and Christian, 1987).

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).

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. Furthermore, a strong commitment by parents to complete therapeutic programs is necessary to achieve positive outcomes. While behavioral treatment methods show the most empirical support to date, there remains a need for additional therapies, which may be more easily administered and used in conjunction with the behavioral methods described. It is important to note that though research has been promising, there has been great variability between studies in their results and 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), meaning that lower functioning individuals are often left out, even though they are perhaps in greatest need of treatment.

Pharmacological 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, Scahill, Klin, and Volkmar 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.

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 (Research Units on Pediatric Psychopharmacology Autism Network 2005). A newer class of neuroleptic, referred to as atypical antipsychotics, reportedly 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 and Abilify are the only drugs approved by the FDA to treat the symptoms (irritability) of autism. A recent meta-analysis of three randomized controlled trials found that the drug was effective in treating the symptoms of irritability and aggression (Jesner et al. 2007). 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. The long-term effects of risperidone are estimated at 1 year (Zuddas et al. 2000) with a relapse rate of 12.5–25 % (Research Units on Pediatric Psychopharmacology Autism Network 2005; Troost et al. 2005). 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.

The use of SSRI agents for the treatment of repetitive, stereotypical, and perseverative behaviors has also been explored (McDougle et al. 1995; Geller et al. 2001). Findings from such studies have been mixed at best (Cook et al. 1992; Hollander et al. 2005). While some studies report “success,” responders often include from 49 to 69 % of the samples (McDougle et al. 1996, 1998; DeLong et al. 2002; Owley et al. 2005). In other studies, the positive response rate is significantly lower than this (McDougle et al. 2000; Couturier and Nicolson 2002; Martin et al. 2003). Based on the research cited, it appears that 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 be only treating certain symptoms and 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. In summary, the research published thus far suggests that some medications may be helpful in managing some of the behavioral disturbances seen in autism.

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). Use of a gluten–casein-free diet has been shown to lead to positive outcomes in some children with autism (Knivsberg et al. 2002; Cade et al., 1999; Reichelt and Knivsberg, 2003). However, 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 and 16 were studied over the course of 12 weeks. The researchers reported no significant differences between groups on their primary measure, the Childhood Autism Rating Scale, while parents reported improvement in their children. The researchers noted that the children were quite heterogeneous (which may have masked any group differences) and noted the relatively small sample size. One of the major problems with the GFCF diet is that it may lead to reduced bone cortical thickness (Hediger et al. 2008). Indeed, in this study, boys between the ages of four and eight who were autistic showed an 18.9 % deviation in metacarpal bone cortical thickness, which was nearly twice that of boys on minimally restricted or nonrestricted 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 (Mariani et al. 1998).

Vitamin supplements and enzymes have been proposed as another treatment for autistic-related symptoms. One supplement that has generated a great deal of interest as a treatment for autism is the gastrointestinal hormone secretin. After receiving much heated attention in the media, 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 12 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 (Wainwright 2002), and some studies have found fatty acid deficiencies in children who are autistic (Bell et al. 2000; Vancassel et al. 2001; Bell et al. 2004). Amminger and colleagues (2007) recently completed a double-blind, randomized controlled trial 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. Potential limitations to this study include that it was conducted with only 12 subjects, and preselection 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 only published study found by the authors 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 months 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, Reichler, DeVellis, and Daly, 1980). Even after the children were divided into subgroups based on age and intelligence, these effects did not diminish. This was not a controlled study, however. 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.

A controversial theory to explain the increase in incidence of ASDs over the past 30 years is that it is 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). In autism, heavy metal toxicity seems to occur from a decreased ability to excrete heavy metals (Adams et al. 2009). Because of this, some health-care providers are performing chelation therapy, which utilizes dimercaptosuccinic acid (DMSA) to clear the body of mercury and other toxic metals.

Results of a study by Holmes (2001) 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). Recently, Adams et al. (2009) reported the results of a 2-phase study intended to determine the efficacy of DMSA/ glutathione in treating children with autism. Overall, there were rated improvements in 3 of every 4 children with 11 % showing a worsening of symptoms. Chelation therapy is considered by some to be a risky treatment, and there have even been reports of death following chelation therapy in autism (Sinha et al. 2006).

Direct treatment of brain anomalies in autism has also been pursued with the use of 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 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). It has been suggested that the increased oxygen delivered by HBOT could counteract the hypoxia caused by hypoperfusion and lead to a reduction in symptoms of autism. Preliminary support for this treatment was reported by Rossignol and Rossignol (2006). While a study by Rossignol et al. (2007) showed empirical support for the possible benefits of HBOT for autistic children, another study (where parents were blinded to the treatment) by Granpeesheh et al. (2010) showed no significant benefits.

In summary, this review of the autism treatment literature reveals there are no 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 disorders. Neurofeedback represents an alternative that may have the potential to decrease symptomatology on a long-term basis with little risk of harm.

6.3 Neurofeedback for ASD

Neurofeedback is designed to use sophisticated computer technology to train individuals to improve poorly regulated brain-wave patterns. In EEG biofeedback, information regarding brain-wave 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 (which measure brain waves) are placed on the scalp and earlobe(s). Individuals instantly receive feedback about the amplitude and/or synchronization of their brain waves and learn to improve their brain-wave

Table 6.1 EEG frequency bands [adapted from Demos (2005) and Thompson and Thompson (2003a, b)]

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	>30 Hz	May be associated with problem solving and memory consolidation	Unknown

functioning. The only way to succeed at the games involved is for children to control and improve their brain-wave patterns (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 or more (e.g., Lubar 1995).

Individuals who participate in EEG biofeedback learn to inhibit brain-wave frequencies that may produce negative symptoms and enhance specific frequencies that produce positive results. Table 6.1 displays the typical EEG brain-wave frequency bands and lists their normal occurrences and respective significance [information adapted from resources contained in Demos (2005) and Thompson and Thompson (2003a, b)]. Within these general frequency bands, there may also be more detailed breakdowns of EEG activity. For example, mu-rhythm abnormalities are associated with excesses in the alpha-frequency band 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 brain waves to meet task demands utilizing neurofeedback. Through the process of operant conditioning, this treatment modality can result in improvement of brain-wave patterns as well as behavior. These changes in EEG patterns have been shown to be associated with regulation of cerebral blood flow, metabolism, and neurotransmitter function (Lubar 1997).

Neurofeedback is a noninvasive treatment with no known significant or lasting negative side effects that has been shown to enhance neuroregulation and metabolic function in ASD (Coben and Padolsky 2007). Positive neurofeedback treatment outcomes are often achieved over the course of several months, in contrast to behavior therapy, which often takes a year or more of intensive training. Furthermore, 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 as in drug therapy and diet therapy (Tansey 1993; Linden et al. 1996; Monastra et al. 2005; Lubar, Swartwood, Swartwood, and O'Donnell, 1995).

Over 30 years of research on using neurofeedback to treat ADHD has consistently shown that it leads to improvements in attention, impulsivity, hyperactivity, and IQ (see Monastra et al. 2005, for a review and analysis). This success was the foundation for the emergence of using neurofeedback with ASD.

6.3.1 QEEG Evaluation and Autistic Spectrum Disorder

Quantitative electroencephalographic (QEEG) evaluation or “brain mapping” is an assessment procedure designed to pinpoint anomalies in brain function (Hammond 2005). QEEG analyses measure abnormalities, instabilities, or lack of proper communications pathways (connectivity) necessary for optimal brain functioning. QEEG maps, collected using 19 electrodes based on the international 10–20 system (Jasper 1958), reflect 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 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).

Coben et al. (2013) identified five relative power subtypes in individuals with autism. However, they noted that 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 normative group. Coben and Myers (2008) used QEEG multivariate connectivity data to develop a typology of autism connectivity patterns including (1) patterns of hyperconnectivity across bilateral frontotemporal regions and between left hemisphere locations and (2) hypoconnectivity involving orbitofrontal, frontal to posterior, right posterior, or left hemisphere sites. A pattern of hypoconnectivity that underlies a mu-rhythm complex was identified as well.

6.3.2 Neurofeedback: Case Studies, Case Series, and Group Pilot Studies

There have been numerous case and group pilot studies conducted with clients diagnosed with autistic spectrum disorders. In general, these studies have shown

that neurofeedback improved symptomatology and these improvements were maintained at follow-up. For a more thorough review of these, please see Coben et al. (2010b).

6.3.3 *Controlled-Group Studies of Neurofeedback for ASD*

There have been two approaches to the research done related to neurofeedback and ASD. Kouijzer and her colleagues have researched the effects of power training and Coben and his colleagues the effects of coherence training. The first study of Kouijzer and colleagues (2009b) investigated the effects of neurofeedback in children with autism. It included 14 children from 8 to 12 years old with a pervasive developmental disorder—not otherwise specified (PDD-NOS)—diagnosis. Excluded were children with an IQ score below 70, children using medication, and children with a history of severe brain injury or comorbidity such as ADHD or epilepsy. Participants were divided into treatment and wait-list control group according to the order of applying. During baseline (Time1), all participants were evaluated using QEEG and a range of executive function tasks, and parents completed behavior questionnaires (CCC and Auti-R). After neurofeedback training (Time2), or a comparable time interval for the wait-list control group, QEEGs and data on executive functions and social behavior were re-collected. One year after ending treatment (Time3), follow-up data including QEEGs, executive function tasks, and behavior questionnaires were collected in the treatment group. Participants in the treatment group had neurofeedback training twice a week, until 40 sessions were completed. In each session, participants were rewarded when inhibiting theta power (4–8 Hz) and increasing low beta power (12–15 Hz) at scalp location C4 according to a protocol including seven 3 min intervals of neurofeedback training separated by 1 min rest intervals. After 40 sessions of neurofeedback, 70 % of the participants in the treatment group had effectively decreased theta power and increased low beta power. Repeated measures MANOVA on the executive functions data collected at Time1 and Time2 revealed a significant interaction between treatment and control group, indicating improvement of participants in the treatment group on tasks measuring attention skills, cognitive flexibility, set shifting, concept generation/inhibition, and planning. Using repeated measures MANOVA to compare questionnaire data collected at Time1 and Time2 revealed a significant interaction effect between treatment and control group, indicating improvement in nonverbal communication and general communication. Time2 Auti-R questionnaire data evaluating changes in behavior over the last 6 months showed significant improvement in social interactions, communication skills, and stereotyped and repetitive behavior for the treatment group, but not for the control group.

In a second study by Kouijzer and colleagues (2010), several methodological improvements were implemented to better identify the effects of neurofeedback. A randomized wait-list control group design was used, and the study was conducted at the schools of the participants ($n=20$). Participants were 8–12 years old and

had diagnoses of autism, Asperger's disorder, or PDD-NOS. Participants in the treatment group had 40 individual neurofeedback sessions using an individualized treatment protocol based on an initial QEEG. However, all treatment protocols included theta inhibition at fronto-central scalp locations. Treatment response was evaluated by QEEG measures taken during rest and task conditions, a range of executive function tasks, and social behavior questionnaires filled out by parents and teachers. All data were collected before (Time1) and after treatment (Time2) and at 6 months follow-up (Time3).

Results of the study showed that 60 % of participants decreased theta power within 40 sessions of neurofeedback. Additionally, repeated measures MANOVA on QEEG data revealed a significant interaction between treatment and control group, indicating a decrease in theta power in the treatment group in two out of four QEEG conditions. Repeated measures MANOVA on Time1 and Time2 executive function data showed a significant interaction between treatment and control group for cognitive flexibility, indicating improvement in cognitive flexibility in the treatment group compared to the control group. Repeated measures MANOVA showed a significant interaction effect for social interactions and communication skills, indicating that parents of participants in the treatment group reported significant improvement in social interactions and communication skills, whereas less or no improvement was reported by parents of children in the control group.

Coben and his colleagues began researching the effects of coherence/connectivity training on autistic symptoms about 6 years ago. Coben and Padolsky (2007) published a study investigating the effects of neurofeedback treatment for autistic disorders. The study included 49 children on the autistic spectrum, with 37 participants receiving QEEG connectivity-guided neurofeedback and 12 participants in a wait-list control group. Treatment included 20 sessions performed twice per week. The control group was matched for age, gender, race, handedness, other treatments, and severity of ASD. According to the parents, there was an 89 % success rate for neurofeedback and an average of 40 % reduction in core ASD symptomatology. There were significant improvements on neuropsychological measures of attention, visual-perceptual skills, language functions, and executive functioning. Importantly, reduced cerebral hyperconnectivity was associated with positive clinical outcomes, and in all cases of reported improvement, positive outcomes were supported by neurophysiological and neuropsychological assessment.

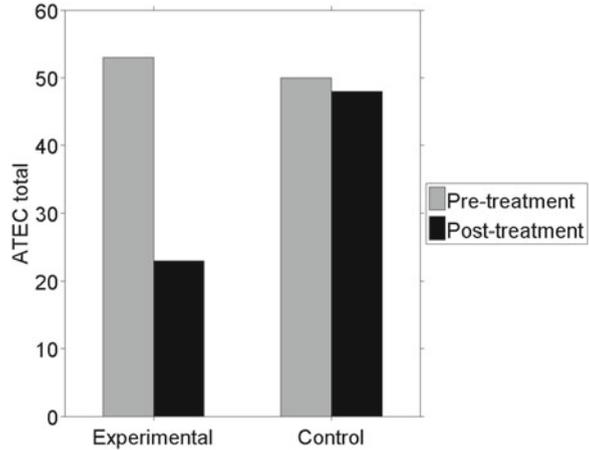
Mu-rhythm abnormalities are a sign of mirror neuron dysfunction, which is thought to be the case in many children with autism (Oberman et al. 2005). In two studies focused on reducing abnormal mu rhythms in children with autism, Pineda and Hecht (2009) found that according to parents, participants showed a small but significant reduction in symptoms but increased ratings of sensory-cognitive awareness. 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 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 nonrandomly assigned to an inter-hemispheric 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 and 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 training. All patients underwent pre- and post-treatment neuropsychological, QEEG, and parent rating scale assessments. Twenty-five individuals were assigned to either an active neurofeedback or a wait-list control group, in a 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 theta power related to brain regions (fusiform gyrus, superior temporal sulcus) associated with enhanced visual/facial/emotional processing.

In the seven controlled-group studies that have been completed, a total of 214 individuals with autism have been studied and 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 nonrandomized 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.

Fig. 6.1 Pre- and post-treatment ATEC scores



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 who have more severe symptoms associated with autism. These populations also should be the focus of future investigations.

6.3.4 *Efficacy of Connectivity-Guided Neurofeedback for Autistic Spectrum Disorder*

Recently, Coben (2009) presented on a study of the effects of an entire course of connectivity-guided neurofeedback treatment on autistic children. This included 110 subjects on the autistic spectrum, with 85 in the experimental and 25 in the control (wait-list) group. The mean age of these subjects was 9.7 years (range 4–20 years). Seventy-seven percent of these subjects were not on medication at the time, while 14 % were on one medication, 7 % on two medications, and 1 % on three medications. The mean IQ of this group was 93 (range 50–130). The mean ATEC score was 50 (range 40–170). There were no significant differences between the experimental and control groups for age, gender, handedness, race, medications, IQ, or ATEC scores.

The experimental group underwent an average of 74 neurofeedback sessions. They were assessed using QEEG, neuropsychological testing, and parent rating scales before treatment and then again after treatment. In order to evaluate the efficacy of neurofeedback treatment for reducing ASD symptomatology, the subjects' scores on the ATEC and neuropsychological testing were compared before and after treatment. A univariate analysis of variance (ANOVA) revealed that ATEC scores changed significantly after treatment ($F=117.213$; $p<0.0001$; see Fig. 6.1). Furthermore, 98.8 % of parents reported a reduction in ASD symptoms on the ATEC after treatment.

On objective neuropsychological testing, 100 % of subjects demonstrated some degree of improvement. An ANOVA revealed improvements on tests of visual-perceptual skills ($F=53.6$; $p<0.0001$), language abilities ($F=31.24$; $p<0.0001$), attentional skills ($F=54.04$; $p<0.0001$), and executive functioning ($F=15.65$; $p=0.00015$). In fact, visuoperceptual skills improved 43 %, language abilities improved 47 %, attentional skills improved 56 %, and executive functioning improved 48 %.

Once it was determined that the therapy was efficacious, the next question investigated was whether it had greater efficacy depending on level of functioning or severity of autistic symptoms. We investigated the effects of pretreatment ATEC and IQ scores on treatment outcome by dividing the groups into quartiles based on ATEC and IQ scores and reanalyzing the data. There were no significant differences for any of these analyses. This revealed that (1) ASD symptomatology improved with treatment regardless of IQ and (2) severity of ASD symptoms did not affect treatment outcomes. These results suggest that neurofeedback is an effective treatment regardless of the child's intellectual ability or severity of symptoms, at least within the parameters of the subjects that were included in this study.

6.3.5 Enduring Effects of Neurofeedback on Children with ASD

Both Kouijzer and Coben, along with their respective colleagues, have studied the enduring effects of neurofeedback after the treatment period has ended. One year follow-up data from Kouijzer et al.'s original study demonstrated enduring effects of neurofeedback treatment (Kouijzer et al. 2009a). Repeated measures MANOVA on the executive function task scores at Time2 and Time3 indicated maintenance of cognitive flexibility, planning skills, and verbal inhibition, improvement of attention, and marginally significant improvement of motor inhibition. No significant decreases in executive function skills were found after 1 year. Repeated measures MANOVA comparing Time1 and Time3 data confirmed maintenance of these effects. Analysis revealed significant increases of all executive functions that improved after neurofeedback treatment, i.e., attention skills, cognitive flexibility, inhibition, and planning. Figure 6.2 shows Time1, Time2, and Time3 scores of the treatment group on tests for attention, cognitive flexibility, inhibition, and planning.

Analysis of behavior questionnaires filled out by parents at Time2 and Time3 showed no loss of nonverbal communication and general communication (CCC), social interactions, communication skills, and stereotyped and repetitive behavior (Auti-R). Comparing Time1 and Time3 behavior questionnaires (CCC) confirmed the positive effect for nonverbal communication, but not for general communication. Figure 6.3 shows Time1, Time2, and Time3 questionnaire data (CCC) for general communication and nonverbal communication of the treatment group.

Detailed information about the results of this study can be found in the original paper (Kouijzer, de Moor, Gerrits, Buitelaar et al. 2009).

Analysis of the 6-month follow-up data from their second study (Kouijzer, van Schie, de Moor, Gerrits, and Buitelaar 2009) revealed enduring effects of

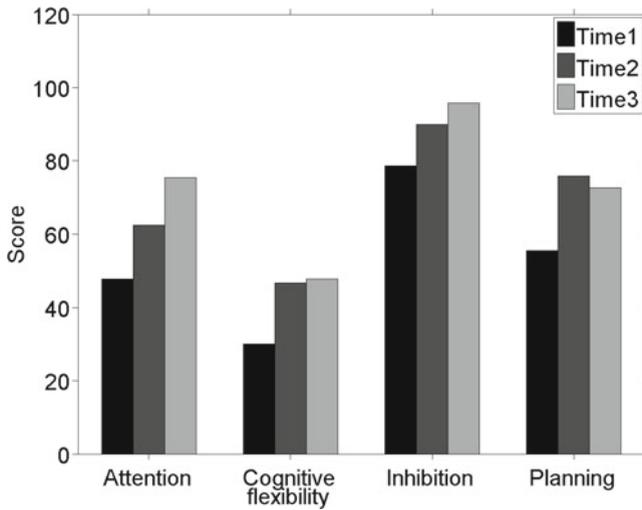


Fig. 6.2 Time1, Time2, and Time3 data of the treatment group on executive function tasks

neurofeedback treatment. Repeated measures MANOVA was used to compare the scores on executive function tasks at Time2 and Time3 and showed no significant changes, suggesting that participants maintained the same levels of executive functioning for at least 6 months. Repeated measures MANOVA comparing Time1 and Time3 data confirmed the previously described effects by revealing a significant increase of cognitive flexibility for the treatment group but not for the control group. Figure 6.4 shows Time1, Time2, and Time3 scores of the treatment and control group on cognitive flexibility.

Repeated measures MANOVA comparing the scores on behavioral questionnaires at Time2 and Time3 showed no effects of group or time, indicating maintenance of the effects in social behavior that were reached 6 months earlier. Repeated measures MANOVA comparing Time1 and Time3 questionnaire data confirmed this effect by showing a significant interaction, suggesting decreases in problem scores on behavior questionnaires for the treatment group, but not for the control group. Figure 6.5 shows Time1, Time2, and Time3 questionnaire data of social interactions and communication skills of treatment and control group.

More detailed information about the results of this study can be found in the original paper (Kouijzer et al. 2009a).

Both studies discussed above indicate maintenance of the effects in executive functions and social behavior from 6 months to 1 year after ending neurofeedback treatment.

A similar study with findings which can be considered complementary to those of Kouijzer and colleagues was recently conducted by Coben at his New York clinic (Coben et al. 2010a). This study assessed 20 patients with ASD in order to investigate long-term clinical effects of neurofeedback in terms of behavioral and

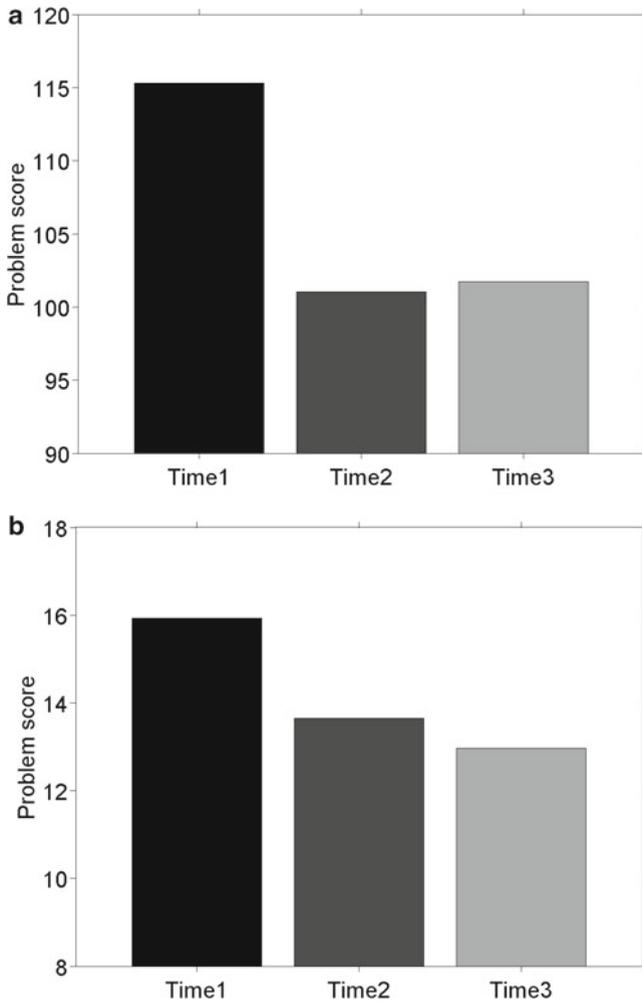


Fig. 6.3 Time1, Time2, and Time3 data of the treatment group on social behavior: general communication (a) and nonverbal communication (b)

neuropsychological measures. The subject pool for this study was predominately male (16 out of 20 individuals) and all Caucasian. The mean age was 9.53 years, with a range of 5–10 years. Most subjects (80 %) were medication free, with only one subject taking more than two medications. Handedness was mostly right handed ($n=16$) with one left handed and 3 ambidextrous subjects. Subjects were administered parent rating scales, including the Autism Treatment Evaluation Checklist (ATEC; Rimland and Edelson 2000), the Personality Inventory for Children (PIC-2; Lachar and Gruber 2001), the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, and Kenworthy, 2000), and the Gilliam Asperger's Disorder Scale (GADS; Gilliam 2001). Subjects were also administered

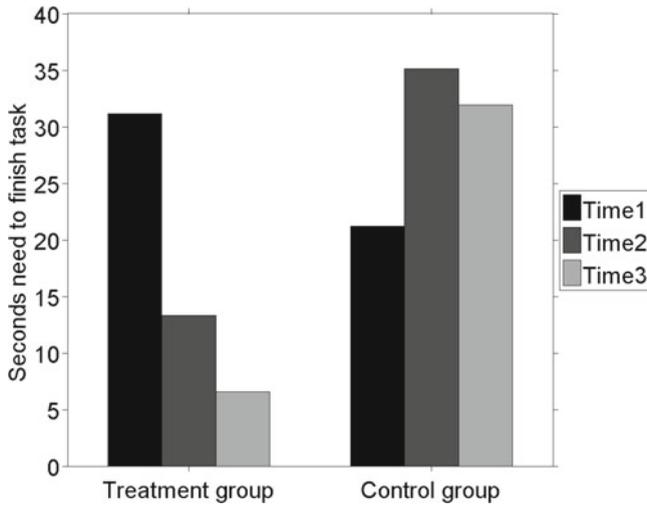


Fig. 6.4 Time1, Time2, and Time3 data of treatment and control group on cognitive flexibility

neuropsychological assessments covering domains of attention/executive functioning, language, and visuospatial processing. After baseline assessments were collected, all subjects underwent at least 40 sessions of neurofeedback training, with an average of 64.5 completed sessions among all subjects. Upon completion of therapy, subjects were reevaluated and pre- and post-treatment scores were compared for significance. After reevaluation, neurofeedback was withheld for between 5 months and 22 months (mean 10.1 months), while no other treatments were administered. Following this break in treatment, subjects were evaluated once again in the same fashion as previously described. Their latter scores were then compared to scores obtained at the end of active neurofeedback training (Time2).

All statistical computations were performed in the statistical package SPSS. Scores prior to treatment on parent rating scales were compared for significance to scores obtained after treatment had ended. Analysis of pre- and postscores obtained from the ATEC revealed significant changes following neurofeedback training. Likewise, changes in scores on the GADS prior to and following treatment were found to be significant. Significant changes were also found to be present following treatment among scores from the BRIEF as well as the PIC-2. Interestingly, when subjects were reassessed following the 5-month to 22-month period of no neurofeedback training, no significant changes were found on any parent rating scale administered (Fig. 6.6). This suggests that changes in parent ratings that were improved by neurofeedback training remained stable during this follow-up period.

Neuropsychological evaluations encompassing the domains of attention, executive functioning, language, and visuospatial processing were also analyzed for significant differences. Significant changes from pre- to post-treatment scores were found among all three domains assessed: attention/executive functioning, language, and visuospatial processing. Interestingly, significant therapeutic changes were also

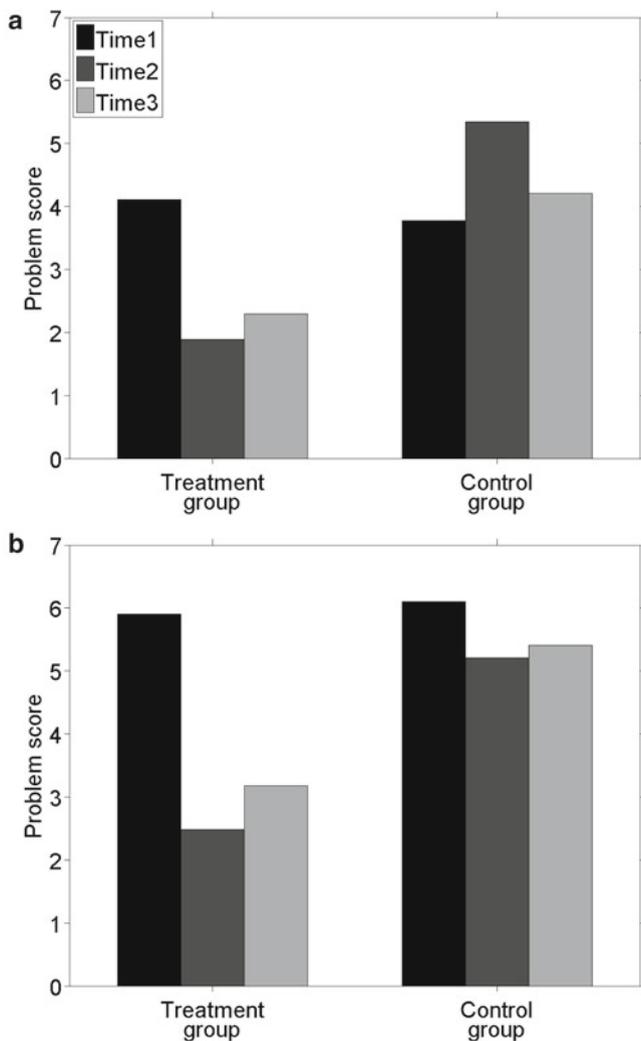


Fig. 6.5 Time1, Time2, and Time3 data of treatment and control group on social behavior: social interactions (a) and communication skills (b)

found after subjects were reevaluated after a lengthy (5–22 months) absence from neurofeedback training. These occurred in the areas of attention, language, and visuospatial processing (Fig. 6.7). This would suggest that neurofeedback training not only led to objective gains in neuropsychological functioning but that these enhancements in functioning continued to improve over the follow-up period when no treatment was being received.

The results of this present study were quite interesting. First, our findings add to the wealth of studies that have shown that from pre- to posttreatment conditions,

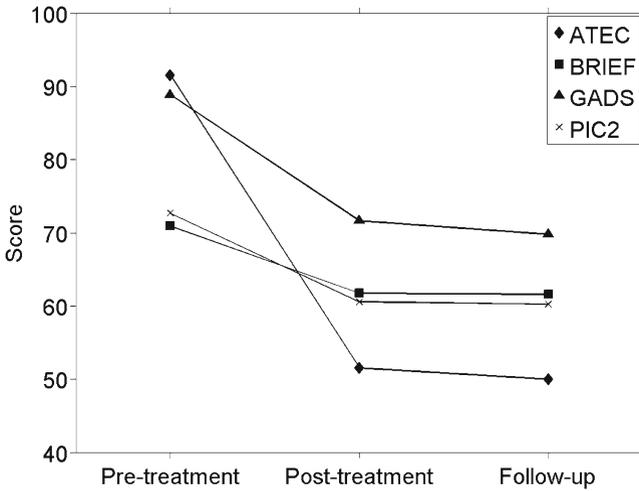


Fig. 6.6 Graph showing the clinical improvements among subjects as assessed by the parents rating scales of ATEC, BRIEF, GADS, and PIC-2 for pretreatment, post-treatment, and follow-up periods

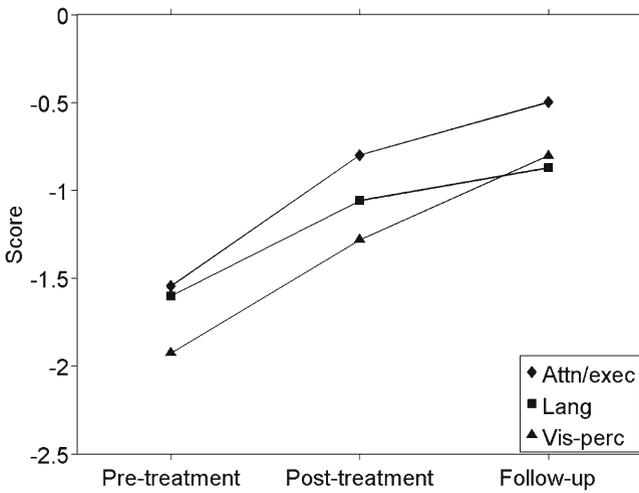


Fig. 6.7 Graph showing the clinical improvements among the domains of attention/executive functioning, language, and visuospatial processing as assessed by neuropsychological evaluations at pretreatment, post-treatment, and follow-up periods

neurofeedback is an effective therapy for treating individuals with autistic spectrum disorders. Additionally, these results show that this treatment was effective in limiting autistic behavioral deficits as well as deficits of a more neuropsychological nature. Furthermore, as our analysis shows, there were no significant increases in autistic pathology when subjects were reevaluated after neurofeedback was

withheld. This finding supports previously found evidence that neurofeedback is capable of creating stable changes within autistic subjects that are not likely to rapidly degrade when treatment ends (Jarusiewicz 2002, p. 749; Coben 2007, p. 740).

Of potentially even greater interest, this study found that during the period in which subjects were receiving no treatment, positive clinical neuropsychological gains were still being manifested within the domains of attention, executive functioning, language, and visuospatial processing. Thus, even without continued treatment, subjects apparently were continuing to improve in these realms. An important implication of this finding is that neurofeedback may indeed change the autistic brain to work in novel and more efficient ways, and these changes may continue to progress even after the treatment has ended. This finding helps further the claim that neurofeedback creates specific neurophysiological changes within the autistic brain (Coben et al. 2009). This is in stark contrast to other commonly administered treatments for autism. For example, Lovaas et al. (1973, p. 1145) performed a study in which applied behavioral analysis (ABA) was administered to a group of children with autism. Upon completion of ABA training, the experimenters reported positive gains in terms of clinical improvements in behavioral deficits. Subjects were then reevaluated between 1 and 4 years later, and subjects who did not continuously receive ABA training had significantly regressed. As our current findings demonstrate, there is no evidence of regression among any of our subjects receiving neurofeedback training. In terms of drug therapies, there is no evidence to our knowledge that would indicate that medications result in enduring clinical gains for subjects with autism when medication is withheld. In fact, numerous studies indicate that prolonged medication use has detrimental effects on autistic individuals (Malone 2002, p. 1149; Anderson et al. 2010).

In terms of the limitations of the current study, the participants consisted of a selected pool of subjects. Subjects were placed in groups by choice of the experimenter rather than by random assignment. When subjects are chosen in that manner, there may be a degree of selection bias associated. We would also recommend that this experiment be replicated with more neuropsychological assessments and parent rating scales included in order to more widely assess the effects of neurofeedback training. This type of investigation could broaden the present findings and help determine if there are other correlations or significant predictors we might not have considered. Also, we would recommend a study with a greater gap between the end of treatment and reevaluation of subjects. Doing this, we believe, would help to assess nature and extent of any positive clinical gains found in subjects when they are no longer receiving treatment, as well as test more fully the limits of enduring effects of neurofeedback treatment.

6.4 Discussion

There are few interventions with proven efficacy for children with autism. Behavioral modification interventions currently have the most empirical support, while pharmacologic interventions, hyperbaric oxygen, and vitamin supplementation have

shown some potential. It is our opinion that neurofeedback is in a similar position with respect to efficacy for ASD, but more research is needed. Neurofeedback is an intervention that may prove to be efficacious in the treatment of symptoms of autism. At present, it should be viewed as possibly efficacious with potential as is the case with most interventions used with this population. Measuring brain-related changes that may occur as a result of neurofeedback is one way of demonstrating its efficacy and mechanism of action. Additional well-designed, more rigorous studies and longer follow-up periods should be included in the future to measure the efficacy of neurofeedback in treating children on the autistic spectrum.

In addition, there is growing evidence that neurofeedback is a therapy capable of creating enduring changes in children with autism. A therapy that can lead to long-lasting effects for children with developmental disorders (and perhaps continuing improvement even after the treatment is stopped) is an enormous asset for children with developmental disorders. Most contemporary treatments require prolonged and lengthy treatment sessions. For example, ABA training can require up to 40 h a week over several months to be effective (Howard 2005, p. 1132). Furthermore, drug therapies usually require years of medication in order to maintain efficacy. In addition, some children require incremental increases in dosages over a period of years for medication use to be clinically viable. Our current results and those of others discussed in this chapter indicate that neurofeedback therapy can reach clinical efficacy relatively quickly and positive gains can be retained for months after treatment has stopped. Outside of the clinical implications, there are ancillary benefits supporting the use neurofeedback. For example, the financial aspects of this treatment should be considered. Presently, the United States alone spends upward of \$3.2 million for the care and treatment for a single individual with autism, a figure that equates to \$35 billion annually (Ganz 2006).

Results of the studies reviewed in this chapter also provide evidence for the safety of neurofeedback. All studies reported no instances of subjects worsening or showing any side effects while undergoing this treatment over an extended period of time. Moreover, there was no evidence of negative side effects when neurofeedback was ceased. In fact, the opposite was found across all studies. This, again, is contradictory to other interventions, most notably drug therapies, which have documented adverse reactions within this population and often have failed to demonstrate positive effects on primary symptoms (Kidd 2002). Investigations into other contemporary treatments (i.e., diet and chelation therapies) have failed to yield adequate evidence in regard to their safety or efficacy (McDougle et al. 2000; Doja and Roberts 2005; Elder et al. 2006).

We speculate that the enduring effects of neurofeedback in children with developmental disorders are the result of this treatments' ability to change the brain in a therapeutic manner. Recently, Coben and colleagues reported specific neurophysiological changes in terms of coherence within and between specific neural regions following neurofeedback treatment for children with autism spectrum disorder (Coben et al. 2009). We would argue that neurofeedback training causes specific neurophysiological changes within the brain, which in turn contribute to the long-lasting effects of this treatment, and this fosters the continued growth and development of cognitive functions. Moreover, we suggest that more research be conducted

into the precise neural areas clinically affected by neurofeedback in an effort to more fully understand the efficacy of neurofeedback for children with developmental disorders. In summary, results of the studies examined add to the growing wealth of investigations into the efficacy of neurofeedback as a treatment for children with developmental disorders. Moreover, these results have found this treatment to be effective over an extended period of time. Consistent with these results, we recommend future studies be conducted that assess the enduring effects of neurofeedback over even longer treatment spans.

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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.

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Using quantitative and analytic EEG methods in the understanding of connectivity in autism spectrum disorders: a theory of mixed over- and under-connectivity

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Neuroimaging technologies and research has shown that autism is largely a disorder of neuronal connectivity. While advanced work is being done with fMRI, MRI-DTI, SPECT and other forms of structural and functional connectivity analyses, the use of EEG for these purposes is of additional great utility. Cantor et al. (1986) were the first to examine the utility of pairwise coherence measures for depicting connectivity impairments in autism. Since that time research has shown a combination of mixed over and under-connectivity that is at the heart of the primary symptoms of this multifaceted disorder. Nevertheless, there is reason to believe that these simplistic pairwise measurements under represent the true and quite complicated picture of connectivity anomalies in these persons. We have presented three different forms of multivariate connectivity analysis with increasing levels of sophistication (including one based on principle components analysis, sLORETA source coherence, and Granger causality) to present a hypothesis that more advanced statistical approaches to EEG coherence analysis may provide more detailed and accurate information than pairwise measurements. A single case study is examined with findings from MR-DTI, pairwise and coherence and these three forms of multivariate coherence analysis. In this case pairwise coherences did not resemble structural connectivity, whereas multivariate measures did. The possible advantages and disadvantages of different techniques are discussed. Future work in this area will be important to determine the validity and utility of these techniques.

Keywords: autism spectrum disorders, EEG/MEG, connectivity analysis, coherence analysis, sLORETA, granger causation analysis

INTRODUCTION

Autistic Spectrum Disorders (ASD) are a heterogeneous group of pervasive developmental disorders including Autistic Disorder, Childhood Disintegrative Disorder, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), and Asperger 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 (NIMH, 2006).

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 (CDC, 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 10-fold increase over a 20 year interval in the United States. These findings make accurate assessment of autistic individuals and their underlying neurophysiology a priority.

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 electroencephalogram (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 the 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.

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; Hughes and Melyn, 2005; Hara, 2007; Parmeggiani et al., 2007). In fact, it has been reported that the autistic population has about 3- to 22-fold increased risk of developing seizure disorders as compared to the normal population (Volkmar and Nelson, 1989). Sub-clinical seizure activity or paroxysmal discharges occur in an even higher proportion of autistics, but the significance of these remain 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).

In a 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. 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. While brain structural imaging may reveal interesting findings, assessment of regional brain dysfunction is more revealing and usually requires functional brain imaging techniques. This would include techniques such as functional MRI, PET, single photon emission computed tomography, magnencephalography (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.

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 ASD and normal controls with conflicting results. Two studies showed decreased delta frontally (Dawson et al., 1982; Coben et al., 2008), 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 (Small et al., 1975; Coben et al., 2008), 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 (Rossi et al., 1995; Chan and Leung,

2006; Coben et al., 2008) 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; Lazarev et al., 2004; Coben et al., 2008). One concern has been that sample sizes by and large have not been large enough to allow for investigation of the observed inconsistencies in findings reported above.

In the largest study of its' kind, we (Coben et al., 2013) included a total of 182 children, 91 on the autistic spectrum and 91 healthy controls. Findings indicated an absolute delta deficit over frontal and central brain regions and theta excesses over frontal, temporal and posterior regions for the ASD sample. There were significant relative theta excesses over frontal and temporal regions, alpha and beta excesses over multiple regions. Interestingly, cluster analytic techniques were used and able to delineate qeeg subtypes of ASD. Furthermore, a discriminant function analysis was able to correctly identify ASD children at a rate of 95%. Despite power subtypes having been shown, VARETA (di Michele et al., 2005) revealed similar sources of activation including temporal, posterior cortical and various limbic regions. These findings raise the likelihood that the study of neuronal networks in autism may lead to a greater understanding of ASD than localization of brain activity. Power asymmetry and coherence findings were also significant consistent with evidence supporting the notion of frontal hypercoherence and anterior to posterior temporal hypo-coherences. 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.

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; Minshew and Williams, 2007; Mak-Fan et al., 2012). 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 (Casanova et al., 2002; Herbert et al., 2004; Carper and Courchesne, 2005; Vargas et al., 2005). This overgrowth, then, leads frontal over-connectivity (Courchesne and Pierce, 2005; Coben and Myers, 2008; 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 hypo-coherences (Coben et al., 2013).

Other data support this hypothesis as well. For example, Mak-Fan et al. (2012) examined changes in diffusivity with age within frontal, long distant, 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 exist and persist in such children. More specifically, frontal and local (short neuronal paths) hyperconnectivity has been shown to be present in autistic samples (Wass, 2011; Li et al., 2014). 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. 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; von dem Hagen et al., 2013). Similarly, low functional connectivity has been shown to relate to poor language processing in autistic children (Kana et al., 2006). Many of these studies used 3-dimensional imaging techniques such as MRI, fMRI or DTI (diffusion tensor imaging). Interestingly, EEG/QEEG studies of coherence have shown similar findings. Coben et al. (2013) have recently shown findings consistent with frontal hypercoherence and bilateral posterior-temporal hypo-coherences. 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 hypo-coherences (Murias et al., 2007; Coben et al., 2008). All of these coherence findings have been based on measurements between pairs of electrodes. There is reason to believe that more advanced statistical approaches to EEG coherence may provide more detailed and accurate information.

PAIRWISE vs. MULTIVARIATE COHERENCE ESTIMATES

Traditionally and historically EEG coherence estimates have arisen from cross correlations between pairs of electrodes (Bendat and Piersol, 1980). Such a calculation is often performed within a given frequency range and is normalized for amplitude or magnitude. As such the following equation serves as the operational definition:

$$\tau_{xy}^2(f) = \frac{(G_{xy}(f))^2}{(G_{xx}(f)G_{yy}(f))} \quad (1)$$

Where: $G_{xy}(f)$ = cross power spectral density and $G_{xx}(f)$ and $G_{yy}(f)$ = auto power spectral densities
The final normalized coherence value is given by Equation (2):

$$\tau_{xy}^2(f) = \frac{r_{xy}^2 + q_{xy}^2}{G_{xx}G_{yy}} \quad (2)$$

Where: r_{xy}^2 = real cospectrum and q_{xy}^2 = imaginary quad spectra
 $G_{xx}(f)$ and $G_{yy}(f)$ = as in Equation (1)

Phase: $159.1549 \tan^{-1}(q/r)/fc$

Where: r and q = as in Eq.2; fc = center frequency of filter

For a more detailed explanation or discussion of these please see Otnes and Enochson (1972) and Thatcher et al. (1986). These concepts have been used and applied commonly. In fact, a search in Google Scholar for “EEG coherence pairs” revealed more than 14,500 citations. While this approach has been commonly used in the past, there are certain limitations in its application and accuracy. First, there is a confound in pairwise coherence measurements, namely the notion of electrode distance. It has been observed that the further the distance between electrodes the lower their coherence value will be regardless of their functional connectivity, with distances as long as at least 5 cm. (Nunez, 1994; Nunez and Srivinasan, 2006; Thatcher et al., 2008). Pairwise coherence measures for nearby electrodes are biased by volume conduction, to a degree that varies as a function of inter-electrode distance such that physically closer pairs manifest higher coherence values. While statistical corrections have been offered for these concerns (Nunez et al., 1997; Barry et al., 2005), multivariate approaches that may eliminate this problem should be desired.

Other reasons for concern include a vast array of possible comparisons (171 comparisons in one frequency band), and that many of these pairs do not correspond to known neuronal pathways. Lastly, pairwise coherence estimates are not precise in their anatomical locations as there is a presumption of a two dimensional and not a 3-dimensional space (Black et al., 2008). It has further been observed that multivariate strategies to assess coherence metrics are more accurate and effective than their pairwise counterparts (Kus et al., 2004; Barry et al., 2005; Pollonini et al., 2010). For example, Duffy and Als (2012) used principal components analysis of coherences (multivariate approach) and demonstrated the ability to distinguish between children with autism and neurotypical controls.

MULTIVARIATE APPROACHES TO COHERENCE ANALYSIS

Multivariate, advanced statistics models, have rarely been applied to the issue of coherence in the autistic brain. With these new advances in analytic methods it is hoped that we will come closer to understanding these dynamic phenomena. Hudspeth (1994) was one of the first to investigate a multifactorial representation of EEG covariance. He and his students obtained multichannel EEG data and computed all combinations and similarities and differences among the waveforms to produce a triangular correlation matrix for each subject. The correlation matrices were then factored with principal components analysis to obtain three eigenvectors and the weighting coefficients required to project each of the waveforms into a 3-dimensional geometric representation of the cortical surface of the brain. When processed in this way, this integration of factored data reduces the redundancy in the EEG waveforms and patterns and correspond to known neural network pathways. This is the predecessor of Duffy and Als (2012) with enhanced complexity. The first three principle components are summed to create a 3-dimensional representation of these multivariate coherences. When EEG data is represented in this way, the resulting eigenimages reveal similarities and differences across systems in the brain often grouped together by cortical function or neuronal systems. Deviations

from these expected relationships points to dysfunctional aspects of coherence. EEG data is gathered based on the classic 10–20 international system/electrode configuration (Jasper, 1958). In this system of analysis, these points in space are redrawn in 3-dimensional space based on each locations' multidimensional relationship with all other locations based on horizontal, sagittal and coronal views. As such, connectivity patterns are determined by the inter-relationships among all combinations of inputs and are thus considered multivariate or multi-source in nature.

A clinical example of this is now presented below in **Figure 1**. This is based on an EEG recording performed with a 12 year old girl diagnosed with autism with her eyes open and fixed on a spot directly in front of her. Her most prominent clinical feature included very limited social skills. The EEG data was consistent with a mu rhythm (Kuhlman, 1978) that does not suppress to movement or observation of social scenes (Oberman et al., 2007) and is, thus, considered indicative of mirror neuron dysfunction (Oberman et al., 2005). This system of coherence assessment was created by Hudspeth (2006) and is contained within the NeuroRep QEEG Software system. The method of calculation has been described above as these eigen images can be viewed as an image in 3-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 hypercoherences and electrodes that are further apart are indicative of greater hypo-coherences. As may be seen in **Figure 1** this analysis reveals a pattern of mixed hypo and hypercoherences with prefrontal and parietal-posterior temporal regions being hyperconnected among themselves and large regions of hypo-coherences across much of the right hemisphere but especially from posterior frontal to posterior temporal regions.

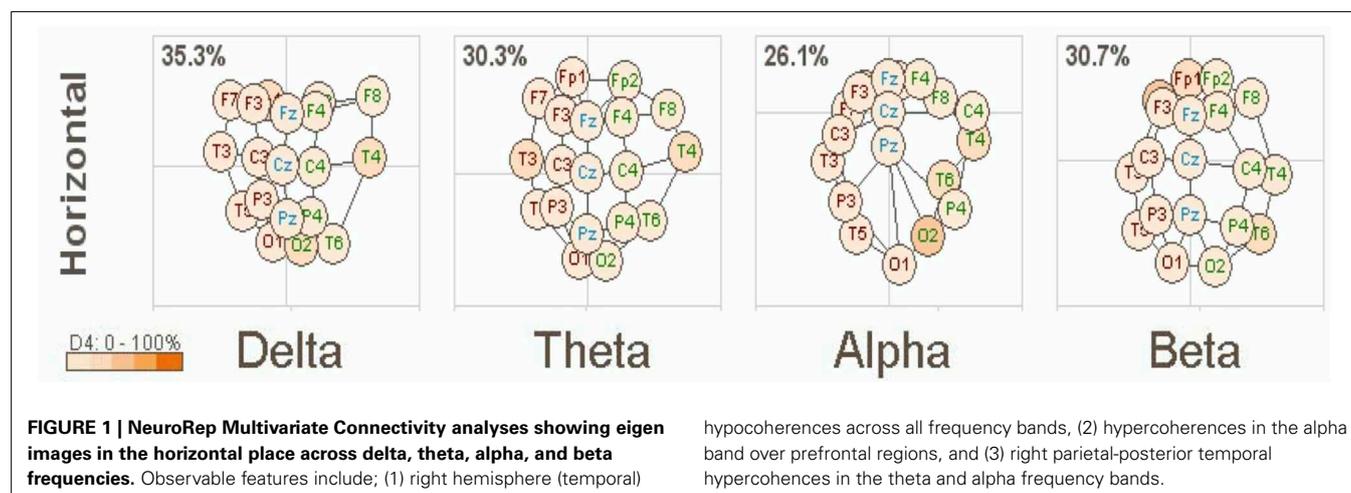
sLORETA FUNCTIONAL CONNECTIVITY

Standardized low-resolution brain electromagnetic tomography (sLORETA) is a method of probabilistic source estimation of EEG signals in standardized brain atlas space utilizing a restricted inverse solution (Pascual-Marqui et al., 1994, 2002). sLORETA

has been used to examine EEG sources in depression (Pizzagalli et al., 2003), epilepsy (Zumsteg et al., 2006), and evaluating temporal changes associated with differential task specific default network activity (Cannon and Baldwin, 2012). Recently, sLORETA and fMRI were shown to localize DMN regions with complementary accuracy (Cannon et al., 2011). Recent statistical and theoretical advances have led to the use of this technology in the measurement of source coherences (Pascual-Marqui, 2007).

There has been rigorous discourse over the localization accuracy of low-resolution electromagnetic tomography (LORETA) and its evolution toward standardized low-resolution electromagnetic tomography (sLORETA) (Pascual-Marqui et al., 1994; Pascual-Marqui, 2002). The most important issue at hand for any EEG localization or functional neuroimaging technique is the fact that none of these methods localize the “true” source, rather they model the source with probabilistic techniques. This includes all methods that utilize statistical/mathematical modeling, including functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) (Knyazev, 2013). Thus, when using sLORETA in this fashion, we do operate under certain assumptions/restrictions. First, we are restricted to cortical gray matter; including the hippocampus and the computations and source estimations are restricted by geometric constraints. Additionally, in the most basic sense it would be optimal to evaluate the source estimates provided by sLORETA to an individual's specific MRI scan, thus we utilize a standardized MRI from the Montreal Neurological Institute with 6340 5 mm³ voxels and with it the potential error (Collins et al., 1994). In the localization of EEG sources, recent works have shown the sLORETA and LORETA methods to improve and even outperform other methodologies in accuracy (Grech et al., 2008; SaediAsl and Ahmad, 2013) with the addition of regularization parameters. Additionally, standardized LORETA is not a modification of the original LORETA, rather it does not utilize the Laplacian operator, instead it utilizes standardized current density.

Importantly, for this particular single case study we extrapolated CSD for each frequency range to enter into bivariate procedures to compute the person correlation coefficient for the mean total relative current source density for each of the ROIs



included in this study. For larger sample sizes, each frequency domain can be analyzed and the results do not correspond to issues with excessively high correlations in neuroimaging studies as reported in Vul et al. (2009), rather it appears that task and subjective mental activity are important to understanding functional coupling that occurs within and between networks in the human brain (Cannon and Baldwin, 2012). The basis for using a correlation procedure is that functional relationships between groups of neurons within the brain can exist, even if the structural relationships are unknown. We have evaluated the use of correlations using two neuroimaging methods (sLORETA/fMRI) with accurate results in the default network (Cannon et al., 2011, 2012). In any experiment utilizing discrete or distributed sources of the EEG volume conduction is a formidable concern. In short, volume conduction decreases as a function of distance from a current source at zero phase lag; however, if volume conduction is a problem in any sense then phase lag differences must be near zero and remain near zero independent of distance (Kauppinen et al., 1999; Thatcher et al., unpublished manuscript).

The distributed source localization problem and its solution as computed by sLORETA can be stated as (Pascual-Marqui, 2002; Liu et al., 2005)

$$\Phi = \mathbf{KJ} + c1 \quad (3)$$

Where Φ is an $N \times 1$ vector containing the scalp electric potentials measured from N_E electrodes on the scalp, \mathbf{J} is a $3M \times 1$ vector representing current sources at M locations within the brain volume, with three orthogonal components per location and c being a common reference. \mathbf{K} is the lead field matrix representing the system transfer coefficients from each source to each measuring point (Pascual-Marqui, 2002). Regularization using a zero-order Tikhonov-Philips cost function permits a unique solution to Equation (1) (Hansen, 1994)

$$\min_{\mathbf{J}} \{ \|\Phi - \mathbf{KJ}\|^2 + \alpha \|\mathbf{J}\|^2 \} \quad (4)$$

Where α is the regularization parameter using the L-curve method. The source estimation is then derived as

$$\hat{\mathbf{J}} = \mathbf{T}\Phi \quad (5)$$

where

$$\mathbf{T} = \mathbf{K}^T[\mathbf{K}\mathbf{K}^T + \alpha\mathbf{I}]^{-1} \quad (6)$$

Substituting (3) into (5) yields

$$\hat{\mathbf{J}} = \mathbf{TKJ} = \mathbf{K}^T[\mathbf{K}\mathbf{K}^T + \alpha\mathbf{I}]^{-1}\mathbf{KJ} = \mathbf{RJ} \quad (7)$$

where \mathbf{R} is the resolution matrix, defined as

$$\mathbf{R} = \mathbf{K}^T[\mathbf{K}\mathbf{K}^T + \alpha\mathbf{I}]^{-1}\mathbf{K} \quad (8)$$

The resolution matrix illustrates a map from the authentic source activity to the estimated activity, with \mathbf{R} being an identity matrix. Thus, the basic functional concept of sLORETA is to normalize the estimation using a block-by-block inverse of the resolution matrix using (8)

$$\hat{\mathbf{J}}_l^T(\mathbf{R}_{ll}) - 1\hat{\mathbf{J}}_l \quad (9)$$

where $\hat{\mathbf{J}}_l$ is a 3×1 vector of the source estimate at the l th voxel and \mathbf{R}_{ll} is a 3×3 matrix containing the l th diagonal block of the resolution matrix. sLORETA was shown to give the best performance in terms of localization error and ghost sources, with different noise levels (Grech et al., 2008).

METHODS

A region of interest (ROI) file with the MNI coordinates for the 15 seed points for the center voxel within Brodmann Area (BA) regions was constructed (see **Table 1**). These ROIs were selected a priori based on their known involvement in the mirror neuron system and social perceptual networks. Each of the ROI values consisted of the mean current source density from each ROI seed

Table 1 | ROIs for this study: in the table from left to right are the x, y, and z MNI coordinates for center voxel, Lobe, structural nomenclature and Brodmann Area.

X-MNI	Y-MNI	Z-MNI	Lobe	Structure	Brodman area
50	20	15	Frontal lobe	Inferior frontal gyrus	45
30	25	-15	Frontal lobe	Inferior frontal gyrus	47
45	35	20	Frontal lobe	Middle frontal gyrus	46
25	55	5	Frontal lobe	Superior frontal gyrus	10
20	45	-20	Frontal lobe	Superior frontal gyrus	11
40	-5	10	Sub-lobar	Insula	13
25	-75	10	Occipital lobe	Cuneus	30
45	-20	-30	Temporal lobe	Fusiform gyrus	20
5	-45	25	Limbic lobe	Posterior cingulate	23
0	20	20	Limbic lobe	Anterior cingulate	33
20	-10	-25	Limbic lobe	Parahippocampal gyrus	28
10	-50	35	Parietal lobe	Precuneus	31
5	30	20	Limbic lobe	Anterior cingulate	24
45	-55	-15	Temporal lobe	Fusiform gyrus	37
40	15	-30	Temporal lobe	Superior temporal gyrus	38

Table 2 | Results for the sLORETA correlation analyses.

		Correlations														
		BA45	BA47	BA46	BA10	BA11	BA13	BA30	BA20	BA23	BA33	BA28	BA31	BA24	BA37	BA38
BA45	Pearson correlation	1	0.584	0.940	0.381	0.358	0.977*	0.553	0.922	0.782	0.547	0.712	0.927	0.531	0.802	0.607
	Sig. (2-tailed)		0.416	0.060	0.619	0.642	0.023	0.447	0.078	0.218	0.453	0.288	0.073	0.469	0.198	0.393
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA47	Pearson correlation	0.584	1	0.817	0.968*	0.967*	0.413	0.909	0.728	0.910	0.883	0.976*	0.804	0.889	0.739	0.993**
	Sig. (2-tailed)	0.416		0.183	0.032	0.033	0.587	0.091	0.272	0.090	0.117	0.024	0.196	0.111	0.261	0.007
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA46	Pearson correlation	0.940	0.817	1	0.670	0.644	0.848	0.723	0.918	0.896	0.783	0.886	0.962*	0.773	0.823	0.820
	Sig. (2-tailed)	0.060	0.183		0.330	0.356	0.152	0.277	0.082	0.104	0.217	0.114	0.038	0.227	0.177	0.180
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA10	Pearson correlation	0.381	0.968*	0.670	1	0.994**	0.185	0.829	0.533	0.781	0.896	0.891	0.630	0.906	0.559	0.941
	Sig. (2-tailed)	0.619	0.032	0.330		0.006	0.815	0.171	0.467	0.219	0.104	0.109	0.370	0.094	0.441	0.059
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA11	Pearson correlation	0.358	0.967*	0.644	0.994**	1	0.167	0.871	0.546	0.800	0.845	0.898	0.633	0.858	0.597	0.951*
	Sig. (2-tailed)	0.642	0.033	0.356	0.006		0.833	0.129	0.454	0.200	0.155	0.102	0.367	0.142	0.403	0.049
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA13	Pearson correlation	0.977*	0.413	0.848	0.185	0.167	1	0.434	0.882	0.678	0.361	0.572	0.858	0.342	0.760	0.450
	Sig. (2-tailed)	0.023	0.587	0.152	0.815	0.833		0.566	0.118	0.322	0.639	0.428	0.142	0.658	0.240	0.550
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA30	Pearson correlation	0.553	0.909	0.723	0.829	0.871	0.434	1	0.806	0.951*	0.609	0.946	0.826	0.619	0.890	0.952*
	Sig. (2-tailed)	0.447	0.091	0.277	0.171	0.129	0.566		0.194	0.049	0.391	0.054	0.174	0.381	0.110	0.048
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA20	Pearson correlation	0.922	0.728	0.918	0.533	0.546	0.882	0.806	1	0.937	0.522	0.858	0.989*	0.515	0.970*	0.779
	Sig. (2-tailed)	0.078	0.272	0.082	0.467	0.454	0.118	0.194		0.063	0.478	0.142	0.011	0.485	0.030	0.221
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA23	Pearson correlation	0.782	0.910	0.896	0.781	0.800	0.678	0.951*	0.937	1	0.685	0.978*	0.958*	0.686	0.951*	0.946
	Sig. (2-tailed)	0.218	0.090	0.104	0.219	0.200	0.322	0.049	0.063		0.315	0.022	0.042	0.314	0.049	0.054
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA33	Pearson correlation	0.547	0.883	0.783	0.896	0.845	0.361	0.609	0.522	0.685	1	0.807	0.642	1000**	0.439	0.824
	Sig. (2-tailed)	0.453	0.117	0.217	0.104	0.155	0.639	0.391	0.478	0.315		0.193	0.358	0.000	0.561	0.176
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA28	Pearson correlation	0.712	0.976*	0.886	0.891	0.898	0.572	0.946	0.858	0.978*	0.807	1	0.908	0.810	0.866	0.990*
	Sig. (2-tailed)	0.288	0.024	0.114	0.109	0.102	0.428	0.054	0.142	0.022	0.193		0.092	0.190	0.134	0.010
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA31	Pearson correlation	0.927	0.804	0.962*	0.630	0.633	0.858	0.826	0.989*	0.958*	0.642	0.908	1	0.635	0.946	0.839
	Sig. (2-tailed)	0.073	0.196	0.038	0.370	0.367	0.142	0.174	0.011	0.042	0.358	0.092		0.365	0.054	0.161
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA24	Pearson correlation	0.531	0.889	0.773	0.906	0.858	0.342	0.619	0.515	0.686	1000**	0.810	0.635	1	0.437	0.830
	Sig. (2-tailed)	0.469	0.111	0.227	0.094	0.142	0.658	0.381	0.485	0.314	0.000	0.190	0.365		0.563	0.170
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA37	Pearson correlation	0.802	0.739	0.823	0.559	0.597	0.760	0.890	0.970*	0.951*	0.439	0.866	0.946	0.437	1	0.807
	Sig. (2-tailed)	0.198	0.261	0.177	0.441	0.403	0.240	0.110	0.030	0.049	0.561	0.134	0.054	0.563		0.193
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BA38	Pearson correlation	0.607	0.993**	0.820	0.941	0.951*	0.450	0.952*	0.779	0.946	0.824	0.990*	0.839	0.830	0.807	1
	Sig. (2-tailed)	0.393	0.007	0.180	0.059	0.049	0.550	0.048	0.221	0.054	0.176	0.010	0.161	0.170	0.193	
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

and one single voxel (its nearest neighbor) for total voxel size 10 mm. The resulting file produced the average current source density for each frequency domain across multiple EEG segments for all subjects for each seed (ROI). The CSD data for each frequency band were organized into Microsoft Excel spreadsheets and then entered into SPSS 19 for analysis. sLORETA images corresponding to the estimated neuronal generators of brain activity within each given frequency range were calculated (Frei et al., 2001). This procedure resulted in one 3D sLORETA image for this single subject for each frequency range. We entered each frequency domain into the analysis for an N of 4 (delta 0.5–4.0 Hz; theta 4–8 Hz; alpha 8–12 Hz, and beta 12–32 Hz). The sequence of steps involved in generating the sLORETA source coherence image is presented in **Figure 2**.

The findings for this same case as described above are presented in **Figure 3**. The most apparent findings from this analysis seem to be regions that are overconnected with each other and that these regions often involve close neighbors or regions of close proximity (see **Table 2**). These include most profoundly regions of the anterior cingulate that are completely ($R = 1.0$) hyperconnected to each other and not to any other ROI. ROIs in and around the right frontal lobe (11, 10, 46, 47) also seem to form a loop of highly connected activity while their connections to other regions are quite limited. The fusiform gyrus is highly connected to the posterior cingulate and pre-cuneus, but again not to other ROIs. What is missing is a link between the fusiform gyrus, superior temporal gyrus, insula and inferior frontal regions that

forms the social perceptual system (Pelphrey et al., 2004). This important neuronal system appears to be underconnected in this case.

EFFECTIVE CONNECTIVITY AS MEASURED BY GRANGER CAUSALITY

One of the critiques of other coherence methods has been that they are largely based on the concept of correlation or similarity. Even sLORETA coherence is still the similarity between sources of EEG activity. An advanced statistical technique for investigated directed causation that uses multiple autoregressive analyses is Granger causality and its related concepts of partial directed coherences (Seth, 2010). Granger causality analysis (GCA) is a method for investigating whether one time series can correctly forecast another (Bressler and Seth, 2010). Granger causality (GC) is a data-driven approach based on linear regressive models and requires only a few basic assumptions about the original data statistics. Recently in neuroscience applications, GC has been used to explore causal dependencies between brain regions by investigating directed information flow or causality in the brain. It uses the error prediction of autoregressive (AR) or multi-variant autoregressive (MAR) models to estimate if a brain process is a Granger-cause of another brain process.

METHODS

To perform such an analysis on this same EEG data stream as used in the two examples above, we utilized the SIFT (Source

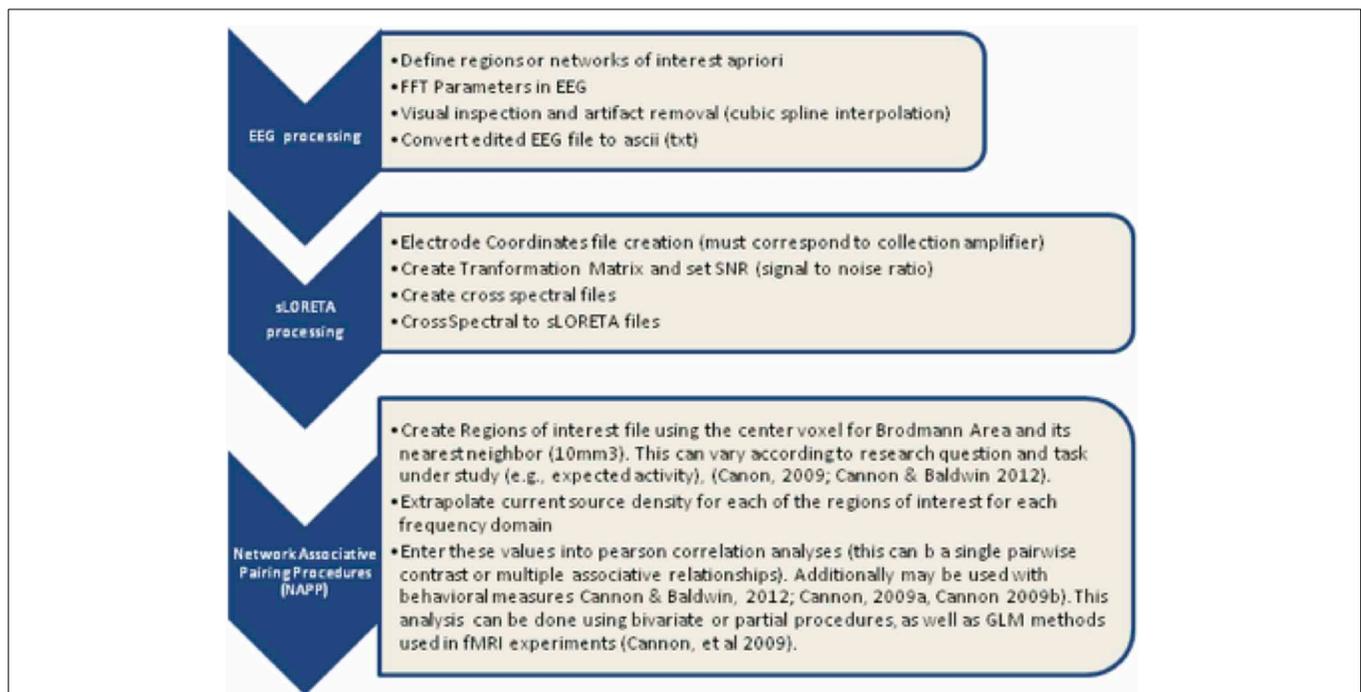
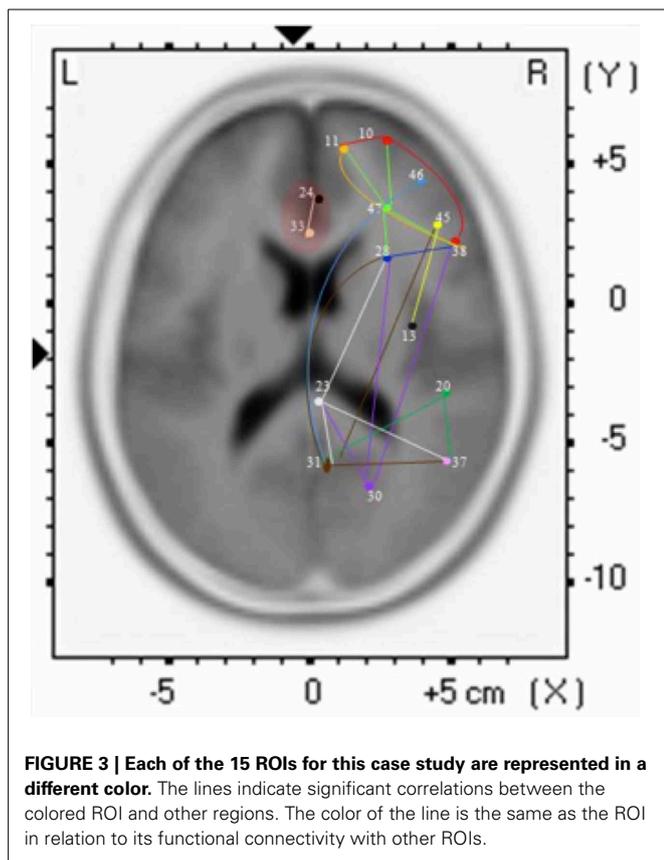


FIGURE 2 | Procedure to examine the associations between the center voxel within a specified Brodmann Area (BA) and its nearest neighbor (10 mm³). Listed in the figure from **top to bottom** are the steps used to process EEG data and create the correlation maps between regions of interest (ROIs). In short, EEG data must be processed first with careful

attention given to artifact contamination and its potential influence across all steps of the sLORETA procedures. The next step is to create the sLORETA files in order to extract the CSD at specified ROIs. Finally, using any statistical program the correlations between the ROI, or networks of interest can be contrasted for functional associations.



Information Flow Toolbox) toolbox from EEGLAB v.12 (Delorme et al., 2011). A key aspect of SIFT is that it focuses on estimating and visualizing multivariate effective connectivity in the source domain rather than between scalp electrode signals. This should allow us to achieve finer spatial localization of the network components while minimizing the challenging signal processing confounds produced by broad volume conduction from “neural” sources to the scalp electrodes. From our eyes open resting EEG data we have virtually epoched this stream into 1-s segments. Independent Component Analysis was then used to extract unique, independent components from the data. To fit multiple component dipoles and determine their locations DIPFIT toolbox was then applied. Then by investigating the dipole locations and the components topographical maps, only good “neural” components that are related to neural process in the brain have been included for further processing. These data were then fit into a MAR model using Vieira-Morf algorithm. For our data the model and after some trials and errors and model validation process, the MAR model order has been set to 5. In addition, the frequency band of interest has been selected from 1 to 30 Hz and the most obvious connectivity measure was Granger-Geweke Causality (GGC).

These methods of operation are summarized in **Figure 4**. This takes the EEG data from sensory to source space via independent component analysis and dipole localization. This diminishes the issue of volume conduction (see Astolfi et al., 2007; Akalin Acar and Makeig, 2013). Once dipole localization has been performed, these data are subjected to MVAR and Granger Causality

(GC) analysis as presented above. Within a reasonable range of values, changes in model order may show little effect on the spectral density (and by extension coherence) (e.g., see Florian and Pfurtscheller, 1995). Our model order has been based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) criteria to maximize model effects. Statistically, the critical issue for GC is the ratio between the number of independent observations (i.e., samples) and the model complexity (i.e., number of parameters). If the number of observations is large relative to the number of parameters then the model order selection criteria are still valid. If the number of observations is small, then we might run into problems with AIC and other asymptotic estimators, but there are corrections for that (corrected akaike information criterion). In our data set (case epoching), we have plenty of data available and the ratio of observations [total data samples within a time window (x trials)] to parameters is >40 suggesting that we have a valid model using AIC (Burnham, 2004).

RESULTS

Our findings for this case are presented in **Figure 5**. This, again demonstrates regions of over and under-connectivity. There appear to be several regions of heightened causality whose major influence is only toward close neighbors. This includes regions of the prefrontal cortex, anterior cingulate, and bilateral inferior parietal lobules. In each instance, these regions are somewhat isolated from each other and other important ICs as well. What is also clear is that there are long connections throughout the right hemisphere that are largely under-connected. These span as far away as the cuneus to the inferior frontal gyrus and include regions of the temporal lobes and underlying areas such as the fusiform gyrus and superior temporal gyrus.

COMPARISON OF COHERENCE TECHNIQUES

While it has not been shown, a pairwise coherence analysis of this case has shown very few significant coherence anomalies. The ones that are present include frontal hypoconnectivity and bilateral occipital-temporal hypoconnectivities. This is the opposite of what is shown in the multivariate analyses. All forms of multivariate analysis shown have suggested a combination of local hyperconnectivity and long distance hypoconnectivity across right frontal to posterior temporolimbic regions. This, in this case, clearly shows a difference between pairwise and multivariate estimates.

Comparing these to know structural connectivity was possible in this case in the form of MR-DTI analysis within this same system of concern (mirror neuron system). This suggests the presence of prefrontal and anterior cingulate hyperconnectivity and dramatic hypoconnectivity from frontal to temporolimbic regions. Comparing this to the multivariate analyses is interesting as there is similarity across all of these. The resemblance of these measures of functional connectivity to the reality of structural connectivity in this case is seen in its' greatest detail in multivariate measures that localize to source space (sLoreta, SIFT GC). As such, one limitation of the first method (Hudspeth NREP) is that it does not source localize activity prior to generating eigenimages of sensory covariances. GC has certain possible advantages including measuring the degree, directionality of connectivity,

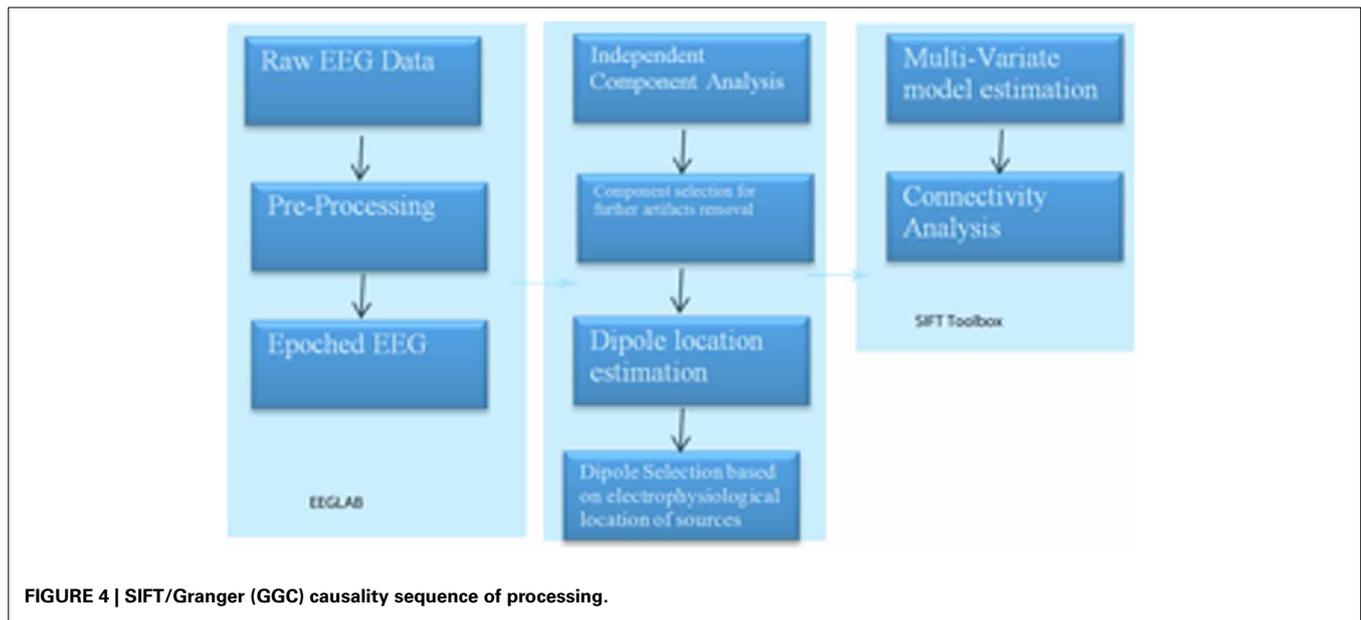


FIGURE 4 | SIFT/Granger (GGC) causality sequence of processing.

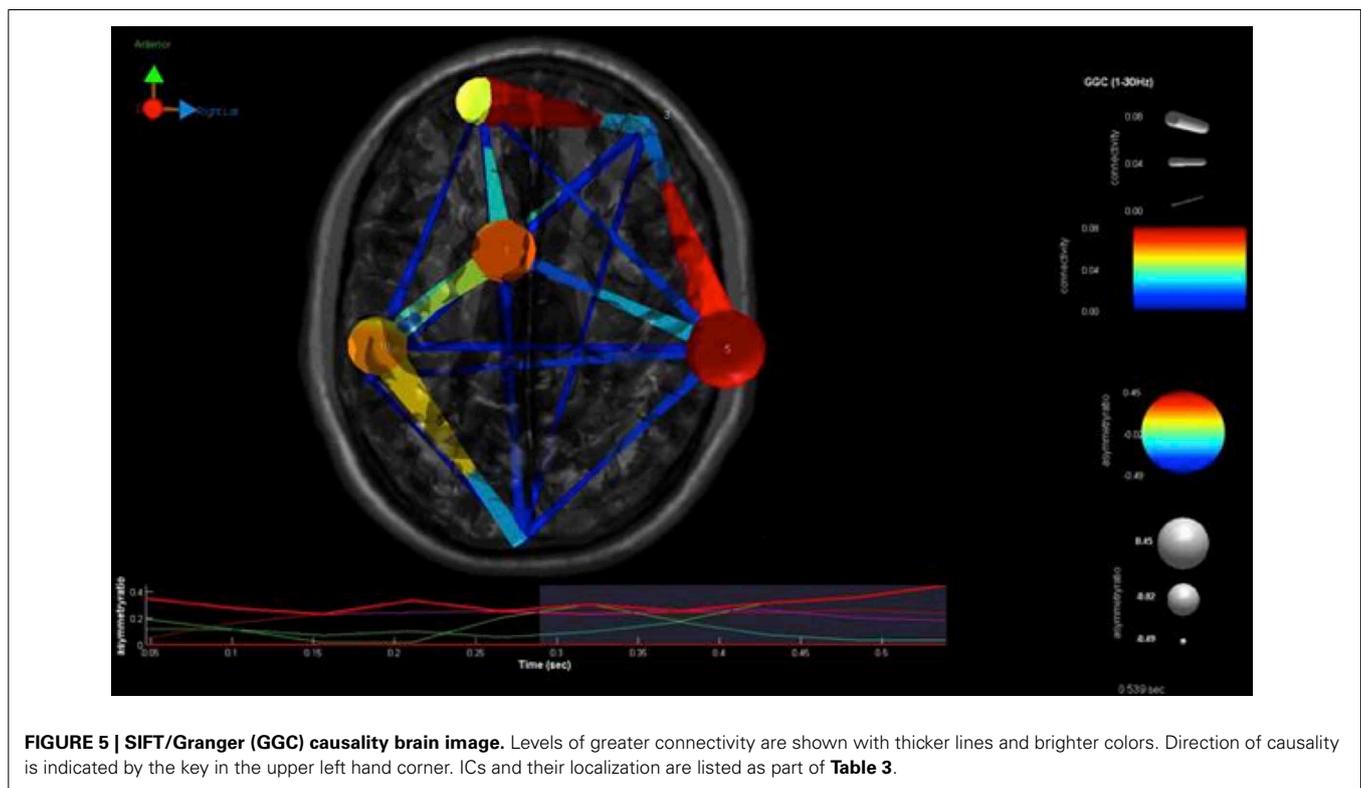


FIGURE 5 | SIFT/Granger (GGC) causality brain image. Levels of greater connectivity are shown with thicker lines and brighter colors. Direction of causality is indicated by the key in the upper left hand corner. ICs and their localization are listed as part of **Table 3**.

reciprocal influences and localization to regions that are deeper than is possible with sLoreta. It should be recalled that these observations are based on theory and one a single case study. Clearly, much more research is needed in this area of study.

DISCUSSION

Neuroimaging technologies and research has shown that autism is largely a disorder of neuronal connectivity. While advanced work

is being done with fMRI, MRI-DTI, SPECT and other forms of structural and functional connectivity analyses, the use of EEG for these purposes is of additional great utility. Cantor et al. (1986) were the first to examine the utility of pairwise coherence measures for depicting connectivity impairments in autism. Since that time research has shown a combination of mixed over and under-connectivity that is at the heart of the primary symptoms of this multifaceted disorder. Nevertheless, there is reason

Table 3 | SIFT/GCC maximal values between ICs.

From To	1	2	3	5	8	9	10	15	18	19
1		0.57	0.50	0.59	0.21	0.22	0.89	0.14	0.36	0.12
2	0.36		0.49	1.51	0.26	0.10	0.50	0.15	0.11	0.28
3	0.04	1.09		0.15	0.52	0.1	0.28	0.10	0.24	0.80
5	0.85	1.31	0.39		0.13	0.09	0.34	0.31	0.05	0.84
8	0.61	0.51	0.82	0.2		0.38	0.99	0.29	1.04	0.13
9	0.24	0.29	0.24	0.08	0.28		0.48	1.22	0.29	0.17
10	1.35	0.35	0.46	0.19	0.72	0.19		0.38	0.92	0.48
15	0.30	0.26	0.41	0.11	0.34	1.07	0.87		0.30	0.15
18	0.39	0.08	0.74	0.11	1.18	0.26	1.87	0.17		0.29
19	0.40	0.66	2.08	2.39	0.31	0.19	1.32	0.18	0.72	

Independent components included: 1 (Brodmann area (BA) 32; Anterior Cingulate), 2 (BA 10; Middle Frontal Gyrus), 3 (BA 40; Inferior Parietal Lobule), 5 (BA 10; Middle Frontal Gyrus), 8 (BA 37; Fusiform Gyrus), 9 (BA 19; Lingual Gyrus), 10 (BA 40; Inferior Parietal Lobule), 15 (BA 22; Superior Temporal Gyrus), 18 (BA 18; Cuneus), and 19 (BA 10; Middle Frontal Gyrus).

to believe that these simplistic pairwise measurements under represent the true and quite complicated picture of connectivity anomalies in these persons. We have presented three different forms of multivariate connectivity analysis with increasing levels of sophistication. These all seem able to capture the complexity of such cases and certainly moreso than pairwise estimates have. There does appear to be a value in using measures that localize the source of EEG activity and judge coherence from these sources. Further, the promise of using MVAR advanced statistical methods to judge effective connectivity and causation is exciting.

Clearly, there is much work to be done to further the scientific underpinnings of these approaches. Future work should extend these forms of analysis to greater sample sizes of autistic children and adults to judge their validity and utility. Comparing findings from autistics to other diagnostic and typically developing samples will be crucial. Lastly, the true value of any form of assessment for autistic children may be in it's applicability to further treatment outcomes for these children. Coben (2013) has shown that such metrics may be used to engineer more effective treatment plans than traditional neurofeedback with impressive outcomes as a result. It is hoped that advancements with such assessment techniques will further sharpen such treatment successes and decrease durations of treatment.

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