

Resting-state QEEG Neuro-Biomarkers for Diagnosis and Treatment Planning of Autism Spectrum Disorders

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Abstract

Background: Autism Spectrum Disorder (ASD) is a combination of complex neurodevelopment disabilities. Early resting-state EEG investigations of autism failed to identify consistent patterns of atypical neural activity. The evidence for the U-shaped profile of electrophysiological power alterations in ASD is primarily supportive, but a more hypothesis-driven effort is needed to confirm and validate it.

Aim of study: The primary objective of the present study was to investigate the resting-state QEEG neuro-biomarkers by amplitude analysis as a diagnostic tool for autistic children, compared with a normative group while recording qEEG during an eyes-open condition.

Patients and Methods: After excluding those with less than one-minute artifact-free EEG data or too many artifacts, the final participants were ($N = 34$) autistic children. The age range was 2-11 years (*mean age* $6.235 \pm SD 2.7198$ years), including 30 males (*mean age* $6.1667 \pm SD 2.730$ years) and four females (*mean age* $6.75 \pm SD 2.986$ years). For the qEEG recording, BrainMaster Discovery 20 module and BrainAvatar 4.0 Discovery (Acquisition software) were used.

Results: After calculating and analyzing all the QEEG data, the findings were categorized and confirmed the U-shaped power profile as an autism signature and as a diagnostic sign, characterized by excessive absolute power in low-frequencies (delta, theta) and high-frequencies bands (beta, hiBeta) and reduced absolute-power in a midrange frequency band (alpha).

Conclusions: Recent literature and our findings have shown that ASD individuals have disturbances of neural connectivity. Neurofeedback (NFB) treatment seems to be an excellent approach to regulating such disorders when using QEEG neuro-biomarkers as a part of treatment planning.

Keywords: Autism Spectrum Disorder (ASD), Resting-state QEEG, Neuro-Biomarkers, Autism Signature, Quantitative Electroencephalography, U-shaped power profile.

Introduction

Autism Spectrum Disorder (ASD) is a complicated neurodevelopmental disability that can clinically be characterized by impairments in language communication, various cognitive deficiencies, and lessened social interaction. Furthermore, it is characterized by repetitive, stereo-typed, and restricted patterns of behaviors, activities, and interests ^(1,2).

Symptoms of ASD usually appear in early childhood ⁽³⁾ and can be assessed and diagnosed in children as young as 1.5 years old ⁽⁴⁾; the American Academy of Pediatrics (AAP) recommends developmental screening by the age of two years of all children. Nevertheless, many children – specifically those with only mild autism or limited speech delays may not be identified until they are of school-age ⁽⁵⁾.

Despite extensive research and investigations, and advancement in recognizing pathophysiological and etiological mechanisms, the exact causes of ASD remain unknown, limited, and poorly comprehended ^(2,6). Nonetheless, it is a highly prevalent disorder impacting children and keeps increasing to be the most increased prevalence rate, indicating a much higher prevalence than previously thought⁽⁷⁻¹⁰⁾. As estimated by the Centers for Disease Control and Prevention (CDC)⁽¹¹⁾ and Autism and Developmental Disabilities Monitoring (ADDM) Network, the prevalence rate for ASD is 18.5 per 1,000, i.e., 1 in 54 children, and ASD was 4.3 times as prevalent among boys as among girls ^(11,12). In 2021, the CDC changed the prevalence to 1 in 44 (2.3%) in children aged eight years ⁽¹³⁾

Diagnosis and assessment of ASD: Improvements in the investigation of early diagnosis have resulted in the more initial diagnosis of autism ⁽¹⁴⁾. A diagnosis accurately describes a child's difficulties ⁽¹⁵⁾. Accordingly, reliable and valid

diagnostic approaches are essential to help specialists make proper assessments and diagnoses of autism ⁽¹⁶⁾. Moreover, a diagnosis can sometimes help make prognostic statements about the future of the child's health ⁽¹⁵⁾.

The diagnosis and assessment of autism can be made in various age groups. Even though some investigators and scientists from different locations worldwide also indicated that autism already exists at birthtime. Still, it is very demanding to form an earlier diagnosis ⁽¹⁷⁾. Regardless, there are no consistent universal instrumentations for evaluating and diagnosing autism, but the clinical diagnosis by The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) ⁽¹⁸⁾, and even if there existed, not each and every country has the adequate resources to manage such procedures ⁽¹⁹⁾. This can lead to consideration and explain the various rates of autism prevalence worldwide.

EEG and QEEG irregularities in autistic children: Electroencephalo-graphy (EEG) has been confirmed to be an exceptional instrument for studying complex neurotic and psychiatric disorders ^(20,21). The EEG characteristics of frequency, amplitude and coherence during numerous tasks or conditions can be identified and analyzed quantitatively, i.e., the brain's activities can be recognized under different tasks and assessed from a more exhaustive viewpoint⁽²²⁾.

Quantitative EEG (QEEG, brain mapping, or mind mapping) is considered an assessment approach designed to identify abnormalities, and it can be applied to analyze dysregulation in brain functions and brainwaves ⁽²³⁻²⁵⁾. Johnstone and Gunkelman ⁽²⁶⁾ stated that QEEG assessment "refers to signal processing and extraction of features from the EEG signal" ⁽²²⁾. Until lately, no one could

pinpoint any “biomarkers” for ASD. QEEG can provide a newfound physiological means for assessing, studying, diagnosing, and a better understanding the autistic children’s brains ⁽²⁴⁾.

QEEG and neurofeedback treatment

QEEG was one of the earliest methods that have been used for assessing autistic children, for evaluating underlying neurophysiological patterns associated with the symptoms and difficulties ^(27,28). Numerous studies have demonstrated EEG’s potential usefulness and advantages as a neuro-biomarker related to the efficacy of treatment ^(29,30). QEEG is considered the first stage in neurofeedback therapy. As a valuable diagnostic tool, it can evaluate and identify learning disabilities, depression, ADHD, anxiety, OCD, seizure disorders, and other disorders ⁽²⁴⁾.

Neurofeedback (NFB) (sometimes referred to as EEG biofeedback) is a treatment approach designed to let the clients control their brainwaves’ oscillation and improve their dysregulated brainwave patterns by utilizing a device that delivers information about brainwave activity. The main aim of the NFB technique is to enhance cognitive or behavioral processes related to brainwave activity. The NFB treatment approach, despite that available for a while, is swiftly earning attention and interest as a treatment and intervention approach for many disorders ⁽³¹⁻³⁴⁾. Present evidence displays that the approach may also be applied positively in the management of autism, as the QEEG investigations indicate under- and over-brain connectivity ⁽³⁾. A wide variety of significant EEG differences associated with ASD have been reported ^(27,35-37), a significant improvement in autism behaviors and symptoms ^(3,37,38), and symptoms benefited include; seizures ⁽³⁹⁻⁴¹⁾, hyperactivity ^(42,43), attention problems

^(44,45), anxiety ⁽⁴⁶⁾, impulsivity, inattention, and response variability ^(47,48), and some executive test performance ^(49,50).

Resting-state QEEG discoveries in autism:

Resting-state QEEG investigations are usually utilized to monitor brainwave frequencies in the absence of sensory stimulation or overt task performance and to identify anomalies, which evoked potential research investigations, the most extensively used methods in QEEG studies with autism, are not well convenient ⁽⁵¹⁾. Usually, resting-state methods do not include any response from the patients. This component is predominantly hopeful for investigating more severely impaired and younger subjects who may not be capable of accomplishing tasks correctly due to physical, developmental, or cognitive challenges. This approach is essential for investigating the irregular maturational path in autism through the early stages of childhood ⁽²⁾. The investigations on resting-state QEEG in typically-developed subjects show increased alpha (α) power and coherence in individuals with autism ⁽⁵²⁾, in addition to reduced power in low-frequency bands (delta Δ , theta θ) in adults relative to children ⁽⁵³⁾. No resting-state EEG research studies have investigated ASD associated with the co-occurring medical, developmental, psychiatric, and neurological disorders ⁽⁵⁴⁾.

Resting-state QEEG investigations have indicated that 20% of autistic subjects show epileptiform discharges at rest, generally without any apparent seizures ^(55,56). Higher rates of epileptiform activity have also been noticed in sleep studies; e.g., Chez, Chang ⁽⁵⁷⁾ said that 61% of autistic patients with no clinical history of seizures showed epileptiform anomalies. Heunis, Aldrich ⁽⁵⁴⁾ stated that 30% of individuals with ASD have epilepsy. Moreover, resting-state QEEG

data has promise as an assessment and method for monitoring prognosis and treatment follow-up ⁽²⁾. Furthermore, experimental studies recommend that increased resting-state power of gamma fluctuations is associated with autism ⁽⁵⁸⁾.

Newborns at high risk for autism show unique EEG patterns before the onset of the complete disorder, highlighting its potential utility as a neuro-biomarker before behavioral exhibitions of autism emerge ⁽⁵⁹⁾. Even though investigations using qEEG biomarkers in autism clinical trials have mainly focused on theta and alpha activity, beta-band activity abnormalities (13–30 Hz) relevant to ASD have been reported ⁽⁶⁰⁻⁶⁷⁾.

Pineda, Brang ⁽⁶⁸⁾ reported that autistic patients who undergo NFB sessions on management of the alpha-or mu-band showed reduced mu power and coherence, in addition to improved attention and reduced scores on some autism tests ⁽⁶⁹⁾.

Early resting-state QEEG investigations of autism failed to recognize reliable shapes of atypical neural activity⁽⁷⁰⁻⁷⁴⁾. The documented prevalence of EEG anomalies in autistic subjects varied significantly among investigations, which may be due to the absence of standardized diagnostic methodologies at the time or to the limits in EEG data acquisition technology (e.g., number of electrodes) and analysis (e.g., different approaches to quantification, and qualitative conclusions).

Regardless of these unique benefits, few investigations have used resting-state QEEG to investigate the brain alterations in autistic individuals. As stated by Wang, Barstein ⁽²⁾, the available evidence for the model of a U-shaped pattern profile of electrophysiological power alterations in autistic subjects, i.e., increased the low power spectrum, while a decrease of the power in the midst frequencies, as

mentioned above, is generally supportive. However, the additional hypothesis-driven effort is essential to validate and confirm it. Thus, the present research study aimed to investigate the resting-state QEEG neuro-biomarkers by amplitude analysis as a diagnostic tool for autistic children compared to a normative group while recording EEG during an eyes-open condition.

Methods

The study design of the current research study is to provide opportunities for enhancing the understanding of ASD biomarkers in terms of biomarker data acquisition and clinical data collection.

A total of 45 autistic children were selected from the outpatient clinic of the Iraqi Association for Psychotherapy (IAP), Baghdad–Iraq, who were blindly clinically assessed and diagnosed by two specialists; a psychiatrist and a doctoral-level licensed clinical psychologist, free of drug treatment, based on the following inclusion criteria:

Inclusion Criteria: According to the “International Statistical Classification of Mental Disorders [ICD-10]” ^(75,76) and the “Diagnostic & Statistical Manual of Mental Disorders 5th edition [DSM-5]”, the research sample had a documented diagnosis code of ASD; “Level 1: Requiring support.”, “Level 2: Requiring substantial support.” or “Level 3: Requiring very substantial support.”⁽¹⁸⁾, as stated in the records, patient database, and case folders.

According to the standards recommended by Thatcher ⁽⁷⁷⁾, only data that had at least one minute of artifact-free EEG data were selected. After excluding those with less than one-minute artifact-free EEG data or too many artifacts, the final participants were ($N = 34$) autistic children. The age range was 2-11 years (*mean* age $6.235 \pm SD 2.7198$ years), including 30 males (*mean* age $6.1667 \pm$

SD 2.730 years) and four females (*mean* age $6.75 \pm SD 2.986$ years), gender ratio (male/female) was 7/1 (Table 1). The normative sample was recruited from the qEEG-Pro database ⁽¹⁾.

All parents/guardians of the participants were asked to read, complete, sign, and dispatch the Consent Form to the principal investigator. Participants who had a previous history of mental retardation, epileptic symptoms, neurological problems, or abnormal developmental milestones other than those conditions or symptoms directly related to autism were excluded from the study.

For the QEEG recording, BrainMaster Discovery 20 module and BrainAvatar 4.0 Discovery (Acquisition software) (BrainMaster Technologies, Inc.) were used (Figure 1). Additionally, *Autism Spectrum Rating Scales (ASRS)* (78-80) were used to assess and diagnose ASD.

Beginning on January 13th, 2020, and ending on March 15th, 2020, the investigator interviewed the parents of the ASD patients to select 45 children having autism to be the subjects of the current research study, where parents/guardians were asked to fill out the demographic data form, the child case history, along with the Informed consent.

Collecting an EEG record typically takes about 60–90 minutes. Since some children with autism have some sensitivity issues, it has been recommended that parents/ guardians bring their child to the examination office at a convenient time prior to the examination session to familiarize the child with the procedure settings and the clinicians. Moreover, instruction is delivered to the family to wash and clean the child's hair before the EEG data acquisition (the hair should be dry by the time of the recording). Moreover, any hair sprays, mousses, and

gels are forbidden.

EEG recording was done in a laboratory that belongs to the Iraqi Association for Psychotherapy. Each child was tested individually in white-noise-free controlled rooms, with controlled temperatures from 24°-26°C. One family member and a trained specialist were present during the EEG recording sessions and the in-charge clinician. All subjects were seated in a comfortable chair. Before the EEG session, the child's parents were given a brief verbal explanation and a written description of the procedure. Informed consent was collected from the parents/guardians of all subjects. Before the EEG assessment, after the parents had indicated that they understood the process, an EEG cap with 20 electrodes, based on the International "10–20" system ⁽⁸¹⁾: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. Referenced to linked-ears were positioned on the head of each child. Then we used a NuPrep gel to carefully clean and prepare the skin, scalps, and ears of the autistic child from any grease and dirt. Then we applied a conductive gel to each electrode hole in the EEG-Cap and connected it to the device's input of the digital EEG (BrainMaster Discovery Acquisition) device.

Usually, it is very challenging to perform EEG recording with autistic children, either in the eyes-open (EO) or eyes-closed (EC) resting condition, as autistic children are typically uncooperative during the investigational session ⁽⁸²⁾. It is challenging to do the EEG-recording due to their restless hyperactivity, lower intellectual abilities, and refusal of sensory contact ⁽⁸³⁾. Accordingly, our EEG recordings were conducted during the (EO) condition. During recordings, instructions were given to all the subjects to sit, as far as they could, in a state of calm, quiet, natural, eyes-

open rest (blinking allowed). To keep the participants engaged and conscious during the session, they were instructed to watch on a computer monitor, which displayed some swimming fishes in various colors or frogs. We recorded (8-10 min.) of uninterrupted EEG signals in the (EO) condition.

Each raw EEG data file was uploaded to the qEEG-Pro website (QEEG Professionals, The Netherlands: <https://q EEG.pro/>) and using the Standardized Artifact Rejection Algorithm (S.A.R.A.)⁽⁸⁴⁾.

This process eliminates segments from an EEG recording likely due to other sources, such as muscle tension, eye blinks, and other artifacts. Using such an automated process ensures that each file is handled in the same form and lessens the possibility of bias in the artifact elimination process. Raw data files were then visually inspected, and according to the standards proposed to yield a reliable measure⁽⁷⁷⁾, only recordings with at least one minute of artifact-free QEEG data were selected.

After the automatic processing of the digital data, it is compared statistically to an age and gender matched normative database banks of typically-developed subjects to produce a profile of irregularities. These database banks rely on individuals who have been regarded as typically-developed subjects based on standard screening and surveying tools for medical, behavioral, and psychological history⁽²²⁾. Consequently, these QEEG reports become the basis for our further quantitative analysis.

Using Microsoft Excel⁽³⁶⁵⁾ and Statistical Package for the Social Sciences (SPSS) v.23.0, all data were analyzed to determine whether the research would fulfill its aims. The researcher checked the data void of errors; then, the 'Brain Discovery' software for analyzing and extracting the results.

Normal distribution for absolute values was achieved through log-natural transformations and confirmed with the *ShapiroWilk's W* test. Descriptive statistics, a series of *t*-tests (two-sample assuming equal variances), and a series of *t*-tests (one-sample test) was conducted to analyze study data, the gender differences (male and female), and age levels (2-11 years old). *Cohen's d*⁽⁸⁵⁾ will also be used to measure the *Effect size* of our outcomes.

Results

Our study sample included ($N=34$) autistic children. The age range was 2-11 years (*mean* age $6.235 \pm SD 2.7198$ years), including 30 males (*mean* age $6.1667 \pm SD 2.730$ years) and four females (*mean* age $6.75 \pm SD 2.986$ years). Clinical evaluation, and the *Autism Spectrum Rating Scales (ASRS)*⁽⁷⁸⁻⁸⁰⁾, confirmed ASD.

To characterize the resting state QEEG, the oscillatory patterns were broken down into bands of frequencies that share physiological properties. The following EEG measures were computed: relative power, total power, percent coherence, and amplitude asymmetry⁽⁸⁵⁾.

Descriptive statistics were calculated for each Z-score (Table 2). The absolute power of each frequency band for the participants was averaged. The topographic maps representing the absolute powers of Z-Delta, Z-Theta, Z-Alpha, Z-Beta, and Z-hiBeta are presented in Fig. 2.

In the present research study, each frequency band's absolute and relative power among the 19 channels for ASD samples were averaged. The topographic maps demonstrate the mean absolute and relative powers of the delta, theta, alpha, beta, and hiBeta. After calculating and analyzing all the QEEG data, the findings of this research study were categorized under the U-shaped power profile, as

discovered by (2), characterized by excessive absolute power in low frequencies (delta, theta) and high-frequencies bands (beta, hiBeta) and reduced absolute-power in a midrange frequency band (alpha) comparing to the normative group. In the experimental ASD group, QEEG presented remarkably increased electrical potentials through all sensors. The irregularly low activity in the average alpha spectrum is outstanding. With regards to connectivity, the main findings showed occipital lobe hyperconnectivity as well as hypo-connectivity of the frontal region to other regions of the brain and diminished connectivity in language areas.

Figure 3 displayed the main general characteristics of qEEG brain mapping, along with Z-scores in two subjects of our sample. Absolute power for delta and theta increases. Moreover, the power of beta and hiBeta brainwaves, due to high nervousness, was also increased in our cases. It is essential to consider that, mostly, alpha brainwaves are positively correlated to cortical information processing, i.e. cognitive abilities. Children with neurological and developmental disorders such as autism showed significantly more delta and theta but less alpha power, corresponding to their cognitive impairment.

The amount of energy in μV^2 (absolute power) of each frequency band for all the ASD groups was calculated and averaged for all the Z-scores at each electrode site (Laplacian Montage), then we used only the Z-scores for each band (Z-Delta, Z-Theta, Z-Alpha, Z-Beta, and Z-hiBeta) for all the study sample (34 children). All measures showed a U-Shaped power profile (Table 3).

Then, a series of *t*-tests (one-sample tests) for all the Z-scores were calculated, and it was found that all the results were significant at ($p < 0.001$). The results showed a U-shape power profile in all the Z-Scores curves (Figure 4).

After calculating the total average for each band for Z-Scores for (Z-Delta, Z-Theta, Z-Alpha, Z-Beta, and Z-hiBeta) for all the study samples, a U-Shaped power profile, which represents a QEEG neuro-biomarkers in ASD, i.e., Autism Signature has been found (Figure 5).

Finally, *Cohen's d* ⁽⁸⁶⁾ to measure the *Effect size* of the results was calculated (see Table 4). It has been found that Z-Delta (measured by Laplacian Montage) significantly differs from the delta brainwave of the Normative Group, *Effect Size (d) = 0.92*: large *effect size*), Z-Theta (measured by Laplacian Montage) significantly differs from the theta brainwave of the Normative Group, *Effect Size (d) = 0.819*: large *effect size*), Z-Alpha (measured by Laplacian Montage) significantly differ from the alpha brainwave of the Normative Group, *Effect Size (d) = 0.713*: medium-large *effect size*), Z-Beta (measured by Laplacian Montage) significantly differ from the beta brainwave of the Normative Group, *Effect Size (d) = 0.782*: medium-large *effect size*), and Z-hiBeta (measured by Laplacian Montage) significantly differ from the hiBeta brainwave of the Normative Group, *Effect Size (d) = 0.881*: large *effect size*).

Table 1: Descriptive statistics of (Ages) of all the study subjects of ASD children (females and males).

Descriptive statistics	Total Sample	Female	Male
Mean	6.235294118	6.75	6.166666667
Standard Error	0.466447918	1.493039406	0.498465077
Median	6	6	6
Mode	6	6	8
Standard Deviation	2.719835373	2.986078811	2.730205668
Sample Variance	7.397504456	8.916666667	7.454022989
Kurtosis	-0.94172445	2.602498035	-1.03949152
Skewness	0.178009534	1.380236621	0.106706849
Range	9	7	9
Minimum	2	4	2
Maximum	11	11	11
Sum	212	27	185
Count	34	4	30
Largest(1)	11	11	11
Smallest(1)	2	4	2
Confidence Level (95.0%)	0.948995425	4.75151774	1.019475551

Table 2 : Descriptive statistics of (Z-scores) of all the study subjects of ASD children (females and males).

Descriptive statistics	Z-Delta	Z-Theta	Z-Alpha	Z-Beta	Z-hiBeta
Mean	1.675232	0.8317337	0.6105263	0.8442724	1.4026315
Standard Error	0.123567	0.1016104	0.1045351	0.116998	0.1313472
Median	1.547368	0.7605263	0.6657894	0.8947368	1.3631578
Mode	2.021052	#N/A	#N/A	#N/A	0.5263157
Standard Deviation	0.720513	0.5924855	0.6095397	0.6822104	0.7658794
Sample Variance	0.519139	0.3510391	0.3715386	0.4654110	0.5865713
Kurtosis	1.664550	0.7969451	0.1781022	0.6401517	-0.2679363
Skewness	1.161626	0.4543409	-0.3939609	0.0318140	0.2643670
Range	3.310526	2.8	2.6736842	3.4052631	3.3368421
Minimum	0.521052	-0.363157	-0.8263157	-0.768421	-0.1684210
Maximum	3.831578	2.4368421	1.8473684	2.6368421	3.1684210
Sum	56.95789	28.278947	20.757894	28.705263	47.689473
Count	34	34	34	34	34
Largest(1)	3.831578	2.4368421	1.8473684	2.636842	3.1684210
Smallest(1)	0.521052	-0.363157	-0.8263157	-0.7684210	-0.1684210
Confidence Level (95.0%)	0.2513990	0.2067279	0.21267845	0.2380344	0.26722798

A Z-score is a value of the standard deviation from the mean of the normative group.

Table 3: The Z-scores for each band (Z-Delta, Z-Theta, Z-Alpha, Z-Beta, and Z-hiBeta) for each child for the whole study's sample according to their gender.

No.	Gender	Z-Delta	Z-Theta	Z-Alpha	Z-Beta	Z-hiBeta
1	Male	0.673684211	0.263157895	0.242105263	0.489473684	1.405263158
2	Male	1.031578947	0.736842105	0.5	0.731578947	1.168421053
3	Male	3.831578947	2.436842105	1.368421053	2.636842105	3.168421053
4	Male	1.194736842	0.978947368	0.936842105	0.963157895	1.189473684
5	Male	1.426315789	0.989473684	0.715789474	1.847368421	2.515789474
6	Male	3.121052632	1.184210526	0.7	0.363157895	0.784210526
7	Male	2.073684211	1.652631579	1.526315789	1.442105263	1.957894737
8	Female	1.942105263	0.873684211	1.1	1.657894737	2.157894737
9	Male	1.9	0.447368421	0.4	0.163157895	0.526315789
10	Male	3.194736842	1.542105263	1.847368421	1.615789474	2.884210526
11	Male	1.557894737	0.715789474	0.352631579	-0.06315789	0.310526316
12	Male	1.642105263	0.663157895	0.584210526	0.168421053	0.568421053
13	Male	1.536842105	0.747368421	0.768421053	0.773684211	1.321052632
14	Male	2.152631579	0.963157895	0.721052632	1.247368421	1.936842105
15	Male	1.357894737	0.589473684	0.394736842	1.357894737	2.389473684
16	Male	1.710526316	1.126315789	0.968421053	0.710526316	1.1
17	Male	1.457894737	1.2	1.273684211	1.268421053	1.731578947
18	Male	2.021052632	1.947368421	1.110526316	1.184210526	2.015789474
19	Male	1.021052632	0.221052632	0.289473684	1.047368421	0.852631579
20	Female	1.094736842	0.163157895	-0.25789473	0.852631579	1.952631579
21	Male	1.836842105	1.215789474	1.121052632	0.936842105	1.421052632
22	Male	1.615789474	0.905263158	0.484210526	1.173684211	1.805263158
23	Male	1.2	0.136842105	-0.10526315	0.231578947	0.568421053
24	Male	1.394736842	0.7	0.842105263	0.847368421	1.436842105
25	Male	2.710526316	0.715789474	-0.13157894	-0.10526315	0.689473684
26	Female	0.521052632	-0.36315789	-0.72631578	-0.27894736	0.526315789
27	Male	0.868421053	-0.23157894	-0.82631578	-0.76842105	-0.16842105
28	Male	2.221052632	1.731578947	1.436842105	1.610526316	2.078947368
29	Female	1.221052632	1.031578947	0.952631579	1.010526316	1.168421053
30	Male	2.021052632	0.310526316	-0.06842105	0.215789474	0.636842105
31	Male	1.063157895	0.205263158	0.168421053	0.457894737	1.052631579
32	Male	1.826315789	0.752631579	0.631578947	0.678947368	0.952631579
33	Male	1.121052632	0.768421053	0.394736842	1.026315789	1.726315789
34	Male	1.394736842	0.957894737	1.042105263	1.210526316	1.857894737

Table 4: *t*-test (one-sample test) results for all the Z-scores of all research study participants and the *Effect size* for each *t*-test.

	Z-Delta	Z-Theta	Z-Alpha	Z-Beta	Z-hiBeta
Mean	1.6752	0.8317	0.6105	0.8443	1.4026
Variance	0.7205	0.5925	0.6095	0.6822	0.7659
Stand. Dev.	0.8488	0.7697	0.7807	0.826	0.8752
N	34	34	34	34	34
T	13.5575	8.1853	5.8408	7.2162	10.6785
d.o.f	33	33	33	33	33
critical value	2.035	2.035	2.035	2.035	2.035
Cohen's d	4.72012	2.849755675	2.033505546	2.51236	3.717776498
Effect Size (r)	0.92076	0.818533536	0.712955982	0.78237	0.880656892



Figure 1: Brain Master Discovery 20 with Impedance Lid BrainAvatar 4.0 Discovery Acquisition system.

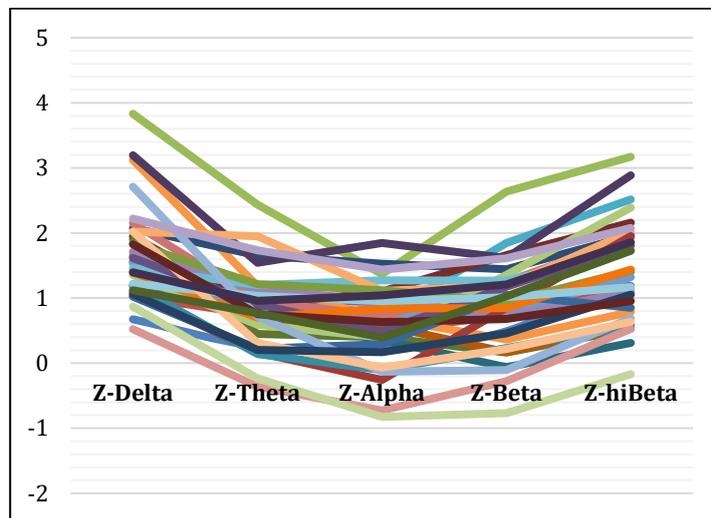


Figure 2: All the Absolute power of the frequency bands for the assessed ASD group.

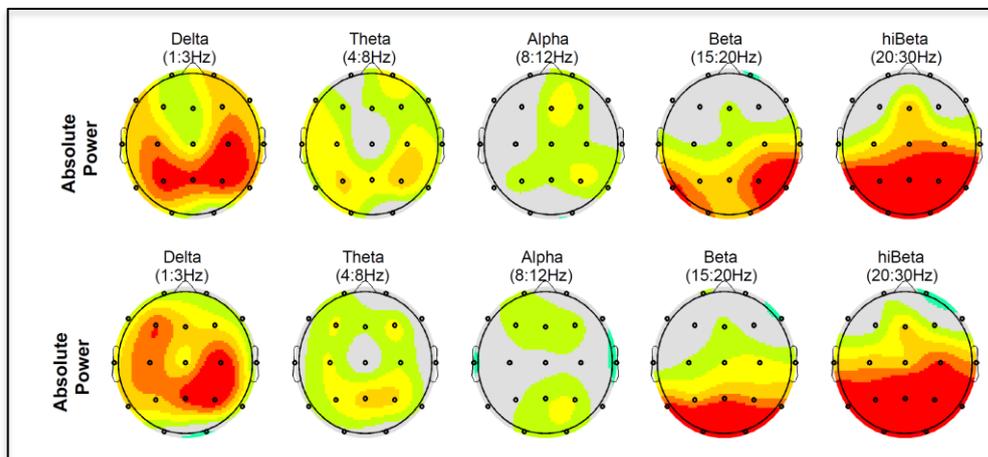


Figure 3: Summary information for absolute power for main brainwaves in two autistic children of our research.

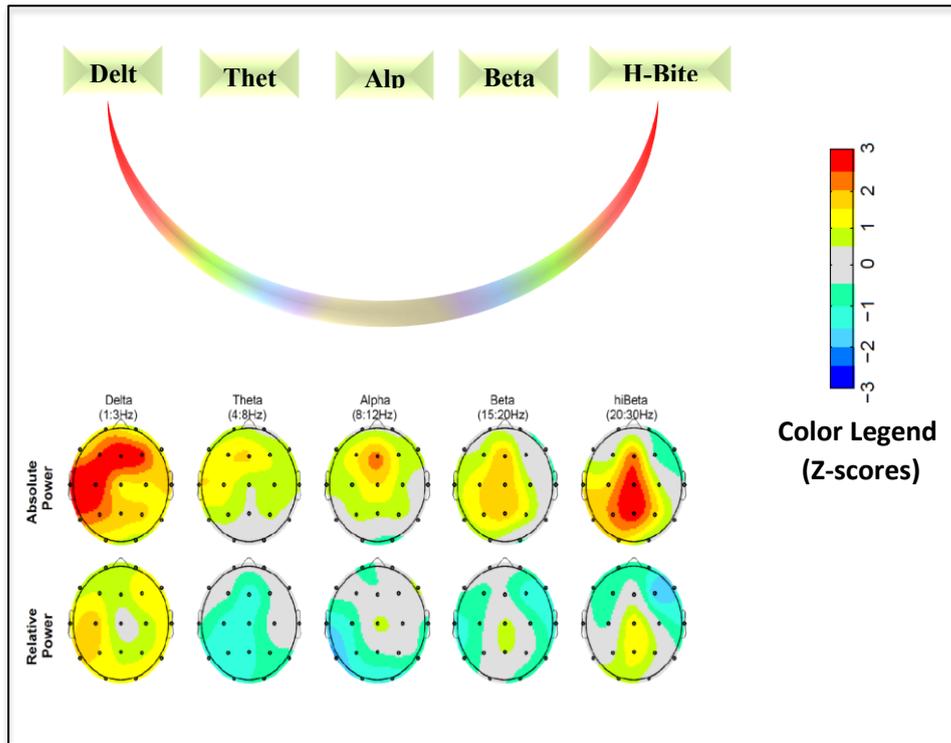


Figure 4: The U-Shape power profile as a final result of the resting-state QEEG neuro-biomarkers in autism spectrum disorders (Autism Signature).

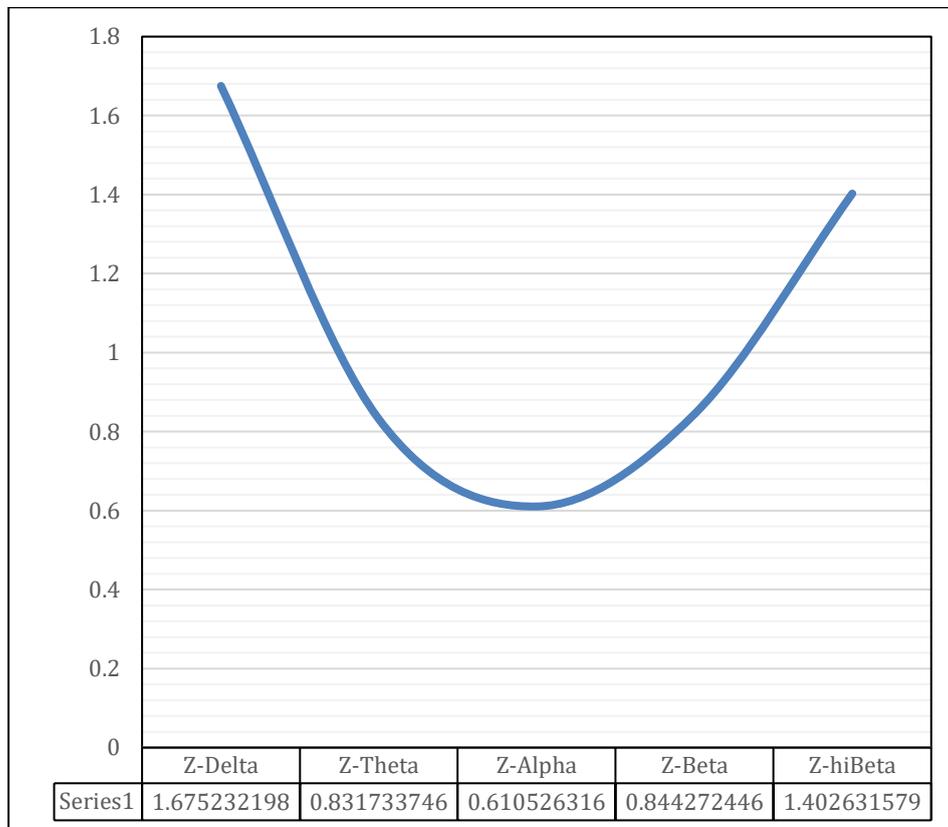


Figure 5: The U-shaped power profile as a final result of the resting-state QEEG neuro-biomarkers in autism spectrum disorders (Autism Signature).

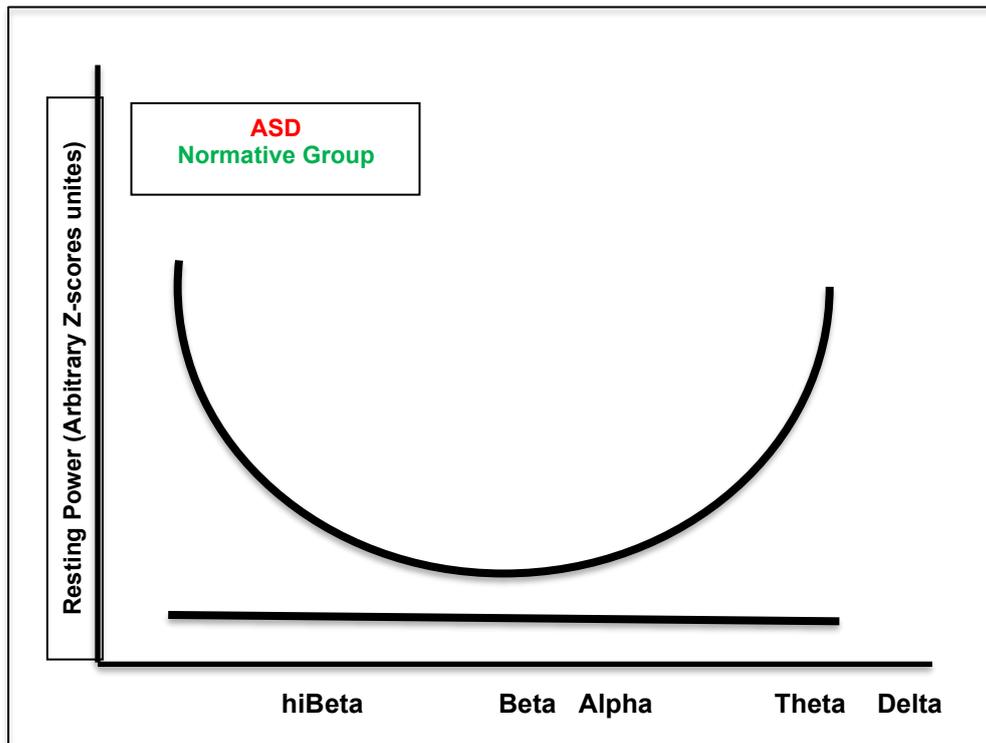


Figure 6: Illustration of the abnormal power pattern as a U-shaped profile in the ASD group compared to the normative group (Autism Signature).

Discussion

The findings of the present study have revealed that children with ASD demonstrated significantly excessive absolute power in low-frequencies (delta, theta) and high-frequencies bands (beta, hiBeta) and reduced absolute-power in a midrange frequency band (alpha) compared to the normative group, which may result from abnormal GABAergic tone in inhibitory circuits. This finding (U-shaped profile) is similar to results from Wang and his colleagues ⁽²⁾, but the current research disagrees with them regarding the differences between the ASD and the normative group profile, as the normative group in our study has a semi-straight line but not as an upside-down (U-shaped profile) (Figure 6). This pattern might indicate a unique QEEG endophenotype of the resting-state QEEG neuro-biomarkers in ASD. Additionally, these findings may explain some of the stereotypes,

hyperactivity, and repetitive behaviors in autistic children.

These results also disagree with Linden and colleagues who have studied subtypes of autism over the past twenty years ^(3,28,87). In (2004), Linden's paper identified four distinctive QEEG profiles of autism and two others for Asperger's syndrome ⁽⁸⁷⁾. Later, Coben, Linden ⁽³⁾, and recent studies extended the number of autism subtypes and have pinpointed six endophenotypes found in ASD. In addition to two more patterns specifically for Asperger's syndrome ^(22,24). However, this study discovered one unique pattern profile, as stated above.

Here, EEG power spectra increased delta and theta power in central and frontal areas of the brain, which was previously documented in autistic patients ^(83,88,89). These findings revealed a pattern of underconnectivity in autistic children, i.e., a decreased delta and theta coherence across the brain. Delta and theta

coherence were low across the frontal area, indicating the deficit in the executive functions in the frontal lobes of autistic children. Generally, delta and theta waves are presented at high levels during sleep stages; but in autistic children, they are abnormally high and constantly peak, even when awake⁽⁹⁰⁾. The excess in delta power has also been found in relative power^(88,91) and absolute power^(83,88,92).

High levels of theta waves may be related to a lack of attention and some depressive disorders. At the same time, a healthy level of delta waves is good for emotional connection, creativity, and intuition. Moreover, increased delta and theta waves activity was reported in schizophrenic patients compared to healthy controls⁽⁹³⁾. Accordingly, we can see some evidence of similarities in power spectra between schizophrenic and autistic patients. On the other hand, high delta and theta power activities in autistic children may be correlated with a lack of reading, deficiencies in other daily and educational activities, inaccuracy in reactions, and perceptual speed problems.

For this reason, these autistic children may have struggled to process all the incoming peripheral perceptual information adequately and fail in the tasks that require multiple cognitive processes⁽⁹⁴⁾. While reduced alpha power was also noted as well as irregular beta and gamma power by Kouijzer, van Schie⁽⁹⁵⁾, the decrease in alpha correlates with reduced limbic system activation in subcortical structures such as the midbrain, brainstem, and hypothalamus. High beta and gamma power in the sample of the present study may indicate a deficit in verbal learning performance. Generally, spectral changes in subjects with autism were more evident than in control normative subjects⁽⁸²⁾.

The impact of anxiety on alpha wave activity, in general, can be complicated, as

the present finding of decreased alpha in ASD is the opposite of what has been found by Cornew, L. et al. (2012)⁽⁹⁶⁾.

According to these results, QEEG can be used as a diagnostic and treatment planning tool for ASD. Nine previous studies reported the use of QEEG in ASD children; five used QEEG as a diagnostic neuro-biomarker, and four used QEEG in the course of ASD treatment^(82,97-104). Compared with other investigations, it is essential to consider that the resting-state QEEG was recorded in an eyes-open (EO) condition, which might clarify a decrease in the alpha activity. Additionally, autistic children showed significantly higher intrahemispheric long-range coherence in the left hemisphere than in the normative group. The ASD participants did not exhibit significant alterations comparing both hemispheres for the resting control condition.

Moreover, one of the limitations of our research study is the relatively small number of the research sample ($N=34$), although a detailed statistical power analysis processing showed that our research results were reliable and significant.

Conclusions

1. The outcomes are reassuring for developing a new essential and contributory technique for examining, assessing, and differential diagnosis of neurodevelopmental disorders such as autism.
2. No classical paper-based psychological tests and scales are required.
3. QEEG is more comfortable and not extended compared to some other techniques (for example, positron emission tomography (PET), computerized tomography CT), and potential clinical evaluation of neuropsychiatric disorders⁽¹⁰⁵⁾ has been evaluated.
4. It is essential to perform further data analysis for a more extensive research sample to represent the results better.

5. Evaluating and developing treatment, therapeutic, and training plans, according to the founded neurobiomarkers (signature), help autistic children and allow them to lead a healthy life.

6. The current results emphasize the hypothesis that autism signature can be found as a U-Shape power profile.

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