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Quantitative Electroencephalographic Abnormalities in children with Autism Spectrum Disorder in Relation to Behavioral and Language Dysfunction

A Thesis

Submitted to the council of College of Medicine/ University of Babylon in Partial Fulfillment of the Requirements for Degree of Master of Science in Medical Physiology

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بسم الله الرحمن الرحيم

{يرفع الله الذين آمنوا منكم

والذين أوتوا العلم درجات والله بما تعملون خبير}

صدق الله العلي العظيم

سورة المجادلة - الآية (11)

Supervisor Certificate

I certify that this thesis entitled **"Quantitative electroencephalography abnormalities in patients with Autism Spectrum Disorder in relation to behavioral and language dysfunction"** was carried out under my supervision at College of Medicine / University of Babylon, as a partial fulfillment of the requirements for the degree of ***"Master of Science in Medical Physiology".***

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Dedication

This project is dedicated to my family. A particular thanks to my beloved parents, thank you both for giving me strength to reach for the stars and chase my dreams, your words of support and push for tenacity still ring in my ears.

My sisters, and brother in law, you have made me stronger, better, and more fulfilled than I could have ever imagined.

To all my best friends, thank you for your understanding and encouragement in my many, many moments of crisis. Your friendship makes my life a wonderful experience.

This thesis is only a beginning of my journey…

SHAMS K.

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جمهورية العراق
وزارة التعليم العالي والبحث العلمي
كلية الطب- جامعه بابل

تغييرات كهربائية الدماغ الكمية لدى المصابين باضطراب طيف التوحد ومدى علاقتها بالمشاكل السلوكية واللغوية

رسالة مقدمة الى

كلية الطب- جامعه بابل

وهي جزء من متطلبات نيل درجة الماجستير في علم الفسلجة الطبية

من قبل

شمس كريم عبد حمادي الجبوري

بكالوريوس طب وجراحة عامة- كليه الطب جامعه بابل

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الخلاصة

اضطراب طيف التوحد هو مرض نمائي عصبي منتشر يصيب حوالي 16% من سكان العالم من الأطفال حيث يتم وصف التواصل الاجتماعي / التفاعل وأنماط السلوك المقيدة والمتكررة على أنها إعاقات أساسية في هذا الاضطراب. لا يزال الأصل والمسبب الرئيسي لهذا الاضطراب مجهولاً الى حد كبير بالرغم من الأبحاث المكثفة، وعدم وجود معلومات موثوقة حول المسببات لهذه المشاكل تحد من الخيارات المتاحة لعلاج مرض التوحد. من اجل فهم وظائف الدماغ المحددة في سلوك التوحد، استخدمت العديد من الأبحاث طرائق التصوير العصبي والفسيولوجية العصبية التي وجدت بدورها ان الأطفال المصابين بالتوحد لديهم نشاط دماغي غير عادي وأنماط اتصال مختلفة مرتبطة بسلوكيات التوحد الغير نمطية، ويعد فهم هذه النتائج وربطها بالنتائج التشريحية العصبية والاعراض السلوكية امراً بالغ الأهمية لفهم نشأة اضطراب طيف التوحد. يمكن قياس العمليات الفيسيولوجية العصبية وراء اضطرابات النمو العصبي باستخدام تخطيط كهربائية الدماغ الكمي، حيث يستطيع هذا الجهاز وعلى مدى نطاقات تردد موجات الدماغ المختلفة، ان يقوم بقياس الطاقة المطلقة، والطاقة النسبية، وعدم التناسق السعة، وتأخر الطور، بالإضافة الى جميع الأنماط الحرجة المطلوبة في الأداء العقلي الأمثل. كما يتميز جهاز تخطيط الدماغ الكمي بأنه اقل كلفة وأسهل في التنفيذ وغير مؤذ باي شكل من الاشكال مقارنة بطرائق التصوير العصبي الأخرى على سبيل المثال، ولقد تم اقتراحه كأداة تقييم سريرية محتملة للمشاكل العصبية والعقلية. علاوة على ذل تم اقتراح استخدام تخطيط الدماغ الكمي لتتبع ومراجعة نتائج العلاج لدى الأطفال المصابين باضطراب صيف التوحد.

تهدف هذه الدراسة الى اختبار وجود تغييرات او شذوذ في فعاليات الدماغ الكهربية ونوعها، واختبار إذا كانت هذه التغييرات مرتبطة بوجود اضطرابات السلوك واللغة المصاحبة لمرض التوحد ومرتبطة بشدة هذه التغييرات، بالإضافة الى اختبار إمكانية استخدام جهاز تخطيط الدماغ الكمي كأداة في تقدير مستوى شدة اضطراب طيف التوحد.

أجريت هذه الدراسة المقطعية في معاهد التوحد في مدينة الحلة خلال الفترة من سبتمبر 2021 حتى مارس 2022 وبلغ اجمالي عدد الأطفال المشاركين في الدراسة (53) طفلا تتراوح أعمارهم بين (3-12) عاما (41 ولدا و12 بنتا). وتم اختيار جميع الأطفال المشمولين بهذه الدراسة من مراكز التوحد بما في ذلك مركز الامام الحسين(ع) للتوحد، مركز بابل للتوحد والنطق، مركز ملاك الرحمة للتوحد، ومركز AUTISM للتوحد. ولقد تم تضمين جميع الأطفال المسجلين في هذه المراكز المذكورة

أعلاه واللذين استوفوا معايير التشخيص العالمية الخاصة بالتوحد والذين تم تشخيصهم مسبقا من قبل طبيب نفسي مختص. اما الأطفال المصابين بالصرع او افرازات الصرع في تخطيط كهربائية الدماغ حتى في غياب نوبات الصرع سريريا، او أولئك المصابين بحالات عصبية أخرى (مثل متلازمة داون والتصلب الدرني) بما في ذلك ضعف السمع او البصر او التخلف العقلي، او كانوا يتناولون ادوية تؤثر على الحالة العصبية او النشاط الكهربائي للدماغ فقد تم اقصائهم من الدراسة.

خضع جميع المشاركين، بعد الحصول على اذن شفهي من الوالدين او ولي امر الطفل، لتقييم كامل بما في ذلك التاريخ الصحي للطفل وفحص سريري شامل، وتم تقييم درجة الشدة لاضطراب طيف التوحد باستخدام مقياس جيليام الإصدار الثالث، ثم تم تسجيل تخطيط كهربائية الدماغ لكل طفل لمدة 20-30 دقيقة. بعد ذلك تم فحص هذه التسجيلات واختيار 5 أجزاء كل منها تمتد من 8 الى 10 ثوان بشرط ان تكون خالية من المشتتات مثل حركة العين او التأثيرات العضلية. وتمت معالجة هذه الأجزاء المنتقاة بواسطة برنامج ((KT88-1016) وتحويلها الى قراءات كمية باستخدام خوارزميات محوسبة (مثل طريقة ووربيه للتحويل وطريقة ولش) وبالتالي تم الحصول على خريطة للموجات الكهربائية بترددداتها المختلفة وتوزيها في مناطق الدماغ. أظهرت هذه الدراسة وجود علاقة طردية بين الزيادة في القوة الطيفية لموجات دلتا في جميع أجزاء الدماغ ومستوى شدة طيف التوحد. كما وقمنا بتقييم قوة الطيفية لموجات الدماغ المختلفة في تحديد شدة اضطراب التوحد باستخدام منحنى روك واظهرت النتائج ان موجة دلتا تمتلك دقة عالية أكثر من 90% مع حساسية ونوعية عالية للاختبار كلما زادت شدة الاضطرابات التوحدية. كما وأظهرت موجة الفا زيادة كبيرة بالقوة الطيفية في جزء الدماغ الايسر كلما زادت حدة الاضطرابات السلوكية.

استنتجت الدراسة ان الأطفال المصابين باضطراب طيف التوحد يعانون من اختلالات في كهربائية الدماغ التي قد تكون وراء اعراضهم، ومن هذه الاختلالات، زيادة القوة الطيفية لموجات دلتا والفا الدماغية وانعدام تماثل القوة بين نصفي الدماغ الأيمن والايسر.

هذه الاستنتاجات تقترح استخدام جهاز تخطيط كهربائية الدماغ الكمي كأداة مناسبة، غير مؤلمة، ومتوفرة بسهولة لتصنيف مستوى شدة اضطراب طيف التوحد وتعزيز التشخيص والتقييم لهذا الاضطراب من قبل الأطباء النفسيين المختصين.

المصدر: المعجم الطبي الموحد

Summary

Autism spectrum disorder (ASD) is a prevalent neurodevelopmental disorder that affects approximately 16% of the global child population. Social communication/interaction and limited, repetitive patterns of behavior are characterized as core impairments. To explain the specific brain functions in autism behavior, several researches have employed neuroimaging and neurophysiological approaches. These methods revealed that children with ASD had unusual brain activity and connection patterns, which were linked to atypical autistic behaviors. The neurophysiological processes behind neurodevelopmental disorders can be measured using quantitative electroencephalography (qEEG). One of the novel methods of qEEG is power spectrum analysis of different frequency bands of EEG which transforms the graphical pattern of EEG frequencies into quantitative numerical values that can be easily interpreted. Over the various frequency bands, it offers “absolute power, relative power, amplitude asymmetry, coherence, and phase lag, as well as all critical patterns required in optimal mental performance”. When compared to other neuroimaging procedures, qEEG has the advantages of being cost effective, easier to execute, and noninvasive. It has been suggested that it be used as a possible clinical evaluation tool for neurological and mental problems. Furthermore, it has been suggested that qEEG might be used to track and review therapy results in children with ASD.

In this study, the researcher aims to test the presence of EEG abnormalities and their type, test if EEG abnormalities are related to the presence of behavior and language dysfunction, test if these abnormalities correlates with the severities of the dysfunctions and test the possibility of using qEEG as an assessment tool in grading ASD severity level.

This is a cross-sectional study conducted in 4 autism institutes in Al-Hilla city, through the period from September 2021 till March 2022. Fifty-three children with age ranging between 3 to 12 years old, (41 boys and 12 girls) were included. All the children engaged in the study aged 3-12 years that fulfilled the DSM-V criteria of ASD, and have already been diagnosed by a specialized psychiatrist are included in the study, and those who had any association with clinical epilepsy, or epileptic discharges on EEG even in absence of clinical seizure, had other neurological or chronic medical conditions (e.g Down syndrome and tuberous sclerosis) including visual, auditory or mental impairment or were taking medications affecting the neurological condition or the brain electrical activity during the study period were excluded. All participant, after taking verbal permission from the parents or caregiver, underwent full assessment including history, clinical examination, ASD severity assessment via Gilliam autism rating scale-3rd edition, resting state EEG recording for 20-30 min. These records then were examined visually to select 5 epochs for each child, every epoch was 8-10 sec. in duration and must be artifact free (such as eye blinks, muscle artifacts), the selected epochs were processed via qEEG software(KT88-1016) Using digital techniques (such as the Fourier Transform and the Welch Method), a

head mapping of distinct wavelength was obtained and statistically analyzed.

This study revealed that there were statistically significant differences in delta and alpha power spectrum between ASD patients with different severity level. Also it showed strong positive correlation between increased spectral power of delta wave in all brain regions and the ASD severity level and autism index. Also, we used ROC curve to find the cut-off value with sensitivity and specificity of the different qEEG parameters in determining the severity of ASD symptoms, and the obtained values showed **delta** wave results had significant accuracy >90% with high sensitivity and specificity. Also, we found no statistically significant relation between qEEG parameters compared between both hemispheres and severity of language impairment. On the other hand, statistically significant increase of delta wave power in all brain regions as the severity of behavioral abnormality increases, alpha wave showed significant increase of its power in the left hemispheres. We concluded that children with ASD have qEEG dysfunctions that may underlie their symptomatology, of theses, increased delta and alpha power, and abnormal hemispheric symmetry, so Delta can be used in classifying sever cases of ASD from mild ones, and Delta and alpha waves power spectral analysis can be used as a grading tool of ASD severity level

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List of abbreviations

abbreviation	Meaning
ASD	Autism spectrum disorder
ADOS	The autism diagnostic observation schedule
ADI-R	The Autism Diagnostic Interview-Revised
ASRS	Autism Spectrum Rating Scales
CDC	The Center for Disease Control and Prevention
CARS-2	Childhood Autism Rating Scale: Second Edition
CSWS	continuous slow waves during sleep
DSM	diagnostic and statistical manual of mental disorders
EEG	Electroencephalography
FFT	fast Fourier transformer
GARS-3	Gilliam Autism Rating Scale–Third Edition
Hz	Hertz
ID	Intellectual disability
IQ	Intelligence quotient
PDD	Pervasive Developmental Disorder
PDD-NOS	Pervasive Developmental Disorder-not otherwise specific
QEEG	Quantitative electroencephalography
ROC	Receiver operating characteristic
TR	Text revision
μv	Microvolt
M±SD	Mean and standard deviation
Ωk	Kilo ohm

CHAPTER ONE

INTRODUCTION

1.1. Introduction:

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder that affects about 1 in every 59 children in the United States (1.7%)." Social communication/interaction and limited, repetitive patterns of behavior" are characterized as core impairments. Among other aspects, children and young people with ASD have psychological, academic, healthcare, social, and family support requirements.(Hyman *et al.*, 2020). ASD have been associated with varying co-occurring medical and behavioral issues that influence the individual`s living, (for example, sleeping and nutrition problems, gastrointestinal problems, obesity, convulsions, attention deficit / hyperactivity, anxiousness, and restlessness)(Evans *et al.*, 2014).

Language development and difficulties utilizing language to convey ideas are not core diagnostic criteria for ASD, although they do occur in a subgroup of people with the disorder. Despite years of treatment, over 25% of people with ASD never achieve functional language(Mody *et al.*, 2013). Language deviance, as well as language delay, is a defining feature of more severe ASD subgroups(Boland & Verduin, 2021).

Standard-EEG is a far more widely available approach and costs less overall for processing and interpretation(Boutros *et al.*, 2015), However, Computerized evaluation of EEG data will reduce the time

required for interpretation while reducing subjectivity and visual bias. (Lodder & van Putten, 2011). The frequency spectrum is most commonly estimated using Fourier or Wavelet analysis. Many studies that use qEEG compare an individual pattern of properties including "absolute and relative EEG power, coherence, peak alpha frequency, asymmetry" and other factors to a database(Johnstone & Lunt, 2011).

Several studies have highlighted the ability of qEEG to distinguish ASD patients from controls or distinct subgroups of ASD patients. Furthermore, qEEG has been used in a neurofeedback approach as a tool for therapeutic intervention, however its usage in ASD is currently under-reported in the literature(Billeci *et al.*, 2013).

Several patterns of EEG have been recognized in ASD patients over the past few years, by examining the power oscillations of various wavelengths, it is likely to spot deviances from normal patterns that show the underlying system's activity(Chan *et al.*, 2007), of these frequently reported patterns**:- 1-** An upsurge in slow wave activity (delta, theta), In 30-40% of ASD children, this activity is associated with cortical slowness, inattention, impulsivity, and hyperactivity, **2-** High Beta activity has been reported in children with ASD, and it is connected to worrying, over-focusing, and anxiety. It is observed in roughly 50-60% of children with ASD(Linden, 2009; Rondeau, 2010)**. 3-** The existence of an unique rhythm, the "mu" rhythm, which is a distinct waveform that arises in the 8-13Hz (alpha) frequency range, may explain some of the dysfunctional behaviors associated with ASD, such as:- restricted imitation behavior, or the inability to watch and replicate a taught activity(Coben et al., 2008; Linden, 2009), **4-** 20% of people with ASD have epileptiform activity at rest, even when no

clinical seizures are present(Hughes & Melyn, 2005), **5-** In people with ASD, EEG tests show that the left hemisphere has more power than the right hemisphere across all frequency bands. This asymmetry is substantially greater than the moderate individually variable asymmetries seen in most persons in their early stages of development(Sutton et al., 2005; Wang et al., 2013). **6-** Hyper- or hypoconnectivity refers to anomalous connection of distinct brain areas to themselves and to one other(Pop-Jordanova *et al.,* 2010).

1.2. Aims of study:

This study aims to:

1. Test the presence of QEEG abnormalities and their type.
2. Test if QEEG abnormalities are related to the presence of behavior and language dysfunction.
3. Test if these abnormalities correlates with the severities of the dysfunctions.

CHAPTER TWO
REVIEW OF LITERATURES

2.1. Autism spectrum disorder

2.1.1. Definition:

Autism spectrum disorders (ASD), are a diverse group of conditions characterized by some degree of difficulty in social interaction and communication. Other characteristics are atypical patterns of activities and behaviors, such as difficulty with transition from one activity to another, a focus on details and unusual reactions to sensations(WHO, 2021).

Autism is known as a "spectrum" disorder because there is wide variation in the types and severity of symptoms people experience (Zeldovich, 2018). ASD occurs in all ethnic, racial, and economic groups. These disorders all share common features of impaired social relationships, impaired communication and language, and stereotypic motor mannerisms or a narrow range of interests (Duchan & Patel, 2012).

2.1.2. History of Autism:

The first case of ASD was documented in 1800 by Dr. Jean-Marc-Gaspard Itard, a French doctor, who was interested in a boy who had been discovered undressed, damaged, and abandoned in the wilderness. The wild child was deaf to speech, silent, and spent much of his time rocking back and forth. (Pearson *et al.*, 2001).

Against existing medical opinion, which disregarded him as an imbecile, Itard became interested in the child and tried out several behavioral techniques in order to assist him. Later, he published his notes in a book called **The Wild Boy of Aveyron**, which established a thoughtful approach to treatment that would be remarkable in the decades to come.(Zeldovich, 2018).

In 1943 Leo Kanner, a psychiatrist, published the first description of infantile autism, since then the medical and sociocultural construct of autism has changed greatly and continue to recast(Kanner, 1943). Viennese pediatrician Hans Asperger, who observed autism-like behaviors and difficulties with social and communication skills in boys who had normal intelligence and language development in 1940s and described it as Asperger`s syndrome (Frith & Mira, 2016),

The concept of autism continued to evolve over the next 100 years with many other similar cases reported here and there, and multiple theories about its causes, clinical features, diagnosis and treatment have been implicated. This development was continued by the efforts of many physicians, psychiatrists and pediatricians from all over the world until the introduction of diagnostic and statistical manual of mental disorders (DSM) in 1952 that is released by American psychiatric association. It declared the first widely agreed definition and characterization of autism (Pearson *et al.*, 2001).

The growth of criteria for ASD between 1952 and 2022 may be seen in the history of the DSM classification of autism as following:

- Children with autistic-like symptoms were classed as "childhood schizophrenic" in the **DSM-I**.(American Psychiatric Association, 1952).
- In **DSM-II**, children were still characterized as "childhood schizophrenic," with criteria for diagnosis including “autistic, atypical, and withdrawn behavior”(American Psychiatric Association, 1968).
- The **DSM-III** was a significant diversion in the history of autism, where it was classified as a unique diagnostic category, with 'infantile autism' as the only kind. To be diagnosed with autism, a child must exhibit six signs and symptoms. (American Psychiatric Association, 1980),
- **DSM-IIIR** Autistic disorder was defined by sixteen enumerated symptoms, with an individual required to exhibit no less than 8 of them to be diagnosed with autism. (American Psychiatric Association, 1987).
- In **DSM-IV** There are now several subtypes of autism, as well as a class of pervasive developmental disorders. Sixteen symptoms were identified, and an individual required to have 6 of them to be diagnosed as autistic. 2 of the 6 symptoms must be based on "qualitative impairment in social interaction", one on confined and repetitive conduct, and one on qualitative impairment in communication(American Psychiatric Association, 1994).

- **DSM-IV-TR:** "Autistic Disorder, Asperger's Disorder, Rett Syndrome, Childhood Disintegrative Disorder, and pervasive developmental disorders-not otherwise specified " were grouped together under the diagnostic umbrella of Pervasive Developmental Disorder (PDD). A child would need to exhibit 2 symptoms of impaired social interaction, as well as communication limitations and repetitive and stereotyped behaviors(American Psychiatric Association, 2000).
- **DSM-V** Autism Spectrum Disorder was designed to reflect three distinct conditions (autism, Asperger's Syndrome, and pervasive developmental disorders-not otherwise specified). To be diagnosed with ASD, a person must have core symptoms such as “impaired social interaction and communication”, as well as indicators of “restrictive repetitive behaviors”.(American Psychiatric Association, 2013).
- **DSM-VTR (text revision)**: This was released in March 2022(American Psychiatric Association, 2022), it included small modifications add some clarity to the definition of autism, but they are unlikely to change diagnostic practice, the DSM-V indicated that an autism diagnosis requires deficits in “social-emotional reciprocity, in nonverbal communicative behaviors used for social interaction, and in developing, maintaining and understanding relationships”. The DSM-5-TR adds two words to that description: “as manifested by all of the following”. The addition could help to dispel “a serious ambiguity” that left many clinicians confused about whether a diagnosis required any or all of those deficits instructs clinicians to use additional diagnostic

codes whenever appropriate, but it no longer requires specifiers to be diagnosable conditions broadening the idea of specifiers, this second change now makes it possible for clinicians to indicate co-occurring problems, such as self-injury, that don't "rise to the level of disorder"(Hess, 2022).

2.1.3. Epidemiology:

It is estimated that worldwide incidence of ASD about 1 in 160 children. This estimate represents an average figure, and reported prevalence fluctuates noticeably across studies. Some well-controlled studies have, however, reported rates that are markedly higher. The prevalence of ASD in many low- and middle-income countries is unknown (WHO, 2021).

In the last decades, a large increase in the prevalence of ASD has been observed, resulting in claims about an "epidemic" of the disorder (Chiarotti & Venerosi, 2014), This rise may be attributed to a variety of factors, including a broadening of diagnostic criteria as a result of ongoing DSM revisions, increased awareness of people about the disorder and its symptoms, increased universal screening for it, and availability of early intervention and school-based services for autistic children. (Hyman, *et al.,* 2020).

The World Health Organization estimates the international prevalence of ASD at 0.76%; however, this only accounts for approximately 16% of the global child population (Hodges *et al*., 2020). The Centers for Disease Control and Prevention estimates that

around 1.68 percent of US children aged 8 years (or 1 in 59 children) have ASD. (Hodges *et al.*, 2020).

There is a shortage of data on the prevalence of ASD in the Middle East and North Africa. However, a recent research done between 2011 and 2018 showed the incidence of ASD in Oman to be 20.35 per 10.000, with this prevalence augmented 15 times since 2011.(Al-Mamri *et al*., 2019). More recently, in Saudi Arabia, a cross-sectional study involving 37 ASD clinics and schools in Makkah and Jeddah in 2020 revealed that the prevalence of ASD in both cities was 2.81 per 1,000 children. (Slama *et al*., 2022).

As for ASD prevalence in Iraq, in spite of extensive research, more than dozen published papers about ASD in Iraq, but none of them mentioned the prevalence of the disease in the country. AL-MONITOR journal published an article in 2014 under the title (Iraqi government fails to address rise in autism) that talked about the increase in the ASD prevalence as seen in International researches that discussed the topic of autism in Iraq, the Autism Research Center at Cambridge University prepared one of these in 2011, Autism was observed at greater levels after 2003, according to the research, than in previous years, it also noted that Autism impacted 75 out of every 1,000 children aged 5 to 10 years old, the journal referenced another report that Guilford University website posted in 2012, this report stated there are 5,000 Iraqi children with autism, and perhaps there are more cases undiagnosed owing to a lack of resources and specialized institutes(Sakr, 2014). An online website listed the Autism Rates by

Country, and mentioned the prevalence of ASD in Iraq to be 89.4 per 10,000children in 2022(Autism Rates by Country,2022).

Additionally, the prevalence of autism is significantly higher in people with moderate to profound intellectual disability (e.g. more than 50% may present concomitant physical or mental conditions) (Baxter *et al*., 2015). ASD also shows sex predilection property with male-to-female ratio of incidence of this disorder is 4:1, regardless of social or cultural classes (Verduin & Ruiz, 2021).

Precise prevalence estimations are vital for planning policy and service needs and identifying probable risk factors for ASD. The increase in ASD prevalence world- wide has raised concern among national governments and international agencies to take action in terms of advocacy and policy, research and service development (Al-Mamri *et al.*, 2019).

2.1.4. Etiology of Autism spectrum disorder:

Available scientific evidence proposes that there are probably several risk factors that increase the likelihood of a child to develop ASD, including environmental and genetic factors (WHO, 2021). Several hypotheses have been proposed to explain the underlying pathophysiology of ASD. Despite the fact that none of them can entirely explain the neurological abnormalities in ASD patients, these theories were useful in emphasizing the most essential pathways in the evolution of this complex condition. (Yenkoyan *et al*., 2017).

a) **Genetic factors**: play a role in ASD susceptibility, with siblings of patients with ASD showing an increased risk of diagnosis when compared to population norms, and a much higher, although not

absolute, concordance of autism diagnosis in monozygotic twins (Hodges *et al.*, 2020). Genetic defects in more than 100 genes and loci, and hundreds of copy number variants and single nucleotide polymorphisms have been connected to about 20% of ASD cases (Campbell *et al.*, 2016). A recent study discovered 16 newly identified genes connected with ASD, raising new potential processes such as cellular cytoskeletal structure and ion transport. (Hodges *et al.*, 2020). Several syndromes caused by a single gene mutation increase the risk of ASD; the most common are Fragile X syndrome, caused by a mutation in (Fragile X Mental Retardation 1) gene, Rett syndrome, caused by a mutation in (methyl CpG binding protein 2) gene, tuberous sclerosis, caused by mutations in (Tuberous sclerosis 1) or (Tuberous sclerosis2), and Timothy syndrome, caused by a mutation in (Calcium Voltage-Gated Channel Subunit Alpha1 C) (Verduin & Ruiz, 2021; Yenkoyan *et al*., 2017).

b) Studies over the years suggesting a significant role for multiple **gene-environmental interactions**, which may be one of the main causes of the broad inter-individual diversity of ASD. Possible environmental risk factors include “advanced parents' age, pregnancy complications and maternal conditions, organic toxicants, air pollution, or medication exposure during pregnancy”. (Donald *et al.*, 2018).

C) It has been claimed that among **environmental factors** related to ASD are toxins (environment-polluting matters, insecticides, thimerosal in vaccines, lead), viruses (prenatal exposure to influenza, rubella, and cytomegalovirus infections), and premature birth with

premature retinopathy (Iseri & Guney, 2015). However, existing epidemiological data show that there is no convincing evidence of a link between the measles, mumps, and rubella vaccination and ASD. Previous research that suggested the causal association were revealed to have methodological problems. (WHO, 2021).

Because of the variety of causes, it is difficult to decide which one is deemed the principal cause for each case. All of these variables are most likely significant in some manner, but the extent to which they are significant or how they interact remains unknown..(Donald *et al.*, 2018).

2.1.5. Clinical features of Autism Spectrum Disorders:

Symptoms of ASD manifested as: Abnormalities in understanding the intent of others, diminished interactive eye contact and atypical use and understanding of gestures, atypical development of social communication and pretend play as well as interest in other children (Evans *et al*., 2014; Hodges *et al*., 2020). Symptoms of ASD are further shaped by deficits in imitation and of processing information across sensory modalities such as vision and hearing (Hyman, Levy, & Myers, 2020).

Autism spectrum disorder normally manifests itself in the second year of life, however in extreme cases, a lack of age appropriate interest in social interactions may be observed as early as the first year. On the other hand, in milder cases, fundamental ASD abnormalities may not be detected for several years. (Verduin & Ruiz, 2021). Although ASD can get diagnosed before the age of 3, many children do not officially get diagnosed until they are 5 or older, this

delay in diagnosis has a devastating impact on society's health and therefore increase the importance of screening children (Fekar Gharamaleki *et al.,* 2021).

Correct early diagnosis of ASD has multiple repercussions**:**

First, early diagnosis allow the individual to receive services for treatment sooner, which has been linked to a better outcome (Fernell *et al*., 2013), Studies of the effects of early intervention have found that it can enhance children's verbal skills and severity of symptoms. Furthermore, these studies concluded that the younger the children are at the time of intervention, the greater the improvement in symptoms (Ben Itzchak & Zachor, 2011). (Dawson et al., 2012)concluded from that this improvement has led to not only a reduction in symptoms but a normalization of patterns of brain activity.

Second, children with ASD have notable, weighty medical and educational needs, and their families are far more likely to report financial, employment and time burdens in comparison with the families of children with other special health care needs (Kogan *et al*., 2008). So, accurate and early diagnosis may reduce the time and financial burden that an ASD diagnosis can have on individuals and their families via early intervention and reduced symptom expression.

Third, mothers of children diagnosed with autism report high levels of parenting stress and were more likely to report poor or fair mental and emotional health than mothers in the general population, even after improvement of the child's social skills (Montes & Halterman, 2007). This highlights the need for accurate diagnosis to

decrease the burden of ASD on the patients and their families by providing support as early as possible.

2.1.6. Language impairment in Autism Spectrum Disorder:

Language is a one-of-a-kind human cognitive skill that evolved primarily for social interaction. (Dunbar, 2009; Tomasello, 2008). Given the importance of language in human intellect and our current existence, any deviance of language accordance with expectations is reason for serious concern. language acquisition impairment has obvious ramifications for communication and socializing, but it also has consequences for cognitive growth, behavioral regulation, and emotional well-being.(Stefanatos & Baron, 2011). Language deviance in ASD can manifest as delayed onset of speech , slow or abnormal growth of linguistic skills, or regression of previously learned verbal skills, as seen in roughly 25% to 30% of cases (Landa *et al*., 2007; Stefanatos, 2008).

Language development and difficulty in using language to communicate ideas are not among the core criteria for diagnosing ASD, however, they occur in a subset of those individuals with ASD. Language abnormality, as well as delayed language, is a feature of more sever ASD subgroups, even when they have a large vocabulary, children with low functioning ASD have obvious trouble putting coherent words together. When children with ASD begin to talk fluently, their discussions may contain information that is not conveyed by standard diction or tone. (Boland & Verduin, 2021).

Language ability in ASD is highly divers, according to experts. On one side, there are ASD children who have a typical level of vocabulary, grammatical understanding, and articulation abilities, while on the other side, a considerable section of ASD population stays largely non-verbal. (Kjelgaard & Tager-Flusberg, 2001), Language impairment in ASD most notable features include:

1-Switching pronouns ("you" for "I"),

2- "Metaphorical language" constituted by linguistic utterances that seemed to have little or no relation to the context of the conversation,

3- Repetition or echoing of words or sounds, both immediate and delayed (echolalia).

4-Unresponsiveness to spoken instructions or requests.

5- Restricted ability to comprehend words(Stefanatos, 2008).

Analyzing data collected from more than 100 children, Kanner in 1950 was able to identify the disorder, "associated with the kind of language that does not seem intended to serve the purpose of interpersonal communication" (Kanner, 1951).

Augmented white-matter proportion was seen in the right arcuate fasciculus, as well as the left inferior Fronto-occipital and uncinate fasciculi, according to a recent meta-analysis. (Radua *et al.*, 2010), Language and social cognition rely heavily on these pathways. Other scientists, on the other hand, have discovered regional decreases in gray matter thickness that fluctuate with the severity of language disability observed across ASD subtypes. For example, children with

less severe ASD had smaller gray matter size in fronto-striatal section containing Broca's area, while those with Asperger's Disorder, who by definition have minimal language abnormality, had decreased gray matter portions in caudate and thalamus when compared to healthy controls. (McAlonan *et al*., 2008).

An article published 2008 about ASD and Specific Language Impairment, there was limited evidence that the co-occurrence of language deviance and ASD was linked to more severe symptoms or higher functional disability. The children with ASD and a language impairment group, on the other hand, were significantly behind in everyday adaptive communication and daily living skills, but not in social adaptive abilities. (Loucas et al., 2008).

In research conducted by Dorenbaum and his colleagues in1987 abnormal EEG activities were found in the temporal region, other authors also suggested that language impairments in ASD children may signify dysfunction of the temporal lobe, other methods of assessing temporal lobe dysfunction may be needed such as “brain stem evoked responses, REM sleep patterns, cerebral metabolism studies and neuropathologic studies”(Dorenbaum *et al.*, 1987).

A study done by (De Fossé *et al*., 2004) to test the asymmetry of “Language-Association Cortex” in boys with ASD and specific language impairment disorders found that in contrast to both the normal control group and the boys with autism who showed normal language skills and had Language-Association area larger in left hemisphere, right-handed language impaired boys with ASD and boys with specific language impairment may exhibit an abnormal volume symmetry

(larger in right hemisphere) in the inferior frontal gyrus, including Broca's. and so they concluded "Linguistically unimpaired boys with autism exhibited identical asymmetry compared to the control group, suggesting that Broca's area asymmetry reversal is connected more to language impairment than particularly to autism diagnosis,".

2.1.7. Epilepsy in ASD:

The co-occurrence of ASD and epilepsy is well documented, but the mechanisms underlying this relation still not yet fully explained (Lee et al., 2015; Taft & Cohen, 1971), around 16% co-existence of epilepsy and ASD was reported in 2002 (Levy et al., 2010)while some other reports suggested that nearly 20–25% children with ASD have epilepsy (Woolfenden et al., 2012). Though epilepsy affects roughly 2% of the general population, reports found that epilepsy affects about 25% of those with ASD, (Spence & Schneider, 2009).

Regarding the onset, (Tuchman & Cuccaro, 2011) tested the relationship between ASD and epilepsy by revision of previous studies, they found that onset for epilepsy in ASD shows two main spurs, early childhood (age: 2–5 years) and a greater one in adolescence.

In children diagnosed with epilepsy, reduced IQ is a well-known risk factor for developing ASD. (Viscidi *et al*., 2013). Epilepsy was also shown to be more common among those with ASD and intellectual impairment, defined as an IQ of 70 or below. The ASD plus ID group had a prevalence rate of epilepsy of 21% compared to 8% in the group of ASD alone. Other possible risk factors include advanced age, female

gender, limited linguistic ability, and a record of regression, however they are not clinically predictive once other aspects are taken into account. (Lee *et al*., 2015).

According to evidence, ASD patients with epilepsy may have seizures that may not match the criteria for particular electro-clinical syndromes. (Viscidi *et al*., 2013). Several particular epilepsy disorders, on the other hand, seem to be potential causes for subsequent ASD diagnosis" Infantile spasms and Lennox–Gastaut syndrome" are among them. In 2012, Zappella published a research that revealed a connection among "continuous slow waves during sleep (CSWS) and Landau–Kleffner syndrome" in people with ASD. (Zappella, 2012). Even with reported of considerable comorbidity associated with epileptic activity in ASD, it's unclear if the existence of these activities on EEG without clinical seizures affects ASD symptom presenting. (Boutros *et al*., 2015).

The disparity in rates is attributable in great part to the differences in the groups being researched, particularly in terms of cognitive ability and age. Furthermore, the prevalence also varies due to the various approaches used in ASD diagnosis. Many variables have been linked to increased chance of developing epilepsy in ASD children, including skill regression (language and social function) and female gender; nevertheless, the most reliable data indicate that cognitive abilities is the most significant risk factor.(Tuchman & Cuccaro, 2011).

ASD and epilepsy have been connected to a number of conditions characterized by genetic mutation or alteration, for

instance: "Tuberous sclerosis, Fragile X syndrome, Down syndrome" *(Lee et al.*, 2015).

2.1.8. Diagnosis: -

There is often nothing about how people with ASD look that sets them apart from other people. They may communicate, interact, and learn in ways that are different from most other people. The abilities of people with ASD can vary significantly (Hyman, Levy, & Myers, 2020).

Although ASD symptoms are neurological in nature, they appear as behavioral traits that vary according to age, language abilities, and cognitive skills. According to the DSM-V, the Core diagnostic characteristics are classified into two domains: social communication/interaction and confined, repetitive patterns of behavior. (Hyman, Levy, Myers, et al., 2020; Lobar, 2016).

To meet DSM-5 diagnostic criteria for ASD, a child must demonstrate persistent deficits in each of three areas of social communication and interaction (see A.1. through A.3. below), as well as at least two of four types of restricted, repetitive behaviors (see B.1. through B.4. below):

A. Deficits in social communication and social interaction that persist across many situations, as evidenced by the following examples:

1. A loss of social-emotional communication, which can range from an unusual social approach and refusal to engage in conventional back-and-forth dialogue to restricted sharing of interests, feelings, or affect, as well as an inability to initiate or respond to social contacts.

2. Deficiencies in nonverbal communicative behaviors used for social interaction, from a total lack of facial expressions and nonverbal communication to poorly coordinated verbal and nonverbal communication, irregularities in eye contact and body language, or deficiencies in understanding and use of gestures.
3. Deficiencies in establishing, maintaining, and comprehending relationships, such as difficulty with modifying behavior to fit different social situations, difficulties with sharing, imaginative play or making new friends, and a lack of interest in peers., to name a few.

Specify **current severity:**

B. Severity is based on social communication impairments and restricted, repetitive patterns of behavior:

Restricted, recurring behavior patterns, interests, or activities, as evidenced by at least two of the following, present or past:

1. Stereotyped, or repeated motor activity, usage of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Sameness obsession, rigorous adherence to routines, or ritualized verbal or nonverbal behavior patterns (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3. Interests that are abnormally confined, fixed, and intense or focused (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4. Hyper- or hyporeactivity to sensory input, as well as unusual interest in sensory components of the environment (e.g., seeming indifference to pain/temperature, negative reaction to certain noises or textures, obsessive sniffing or touching of items, visual obsession with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

C. Symptoms must appear throughout the early stages of development (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms result in clinically severe impairment in social, vocational, or other areas of present functioning.

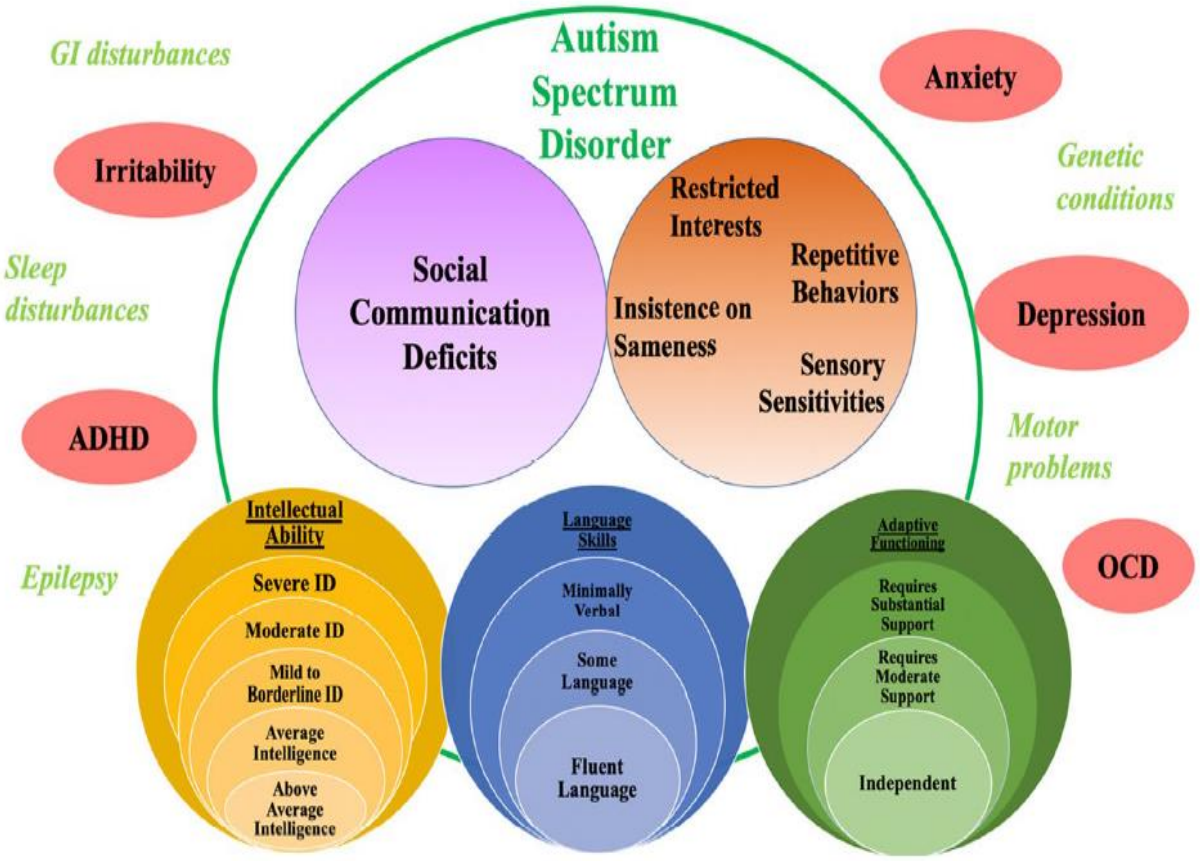
E. Intellectual impairment (intellectual developmental disorder) or global developmental delay are not superior explanations for these issues. Autism spectrum disorder and intellectual impairment commonly co-occur; to establish comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below the predicted level for general development.

Autism spectrum disorder diagnosis should be provided to those who have a well-established DSM-IV diagnostic of autistic disorder,

Asperger's disorder, or PPD-not otherwise specific. Individuals with significant social communication difficulties who do not otherwise fulfill autism spectrum disorder criteria should be tested for social (pragmatic) communication disorder.

***Specify* if:**

Whether or not there is a concomitant intellectual disability Whether or whether there is a language handicap, linked to a known medical or hereditary issue, as well as an external element, Linked to a different neurodevelopmental, mental, or behavioral issue, With catatonia(American Psychiatric Association, 2013).



Figure(A):DSM-V diagnostic symptoms and differential diagnosis of ASD(Rosen *et al.*, 2021)

In 2021, one of the first reports that uses machine learning to identify a set of biomarkers that demonstrate an association with maternal antibody-related-ASD with 100% accuracy. This is a novel serological risk assessment test for women at high risk of having a child with ASD; Around 20 percent of diagnoses appear to be linked with some kind of maternal autoantibody response, making it a major factor in the development of ASD(Ramirez-Celis *et al.*, 2021).

Biological diagnostic indicators are currently not official; thus the diagnosis relies on a thorough examination of the individual. Interviews with the child and his family, as well as an assessment of data and historical information, should all be part of a regular psychiatric evaluation. The fundamental symptoms of ASD should be observed and assessed.(Wiggins *et al.,* 2019)

The 'gold standard' diagnosis of ASD is time-consuming approach that necessitates the use of a skilled multi-disciplinary team (MDT) to assess behavior, history, and parent-report data in order to reach a diagnosis. To aid with this judgment, a variety of tools have been created. The optimum diagnostic equipment must be discovered in order to improve diagnostic operations. (Falkmer *et al.*, 2013).

The age and developmental stage of the patient may necessitate certain alterations to the evaluation processes. Clinicians should be aware of any ethnocultural, or socioeconomic characteristics that might influence the evaluation. A number of tools for assessing ASD have been created. In fact, all of these tools have varying degrees of utility in routine clinical practice, and some need special training. (F. Volkmar et al., 2014).

2.1.9. Commonly used scales:

1. Childhood Autism Rating Scale: Second Edition (CARS-)

This questionnaire was developed in 2010 for two separate age groups: 0-6 years old and above 6 years old. This exam has 75 % content validity, 76 % reliability, 81 % sensitivity, and 87 % specificity.(Fekar Gharamaleki *et al*., 2021). It is one of the most commonly used scales for diagnosing ASD

2. **The autism diagnostic observation schedule (ADOS)**

ADOS is a standardized diagnostic observation tool that helps evaluate the social and communication deficits associated with ASD-related behavior It includes the observation of a subject performing different imaginative activities and socials tasks that normally provoke spontaneous behavior (Fakhoury, 2015).

3. The Autism Diagnostic Interview-Revised (ADI-R):

ADI-R and ADOS are often administered together to improve arrangement with clinical judgments by using multiple sources of information attained on an individual's past and current behavior. It is known to be reliable in older children(Oh *et al*., 2021). typically takes 1–2 hours and focuses on the child's current behavior or behavior at a certain point in the areas of mutual social interaction, communication and language, and patterns of behavior(Evans *et al*., 2014).

4. **The Gilliam Autism Rating Scale–Third Edition (GARS-3**):

With the change in the DSM-5, some of the subjective rating scales were upgraded to better match the new diagnostic criteria. Two of

these scales are the Gilliam Autism Rating Scale (GARS) and the Autism Spectrum Rating Scales(ASRS) (Amy Langenderfer, 2020).

GARS-3 is a norm-referenced tool designed to screen for ASD in individuals between the ages of 3 and 22. The GARS-3 was updated to reflect the DSM-5 changes. In addition, the GARS-3 underwent confirmatory and exploratory factor analyses to establish the theoretical and empirical strength of its subscales (Fekar Gharamaleki et al., 2021; Karren, 2017).

This test is intended to assist in distinguishing children with ASD from those who have other types of mental and behavioral disorders and determine the severity of the condition. The scale consists of 56 items describing characteristic behaviors of individuals with autism. These items are grouped into six subscales: (Kong *et al.,* 2020).

- Restrictive, repetitive behaviors,
- Social interaction,
- Social communication,
- Emotional responses,
- Cognitive style,
- Maladaptive speech

The GARS-3 is able to accurately discriminate children with ASD from children without autism (i.e., sensitivity = 0.97, specificity = 0.97). The GARS-3 takes only 5-10 minutes to administer. Results are expressed as standard scores, percentile ranks, severity level, and probability that the individual does have ASD (Gilliam, 2014).

2.2 Electroencephalography:

German neuropsychiatric from Jena, **Hans Berger** (1873-1941) was the one who discovered the electroencephalography (EEG), and the first human EEG record was done on a 17-year old boy during neurosurgical operation (Mecarelli, 2019). EEG is a real-time, measurement of the brain's electric fields, it is completely non-invasive procedure that can be applied repeatedly to patients, normal adults, and children with virtually no risk or limitation (Teplan, 2002). Electrodes placed on the scalp record voltage potentials that results from current flow in and around neurons. EEG is nearly a century old: this long history has given EEG a rich and diverse spectrum of applications (Biasiucci *et al.*, 2019). The postsynaptic potentials produced by neurons of the cerebral cortex are the electrical potential detected by EEG. PSPs are the synchronized activity alternating between excitatory and inhibitory postsynaptic potentials in the apical dendrites of neurons; activity captured by the EEG is the synchronous energy oscillating across EPSPs and IPSPs. It is caused by the interplay between he cortex and the thalami. (Sazgar & Young, 2019).

Hans Berger had just two electrodes available when he obtained the very first human EEG, which he placed in the front and posterior areas of the scalp. Berger continued to use this approach for years, believing it to be an effective methodology for determining global activity of the cerebral cortex. Other studies later on pointed out that EEG activity varied greatly by the site of the scalp from where it was recorded. (Mecarelli, 2019)

A committee lead by H. Jasper developed an electrode placement method that could be utilized in all laboratories. The first standardized

method, known as the "International 10-20 system" (SI 10-20) was introduced in 1949 and released by Jasper in 1958.(Mecarelli, 2019).

2.2.1. physiological mechanism

The EEG records oscillations in brain electrical activity over time. This electrical activity typically between -100 and +100 micro volts. The data appears as positive and negative deflections that may be analyzed for frequency and magnitude, all of which could have psychological, neurological, or physiological implications. (Read & Innis, 2017). Differences of electrical potentials are caused by summed PSPs from pyramidal cells that create electrical dipoles between soma (body of neuron) and apical dendrites (neural branches) (Teplan, 2002), these PSPs are the voltages that emerge from a nerve impulse when transmitters are discharged and attach to a postsynaptic neuron, affecting the movement of ions along a cellular membranes. (Ganong *et al.,* 2019).

Neurons of the cortex are grouped in a columnar arrangement with their electrical fields oriented in the same direction. This allows for the summation of signals from numerous neurons. (Aminoff, 2012). Only the activity at the ends of electrical dipoles of simultaneously discharging neurons that are positioned perpendicular to the scalp can be detected by EEG. The contra-polar dipole are not detected(Guyton, 2020).

Certain cortical neurons, such as those in the amygdala, are not organized in this columnar fashion and hence cannot be spotted by EEG. Dipoles having conflicting polarity directed toward one other

cancel each other out, resulting in none of the dipole being recorded. (Read & Innis, 2017). Electrodes are placed on the scalp and linked to the EEG recording system to pick up this activity. Brain complex, cortico-spinal fluid, cranium, and scalp form a volume conductor that modifies the magnitude and shape of the electrical signal generated by cortical neurons.(Sazgar & Young, 2019). According to estimate, a potential is captured at the scalp if 6 cm^2 of cortical surface area is simultaneously stimulated. (Misulis, 2014)

2.2.2. Frequency bands

Continuous electrical activity in the brain is demonstrated by recorders from the brain surface or even the outside surface of the head. The amount of activation of different areas of the brain is linked to sleep, alertness, or brain conditions such as epilepsy or even psychoses determines the strength and rhythm of this electrical activity. Brain waves, shown in figure (2-2), are the undulations in recorded electrical potentials. (Guyton, 2020)

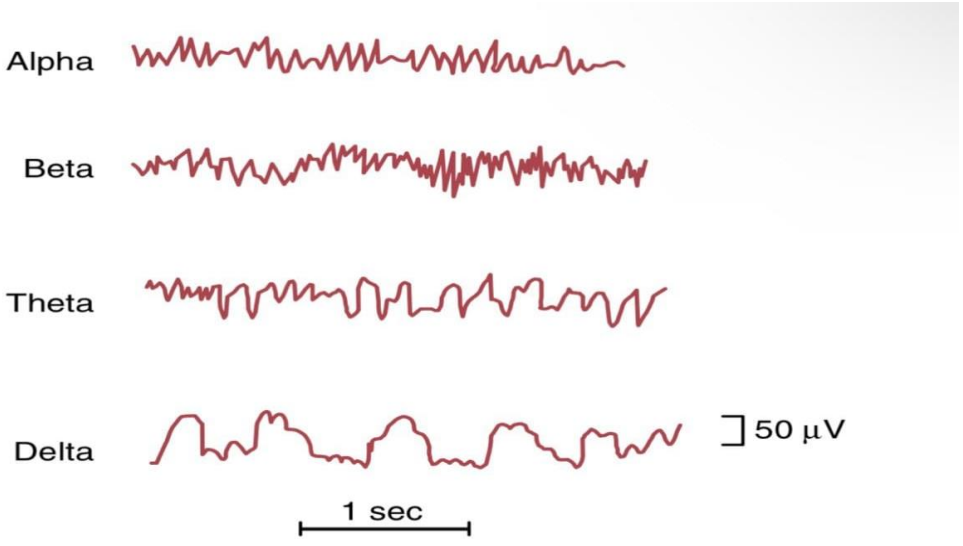


Figure (B), normal brain waves (Guyton, 2020).

The standard EEG clinical bands are the delta (0.1-3.5Hz), theta (4-7.5Hz), alpha (8-13Hz), and beta (14-30 Hz) bands. EEG signals with frequencies greater than 30 Hz are called gamma waves(Anilkumar, 2019).

Alpha waves are seen in all ages and commonly found in awake and relaxed adults, with closed eyes. It is generated on both sides of the brain, but slightly higher in amplitude on the non-dominant side, occipital and partial regions of the brain. It acts like a link between conscious and subconscious mind. Alpha waves are in the range of 8 to 13 Hz (Kumar & Bhuvaneswari, 2012).

Beta waves occur at frequencies greater than 14 cycle second and as high as 30 Hz. They are recorded mainly from the parietal and frontal regions during specific activation of these parts of the brain. It is mainly seen during period of mental activity as well as during drowsiness. Also beta waves is activated by administration of certain medications like benzodiazepines(Ganong *et al.,* 2019) and chloral hydrate(Sazgar & Young, 2019).

Theta waves have a frequency range of 4–7.5 Hz. It is typical in early childhood and during sleep in adult EEG, as well as in fronto-central regions of young adults. In the absence of sleepiness, generalized theta activity in an adult patient may suggest widespread cerebral disruption, encephalopathy, and/or drug impact; focused and asymmetrical theta frequency may suggest local disruption of brain activity(Sazgar & Young, 2019).

Delta is the frequency range up to 3.5 Hz, delta waves tend to be the highest in amplitude and the slowest waves. It is seen normally in adults in slow wave sleep and it is the normal brain activity in babies. It may occur specific focus with subcortical lesions, and generalized with diffuse lesions, metabolic encephalopathy hydrocephalus or deep midline lesions. It is usually most prominent frontally in adults and posteriorly in children (Cox, 2007).

2.2.3 Methods of EEG interpretation:

There were two primary components of standard-EEG analysis prior to the adoption of automated quantified methodologies. The first step is to spot evident anomalies in brain electrical activity, such as "epileptic spikes or sharp waves", as well as noticeable inconsistencies that are most likely caused to artifacts. The second component is the evaluation of background continuous activity, which is subjectively interpreted through inspection and is depending on the examiner's experience, attention to detail, and evaluation of tiny abnormalities. Quantified EEGs are most useful in this situation. (Cantor, 1999). When EEG is examined visually there is frequently substantial lack of agreement on the presence and significance of EEG "abnormalities" and many patterns are considered as “normal variants” or "maturational". There are many studies about the inter- and intra-rater reliability in evaluation of EEG signals (Johnstone & Lunt, 2011).

Standard-EEG is a far more extensively used technology that also costs less to analyze and interpret brain electrical activity.

Furthermore, conventional EEG remains the sole method for identifying paroxysmal or epileptiform activity that is trustworthy. (Boutros *et al.,* 2015)**.** However, Automated interpretation of clinical EEG recordings will reduce subjectivity and visual bias from analysis and can reduce the time required for interpretation (Lodder & van Putten, 2011).

The expression "quantitative EEG" (QEEG) denotes to the digitized EEG's quantitative analysis method. The frequency range is most typically estimated using Fourier or Wavelet analysis. Many researches that use QEEG compared an individual pattern of properties including "absolute and relative EEG power, coherence, peak alpha frequency, asymmetry, and other parameters" to a database. (Johnstone & Lunt, 2011).

Automated presentation tools have been created to enhance the presentation of the distribution of specific frequency band powers, amplitudes, and symmetry in EEGs. These approaches examined visually frequency-analyzed EEGs across time using" compressed spectral arrays" or, subsequently, "density spectral arrays". Bickford and his coworkers were first to bring the CSA to the public's attention. (Bickford RG, Fleming N, 1971).

The CSAs split the EEG recordings into sequences and transform each section (epoch) to a power spectrum analysis utilizing advanced mathematical algorithms such as Fast Fourier transformers. Then, using the concept of concealed line suppression, consecutive spectra are placed one over the other, ensuring that no subsequent line spectrum overlaps a previously drawn spectrum, resulting in a three-

dimensional image. The final stage in the CSA is to form the CSA of individual EEG channels it in to an array that corresponds to the location on the head where they were collected. (Cantor, 1999).

Power spectra represent the magnitude or magnitude-squared power of complex activity patterns as a function of EEG frequency (measured in cycles per second, Hertz). Because EEG signals themselves occupy a wide spectrum of frequencies (from 0.1 Hz and below to 250 Hz and above), power spectral averages can capture information about parallel EEG processes occurring in distinct frequency ranges that contribute to different aspects of cognitive, sensory, or motor processing (Dimitrov et al., 2017; Loo et al., 2016). Both spectral analysis and coherence estimation approaches have been employed to analyze ASD children using qEEG, and while the methodology and research procedures have differed, these findings have consistently revealed certain aberrant EEG features in these patients. (Machado *et al.*, 2015).

2.2.4. Applications of quantitative electroencephalography:

The regular use of qEEG is now under controversy; it has, for example, been used to anticipate therapy outcome in neuropsychiatric illnesses. few of the clinical applications of qEEG include:

1. **Epilepsy**

In epilepsy, EEG is a typical evaluation technique. Although QEEG is not as widely used, it may quickly diagnose epileptic discharges and distinguish between different subtypes of epilepsy. Some authors suggest that various types of seizures exhibit distinct QEEG patterns,

enhancing the sensitivity of seizure detection and boosting diagnosis, and discovered that the sensitivity of QEEG in seizure diagnosis range from 43% to 72% in their trials. (Livint Popa *et al*., 2020).

2. **Schizophrenia**

Numerous QEEG researches have been performed to properly analyze schizophrenic patients. A decrease in alpha power is frequently associated with a change in alpha mean frequency or decreased alpha responsiveness. (Chabot *et al.*, 2005)

3. **Learning disorders:**

The utility of QEEG in addressing learning difficulties and assessing learning disorders has been demonstrated in several research, with QEEG discriminating accuracy ranging from 46% to 98 percent(Kanda *et al.,* 2009).

4. Attention disorders:

Attention deficit hyperactivity disorder (ADHD) is a common childhood neuropsychiatric disorder that affects 3–5% of school-aged children. (Coburn *et al.*, 2006). The use of qEEG in the assessment of ADHD may have significant role. Adults and children with ADHD have higher EEG power. Adolescents with ADHD, on the other hand, have less power. With a precision of 46-98 %, QEEG may be utilizes to assess response to therapy, and numerous studies have stressed its significance as a diagnostic instrument in learning disorders, measuring spectral power and coherence.(Bresnahan & Barry, 2002).

5. Depression:

standard EEG reveals 20% to 40% of the alterations seen in the EEGs of individuals with depression. (Kanda *et al.*, 2009). There are several researches on QEEG in depression, and it have been replicated widely in academic institutions. With 72%–93% sensitivity and 75%–88% specificity, the validity of these QEEG results in diagnosing depression has been proven and reproduced in large samples. (Coburn *et al.*, 2006).

6. **Encephalopathies and delirium:**

"Creutzfeldt-Jakob disease, uremic, hypoxic-ischemic, hepatic, methamphetamine abstinence, baclofen overdose, acute lymphoblastic leukemia, and coma" are among the encephalopathies for which QEEG is described as a tool for evaluation, it may be a useful adjuvant to the EEG in encephalopathies in situations where the diagnosis is not completely clear. The approach was also used to characterize encephalopathy linked to the Chernobyl disaster's exposure(Kanda *et a*l., 2009).

7. Dementia:

Several QEEG studies of dementia patients report high correlations between the severity of cognitive impairment and amount of EEG slowing. These features are absent in depression and are localized in multi-infarct dementia, which enables these disorders to be differentiated from Alzheimer's dementia.(Chabot *et al*., 2005)

8. Intensive care unit and operating room monitoring

When visual assessment can`t notice, and clinically evaluate changes, more effectively, spectral analysis may be used to enhance EEG. (Nuwer, 1997). The relevance of qEEG in the early identification of acute severe brain ischemia and post-SAH (subarachnoid hemorrhage) vasospasms has been shown. It provides information regarding diagnosis as well as prognoses in unconscious patients that cannot be accessed any other way.(Lieber AL, 1988). QEEG appears to be helpful in assisting clinicians in determining the best moment to unplug the patient from the ventilator*(Kanda et al.,* 2009).

9. **Neurofeedback**

It entails recording, evaluating, and displaying QEEG analysis data of patients in near real-time designed to motivate changes to the brain electrical events. In 2008, Johnston proposed that QEEG may aid in the design of neurofeedback protocols. (1) generalized regulation or arousal-based symptoms, (2) recognizing target areas of interest for training, and (3) analyzing connection across brain areas, both in and between hemispheres, were the three key topics Johnston addressed(Johnstone & Lunt, 2011).

2.2.5. EEG application in autism spectrum disorder:

The identification of generalized or localized spikes, that appear at a greater rate in ASD, has been the primary method for recording and determining the kind of epileptiform and aberrant paroxysmal activity. (Jeste & Tuchman, 2015).

Low-functioning children with ASD, normal children, and children with intellectual disability, all of the same age, were examined in one of the earliest studies that investigated resting EEG in ASD patients. The ASD patients displayed remarkably higher slow wave activity and lower alpha, as well as less intra and inter symmetry in comparison to the normally developed children and those with ID.(Cantor *et al*., 1986).

Resting EEG researches have demonstrated that 20% of people with ASD have epileptiform discharges at rest, even when no clinical seizures are present. (Hughes & Melyn, 2005). During sleep investigations, higher rates of epileptiform discharges have been recorded; for example, (Chez *et al.,* 2006) found that 61% of people with ASD who had never had a clinical seizure displayed epileptiform activity, EEG results vary widely with published frequencies of epileptiform EEG abnormalities in children with ASD varying from 6-85.8% (M Thodeson *et al.*, 2018)Moreover, paroxysmal discharges and slow focal activity were recorded in the temporal region in EEG of patients with this disorder, especially those with developmental regression (Boutros *et al.,* 2015). The significance of epileptiform EEG abnormalities in children with ASD is unclear and careful clinical correlation is required while making treatment decisions (M Thodeson *et al*., 2018)

Several studies have highlighted the ability of QEEG to distinguish ASD patients from norms or distinct subgroups of ASD patients. Furthermore, qEEG has been used in a neurofeedback technique as a

tool for therapeutic intervention, however its usage in ASD is currently under-reported in the literature. (Billeci *et al.,* 2013)

By examining the power fluctuation of various frequency bands, it is possible to spot deviations from normal rhythms that show the underlying system's organization. (Billeci *et al.,* 2013).

A study done by Rondeau (2010) recognized three recurring patterns of EEG in ASD children, these are:-

1. Excess slow wave activity (delta, theta). There may also be excess fast (alpha, beta) brainwaves present relating to hyper- or hypofuncioning of the localized area.

2. Repeated pattern in ASD has also been mentioned in2008 by (Coben et al., 2008), and liked to clinical symptoms of autism, is the presence of a specific rhythm, the "mu" rhythm, this is a distinctive waveform appears at 8-13Hz (alpha) frequency range, this finding might explain some of the dysfunctional behaviors of ASD, such as:- limited imitation behavior , or disability to observe and mimic an instructed task.

3. Pattern frequently observed in ASD is aberrant connection in the brain regions to themselves and to each other, this is called "hyper- and hypoconnectivity". hyperconnectivity usually found with complaints of sensory integration, language abnormalities and emotional impairment.

A research done by Dr. Linden in the period between 2004-2009 found similar patterns, he recognized six QEEG paradigms in ASD and two in Asperger's, recording 19 channel EEG and analysis of the raw

data, absolute power, relative power and multivariate connectivity. The subtypes found in Autism are: (Linden, 2009)

1) High Beta activity which is linked to obsessing, over focusing and anxiety, this is the most common subtypes found in around 50-60 % of the children with ASD.

2) Cortical slowness and attention problems, impulsive, and hyperactive behavior are all symptoms of high Delta/Theta activity, and in 30-40% of ASD children.

3) Abnormal EEG/epileptogenic activity, in 33%,

4) Metabolic/Toxic in the form of low EEG voltage, in 10%.

5) Mu activity which relates to social abilities

6) abnormal coherence pattern.

Fauzan & Amran (2015) concluded that each of the studied subjects had different level of severity(behavioral and biochemical), children with high intellectual disabilities might show increased delta activity in frontal-temporal brain regions while children with lower disabilities showed more theta activity. They also suggested that these alterations were a result of the reduced mental abilities, if not, the decrease in abnormalities might result from maturity factors.

In a neurophysiological context, EEG power is the totals of simultaneously firing neurons. Because the density of the cortex is linked to intellect, it's likely that EEG power can be used to assess the performance of cortical processing of information.(Kanda *et al*., 2009)

In terms of spectral analysis, Cantor and his colleagues (1986) and Cantor and Chabot (2009) observed lower Alpha power, although other writers challenged their findings, indicating a decrease in this EEG frequency band bilaterally and frontally(Macha*do et al.,* 2015).

In the subject of ASD research, rest-state qEEG is one of the most often used methods. Neuro-oscillations recording that replicates the simultaneous firing of a network of neurons regulated by excitatory/inhibitory collaborations. The balanced excitatory and inhibitory activity may be obtained from qEEG at rest in vivo, which might alter the social and cognitive abilities of people with ASD. (Billeci *et al*., 2013).

Thus, atypical patterns may be identified by monitoring power variations of brain frequencies, demonstrating the architecture of the underlying system.

2.2.5.1. Abnormal hemispheric symmetry

Changes in hemispheric symmetry of brain neurophysiological activity have been observed in children with ASD additional to spectral power abnormalities. In ASD, the large number of resting-state EEG investigations show increased power of left hemisphere vs to the right across all frequency bands. (Wang et al., 2013b). This asymmetry is significantly larger than the moderate asymmetries seen in most individuals in their early stages of development(Sutton *et al.*, 2005).

According to Cantor and colleagues in 1986, ASD Children showed increased power in the delta frequency in the posterior-temporal, midline, and occipital areas of the left hemisphere(Cantor *et al.*, 1986).

Similarly, Stroganova and his fellow researchers in 2007 found increased delta power in the left side of the brain among ASD children in the frontal, temporal, and parietal areas. Just as well, theta band dominated in frontal, parietal, temporal and occipital area of the left rather than right hemisphere(Stroganova *et al.,* 2007).

In the posterior-temporal, midline, and occipital areas, Cantor and coworkers were able to reproduce the beta band dominance in the left side(Cantor, 1999). Alpha band dominance over the left hemisphere among ASD children was mentioned in several studies at mid-frontal, temporal, parietal midline and occipital areas(Daoust *et al.*, 2004; Sutton *et al.*, 2005).

Given the usual linguistic impairments reported in ASD, left-hemisphere asymmetries in the brain is of clinical importance. (Dawson *et al.*, 1989; De Fossé *et al.,* 2004).

CHAPTER THREE

Materials and Methods

3.1. Materials

3.1.1. Subjects:

This cross-sectional study was conducted in the autism institutes in Al-Hilla city, including AL-IMAM HUSSAIN center for autism, BABYLON center for autism and speech rehabilitation, MALAK AL-RAHMA center for autism, and AUTISM rehabilitation center through the period from 27th of September 2021 till 1st of March 2022.

Fifty-three children with age ranging between 3 to 12 years old, (41 boys and 12 girls).

3.1.1.1. Inclusion criteria

All the children attending the above-mentioned autism centers aged 3-12 years that fulfilled the DSM-V criteria of ASD, and have already been diagnosed by a specialized psychiatrist are included in the study.

3.1.1.2. Exclusion criteria

i. Association with clinical epilepsy, or epileptic discharges on EEG even in absence of clinical seizure.
ii. Presence of other neurological or chronic medical conditions (e.g Down syndrome and tuberous sclerosis) including visual, auditory or mental impairment.
iii. children taking medications affecting the neurological condition or the brain electrical activity during the study period.

Sample size: due to the lack of data regarding the prevalence of ASD in Iraq, and following the advice of the statistician a convenient sample

was selected, were all eligible children attending the above-mentioned autism centers in Al-Hillah city that fitted the inclusion criteria were sampled.

One of the factors that limited sample selection is the fact that the recording of EEG requires patient to be restful with minimal movement and to cope with the technician instructions to perform specific protocols during the recording period to acquire reliable EEG data with minimal artifact. This was important challenge to the researcher especially for the autistic children who already are hyperactive, have attacks of fear and getting away from strangers.

So, all cooperative children, who tolerated staying still during the period of EEG recording were selected. We avoid the use of sedative drugs (benzodiazepines, barbiturates and chloral hydrate) which are commonly used in clinical EEG recording because they might result in generalized beta activity which would impede the calculation of quantitative EEG findings (Hartman, 2005).

With patience, adequate preparation and the presence of familiar persons in the recording room, the researcher was able to carry out the procedure with minimal difficulty and without sedation.

3.1.2. **Ethical approval:**

The committee on publishing ethics in Babylon University/College of Medicine gave its approval to this work. and verbal consent of participation was obtained from the children`s parents or their care-giver.

3.1.3. Instruments used in this study:

Table (3-1) show the instruments used in this study:

Instrument	Supplying company	Country
18-channel EEG machine	Contec	China
Reusable cup Electrodes	Contec	China
EEG paste (Elefix)	Nihon Kohden	Japan
Skin preparation gel	Nihon Kohden	Japan
QEEG software (KT88-1016)	Contec	China

3.2. Methods

All subjects enrolled in the study underwent the following procedures.

1- History and clinical examination
2- Autism rating scale assessment
3- Electroencephalographic recording

3.2.1. History and clinical examination

All of the subjects had their history taken in detail, including demographic and clinical data which were collected based on specially designed questionnaire shown in table **(3-2)**. In addition to that, all children underwent clinical evaluation, with a simple hearing assessment.

Table (3-2): demographic data of the subjects**:**

Demographical data of the children
• Name of the child • Age of the child at the time of the assessment • Gender of the child • Father`s age at the child`s birth • Educational level of the father • Mother`s age at the child`s birth • Mother`s level of education. • degree Parental consanguinity • No. of siblings • Family members with ASD, and their relation to the child • Duration of enrolment in the institute • Drugs the child is using at the time of the assessment • Any other medical condition

3.2.2. Gilliam Autism Rating Scale

An interview with each child, his teacher and caregiver were conducted in the institution, after explaining detailed information regarding the scale, the questions and their grading. The researcher attended online webinars about GARS-3 prior to the data collection, it took about 20-30 min per child to fully complete the scale filling.

The examiner adds up raw scores for each one of the sub - scales (or four if the person being evaluated is deaf). Using Appendix (A) at the back of the Examiner's Manual, these raw results are transformed into rankers and scaled scores. Raw scores were transformed using a direct linear transformation to produce a distribution with a mean of 10 and a

standard deviation of 3. Scaled scores, according to the GARS-3 handbook, are excellent for comparing an individual's performance to norms and may be statistically modified, making them perfect for study. (Gilliam, 2014; Karren, 2017).

The Autism Index (AI) values are acquired by translating the total of the subscale scores. The greater a patient's Autism Index, the more likely he or she has ASD. GARS-3 assigns four levels of likelihood of having ASD:

level 0: AI= 4, “unlikely;”

level 1: AI range from 55 to 70, demanding “minimal support;”

level 2: AI range from 71 to 100, “very likely” needs large assistance;

level 3: AI 101, “very likely,” need a significant amount of assistance (Kong *et al.*, 2020). On a subscale, higher scaled scores indicate more severe symptoms (Karren, 2017).

On the other hand, the scale enables us to grade severity of ASD:

an autism index between 55-70 is regarded as mild,

autism index between 71-100 as moderate,

and autism index >100 is considered severe ASD (Gilliam, 2014).

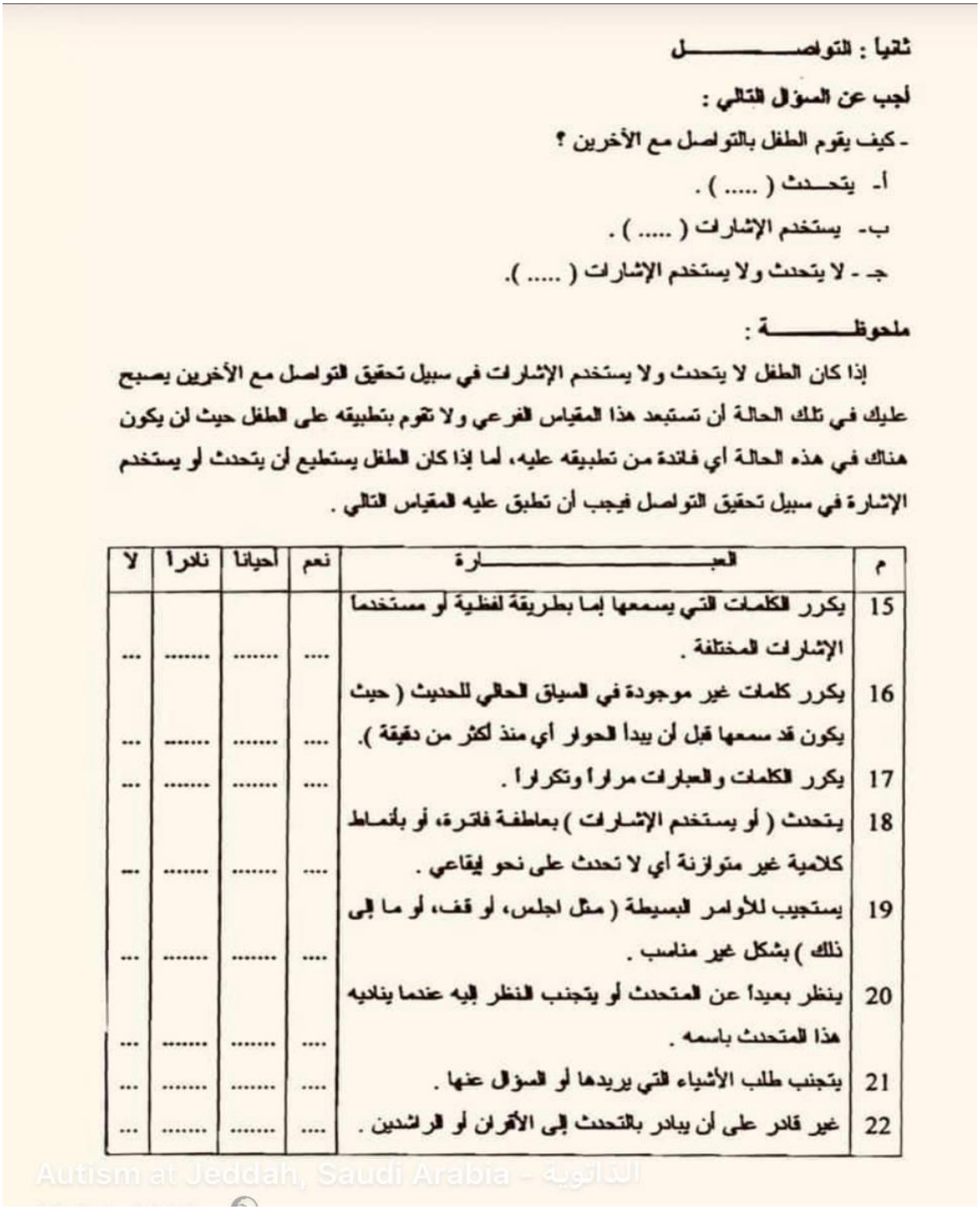
3.2.2.1. Severity of language abnormality:

Gilliam autism rating scale-3rd edition asses’ communication as a separate domain, this includes both sign language and spoken language. It is done by scoring questions (15 -22), figure (3-A), then the raw score of this domain is converted into slandered score in appendix A, and finally the autism index is determined based on a rank that extends from 1(no autism) to 19 (very sever autism). Figure (3-B)(Karren, 2017).

3.2.2.2. Severity of behavioral abnormality:

Abnormal restrictive behavior is the first domain assessed in GARS-3, it is examined by answering questions (1-14), then the raw score of

this domain is converted into slandered score in appendix A, and finally the AI is determined based on a rank that extends from 1(no autism) to 19 (very sever autism). Figure (3-B)(Gilliam, 2014).



ثانيا : التواصـــــــــــل

أجب عن السؤال التالي :

- كيف يقوم الطفل بالتواصل مع الآخرين ؟

أ- يتحـــدث (.....) .

ب- يستخدم الإشارات (.....) .

جـ - لا يتحدث ولا يستخدم الإشارات (.....).

ملحوظـــــــــة :

إذا كان الطفل لا يتحدث ولا يستخدم الإشارات في سبيل تحقيق التواصل مع الأخرين يصبح عليك في تلك الحالة أن تستبعد هذا المقياس الفرعي ولا تقوم بتطبيقه على الطفل حيث ان يكون هناك في هذه الحالة أي فائدة من تطبيقه عليه، أما إذا كان الطفل يستطيع أن يتحدث أو يستخدم الإشارة في سبيل تحقيق التواصل فيجب أن تطبق عليه المقياس التالي .

م	العبـــــــــــــــارة	نعم	أحياناً	نادراً	لا
15	يكرر الكلمات التي يسمعها إما بطريقة لفظية أو مستخدماً الإشارات المختلفة .	....	.....	.....	...
16	يكرر كلمات غير موجودة في السياق الحالي للحديث (حيث يكون قد سمعها قبل أن يبدأ الحوار أي منذ أكثر من دقيقة).	....	.....	.....	...
17	يكرر الكلمات والعبارات مراراً وتكراراً .	....	.....	.....	...
18	يتحدث (أو يستخدم الإشارات) بعاطفة فاترة، أو بأنماط كلامية غير متوازنة أي لا تحدث على نحو إيقاعي .	....	.....	.....	...
19	يستجيب للأوامر البسيطة (مثل اجلس، أو قف، أو ما إلى ذلك) بشكل غير مناسب .	....	.....	.....	...
20	ينظر بعيداً عن المتحدث أو يتجنب النظر إليه عندما يناديه هذا المتحدث باسمه .	....	.....	.....	...
21	يتجنب طلب الأشياء التي يريدها أو السؤال عنها .	....	.....	.....	...
22	غير قادر على أن يبادر بالتحدث إلى الأقران أو الراشدين .	....	.....	.....	...

Figure (3-A): sample of GARS-3 questions and their scoring system(Gilliam, 2014).

القسم الأول : معلومات عامة :

اسم المفحوص : ..... الجنس : ..... (ذكر / أنثى)

العنوان : ..... المدرسة : .....

تاريخ الميلاد : ...../...../..... السـن : .....

اسم الفاحص : ..... وظيفتـه : .....

تاريخ تطبيـق المقيـاس : ...../..../.....

القسم الثاني : الدرجـات :

الاختبارات الفرعية	الدرجة الخام	الدرجة المعيارية	الرتب المئينية للتوحد	الخطأ المعياري للقياس
السلوكيات النمطية	.....	.....	.....	1
التواصـل	.....	.....	.....	1
التفاعل الاجتماعي	.....	.....	.....	1
الاضطرابات النمائية	.....	.....	.....	1
مجمـوع الدرجـات المعيـاريـة	.....	//////////////////////////////////		
معامل أو نسبة اضطراب التوحد	.....	.....	.....	3

القسم الثالث : الدليل التفسيري للدرجات :

الدرجات الخام للمقاييس الفرعية	معدل أو نسبة اضطراب التوحد	مستوى الشدة	احتمال وجود اضطراب التوحـد
19 -17	131 -	مرتفع	مرتفع جداً
16 -15	130 -121		مرتفـع
14 -13	120 -111		فوق المتوسط
12 -8	110 -90		متوسط
7 -6	89 -80		أقل من المتوسط
5 -4	79 -70		منخفض
3 -1	69 -	منخفض	منخفض جداً

Figure (3-B): standard score, autism index and their corresponding severity level of ASD(Gilliam, 2014).

Then the children were divided into 3 groups (mild, moderate and sever) based on ASD severity level measured via GARS-3.

3.2.3. Electroencephalogram recording:

The children`s parents or care-givers were instructed to prepare the children for the EEG examination, such as washing and trimming their hair the day before the record. The EEG recording lasted for a minimum of 30 minutes. The children were asked to stay calm, not moving their body or blinking their eyes. Also recording was obtained under an eyes-closed, and eyes-opened conditions (rest-state EEG), the recording process was done firstly under the directions of the supervisor, then a skilled technician, and by the end of the data collection the researcher was able to perform the EEG recording alone. The children were placed in a quiet, dimmed room and made familiar with the device and the procedure first. Then, we made sure that the child`s position during the recording is relaxed enough to eliminate any undesirable movement, a lying position reduced the occurrence of some artifacts resulting from squirmy movement, on the other hand it may cause the child to fall asleep, especially in the setting of a darkened noiseless room, so the subjects were alerted upon any signs of fatigue, sleep or reduced alertness.

Electrode placement was done according to the 10-20 system. To ensure appropriate coverage of all parts of the brain, the scalp is subdivided into proportionate intervals from major skull features (nasion, preauricular points, inion). The notation 10-20 indicates proportionate spacing in percentages between the ears and the nose, where electrode locations are selected as illustrated to the left of the diagram, **figure(3-C)**(Sazgar & Young, 2019). As seen to the right,

electrode positions were labeled according to nearby brain areas: "F (frontal), C (central), T (temporal), P (posterior), and O (occipital)". **figure (3-c)**. On the left side of the head, the letters are represented by odd numbers, whereas on the right they are represented by even numbers. From the standpoint of the individual, the left and right sides are decided by convention. (Teplan, 2002). The EEG is then stored on a computer.

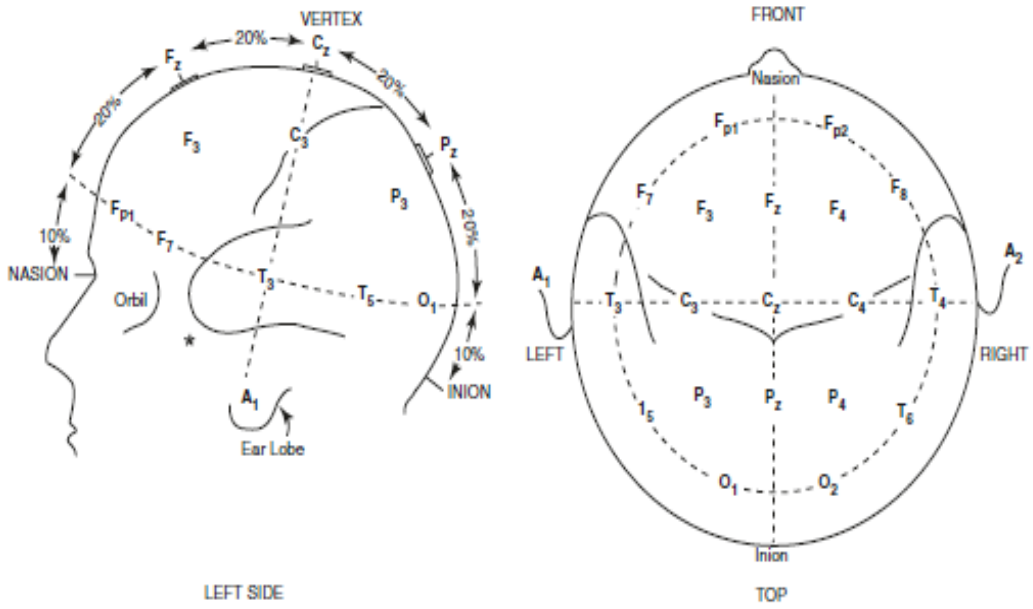


figure (3-c): The international 10–20 system is used for electrode placement(Sazgar & Young, 2019).

3.2.4. Quantitative electroencephalographic analysis

Before the processing phase, the record was inspected visually to select 5 epochs for each child, every epoch was 8-10 sec. in duration and must be artifact free (such as eye blinks, muscle artifacts) as shown in **figure (3-D)**.

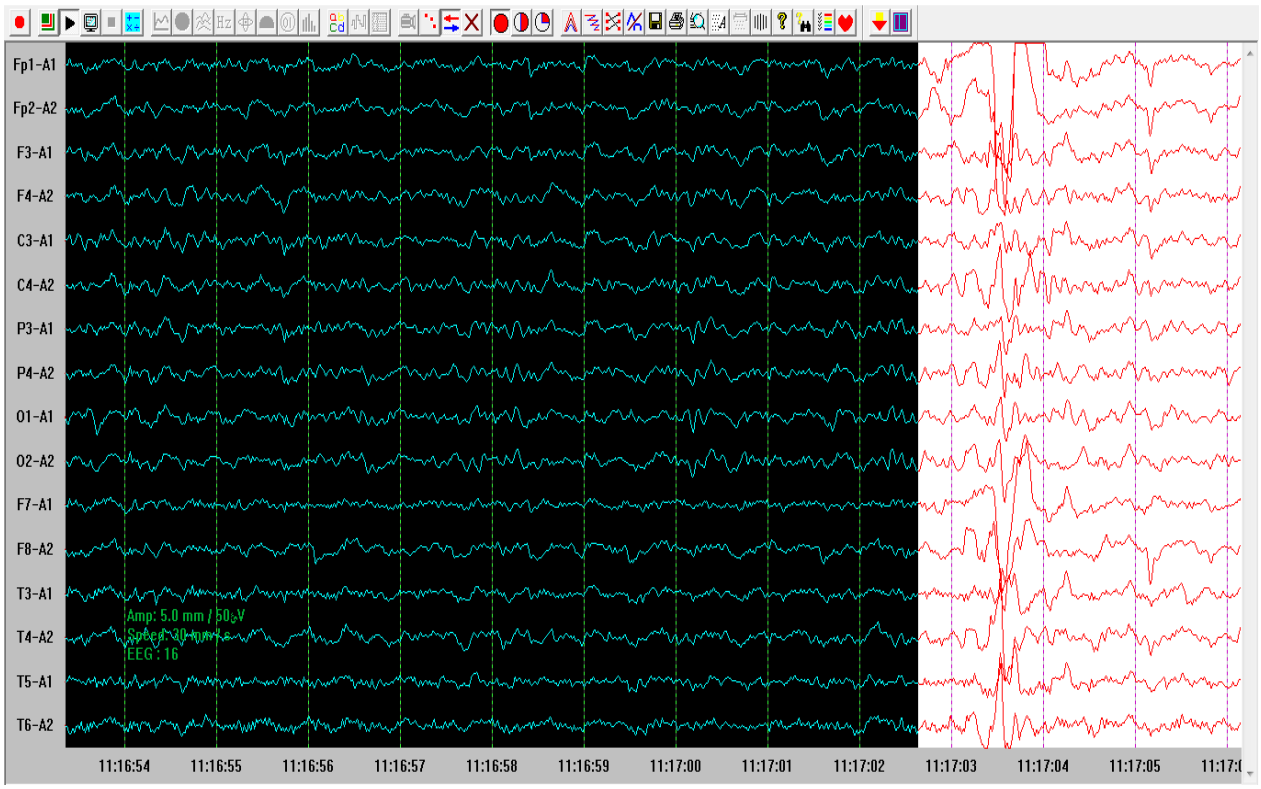


Figure (3-D): selection of an artifact free epoch.

The selected epochs were processed via QEEG software(KT88-1016) and mathematical formulas (e.g., Fourier Transform and Welch Method) were used to transform the data into frequency domain, and a scalp map of various frequency bands was obtained. (Coben *et al*., 2008).

The sensitivity was set at 7 µV, low-frequency filter 1Hz, high-frequency filter 70 Hz and 50-Hz notch filter. Epochs, which were subjected to Fourier power spectral analysis and application of the Hanning window band pass, to determine the magnitude of each frequency band in microvolt. The frequency bands were classified into "delta (0.8–3.9 Hz), theta (>4-7.9 Hz), alpha (>8–12.9 Hz), and beta (13–30 Hz)" as shown in **figure (3-E)**. Data was recorded from 18 electrode sites, as following "FP1, FP2, F3,F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1, and O2" were analyzed (Azouz *et al*., 2018).

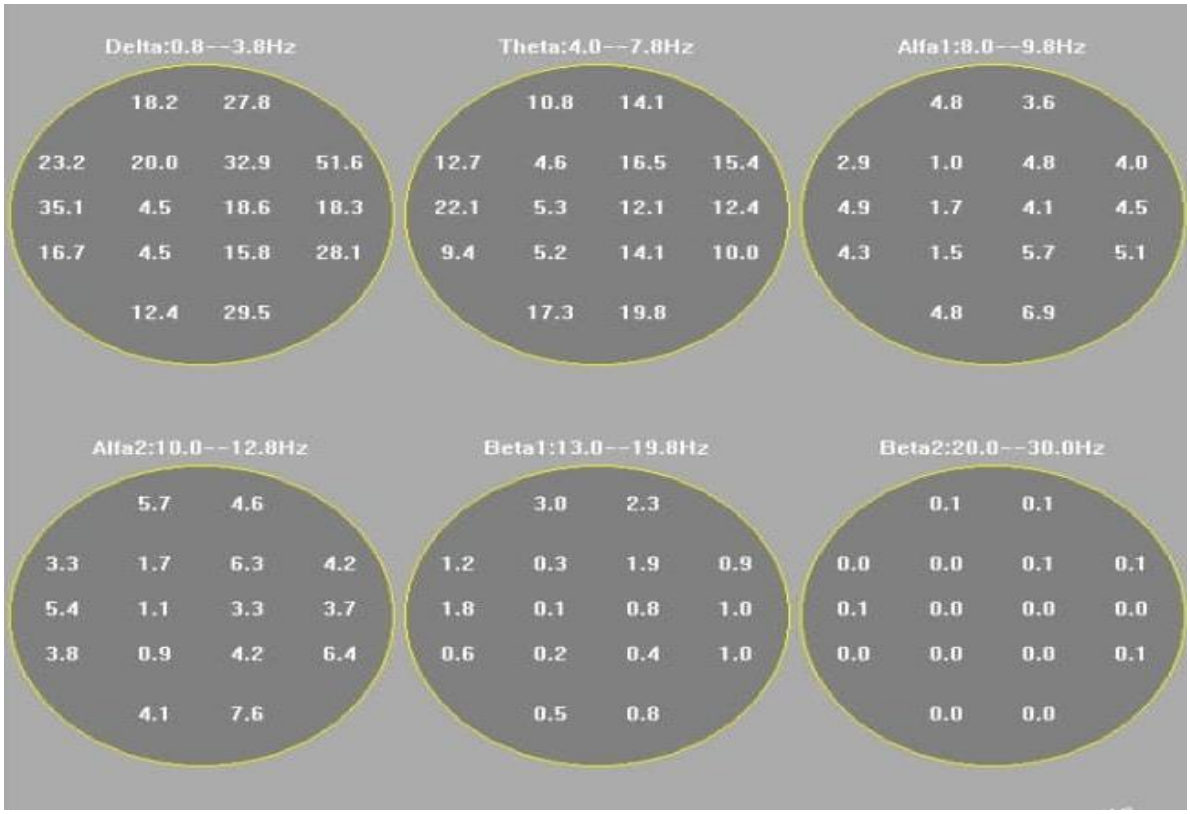


Figure (3-E): frequency bands and spectral power analysis by qEEG software.

Some features of QEEG that can be used are "absolute power (the average amount of power μV in each frequency band or wavelength and the total frequency spectrum recorded from each electrode site), and relative power (the percentage of total power contributed by each frequency band or wavelength in the spectrum from each electrode site)"(Simkin, 2014).

To limit the number of statistical tests, the absolute and relative power values from 16 electrodes were divided into six zones. These areas are depicted in **table (3-3)**.

Table (3-8): the cortical regions examined

Cortical region	Electrodes
1. Left hemisphere	Fp1, F3, F7, T5, T7, C3, P3 and O1
2. Right hemisphere	Fp2, F4, F8, T4, T6, C4, P4 and O2
3. Frontal	Fp1, F3, F8, Fp2, F4 and F7
4. Temporal	T4, T5, T6, and T7
5. Central	C3, C4 and Cz
6. Prieto-occipital	P3, P4, Pz, O1, O2 and Oz

3.3. Statistical analysis

The collected data were inputted on the computer and processed using Statistical package for Social Science (SPSS 23.0 for windows; SPSS Inc, Chicago, IL, 2015). Data were supplied and appropriate analysis was performed based to the type of data gathered Continuous data are given as mean and standard deviation (M±SD), and categorical variables are presented as percentage. The student t-test and ANOVA test was used to compare the data of baseline characteristics between different levels of ASD severity. Pearson`s (r) correlation coefficients were calculated to measure association of continuous data, also the receiver operating characteristic (ROC) curve were used to define cut off value with sensitivity and specificity for QEEG in grading ASD severity.

The differences are considered significant when the probability (P) is less than 0.05 ($p<0.05$)) (Wayne W. Daniel, 2018).

CHAPTER FOUR

RESULTS

4.1. Demographic data:

Our sample was mostly boys (male/ female ration= 3.4:1), the mean of their ages was 6.18± 2.1 years. A minority of patients (35.8 %, 19 child) had positive family history of a similar condition. Drugs used by the children at the time of the study included: omega-3 supplement, multivitamins supplement, Risperdal (atypical antipsychotic drug, effective for short-term treatment of aggression, temper outbursts, and self-injurious behavior in ASD children) which don`t have any record of affecting the electrical activity of the brain. The demographic data collected is shown in **table (4-1).**
Regarding the parents, fathers were in the thirties and the mothers in mid-twenties with only small percentage of them are related. Parental educational level is shown in figure **(4-A).**

The children were divided into three groups based on the severity of ASD (mild, moderate and severe) as seen in figure(4-B) and it show 29 childe has moderate ASD symptoms, 16 was mild, and only 8 sever. This can be explained by the fact that EEG recording requires the child to be calm which is difficult in severe cases, as for the mild cases, cases number was already low in comparison to moderate cases, we believe it is due to low index of suspension among parents.

Table (4-1): the demographic data of study participants

Variable	Finding
Male: female ratio	3.4:1
Positive family history	19 (35.8%)
Age(years)	6.18 ± 2.1
Father`s age(years)	31.5± 6.7
Mother`s age(years)	26.04 ± 5.3
Positive Parental consanguinity	19 (17.9%)
Positive drug history	20 (18.9%)
Duration of enrolment in the centers (months)	22.5 ± 15.7

Numbers are expressed as percentages (%), mean± standard deviation

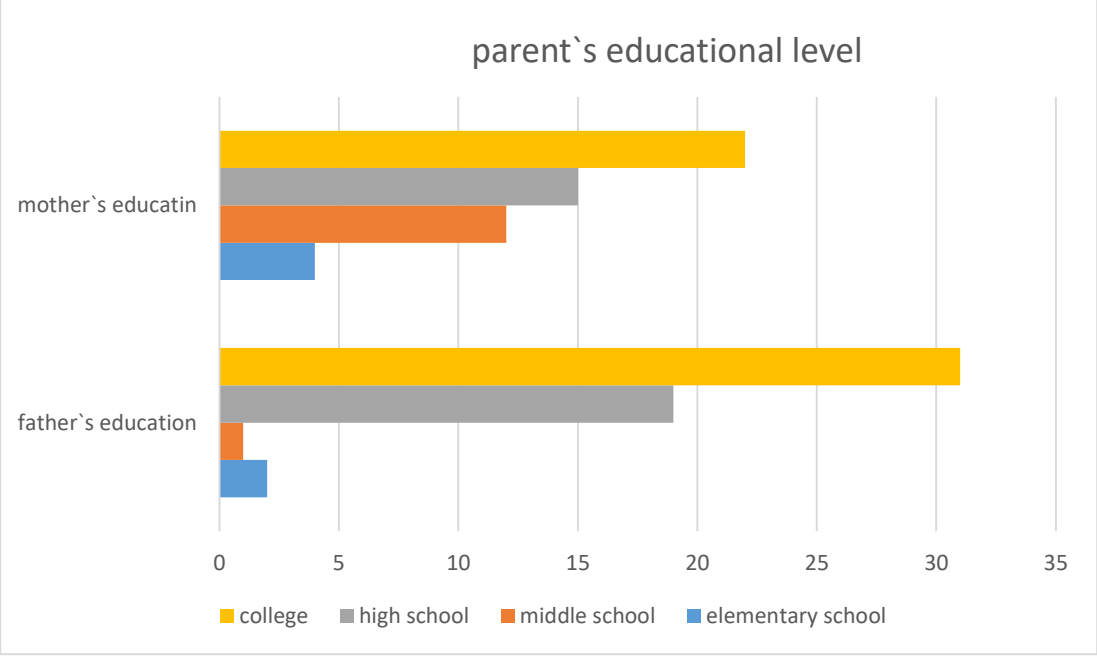


Figure (4-A): educational level of the ASD parents.

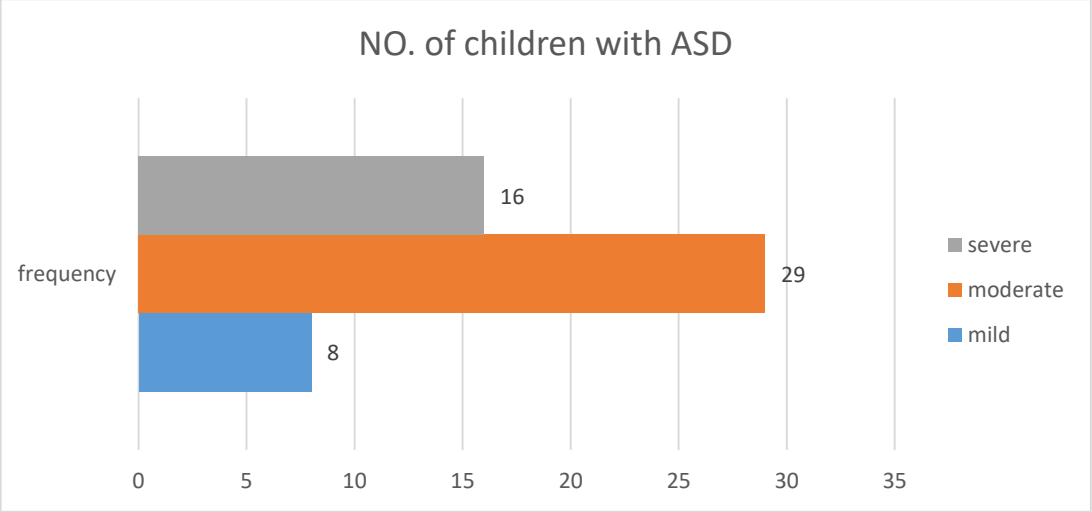


figure (4-B): number of children in each severity level of ASD.

4.2. Quantitative electroencephalography parameters and autism spectrum disorder severity:

The following tables show the QEEG parameters measured in μV of the different wave frequencies (alpha, beta, delta and theta), in both hemispheres and in different brain regions (frontal, central, temporal, and Prieto-occipital) for children with ASD. The statistical analysis showed significant increase of delta wave absolute power in all brain regions as the severity of the ASD increases, with P value <0.001.

Alpha wave also demonstrated an increase in absolute power seen in the right hemisphere and in the total power with a p value <0.005. On the other hand, neither theta frequency nor beta frequency displayed significant change with increase of the ASD severity.

Table (4-2): distribution of Delta wave power according to ASD severity.

Delta wave power at different head regions	ASD severity level		
	Mild	Moderate	Severe
Frontal	15.7 ± 3.6 aa	20.4 ± 2.8 bb	29.9 ± 2 cc
Temporal	11.9 ± 2.4 aa	19.6 ± 3.7 bb	27.3 ± 5.3 cc
Central	16.1 ± 3.1 aa	21.8 ± 2.7 bb	28.9 ± 3.7 cc
Prieto-occipital	18.2 ± 3 a	21.4 ± 4 bb	28.8± 6.9 cc
Left hemisphere	16.2 ± 3.1 aa	22.3 ± 2.3 bb	28.6 ± 3.6 cc
Right hemisphere	16.2 ± 2.7 aa	25.1 ± 1.9 bb	30.4 ± 3.8 cc
Total delta power	15.5 ± 2.3 aa	20.8 ± 2.3 bb	28.7 ± 2.7 cc

Values are expressed as mean ± standard deviation
a, aa significant difference between mild and moderate at p<0.05 and p<0.01 respectively
b, bb significant difference between moderate and severe at p<0.05 and p<0.01 respectively.
c, cc significant difference between mild and severe p<0.05 and p<0.01 respectively.

Table (4-3): distribution Alpha wave power according to ASD severity.

Alpha wave power at different head regions	ASD severity level		
	Mild	Moderate	Severe
Frontal	4.9 ± 1.5	4.5± 2	3.9 ± 2.3
Temporal	4.5 ± 2	3.9 ± 1.8	4.8 ± 5.4
Central	6.5 ± 1.6	5.5 ± 1.7	5.8 ± 4.8
Prieto-occipital	6.1 ± 2.2	6.5 ±3	7.4 ±7.6
Left hemisphere	6.4 ± 1.7	4.6 ± 1.8	5.2 ± 4.9
Right hemisphere	**6.9 ± 1.9 a**	4.7 ± 1.5	5.2 ± 4.5
Total alpha power	**6.6 ± 1.4 a**	4.7 ± 1.6	5.2 ± 4.7

a, significant difference between mild and moderate at p<0.05
Values are expressed as mean ± standard deviation.

Table (4-4): distribution of Beta wave power according to ASD severity.

Beta wave power at different head regions	ASD severity level		
	Mild	Moderate	Severe
Frontal	1 ± 0.5	0.9 ± 0.8	1 ± 0.5
Temporal	1 ± 0.9	0.6 ± 0.3	0.8 ± 0.5
Central	1 ± 0.5	0.9 ± 1	**1.1 ± 0.7**[c]
Prieto-occipital	1.1 ± 0.5	0.9 ± 0.9	0.9 ± 0.5
Left hemisphere	0.99 ± 0.6	0.9 ± 0.7	1 ± 0.7
Right hemisphere	1.1 ± 0.9	0.9 ± 0.6	0.9 ± 0.4
Total delta power	1 ± 0.7	0.9 ± 0.7	1 ± 0.5

Values are expressed as mean ± standard deviation

c, significant difference between mild and severe $p<0.05$

Table (4-5): distribution of Theta wave power according to ASD severity.

Theta wave power at different head regions	ASD severity level		
	Mild	Moderate	Severe
Frontal	16.5 ± 3.8	17 ± 5.9	17.9 ± 6.7
Temporal	14.6 ± 3	14.6 ± 5.8	17.7 ± 6.7
Central	16.2 ± 2	23 ± 9	25.4 ± 7.3
Prieto-occipital	16 ± 1.9	22.8 ± 8.5	25.1 ± 6.9
Left hemisphere	15.6 ± 3.2	18.8 ± 6.3	20.8 ± 7.9
Right hemisphere	16.3 ± 3.3	18.7 ± 5.9	20.9 ± 6.6
Total delta power	15.9 ± 3	18.7 ± 5.8	20.9 ± 6.9

Values are expressed as mean ± standard deviation

4.3. Correlation between autism index and quantitative electroencephalographic data:

Autism spectrum disorder severity was assed viaGARS-3, the scores of this scale are calculated to measure the autism index which increases as the severity of the symptoms increases.

Strong positive correlation between AI and the absolute spectral power of the delta and alpha waves in different brain regions was found with p value<0.0001, and <0.05 respectively.

Neither the absolute power of the total nor the regional theta and beta waves were significantly associated with the disease severity index. These findings are shown in **table (4-6).**

Table (4-6): correlation between autism index and QEEG parameter.

QEEG Power at different head regions	r value	P value
Delta frontal	0.810	0.0001
Delta temporal	0.692	0.0001
Delta central	0.728	0.0001
Delta Prieto-occipital	0.567	0.0001
Delta left hemisphere	0.751	0.0001
Delta right hemisphere	0.706	0.0001
Total delta	0.798	0.0001
Alpha frontal	0.004	0.079
Alpha temporal	0.129	0.035
Alpha central	-0.015	0.019
Alpha Prieto-occipital	0.129	0.035
Alpha left hemisphere	-0.006	0.039
Alpha right hemisphere	-0.039	0.005
Alpha total	-0.023	0.038
Beta frontal	0.091	0.519
Beta temporal	0.043	0.762
Beta central	0.048	0.735
Beta Prieto-occipital	0.035	0.802
Beta left hemisphere	0.134	0.337
Beta right hemisphere	0.02	0.822
Beta total	0.059	0.676
Theta frontal	0.128	0.362
Theta temporal	0.241	0.082
Theta central	0.224	0.108

Theta Prieto-occipital	0.163	0.243
Theta left hemisphere	0.169	0.227
Theta right hemisphere	0.231	0.096
Theta total	0.207	0.137

(r): Pearson's correlation coefficient

4.4. Receiver operating characteristic curve analysis:

Receiver operating characteristic curve analysis was done to find the cut-off value with sensitivity and specificity of the different qEEG parameters in determining the severity of ASD symptoms, results are displayed in the following figures and tables.

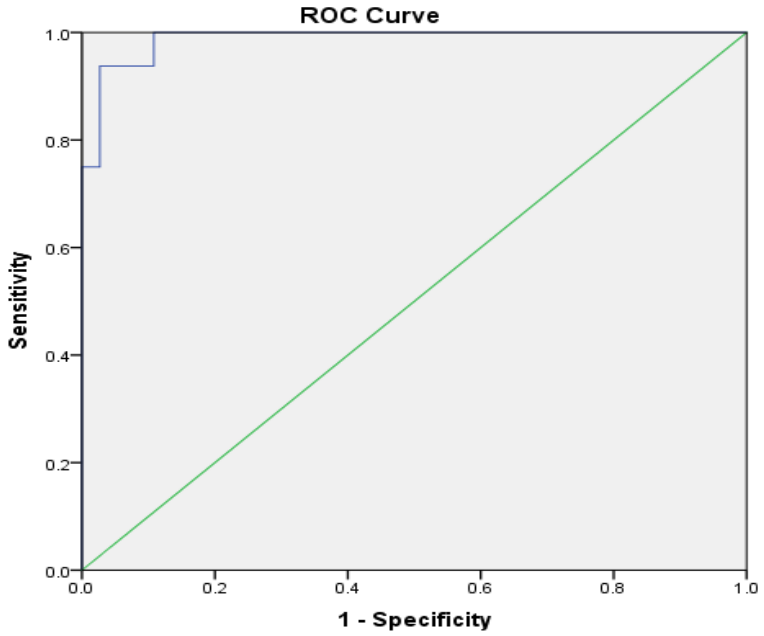


Figure (4-C): ROC curve analysis for assessment of ASD severity (severe ASD) by measuring the power of the total delta wave (μv).

Table (4-7): ROC curve analysis of total delta frequency in severe ASD.

QEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95 Confidence Interval	
					Upper bound	Lower bound
Absolute Total delta	0.988	27.4	75%	100%	0.968	1.00

AUC:area under the curve, CUV:cut-off value

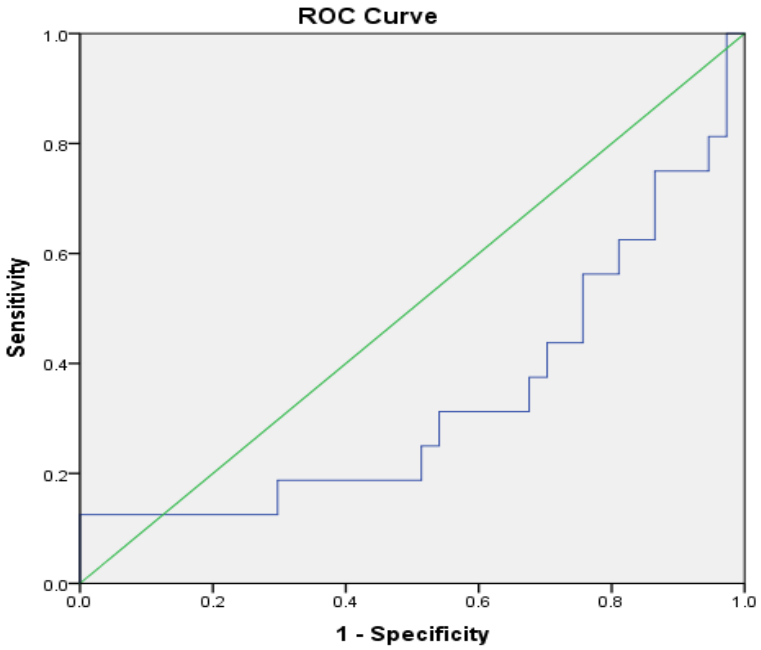


Figure (4-D) ROC curve analysis for assessment of ASD severity (severe ASD) by measuring the power of the total alpha wave (μv).

Table (4-8): ROC curve analysis of total alpha frequency in severe ASD.

QEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Upper bound	Lower bound
Absolute Total alpha	0.334	5.3	19%	43%	0.162	0.507

AUC:area under the curve, CUV:cut-off value

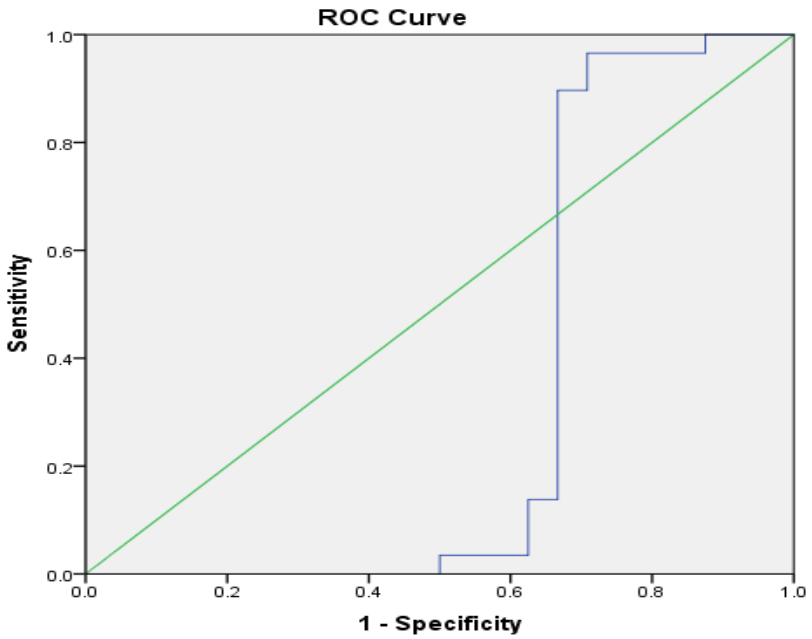


Figure (4-E) ROC curve analysis for assessment of ASD severity (moderate ASD) by measuring the power of the total delta wave (μv).

Table (4-9): ROC curve analysis of total delta frequency in moderate ASD.
AUC: area under the curve, CUV: cut-off value

QEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Upper bound	Lower bound
Absolute Total delta	0.333	21.0	0.448	0.667	0.152	0.515

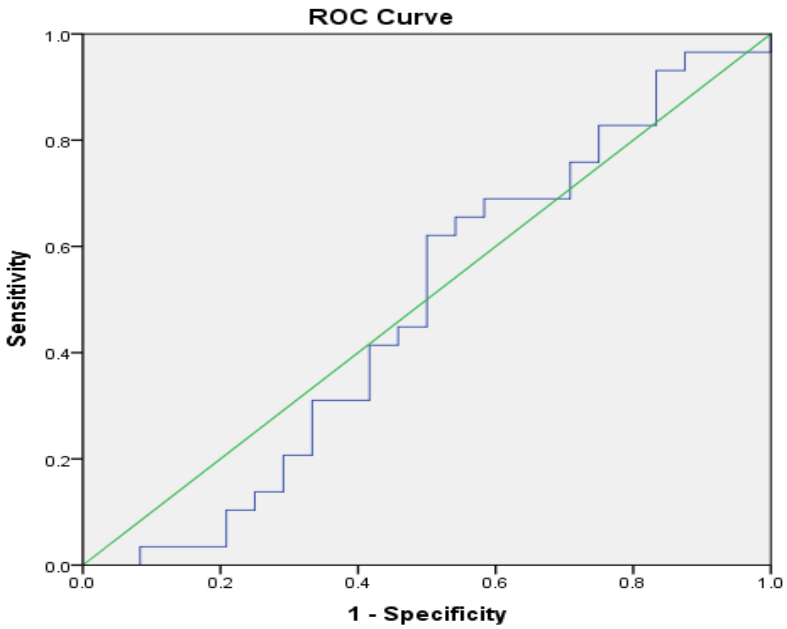


Figure (4-F) ROC curve analysis for assessment of ASD severity (moderate ASD) by measuring the power of the total alpha wave (µv).

Table (4-10): ROC curve analysis of total alpha frequency in moderate ASD.

QEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Upper bound	Lower bound
Absolute Total alpha	0.484	4.6	0.448	0.458	0.321	0.647

AUC: area under the curve, CUV: cut-off value

4.5. multinomial logistic regression between qEEG parameters and ASD severity:

The following tables display the relation between the different QEEG parameters and the increase in ASD severity. There is statistically significant association between power of delta frequency and ASD severity in all regions mostly in the frontal region with odds ratio of 8.5 at p value of 0.001 as shown in table (4-11):

Table (4-11) multinomial logistic regression regarding the delta wave spectral power, between the moderate and severe ASD patients in reference to the mild.

Delta wave absolute power at different head regions	ASD severity	Significance	*Exp(B	*95% Confidence Interval for Exp(B)	
				Upper bound	Lower bound
left hemisphere	moderate	0.005	2.1	1.2	3.5
	Severe	0.007	3.7	2.8	5.9
right hemisphere	moderate	0.0001	3.7	2.2	8.1
	Severe	0.0001	6.1	1.2	1.2
Frontal	moderate	0.010	2.1	1.2	3.9
	Severe	0.001	8.5	2.3	3.1
Temporal	moderate	0.006	1.9	1.2	3.0
	Severe	0.0001	2.8	1.6	4.8
Central	moderate	0.010	2.0	1.1	3.4
	Severe	0.0001	5.8	2.4	4.1
Prieto-occipital	moderate	0.033	1.4	1.0	1.9
	Severe	0.001	1.8	1.3	2.7
Total	moderate	0.083	8.5	0.7	9.7
	Severe	0.012	5.5	2.0	3.1

***Exp(B):** exponential value of B. When Exp(B) is less than 1, increasing values of the variable correspond to decreasing odds of the event's occurrence.
****confidence interval:** is a range of values that's likely to include a population value with a certain degree of confidence.

While none of the brain regions showed statistically significant change in alpha, theta and beta frequency power in association with increase in ASD severity, as seen in the following table:

Table (4-12): multinomial logistic regression regarding the alpha wave spectral power, between the moderate and severe ASD patients in reference to the mild.

Alpha wave power at different head regions	ASD severity	significance	Exp(B)	95% Confidence Interval for Exp(B	
				Upper bound	Lower bound
left hemisphere	Moderate	0.185	0.854	0.676	1.079
	Severe	0.476	0.921	0.734	1.156
right hemisphere	Moderate	0.091	0.802	0.620	1.36
	Severe	0.262	0.866	0.674	1.114
Frontal	Moderate	0.153	0.759	0.519	1.108
	Severe	0.263	0.790	0.523	1.193
Temporal	Moderate	0.599	0.938	0.740	1.190
	Severe	0.857	1.021	0.814	1.281
Central	Moderate	0.371	0.896	0.704	1.140
	Severe	0.625	0.939	0.730	1.208
Prieto-occipital	Moderate	0.814	1.024	0.838	1.252
	Severe	0.565	1.062	0.866	1.302
Total	Moderate	0.127	0.823	0.641	1.057
	Severe	0.357	0.893	0.702	1.136

4.6. Relation between severity of language impairment in ASD and asymmetry:

Language impairment severity was assessed via GARS-3 which allows the severity assessment of each domain separately. And the association between impairment level and the asymmetry of the left and right hemispheres was found to be statistically insignificant (except for the

moderate severity and this can`t be utilized effectively in clinical practice) with p value > 0.05, as shown in the following table:

Table (4-13) relationship between severity of language impairment in ASD patients and QEEG power spectral left VS right hemisphere asymmetry.

Severity of Language impairment in ASD patients	P value	95% Confidence Interval of the differences	
		Lower bound	Upper bound
Mild	0.603	-36.6	32.6
Low moderate	0.357	-3.56	9.15
Moderate	0.030	2.06	9.6
High moderate	0.750	-30.0	25.3
no communication	0.49	0.053	20.10

4.7. Quantitative electroencephalography parameters and severity of behavioral abnormality:

Severity of behavioral abnormality was assed via Gilliam autism rating scale- third edition, which allows for the assessment of each domain separately. The following table show the qEEG parameters measured in μV of the delta and alpha waves frequency in both hemispheres and in different brain regions (frontal, central, temporal, and Prieto-occipital) for children with ASD. The statistical analysis using ANOVA test showed significant increase of delta wave power in all brain regions as the severity of behavioral abnormality increases, with P value <0.001and <0.05 as shown in **table (4-14).** Alpha wave showed significant increase of its absolute power in the right hemispheres, while power analysis in all other regions were insignificant as shown in **table (4-15).** Analysis of both theta and beta was statistically in significant.

Table (4-14) distribution of Delta wave power according to the severity in behavioral abnormality.

delta wave power at different head regions	Severity of behavioral abnormality in ASD patients				
	Mild	Low moderate	Moderate	High moderate	Severe
Frontal	17.6 ± 3.6	20.1±2.9	**23.8 ±5.7** [b]	**29.4 ± 2.4** [dd]	**29.8± 0.5** [ee]
Temporal	15.3 ±4.3	20.1±2.9	**21.8 ±5.9** [b]	**29.0± 4.6** [dd]	**27.3 ±1.6** [e]
Central	19.1± 4.1	22.3±2.7	24.0± 6.0	**26.3±2.7** [dd]	**32.5 ±0.14** [ee]
Prieto-occipital	19.3± 2.9	21.2±4.0	24.5 ±7.6	**26.0± 3.4** [dd]	**35.1±2.1** [ee]
left hemisphere	18.6 ± 4.1	**22.6 ± 1.8** [a]	**24.4±5.2** [b]	**26.4±0 .9** [dd]	**33.2±1.8** [ee]
right hemisphere	19.4± 4.4	**25.6 ±1.6** [aa]	**27.3± 4.6** [bb]	**28.1± 1.8** [dd]	**32.9 ±5.7** [e]
Total	17.8±3.3	20.6±2.0	23.5 ± 5.4	**27.7± 0.9** [dd]	**31.2 ± 0.04** [ee]

a, aa significant difference between mild and low moderate at p<0.05 and p<0.01 respectively
b, bb significant difference between mild and moderate at p<0.05 and p<0.01 respectively
d, dd significant difference between mild and high moderate p<0.05 and p<0.01 respectively
e, ee significant difference between mild and severe p<0.05 and p<0.01 respectively

Table (4-15) distribution of alpha wave power according to the severity in behavioral abnormality.

Alpha wave power at different head regions	Severity of behavioral abnormality in ASD patients				
	Mild	Low moderate	Moderate	High moderate	Severe
Frontal	4.6±1.9	3.5± 1.8	4.1±1.7	3.0±1	6.6±4.1
Temporal	4.6±2.1	3.6±1.7	4.3±3.7	2.7±0.6	10.7±3.1
Central	6.0±1.6	6.0±2.3	5.7±2.9	3.8±2.6	10.6±1.6
Prieto-Occipital	5.9±1.8	6.2±3	7.4±5.5	4.8±2.6	12.6±3.6
Left Hemisphere	5.8±1.1	4.3±1.8	5.4±2.9	3.1±1.5	10.4±2.5
Right Hemisphere	5.8±2.7	4.5±2.4	5.1±3.2	**3.2±1.3** [d]	10.7±2.5
Total	5.8±1.7	4.4±2	5.3±3	3.3±1.4	10.5±3

d, significant difference between mild and high moderate p<0.05

In the following tables we examined the relation between QEEG parameters measured in μV of in alpha and delta frequencies, in left and right anterior head region (mid-frontal, lateral frontal, central, parietal) and the severity of behavioral abnormality, and found significant asymmetry between alpha absolute power between right and left (higher in right) frontal head region in all severity levels of behavioral abnormalities with p value <0.005 as shown in table (4-16). Also, analysis of delta power found significant asymmetry with p value <0.05 in almost all levels of ASD severity, table (4-17).

Table (4-16): relationship between severity of behavioral abnormality in ASD patients and alpha wave power spectral left VS right frontal asymmetry.

Behavioral abnormality severity	p value	95% Confidence Interval of the differences	
		Lower bound	Upper bound
Mild	0.005	0.59	0.95
Low moderate	0.005	0.6	1.40
Moderate	0.003	0.91	1.14
High moderate	0.001	0.10	1.51
Severe	0.000	0.89	1.50

Table (4-17) relationship between severity of behavioral abnormality in ASD patients and delta wave power spectral left VS right frontal asymmetry

severity of Behavioral abnormality	p value	95% Confidence Interval of the differences	
		Lower bound	Upper bound
Mild	0.059	1.37	1.98
Low moderate	0.015	0.87	1.54
Moderate	0.067	-0.045	1.277
High moderate	0.009	-4.86	-0.42
Severe	0.008	-4.97	6.57

CHAPTER FIVE

DISCUSSION

5.1. demographic data:

5.1.1. Effect of gender:

Numbers of the sample show high sex predilection in people with ASD. According to a significant systematic review and meta-analysis the gender disparity in males is expected to be up to triple than that in girls. (Loomes *et al.*, 2017), while other studies suggested that males are about four times more likely to be diagnosed with ASD than females (Werling *et al*., 2016; Zhang *et al*., 2020).

Numerous concepts have been offered to clarify the higher risk of ASD among boys, of these, is the "multiple threshold liability model" which propose that multiple genetic factors cause the susceptibility to develop ASD, and a greater threshold of genetic liability is essential for girls in comparison to boys; , this is also known as the "female protective model" (Robinson *et al*., 2013; Werling *et al.*, 2016).

Another research suggests that genes of sex chromosomes and/or sex hormones, particularly testosterone, may temper the effects of genetic variation on the presentation of an autistic phenotype (Zeestraten *et al*., 2017).

The researcher believe the sex predilection here may be affected by sociocultural factors, with the possibility that boys may get more attention than girls.

5.1.2. Family history:

Family history of ASD in children recruited for this study was positive in 19 (35.8%) of cases, whereas 34 (64.1%) children have negative family history as seen in **table (4-1),** indicating a possible association between positive family history and ASD.

In a large population-based longitudinal study evaluating familial risk of ASD conducted on children born in Sweden, the heritability of ASD was estimated to be approximately 50% (Sandin *et al.,* 2014). This is considerably lower than the 90% percentage of heritability found in earlier twin studies (Steffenburg *et al.,* 1989 and Bailey *et al*., 2013) and closer to the 38% reported in a recent California twin study (Hallmayer *et al*., 2011). If a full sibling gets the diagnosis, the chance of ASD increases tenfold, and if a relative has it, the risk increases nearly twofold (Sandin *et al.*, 2014). furthermore, in families of ASD children, different medical, developmental, and neuropsychiatric disorders are more common (Mostafa & Shehab, 2010).

5.1.3. Parental age and educational level:

The mean paternal age is 31 years and maternal age is 26 years, many literatures suggests an elevated risk of ASD with increased mother`s and father`s age individually (Shelton *et al.*, 2010). A study lead in families with one child diagnosed with ASD found that there was no link between maternal age and ASD incidence for siblings of ASD children, while there was a link between younger fathers at the time of conception and ASD among siblings of children with ASD (Hallmayer *et al.*, 2011)

There have been several studies investigating the relationship between parental level of education and ASD in their children. In this

study we found that more than 50% of the fathers and 40% of the mothers are college graduates, as shown in figure **(4-A).** In the United States, numerous studies found that autism rates are higher among children with parents educate at high levels(Mazurek *et al*., 2014 and Dickerson *et al*., 2017). However, in Sweden, no important relationships with parental education levels were observed (Rai *et al*., 2012). In contrast, a new survey among children of women with A-level or higher education had twice the risk of ASD diagnosis as those of mothers with lower levels of education(Kelly *et al*., 2019). The researcher believes these results are due to high index of suspicion among the educated parents so the ASD cases are diagnosed more efficiently than those raised by uneducated parents.

5.2. Comparison and association between quantitative electroencephalographic parameters and autism spectrum disorder severity:-

Autism spectrum disorder is widely regarded as a permanent impairment with an unknown origin, several researchers have examined the oscillatory activity of QEEG in ASD, but none of them was able to confirm whether these changes are a cause of ASD or a result.

In this study we found statistically significant increase of delta wave absolute power in all cortical regions as the severity of the ASD increased, **table (4-2)**.

On reviewing literatures about the delta activity in ASD, we found conflicting results that ranges from decreased delta power in all or regional head areas, to the more common and agreeable results of increased delta spectral power in ASD patients (Coben *et al*., 2008) some authors findings go in the same direction of the results of this study in showing increased delta spectral power in all head regions

and also in every regions separately (Stroganova *et al.*, 2007; Elhabashy *et al*., 2015). While other researchers found increased spectral power of delta wave in frontal regions (Kawasaki1 *et al*., 1997; Stroganova *et al.,* 2007; Pop-Jordanova *et al.*, 2010), or Centro-Parietal head regions like Chan and his study group in 2007.

In addition, One of the earliest studies by (Cantor *et al.,* 1986) described higher delta frequency activity among children with ASD in comparison to mental age-matched control subjects. And many other studies were able to replicate this increased delta in ASD (Chan *et al*., 2007; Murias *et al.*, 2007).

We propose that in certain circumstances, enhanced low-frequency activity in individuals with ASD (delta wave) may represent a compensating strategy to prevent the activation of high excitatory frequencies caused by GABAergic system malfunction similar to the theory mentioned by(Ma *et al.*, 2005), this interrupted inhibitory control system could be connected to high levels of inattentiveness and impulsivity noticed in ASD patients (Mosconi *et al.,* 2009)

In this study, alpha wave also demonstrated an increase in power seen in the right hemisphere and in the total power **table (4-3)**. Some inconsistent results, regarding alpha wave power in ASD, in comparison to typically developed children, was found to be reduced (Cantor *et al.,* 1986; Chan *et al.,* 2007), unchanged (Stroganova *et al*., 2007), or even higher (Mathewson *et al.*, 2012). A greater alpha power shows the suppression of non-essential activity and, as a result, improved task performance. (Klimesch *et al.*, 2007) that can be described by the “neural efficiency” hypothesis (Doppelmayr *et al.,* 1998).

The researcher believes alpha power at Rest has a positive relationship with various cognitive rigidity features, such as the inability to adjust to changes and an inclination for repeated activities(Precenzano *et al.,* 2020).

In a study by Fauzan and his colleagues in 2015, one of the QEEG patterns they found was extra slow wave activity (delta, theta) or extra rapid wave activity (alpha, beta) associated to "hyper- or hypofunctioning" of the precise area(Fauzan & Amran, 2015),

A recent study done in Al-Nahrain University/ college of medicine showed a very similar results to this one regarding the delta and alpha frequencies, where the total absolute and regional delta-theta activity were significantly higher in patients versus controls, they also proposed might be relating to hyper or hypo functioning of the localized area especially at the frontal lobe suggesting faulty neural integration between frontal and the posterior regions. In addition, they found increased absolute total alpha activity and reduced central and temporal regional alpha activity in patients versus controls (Jasim *et al.,* 2021)

Agreeing with that, Wang and his colleagues (2013) released a review of researches that recorded resting-state EEG for ASD children and found a U-shaped pattern of broadly spread EEG power modifications, with raised power in low-frequency and high-frequency waves, till now, there is no agreeable theory that explain the cause of abnormal delta and alpha spectral power and distribution in ASD patients and whether they are the cause or result of the ASD symptoms and signs. Some researchers blame the function of some neurotransmitter molecules like gamma-aminobutyric acid (GABA) in inhibitory circuits might cause an imbalance between inhibition and

excitement in the brain, and that this could be at least partly to blame for the widespread dysfunctions (Tierney *et al*., 2012).

5.3. Relation between quantitative electroencephalography parameters and Autism index:

In this study we found a positive association between the absolute spectral power of the delta and alpha waves and the increment of AI (which reflects the increase in ASD symptoms severity measured by GARS-3), On the other hand, other frequency bands (beta, and theta) showed insignificant association with autism index increase, **table (4-6).**

There is only few studies that investigate the statistical association between different QEEG parameters and ASD severity such as: the higher-order spectra bi-spectrum (Pham *et al.,* 2020)(The higher-order spectrum is an extension Fourier spectrum that uses higher moments for spectral estimates), as for the power spectral analysis, positive correlation between absolute power delta/theta bands of QEEG and the severity score of the disease measured by CARS was reported by (Jasim *et al.*, 2021).

In this study we also tried to find the degree of this association between the QEEG absolute spectral power and the severity of ASD, and we found that there is statistically significant association between power of delta frequency and ASD severity in all regions mostly in the frontal region, where the power of the delta frequency increased about eight times in severe cases in comparison with mild cases, in the left hemisphere delta power increased about six folds in severe ASD in comparison to mild ASD as shown in **table (4-11)**, these results suggests that delta power can be utilized in the determination of ASD

severity and support the ASD diagnosis or follow up the response to treatment, adjuvant to the available scales and instruments in an objective rather than subjective way.

On the other hand, none of the brain regions showed statistically significant change in alpha in **tables (4-12)**, theta and beta frequency power in association with increase in ASD severity,

5.4. Receiver operating characteristic curve analysis of Quantitative electroencephalographic parameters:

All previous studies measured the ROC curve to assess QEEG validity in differentiating ASD patients from controls, and up to the researcher`s knowledge, this is the first study that measure ROC curve to test the validity of QEEG in the assessment of ASD severity.

The optimal cut-off value for the diagnosis of severe ASD of the total **delta** frequency power for was 27.4 μv with good sensitivity and specificity as shown in figures (4-C and 4-D), and tables (4-7 and 4-8).

Receiver operating characteristic curve analysis of QEEG parameters in the diagnosis of moderate cases results had low sensitivity and specificity for all frequencies.

Based on ROC curve analysis of this study, **delta** wave results had high AUC (>90%) suggesting that this QEEG parameter has a good accuracy for classifying sever cases of ASD from mild ones.

5.5. Relation between severity of language impairment in autism spectrum disorder and asymmetry of quantitative electroencephalographic data:

EEG asymmetry in children with autism has been mentioned in many literatures, several studies have examined language impairment

in ASD patients, hemispheric asymmetry and the relation between them. In this study we found no significant relation between power asymmetry and the level of impairment as seen in **table (4-13).**

A research performed by(Dorenbaum *et al.*, 1987) agree with the findings of this study, they stated "We did not find a statistically significant correlation between EEG changes and speech performance", Neither expressive, nor receptive language displayed statistically significant correlation with EEG changes, The EEGs of the most actively communicative kids varied from normal to seriously abnormal, while the majority of verbal children with a moderate degree of communication skills had typical EEGs. In another study done by (Burnette *et al.,* 2010) initial correlation analyses showed insignificant association between verbal IQ and EEG abnormal symmetry in all examined children, within the high functioning ASD children or comparison group alone.

To our knowledge, no additional studies associated absolute spectral power analysis with language impairment. Other studies used imaging techniques to asses asymmetry, they proposed that the asymmetry is related to the language impairment rather than to the autism itself as they found that the volume of the speech association cortex in ASD children was of no significant difference from normal children, and the hemispheric asymmetry was also insignificant (De Fossé *et al.*, 2004). And based on these results, the researcher believe that EEG abnormality associated with ASD is not related to the presence or absences of language abnormality, and can`t be linked to the severity of the deviance.

5.6. Quantitative electroencephalographic parameters and severity of behavioral abnormality:

To understand the etiology of ASD, understanding and correlating the neuroanatomical findings and behavioral symptoms is important (Sheikhani *et al.*, 2012; Szachta *et al.*, 2016). Individual characteristics and subgroups in ASD children may benefit from psychophysiological monitoring of processes connected with social behavior(American Psychiatric Association, 2022; Dawson et al., 1995; Modahl et al., 1998).

In this study statistically significant increase of delta wave power in all brain regions as the severity of behavioral abnormality (measured via GARS-3 as a separate domain) increases**, table (4-14).**

Alpha wave showed significant increase of its absolute power in the right hemispheres, **table (4-15)**, while power analysis in all other regions were insignificant. We also found statistically significant asymmetry between alpha and delta absolute power in right and left (higher in right) frontal head region at all severity levels of behavioral abnormalities, **table (4-16,17).**

A study done by Sutton and his colleagues (2005) to test if fields of behavior and social symptoms are linked to EEG asymmetry at anterior head region in ASD showed very similar results, it resulted in the conflicting assumption that asymmetry at left frontal cortex in ASD would worsen social impairments, also, increase the associated emotional complications including “obsessive compulsive symptoms and expressed anger”. He confirmed the assumption that variation of EEG asymmetry in the frontal area perhaps may modify the expression of ASD by observing the relationship between frontal head region EEG

asymmetry at rest and severity degree of the symptoms and social/emotional behavior in ASD children and adolescents.

Likewise, wide research literature signifying links between "approach behaviors" and increased easting-state cortical activity frontal head region at the left rather than right hemisphere, and between "avoidant behaviors" with higher right rather than left resting activity(Harmon-Jones & Allen, 1998;Davidson, 2002; Pizzagalli et al., 2005).

(Sutton et al., 2005) explained that if "approach-avoidance behaviors" alter the symptoms of ASD or its phenotype, then measuring anterior EEG asymmetry at rest, or standard brain activity, might be connected with essential differences in expression of ASD symptoms(Sutton *et al.,* 2005). Agreeing with this theory, reports of parents on a "symptom checklist" which found that 8- to17-year-old subjects with mild ASD who showed left frontal EEG asymmetry also showed fewer or less severe symptoms of social disabilities or limitations in comparison children with right frontal EEG asymmetry(Burnette *et al*., 2010).

Because left anterior EEG asymmetry is linked to "approach behavior" and right anterior asymmetry is linked to withdrawal, the researchers translated their findings to mean that the manifestation of social symptoms was weaker or less evident in autistic children who were inclined to approach behavior.

Because effective communication and information integration across brain areas are essential for proper brain function, disturbances in this communication can induce cognitive and behavioral issues, and as a result, we suggest that left frontal asymmetry may be related to

the intensified abnormal behavior in children with autism. Furthermore, opposing to anticipations based on previous work (F. R. Volkmar et al., 1989) proposed the left and right frontal EEG groups did show difference on IQ proposing that cortical processes associated with approach behavior or avoidance behavior may differentiate subgroups of children with autism based exclusively on phenotypic expression with disregard to the differences in IQ(Burnette *et al.,* 2010).

Accordingly, subjects with relatively higher right anterior versus left anterior brain activity are more likely to exhibit limited movement towards goals and withdrawal from new situations and social communications (Gray, 1994; Sutton & Davidson, 1997; Davidson, 2002)

These results indicate that anterior EEG asymmetry might be a measure of motivation, emotion, and behavior control that refracts autistic symptoms into significant individual variations in social expression among better functioning children. Of course, more focused study is required before the clinical application of EEG asymmetry assessment can be fully realized. We require a deeper knowledge of the best procedures for collecting and calculating EEG asymmetry, as well as psychometrics and the validity of equivalency measurement among children.

CHAPTER SIX

Conclusions

1. Children with ASD have abnormal QEEG (increased alpha and delta wave spectrum power) and this might underlie the symptomatology and etiology of the condition.
2. Increased absolute spectral power of alpha and delta frequency QEEG pattern positivity was related to the severity level of behavioral abnormality clinically.
3. There is no association between QEEG patterns and language dysfunction in ASD patients.

Recommendations

1. Further research with larger sample size studying the qEEG parameters in correlation with ASD need to be done.
2. Increased Delta spectral power can be used as an additional tool in the grading tool of ASD severity level.
3. This study can't assess the long-term effects of EEG abnormalities on the brain development of children with ASD since the data in this study was obtained at a single time point. To demonstrate the temporal sequences and the long-term effect, longitudinal studies is recommended.
4. It is believed that integrating different EEG methodologies with well-established ones might lead to a fresh viewpoint on ASD evaluation, as well as new early diagnosis, intervention, and preventive measures.

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