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Original Article

Visual Evoked Potential Findings and Correlation between Visual Evoked Potential and Clinical Severity in Children with Autism Spectrum Disorder

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Abstract

Background: Autism spectrum disorder (ASD) is a heterogeneous behavioral disorder that is characterized by qualitative deficits in social communication and interaction and restricted, repetitive behavioral patterns, activities, and interests. For an optimum outcome in children with autism, early intervention (preferably before three years of age) is essential. Hence, there is a critical need to improve the awareness of ASD to enable earlier detection and intervention. The present study aims at achieving the following: (1) Investigating neural transmission within the visual system using visual evoked potentials (VEPs) as an index of the myelination process of the visual pathway. (2) Correlating the changes in the VEPs with the clinical severity of autism. (3) Investigating the possible gender differences in VEPs in autistic children. **Materials and Methods:** The study was conducted on 60 preschool children (11 females and 49 males) who were recruited from the autism center and the pediatric neurology ward and who met the DSM-V criteria for autism in the Pediatric Hospital for the period from 12 December 2019 to 1 June 2021. Their mean age was 4.5±1.17 years. Another 50 (40 males and 10 females) age- and gender-matched normally developed children served as the control group. Both groups were subjected to a detailed history, as well as complete physical and neurological examinations. The VEPs were assessed for all of them. The autistic children were excluded from the study if they had any motor, visual impairment, inborn errors of metabolism, epilepsy, other chronic medical or neurological disorders, or if they were taking medications during the period of study. **Results:** The P100 wave latency of the VEPs was significantly prolonged in both eyes of autistic children as compared with that of the control group. The N75-P100 amplitude was significantly lower in the left but not the right eye of patients when compared with those of normally developed children. Neither the P100 wave latency nor the N75-P100 amplitude of both eyes was associated with the gender or severity of illness. **Conclusion:** There are distinct changes in VEPs in autistic children, especially the abnormal prolongation of conduction time, suggesting that autistic children may have brainstem and visual pathway dysfunction. Gender and disease severity score have no impact on VEPs.

Keywords: Autism spectrum disorders, childhood autism rating scale, diagnostic statistical manual of American psychiatric association, pattern-reversal visual evoked potentials, visual evoked potential

Introduction

ASD refers to a lifetime, generally stable condition of a group of pervasive neurodevelopmental disorders that involve moderately to severely disrupted functioning regarding social skills and socialization, expressive and receptive communication, and repetitive or stereotyped behaviors and interests.[1,2]

It is known as a "spectrum" disorder, because there is wide variation in the type and severity of symptoms that people experience. The broad terms encompassing autistic disorder, Asperger disorder/syndrome, and pervasive developmental disorder are not otherwise specified. These disorders all share common features of impaired social

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relationships, impaired communication and language, and stereotypic motor mannerisms or a narrow range of interests.[3]

The most recent global burden of disease estimates revealed 62.2 million people with ASD around the world in 2016.[4] The prevalence has been steadily increasing over the past two decades, with current estimates reaching up to 1 in 36 children. Community-based prevalence rates for ASD in the general population show considerable variation across studies, though recent systematic reviews and large-scale epidemiological research estimate rates of between 0.7% and 1.1%.[5-7] Similar prevalence estimates have been reported in adults.[8] Over the past decade or so, studies across the world have estimated an increase between 50% and more than 2,000% in cases of autism.[9]

In addition, the prevalence of autism is significantly higher in people with moderate to profound intellectual disability; comorbidities are common (e.g. more than 50% may present concurrent physical or mental conditions).[7,10]

ASD seems to affect more males than females, with approximately four affected males for every one affected female.[11,12] Intelligence level affects this sex ratio: Males are substantially overrepresented among high-functioning cases, and males and females are more equally represented among cases with severe intellectual disability. Girls have been reported to show more social communication and had fewer repetitive behavior symptoms.[13]

In some countries, the prevalence of diagnosed ASD is lower among children of women from minority ethnic groups. For example, children of Indigenous women in Australia[14] and Canada[15] have a lower prevalence of diagnosed ASD than the children of Caucasian women.

In the United States, children born to Hispanic and Black women have a lower prevalence of diagnosed ASD than children born to Caucasian women. In addition, some studies indicate that the proportionate distribution of ASD with (vs without) intellectual disability is higher in the children of Hispanic, Asian, or Black women than the children of Caucasian women.[16]

The exact pathomechanism of ASD is not known so far, although several factors have been implicated in its pathogenesis of autistic disorders. The mechanism that leads to ASD is very complex, involving genetic, epigenetic, immune, and environmental factors that could act in different proportions, at different developmental stages (prenatal, perinatal, or postnatal), and on different pathways.[17,18]

Environmental factors involved in autism determinism could be very diverse and include classical extrinsic factors (toxicants, environmental pollutants, medications, food additives, electromagnetic fields, and even social influences), maternal disorders or lifestyle factors, as well as intrinsic factors (hormones, inflammatory mediators, microbiota, and other biological molecules) that make up the microenvironment around the developing fetal or neonatal brain.[19]

Recent studies have suggested that autistic symptoms are continuously distributed in the population, forming a broad spectrum as the disorder may take many forms from mild-moderate-severe with a variety of impairments. This increasing heterogeneity of the disorder can cause difficulty in measurement and assessment. Measures should be able to quantify subtle differences in the degree of impairment across the spectrum and alert clinicians to the severity of symptoms, including those that may be sub-thresholded.[20]

There is a critical need to identify children with autism at a very young age so that they can access evidence-based interventions that can significantly improve their outcomes and that financially benefit society by reducing the need for costly services later in life. To make early identification easier to achieve, valid screening and diagnostic instruments are needed that are, ideally, simple and brief, available at no charge, cost-effective to administer, accurate when completed by both clinicians and parents, appropriate for toddlers as well as older children, and designed for individuals at both the low and high ends of the autism spectrum.[21]

Currently, biological diagnostic markers are not available and diagnosis rests on careful examination of the child. A standard psychiatric assessment should be followed, including interviews with the child and family and a review of records and historical information. Observation and assessment should include the core symptoms of ASD and according to DSM-V, which specifies that people with ASD must meet all three social criteria (i.e., deficits in social–emotional reciprocity, deficits in nonverbal communicative behaviors, and deficits in developing, understanding, and maintaining relationships). In addition, two of the four behavioral criteria (i.e., repetitive speech or motor movements, insistence on sameness, restricted interests, or unusual response to sensory input) should be met.[22]

The child's age and developmental level may dictate some modification in assessment procedures. Clinicians should be sensitive to ethnic, cultural, or socioeconomic factors that may affect the assessment. Various instruments for the assessment of ASD have been developed. Among all these scales and assessments, Childhood Autism Rating Scale (CARS) is promising as a diagnostic measure because of its simplicity, conceptual relevance, high concordance with DSM-V, diagnosis of autism, acceptability, cost-effectiveness, utility among different populations, and strong psychometric properties when validated.[23]

The CARS is a 15-item behavior-rating scale designed to detect and quantify symptoms of autism as well as to distinguish them from other developmental disabilities.

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Each item on the CARS is scored on a Likert scale, from 1 (no signs of autism) to 4 (severe symptoms). The maximum CARS score is 60, and the cutoff for a diagnosis of autism is 30. Children with scores of 30.5 to 37 are rated as mildly moderately autistic, and those with scores of 37.5 to 60 are rated as severely autistic.[24]

The scale assesses behavior in 14 domains that are generally affected by severe problems in autism, plus one general category of impressions of autism, to identify children with autism, as differentiated from the other developmental disorders. The 15 items in the scale are: relating to people; imitative behavior; emotional response; body use; object use; adaptation to change; visual response; listening response; perceptive response; fear or anxiety; verbal communication; nonverbal communication; activity level; level and consistency of intellective relations; and general impressions.

The examiner assigned a score of 1 to 4 for each item: 1 indicates behavior appropriate for age level, whereas 4 indicates severe deviance regarding normal behavior for the age level. The scores for the single items are added together to obtain a total score, which classifies the child as not autistic (below 30), mild or moderately autistic (30–36.5), or severely autistic (above 36.5).[23]

Sensory processing concerns have been a key feature of ASD clinical descriptions, as observed from the original independent seminal reports by Asperger and Kanner to first-person accounts.[24] Although sensory hyper- and hypo-responsiveness are not unique to ASD, they appear to be more prevalent in this population than in other developmental disabilities.[25,26]

There is limited consensus regarding the pattern of these sensory deficits in ASD. However, historically, proximal senses such as touch, smell, and taste were believed to be particularly at risk and to indicate developmental immaturity.[27,28] Interestingly, these tend to be the least well studied of the sensory modalities, whereas there is mounting evidence for disruption of the auditory and visual processing pathways and a surging interest in multisensory integration.[29]

Individuals with ASD exhibit atypical visual behavior that can be construed as attempting to avoid visual input (e.g. covering eyes at bright lights) or to seek additional visual stimuli (e.g. twisting fingers in front of eyes).[26]

There is a considerable discrepancy in neurophysiological findings. There are suggestive reports in the visual domain of enhanced detail perception, particularly for simple stimuli with impairment in more complex tasks.[30] Some threshold studies show no difference between ASD individuals and controls in contrast sensitivity for low versus high spatial frequencies or motion/form processing.[31,32]

Other VEP studies indicate that individuals with ASD possess atypical early peaks with impairments in object boundary detection,[33] decreased contrast-detection ability in both still and moving stimuli at a range of signal/noise ratios,[34] and undifferentiated responses for mid and high spatial frequency gratings.[35]

An fMRI study with eye tracking shows that activation of the fusiform gyrus and the amygdala is reduced in an ASD cohort, as well as their unaffected siblings, but that it correlates positively with fixation time on the eye region of the face.[36]

An event-related potentials study again highlights group differences that are dependent on directed attention such that ASD individuals do not show the expected increase in the N170 (face processing) wave with directed attention.[37]

An EEG study assessing γ-band activity, believed to represent the binding of visual information, gives convergent evidence for a neurophysiologic difference in Asperger syndrome face processing.[38] Further, the type of visual information matters; children with ASD may respond more robustly than controls to neutral and detailed, high-spatial frequency information and less robustly to the rapid low-frequency processing that is so critical to our fast-paced social world.[39]

The emotional valence of face processing has been investigated with a study suggesting hyperactivity in the right amygdala with altered connectivity between the frontal and temporal lobes.[40] It is a challenge to interpret whether these differences represent primary cortical abnormalities, result from decreased visual exploration in early infancy, or are secondary to a primary social cognitive deficit.

Speaking to a genetic underpinning for these differences, inefficient motion processing has been found in siblings of individuals with ASD as well.[41] Following theories of increased local cortical activity[42] with impaired long-range connectivity,[43] individuals with ASD appear to be over-recruiting their left primary cortex compared with typically during a motion coherence fMRI study.[44]

Pattern-reversal VEPs stimuli can be produced by alternating black/white to white/black checkerboard stimulation without a change in the overall luminance of the screen at a specific reversal rate. Pattern-reversal VEP waveforms are more consistent regarding morphology and timing as compared with VEPs produced by other stimuli. The pattern-reversal VEP waveform comprises N70, P100, and N145 peaks.[45]

The P100 wave is the most robust peak with comparatively minimal interindividual variability, nominal within-subject inter-eye difference, and negligible variation with high repeatability [Figure 1].

Several studies have revealed VEP abnormalities in various neurological and psychiatric disorders such as Alzheimer's disease,[46] migraine headache, and schizophrenia.[47,48]

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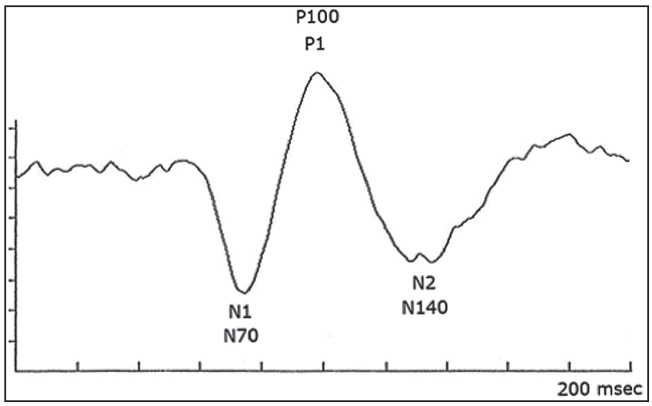

Figure 1: Representative normal pattern-reversal visual evoked potential recorded from the mid-occipital scalp using checkerboard pattern stimuli

The abnormalities of VEP can also be found in children with developmental delays. A previous study has shown prolonged VEP latencies in slow learners.[49] In children with attention deficit hyperactivity disorder (ADHD), the VEP waveforms are slightly more prolonged than in healthy children.[50] Moreover, alterations in the VEP waveforms were also found in patients with dyslexia[51] and fragile X syndrome.[52] The prolongation of the VEP waveforms usually reflects delayed nerve conduction, which is commonly observed in children with developmental delays.

Children with autism usually show some abnormalities in the visual system, such as poor eye control and hypersensitivity to light. These abnormal findings may result either from atypical sensory processing or from defects in neural networks of social cognition. A recent study using a steady-state VEP showed hyperresponsivity to visual stimuli in patients with high-functioning autism.[53] However, there is a current lack of studies that use VEP testing in children with ASD as a brain maturation index.

Two recent studies examine the VEPs in children with ASD; a significantly longer N145 latency[54] and decreased P100 amplitude in adolescents and young adults with ASD[55] were demonstrated.

Materials and Methods

A prospective case-control study was conducted at the Autism Center, Baghdad Teaching Hospital, Pediatric Hospital, Medical City for the period from 12 December 2019 to 1 June 2021.

Subjects

The study was conducted on 60 preschool children (11 females and 49 males) who were recruited from the autism center and the pediatric neurology ward in the Pediatric Hospital of Baghdad Medical City and met the DSM-V criteria for autism. Another 50 age- and gender-matched normally developed children who did not fulfill the criteria of any pervasive developmental disorder served as the control group.

The autistic children were excluded from the study if they had any motor, visual, inborn errors of metabolism, epilepsy, other chronic medical or neurological disorders, or if they had been taking medications during the period of study.

Methods

All the studied children were subjected to the following:

History and clinical examination

The children's entire physical and medical history was recorded; patient demographics were registered. Again, a physical, neurological, and psychiatric examination for clinical assessment of ASD according to DSM-IV criteria was also done.

Childhood Autism Rating Scale

This is a 15-item measure intended to assist in distinguishing children with ASD from children with other types of delays. The CARS consists of 14 domains assessing behaviors associated with autism, with a 15th domain rating general impressions of autism.[56] It is an observational scale in which each item is rated from 1 (within normal limits) to 4 (severely abnormal), and ratings include a consideration of "peculiarity, frequency, and duration" of the behavior rated. It yields a total score ranging from 15 to 60. Scores of 30–36.5 suggest mild to moderate autism, and scores of 37–60 suggest severe autism.[57]

Pattern-reversal visual evoked potentials

The pattern-reversal VEPs were recorded using the Roland RETI system (Roland, Germany). Table 1 illustrates the patient-related factors during recording:

Recording parameters

- The test was performed in a moderately lit room.
- The video monitor was placed at a distance of 1 m (range = 75–150 cm) calibrated exactly by a measuring tape from the nasion to the screen.

Table 1: Patient-related factors during PRVEP recording

Patient variables	PRVEP testing parameters
Eye drops	No pharmacologic eye drops before the test
Instruction to the patient	Keep alert and maintain focus on a red cross at the center of the checkerboard pattern
Patient's position	Comfortably sitting or partially reclining with the visual monitor placed at eye level
Mode of stimulation	Monocular stimulation with a nonstimulated eye covered by a dark light-tight patch
Patient monitoring	Monitor the patient's cooperation and alertness throughout the test

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- High contrast (> 80%) black and white checks are displayed on the monitor and they are reversed abruptly with a reversal rate of <4 reversals/sec (blacks turn into whites, and whites turn into blacks) during visual stimulation.
- Total luminance of the screen does not change during the check reversals "assured by having an equal number of white and black checks across the monitor."
- The bandpass filter should be set at 1–300 Hz.
- The analysis time (sweep duration after stimulus) is set at 500 msec.
- Standard skin disk electrodes are secured on the skin with electrode paste or collodion.
- Electrode impedances are maintained below 5 kΩ, with an abrasive gel to the scalp.
- The PRVEPs are obtained using full-field stimulation.
- Each eye is tested by two different check sizes: large checks of 40′–60′ and small checks of 10′–15′ of visual arc.
- 100–200 averages per replication are needed. The number of replications is at least two averages to demonstrate PRVEP reproducibility.

Electrodes location

The scalp electrodes were placed relative to bony landmarks, in proportion to the size of the head, according to the International 10/20 system.[58] The anterior/posterior midline measurements are based on the distance between the nasion and the inion over the vertex [Figure 2]: The active electrode is placed on the occipital scalp over the visual cortex at Oz, and the reference electrode is placed at Fz. A ground electrode is attached to the vertex (Cz).

PRVEP components

A typical PRVEP waveform consists of N75, P100, and N145 peaks [Figure 3]. These peaks are designated as negative and positive followed by the typical mean peak time. The standard measure of VEP amplitude is the height of P100 from the preceding N75 peak.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 77 (including the number and the date in 17/10/2019) to get this approval.

Results

One hundred and ten children were enrolled in this study: 60 were diagnosed as having ASD (49 males and 11 females), and 50 were normally developed children (40 males and 10 females). No significant difference was noticed between the two groups regarding gender (P = 0.825). Also, no significant difference (P = 0.390) was found in terms of age between the children with ASD (4.5±1.17 years) and the normally developed children (4.68±0.97 years).

Visual evoked potential data

The P100 wave latency was significantly prolonged (P < 0.001) in both eyes of children with ASD as compared with that of the ND group. Moreover, the N75-P100 amplitude was significantly lower (P < 0.001) in the left but not the right eye of patients when compared with the ND group [Table 2].

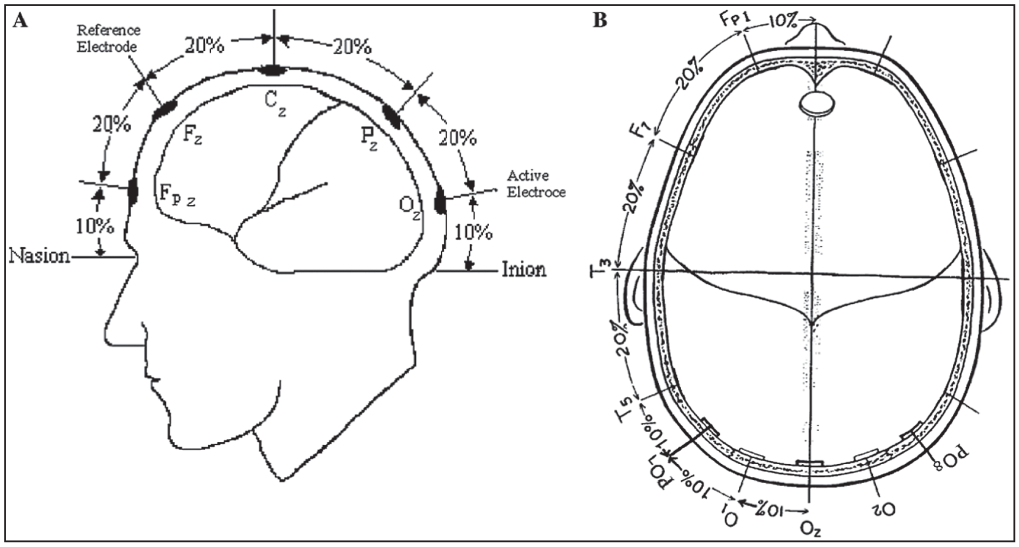

Figure 2: Visual evoked potential electrode locations. (A) Location of active and reference electrodes for standard responses. (B) Locations of the lateral active electrodes. O1 and O2 are indicated along with the midline active electrode location, OZ[59]

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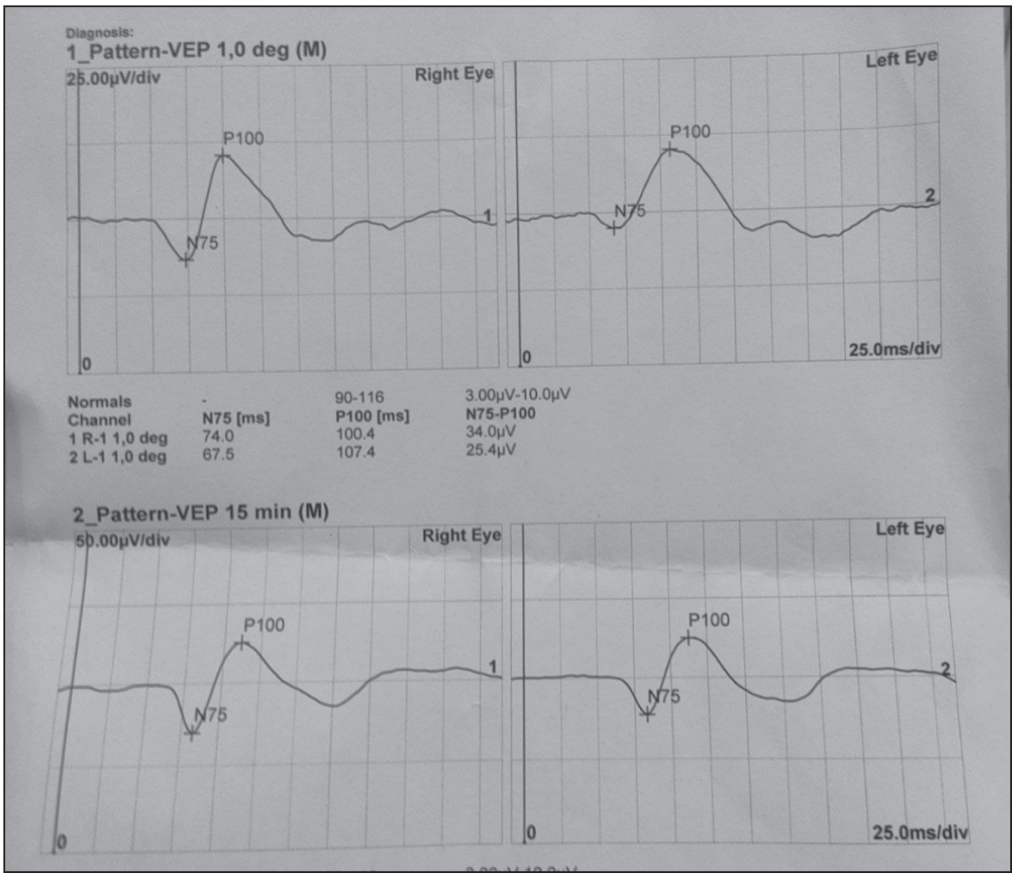

Figure 3: Typical visual evoked potential record

Table 2: Visual evoked potential parameters in patients with autism spectrum disorder and controls

Variables		ASD (n = 60)	Controls (n = 50)	P Value
P100 latency (ms)	Right	119.2 ± 7.06	110.51 ± 6.27	<0.001[a]
Mean ± SD	Left	118.58 ± 6.26	110.02 ± 6.19	<0.001 [a]
N75-P100 amplitude (µV)	Right	12.33	15.4	0.017[b]
	Left	11.04	16.55	<0.001 [b]

ASD = autism spectrum disorder, SD = standard deviation

[a]*t* test

[b]Mann–Whitney *U* test

Gender and visual evoked potential data

Neither the P100 wave latency nor the N75-P100 amplitude of both eyes was associated with the gender of children with ASD [Table 3].

Disease severity score and visual evoked potential data

Likewise, both VEPs parameters of both eyes show no significant association with disease severity score in children with ASD [Table 4].

Discussion

Gender effect

Out of the 60 children with ASD who had enrolled in this study, 49 (81.7%) were boys and 11 (18.3%) were girls. These percentages support a strong gender dimorphism, as males are about four times more likely to be diagnosed with ASD than females.[60,61] However, a large systematic review and meta-analysis report that the gender difference is likely to be closer to three times, rather than four times, higher in boys.[12]

Several plausible theories have been proposed to explain the increased risk of ASD in males.[62] Among these is the multiple threshold liability model, which hypothesizes that multiple genetic factors contribute to the liability for developing ASD, and a higher threshold of genetic liability is required for females as compared with males; thus, this is also known as the "female protective model."[11,63] Another study suggests that sex chromosomal genes and/or sex hormones, especially testosterone, may modulate the effects of genetic variation on the presentation of an autistic phenotype.[64]

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Table 3: Association of gender with visual evoked potential parameters in patients with autism spectrum disorder

Variables		Males (n = 49)	Females (n = 11)	P Value
P100 Latency (ms)	Right	119.18 ± 6.64	119.27 ± 9.07	0.969 [a]
Mean ± SD	Left	118.96 ± 5.87	116.94 ± 7.87	0.338 [a]
N75-P100 amplitude (μV)	Right	12.25	12.5	0.947 [b]
	Left	11.4	8.04	0.785 [b]

SD = standard deviation

[a]*t* test

[b]Mann–Whitney *U* test

Table 4: Association of Childhood Autism Rating Scale with visual evoked potential parameters

Parameters		Mild (n = 31)	Moderate (n = 22)	Severe (n = 7)	P Value
P100 wave latency (ms)	R	118.35 ± 7.25	120.46 ± 5.52	118.97 ± 7.06	0.567 [a]
Mean ± SD	L	118.53 ± 6.36	118.27 ± 5.17	119.81 ± 9.38	0.853 [a]
N75-P100 amplitude (μV)	R	12.4	11.15	12.8	0.653 [b]
	L	9.5	11.4	12.5	0.293 [b]

CARS = Childhood Autism Rating Scale, R = right, L = left, SD = standard deviation

[a]ANOVA

[b]Kruskal–Wallis test

The visual evoked potentials

One of the present studies aims at investigating early visual responses in children with ASD. To this end, P100 amplitudes and latencies evoked by pattern-reversal checkerboards were measured in children with ASD and their control peers. A smaller N75-P100 amplitude to left eye stimulation and delayed P100 latency of both eyes were observed. In ASD, vast literature showing VEPs differ in references to controls.[53-55,65-73]

Other studies reported a larger evoked response amplitude for autistic children in contradiction to the results of this study,[40,53,73,74] at least for some stimulus conditions or participant groups. Several other studies reported response components that are not altered.[67,71]

Studies dealing with the use of VEP testing in children with ASD as a brain maturation index are scarce. Children with autism usually show some abnormalities in the visual system, such as poor eye control and hypersensitivity to light. These abnormal findings may result either from altered sensory processing[75] or from defects in neural networks of social cognition.[75] These alterations include both hyper- and hyposensitivity to visual stimuli.[53,76]

In the current study, children with ASD differed from controls by exhibiting a hemispherical effect showing reduced amplitude in the left than in the right hemisphere. On the contrary,[69] in the ASD group, a selective amplitude reduction over the right hemisphere to steady-state VEPs pattern reversal was observed.

Neither the P100 wave latency nor the N75-P100 amplitude of both eyes was associated with the gender and severity score in children with ASD. Contrary to these results,[54] longer N145 latency but not P100 and N75-P100 amplitude was found to be correlated with a higher clinical severity score measured by Autism Treatment Evaluation Checklist within the sensory/cognitive awareness subdomain. Moreover, a negative significant correlation was found between the P100 latency and the Vineland Adaptive Behavior Scales 2nd edition scores only in the subdomain of socialization. Specifically, the longer P100 latency correlated with a lower score within the interpersonal relationships subdomain.

Interestingly, the correlation between N145 latency and Vineland Adaptive Behavior Scales 2nd edition scores was negatively significant for the socialization domain and all its subdomains. This correlation was assumed to be a delayed neural communication within other neural circuits, apart from the visual pathway. Further, this evidence supported the possibility of using VEP, along with clinical parameters, for the assessment of ASD severity.[54]

Normal brain function requires an appropriate level of synaptic contacts, and an appropriate speed of neural transduction.[54] Increased electrical conduction is strongly dependent on the presence of myelin around the nerve fibers, which is crucial for rapid neural communication. Myelination is an important brain maturation process that occurs in a region-specific manner[77] and begins in the sensory pathways, which include the visual system, followed by the motor pathways since the early developmental period.

Ophthalmological issues were present in a surprisingly high number of ASD candidates.[78] In the current study, these issues were controlled by excluding visually impaired children with ASD, so the findings were not biased by the inclusion of such participants. The VEP abnormalities are closely correlated with white matter damage of parallel

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visual pathways.[79] Consequently, the current study suggests that these abnormalities in sensory responses are not linked to visual disorders, rather they are due to the slower neural communication and altered connectivity within the visual pathways, which might contribute to the impaired social communication observed in ASD.

Conclusion

(1) There are distinct changes in VEPs in children with ASD, especially the abnormal prolongation of conduction time, suggesting that ASD children may have visual pathway dysfunction.
(2) This suspected dysfunction in the brainstem and optic nerves, affecting the processing of sensory afferents through the visual pathways, can be part of a generalized neurological dysfunction process that explains a change in the social, cognitive, language, poor eye control, and hypersensitivity to light that are part of autistic behavior.
(3) Gender and disease severity score have no impact on VEPs data.

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Conflicts of interest
There are no conflicts of interest.

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