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BIOMARKERS OF VISUAL PERCEPTION DYSFUNCTION IN AUTISM: PROGRESS AND DIRECTIONS IN EEG RESEARCH

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SUMMARY

Background: As the world moves towards the Fourth Industrial Revolution, there is a need for formulations of neurophysiological biomarkers that ensure the accuracy of the diagnosis of visual perception dysfunction in individuals with Autism Spectrum Disorder (ASD). Biomarkers of visual perception dysfunction in ASD using EEG complements behavioral methods of diagnosis and allows for a more direct assessment of the dysfunction, identifying rapid, implicit neural processes that are not revealed through behavioral measures alone. This paper aims to review the neural biomarkers of the five domains of visual perception dysfunction (visual discrimination (VD), visual spatial relations (VSR), visual form constancy (VFC), visual memory (VM) and visual closure (VC)) in individuals with ASD. This paper shall help researchers gain new insight into the current trends and progress in EEG methods in ASD and discover gaps in the subject literature.

Material/ Methods: A systematic literature search on PubMed was conducted to report findings of EEG studies that: 1) assessed the severity levels in patients with ASD and 2) investigated the neural biomarkers of visual perception dysfunction in ASD.

Conclusions: Spectral analysis, functional connectivity analysis and event-related potential (ERP) are useful in modern medicine to identify the biomarkers that distinguish the levels of the severity of visual perception dysfunction in ASD.

Key words: visual perception dysfunction, biomarkers, autism, EEG, ERPs

INTRODUCTION

Autism is perceived as one of the fastest-growing disorders globally, with the prevalence of 1 in every 59 children born with ASD [1]. Diagnosis for ASD maybe delayed until pre-school and primary school [2–6], preventing early intervention [7]. Assessing children with ASD behaviorally could be challenging because of their decreased attention and engagement to a particular task and difficulty following verbal instructions [2,8]. Inaccurate diagnosis may affect students' passion for learning, hence, affecting their future. Thus, there is a need for formulations of neuromarkers that allow for a more direct assessment of the dysfunction, ensuring the accuracy of the diagnosis of visual perception dysfunction in children with Autism.

Visual perception is responsible for the reception and cognition of visual stimuli. It provides a vital input channel to academic, social and cognitive abilities, such as reading, writing, spelling, and mathematical problem solving [9]. In individuals with ASD, Visual Perception Dysfunction may be influenced by the higher-order dorsal-cognitive system at the frontal brain region [10]; however, studies have also shown early visual perception dysfunction related to the parietal and occipital brain regions [11]. Deficits in neural connectivity network of visual cortex in ASD have also been predicted by [12].

PROGRESS IN METHODOLOGY

Brain structure and EEG features are closely correlated to the severity of illness [13]. Furthermore, EEG biomarkers could be used to diagnose various physiological and pathological conditions, including ASD. Indubitably, EEG biomarkers have the potential to be used not only for clinical diagnosis but also for predicting stages or severity of ASD.The severity of ASD vary considerably [14]; however, most EEG studies are restricted to only distinguishing individuals with ASD from healthy controls without determining the severity levels of the autistic features [15,16].

To review the state-of-the-art EEG neuromarkers reported in ASD, and the association of these biomarkers with ASD severity, we conducted a systematic search on PubMed for studies between 2011-2021 using three keywords with the Boolean operator "AND". The first keyword was "severity". The second keyword was "Autism" and the third term was either "EEG" or "ERP". The search process, last performed in August 2021, yielded 182 records, including 56 duplicates. The original 126 publications were screened to exclude 49 non ASD articles, 26 non-EEG studies, 26 ASD studies without the inclusion of severity factor and 12 review articles. The remaining 13 eligible articles, which evaluated Autism symptom severity, were summarized in Table 1.

Based on Table 1, out of the 13 studies in 2011 to 2021 that included assessment of severity levels in ASD research, only three studies were related to visual processing. All studies showed either significant correlation between EEG features in ASD with symptom severity or distinct EEG features between several severity groups.

The underlying cause of ASD has yet to be unveiled; thus, the identification of EEG biomarkers that capture and quantifies brain processes, pathways and connectivity, are highly sought upon. From Table 1, the identification of biomark-

ers using EEG is based upon three different approaches [28]. A summary of the state-of-the-art techniques of identification of EEG biomarkers in ASD research is illustrated in Figure 1.

The spectral analysis approach analyses the spectral biomarkers [29] using Fourier transform techniques. Time-frequency wavelet transform [30] and the statistical auto-regressive moving average (ARMA) method also fall under this cate-

Table 1. Summary of the State-of-The-Art in ASD EEG Research that evaluated Autism symptom severity

Study	Type of EEG Analysis	Visual task?	Severity measures	Findings
[15]	Nonlinear EEG Analysis (resting-state)	No	Mild and severe Autism	In the severe ASD group, there are more minor IMFs, more stochastic SODP plotting, fewer CTM values, and higher ellipse area values.
[17]	ERP	No	Autism Spectrum Quotient (AQ) scores	In the visual-auditory priming test, there were significant associations between electrophysiological aspects of cross-modal priming and AQ scores.
[18]	ERP	No	Mild, moderate and severe Autism	Smaller N1a and larger N1b amplitudes werecorrelated with lower severity symptoms.
[19]	Spectral EEG	Yes	ADOS (Autism Symptom Severity)	Slower neural binocular rivalry alternations for individuals with ASD is correlated with symptom severity and complimenting behavioral results.
[20]	Functional connectivity (phase lag index)	No	ADI-R RRB (Autism Diagnostic Interview-Revised Restricted and Repetitive Behaviours) scale	The higher functional connectivity within thefronto-central regions is correlated with the severity of ADI-R RRB in infants with later ASD
[21]	Nonlinear EEG Analysis	No	Autism Diagnostic Observation Schedule Calibrated Severity Score (ADOS-2 CSS)	Nonlinear EEG characteristics recorded at each age, starting at 3 months were used to predict the severity of ASD symptoms.
[16]	Nonlinear EEG Analysis	No	Mild and severe ASD	Those with mild ASD had greater average multiscale entropy (MSE) values than children with severe ASD.Children with mild ASD had different MSE topographical cortical representation and MSE curve plotting than children with severe ASD.
[22]	Spectral EEG	No	ADOS and Multi-dimensional Scale for Pervasive developmental disorder and Attention-deficit/hyperactivity disorder (MSPA)	Higher theta-wave activity at the frontal cortex in adults with ASDwas correlated to the severity of ASD
[23]	Spectral EEG	No	Social Responsiveness Scale (SRS)	Decreased resting gamma power at right lateral electrodes in boys with ASD in comparison to controls. Reduced resting gamma power is correlated to increased severity.
[24]	ERP	Yes	ADOS	At the age of three, faster ERP in the left hemisphere to neutral faces predicted ASD symptom improvement and reduced ASD severity in adolescence.
[25]	Functional connectivity	No	ADI-Revised (ADI-R) and AQ	Compared to controls, children with ASD showed higher coherence in short-distance and long-distance electrode pairs within certain regions and frequencies. The abnormal coherence was correlated with symptom severity.
[26]	Functional connectivity	Yes	ADOS	Increased short-range lateral inhibition is linked to more severe ASD symptoms.
[27]	Spectral analysis	No	AQ	Greater ASD symptom severity is related to decreased left frontal alpha power and increased right parietal alpha power in adolescents with ASD.

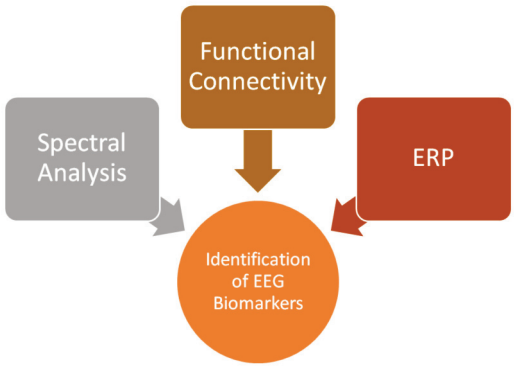

Figure 1. The three main analysis techniques to identify EEG biomarkers in Autism research

gory [28]. EEG signals are decomposed into frequency bands that reflect rhythmic activities related to behavioural significance in this approach. Visual studies such as [31,32] established atypical EEG power distribution to individuals with ASD.

Functional connectivity and nonlinear analysis methods investigate underlying neural interactions between regions of the brain. Techniques such as coherence [33,34] and parameters such as entropy [35] and Lyaponov Exponent [36] have been widely used as EEG biomarkers. In visual perception studies [31,32], altered functional connectivity in individuals with ASD has been detected.

The third approach uses ERP for the extraction of mean EEG responses that are time-locked to stimulus processing [37]. This is a well-established approach that has been used to index biomarkers [38] of various mental illnesses and psychological disorders such as PTSD [39], Vascular Dementia [40], Anxiety Disorders [41,42] and ASD [43]. In studies such as [44-46], a typical ERP responses in individuals with ASD were observed.

EEG NEUROMARKERS

Recent articles that identified EEG biomarkers of visual perception dysfunction in ASD were determined according to a systematic search on PubMed for studies between 2011-2021 using three keywords with the Boolean operator “AND”. The first keyword was either “visual discrimination” or “visual spatial relations”, or “visual form constancy” or “visual memory” or “visual closure”. The second keyword was “Autism” and the third term was either “EEG” or “ERP”. The search process, last performed in August 2021, yielded a total of 84 records, including 24 for visual discrimination, 45 for visual memory, 15 for visual spatial relations, 0 for visual form constancy and 0 for visual closure. There were 30 duplicate articles. The original 54 publications were screened to exclude 19 non ASD articles, 14 non-EEG and 2 review papers. The remaining 19 eligible articles which investigated the neuromarkers of the five domains of visual perception dysfunction; visual discrimination, visual spatial relations, visual form constancy, visual memory and visual closure in individuals with ASD, were summarized in Table 2.

Table 2. Summary of articles thatInvestigated the Neuromarkers of the Five Domains of Visual Perception Dysfunction

Study	EEG Analysis	Task / Stimuli	Visual Perception Domain	Biomarker	Participant	Result
[47]	ERP	Memorizing images and colors of drawings of objects	Visual Memo-ry	The early old-new effect seen in TD was reduced in ASD.The ASD group's late posterior negativity effect was not specific to this time window.	15 adults with ASD and 18 matching controls	In this task, early and late effects may influence atypical episodic memory judgements in ASD.
[48]	ERP	Two photographs of familiar and unfamiliar faces	Visual Memory	N290 peaked faster in TD 18to30, ASD 18to30, and finally TD 12to17. The ASD 18-30 group had a stronger P400 response to the familiar face than the unfamiliar face.	24 18-to 47-month-old children with ASDand 32 12-to 30-month-old typically developing (TD) children (C)	Facial familiarity neural responses in early ASD are delayed, evidenced by the task's atypical early and late effects.
[44]	ERP	Digital images of faces and houses in gray-scale	Visual Memory, Visual Discri-mina-tion	At the P1 and P1-N170 slopes, controls demonstrated differential responses to upright vs inverted faces, but this effect was not evident in participants with ASD.	39 individuals with ASD and 38 controls (adults)	The atypical P1 and N170 responses were associated with improved face memory and social skills performance in the ASD group.
[45]	ERP	Passive repetition detection of unfamiliar photographs of faces and houses	Visual Memory	Larger parietal P600 for the repeated faces in TDC. The effect was absent in children with ASD.	13 children with ASD and 11 TDC	The control group processed repeated social stimuli to a greater extent to establish perceptual familiarity
[49]	ERP, functional connectivity	two-choice recognition task (ownname, close other's, and famous names)	Visual Memory	In the ASD group, P300 to own-name and a close other's name both increased, whereas only P300 to own-name was increasedin the control group.Within the beta band, individuals with ASD showed disruption of fronto posterior task-related connectivity.The ASD group has weaker frontal connections and stronger occipital connections.	15 young males with ASD and 15 controls	Individuals with ASD have a lack of self-preference effect and a dysfunctional attentional network when it comes to recognizing visually presented names.
[50]	ERP	face and name detect-iontask (own, close-other, famous, and unknown)	Visual Memory	In the ASD group, P300 to own-name and a close other's name both increased, whereas only P300 to own-name increased in the control group. Attenuated face and name processing at the N170 window in the ASD group.	23 adolescents with ASD and 23 controls	Atypical brain organization in ASD due to less lateralization of face and name processing at the N170 window.

Table 2 above summarizes the EEG biomarkers of VD, VSR, VFC, VM and VC in ASD using various EEG analysis techniques. With the exception of one study, all studies showed a typical ERP, connectivity and spectral EEG responses

[51]	Spectral EEG	Face recog-nition task (neutral, positive, negative)	Visual Memory	Children with ASD had greater absolute theta activity at the P7 electrode compared to TDC.In the ASD group, overnight Reaction Time improvement for positive and negative faces correlated with theta and beta activity.	13 high-functioning male children with ASD and 13 TD male children	ASD and controls have a different network for facial image processing during sleep
[52]	Spectral and functional connectivity analysis	9 categories of face stimuli (photograph, Mooney)	Visual Discrimina-tion, Visual form constancy	Decreased EEG responses in the beta and gamma bands to face stimuli in adults with ASD.	10 adults with ASD and 16 controls	Overall classification accuracy was above 95%
[46]	ERP	Target-to-probe	Visual Spatial Rela-tions	Increased N2 ERP component in the TD group, with cortical sources in the ventral visual stream. Children with ASD did not show this effect. Weaker suppression predicted higher ASD severity.	18 children with ASD and 18 TDC	The attentional focus of children with ASD is defined by a weak suppression that surrounds the attended area.
[53]	ERP	Cued Posner Spatial Attention Task	Visual Spatial Relations	In incongruent trials in both types of spatial location, the ASD group showed prolonged and more negative frontal N100 potentials, as well as prolonged frontal P200 potentials.	30 children with ASDand 30 TDC	Congruence and spatial location have a greater negative impact on attentional selectivity processes in the ASD group.
[54]	ERP	Discrimination Tasks:1)Facial images (familiar and unfami-liar) and an object. 2) Facial identity	Visual Discrimination	P300 amplitude was higher in TDC when they perceived familiar faces than unfamiliar faces.This effect was reduced in children with ASD.	9 children with ASD and 9 TDC	Attentional resource allocation during face identification in children with ASD may influence the attenuated familiarity effect on P300.
[55]	Functional connectivity	Face perception task (fearful, happy and neutral)	Visual Discrimination	Synchrostates obtained while the children were performing face perception task can effectively distinguish children with ASD and TDC.	12 children with ASD and 12 TDC	The overall classification accuracy was 94.7%.
[56]	ERP	Visual statistic-al learning para-digm (oddball para-digm)	Visual Discrimination	ASD group showed reduced amplitude differences between expected and unexpected conditions duringP300 (attention to novelty) and N1 (early visual discrimination).	68 children with ASD and 35 TDC	The ASD group showed reduced learning, evidenced by the N1 and P300 effects.

[57]	ERP	Face process-ingdiscri-minationtasks: 1)Gender task 2) Affect task (angry or happy)	Visual Discrimination	Children with ASD had smaller Error-Related Negativity amplitude differences between right and wrong responses (ERNdiff) than TD children in the gender task.	42 children with ASD and 42 TDC	Children with ASD had enhanced ERNdiff in the affect task, similar to the TD group, compared to the gender task. Error-monitoring ability was not associated with severity.
[58]	Spectral analysis and Function-al connect-ivity	Visual Crowding Task	Visual Discrimination	The ASD group showed no desynchronization after stimulus onset in the beta band. Reduction in occipital-inferotemporal beta band functional connectivity is linked to severity in ASD.	22 children with ASD and 22 TDC	In children with ASD, detail-oriented processing is attributed to abnormal oscillatory activity in the beta band
[59]	Spectral EEG analysis FPVS-EEG	Neutral and fearful oddball	Visual Discrimination	Lower amplitudes in the ASD group for fear detection in a stream of neutral faces	23 8-12-year-old TD boys and 23 boys with ASD	Boys with ASD have reduced sensitivity to fearful faces than TD boys.
[60]	Spectral (FPVS-EEG)	Face discrimination	Visual Discrimination	Reduced neural responses at the occipito-temporal cortex (right-lateralized) in ASD in individual face discrimination.	23 8-12-year-old boys with ASD and 23 TDC	Boys with ASD exhibit atypical processing strategies when it comes to individuating faces.
[61]	Spectral (Time Frequency)	Orientation Discrimination Task	Visual Discrimination	Superior orientation discrimination in ASD. Peak frequency ofvisually induced gamma activity is higher in ASD.	28indivi-duals with ASD and 39 controls	Increased occipital inhibition in ASD, which may be mediated through increased GABA levels.
[62]	Spectral (FPVS-EEG)	Face discrimination and face memory	Visual Memory	Nil	16 high-function-ing ASD adults, 16 controls	Face memory, rather than face perception, suffers from behavioral face recognition impairments in ASD.

in individuals with ASD compared to matching controls. However, some studies showed EEG effects that are not reflected in the behavioral tasks. This may be due to the explicit nature of the behavioral tasks, allowing compensatory strategies and the influence of other factors beyond what is measured [60,62].

The Test of Visual Perceptual Skills (Non-Motor) (TVPS) is a standardized test commonly used to measure the five (and growing) domains of the visual perceptual skills. The test has been used many times over to assess visual perception dysfunction in individuals with ASD [3,63], Dyslexia [64], Cerebral Palsy [65] and other disorders. However, none of the study in Table 2 investigated all five domains of visual perception dysfunction in one study. We also observed fewer research papers in the VSR and VFC, and none in the VC domain of the visual perception dysfunction in ASD.

GENERAL DISCUSSION

To the best of our knowledge, this is the first systematic literature search to report findings of EEG studies that assessed severity levels in patients with ASD, and EEG studies that investigated the neural biomarkers of the five domains of visual perception dysfunction in ASD.The three main analysis techniques reported here are ERP, spectral analysis and functional conectivity. It is interesting to note that only 23% of the studies that evaluated Autism symptom severity were related to visual processing, although extracted EEG features are strongly related to the severity of illness.The findings here are in accordance with [15,16].

A possible explanation for this is the inability of some visual perception studies to establish a link between the EEG features and Autism symptom severity. Furthermore, certain limitations of visual perception studies are their inability to establish a link between behavioral reaction time and the atypical EEG feature sin ASD. Recent findings [66,67] established the importance of assessing severity of Autistic symptoms for early and impactful intervention.

Although there is a need for formulations of neuromarkers that ensures the accuracy of the diagnosis of the disorder, up to now, there are no standardized neural biomarkers that distinguish the levels of severity of all five domains of visual perception dysfunction (VD, VSR, VFC, VM and VC) in individuals with ASD, compared to standardized observational or behavioral measurements such as the TVPS. A possible reason behind this may be that the study of EEG biomarkers in this area is still in a premature state. Identifying the biomarkers that distinguish the levels of severity of visual perception dysfunction in ASD may lead to a complementary approach to diagnosing the dysfunction by medical professionals and assessment centres.

Future work should be designed to replicate the atypical ERPs, spectral EEG and connectivity findings discussed in Table 2, and establish correlations between the EEG features with the level of Autism severity. More studies of the VSR, VFC, and VC domains should be conducted so that specific intervention and therapy could be taken to improve these visual perception domains in individuals with ASD. Future visual processing studies in ASD may also be labeled according to the specific domains of the visual perception dysfunction to ease research and development in this area of study [68]. The researchers anticipate that the results achieved from these studies may spark increased interdisciplinary research in the field of psychiatry, psychology, neuroscience, engineering, and medicine, aiming to resolve visual perception dysfunction suffered by individuals with Autism.

CONCLUSION

In this paper, we discussed current literature of the neural biomarkers of the five domains of visual perception dysfunction: visual discrimination (VD), visual spatial relations (VSR), visual form constancy (VFC), visual memory (VM) and visual closure (VC) in individuals with ASD. We discussed current EEG method-

ologies and research trends and progress in visual perception dysfunction in ASD, the gaps and limitations of the studies.

We anticipate that extensive research in the replication of results and more studies that focuses on all domains of visual perception dysfunction may spark increased interdisciplinary collaboration in the field of psychiatry, psychology, neuroscience, engineering, and medicine, aiming to resolve visual perception dysfunction suffered by individuals with ASD. By assisting educators, assessment centers and medical professionals in the diagnosis of visual perception dysfunction in individuals with Autism, the neuromarkers of visual perception dysfunction may lead to the increase of the quality of lives of children suffering from Autism with early detection. Furthermore, these neuromarkers may provide a basis for designing new drug treatments for Autism that work directly in the brain to decrease the severity of the dysfunction.

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