Gaze Behaviour in Infants with Early-Onset Epilepsy and Its Association to Future Neurocognitive Development

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Abstract: The analysis of gaze behaviour is nowadays commonly employed to help with the diagnosis and exclusion of differential neurological conditions as well as to help researchers better understand cognition in the early stages of life. However, its application in the developmental evaluation and follow-up of children with early-onset epilepsy has not been profoundly studied yet. Therefore, the current study aimed to investigate the association between the gaze behaviour of infants with early-onset epilepsy and their future neurodevelopmental outcome. To study the association and its predictive ability, three models were created. Sixty-three infants with epileptic seizure onset before 12 months of age participated in the study with the voluntary consent of their parents. Infants' gaze behaviour was recorded with Tobii Pro-X3-120 at two measure points. The results showed infants' initial ability to fixate their gaze, changes in their gaze shift probability in the first 12 months of life, and structural aetiology to be significantly associated with the infants' developmental outcome at 24 months of age. Where the structural aetiology was significantly associated with poorer developmental outcome, good initial fixation ability and improvements in the infants' gaze shift probability during their first year of life were significantly associated with more positive outcome. These findings suggest that gaze behaviour at an early age is an essential predictor of later development in infants with early-onset epilepsy. Hence, eye-tracking could provide means to evaluate the later neurocognitive outcome of infants with early-onset epilepsy at an early age.

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Tiivistelmä: Katsekäyttäytymisen analysointia käytetään nykypäivänä yleisesti auttamaan erilaisten neurologisten sairauksien diagnosoinnissa ja poissulkemisessa sekä auttamaan tutkijoita ymmärtämään paremmin kognitiota aikaisissa elämänvaiheissa. Sen käyttöä imeväisiän epilepsiaa sairastavien lapsien kehityksen arvioinnissa ja seurannassa ei kuitenkaan ole vielä tutkittu perusteellisesti. Siksi tämän tutkimuksen tavoitteena oli tutkia imeväisiän epilepsiaa sairastavien imeväisten katsekäyttäytymisen yhteyttä heidän myöhemmin toteutuneeseen hermoston kehitykseen. Yhteyden ja sen ennustekyvyn tutkimiseksi luotiin kolme mallia. Kuusikymmentäkolme lasta, joiden epileptiset kohtaukset alkoivat ennen 12 kuukauden ikää, osallistuivat tutkimukseen vanhempien vapaaehtoisella suostumuksella. Imeväisten katsekäyttäyminen nauhoitettiin Tobii-Pro-X3-120:lla kahdessa mittauspisteessä. Tulokset osoittivat, että imeväisten alkuperäinen kyky kiinnittää katse, muutokset katseen siirtämisen todennäköisyydessä ensimmäisen 12 elinkuukauden aikana sekä rakenteellinen etiologia olivat merkittävästi yhteydessä imeväisten kehitystulokseen 24 kuukauden iässä. Siinä missä rakenteellinen etiologia liittyi merkitsevästi huonompaan kehitystulokseen, hyvä alkuperäinen katseenkiinnittämiskyky ja katseen siirron todennäköisyyden paraneminen ensimmäisen elinvuoden aikana olivat yhteydessä merkittävästi positiivisempaan tulokseen. Nämä havainnot viittaavat siihen, että katsekäyttäytyminen varhaisessa iässä on olennaista myöhemmän kehityksen kannalta imeväisille, jotka sairastavat imeväisiän epilepsiaa. Näin ollen katseenseuranta voisi tarjota keinoja arvioida imeväisiän epilepsiaa sairastavien imeväisten myöhemmin toteutuvia neurokognitiivisia tuloksia jo varhaisessa iässä.

Gaze Behaviour in Infants with Early-Onset Epilepsy and Its Association to Future Neurocognitive Development

Within the first year of life, newborns' eyesight undergoes several changes – they start to perceive movement and develop three-dimensional vision in addition to a farther colour range. In the first months of life, typically developing infants can already shift their fixation from a central target to a salient target appearing in the periphery when absent of other visual or auditory distractors (Atkinson & Braddick, 2012). The ability to shift attention from one visual input to another is a relevant feature of human development, allowing infants to focus on processing and learning relevant events while building the foundation for selective attention (Kulke et al., 2015). Although some very young newborns may experience 'sticky fixation' – appearing unable to shift their attention from the central stimulus – this rarely occurs in healthy infants after two months of age (Kulke et al., 2015).

Where gaze behaviour knowingly plays a salient role in nonverbal communication, it is also the primary control point for visual information intake. Therefore, observing how an individual responds to various stimuli can provide insight into cognitive processes such as attention, memory, and processing speed (Boardman & Fletcher-Watson, 2017). Over the last few decades, eye-tracking has been one of the predominant research methods for gaining insights into early neurocognitive development (Hessels & Hooge, 2019). By tracking participants' gaze to visual stimuli, eye-tracking techniques have provided researchers with a simple, non-invasive window into complex cognitive processes.

One of the well-known behavioural techniques using a shift of gaze to examine attention in young infants is the fixation shift paradigm (Kulke et al., 2015). With the fixation shift paradigm, it is possible to compare infants' ability to make a gaze shift under two conditions: 'non-competition' and 'competition'. In the non-competition, the central target disappears as a lateral target appears, and in the competition, the central target remains on the

screen (Atkinson & Braddick, 2012). Sub-cortical systems have been suggested to underpin the initial attentional ability of newborn infants, followed by the cortical systems at a few months post-term enabling infants to disengage attention from one visual object to another (Atkinson & Braddick, 2012). In typically developing infants, gains in shifting attention with age can be observed along with cortical development – especially under the competition fixation shift paradigms (Kulke et al., 2015). Therefore, challenges with the fixation shift paradigm in early infancy may indicate abnormal or delayed cortical development (Kulke et al., 2015).

While abnormal gaze behaviour can aid in the diagnosis and narrowing of differential neurological conditions as well as help researchers better understand cognition before infants can even talk (Shaikh & Zee, 2017), its use in the developmental evaluation and follow-up of children with early-onset epilepsy has not been profoundly studied yet. Therefore, this thesis focuses on eye-tracking data from infants with early-onset epilepsies to determine if infants' initial gaze behaviour differs significantly among the three developmental outcome groups at the age of two, and if so, whether it is possible to predict infants' future development based on these differences.

Epilepsy

Epilepsy is a neurological condition expressed by paroxysmal and recurring epileptic events caused by chronic structural, functional, or both alterations in the brain (Gast et al., 2016). While epilepsy is widely known for its long-term predisposition to trigger spontaneous epileptic seizures, it also has a variety of neurobiological, cognitive, and psychosocial consequences. (Zentner, 2020; Kim et al., 2021). Particularly recurring seizures may induce severe brain damage in highly vulnerable areas such as the hippocampus, entorhinal cortex, amygdala, thalamus, and other limbic structures (Dingledine et al., 2014). The neuronal death resulting from the seizures may be limited or widespread, depending on the aetiology.

Epilepsy and seizures can develop at any age, with a wide range of impacts that differ from individual to individual. However, the disease's heavy burden is not evenly distributed showing the incidence being higher in the youngest and oldest populations (Beghi, 2019). According to Aaberg et al. (2017), one out of every 150 children is diagnosed with epilepsy within their first ten years of life, with the highest incidence rate occurring during the first year of life. A recent Scottish population-based prospective nationwide study, nonetheless, has revealed early-onset epilepsies to be 30 per cent more prevalent than previously thought (Symonds et al., 2021).

Early-Onset Epilepsy

Childhood-onset epilepsies vary from those with onset later in life in several aspects, including seizure type, aetiologies, reaction to anti-seizure therapy, and electroencephalogram patterns (Kim et al., 2021). Despite the epilepsy type, onset in infancy is often linked to a particularly high risk of a poor outcome (Nickels, 2019) with only 21 to 38 per cent of the children achieving normal development (Gaily et al., 2016). The reason behind the poor outcome expectation is related to the early-onset types often being resistant to treatment and commonly accompanied by cognitive and behavioural comorbidities (Symonds et al. 2021).

Among different aetiologies, genetic, structural, or unknown origin are the most common for early-onset epilepsies. Genetic epilepsies are typically defined as epilepsies produced directly by a mutation (Howard & Baraban, 2017), and structural epilepsies as having a distinct structural brain abnormality, such as trauma or infection, that has been demonstrated to be associated with a substantially increased risk of epilepsy (International League Against Epilepsy, 2022). The definition of epilepsy syndrome includes epilepsy syndromes in infancy that can vary from self-limited familial syndromes, with good seizure and developmental outcome, to early-onset epileptic encephalopathies with poor prognosis and severe psychomotor retardation (Lee, 2018).

Neurocognitive Impairment

In a recent German population-based nationwide study (Sorg et al., 2022), children with epilepsy were 10.5 times more likely to exhibit cognitive impairment than their age-matched controls, with the highest relative risk in epilepsy patients with seizure presentation within the first two years of life. Epileptiform discharges propagating widely at a young age often have a negative impact on neurodevelopmental processes such as synaptogenesis and apoptosis (Kim & Ko, 2016). Aberrant synaptogenesis and apoptosis may cause the brain to become inappropriately hardwired and susceptible to continued high levels of excitation, resulting in sustained, intractable seizures alongside accompanying cognitive and motor impairments (Zupanc, 2009).

Much of the cognitive impairment seen in people with epilepsy is related to the underlying aetiology (Holmes, 2016). While aetiology undoubtedly plays a critical role, there is also evidence of the impact of early-life seizures on cognitive impairment, regardless of the aetiology (Holmes, 2016). For example, studies have shown prolonged or recurrent seizure activity during infancy to result in irreversible alternations in how the immature brain develops and forms synapses, with long-term effects on learning and memory (Holmes & Ben-Ari, 2001; Holmes, 2015). Moreover, in a study by Korman et al. (2013) that looked at the neuropsychological function in children with focal dysplasia, age at onset of epilepsy was shown to be an independent contributor to cognitive dysfunction by disrupting critical periods of development. Thus, both age of onset and underlying aetiology may play a role.

Gaze Behaviour Abnormalities

In addition to the effects on cognitive function, some studies have shown epilepsy to result in gaze behaviour abnormalities. Research done with paediatric epilepsy patients aged seven to eighteen revealed several abnormalities of saccadic eye movements in the affected children compared to healthy controls, including impaired and more variable processing speed,

reduced accuracy, increased peak velocity, and a higher number of inhibitory errors (Asato et al., 2010; Lunn et al., 2016). The younger unmedicated individuals also exhibit difficulties monitoring their own mistakes, indicating a deficiency in error monitoring (Lunn et al., 2016). According to Lunn et al. (2016), the saccadic abnormalities found in the study imply abnormal development of cortical and subcortical functional connectivity as well as disrupted neurotransmission.

The idea of saccadic pattern abnormalities resulting from compromises in early childhood brain maturation is consistent with the findings from Mrabet et al. (2018) that demonstrated eye movement abnormalities in genetic epilepsy patients to be consistent with the anatomic alterations seen in the patients' brains. Moreover, the preliminary findings from our laboratory (Knapič, 2020) showed infants' initial ability to shortly fixate their gaze, as well as improvements in this ability through time, to be associated with the infants' later cognitive performance at the age of two. Thus, based on these findings, patients' abnormal gaze behaviour could be an informative indicator of the infants' neurocognitive state, progression, and future neurodevelopmental outcome.

Practical Implication

While global, standardized instruments for assessing the developmental status of infants and toddlers have their place in the early assessment, relying solely or primarily on such tests to examine the effects of clinical trials or interventions may underestimate or miss specific effects on early cognition (Brito et al., 2019). Thus, the addition of biological indicators or functions could strengthen the assessments of early-childhood development. As eye-tracking is non-invasive and relatively quick, it is a very profitable method with several applications in the analysis. Epilepsy knowingly affects the formation of interrelationships between cognitive domains, resulting in a weakened, less put-in-place network structure, with attention and executive function being the two most poorly integrated domains (Kellermann et al., 2015).

Hence, the early, serial assessment of fixation and gaze shift behaviour - especially in patients with epilepsy - could be a valuable predictor of an individual's later cognitive development. Moreover, early detection could also lead to early interventions, such as rehabilitation measures or parental support of early interaction, improving patients' quality of life and cognitive performance.

Aims of the Study

This thesis aims to build on earlier findings from our laboratory to gain a more comprehensive understanding of the gaze behaviour in infants with early-onset epilepsies in terms of aetiology, age at onset, and gender, as well as complete the analyses with additional eye-tracking measures. The data used for the analyses is secondary data from a prospective study of infantile epilepsies, with the broader goal of determining infants' visual ability to orient and fixate gaze on a screen, re-orient visual attention, and the progression of these visual abilities over time, as well as their relationship to cognitive development. This thesis is also part of a broader initiative at the BAby Brain Activity (BABA) centre, which focuses on examining and improving eye-tracking-based assessments of newborn neurocognitive development.

I will begin by investigating if there are any notable differences in the infants' gaze behaviours between different developmental statuses at 24 months of age. If so, I will move on to the main study, which examines whether it is possible to predict the infants' developmental outcome at the age of two based on differences observed between their baseline and one-year measurement, when adjusted for gender, aetiology, and age. To better address the main research question, this thesis also intends to account for the potential influence of infants' ages during measurements as well as the potential impact of intra-individual dependency between measures. Moreover, I have limited the follow-up period to a time window of twelve months to investigate the significance of change occurring in the early stages for the infants' later

development in this clinical group. The original plan of this study also included epilepsy syndrome as one of the control variables, but since the syndrome classification integrates a strong assumption about the infants' development, it was left out from the final analyses.

Based on our preliminary findings and previous literature, I hypothesise that the different cognitive-developmental groups should be already noticeable from the infants' first gaze behaviour measurements and that any changes seen in individuals within the two measure points should be associated with changes in that individual's overall development. I also hypothesise aetiology to be significant predictor of the infants' later developmental outcome.

Methods

Participants

Sixty-three infants with epilepsy diagnosis and seizure onset before 12 months of age participated in the study with the voluntary consent of their parents. Thirty-four (54%) participants were male and twenty-nine were female (46%). All participants were treated at the Children's Hospital of Helsinki University Hospital (HUS) and the families were residents of the Helsinki University Hospital Specific Catchment Area. The recruitment was conducted as part of an ongoing clinical prospective study on epilepsy in children. Infants' parents and guardians signed a written informed consent before the infants participated in the study. Ethics approval for this study was granted by the HUS Ethics Committee for gynaecology and obstetrics, paediatrics, and psychiatry.

Apparatus and Materials

Gaze Behaviour

Infants' gaze behaviour was recorded with Tobii Pro-X3-120, which is an automated screen-based eye-tracker with a sampling rate of 120 Hz. Tobii Pro-X3-120 detects gaze using an infrared light reflection technology combined with image recognition algorithms, allowing in-depth study into the timing and duration of fixations (Tobii AB, 2017). The stimulus was

shown to the infants on a 24" ASUS VE247 computer screen with a 60 Hz refresh rate. MATLAB environment-based software used in this study was created in an Infant Cognition Lab at the University of Tampere, Finland (Leppänen et al., 2015).

Developmental Outcome

The classification of the infants' neurodevelopmental outcome at 24 months of age was done by a paediatric neurologist based on the results from the Bayley III cognitive scale (Bayley, 2006) and the Griffiths scales of child developmental scales (Green et al., 2016). Based on the results, infants were divided into three groups (Table 1). Children in the first group were those whose development at 24 months was assessed to be typical. The second group consisted of children who, at the age of 24 months, either had a slight delay in their overall development or more specific and restricted developmental issues. Lastly, the third group consisted of children who at 24 months showed vast developmental delay or intellectual disability.

Aetiology

Aetiology was also classified by a paediatric neurologist around the time of onset with the consideration of additional findings, such as gene test results, during the follow-up visits. Based on the classification, I divided infants into four aetiology groups: genetic, genetic-structural, structural, and unknown. Since there were only four infants with a genetic-structural aetiology, I considered structural and genetic-structural as one group for this study. This decision was done based on the four infants having a gene alteration, such as a pathogenic ARX-gene mutation, causing changes in brain structure. Thus, infants in the genetic group had epilepsy caused by a known or presumed genetic defect, infants in the structural group due to a distinct structural brain abnormality, and infants in the unknown group for an unknown underlying cause.

Table 1

Developmental Outcome Classification

Typical	The test score is above -1*SD* of the test normative mean (Bayley III) **or** The developmental quotient is above 80 (Griffiths)
Mild	The test score is below -1*SD* but better than or equal to -2*SD* of the norm in all domains **or** The test score is lower than -2*SD* in one domain but scores in the other domains were within age-appropriate development **or** The overall developmental quotient was 70-79 (Griffiths)
Global	The test scores in two or more domains are below -2 *SD* of the norm (Bayley III) **or** The test scores are below a developmental quotient of 70 (Griffiths) **or** If clinically observed large developmental delay in all areas that formal assessment by Bayley III at 24 months was not applicable

Note. This table illustrates the paediatric neurologists' classification criteria for infants' neurodevelopmental outcomes at 24 months of age. Aetiology was classified around the time of onset, with the consideration of additional findings during the follow-up visits.

Procedures

Data Collection

Infants' gaze behaviour was assessed over multiple visits, with each visit consisting of a series of repeated tests. Infants were first tested around the time of onset, a month later after the first visit, and then around the age of 7, 9, 12, 18, and 24 months. The study visits were mostly conducted in conjunction with clinical follow-up appointments. Due to severe alterations in vigilance or other reasons causing an inability to orient to screen related to the infants' condition, all individuals could not complete every visit. The median number of successful visits per infant was four and each visit was performed in accordance with the family's schedule and the infants' vigilance state.

Before each eye-tracking session, an experienced nurse or technician first evaluated the infants' alertness. If an infant was too sleepy or inactive to engage in the eye-tracking test, it

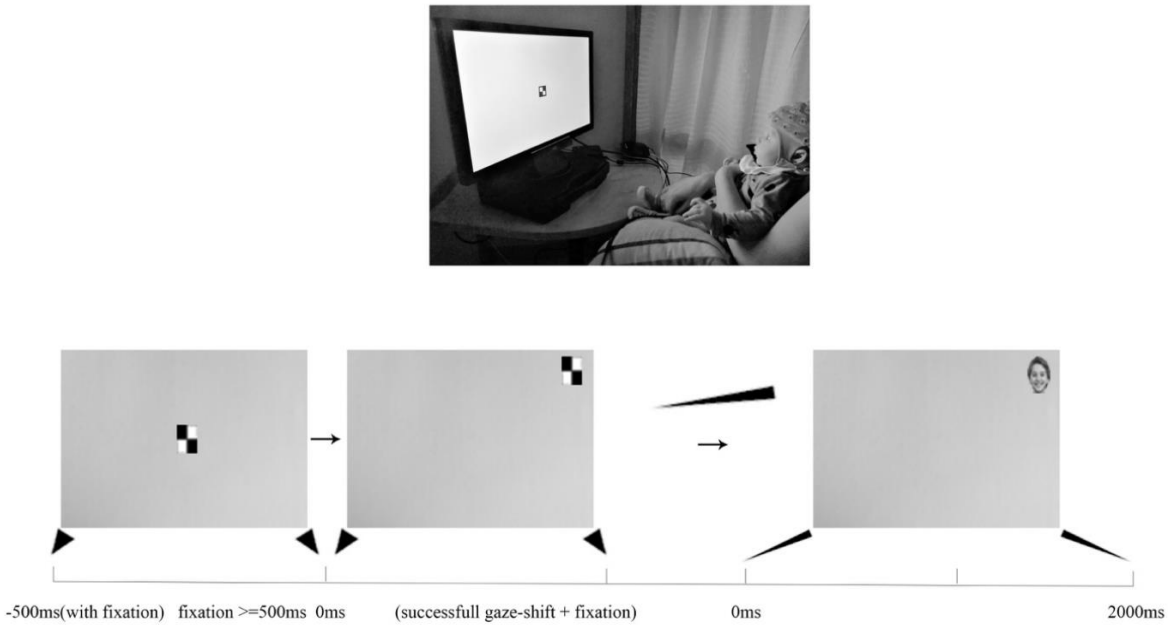
was done on a different day or later that day, after a nap or a sleep EEG. During the eye-tracking, infants sat on their parent's or guardian's lap and watched visual stimuli presented on a computer screen at a 50 to 60-centimetre distance while the eye movements were recorded by the eye-tracker. Parents and guardians were instructed to look away from the screen. Data was gathered separately for both eyes and then analysed collectively in situations where data from both eyes was available. All visits lasted between 10 to 15 minutes.

During each visit, infants completed two distinct tests that alternated throughout the measure-time: SRT (three blocks) and FACE (two blocks). In the SRT test (Figure 1), each trial began with an animated checkerboard fixation stimulus in the centre of the screen, accompanied by a sound. The animated checkboard remained on the screen with the sound until the infant fixated on it. Following a successful fixation, the stimulus and sound stopped, leaving a stationary central stimulus on the screen for 500 milliseconds until the experiment trial began. The central target faded away with the peripheral target emerging in one of the corners of the screen. The periphery stimulus remained the same, a still image of a checkerboard. When an infant turned their focus successfully to the location of the new peripheral stimulus and fixated on it, the checkboard transformed into a happy smile. The smiley stimulus remained on the screen for 2000 milliseconds before the start of the next trial. If an infant did not fixate their gaze, the technician moved on to the next trial. Each SRT test set had 36 trials in total.

The FACE test was designed to measure how different facial expressions, such as neutral, fear, and happiness, affect an infant's gaze fixation on a target. In contrast to the SRT test, it was an overlap paradigm where both stimuli remained on the screen simultaneously. However, since the FACE test data will not be included in this thesis, I will not go into further detail on its methodology.

Figure 1

Schematic of the procedure of the SRT test



.*Note.* EEG cap was not used as part of this experiment. Figure adapted from "Eye-Tracking Based Neurocognitive Screening for Epilepsy in Infancy" by Knapič, 2020, Master's thesis, Umeå University, Umeå, Sweden.

Data Diagnostics

Prior to running the data analyses, I pre-processed the raw data using in-house created software with MATLAB library routines (Mathworks, Natick, MA). Pre-processing procedures, such as moving median filter and interpolation, are often employed to enable automated, standardised SRT analysis and overcome the difficulties of analysing SRT utilising eye-tracking data from participants with high attrition, like infants. As a result, the pre-processing script in this study also incorporated interpolation and the application of a median filter, giving a more robust estimate of gaze behaviour trends. The script was also written to detect technical artefacts and missing samples in the raw data and remove them from the data set, as well as to distinguish SRTs using a simple algorithm that detects the last point of gaze

in the area of interest. The time frame for gaze shift in this study was restricted to 1000 milliseconds due to the frequency with which infants' reactive gaze shift occurred within that time range. Infants' fixation ability was calculated from the time window of 500 milliseconds where only a stationary central stimulus was on the screen. All MATLAB routines used in this study are open source and available at http://www.uta.fi/med/icl/methods.html (Leppänen et al., 2015).

After pre-processing the data, I excluded 11 infants from the data set. Four of the excluded infants had inadequate data, one withdrew in the middle of the study, and two did not meet the criteria for early-onset epilepsy. The rest four had inadequate data for their initial visit, which was relevant to this study. I also excluded failed measures from the data set and calculated the gaze behaviour median values for each visit from the accepted measurements. In the SRT test, three successful measures on the same visit were required. Based on this requirement, nine SRT measures were removed from the data set. After the data manipulation, the final number of participants included in the study was fifty-two, with an average age of 6.69 months (SD = 3.33) and a median of 6.20 on the initial visit.

Statistical Analyses and Parameters

Statistical Analyses. I started by performing Kruskal-Wallis pairwise comparisons to examine if infants' initial gaze behaviour differed significantly among the three developmental outcome groups at 12 and 24 months of age. To assess the significance of the initial gaze behaviour and changes in that behaviour over time in predicting the infants' developmental outcome at 24 months of age, I implemented three multinomial ordinal regression models with a logit link function. This decision was based on the response variables being a class variable and the study's aim of examining the association of numerous factors with a child's development as well as the ability to classify children into developmental categories. Usually, a repeated measurement setup would be employed for this type of time series study. However,

infants' measurement ages and successful measurement points, as well as the number of available measurement points, differed notably in this study (see Figure 2), making such analysis challenging. Moreover, due to the size of the data and lack of longitudinal reference data, I chose to keep the analysis as simple as possible. Because of the large variability in age at infants' first successful visit, I only included visits that were completed before 11 months of age in the regression analysis. Additionally, a 12-month ± one-month rule was applied for the 12-month measure point for the analysis. R programming, IBM SPSS Statistics, and GraphPad Prism version 9.0.0. were used for the analyses.

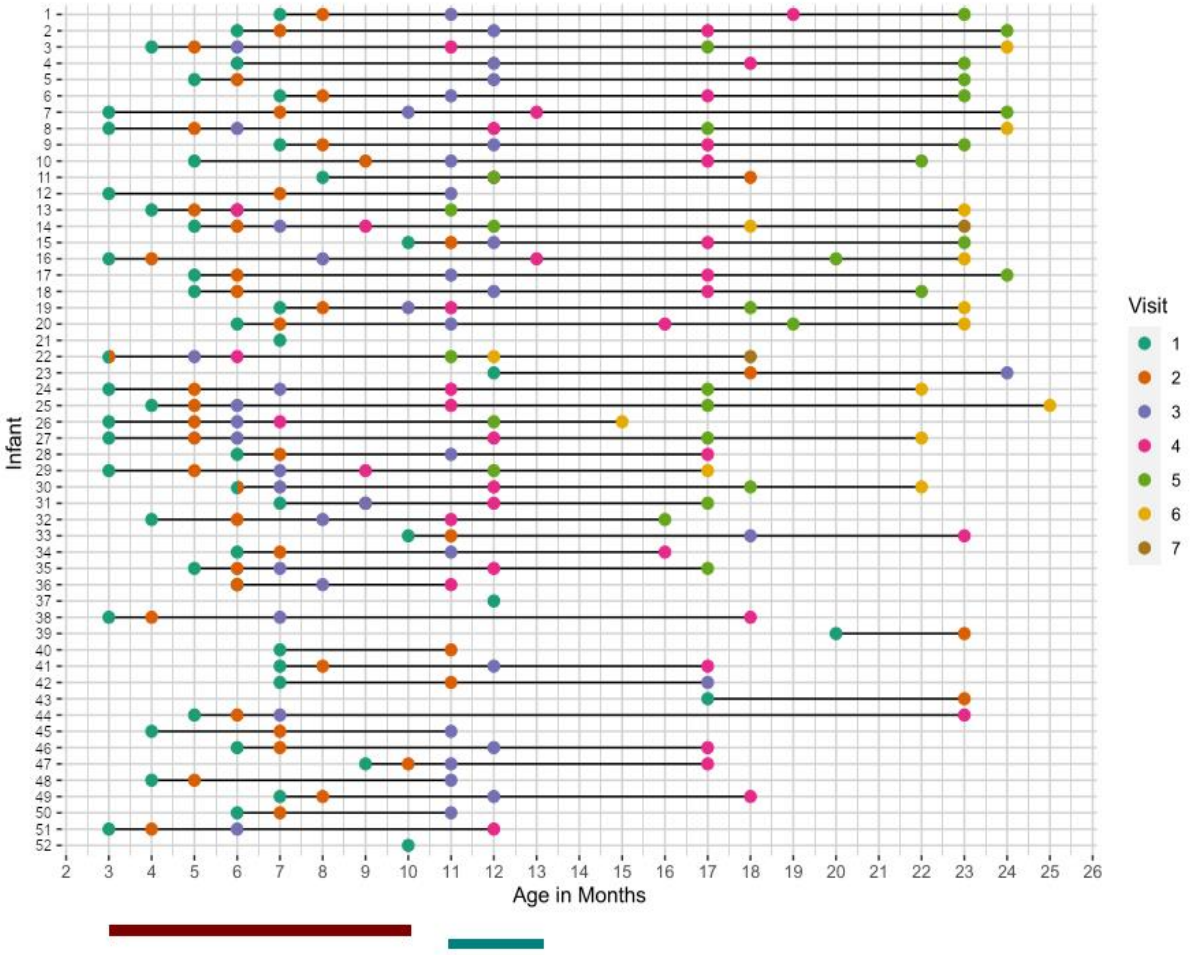
Parameters. At its most basic level, infants' ability to fixate on a screen and the probability of gaze shift following a successful fixation can be evaluated at the first measurement point and a later measurement point as it stands. The former approach, however, inevitably leads to a high level of covariation among the variables, affecting parameter estimate accuracy. Therefore, to determine the best way of employing gaze behaviour parameters in this study, I created three regression models (Figure 3). The gender of the infants, age at onset, and aetiology were included in all three models as control variables in addition to the gaze behaviour parameters. For simplification, I did not consider the dependence between measurements and age standardization in the same model. It should also be noted that due to the small sample size, and in particular the partly small subgroups, the results of the multinomial logistic regression analyses should be considered indicative.

Due to the probability of gaze shift in these infants being clearly lower than the expected probability in the literature for infants of similar age, I also created a gaze shift probability classification variable (see Table 2) that combines fixation and gaze shift ability. The goal of this study was to investigate the essential developmental features in this group of infants, and therefore using such a classification offered a better way of describing their gaze shift development without excluding the infants who were unable to fixate on screen from the

analysis. In addition to the former, infants' fixation ability was used as a continuous variable in this study. The studied parameters can be found in more detail in Table 3.

Figure 2

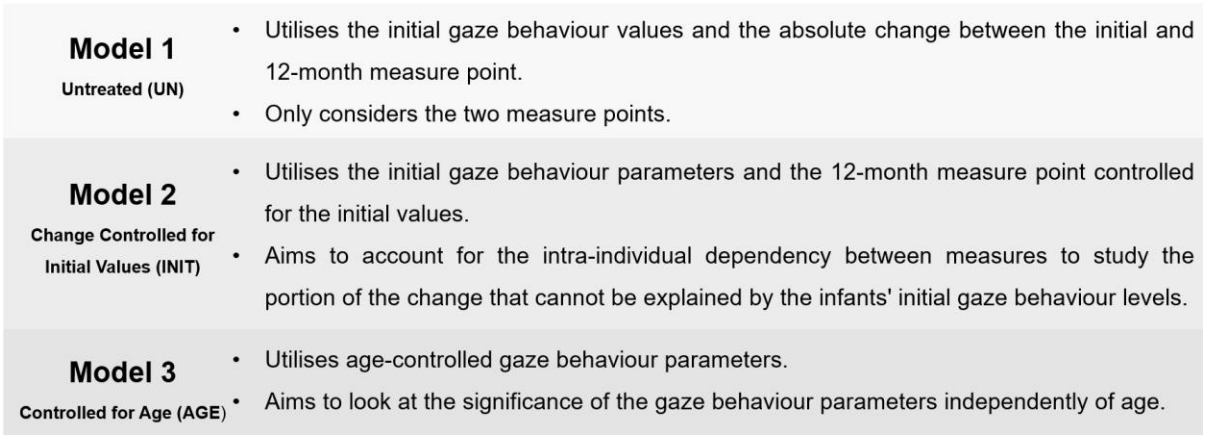
Infants' Age in Months During Visits



Note. This figure illustrates how many visits each infant completed and at what age. The number and time of visits varied, with infants' age ranging from three to twenty months at their first successful visit. Only initial visits that were taken within three to ten months (marked with a red horizontal line) were used in the regression analysis. Additionally, a 12-month ± one-month rule was applied for the regression analysis, with the accepted ages for the 12-month measure point being eleven to thirteen months (marked with a blue horizontal line).

Figure 3

Multinomial Regression Models



Note. Aetiology, the age of onset, and the gender of the infants were included in all three models as control variables.

Table 2

Gaze Shift Probability Classes

Class	Description	Shift Probability Value	Initial Visit (*N* = 52)	12-Month Measure Point (*N* = 48)
1	Non-sufficient fixation	No value	17	17
2	Sufficient fixation without shift	0	18	10
3	Good fixation with low to moderate shift probability	0.01 – 0.75	4	2
4	Good fixation with high shift probability	> 0.76	13	19

Note. Infants' gaze shift probabilities were calculated by dividing the number of successful gaze shifts (shift <1000ms) by approved trials and then divided into four categories, each with its own classifying description. The last two columns present the number of infants within each class based on their initial shift probability value and the value at the 12-month fixed measure point, including the accepted 11-month and 13-month measures.

Table 3

Description of Parameters

Parameter	Description	Computation
Aetiology	Aetiology of epilepsy	
Age initial	Infants' age in their first visit	Full term birth: Age in days divided by 30.5 (n = 45) Preterm birth: Actual age in days – days preterm divided by 30.5 (n = 7)
Develop outcome24mos	Infants' developmental outcome at the age of 24 month	Classification into three groups: typical, mild, global
Fix initial	Ability to fixate on the screen in first visit	Median proportion of fixation to the central stimulus, when only fixation stimulus was presented
Fix abs	Difference between initial visit and 12-month visit	Absolute difference between 12-month fixation ability and initial fixation ability
Shift prob initial	Shift probability class in first visit	
Shift prob abs	Difference between initial visit and 12-month visit	Absolute difference between 12-month shift probability class and initial shift probability class
Fix change INIT	Change in the infants' ability to fixate on the screen between first visit and 12-month visit	Standardised residuals of 12-month fixation ability from a linear regression, when change is predicted by initial fixation values
Shift prob change INIT	Difference between expected and observed shift probability class at the 12-month visit	Expected shift probability class at 12-month measure point minus observed probability class at 12-month measure point
Fix change AGE	Difference between initial visit and 12-month visit	Absolute difference between age-standardized 12-month fixation ability and initial fixation ability
Shift change AGE	Difference between initial visit and 12-month visit	Absolute difference between age-standardized 12-month shift probability class and initial shift probability class

Note. 12-month measure point also includes the measures of 11- and 13-month-old infants.

Results

Data Description

Participants

Out of the fifty-two infants who were included in this study, 54% were male (n = 28) and 46% female (n = 24). Sixteen had genetic aetiology, thirteen structural, and twenty-three unknown. By 24 months of age, twelve infants were classified to have typical development, ten with a mild delay, and twenty-eight with a global developmental delay. Infants' ages ranged from three to twenty months at their first successful visit with the majority lying between three and seven months. Since the majority of the initial gaze behaviour measures were taken around the time of epilepsy onset, infants' initial age will also be referred to as the age of onset in this study despite a small proportion of the infants having their onset well before their initial visit.

Gaze Behaviour

Fixation ability. The initial fixation ability median of the infants was 0.88 with an average of 0.72 (SD = 0.32, N = 52), indicating a left-skewed distribution with more values concentrated on the right side of the distribution. At the 12-month measure point, infants' fixation ability median was 0.96 with an average of 0.83 (SD = 0.24, N = 48).

Gaze Shift Probability. The initial shift probability median of the infants was 0 with an average of 0.42 (SD = 0.46), with seventeen infants having no value (N = 35) due to non-sufficient fixation. Equivalently to the initial fixation ability values, the mean and median of the initial gaze shift probability values indicate an asymmetric distribution of data. At the 12-month measure point, infants showed a median gaze shift probability of 0.95 (M = 0.64, SD = 0.46), with seventeen infants having no value for the gaze shift probability (N = 31) due to non-sufficient fixation. It should be noted that infants' shift probability classification fluctuated in both directions with some infants' gaze shift probability increasing and others lowering. At the

12-month measure point, out of the 48 infants, eight had shifted to a lower class, twenty-six remained in the initial class, and fourteen had shifted to a higher class.

SRT. The initial SRT median for the fifteen infants who were able to successfully shift their gaze from one fixation point to another was 463 milliseconds with an average of 446.52 (*SD* = 102.77), showing close to normal distribution. At the 12-month measure point, infants showed minor improvement in their SRTs, with a 407.69-millisecond median and an average of 411.75 (*SD* = 76.00, *N* = 19).

Data Exclusion

To be included in the multinomial ordinal regressions, infants needed to have completed at least two eye-tracking measurements of which the first was before turning 11 months and the second one within 11 to 13 months of age. Therefore, data from eight participants were removed from the multinomial ordinal regression due to their first visit occurring after the 12-month measure point or a lack of two successfully completed visits before 14 months of age (*n* = 44). Additionally, because of the scarceness of the SRT data, I chose not to include SRTs measures in multinomial ordinal regression models. Only fifteen infants out of the thirty-two (47%) had an adequate measure for their initial visit. Moreover, out of the 19 infants who had a measure at the 12-month measure point, only ten had a measure for their first visit. As a result, the sample size for multivariate analysis would have been insufficient to yield any relevant results. Future research, however, may examine SRTs independently at each age point and see whether the inclusion of SRTs would benefit the small subset of infants.

Statistical Results

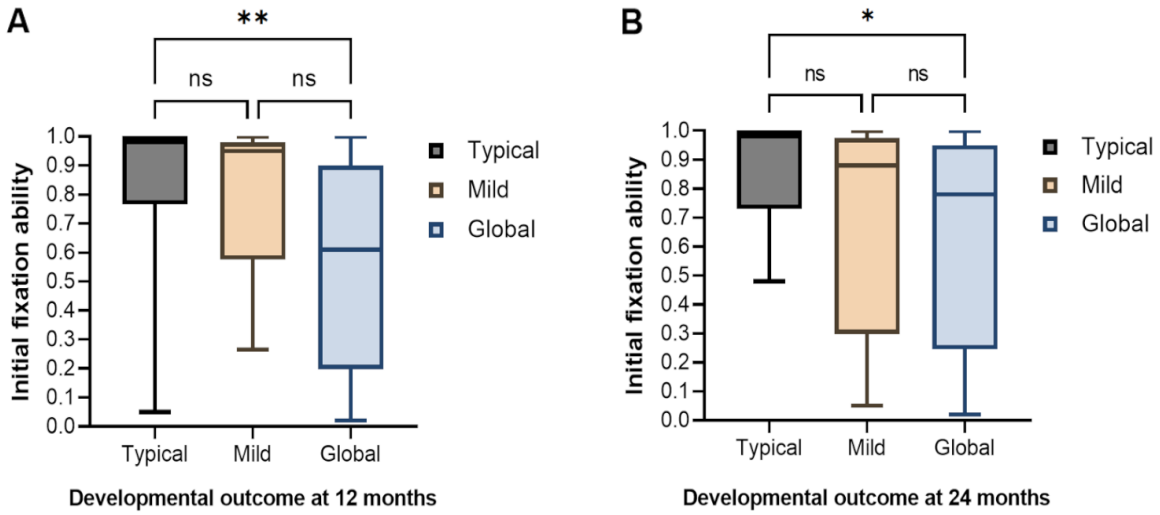
Pairwise Comparison Between Developmental Groups for Initial Gaze Behaviour

The results of the Kruskal-Wallis H test revealed statistically significant difference in initial fixation between the developmental outcome groups at 12 and 24 months of age (12-month measure point: $H(2, N = 52) = 12.69$, $p = 0.002$; 24-month measure point: $H(2, N = 52)$

= 6.49, p = 0.039). Additionally, the results from a post hoc with Bonferroni correction showed a significant difference between the typical and global developmental delay outcomes at both measure points (Figure 4), indicating that infants with global developmental delay had significantly lower median values for fixation ratio during the initial visits compared the typical group. The developmental outcome groups did not differ significantly in terms of initial gaze shift probability (12-month measure point: $H(2, N = 52) = 0.62$, $p = 0.734$; 24-month measure point: $H(2, N = 52) = 2.70$, $p = 0.260$) nor initial SRT (12-month measure point: $H(2, N = 15) = .08$, $p = 0.961$; 24-month measure point: $H(2, N = 15) = 1.72$, $p = 0.424$).

Figure 4

Independent-Samples Kruskal-Wallis Test of the Studied Gaze Behaviour



Note. Kruskal-Wallis pairwise comparisons were performed to examine if infants' initial gaze behaviour differed significantly among the three developmental outcome groups at 12 and 24 months of age. (A) Pairwise comparison between the typical (n = 20), mild (n = 11), and global (n = 21) developmental outcome group at 12 months of age. (B) Pairwise comparison between the typical (n = 14), mild (n = 10), and global (n = 28) developmental outcome group at 24 months of age. Boxplots illustrate the median, interquartile range, and minimum and maximum. **p <.01, *p <.05.

Associations with Developmental Outcome

Full Model Evaluation. Model 1-UN showed significant improvement over a null model (X^2(10, N = 44) = 22.95, p = .011), suggesting that when all six predictor variables were included in the model, it explained the infants' developmental outcomes better than the null model. Similar results were achieved with Model 2-INIT (X^2(10, N = 44) = 19.39, p = .036) and Model 3-AGE (X^2(8, N = 44) = 23.58, p = .003).

Individual Parameters. The statistical significance of individual parameters was tested using Wald chi-square statistics (Table 4). In all three models, gender of the infants, age at epilepsy onset, genetic aetiology, and initial gaze shift probability, were all non-significantly associated with infants' developmental outcome at 24 months of age.

Model 1-UN. The results from Model 1-UN showed structural aetiology to be significantly associated with a higher probability of being in higher outcome categories than when the aetiology is unknown and other factors held constant. The lowest category refers to typical development and the highest category to global developmental delay. Therefore, in this group of infants, the atypical developmental outcome is more likely with structural aetiology compared to unknown aetiology. Additionally, better fixation ability in the initial visit and a positive change in gaze shift probability were both associated with a higher likelihood of being in lower outcome categories. Since the lowest category refers to typical development and the highest category to global developmental delay, having good initial fixation and making a positive improvement in gaze shifting by the age of 12 months is associated with a more probable positive developmental outcome and less probable unfavourable outcome at 24 months of age.

Model 2-INIT. The results from Model 2-INIT showed a significant association between infants' initial fixation ability and a more positive developmental outcome at 24 months of age. In contrast to Model 1-UN, structural aetiology was not found to be significantly

associated with infants' later developmental outcome when intra-subject dependency was controlled. Additionally, neither the change in infants' fixation ability nor the change in gaze shift probability, after controlling for the initial measures, showed a significant association with infants' developmental outcome.

Model 3 - AGE. The results from Model 3-AGE yielded similar results with Model 1-UN, showing global developmental delay being more likely with structural aetiology compared to an unknown one, and a good initial fixation and positive improvement in gaze shifting by the age of 12 months being associated with a higher likelihood of a positive developmental outcome.

Table 4

Multivariate Analysis of Associations

Predictors	***df***	***β***	**SE *β***	**Wald's X^2**	***p***	**OR**	**OR 95% CI**
Model 1 - UN							
Aetiology: genetic	1	1.10	.83	1.76	.184	3.00	(.59 - 15.22)
Aetiology: structural	1	2.48	1.22	4.16	.041	12.00	(1.10 - 128.84)
Aetiology: unknown	.	0[a]	.	.	.	.	.
Gender: female	1	-.12	.77	.02	.881	.89	(.20 - 4.02)
Gender: male	.	0[a]	.	.	.	.	.
Shift_prob_init = class 1	1	-.21	.97	.05	.828	.81	(.12 - 5.41)
Shift_prob_init = class 2	1	-.43	.98	.19	.662	.65	(0.10 - 4.42)
Shift_prob_init = class 3	1	.18	1.79	.01	.919	1.20	(.04 - 39.87)
Shift_prob_init = class 4	.	0[a]	.	.	.	.	.
Age_init	1	-.04	.22	.03	.864	.96	(.63 - 1.47)
Fix_init	1	-7.57	3.25	5.20	.023	<.001	(<.001 - .35)
Fix_abs	1	-5.42	3.34	2.64	.104	.004	(<.001 - 3.07)
Shift_prob_abs	1	-.81	.40	4.05	.044	.45	(.20 - .98)
Model 2 - INIT							
Aetiology: genetic	1	0.88	.81	1.18	.278	2.40	(.49 - 11.68)
Aetiology: structural	1	1.93	1.10	3.10	0.80	6.90	(.79 - 59.86)
Aetiology: unknown	.	0[a]	.	.	.	.	.

Table 4 Continued

Multivariate Analysis of Associations

Gender: female		-.07	.80	.007	.931	.94	(.21 - 4.12)
Gender: male	.	0[a]	.	.	.	.	.
Shift_prob_init = class 1	1	-.54	.94	.31	.575	.59	(.09 - 3.72)
Shift_prob_init = class 2	1	-.44	.96	.21	.646	.64	(.10 - 4.24)
Shift_prob_init = class 3	1	-.19	1.85	.01	.916	.82	(.02 - 30.66)
Shift_prob_init = class 4	.	0[a]	.	.	.	.	.
Age_init	1	.19	.21	.80	.374	1.21	(.78 - 1.84)
Fix_init	1	-3.59	1.81	3.92	.048	.03	(.001 - 1.00)
Fix_change_score	1	-1.18	.62	3.63	.057	.31	(.09 - 1.04)
Shift_prob_change_score	1	.33	.32	1.10	.269	1.40	(.75 - 2.58)
Model 3 - AGE							
Aetiology: genetic	1	1.07	.77	1.93	.164	2.92	(.64 - 12.26)
Aetiology: structural	1	2.29	1.12	4.19	.041	9.89	(1.10 - 88.72)
Aetiology: unknown	.	0[a]	.	.	.	.	.
Gender: female	1	-.184	.72	.07	.797	.83	(.20 - 3.39)
Gender: male	.	0[a]	.	.	.	.	.
Age_init	1	-.23	.21	1.19	.275	.79	(.52 - 1.20)
Fix_init_stand	1	-1.89	.77	5.96	.015	.15	(.03 - .69)
Shift_prob_init_stand	1	.131	2.84	.21	.645	1.14	(.65 - 1.99)
Fix_abs_stand	1	-1.26	.74	2.94	.086	.28	(.07 - 1.20)
Shift_prob_abs_stand	1	-.74	.40	4.02	.045	.48	(.23 - .98)

Note. This table represents the associations between infants' gender, aetiology, age at onset, and gaze behaviour parameters per model. Infants' developmental outcome at the age of 24 months was included in the model as a dependent variable.

Classification Results. I used a classification table to compare the degree to which the predicted probabilities of each model agree with the actual outcomes (Table 5).

Sensitivity. All three models had a high sensitivity for the global developmental delay group, meaning that the models could predict true positives 85 to 88 per cent of the time. On the other hand, the sensitivity for the mild delay developmental group was moderate in each model. Model 1-UN and 3-AGE showed a higher sensitivity for the typical group than Model 2-INIT. Using age-controlled gaze behaviour parameters (Model 3-AGE) resulted in the

highest sensitivity for mild developmental delay. Similarly, controlling the follow-up value for the initial gaze behaviour values (Model 2-INIT) showed the highest sensitivity for global developmental delay.

Specificity. Specificity was highest in the mild developmental delay group in all three models (0.93 - 1%), meaning that all models performed best at identifying individuals who do not have a mild delay. The specificity for typical and global developmental delay outcome ranged between 71 to 84 per cent depending on the model. The highest specificity for the mild developmental delay was achieved by controlling the follow-up value for the initial gaze behaviour values (Model 2-INIT) and the highest specificity for individuals with global developmental delay by using age-controlled gaze behaviour parameters (Model 3-AGE).

Overall Fit. Since the goal of this study was not to find the best prediction model but rather to investigate the relationship between infants' gaze behaviour and later developmental outcome and the predictive ability of that association, I focused on looking at the overall differences between the models. With the former, I also aimed to determine the necessity of controlling for the factors influencing the gaze behaviour measurements, for example, the age of the infants and intra-individual dependency between the measures.

Sensitivity, specificity, and the overall accuracy – measured as the degree to which the probability of belonging to a developmental outcome group agrees with the actual outcomes at 24 months of age – were very similar between Model 1-UN and Model 3-AGE. On the other hand, the results from Model 2-INIT showed slightly poorer accuracy compared to the other two models with more varying sensitivity and specificity. Based on these findings, employing age-controlled gaze behaviour parameters with early-onset epilepsy infants appears to be particularly beneficial in identifying true positives of the mild developmental group – which all three models pointed challenging.

Table 5

The Observed and Predicted Developmental Outcome Groups at 24 Months of Age

MODEL 1 - UN	Pred. Group			
Developmental Outcome	Typical	Mild	Global	% Correct
Typical	12	2	3	0.71
Mild	4	10	4	0.56
Global	3	1	22	0.85
Overall % correct				**0.72**

Specificity: Typical 0.84, Mild 0.93, Global 0.80

MODEL 2 - INIT	Pred. Group			
Developmental Outcome	Typical	Mild	Global	% Correct
Typical	12	0	6	0.66
Mild	5	10	5	0.50
Global	3	0	22	0.88
Overall % correct				**0.70**

Specificity: Typical 0.82, Mild 1.0, Global 0.71

MODEL 3 - AGE	Pred. Group			
Developmental Outcome	Typical	Mild	Global	% Correct
Typical	12	2	3	0.71
Mild	4	10	3	0.59
Global	3	1	22	0.85
Overall % correct				**0.73**

Specificity: Typical 0.84, Mild 0.93, Global 0.82

Note. The predicted values for different models were acquired from the multivariate ordinal regression.

Partial model evaluation. To assess the independent contribution of gaze behaviour parameters in the prediction of infants' future developmental outcomes, I reran all three models only using the gaze behaviour parameters as predictors. All three models remained to show significant improvement over the null model (Model 1-UN: $X^2(6, N = 44) = 17.56$, $p = .007$; Model 2-INIT: $X^2(6, N = 44) = 14.95$, $p = .021$; Model 3-AGE: $X^2(4, N = 44) = 17.09$, $p = .002$). On the contrary, when aetiology and infants' initial age were used in the model as the only predictors, the model's significant improvement over a null model became non-significant, $X^2(4, N = 44) = 7.89$, $p = .096$). Moreover, when only gaze behaviour parameters

were included in the analysis, all models' prediction accuracy for the infants' developmental outcome at 24 months of age remained relatively similar (Model 1-UN: 72%; Model 2-INIT: 70%; Model 3-AGE: 73%). These finding illustrates the importance of gaze behaviour parameters in enhancing model prediction ability.

Summary of the findings

Infants with global developmental delay at 12 and 24 months of age showed significantly lower median values for fixation ratio compared to the infants in the typical developmental group. Infants' initial ability to fixate their gaze and changes in their gaze shift probability within the first year of life, were both associated with the infants' later developmental outcome at 24 months of age, and the association persists even when the aetiology, the age of onset, and the gender of the infants were considered. With the methodology used in this study, it was possible to identify infants with typical development and global developmental delay 71 per cent and 85 per cent of the time, respectively. The identification of infants with mild developmental delay was moderate, with 59 per cent of the infants getting identified correctly.

Discussion

This study investigated the association between the gaze behaviour of infants with early-onset epilepsy and their future developmental outcome. The results showed infants' initial ability to fixate their gaze, as well as changes in their gaze shift probability within the first year of life, to be associated with their later developmental outcome at 24 months of age. The associations persisted even when aetiology, age of onset, and infants' gender were considered. Based on these findings, by examining the gaze behaviour of infants with early-onset epilepsy at an early stage using simple eye movement tasks, it is possible to identify infants with typical development and infants with global developmental delay quite successfully. The identification of infants with mild developmental delays was moderate.

Taking into account the dependency between eye movement measurements taken at two different time points weakened the predictive power of the gaze parameters. The former could be explained by the deviation from the expected gaze behaviour being minor in most infants. It is also possible that better-than-expected, in-line-with-expectation or weaker-than-expected change is associated with various connections to the infants' development that cannot be reached with this approach. In contrast to controlling for intra-individual dependency between the measures, standardizing the measurements in relation to the initial measurement age did not change the associations between the gaze behaviour parameters and later developmental outcome significantly. This may indicate that although the measurement results are to some extent related to the infants' age, the connections between gaze behaviour and later development do not seem to be explained by the variation in the infants' measurement age. However, even if the standardization of the measurements in relation to the measurement age did not change the associations significantly, the precision of the fixation ability parameter estimates improved. Thus, it might be that age-controlled fixation measures are necessary for more precise estimates.

The results of this study are consistent with my hypothesis and with the findings from Knapič (2020), where higher initial fixation ability was significantly associated with a better neurodevelopmental outcome. In contrast to Knapič (2020), this study did not find evidence of an association between changes in infants' fixation ability and later developmental outcome. The variation between the results of this study and Knapič's (2020) might be attributable to different computation methods utilised. Moreover, where Knapič (2020) looked at the mean change of the fixation across all visits during the whole 24-month follow-up period, I looked at the change between the initial visit and the 12-month measure point. Since infants' gaze behaviour fluctuated throughout the 24-month follow-up period, looking at the difference between two measure points in comparison to the mean of the whole follow-up period may

give very different values. Moreover, given that the shift probability classification of this study also included infants' fixation ability at a coarser level (non-sufficient, sufficient, or good), it is also possible that such changes in the infants' fixation ability are conveyed through the shift probability parameter.

After the first two to three months of life, the visual system in typically developing infants generally progresses to the point where an infant can successfully fixate and track objects (Atkinson & Braddick, 2012). The infants of this study, however, showed a clear deviation from the typical visual developmental milestones, with some of the infants being unable to fixate their gaze and having difficulties shifting their gaze at one year of age. Along with their medical condition, the fluctuating state of alertness of the infants may have also affected their fixation ability during testing. The drastic improvement seen in the infants' gaze shift probability within the first year could be a marker of the development of circuits between subcortical and cortical areas essential for normal visual development (Braddick & Atkinson, 2011). As subcortical-cortical functional connectivity provides the basis for decision-making, learning abilities, and sensorimotor processing (Canini et al., 2020), improvements in the connectivity should result in higher cognitive efficiency. The former idea is consistent with the findings of this study where an improvement in gaze shift probability by 12 months of age was associated with a more favourable outcome at 24 months of age.

The lack of significant association between changes in fixation ability within the first year of life and the later developmental outcome could be related to subcortical systems underpinning the initial attention ability (Atkinson & Braddick, 2012) and serving as a foundation for the more polished visual skills controlled by the cortical systems (Braddick & Atkinson, 2011). A potential subcortical system impairment would therefore raise the risk of less favourable developmental outcomes in demands that rely on this system, such as cognition. However, as mentioned earlier, infants' fixation ability was also included in the shift probability

classification used in this study. Therefore, since the gaze behaviour parameters overlap through the shift probability parameter, the significance of changes in fixation ability within the first years of life for the infants' future developmental outcome cannot be ruled out.

Similarly to other studies that have investigated early-onset epilepsy patients (Gaily et al., 2016; Symonds et al., 2021), structural aetiology was significantly associated with poorer developmental outcome. This finding is consistent with my hypothesis, which suggested aetiology to be a significant predictor of the infants' later developmental outcome. Since ongoing seizures due to drug resistance are commonly seen in infants with structural aetiologies (Balestrini et al., 2021), the more adverse prognosis compared to other aetiologies could be explained by the poorly controlled seizures that are commonly linked to impaired cognitive function, with the most severe consequences in infancy (Holmes, 2016). However, given that this study did not look at infants' seizure outcomes, it cannot be verified how well seizures were managed in each aetiology group or whether any of the infants were resistant to medication.

Implications

The results of this study imply that early childhood gaze behaviour is an essential factor in predicting the developmental outcome of infants with early-onset epilepsy at 24 months of age. In other words, infants' developmental outcome at two is better explained by infants' gaze behaviour than infant's aetiology, age at onset or gender – with the results remaining regardless of the measurement age. Based on this finding, it could be expected that infants with early-onset epilepsy who (i) show poorer initial ability to steadily fixate their gaze during the initial visit and (ii) deteriorate in their ability to make reliable gaze shifts within the first year of life are more prone to a poor developmental outcome. However, due to the small sample used in this study, these results should be verified in a larger patient population.

Applications

Based on the findings of this study and Knapič's (2020), we have a good indication of the importance of gaze behaviour in predicting the future neurodevelopmental outcome of infants with early-onset epilepsy. Assessing gaze behaviour at a relatively young age can already provide a moderately good prognosis for the infants' future development within this clinical group of infants. If these findings replicate in larger samples and the model is further refined for higher accuracy and better sensitivity to the mild delay group by including SRT measures and several measure points, serial eye-tracking could be a valuable addition to the current approaches used in clinical and paediatric epilepsy research settings. Moreover, with the results of this study, it is also possible to create individual metrics, limiting values, and prediction probabilities in the future.

In a systematic review from Tao et al. (2020) that investigated adult patients with neurological disorders commonly associated with mild cognitive impairments, eye-tracking technology was found to facilitate the assessment of cognitive impairment with higher temporal resolution and finer granularity than traditional cognitive assessments. Even if the aforementioned systematic review only consisted of adult participants, based on the findings of this study, eye-tracking could be equivalently used with early-onset epilepsy patients to not only facilitate the assessment of cognitive impairment and future developmental outcome but to also learn more about the relationship between early-onset epilepsy in terms of gaze behaviour – especially when more refined analyses of gaze behaviour can be applied. Additionally, by utilising serial eye-tracking, researchers may be able to learn more about the progression of early-onset epilepsies and condition-related changes in their neurodevelopment.

Limitations

Some prominent limitations of this study are the small sample size and inconsistency in the fixed measure points. Ideally, all infants would have completed all visits at the

predetermined measuring points. However, this was not always possible due to the condition of some of the infants as well as scheduling difficulties. This study also did not look at the effects of more specific but relevant clinical features, such as anti-seizure medication, which is another limitation of this study. The initial eye-tracking sessions were meant to be done before the infants' anti-seizure medication began. However, for clinical considerations, this was not feasible in most of the cases. Also, infants' seizure activity or eye disorders and diseases, such as strabismus and hyperopia, were not considered in this study. If the start of anti-seizure medication, seizure activity, and eye disorders and diseases had been considered, the prediction model utilised in this study could have resulted in higher accuracy. Lastly, the high variation in the temporal distance between the two measurements – caused by the different timings of infants' initial gaze behaviour measures – may have affected the results.

Future Studies

To address the issue of lack of control for certain factors, future studies should also control for the possible effects of anti-seizure medication, seizure activity, and eye disorders and diseases. Adding SRT as one of the gaze behaviour parameters could also bring additional information about the abnormal neurodevelopment related to infants' cognitive difficulties in infants who are able to fixate and shift gaze reliably, allowing more accurate predictions of their future developmental outcome. Also, even if the age standardization should have helped with the issue related to the high variation in the temporal, future studies should further investigate whether the temporal distance matters in terms of results. Moreover, another aspect of this study that was left out was the examination of how gaze behaviour develops in different aetiology groups and whether there are any initial differences. It could be interesting to see if any gaze behaviour abnormalities are, for example, aetiology specific. Lastly, to increase the validity of the results, future studies should also include a healthy control group to see how the gaze behaviour values and fixed measure points are associated with typical infants.

Conclusion

The current study investigated whether gaze behaviour in infants with early-onset epilepsy is associated with the infants' neurocognitive development at 24 months of age. The results of the multinomial ordinal regression showed better fixation ability during the initial visit and improved ability to make reliable gaze shifts within the first year of life, both to be associated with better developmental outcome at 24 months. Structural aetiology was significantly associated with a higher probability of an atypical developmental outcome. Based on these findings, good fixation ability and developing gaze behaviour are significant indicators for later positive developmental outcome in infants with early-onset epilepsy. With more research, eye-tracking could provide a quick, non-invasive, and unbiased method for evaluating the later neurocognitive outcome of infants with early-onset epilepsy at an early age.

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