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Pattern visual evoked potentials show an inferior–superior topographic shift through maturation in childhood

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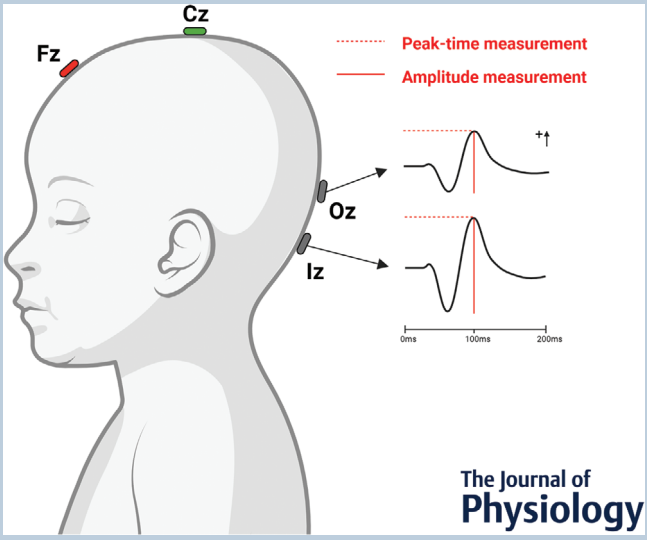

Abstract The pattern-reversal visual evoked potential (prVEP) is an established routine clinical test. Its objectivity is particularly valuable for assessing visual pathway function in children. International standards specify at a minimum that an active electrode is placed on the occiput at Oz, but we find an additional inferior electrode at the inion (Iz) provides larger and more sensitive prVEPs in young persons. This study assesses the significance and age-dependence of these observations. PrVEPs were recorded from 1487 patients considered ophthalmologically normal aged <20 years old, to a range of check widths including International Society for Clinical Electrophysiology of Vision (ISCEV) standard large (50′) and small (12.5′) check widths. P100 peak-time and amplitude from both electrode sites were analysed. A subset of 256 children were studied longitudinally by fitting logistic regression models including a random effect on subjects. PrVEPs were largest over the Iz electrode for the majority of infants and children. This transitioned with age to become equal or smaller at Oz as a function of check width. For ISCEV standard large and small check widths,

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transition periods were ∼8 and ∼12 years of age, respectively. We estimated abnormal result classifications of 3.7% with use of an Oz electrode alone, which decreases to 0.0–0.5% when adding or using an Iz electrode. The inferior dominance of prVEP topography in children may be explained by age-related anatomical changes altering the cortical dipole, combined with physiological maturation of the neural generators of the prVEP. We recommend the Iz electrode is used routinely in recording of prVEPs in children.

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Abstract figure legend Schematic representation of prVEP response measurement. Responses were recorded from mid-occipital (Oz) and inion (Iz) electrodes simultaneously, referred to a mid-frontal electrode (Fz) and ground centrally (Cz). Peak-time was taken from stimulus onset (0 ms) to peak of the P100 component (red dashed line). Amplitude was taken from the N75 trough to P100 peak (red vertical line).

Key points

- Pattern visual evoked potentials (PVEPs) are an established clinical test which provide objective assessment of visual pathway function. These are particularly valuable in providing objective information of vision in children.
- International standards specify the active recording electrode should be placed at the mid-occiput (Oz), but we find that pattern-reversal visual evoked potential amplitudes are larger for a lower placed electrode (Iz) in young persons.
- This was assessed in 1487 patients who had simultaneous PVEP recording at both electrode positions, and it was found that the majority of PVEPs in children were larger over the Iz electrode.
- The developmental differences in PVEP distribution transitioned to be equal between Iz and Oz with increasing age as a function of check width, at ∼8 and ∼12 years old for large and small check widths, respectively.
- These differences will improve diagnostic accuracy of paediatric PVEPs. We hypothesise these changes reflect developmental anatomical and neurophysiological changes altering the PVEP dipole.

Introduction

The visual evoked potential (VEP) is an important clinical tool in the assessment of the visual pathway. It is a cortical response which depends upon afferent signals from the retina, optic nerve and visual pathway. The VEP can detect and localise visual pathway pathology in many conditions (Marmoy & Viswanathan, 2021).

There are international standards (International Society for Clinical Electrophysiology of Vision; ISCEV) and recommendations (International Federation of Clinical Neurophysiology; IFCN) for performing the clinical VEP,

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which can be elicited to pattern reversal (prVEP), pattern onset–offset or flash stimuli (Holder et al., 2010; Odom et al., 2016). The prVEP has the clinical advantage of producing the lowest inter- and intra-subject variability, and therefore it is the most commonly used modality (Odom et al., 2016). Electroencephalographic (EEG) activity time-locked to each black to white phase reversal of a high contrast checkerboard stimulus is averaged to produce a triphasic prVEP in healthy individuals. The prVEP components are named according to their polarity (N, negative; P, positive) and peak-time (milliseconds), namely N75, P100 and N135, respectively. Scalp electrodes are placed according to the international 10−20 system and ISCEV standard prVEPs specify a minimum of an active, reference and ground electrodes at Oz, Fz and Cz (or around C3/C4), respectively (Klem et al., 1999). The prVEP is an objective test of the functional integrity of the macular pathway and can give early indications of vision levels or visual pathology. This is particularly important for children who have lower cooperation or are unable to tolerate subjective testing.

At the authors' institution, Great Ormond Street Hospital for Children (GOSH) in London, UK, prVEPs are recorded in accordance with specifications in the ISCEV standards but with an additional midline electrode positioned 10% of the nasion–inion distance below Oz over the bony protuberance known as the inion, termed Iz according to the 10–10 system nomenclature (Nuwer et al., 1998). We have frequently observed the prVEP in young children to be larger over this electrode relative to the ISCEV standard Oz placement. We hypothesised that prVEPs are larger at Iz in the early years of life but decrease in amplitude with age as the spatial tuning of the prVEP and visual pathway anatomy matures. We designed this study to address this hypothesis and to identify the age range when children have more than a 10% amplitude difference between Oz and Iz electrodes for a given check width, which may guide those performing paediatric prVEPs to use an Iz electrode in addition to the standard Oz electrode placement. We also explored the intra-subject differences in a subset of participants through longitudinal measures.

Methods

Ethical approval

This study was approved by the Great Ormond Street Hospital/UCL Institute of Child Health joint research and development office (ref. 19SS02). Data were anonymised and retrospectively collected, and in accordance with these approvals no consent procedures were required. The study conformed to the standards set by the *Declaration of Helsinki*, except for registration in a database.

Study design

This study utilised all eligible prVEP recordings of patients under the age of 20 years seen at GOSH between 2016 and 2020. The eligibility criteria included a normal prVEP recording, with both eyes open to at least a 50 min of arc (′) check width (ISCEV large check), compared to laboratory reference ranges. Laboratory reference ranges were originally derived from 219 healthy children aged 2 weeks to 16 years (163 children between 0 and 12 months and 56 children over 1 year). The largest P100 amplitude measured either from Oz or Iz was used as a single data point from each child in these reference data. P100 amplitudes equal to or larger than this were regarded as clinically normal, falling within the 2.5th–97.5th centile. Patients with an identified abnormality of the prVEP or clinical examination at our institution were excluded. In addition to the P100 amplitude and peak-times to 50′ check widths, prVEPs measures to a range of check widths (6.25′–200′) were included. Some patients were seen more than once within the sampling period, and therefore the last visit was compared to the initial data point to calculate the intra-subject rate of amplitude difference between Oz and Iz longitudinally.

Data acquisition

PrVEPs were recorded to a range of high contrast reversing checkerboards (Michelson contrast ∼96%) presented on a plasma display screen (Model PDP433MXE; Pioneer Electronics Corp., Tokyo, Japan), subtending 28° visual field at 1 m with a mean luminance of 82 cd/m^2. Check widths ranged between 200′ and 6.25′ and included ISCEV standard 'large' (50′) and 'small' (12.5′) checks. Patient fixation was directed to a small fixation point in the centre of the stimulus by an experienced member of staff and monitored with closed-circuit television. Intermittent averaging was performed and stimulus alternated with a video of choice in younger children to maintain alertness.

Ag–AgCl electrodes were applied to the occiput over O_1, Oz and O_2 locations, with the addition of the Iz electrode, using a conductive paste (Elefix paste, Nihon Cohden, Tokyo, Japan) following preparation of the scalp (NuPrep gel; Weaver and Company, Bromley, UK) to ensure impedances were maintained below 5 kΩ. These electrodes were referred to a mid-frontal reference electrode (Fz) with a ground electrode placed centrally (Cz). The time-locked background EEG was band-pass filtered (0.312–100 Hz). An epoch of 300 ms, including a 15 ms pre-stimulus interval, ensured capture of the entire prVEP waveform. PrVEPs recorded from Oz and Iz were recorded simultaneously to the same stimulus. Between 30 and 100 trials were obtained per average, dependent on the child's cooperation, with a minimum of two averages obtained for each check-width. P100

amplitude and peak-time at Oz and Iz were measured from N75 trough (Fig. 1) to P100 peak using an Espion Diagnosys E3 system (Diagnosys LLC, Cambridge, UK) by two independent scientists and verified by the principal investigator (O.R.M.) using a stratified audit sample method to ensure data quality.

The primary outcome of interest was the difference between Iz and Oz amplitudes as a proportion of the Oz amplitude (Proportional amplitude difference = (Iz – Oz)/Oz). This was smoothed with a 3 months' rolling mean in favour of longer-term trends rather than short-term fluctuations in order to find the age cut-off point in months where one electrode placement is preferred over the other to produce larger amplitudes (Zeileis & Grothendieck, 2005). The clinical threshold was set at 10%, and greater differences indicate a preference for the Iz placement, whilst smaller differences indicate preference for the Oz placement. A 10% difference was chosen as this follows the coefficient of variability for the prVEP (Mellow et al., 2011). We also explored peak-time differences between Iz and Oz amplitudes as a function of age to the ISCEV large and small check width equivalents.

For the subset of patients who had repeated prVEPs recorded to the 50′ check width, the secondary outcome was the annual intra-subject rate in the proportional difference of amplitude. This was calculated by subtracting the proportional difference in amplitude (PDA) at the first measurement from the one at the last measurement, divided by the age difference when these measurements were taken: $(PDA_{last} - PDA_{first})/(Age_{last} - Age_{first})$. A negative rate means that the proportional difference in amplitude decreases with increasing age, whereas a positive rate means the opposite.

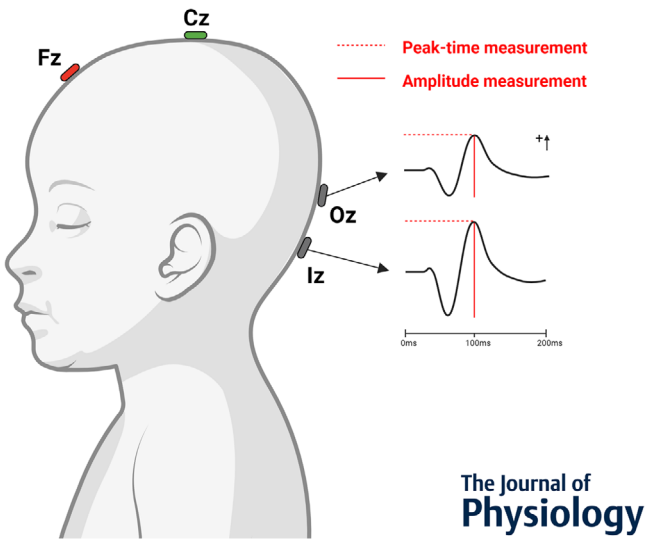

Figure 1. Schematic representation of prVEP response measurement
Responses were recorded from mid-occipital (Oz) and inion (Iz) electrodes simultaneously, referred to a mid-frontal electrode (Fz) and ground centrally (Cz). Peak-time was taken from stimulus onset (0 ms) to peak of the P100 component (red dashed line). Amplitude was taken from the N75 trough to P100 peak (red vertical line).

Statistical methods

Complete case analyses were carried out in R version 4.1.0 (R Core Team, 2021). Summary statistics included median and interquartile range (IQR) of Iz and Oz amplitudes and patient age by check width used. A cross-sectional analysis made use of all subjects' first or only prVEPs recordings. Bland–Altman's limits of agreement were calculated to compare the differences in peak-time and amplitude obtained from the different electrode placements (Bland & Altman, 1986). We found no significant differences between prVEP P100 peak-times between Oz and Iz electrode sites for 50′ and 12.5′ check widths when observing the linear regression and Bland–Altman plots. No further analysis therefore took place for prVEP peak-time. A significant difference was observed for amplitude, following which the distribution between Iz and Oz amplitude was determined by visualising the 3 months' rolling mean by age and check width with the best fitted line using local regression smoothing (loess) (Cleaveland et al., 1992). For the ISCEV standard large check width of 50′, the best fitting model considered was a $\log_{10}$ transformation of age in months. Following this, a logistic regression on the rolling mean (3 months) was fitted for each check width with age as a fixed effect. Values exceeding the 10% threshold using smoothed functions of age were modelled as a fixed effect and the individual's identity as a random effect. Inference on the age at which the rolling mean passed the 10% threshold was performed via the delta method applied using the R package msm (Jackson, 2011). The 99% confidence interval (CI) derived was used to form a 'transition period' whereby the difference around a 10% threshold showed no preferred electrode placement. Sensitivity, specificity and area under the receiver operating characteristic curve (AUC–ROC) were calculated for each age period to quantify the classification performance of the model, where one electrode placement was preferred over the other for a given check width. The sensitivity analysis included optimising the AUC from 1 year before to 1 year after the transition period by sliding it 1 month ahead each time. Furthermore, the rate of abnormality in amplitude (<7 μV) for 50′ check widths was calculated for each electrode, relative to the other being normal. This was considered 'classified abnormal', as this would fall outside of the 95% reference range confidence limits.

Longitudinal analysis was restricted to the subjects with repeated prVEPs recordings to a 50′ check width. The annual intra-subject rate in the proportional amplitude difference by age at first measurement was visualised,

Table 1. Population characteristics at the first prVEP measurement

Check width (min of arc, ′)	*n*	Amplitude (μV)		Age in months (IQR)
		Oz (IQR)	Iz (IQR)	
100′	740	21.0 (14.0–30.0)	21.5 (15.8–30.0)	43.4 (18.4–79.2)
50′†	1487	23.0 (15.0–33.0)	24.0 (17.0–35.0)	54.9 (24.7–87.5)
25′	1419	22.0 (14.0–33.0)	24.0 (16.0–34.0)	55.5 (25.6–87.6)
12.5′‡	1267	20.0 (13.0–31.0)	22.0 (15.0–33.0)	57.8 (29.1–89.5)
6.25′	857	16.0 (11.0–26.0)	19.0 (13.0–27.0)	59.8 (32.9–90.5)

†This check width equates to the ISCEV standard 'large check'. ‡This check width equates to the ISCEV standard 'small check'.

and the best fitted line using loess was added. A linear mixed-effects regression model on the annual intra-subject rate was fitted with age at first measurement as fixed effect, and the subject's identifier as a random effect on the model's intercept. The delta method was used to perform inferences on the age at which the rate was zero, i.e. when the proportional amplitude difference did not change with age.

Results

Study sample

The sampling period contained a total of 7696 records, of which 2140 prVEPs (27.8%) were considered 'normal' during initial screening when compared to laboratory reference data. All of these records had their raw data re-examined to measure P100 peak-time and amplitude, of which 653 records were excluded due to missing (i.e. one electrode site not applied or grounded) or sub-optimal quality (i.e. noisy or variable) data. The resultant sample size (2140 − 653 = 1487 (69.5%)) ranged from 740–1487 patients per check width (Table 1). Due to the limited observations of prVEP recordings at 200′ check width ($n = 176$), these were not considered in the full analysis. Patient age ranged from 1.6 months to 19.7 years, often with younger patients having more prVEPs to large check widths and older patients having more prVEPs to smaller check widths.

Differences in Iz and Oz amplitudes according to check width

For each check width, the proportional difference in amplitude decreased with increasing age (Fig. 2). The trend was best fitted by transforming age in months to its logarithm in base 10 for the ISCEV standard 'large check' of 50′ as well as for check widths of 25′ and 100′. For the 100′ check width, there was a big spike in the proportional difference at 42 months (3.4 years) caused by one subject with extremely different Oz–Iz measurements.

For the 50′ check width, the proportional difference in amplitude hit the 10% clinical threshold at 101.5 months (99% CI: 94.9–108.1) (Fig. 3). The Iz electrode placement was the preferred position up to age 94.9 months (7.9 years) with a sensitivity of 83%, whereas the Oz electrode placement was the preferred position from age 108.1 months (9.0 years) with a specificity of 80%. The smaller the check width, the later the age at which transition from Iz to Oz took place, ranging from 83 months (6.9 years) for larger 100′ check widths, to 249 months (20.7 years) for 6′ widths (Table 2).

The classification performances for the logarithmic model to the data for check widths 100′, 50′ and 25′ were good (AUC–ROC 73−81%), but for check widths 12.5′ and 6.25′ were poor (AUC–ROC 40−50%). When optimising the classification performance of the age period for each electrode position, the transition period was found up to 11 months earlier for the three largest check widths, whereas the smallest check widths still performed poorly (Table 3). The optimised age periods for the 50′ check widths were Iz up to age 86 months (7.2 years) and Oz from age 99 months (8.3 years).

Longitudinal assessment of Oz–Iz differences

There were 256 subjects with repeated prVEPs for 50′ check widths. The first prVEP was recorded between ages 2.4 months and 14.6 years, and the last recording was on average 1.4 (IQR, 1.0–2.1) years later. The annual intra-subject rate in the proportional difference of amplitude had a median of −0.03 (IQR, −0.31 to +0.17). The linear regression model on the annual rate had a significant intercept of −0.310 (standard error (SE), 0.116; $P = 0.008$) and for age at first measurement the effect of 0.046 did not reach statistical significance (SE, 0.023; $P = 0.052$). This meant that the annual rate was on average negative up to an age of 6.7 years (95% CI, 6.5–6.9) and positive, though not significantly, afterwards (Fig. 4). This demonstrates that within subjects, up to the age of 6.7 years there is a trend for the proportional difference in amplitude between electrode sites to reduce.

Table 2. Transition period and classification performance of each electrode position

Check width	Age in months at 10% threshold (99% CI)	AUC–ROC	Sensitivity Iz over Oz (age < LCI)	Specificity Oz over Iz (age > UCI)
100′	83.2 (72.6–93.7)	0.739	0.90	0.58
50′	101.5 (94.9–108.1)	0.814	0.83	0.80
25′	133.4 (124.3–142.5)	0.774	0.93	0.62
12.5′	157.4 (145.1–169.8)	0.401	0.97	0.23
6.25′	248.7 (224.8–272.6)	0.500	1.00	NA[†]

99% CI is the transition period of no preferred electrode position. Ages younger than the lower confidence interval (LCI) is the period of Iz position, whilst ages older than the upper confidence interval (UCI) is the period of Oz position. [†]No data were available above age 272.6 months (22 years).

Diagnostic accuracy findings

Lastly, we calculated the performance of each electrode producing an abnormal result, relative to the abnormality in the other electrode for 50′ check widths (Table 4). The conventional Oz electrode placement provided an abnormal classification result in 3.7% of patients, whereas when using the Iz electrode only 0.5% of patients had an abnormal classification. This resulted in a higher negative predictive value and specificity of prVEPs when using an Iz electrode of 99.4% and 99.5%, respectively, relative to 96.3% and 96.4%, respectively for using the Oz electrode alone.

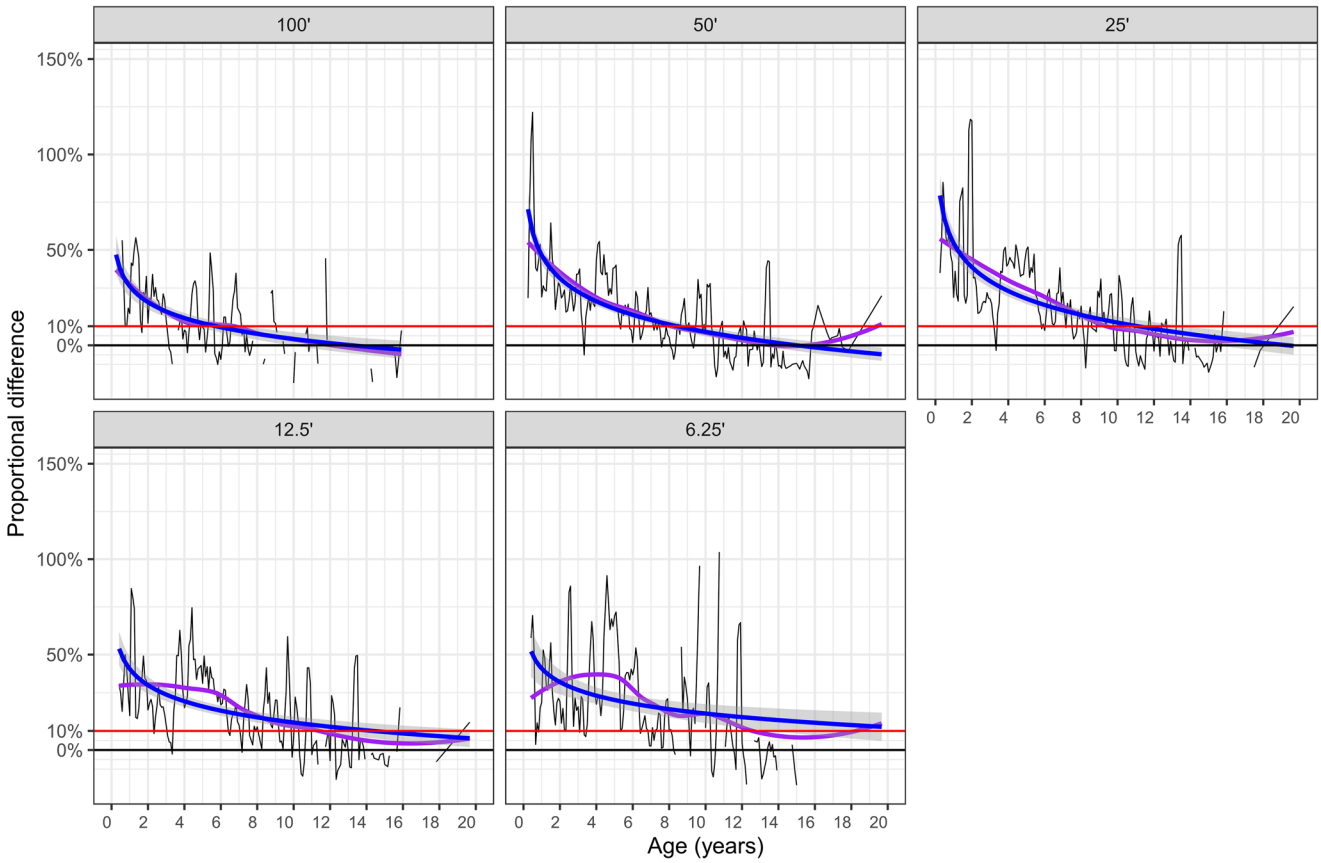

Figure 2. Illustration of differences in amplitude between electrode sites by age and check width
This figure demonstrates the proportional prVEP amplitude difference between Iz and Oz electrode sites to a variety of check widths as a function of age. Black, 3 months' rolling mean of the proportional difference in amplitude; purple, best fitted line with local regression smoothing; blue, logistic regression (base 10) with 95% confidence interval in grey; red, clinical threshold of 10% with higher/lower values indicating preference for Iz/Oz electrode, respectively.

Table 3. Sensitivity analysis of the two years around the transition period

Check width	Range of AUC–ROC	Best performance of the model compared to original transition period	Best performing transition period of the model (months)
100′	0.712–0.788	6 months earlier	66–88
50′	0.790–0.832	8 months earlier	86–99
25′	0.282–0.814	11 months earlier	113–131
12.5′	0.342–0.481	12 months later	157–182
6.25′[†]	0.490–0.500	Same	225–236

[†]Oldest participant was 236 months of age (19.7 years), and therefore the 2 years before this age was considered.

Discussion

In a very large cohort of young people we have demonstrated that recording prVEPs from a more inferiorly located electrode, Iz, compared to the ISCEV VEP standard electrode position, Oz, improves diagnostic accuracy, specifically for negative predictive value and specificity. We have shown through cross-sectional analysis that the prVEP P100 is larger over the Iz electrode site in the majority of children under the age of 7.9 years for the ISCEV large check width and under 12.1 years for the ISCEV small check width. The addition of an Iz electrode in paediatric prVEP recording improves diagnostic specificity from 96.4 to 99.5 when comparing to an Oz electrode alone. These data suggest an additional inion electrode for recording paediatric prVEPs would be highly beneficial for all patients under the age of 12, or at least under the age of 8 if only recording to an ISCEV standard large check width. This observation was supported by our longitudinal data which demonstrated an Iz dominance up to the age of 6.7 years. This study, comprising prVEP data in the normative reference range from a large cohort of children, is to our knowledge the first to formally assess the differences in prVEP peak-time and amplitude between the standard and lower midline VEP electrode placements, thereby establishing age periods when one position is preferred over the other to increase diagnostic accuracy. These significant improvements in diagnostic accuracy advocate the use of the Iz electrode in the routine recording of paediatric prVEPs.

Whilst the difference between Oz and Iz amplitudes for prVEPs in children has not been reported previously, Kobayashi & Toyomura (1981) reported, in a cohort of 74 children age 1−13 years old, that VEPs to flash stimuli in 80% were larger over the inion, rather than other occipital electrodes of more conventional placement. These authors found a similar age-dependence, reporting that flash VEPs at the inion showed dominance until age 5−6 years and the midline Oz flash VEP then became equal or positive

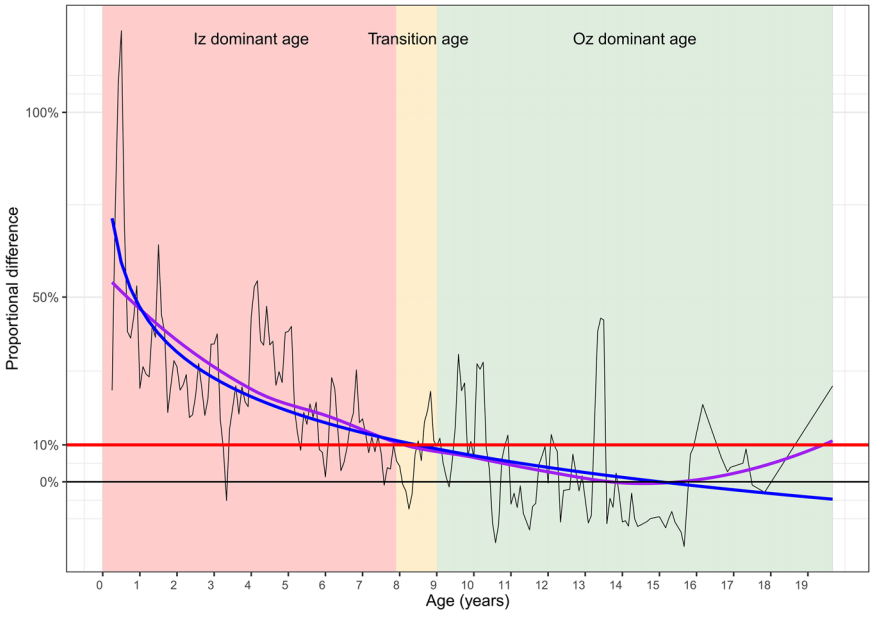

Figure 3. Difference in amplitude between electrode position by age for ISCEV large check (50′)
This figure demonstrates the proportional difference between Iz and Oz electrode prVEP amplitudes produced by the ISCEV large check (50′). Black, 3 months' rolling mean of the amplitude proportional difference; purple, best fitted line with local regression smoothing; blue, logistic regression (base 10); red, clinical threshold of 10% with higher/lower values indicating preference for Iz/Oz electrodes, respectively. Pink area, Iz as preferred electrode position; yellow area, transition period of no preferred midline electrode position; green area, Oz as preferred electrode position.

for 7–8 year olds. This corresponds to the transition period we observed for prVEPs produced by large checks. To our knowledge, no further studies have explored this in children though it has been demonstrated that both full-field pattern reversal and pattern onset–offset VEPs are largest at Oz in adults (Lesevre & Joseph, 1979).

We hypothesise that these findings may be explained by the anatomical growth of the skull and brain shifting the electromagnetic orientation of the VEP signal (i.e. cortical dipole), and the development of receptive fields and foveal bias at the occipital lobe in the first 5 years of life. Together these alter the topography of the scalp recorded prVEP (Gomez et al., 2018).

It is a reasonable assumption that anatomical changes with age may alter the cortical dipole of the prVEP. Cortical dipoles refer to the orientation of the electromagnetic field generated by neurons when there are two equal but opposite electrical changes. This results in an electrical potential (such as the prVEP) which can be recorded using scalp electrodes. These dipoles can be modelled to identify the anatomical correlate for the underlying neural sources or generators of the signal of interest (Niedermeyer, 1996). The finding of changing amplitude between Iz to Oz with increasing age implies that the prVEP cortical dipole alters orientation to produce a larger P100 superiorly during development. As the P100 component is maximal over the occipital pole of the brain, this suggests that the occipital pole may be located more inferiorly relative to the occipital scalp electrodes in children than adults (Jeffreys & Axford, 1972).

Presuming the generators of the prVEP are oriented differently in youth, we must consider the alterations in brain anatomy within changing skull morphology which may also be responsible. Total brain volume rapidly increases within the first year of life, reaching 80–90% adult values by the second year (Pfefferbaum et al., 1994). This includes the occipital lobe, which continues to have

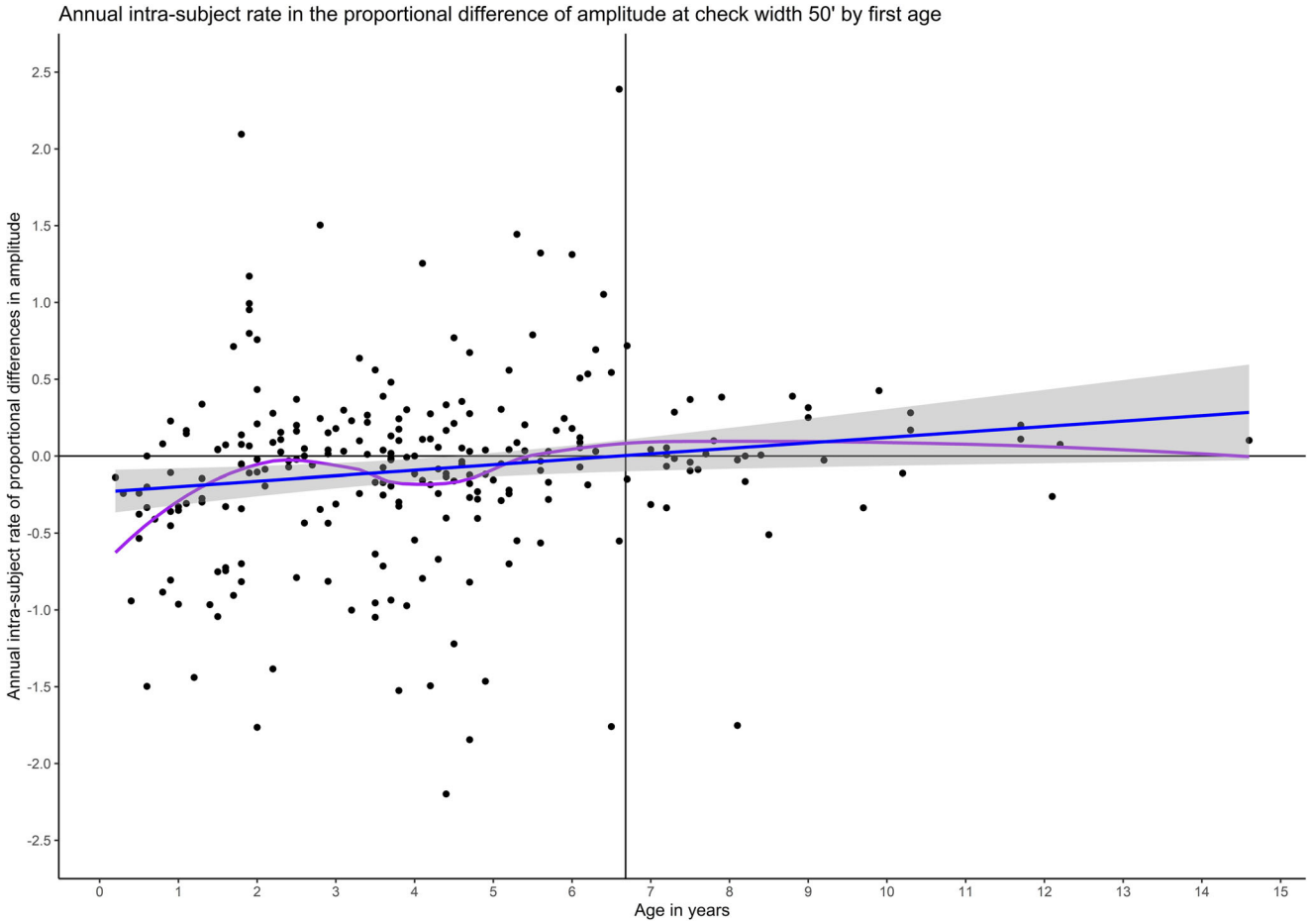

Figure 4. Longitudinal differences in amplitude between Iz and Oz electrodes between first and last visits for 50′ check widths
Black, annual intra-subject rate at first observed age; blue, mixed-linear regression with 95% CI in grey; purple, best fitted line with local regression smoothing; negative rate means that the proportional difference in amplitude decreased with increasing age, whereas a positive rate means that it increased with increasing age.

Table 4. Accuracy measures for detecting an abnormal prVEP (<7 μV) for a 50′ check width

	50′ check width performance ($n = 1487$)	
	Iz normal	Iz abnormal
Oz normal	1424 (95.8%)	8 (0.5%)
Oz abnormal	55 (3.7%)	0 (0%)
Diagnostic accuracy of Oz electrode	Percentage	
Negative predictive value	96.3	
Specificity	96.4	
Diagnostic accuracy of Iz electrode	Percentage	
Negative predictive value	99.4	
Specificity	99.5	

a small but linear growth in volume until 7–13 years, and thereafter occipital pericalcarine areas can continue to grow even when other brain regions may decrease or plateau in volume (Thompson et al., 2020). In the proximity of the occipital lobe, the cerebellum has a marked volume increase of 240% in the first year of life (Knickmeyer et al., 2008). Given that the cerebellum abuts the occipital lobe and is spatially restricted by the occipital bone inferiorly, its significant volume increase may move the occipital lobe slightly superiorly and consequently shift the generator of the prVEP superiorly as observed in our Iz–Oz amplitude differences. Kabdebon et al. showed using MRI techniques in infants that occipital electrodes are situated at the inferior portion of the occipital lobe, whereas in adults Okamoto et al. demonstrated occipital electrodes to be situated superiorly overlaying the 'mid-occipital' region (Kabdebon et al., 2014; Okamoto et al., 2004). Therefore, if both Oz and Iz electrodes are inferiorly located relative to adults over the inferior occipital lobe, we would expect both electrodes to show amplitude changes with age and not show the disparity observed between electrode site amplitudes as observed in these findings.

It is also important to consider how electrode–brain distance may influence our findings, specifically the relationship between electrodes placed according to the international 10−20 system and the cortex. Kabdebon et al. demonstrated that electrode–brain distances in infants are largest anteriorly and superiorly at ∼11 mm with a gradient decrease to be smallest posteriorly and inferiorly at ∼4 mm (Kabdebon et al., 2014). Based on these findings we may hypothesise that a larger Iz prVEP amplitude simply reflects a smaller brain–electrode distance than at Oz. This anterior–posterior gradient is not observed in adults, and therefore the equalisation of electrode–brain distances with age may coincide with Iz–Oz transitional periods observed in our data (Okamoto et al., 2004). Other studies have demonstrated that electrode–brain distances increase with age, possibly reflecting changes in skull thickness, cerebrospinal fluid (CSF) volume, brain volume and cortical folding (Fu & Richards, 2021). These studies have postulated that the posterior–anterior gradient of cortical maturation and related volume changes may consequently affect electrode brain differences which decrease with increasing age (Beauchamp et al., 2011; Fu & Richards, 2021; Gilmore et al., 2007). The differences between Iz and Oz in younger age may reflect these complex differences in skull thickness, posterior–anterior cortical maturation and CSF volume between cortex and electrode that become less marked with increasing age.

In addition to structural changes of the skull and brain, physiological maturation of the visual system may also play a role. The early negative trough N75 of the prVEP has been associated with activation of the striate cortical lamina 4C, and the main positivity P100 has been suggested predominantly to reflect striate processing, with some possible extra-striate involvement (Clark & Hillyard, 1996; di Russo et al., 2002). This is similar for the early C1 component of the pattern onset VEP, whereby only the initial 10−15 ms of the response is considered to represent purely striate cortex activity, after which extra-striate processing has been implicated for later C2 or C3 components (Foxe & Simpson, 2002). The changing balance of contributions between striate and extrastriate areas with maturation may alter the topographic orientation of the prVEP. This idea is supported by previous works, whereby a maturation of the pattern onset VEP in infants has been observed to be dominated by the C1 early positivity, likely reflecting striate cortex activation, following which

the morphology of C2–C3 components, which have extra-striate involvement, evolve and become more distinct with age (Thompson et al., 2017). Furthermore, the transition periods observed within our data are consistent with key milestones of visual maturation (i.e. the critical period (Wiesel & Hubel, 1963)), in which cortical synaptogenesis and plasticity, receptive field development, neural myelination and inter-laminal connections take place (Siu & Murphy, 2018). These complex neurobiological milestones are associated with maturation of binocularity, ocular dominance and visual acuity, which is similar to the spatial tuning we observe in the prVEP with age (Almoqbel et al., 2017). It is possible, therefore, that the transition periods observed in this study reflect these events of neuro-biological maturation within the visual system, which alter the geometry of the prVEP signal in developing brains.

A limitation of this study is that all children irrespective of age had prVEP recordings for the standard large check width, but not necessarily for other check widths. This led to fewer datapoints for some check widths, which may explain the lower classification performances of the smallest check widths. This data sampling is attributable to the maturation of spatial tuning observed in children who produce prVEP to smaller check widths as they get older, just as their visual acuity develops to enable them to see finer detail or smaller letters on a chart. Thus older children and adults, with more mature visual systems, produce prVEPs to smaller check widths than young infants. Another limitation of the study is that we could not assess prVEP differences by sex or ethnicity, however the data were sampled from a large clinical cohort of mixed ethnicity and sex, so are likely to reflect a varied and heterogeneous sample. The findings of the cross-sectional analysis of the proportional difference in amplitude by age correspond with the longitudinal analysis of the intra-subject rate in the amplitude proportional difference, and thus ecological fallacy can be excluded.

To conclude, our data show prVEPs are larger over the inion electrode (Iz) in the majority of children. Furthermore, we demonstrate a risk of higher abnormal test classifications if using the conventional electrode placement (Oz) alone when performing prVEPs in children. We therefore recommend the use of an additional inferior electrode placed over the inion to record paediatric prVEPs. Our data suggest at a minimum that the inion electrode should be used in all children under the age of 7.9 years (∼8 years old), but if using multiple check widths smaller than the ISCEV large check, then the inion electrode is advantageous in children under the age of 12.1 years (∼12 years old).

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Additional information

Data availability statement

The data used in this study are not publicly available for use in a data repository or database as this does not conform to ethical approvals granted from our institution.

Competing interests

The authors declare no competing interests.

Author contributions

The authors (O.R.M., L.A.H., M.C., D.A.T.) have made significant contributions to conception, acquisition, analysis or interpretation of study data. All authors (O.R.M., L.A.H., M.C., D.A.T.) have contributed in drafting of the work and/or revising it critically. Accordingly, all authors (O.R.M., L.A.H., M.C., D.A.T.) qualify for authorship and agree to be accountable for all aspects of the work. All authors (O.R.M., L.A.H., M.C., D.A.T.) have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Statistical Summary Document
Peer Review History

Translational perspective

The pattern reversal visual evoked potential (prVEP) is a neural response recorded from averaged background electroencephalographic brain activity time-locked to a reversing checkerboard visual stimulus. The response obtained informs us about the integrity of the visual system, which is particularly useful in children, where subjective tests of vision are more challenging. International standards specify that to record the prVEP, using the international 10−20 system of head measurement, an active electrode should be used at a site named 'Oz', which is 10% of the total nasion–inion distance. We have found that in young children, larger responses are elicited at a lower region of the head over the inion (Iz) itself. We hypothesised that this difference was largest in young children and decreased with age by studying 1487 children who had normal prVEPs recorded using Oz and Iz electrodes simultaneously. It was found that a majority of children had a larger prVEP over Iz, which became less marked with age and had a transition period around 8 years of age for large check widths and 12 years of age for small check widths. These findings suggest that either the anatomical development of the brain and skull may alter the geometry of the neural generators for the prVEP, or that the processes involved in visual neurodevelopment may alter its orientation. Future work may be directed to exploring anatomical changes of the occipital lobe with age through neuroimaging, or through exploration of potential differences in detailed visual sensitivity and psychophysical changes during development.