Frontal EEG asymmetry and later behavior vulnerability in infants with congenital visual impairment

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Highlights

- We show left frontal asymmetry in VI infants that does not differ from that in sighted infants.
- 22.7% of the VI sample had ‘internalizing’ behavior difficulties at two years.
- Greater left frontal asymmetry was associated with later increased internalizing behavior risk in VI infants.

Keywords: frontal EEG asymmetry, visual impairment, vision, vision disorders, behavior, infancy, children.

Abstract

Objective: Young children with congenital visual impairment (VI) are at increased risk of behavioral vulnerabilities. Studies on 'at risk' populations suggest that frontal EEG asymmetry may be associated with behavioral risk. We investigated frontal asymmetry at 1 year (Time 1), behavior at 2 years (Time 2) and their longitudinal associations within a sample of infants with VI. Frontal asymmetry in the VI sample at 1 year was also compared cross-sectionally to an age-matched typically sighted (TS) group. *Methods:* At Time 1, 22 infants with VI and 10 TS infants underwent 128-channel EEG recording. Frontal asymmetry ratios were calculated from power spectral density values in the alpha frequency band. At Time 2, Achenbach Child Behavior Checklist data was obtained for the VI sample. *Results:* 63.6% of the VI sample and 50% of the TS sample showed left frontal asymmetry; no significant difference in frontal asymmetry was found between the two groups. 22.7% of the VI sample had subclinical to clinical range 'internalizing' behavior difficulties. Greater left frontal asymmetry at one year was significantly associated with greater emotionally reactive scores at two years within the VI sample (r=.50, p=.02). *Conclusions:* Left frontal asymmetry correlates with later behavior risk within this vulnerable population. *Significance:* These findings make an important first contribution regarding the utility of frontal EEG asymmetry as a method to investigate risk in infants with VI.

1. Introduction

Congenital visual impairment (VI) is a rare childhood disorder with conservative estimates of 4-5 per 10,000 with 'blind/severe' VI in the first year of life in the UK (Rahi and Cable, 2003). Lack of visual input from birth is associated with significant challenges in acquiring cognitive/sensorimotor, motor, social, communicative and language abilities with delays of up to 12-24 months (compared to typically developing sighted peers) and especially in children with profound VI (light perception at best; Cass et al., 1994; Dale et al., 2014; Hatton et al., 1997; Levtzion-Korach et al., 2000; Perez-Pereira and Conti-Ramsden, 1999; Sonksen and Dale, 2002; Reynell, 1979; Tadic et al., 2010). Young children with VI are also known to be at increased risk of behavioral difficulties, especially internalizing behaviors, with emotional reactivity (Alon et al., 2010) and withdrawal accompanying developmental setback (Cass et al., 1994; Dale and Sonksen, 2002) in these children. Elevated risk of avoidant, overanxious and oppositional behavior in children with VI has also been reported (Tirosh et al., 1998), as have reactive temper tantrums and aggressive behavior (Margalith et al., 1984; Ek et al., 2005). However, previous studies reporting behavior outcomes in children with VI have been limited by the inclusion of heterogeneous visual disorders, many of which include additional brain involvement (e.g., 12% of Tirosh's sample had abnormal MRIs and the majority of Ek's sample had other paediatric disorders including cerebral palsy). In such a mixed population, intellectual impairment and attention deficit disorder are likely to be widespread and it is difficult to disentangle whether any evident behavior difficulties are attributable to the lack of vision or other underlying brain abnormalities.

The early factors and mechanisms influencing and underlying such heightened risk for behavior difficulties in young children with VI are not yet understood. Reductions in exposure to visual social cues have been hypothesized to predispose children with VI to developing socio-behavioral difficulties (Hobson, 1999); having some functional vision, even low levels of residual 'form' vision, appears to serve a protective role in cognitive and social development compared to those with profound VI. Lack of visual stimulus may affect developmental white matter integrity in the occipital-frontal longitudinal networks (Lao et al., 2015). Notably, a recent neuroimaging study of children with isolated optic nerve hypoplasia who had either mild-moderate or no VI (Webb et al., 2013) demonstrated heightened risk of behavior difficulties (45.5% with behavioral difficulties in the subclinical to clinical range) according to the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2000). Possible neural correlates were proposed on account of the association between white matter integrity in the ventral cingulum area and CBCL total and externalizing scores. However, the brain physiology underpinning behavioral difficulties in the more vulnerable sub-population of children with profound and severe VI has yet to be investigated.

A widely reported neurophysiological marker that has shown reliable associations with infants' and young children's vulnerability to behavioral risk is frontal electroencephalography (EEG) asymmetry (see Peltola et al., 2014, for a review). Frontal EEG asymmetry refers to the difference in EEG power of a *right* hemisphere frontal site minus the EEG power of the corresponding electrode site of the *left* hemisphere (Allen et al., 2004). Therefore, positive EEG asymmetry values indicate greater right than left EEG power, whereas negative values indicate greater left than right EEG power. As power in the alpha frequency band is *inversely* related to

neural activity (stronger power indicating less activity; Allen et al., 2004), positive asymmetry values are considered to reflect greater left frontal activity i.e., greater left frontal asymmetry, whereas negative values reflect greater relative right frontal activity i.e., greater right frontal asymmetry. These differences in frontal EEG asymmetries have been hypothesized to arise from lateralized cortical and subcortical innervation by neurotransmitter (dopamine and serotonin) systems (Davidson, 1995; Wacker et al., 2013) and are modulated by variation in serotonin transporter-linked polymorphic region genotypes in healthy young children (Christou et al., 2016).

Frontal EEG asymmetry studies of typically developing infants have shown overall right-sided asymmetry (Fox et al., 2001; Müller et al., 2015). Infant studies have also shown frontal asymmetry to be a reliable correlate of i) psychosocial risk, with strong evidence for relationships between greater right frontal asymmetry and maternal depression (Dawson et al., 1997; Jones et al., 2009; Lusby et al., 2014); and ii) individual differences in behavior patterns relating to 'approach' and 'withdrawal' tendencies as first posited by Fox and Davidson's model (Fox and Davidson, 1984; Fox, 1989, 1994). Greater right asymmetry has been linked with withdrawal-related behaviors, negative affect (e.g., Davidson, 1990; Diaz and Bell, 2012; Fox, 1994, 1995, 1996, 2001; Hane et al., 2008; Henderson et al., 2001; Missana et al., 2014, 2015), and internalizing behaviors (e.g., Fox et al., 2001), whilst greater left frontal asymmetry was shown to associate with approach-related behaviors, positive affect and positive reactivity (e.g., Degnan et al., 2011; Fox, 1991; Fox et al., 2001; Hane et al., 2008; He et al., 2010; Howarth et al., 2016; LoBue et al., 2011; Missana et al., 2014, 2015) and externalizing behaviors (Smith and Bell, 2010) in typically developing infants.

In atypical paediatric populations however, different directions of asymmetry associations have been reported. For example, an overall greater *left*- than right-lateralized asymmetry was observed in 6- and 12-month old infants at high-risk of autism spectrum disorder (ASD) relative to those at low-risk (Gabard-Durnam et al., 2015). Left frontal asymmetry was associated with higher anxiety-related obsessive-compulsive disorder and anger (Burnette et al., 2011) and greater social anxiety (Sutton et al., 2005) in older children with high-functioning ASD. Frontal asymmetry has been shown to change in typically developing infants across the first two years of life (Fox et al., 1994; Fox et al., 2001) and a reversal of asymmetry occurs by 18 months in high-risk and low-risk groups for ASD (Gabard-Durham et al., 2015). Taken together, the literature provides growing evidence that individual differences in EEG asymmetry provide an early correlate of specific behavior patterns and difficulties in young children and may have the potential to distinguish between typically and atypically developing populations.

Given that behavioral difficulties in young children predict future behavioral risk, academic success and social functioning (Campbell, 1995; Campbell et al., 2006), it is important to examine potential early electrophysiological correlates of behavior vulnerability, which have never been investigated in this vulnerable yet understudied population. A prospective longitudinal cohort study (Dale et al., 2017) has provided the opportunity to investigate these at approximately one and two years of age, which has been shown in other studies to be a relevant age period for examining frontal asymmetry and behavioral risk in typically developing and clinical populations. Cross-sectional comparisons with an age-matched typically sighted group

using the same auditory EEG paradigm at one year will provide insight into any differences between the VI and TS infants at this age. Therefore, our aims were 1) to examine frontal EEG asymmetry in one-year-old infants with profound-severe VI and to compare cross-sectionally with typically sighted infants, and 2) to investigate whether frontal asymmetry has a predictive association with greater behavior risks, particularly internalizing difficulties, at two years within the VI sample. As there is likely to be variation in behavior risks within the VI sample, we anticipated that frontal asymmetry may be associated with greater behavioral risk as in other clinical infant populations. In light of the literature, we hypothesized that frontal EEG asymmetry at one year would show predictive associations with their later behavior risks, particularly in the internalizing domain. As this is the first study to investigate frontal EEG asymmetry in young children with VI, cross-sectional comparisons with the TS group were exploratory, as were the specific directions of this frontal asymmetry in terms of its associations with behavior in the VI sample.

2. Methods

2.1. Study Design

This study is part of a national prospective longitudinal cohort study of infants with congenital VI across England (OPTIMUM, Dale et al., 2017). The study reported here is part of the longitudinal investigations undertaken at the first and second time-points (Time 1 and Time 2 at approximately one and two years).

2.2. Participants

Twenty-two infants with VI (mean age 13.1 months, Standard Deviation [*SD*] =2.5, range 8.2 – 17 months at Time 1; mean age 26.2 months, *SD* = 2.5 at Time 2) comprised the VI group. Participant characteristics of the VI sample are presented in Table 1. Full details of the recruitment process for this sample are published in Dale et al. (2017). Inclusion criteria for the VI group were i) 8-16 months at study entry, and ii) the subgroup of the cohort with 'potentially simple' congenital disorders of the peripheral visual system (CDPVS), i.e., ophthalmological disorders of the globe, retina and anterior optic nerve without known central nervous system involvement in the vision or paediatric diagnosis and chronic VI which is severe-profound at the time of recruitment were included in this analysis (Sonksen and Dale, 2002). The individual visual disorder diagnoses of the VI sample are presented in Table 2. The subgroup of the cohort with 'complex' CDPVS (known CNS involvement, for example septo-optic dysplasia or Joubert syndrome; Sonksen and Dale, 2002), and infants with clinically diagnosed neurological, motor or hearing impairment or severe prematurity were excluded. Broader exclusion criteria of the main study cohort are published in Dale et al. (2017).

Of the sample of n=69 infants with 'simple' CDPVS (77% of total cohort, N=90; Dale et al., 2017), n=20 had assessments in their own home due to geographical constraints and could not attend the electrophysiology lab. The remaining n=49 children were invited to attend the infant electrophysiology lab at Time 1 when they were approximately one year of age. Of these, 13 infants (26.5%) did not participate due to the following reasons: family did not consent to participate (n=5), child fussiness/tiredness (n=2), medical appointments on the same day (n=2),

lab technical issues (n=2) and child having excessively thick hair braiding and therefore unable to wear the EEG net (n=2). In total, 36 infants (73.4% of those invited) attended the lab and attempted EEG recording; of these four refused to wear the EEG sensor net so recordings were obtained for 32 infants. A further five were excluded from analyses because recordings were terminated due to excessive movement artifact in the EEG recording. An EEG data loss rate of 15.6% for movement artifact is relatively low and was viewed as acceptable compared with the mean attrition rate of 49.6% reported in a meta-analysis of infant electrophysiology studies (Stets et al., 2012).

We therefore had a final sample of 27 infants with VI at Time 1 with acceptable EEG data. The parents of five of these 27 infants chose to leave the study by Time 2; therefore longitudinal data were available for 22 of these participants (i.e., corresponding EEG Time 1 and CBCL Time 2 datasets). See Figure 1 for a flowchart of the VI sample numbers and attrition details. Details on the representativeness of our n=22 VI sample relative to the larger 'potentially simple' CDVPS sample who had CBCL data available (total n=47) in terms of age, gender, cognitive level, vision level and maternal education, and other representativeness analyses, are given in the Supplementary Materials (Sections 1 and 2).

Of the 32 typically sighted (TS) infants invited to take part, 7 did not consent and one was excluded due to prematurity. Eleven of the 24 infants invited to the laboratory did not participate due to the following reasons: refusal to wear the net (n=3), child fussiness/tiredness (n=4) and lab technical issues (n=4). A further three infants were excluded from further

analysis due to excessive noise at multiple electrodes. Therefore the final comparison sample consisted of 10 typically sighted infants.

The TS comparison sample comprised 10 infants chronologically age-matched to the VI sample (mean age 11.8 months, *SD* = 2.6; range 8.4 – 16.2 months; Table 1). Inclusion criteria were: age range 9-16 months at study entry, normal eye health and no visual impairment. Infants with clinically diagnosed neurological, motor or hearing impairment, severe prematurity or developmental delays were excluded. The sample was recruited through local university staff and local mother and baby groups. There were no significant age, gender, birthweight, gestational age, developmental quotient, maternal education or maternal depression differences between the two groups, see Table 1.

Ethical approval was obtained from the National Research Ethics Service (NRES) Committee – Bloomsbury (IRAS no. 10/H0713/46) and met standards required by the guidelines set out by the Social Research Association (SRA). Written informed consent was obtained from all parents for participation and publication.

2.3. Measures

2.3.1. Functional vision

Of the Time 1 to Time 2 subsample (n=22), five (22%) had profound vision impairment (PVI; points 0-1, light perception at best) and 17 (77.3%) had severe vision impairment (SVI; points 2-9, ‘form’ vision of differing levels) according to the Near Detection Scale (NDS; Sonksen et

al., 1983), see measurement details in Dale et al. (2017). None of the five with PVI changed vision status to SVI between Time 1 and Time 2. Vision level, vision category (PVI, SVI) and anatomical vision disorder (optic nerve, retina, globe) characteristics of the participants are presented in Table 1.

2.3.2. EEG

EEG Procedure

Parents were invited to attend the laboratory a short time before commencing testing procedures to allow the infant to become familiar with the experimenters and with the experimental setting. Infants were seated on their parent's lap and stimuli were presented via speakers positioned at head level in front of the infant at a distance of approximately 50 cm (Sound Pressure Level = 70 dB). If needed, the infant was entertained with toys and calming music before beginning the experimental procedure. An experienced experimenter (MOR) applied the net to eliminate or minimize infant distress and guarantee accurate placement of the EEG sensors.

Experimental stimuli and design

The use of an auditory paradigm permitted infants with VI and infants who were typically sighted to undertake the same experimental stimuli and design without any modifications. Differing emotional auditory stimuli of positive, negative and neutral valence were utilized for

the current experiment to facilitate the infants' interest and attention during the EEG recording (rather than using 'resting' EEG). Although many infant studies of EEG asymmetry have used resting recording conditions (e.g., Müller et al., 2015; Fox et al., 2001; Henderson et al., 2001; Gabard-Durnam et al., 2015), Coan et al. (2006) argued that the use of emotional stimuli increases the proportion of variance in frontal EEG asymmetry attributable to individual differences and increases the magnitude and reliability of statistical associations between frontal EEG asymmetry and measures of behavior, temperament and psychopathology. Other studies using emotional stimuli rather than resting conditions have also demonstrated reliable frontal asymmetry results and associations with temperament or behavior (LoBue et al., 2011; Missana et al., 2014). Therefore for the current study we used a composite frontal EEG asymmetry derived from the three conditions (mean of the three conditions) described above. Preliminary analyses indicated that the three conditions' FA separately did not predict CBCL outcome differently, therefore a composite score was used for the reasons stated above.

All stimuli were selected from the Montreal Affective Voices (Belin et al., 2008), a standardized set of sounds rated for valence, arousal and intensity, available from the Voice Neurocognition Laboratory website (http://vnl.psy.gla.ac.uk/resources.php). Three categories of auditory stimuli were presented: neutral vocalizations (natural non-speech vocalizations with no emotional content, 'ah' sounds), happy vocalizations (laughing), and sad vocalizations (crying). All voice sounds were adult vocalizations, obtained from different male and female speakers. The three emotion conditions did not differ with respect to their mean intensity (Belin et al., 2008). Each condition was presented as a stimulus sequence lasting 26 seconds and consisted of 10 different sounds interleaved by short rest periods (between 0.35 and 0.45

seconds). The sampling rate of all sound stimuli was 16 bit/22 kHz. A complete session comprised 32 blocks (8 in each stimulus category) for a total of approximately 16 minutes. The order of presentation was randomized across infants across the experimental blocks to reduce potential habituation effects to the emotional condition categories (Blasi et al., 2011; Supplemental Information). There was a mean number of 108 segments of useable EEG data available per infant and condition after artifact rejection and no significant difference in the number of included epochs between conditions (happy condition: mean=89.79, SD=6.47; sad condition: mean=110.9, SD=7.44; neutral condition: mean=112.86, SD=8.99; $F(2,84)= 2.76$, $p>0.05$).

EEG recording

EEG was recorded on a high impedance system using a Geodesic Sensor Net with 128 channels and a NetAmps 200 amplifier (Electrical Geodesics Inc., OR) against a vertex reference. The EEG was recorded at 250 Hz sampling rate with 0.1 to 100 Hz online filter with a common vertex reference (Cz). Channel gains and zeros were measured prior to channel application to ensure accurate scaling of waveforms. Channel impedances on the scalp were measured and adjusted to be below 100 kOhm. The EOG was recorded for vertical and lateral eye movements from outer channels of the EGI sensor nets.

EEG processing

The EEG data was analyzed in Matlab R2014a (The MathWorks, MA) using a combination of

in-house software and EEGLAB functions (Delorme et al., 2011). Channel region selection was based on previous reports of similar analyses in infants using a similar EEG system (e.g., Gabard-Durnam et al. 2015; left frontal: 19, 20, 24, 25, 28, 29; right frontal: 3, 4, 10, 118, 123, 124). The continuous EEG was digitally filtered with a high-pass filter at 1 Hz and a low-pass filter at 40 Hz. Subsequently, a thresholding procedure was applied to identify 'bad' channels or epochs with high amplitude artifact. Channels were defined as 'bad' if amplitudes exceeded the threshold (empirically determined to be optimal at 60 μV absolute amplitude) in more than 30% of epochs. Epochs were defined as 'bad' if any of the frontal channels of interest displayed amplitudes above the threshold after rejection of bad channels. If more than two channels of interest were identified as 'bad', the dataset was rejected from further analysis. Details of rejection threshold and lateral eye movement evaluations are provided in the Supplementary Materials (Sections 3 and 4).

Frontal EEG asymmetry calculation

Following artifact rejection, Power Spectral Density (PSD) was calculated within 1s data segments using a Fast Fourier Transform (FFT) implemented in MATLAB R2014a with 50% overlapping Hanning window with 0.25 Hz resolution. PSD values between 6 and 10 Hz were averaged to obtain the mean alpha power within the typical infant alpha frequency range (Stroganova et al., 1999). Visual inspection indicated that the peak alpha frequency fell within this range for infants who showed a clearly discernible alpha peak. Because not all infants displayed a clearly discernible alpha peak and because peak alpha frequency within the range

varied between infants, the mean power within the frequency range of 6 to 10 Hz rather than individual peak values was selected for further analysis. Mean PSD values were averaged over channels on the left and right side. Subsequently, the Asymmetry Relation Ratio (ARR) was calculated as the difference between log-transformed PSD values on the left and right side divided by their sum (see Equation 1; Allen et al., 2004). This ARR provided a continuous variable that was entered into the relevant analyses.

$$ARR = \frac{\ln(PSD_{right}) - \ln(PSD_{left})}{\ln(PSD_{right}) + \ln(PSD_{left})} \qquad (1)$$

Frontal alpha asymmetry is considered to have good test-retest stability and excellent internal consistency reliability (Tomarken et al., 1992).

2.3.3. Behavior

Behavior at Time 2 in the VI sample was measured using the Child Behavior Checklist (CBCL), a widely used, reliable, and valid standardized questionnaire assessment of children's behavior using parent ratings (Achenbach and Rescorla, 2000). 'Internalizing' problems consist of syndrome scales for emotionally reactive behavior, anxious/depressed behavior, somatic complaints and withdrawn behavior. 'Externalizing' problems consist of syndrome scales for attention problems and aggressive behavior. The CBCL has not been designed or normed for infants with severe VI; one vision-related item (withdrawn subscore – Item 4: "avoids looking others in the eyes*"*) was considered unsuitable and omitted. Therefore, withdrawn,

internalizing, and total scores were calculated on a pro-rata basis to account for this missing item (which was allocated a raw score rating of 0). T-scores of ≥ 64 for summary (internalizing, externalizing, total) scales and ≥ 70 for syndrome (emotionally reactive, withdrawn) scales are considered *clinically* significant; T-score values between 60-63 for summary scales or 65-69 for syndrome scales identify the *subclinical* range (Achenbach and Rescorla, 2000). Raw scores were used for the analyses as Achenbach and Rescorla (2001, p. 89) state explicitly that raw scale scores should be used in statistical analysis in order to take account of the full range of variation in these scales. T-scores were used only for qualitative descriptions according to normal, subclinical or clinical ranges. Higher scores indicate greater severity of behavior difficulties.

2.3.4. Maternal Education

Socioeconomic status (with maternal education as a proxy for socioeconomic status) may be a potential mediator of asymmetry (Tomarken et al., 2004). Full details of maternal education measurement from (1) primary and secondary education to (4) postgraduate training are given in Dale et al. (2017). Maternal educational level information for the current study is presented in Table 1.

2.3.5. Developmental Quotient (DQ)

Cognitive level has also been implicated as a possible influence on asymmetry (Burnette et al., 2011; Sutton et al., 2005). Children were assessed using the Reynell-Zinkin Scales of mental

development for visually handicapped children (Reynell, 1979); the Sensorimotor Understanding subscale was used for this analysis and details of development quotients (DQs) scoring are given in Dale et al. (2017). As the normative values are already significantly adjusted for greater delays in the VI infancy population (Reynell 1979), a higher DQ of 90 was arbitrarily selected as a cut-off for significant delay that may be indicative of intellectual disability. Participant DQ information is shown in Table 1.

2.3.6. Maternal depression

A significant body of literature shows reliable associations between maternal depression and infant frontal asymmetry (Lusby et al., 2014). Maternal depression was measured using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), a self-rating measure based on a four-point Likert scale. HADS information is presented in Table 1.

2.4. Statistical Analysis

EEG Data: Converging evidence from visual inspection of frequency distribution histogram plots, examination of skewness and kurtosis/standard error (<1.96 within normal limits), and the Shapiro-Wilk test confirmed that the EEG data including the frontal asymmetry composite score met the normality assumption for parametric tests for both the sample with VI and the typically sighted comparison group.

CBCL Data: Many of the CBCL composites, including total, externalizing, aggressive, anxiety, pervasive developmental disorder, attention deficit disorder and oppositional defiant scores were normally distributed according to both inspection of the frequency histogram plots and Shapiro-Wilk tests. However, internalizing, emotionally reactive, anxious/depressed, and withdrawn raw scores were not normally distributed according to the Shapiro-Wilk test. Nonetheless, skewness calculations (skewness statistic divided by its standard error) revealed that these variables' values did not fall outwith normal +/- 1.96 limits, and therefore could be considered normally distributed and suitable for parametric analyses. As the NDS data was not normally distributed according to inspection of the frequency histogram plots, the Shapiro-Wilk test and skewness calculations, nonparametric statistics were used for this data.

Independent samples *t*-tests were used to compare the frontal EEG asymmetry scores of the sample with VI and the TS comparison sample. Pearson or Spearman correlations were used as appropriate to examine the within-sample (VI) association between i) the EEG asymmetry composite score and other factors including age, NDS scores, DQ and maternal depression score, ii) CBCL raw variables (total, internalizing, emotionally reactive, anxious/depressed and withdrawn) and age, NDS scores and DQ, and iii) the EEG asymmetry composite score and CBCL raw variables (total, internalizing, emotionally reactive, anxious/depressed and withdrawn). In light of the literature on internalizing behavior in children with VI, for the correlational analyses we focused on the internalizing scale and three of its component syndrome subscales: emotionally reactive, withdrawn, anxious/depressed; and the total scale.

As this is the first study using these methods in this population and due to the small sample size

related to its rarity, we did not correct the results for multiplicity to avoid inflating Type II error and thereby obscuring expected results (Rothman, 1990). Multiple comparisons were kept to the minimum by using hypothesis-led predictions. Multivariate ANOVAs were also used to examine the effect of gender, maternal education and anatomical vision disorder on the EEG and CBCL variables in the sample with VI. An alpha level of .05 was used for all statistical tests and all reported *p* values are two-tailed.

3. Results

3.1. Frontal asymmetry in the VI sample and cross-sectional comparison with TS sample at one year

The sample with VI's (n=22) mean asymmetry score was .008 ± .05, the positive value indicating slightly left asymmetry. Of the VI sample, n=14 (63.6%) had positive scores showing left-sided asymmetry and n=8 (36.3%) had negative scores showing right-sided asymmetry. Independent samples *t*-test revealed no statistically significant difference between the frontal asymmetry scores of the VI and TS groups, $t(9) = .48$, $p=.6$; $d = 0.2$, 95% CI [-.37, .58]. The TS comparison sample's (n=10) mean asymmetry score was -.1 ± .6 (negative value indicating slightly right asymmetry). Of these, n=5 (50%) had positive scores showing left-sided asymmetry and n=5 (50%) had negative scores showing right-sided asymmetry.

3.2. Associations between frontal asymmetry and other factors (Time 1) in the VI sample

Possible variables that may have been associated with frontal asymmetry in the VI sample were

examined. No significant correlations were found between frontal asymmetry scores and vision level (NDS scores), age, DQ or HADS maternal depression scores (Time 1; all *p*s >.05). Multivariate ANOVAs also revealed no significant differences in frontal asymmetry scores according to anatomical vision disorder, gender or maternal education (all *p*s >.05).

3.3. Behavior in the VI sample at two years and associations with other factors

On the CBCL, the majority (86%, n=19) of the VI sample had scores in the normal range for their chronological age on the total domain; 9% (n=2) reached the clinical range and 4.5% (n=1) had scores in the subclinical threshold range (combined clinical and subclinical prevalence: 13.5%). Notably, for *internalizing*, 9% (n=2) of the children reached scores in the clinical range and 13.6% (n=3) had scores in the subclinical range (combined clinical and subclinical prevalence: 22.7%). However, for *externalizing*, all children had scores in the normal range.

No significant correlations were found between the CBCL raw scores and vision level (NDS scores), age, DQ or HADS maternal depression scores (Time 2; all *p*s >.05). Multivariate ANOVAs also showed no significant differences in CBCL scores according to anatomical vision disorder, gender, or maternal education. Only 3 (13.6%) of the VI sample had DQs below 90, indicating that the majority of the sample was in the developmental range that was considered ‘age appropriate’ for their vision level and chronological age.

3.4. Association between frontal asymmetry at one year and behavior at two years within the VI sample

A longitudinal correlation (n=22) between Time 1 EEG and Time 2 behavior (CBCL) showed a significant positive relationship between frontal asymmetry scores and emotionally reactive raw scores on the CBCL: r=.50, p=.02, indicating 'medium' effect size (Cohen, 1992). This indicated that more positive asymmetry scores (i.e., greater left frontal asymmetry) were associated with greater difficulty on the emotionally reactive scale (see Figure 2). Correlations between frontal asymmetry and the total, internalizing and withdrawn CBCL variables were not statistically significant. Correlations between frontal asymmetry and the other CBCL variables (externalizing) were also not statistically significant.

Correlational analyses also confirmed that similar positive associations were evident between each of the three conditions (happy, sad and neutral) frontal asymmetry scores and CBCL emotionally reactive (r=.48, p=.02; r=.5, p=.01, r=.4, p=.04, respectively).

4. Discussion

At one year, we found greater left frontal asymmetry in 63.6% of the VI group, and in 50% of the TS comparison group, with no significant difference in frontal asymmetry between the two groups. 22.7% of the VI sample at two years had 'internalizing' behavior difficulties in the clinical/subclinical range according to the CBCL norms. As hypothesized from the literature, frontal asymmetry at one year correlated with greater behavior risk at two years within the VI sample.

4.1. Frontal asymmetry in the VI and TS samples at one year

Two-thirds of infants within the VI sample showed greater relative left frontal asymmetry at one year; the positive mean FA score shows that on average the VI sample was slightly left lateralized. This is the first study to investigate frontal asymmetry in infants with VI, and our finding resembles a previous report demonstrating predominantly left frontal asymmetry in infants at high-risk of ASD, (Gabard-Durnam et al., 2015). Although these authors interpreted the high-risk ASD sample's left frontal asymmetry (in contrast to low-risk infants' right frontal asymmetry) as an 'atypical' pattern indicative of 'atypical neural organization', the significance of the VI sample's left frontal asymmetry finding is unclear, as no significant difference in frontal asymmetry was found between the VI and TS samples. Also, there was no association between frontal asymmetry and differing gradations of low functional vision level (as measured by the NDS). In the TS sample, frontal asymmetry was distributed equally between right and left lateralization, with the negative mean score indicating slightly right lateralization; mean right-sided asymmetry has also been reported in studies of one-year-old TS infants (Fox et al., 2001; Müller et al.,

2015).

This lack of difference in frontal asymmetry between our VI and TS comparison groups raises the question of whether protective neural processes are compensating for the disruption of visual stimulus to the optic radiation and occipital lobes in the VI sample. Alternatively, a potential difference in frontal asymmetry between the samples could be obscured as both samples may be going through a dynamic change in frontal asymmetry during this age range, with potential reversibility and opposing symmetries as shown by 14 and 18 months in TS and clinical samples (Fox et al., 2001; Gabard-Durnam et al., 2015). However, the majority of our VI sample (60%) and TS sample (80%) were below the age-point at which reversal has been reported for TS infants (14 months; Fox et al.), and age did not correlate with frontal asymmetry in either group. This suggests that these results were not attributable to differing age-related group changes; investigations of VI and TS samples at two and three years of age are required to clarify the frontal asymmetry trajectory in this population.

4.2. Behavior as measured by the CBCL in the VI sample

The majority of the VI sample at two years did not reach the clinical or subclinical range according to the CBCL norms in relation to behavior risk. However, 22.6% showed behavior scores reaching clinically concerning levels according to CBCL norms, specifically in the internalizing scale. This contrasts with the much lower percentage (6.7%) reaching this level on the same scale in a community population of TS infants (Briggs-Gowan et al., 2001). Whilst this finding should be interpreted with caution given

the small sample size, it supports our hypothesis that internalizing behavior is at risk in children with VI. Furthermore, this finding is compatible with reports of higher risk of emotionally reactive, anxiety, avoidant and withdrawal behaviors in young children with VI (Alon et al., 2010; Cass et al., 1994; Dale and Sonksen, 2002; Egan, 1979; Tirosh et al., 1998). Notably, these internalizing difficulties were present despite the fact that the VI sample had no additional CNS involvement and the majority was in the developmental (DQ) range considered 'age appropriate' for their vision level and chronological age.

4.3. Association between frontal asymmetry and later behavior within the VI sample

Greater left lateralized frontal asymmetry at one year showed a statistically significant moderate association with higher emotionally reactive behavior scores (items include "worries", "disturbed by change", and "upset by new people or situations") at two years. This association held whether run with the total sample including profound VI or severe VI only. Whilst we cannot claim that frontal asymmetry plays a key role in determining behavior difficulties in these children, given the limits of this study, our correlation finding suggests that within the VI group there is a subgroup of greater vulnerability with a more left-lateralized frontal asymmetry. This subgroup was also more at risk in relation to emotional reactivity by two years, which is in line with internalizing behavior concerns reported in the clinical literature for children with VI (Cass et al., 1994; Alon et al., 2010; Tirosh et al., 1998). The reasons for this more vulnerable subgroup are unclear; the frontal asymmetry at one year was independent of other factors previously shown to influence this measure in infancy, such as age, gender, DQ level, maternal education and maternal depression. Other reasons for within-sample differences may include genetic or

environmental factors (e.g., parenting style) and need further investigation. Our correlation finding is consistent with other reports showing an association between greater *left* asymmetry and longer-term internalizing risk, particularly social anxiety, worry and obsessive compulsive symptoms, in older children with higher-functioning ASD (Sutton et al., 2005; Burnette 2011) and in adults born with very low birthweight (Fortier et al., 2014). Our association finding differs from previous reports of TS infants demonstrating a relationship between *right* rather than left frontal asymmetry and internalizing or withdrawn behaviors (e.g., Smith and Bell, 2010; Fox et al., 2001). However, this previous work has investigated only those with typically sight (Peltola et al., 2014); infants with VI may differ from those with typical sight.

4.5. Strengths and Limitations

The strengths of this study include 1) the exclusion of those with known additional brain involvement to avoid the potential confound of additional brain damage, 2) the representativeness of the wider cohort of this sample according to national epidemiological and population census data (Dale et al., 2017) and 3) the use of brain electrophysiology, a powerful noninvasive tool for investigating brain activity in infancy, and deployed for the first time with the VI infant population.

However, the methodological limitations must also be considered. The small sample size of our TS group means that our cross-sectional comparison analyses of the frontal asymmetry data at Time 1 may be underpowered and therefore demands cautious interpretation. Furthermore, CBCL data was not available at Time 2 for the TS sample.

This would have been valuable for comparing the longitudinal relationship between frontal asymmetry and later behavior in the VI and TS groups. Another limitation is that behavior was measured only through the parent-reported CBCL; parental report may be valuable however as parents have the opportunity to observe their child across a variety of contexts (Rothbart and Bates, 2006). The CBCL has not been validated with or normed for infants with VI or designed to allow a formal clinical diagnosis. Nonetheless, the CBCL has excellent norms as well as good criterion and construct validity with typically sighted children (Achenbach and Rescorla, 2000), with studies demonstrating a high rate of reliability between CBCL scales and psychological diagnosis (Warnick et al., 2007).

5. Conclusions

This study provides the first evidence of an association between frontal EEG asymmetry and later behavioral difficulties within young children with congenital VI. It makes an important first contribution regarding the utility of frontal EEG asymmetry as a method to investigate risk in infants with VI and marks a significant first step in our understanding of possible neural and behavior vulnerability in this rare population. Further longitudinal investigations as part of this larger study (Dale et al., 2017) will contribute to greater understanding of children with VI who are most at risk, as well as potential protective and/or compensatory factors. This will help tailor targeted interventions for early support for those infants who are at greatest behavioral risk in this vulnerable population.

References

Achenbach TM, Rescorla LA. Manual for the ASEBA Preschool Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families; 2000.

Allen JB, Coan JA, Nazarian M. Issues and assumptions on the road from raw signals to metrics of frontal EEG asymmetry in emotion. Biol Psychol 2004; 67(1-2): 183–218.

Alon L, Cohen-Ophir M, Cohen A, Tirosh E. Regulation disorders among children with visual impairment: a controlled study. J Dev Phys Disabil 2010; 22(1), 57-64.

Belin P, Fillion-Bilodeau S, Gosselin F. The Montreal Affective Voices: A validated set of nonverbal affect bursts for research on auditory affective processing. Behav Res Methods 2008; 40(2): 531–539.

Blasi A, Mercure E, Lloyd-Fox S, Thomson A, Brammer M, Sauter D, Deeley Q, Barker GJ, Renvall V, Deoni S, Gasston D. Williams S, Johnson MK, Simmons A, Murphy D. Early specialization for voice and emotion processing in the infant brain. Curr Biol 2011; 21:1220–1224.

Briggs-Gowan MJ, Carter A, Moye-Skuban, Horwitz S. Prevalence of social

emotional and behavioural problems in a community sample of 1- and 2- year old children. J Am Acad Child Adolesc Psychiatry 2001; 40(7): 811-818.

Burnette CP, Henderson HA, Inge AP, Zahka NE, Schwartz CB, Mundy PC. Anterior EEG asymmetry and the modifier model of autism. J Autism Dev Disord 2011; 41: 1113-1124.

Campbell SB. Behavior problems in preschool children: a review of recent research. J Child Psychol Psychiatry 1995; 36(1):113-49.

Campbell SB, Spieker S, Burchinal M, Poe MD. Trajectories of aggression from toddlerhood to age 9 predict academic and social functioning through age 12. J Child Psychol Psychiatry. 2006; 47(8):791-800.

Cass HD, Sonksen PM, McConachie HR. Developmental setback in severe visual impairment. Arch Dis Child 1994; 70: 192-196.

Christou AI, Endo S, Wallis Y, Bair H, Zeegers MP, McCleery JP. Variation in serotonin transporter linked polymorphic region (5-HTTLPR) short/long genotype modulates resting frontal electroencephalography asymmetries in children. Dev Psychopathol 2016; 28(1):239-50.

Coan JA, Allen JJ, McKnight PE. A capability model of individual differences in

frontal EEG asymmetry. Biol Psychol 2006; 72: 198-207.

Cohen J. "A power primer". Psychol Bull 1992; 112 (1): 155–159.

Dale N, Sonksen P. Developmental outcome, including setback, in young children with severe visual impairment. Dev Med Child Neurol 2002, 44(9): 613–622.

Dale NJ, Tadic V, Sonksen P. Social communicative variation in 1-3 year olds with severe visual impairment. Child Care Health Dev 2014; 40(2): 158-64.

Dale N, Sakkalou E, O'Reilly M, Springall C, de Haan M, Salt, A. Functional vision and cognition in infants with congenital disorders of the peripheral visual system. Dev Med Child Neurol 2017. doi: 10.1111/dmcn.13429

Davidson RJ, Ekman P, Saron C, Senulis J, Friesen W. Approach-withdrawal and cerebral asymmetry; emotion expression and brain physiology. J Pers Soc Psychol 1990, 58: 330-341.

Davidson RJ. Cerebral asymmetry, emotion, and affective style. In R.J.H. Davidson, (Ed.), *Brain asymmetry*. Cambridge: MIT Press; 1995.

Davidson RJ, Lewis DA, Alloy LB, Amaral DG, Bush G, Cohen JD, Drevets WC, Farah MJ, Kagan J, McClelland JL, Nolen-Hoeksema S, Peterson BS. Neural and

behavioral substrates of mood and mood regulation. Biol Psychiatry. 2002 Sep 15;52(6):478-502.

Dawson G, Frey K, Panagiotides H, Osterling J, Hessl D. Infants of depressed mothers exhibit atypical frontal brain activity: a replication and extension of previous findings. J Child Psychol Psychiatry 1997; 38(2):179-86.

Degnan KA, Hane AA, Henderson HA, Moas OL, Reeb-Sutherland BC, Fox NA. Longitudinal stability of temperamental exuberance and social-emotional outcomes in early childhood. Dev Psychol 2011; 47(3):765-80.

Delorme A, Mullen T, Kothe C, Akalin Acar Z, Bigdely-Shamlo N, Vankov A, Makeig S. EEGLAB, SIFT, NFT, BCILAB, and ERICA: New tools for advanced EEG processing. Comput Intell Neurosci 2011; 2011: 130714.

Diaz A, Bell MA. Frontal EEG asymmetry and fear reactivity in different contexts at 10 months. Dev Psychobiol 2012; 54(5): 536–545.

Egan DH. The early development of visually handicapped children. In Visual Handicap in Children (Ed. V.Smith and J. Keen), pp. 139-44. London; 1979.

Ek U, Fernell E, Jacobson L . Cognitive and behavioral characteristics in blind children with bilateral optic nerve hypoplasia. Acta Paediatr 2005; 94: 1421–1426.

Fortier P, Van Lieshout RJ, Van Lieshout R.J, Waxman JA. Are orchids left and dandelions right? Frontal brain activation asymmetry and its sensitivity to developmental context. Psychol Sci 2014; 25(8): 1526–1533.

Fox NA, Davidson RJ. Hemispheric substrates of affect: a developmental model. In Fox NA. and Davidson RJ. Eds. The psychobiology of affective development, 353-382, Hillside, NJ: Erlbaum Press; 1984.

Fox NA. Psychophysiological correlates of emotional reactivity during the first year of life. Dev Psychol 1989; 25: 364-372.

Fox NA. If it's not left, it's right. Electroencephalograph asymmetry and the development of emotion. Am Psychol 1991; 46: 863-872.

Fox NA. Dynamic cerebral processes underlying emotional regulation. Monogr Soc Res Child Dev 1994; 59, 2-3, Serial no. 240.

Fox NA, Rubin KH, Calkins SD, Marshall TR, Coplan RJ, Porges S, Long J, Stewart S. Frontal activation asymmetry and social competence at fours years of age. Child Dev 1995; 66: 1770-1784.

Fox NA, Schmidt LA, Calkins SD, Rubin KH, Marshall TR, Coplan RJ. The role of

frontal activation in the regulation and dysregulation of social behavior during the preschool years. Dev Psychopathol 1996; 8: 89-102.

Fox NA, Henderson HA, Rubin KH, Calkins SD, Schmidt LA. Continuity and discontinuity of behavioral inhibition and exuberance: psychophysiological and behavioral influences across the first four years of life. Child Dev 2001; 72 (1): 1-21.

Gabard-Durnam L, TierneyAL, Vogel-Farley V, Tager-Flusberg H, Nelson CA. Alpha asymmetry in infants at risk for autism spectrum disorders. J Autism Dev Disord 2015; 45(2):473-80.

Hagemann D, Naumann E. The effects of ocular artifacts on (lateralized) broadband power in the EEG. Clin Neurophysiol 2001; 112(2): 215–231.

Hagemann D, Naumann E, Thayer JF. The quest for the EEG reference revisited: A glance from brain asymmetry research. Psychophysiology 2001; 38(05): 847–857.

Hane AA, Fox NA, Henderson HA, Marshall PJ. Behavioral reactivity and approach-withdrawal bias in infancy. Dev Psychol 2008; 44(5): 1491-1496.

Hatton DD, Bailey DB, Burchinal MR, Ferrell KA. Developmental growth curves of preschool children with visual impairments. Child Dev 1997; 68: 788-806.

He J, Degnan KA, McDermott JM, Henderson HA, Hane AA, Xu Q, Fox NA. Anger and approach motivation in infancy: Relations to early childhood inhibitory control and behavior problems. Infancy 2010; 15(3), 246–269.

Henderson HA, Fox NA, Rubin KH. Temperamental contributions to social behavior: the moderating roles of frontal EEG asymmetry and gender. J Am Acad Child Adolesc Psychiatry 2001; 40(1):68-74.

Hobson RP, Lee A, Brown R. Autism and congenital blindness. J Autism Dev Disord 1999; 29 (1): 45-56.

Howarth GZ, Fettig NB, Curby TW, Bell MA. Frontal Electroencephalogram Asymmetry and Temperament Across Infancy and Early Childhood: An Exploration of Stability and Bidirectional Relations. Child Dev 2016; 87(2):465-76.

Jan JE, Farrell K, Wong PK, McCormick AQ. Eye and head movements in children with vision impairment. Dev Med Child Neurol 1986; 28(3): 285-93.

Jones NA, Field T, Almeida A. Right frontal EEG asymmetry and behavioral inhibition in infants of depressed mothers. Infant Behav Dev 2009; 32(3): 298–304.

Lao Y, Kang Y, Collignon O, Brun C, Kheibai SB, Alary F, Gee J, Nelson MD,

Lepore F, Lepore N. A study of brain white matter plasticity in early blinds using tract-based spatial statistics and tract statistical analysis. Neuroreport 2015; 26(18):1151-4.

Levtzion-Korach O, Tennenbaum A, Schnitzer R, Ornoy, A. Early motor development of blind children. J Paediatr Child Health 2000; 36: 226-229.

LoBue V, Coan JA, Thrasher C, DeLoache JS. Prefrontal asymmetry and parent-rated temperament in infants. PloS One 2011; 6(7): e22694.

Lusby CM, Goodman SH, Bell MA, Newport D.J. Electroencephalogram patterns in infants of depressed mothers. Dev Psychobiol 2014; 56(3):459–473.

Margalith D, Jan JE, McCormick A, Tze W, Lapointe, J. Clinical spectrum of congenital optic nerve hypoplasia: Review of 51 patients. Dev Med Child Neurol 1984; 26: 311-322.

Missana M, Grigutsch M, Grossmann T. Developmental and individual differences in the neural processing of dynamic expressions of pain and anger. PLoS One 2014; 9(4): e93728.

Missana M, Grossmann T. Infants' emerging sensitivity to emotional body expressions: insights from asymmetrical frontal brain activity. Dev Psychol 2015;

51(2):151-60.

Müller BC, Kühn-Popp N, Meinhardt J, Sodian B, Paulus M. Long-term stability in children's frontal EEG alpha asymmetry between 14-months and 83-months. Int J Dev Neurosci 2015; 41:110-4.

Peltola MJ, Bakermans-Kranenburg MJ, Alink LR, Huffmeijer R, Biro S, Van IJzendoorn MH. Resting frontal EEG asymmetry in children: Meta-analyses of the effects of psychosocial risk factors and associations with internalizing and externalizing behavior. Dev Psychobiol 2014; 56(5): 1377-1389.

Perez-Pereira M, Conti-Ramsden G. Language Development and Social Interaction in Blind Children. Hove, UK: Psychology Press (Taylor & Francis); 1999.

Rahi JS, Cable N, BCVISG. Severe visual impairment and blindness in children in the UK. *Lancet*, 2003; 362(9393):1359–1365.

Reynell J. Manual for the Reynell-Zinkin scales, developmental scales for visually handicapped children – part 1, Mental Development. Windsor: NFER-Nelson Publishing; 1979.

Rothbart MK, Bates JE. Temperament. In Damon W, Lerner R, Eisenberg N (Eds). Handbook of child psychology: social, emotional and personality development (6th

Ed. Vol. 3, p99-166). New York: John Wiley; 2006.

Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology 1990; 1:43–6.

Smith CL, Bell MA. Stability in infant frontal asymmetry as a predictor of toddlerhood internalizing and externalizing behaviors. Dev Psychobiol 2010; 52(2): 158–167.

Sonksen PM, Dale N. Visual impairment in infancy: impact on neurodevelopmental and neurobiological processes. Dev Med Child Neurol 2002; 44(11): 782–791.

Sonksen PM. The assessment of 'vision for development' in severely visually handicapped babies. Acta Ophthalmol 1983; 61: 82-90.

Stroganova TA, Orekhova EV, Posikera IN. EEG alpha rhythm in infants. Clin Neurophysiol 1999: 110 (6): 997-1012.

Sutton SK, Burnette CP, Mundy PC, Meyer J, Vaughan A, Sanders C, Yale M. Resting cortical brain activity and social behavior in higher functioning children with autism. J Child Psychol Psychiatry 2005; 45: 1-12.

Stets M, Stahl D, Reid VM. A meta-analysis investigating factors underlying attrition rates in infant ERP studies. Dev Neuropsychol 2012; 37(3), 226–252.

Tadic V, Pring L, Dale N. Are language and social communication intact in children with congenital visual impairment at school age? J Child Psychol Psychiatry 2010; 51: 696-705.

Tirosh E, Schnitzer MR, Davidovitch M, Cohen A. Behavioural problems among visually impaired between 6 months and 5 years. Int J Rehab Res 1998; 21: 63-70.

Tomarken AJ, Davidson RJ, Wheeler RE, Kinney L. Psychometric properties of resting anterior EEG asymmetry: temporal stability and internal consistency. Psychophysiology 1992; 29(5): 576–592.

Tomarken AJ, Dichter GS, Garber J, Simien C. Resting frontal brain activity: linkages to maternal depression and socio-economic status among adolescents. Biol Psychol 2004; 67(1-2):77-102.

Wacker, J., Mueller, E. M., Pizzagalli, D. A., Hennig, J., & Stemmler, G. Dopamine D2-Receptor Blockade Reverses the Association Between Trait Approach Motivation and Frontal Asymmetry in an Approach-Motivation Context. Psychol Sci 2013: 24(4), 489-497.

Warnick EM, Bracken MB, Kasl S. Screening efficiency of the child behavior checklist and strengths and difficulties questionnaire: a systematic review. Child and Adolescent Mental Health. 2007;13:140–147.

Webb EA, O'Reilly MA, Clayden JD, Seunarine KK, Dale N, Salt A, Dattani MT. Reduced ventral cingulum integrity and increased behavioral problems in children with isolated optic nerve hypoplasia and mild to moderate or no visual impairment. PloS One, 2013; 8(3), e59048.

Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67: 361-370.

Figure Legends

Figure 1. *Flowchart of the VI sample's participants included at each analysis step*

Figure 2. *Correlation plot showing the significant positive relationship between Frontal EEG asymmetry composite and CBCL-Emotionally Reactive (r=.50, p=.02) in the sample of infants with VI (n=22) who had an EEG at 12 months and a parent rating on the CBCL at 2 years.*