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

Michelle A. O'Reilly [a], Joe Bathelt [b,d], Elena Sakkalou [a], Hanna Sakki [a], Alison Salt [a,c], Naomi J. Dale [a,c,*], Michelle de Haan [d]

[a] Clinical Neurosciences Section, Developmental Neurosciences Programme, UCL Great Ormond Street Institute of Child Health, London, UK
[b] MRC Cognition & Brain Sciences Unit, University of Cambridge, UK
[c] Developmental Vision Service, Great Ormond Street Hospital NHS Foundation Trust, London, UK
[d] Cognitive Neuroscience and Neuropsychiatry Section, Developmental Neurosciences Programme, UCL Great Ormond Street Institute of Child Health, UK

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HIGHLIGHTS

- Left frontal EEG alpha-power asymmetry in congenital visual impairment (VI) infants 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.

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 ($r = 0.50$, $p = 0.02$).
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,

* Corresponding author at: Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH, UK.
E-mail address: n.dale@ucl.ac.uk (N.J. Dale).

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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 et al., 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 reduced white matter integrity in the ventral cingulum and higher 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 dopamine and serotonin neurotransmitter 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). Frontal asymmetry in infant studies has been shown 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 et al., 1990; Diaz and Bell, 2012; Fox, 1994; Fox et al., 1995, 1996, 2001; Hane et al., 2008; Henderson et al., 2001; Missana et al., 2014, Missana and Grossmann, 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; Missana and Grossmann, 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). Furthermore, 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, 1994; Fox et al., 2001) and a reversal of asymmetry occurs by 18 months in high-risk and low-risk groups for ASD (Gabard-Durnam 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 offer 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,