Disrupted developmental processes in the human visual cortex linked to congenital patterned visual deprivation

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Abstract

Sensitive periods are maturational phases wherein the brain shows heighted plasticity in response to environmental experience. Importantly, if sensory experience was not received within such windows, development of the underlying neural architecture was found to be impaired. This dissertation investigated two hypothesized mechanisms underlying sensitive periods in the human visual cortex, by working with rare individuals who were born blind due to dense bilateral congenital cataracts. Due to delayed treatment, these individuals experienced a transient period of congenital patterned visual deprivation.

The first two studies of this dissertation tested the role of two neural processes which, based on non-human animal research, were proposed to underlie sensitive periods of brain development.

First, the maturation of inhibition in the visual cortex was shown to rely on visual experience in non-human animal models, resulting in the establishment of an E/I balance. To investigate whether the development of such an E/I balance in humans is linked to a sensitive period, the first study of this dissertation (**Appendix I**) compared the ratio of excitation to inhibition (E/I ratio) in the visual cortex of CC individuals to aged-matched normally sighted (SC) individuals. Magnetic Resonance Spectroscopy was used to compare the visual cortex concentrations of excitatory/inhibitory (Glutamate-glutamine/Gamma-Aminobutyric Acid) neurotransmitters. Additionally, the aperiodic parameters of the broadband (1-20 Hz) electroencephalogram (EEG) spectrum were compared across occipital electrodes. Previous work has linked the slope of the aperiodic EEG (1/f) distribution to the E/I ratio, whereas the intercept has been related to broadband neuronal firing. Both the neurotransmitter ratio and the aperiodic slope indicated a lower E/I ratio in the visual cortex of CC than SC individuals. Simultaneously, the aperiodic intercept was increased in CC individuals, suggesting increased broadband neuronal firing. These findings suggest that the development of human visual cortex E/I ratio might underlie sensitive period plasticity.

Second, the development of corticocortical projections has been shown to rely on postnatal visual input in non-human animals. Corticocortical projections support the interaction between feedforward and feedback processing, i.e. recurrent processing, in the visual cortex, which is essential for typical visual behavior. Occipital alpha (8-14 Hz) oscillations have been correlated to feedback processing in SC individuals; therefore, the second study of this dissertation compared whether two characteristic EEG alpha-range phenomena manifest to the same extent in CC individuals (Appendix II). CC individuals demonstrated lower stimulus-evoked as well as resting-state alpha amplitudes than

SC individuals. Further, CC individuals with above-threshold evoked alpha activity had better visual acuity than those without a significant evoked alpha peak. This linked reduction of evoked and resting-state alpha activity was interpreted as an impairment in recurrent processing in CC individuals' visual systems.

Together, these studies provide evidence for neural processes which demonstrate (visual) experience dependence, and therefore, might be associated with a sensitive period.

In addition to deleterious effects on visual behavior, the consequences of congenital visual deprivation have been shown to extend to multisensory integration. The third study of this dissertation tested whether congenital visual deprivation affected the development of visuo-haptic integration by investigating whether CC individuals experience the Size-Weight illusion (SWI). The SWI is a robust illusion in typical visuo-haptic development, wherein SC individuals perceive the larger of two objects which in fact weigh the same to be lighter. In this study, CC and SC participants were first presented with visuo-haptic cues of size, i.e. being able to see and feel the objects. Additionally, individuals treated for developmental cataracts and permanently congenitally blind individuals were tested. All groups experienced a robust visuo-haptic SWI. Subsequently, CC participants assessed the weights of stimuli while receiving no haptic size information, i.e. holding them with an attached string. Regardless of whether size information was presented via visuo-haptic or exclusively visual cues, CC participants experienced the SWI to the same extent as SC individuals. These results suggested that the ability to integrate simultaneous visual and haptic size cues did not rely on early visual experience.

1. Investigation of sensitive periods in the human visual cortex

In humans, the postnatal developmental trajectories for sensory and motor processing are amongst the longest in the animal kingdom. Human vision requires years of visual experience to develop adult-like characteristics; when babies are born, their visual acuity is a fraction of adults', they see little color, and have limited control over their eye movements (Braddick & Atkinson, 2011). While basic visual acuity reached adult levels by 4 years of age, aspects of visual perception which require identification of relative positions, such as Vernier acuity (Skoczenski & Norcia, 2002) and visual feature binding (Kovács et al., 1999), appeared to improve until the end of adolescence.

Neural circuits which support these abilities are thought to be fine-tuned during epochs termed sensitive periods (Hubel & Wiesel, 1970; Knudsen, 2004; Maurer & Lewis, 2017; Röder & Kekunnaya, 2021). It was observed that neural structures and functions showed higher responsiveness to environmental experience within such windows, than at other stages of life (Knudsen, 2004). Sensitive periods were further distinguished from adult learning by the observation that when experience was not received within this window, neural structures and functions did not develop to the expected level (Hubel & Wiesel, 1970; Knudsen, 2004). Consequently, one approach to characterizing the neural processes underlying sensitive period plasticity has been via perturbation of input in non-human animal models. This model induces monocular or binocular visual deprivation at various life stages in non-human animals. During or following such deprivation, investigations of the structure and physiology of the visual pathway established the role of visual experience in their respective development (Hensch, 2005; Levelt & Hübener, 2012).

Investigation of the visual systems of humans who were born blind due to peripheral deficits has provided crucial "retrospective" (Lewkowicz & Röder, 2015) evidence that post-natal visual experience is necessary for normal development (Lewis & Maurer, 2005; Röder & Kekunnaya, 2021). Rare individuals born blind due to dense bilateral congenital cataracts, who underwent surgery more than a few weeks from birth, showed persistent deficits of several visual and multisensory functions on a behavioral level (Maurer et al., 2007; Maurer & Hensch, 2012; Maurer & Lewis, 2017; Röder et al., 2020; Röder & Kekunnaya, 2021). Individuals who were born with vision, but developed total cataracts in childhood or adulthood, did not show comparable deficits after surgery (Birch et al., 2009; Bruns et al., 2022; Khanna et al., 2013; Lewis & Maurer, 2005). Therefore, the persistent effects of congenital patterned visual deprivation after sight restoration in humans were attributed to sensitive

periods for typical visual development. However, which neural processes might underlie such sensitive periods in humans has remained an active field of enquiry.

In the following chapters findings from the cataract model are discussed in the context of two neural processes underlying sensitive period plasticity: the maturation of inhibition in the cortex, leading to the establishment of an excitatory-inhibitory balance (Hensch & Fagiolini, 2004), and the elaboration of corticocortical circuitry, which supports feedback processing (Kral, 2013).

2. Role of the excitatory/inhibitory ratio in human visual cortex development

2.1 Background

Animals constantly experience changes in their visual environments, learn to recognize novel signals, and undergo changes to the eyes with age, all of which require the visual system to adapt to variable input. On a neural level, these constant changes in incoming signals to circuits might constitute "destabilizing" events. Yet, the visual cortex appears to process such changes without dramatic alteration of response properties in healthy adults. Hebbian learning provides an incomplete characterization of our adaptability to such changes (Turrigiano & Nelson, 2004), as under purely long-term potentiation or long-term depression, repeated excitation would lead to epileptiform neural activity, and repeated inhibition would lead to silent synapses (L. Chen et al., 2022; Whitt et al., 2013; Wu et al., 2022). Indeed, typical neurons and networks appear to be subject to a negative feedback mechanism, preventing runaway excitation or silencing. The excitatory/inhibitory (E/I) balance was one mechanism proposed to maintain stability, wherein the inhibition generated in a given synapse, circuits or ensembles was proportional to the excitation (Van Vreeswijk & Sompolinsky, 1996; Vogels et al., 2011), thereby regulating one with the other (Isaacson & Scanziani, 2011).

2.2 Measurement of the E/I ratio.

The ratio between measures of excitatory and inhibitory transmission (E/I ratio) in a synapse, circuit, or brain region, is a measure of the E/I balance[1]. Using such a ratio, the proportion of excitation and inhibition was experimentally observed to be "balanced" across various spatiotemporal scales in the visual cortex (Tao & Poo, 2005; Xue et al., 2014), somatosensory cortex (Okun & Lampl, 2008; Z. Zhang et al., 2011), auditory cortex (Wehr & Zador, 2003) and prefrontal cortex (Haider et al., 2006) of non-human animals. Further, the proportion of excitation and inhibition has been demonstrated to alter neuronal tuning (Fang et al., 2021; Ip & Bridge, 2021; Kato et al., 2017; Wehr & Zador, 2003); greater synaptic inhibition is thought to result in sharper tuning and increased stimulus selectivity (Isaacson & Scanziani, 2011).

[1] Models of neural function suggested that excitatory/inhibitory balance is a dynamic property maintained in circuits reflective of interactions between synaptic scaling, Hebbian learning and intrinsic neuronal excitability, rather than a static value. Measured E/I ratios may be reflective of any or all of these.

The relationship between cortical excitation/inhibition, neuronal tuning and visual behavior has been indirectly investigated in humans via quantification of excitatory neurotransmitters Glutamate/Glutamine, and inhibitory neurotransmitter Gamma Aminobutyric Acid (GABA)(Ip & Bridge, 2021; Kurcyus et al., 2018). Non-invasive measures of neurotransmitters GABA (GABA+) and Glutamate/Glutamine complex (Glx) quantified via Magnetic Resonance Spectroscopy (Ip & Bridge, 2021) have demonstrated a regional balance between the inhibitory and excitatory neurotransmitter concentration in neurotypical adult humans (Rideaux et al., 2022; Steel et al., 2020)[2]. Glx and GABA+ concentrations measured via MRS have been linked to performance on orientation discrimination (Edden et al., 2009)[3], contrast sensitivity (Ip et al., 2019)[4], binocular vision (Lunghi et al., 2015)[5] as well as perceptual rivalry (Pitchaimuthu et al., 2017; Van Loon et al., 2013)[6]. Further, invasive local field potentials (Dehghani et al., 2016) and non-invasive EEG/MEG activity have been reported to reflect E/I ratios in humans (Bezalel et al., 2019; Muthukumaraswamy & Liley, 2018). In these signals, the negative slope of the aperiodic (1/f) distribution of the magnetoencephalogram was shown to flatten with pharmacological increase (Muthukumaraswamy & Liley, 2018)[7] and steepen with the pharmacological decrease (Gao et al., 2017; Medel et al., 2020; Muthukumaraswamy & Liley, 2018)[8] of the E/I ratio. It was concluded that the aperiodic neuronal activity recorded from a region might track the E/I ratio of the underlying neural circuits.

In sum, the E/I ratio is considered a modulatory property for typical sensory processing and efficient neuronal coding in typically developed animals (Dehghani et al., 2016; Wu et al., 2022; Zhou & Yu, 2018).

2.3 Developmental maturation of inhibition in the visual cortex.

A well-evidenced account of neural changes underlying sensitive period plasticity is that the balance between excitatory and inhibitory drive on neurons at a synaptic, circuit or regional level is

[2] While (Rideaux, 2021) did not find evidence for an E/I balance with MRS measures, (Rideaux et al., 2022) showed a correlation between GABA+ and Glu concentrations in the visual cortex.
[3] Higher resting visual cortex GABA+ concentration predicted lower discrimination thresholds/better performance
[4] Higher contrast images correlated with higher visual cortex Glutamate concentration during the MRS scan
[5] Resting GABA+ concentration in the visual cortex decreased following monocular deprivation
[6] Increased resting state visual cortex GABA+ concentrations were associated with longer percept durations and fewer switches in binocular rivalry
[7] Tested using anesthetic Ketamine, a non-selective NMDA receptor antagonist reduces GABAergic interneuron firing, increasing the E/I ratio (Muthukumaraswamy & Liley, 2018)
[8] Tested using Propofol, an anesthetic known to enhance GABAergic function, reducing the E/I ratio (Gao et al., 2017; Medel et al., 2020); anticonvulsant Tiagabine, a GABA reuptake inhibitor increasing the GABA concentration and reducing the E/I ratio at the synapse; and anti-epileptic Perampanel, which blocks AMPA receptors, thereby reducing the E/I ratio (Muthukumaraswamy & Liley, 2018)

attained within this window (Froemke, 2015; Larsen et al., 2023; Takesian & Hensch, 2013; Vogels et al., 2011). As the delayed or premature onset of GABAergic inhibitory circuit development in the cerebral cortex was shown to correspondingly affect the onset and closure of the sensitive period (Hensch, 2004; Hensch & Fagiolini, 2005; Wong-Riley, 2021; H. Zhang et al., 2018), a causal link was proposed between sensitive period plasticity and the development of cortical inhibition.

Simultaneously, several non-human animal models demonstrated that visual experience played a crucial role in the maturation of GABAergic circuits (Berardi et al., 2000; Fagiolini & Hensch, 2000; Flores & Méndez, 2014; Hensch, 2004; Sale et al., 2010; Toyoizumi et al., 2013), supporting the role of experience in the development of cortical inhibition, and further linking inhibitory development to the sensitive period. In "prospective" studies of neural changes with age, the E/I ratio across various cortical regions demonstrated a decrease during early development (Larsen et al., 2022; Wong-Riley, 2021; Z. Zhang et al., 2011). Retrospective studies in non-human animals concomitantly demonstrated alterations in the visual cortex E/I ratio corresponding to perturbations of visual experience (Levelt & Hübener, 2012). Dark rearing delayed the maturation of GABAergic circuits (Gianfranceschi et al., 2003; Hensch et al., 1998), thus resulting in "unbalanced" excitatory firing in the visual cortex of dark reared rodents (Benevento et al., 1992; Morales et al., 2002). Further, dark rearing or lid suture followed by reintroduction of visual stimulation has been shown to alter the E/I ratio in V1 pyramidal neurons (Fang et al., 2021; Morales et al., 2002). As detailed in Section 2.2, impaired development of cortical inhibition predicted reduced stimulus selectivity in the visual cortex; such impaired development was proposed to underlie reduced orientation selective neurons in the visual cortices of lid sutured cats (Singer & Tretter, 1976), and fewer direction selective neurons in the visual cortices of dark reared ferrets (Li et al., 2006). Summarily, sub-optimal E/I dynamics following disrupted experience within a sensitive period have been purported to underlie deficits in visual cortex responses, and correspondingly, visual behavior (Baroncelli et al., 2011).

In humans, direct measures of the E/I ratio across visual cortex development are scarce. Post-mortem histological assays[9] provided evidence of a balanced development of excitation and inhibition in the human visual cortex (Murphy et al., 2005; Pinto et al., 2010; Siu & Murphy, 2018). Non-invasive indicators of visual excitation/inhibition are more common; one such index of post-natal

[9] By measuring the ratio of $GABA_A$ receptor subunit expression ($GABA_A\alpha1$:$GABA_A\alpha3$) and NMDA receptor subunit expression (NR2A:NR2B) as a function of age, Murphy et al., (2005) demonstrated that both ratios concomitantly increase in the visual cortex until the age of 6 years. This receptor subunit shift has been noted in mouse models and results in an increased speed of EPSCs and IPSCs (Cho et al., 2009; Philpot et al., 2003).

development of inhibition in the human visual cortex is surround suppression (Angelucci & Bressloff, 2006). Surround suppression is the property of a neuron's "classical" receptive field, wherein stimulation in the "surrounding" receptive field causes a suppressed response, which requires lateral inhibition (Angelucci & Bressloff, 2006; Nurminen et al., 2018). Visual evoked potentials (VEP) were measured in response to grating stimuli in infants and adults to assess the age at which an increased VEP in response to orthogonal (non-suppressed) vs. parallel (surround-suppressed) backgrounds was observable (Morrone & Burr, 1986). This increase in VEP amplitude was only recorded after 6 months of age. Infants tested using moving gratings also demonstrated the behavioral effects of shrinking of the receptive field into the "classical" and "surround" after 6 months of age (Nakashima et al., 2019). These studies suggested that lateral inhibition in the visual cortex of human infants was immature in the first 6 months of life (Braddick & Atkinson, 2011; Morrone & Burr, 1986; Nakashima et al., 2019).

2.4 Alteration of E/I ratio after congenital patterned visual deprivation

Based on the aforementioned findings across non-human animals and non-invasive studies with humans, it was predicted that E/I balance in the visual cortex might be permanently altered due to congenital visual deprivation (Röder et al., 2021). Studies in CC individuals have provided evidence consistent with this hypothesis.

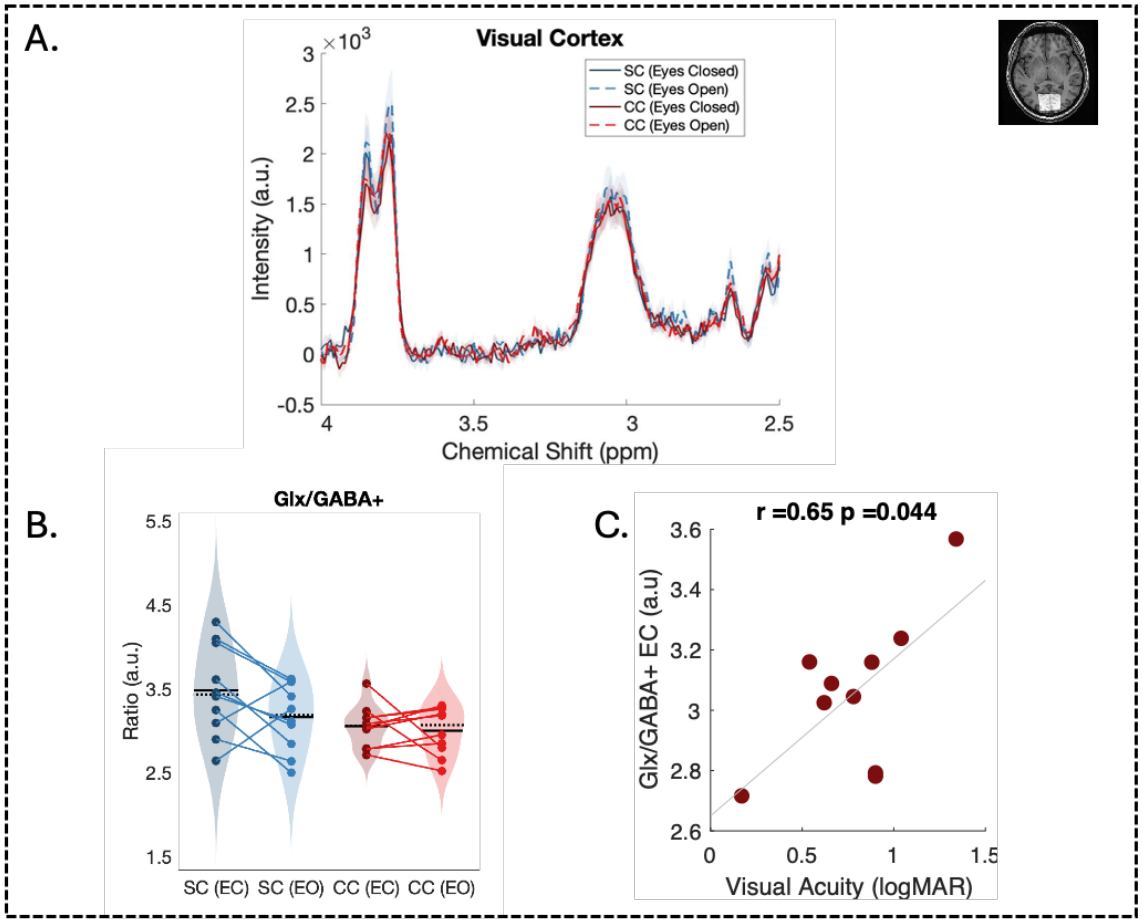
2.4.1 Physiological evidence consistent with an altered E/I ratio linked to congenital visual deprivation.

The crucial link between the development of cortical inhibition in humans and sensitive period plasticity was suggested by recent studies using a retrospective approach to indirectly assess E/I dynamics (Ossandón et al., 2023; Pant et al., Under Review; Raczy et al., 2022). Three findings from these studies suggested that increased excitation in the visual cortex, attributable to congenital blindness, might persist following sight recovery. First, an increased aperiodic (1/f) intercept in electroencephalography (EEG) recordings was found in 10 CC individuals compared to age-matched, normally sighted controls while participants kept their eyes open at rest, eyes closed at rest, and watched flickering visual stimuli (1-30 Hz, **Pant et al., Under Review**) (**Appendix 1**). This intercept has been related to neuronal firing (Manning et al., 2009; Winawer et al., 2013), and was used as an indirect assessment of broadband neural activity in the occipital cortex of CC vs SC individuals **(Pant et al., Under Review) (Appendix I).** An increased aperiodic intercept was reported at occipital electrodes in CC compared to SC individuals, across both resting state and flickering stimulation

conditions (Figure 1.1). This finding suggests increased spontaneous firing in the visual cortex of CC individuals, consistent with the hypothesized impairments in inhibitory development. Second, when the slope of the aperiodic spectrum in the 20-40 Hz range was compared across CB, CC and SC groups (Ossandón et al., 2023), this slope was flatter (i.e., less negative) across occipital channels of CB and CC individuals, compared to SC individuals. A flatter aperiodic slope was observed in CB individuals during eye closure, and CC individuals across both eye closure and eye opening at rest. As the aperiodic slope has been reported to track the E/I ratio (Gao et al., 2017; Muthukumaraswamy & Liley, 2018) (see Section 2.2), the authors interpreted these results as reflective of a higher E/I ratio in the visual cortex, during and following congenital visual deprivation. Third, an fMRI study comparing the amplitude of low-frequency fluctuations (ALFF)[10] in BOLD activity found increased ALFF during eye opening in CC compared to SC individuals. The authors suggested that neuronal activity was increased in the visual cortex during eye opening, as a consequence of transient congenital visual deprivation (Raczy et al., 2022).

MRS findings from permanently congenitally blind (CB) individuals also appeared consistent with the prediction that inhibitory circuits require visual experience for typical development in humans. Glutamate/Glutamine (Glx) concentration was increased in anophthalmic individuals' visual cortices (Coullon et al., 2015), and a trend towards decreased GABA+ concentration was observed in the visual cortex of CB individuals (Weaver et al., 2013). As GABA+ and Glx concentrations are considered measures of inhibitory and excitatory neurotransmission, respectively, these changes were interpreted as a shift towards excitation in the CB visual cortex.

[10] The amplitude of low-frequency (0.01-0.1 Hz) fluctuations of blood oxygen level dependent (BOLD) fMRI signals have been suggested to arise from underlying spontaneous neuronal activity (Zeineh et al., 2018).


A.
Visual Cortex
SC (Eyes Closed)
SC (Eyes Open)
CC (Eyes Closed)
CC (Eyes Open)
Intensity (a.u.)
Chemical Shift (ppm)
B.
Glx/GABA+
Ratio (a.u.)
SC (EC) SC (EO) CC (EC) CC (EO)
C.
r =0.65 p =0.044
Glx/GABA+ EC (a.u)
Visual Acuity (logMAR)

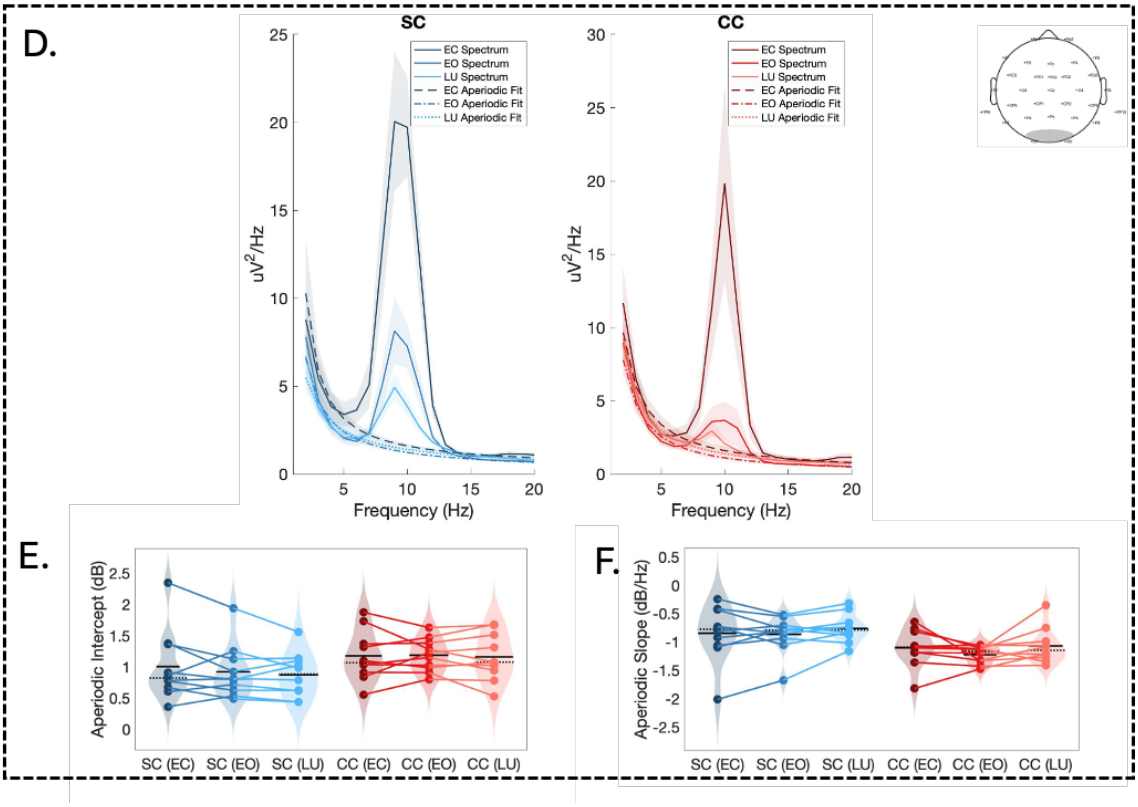

D.
SC
CC
EC Spectrum
EO Spectrum
LU Spectrum
EC Aperiodic Fit
EO Aperiodic Fit
LU Aperiodic Fit
uV²/Hz
Frequency (Hz)
E.
Aperiodic Intercept (dB)
SC (EC) SC (EO) SC (LU) CC (EC) CC (EO) CC (LU)
F.
Aperiodic Slope (dB/Hz)
SC (EC) SC (EO) SC (LU) CC (EC) CC (EO) CC (LU)

Figure 2.1. Magnetic Resonance Spectroscopy and Electroencephalography measures of visual cortex excitatory/inhibitory ratio in congenital cataract-reversal individuals. A. Magnetic Resonance Spectra of congenital cataract-reversal (CC, red) and normally sighted (SC, blue) individuals, showing peaks of Glutamate/Glutamine complex (Glx, left) and Gamma-Aminobutyric acid (GABA+, right) are displayed. Spectra are shown for the eyes open (EO) and eyes closed (EC) conditions for both groups. Inset shows an exemplar for visual cortex placement from one participant. The standard error of the mean is shaded. B. Ratio of Glx to GABA concentration in the visual cortex of CC (red) and SC (blue) individuals quantified from MRS spectra. The solid black lines indicate mean values and dotted lines indicate median values. The coloured lines connect values of individual participants across conditions. C. Correlation between visual cortex Glx/GABA+ concentration in the eyes closed condition with visual acuity assessed in the CC group. D. Electroencephalography (EEG) spectra (solid lines) with the aperiodic fit (dashed lines) are shown for CC (red) and SC (blue) individuals in the eyes closed (EC), eyes open (EO) and flickering visual stimulation (LU) conditions. Inset shows electrode montage used for recordings, with grey shading around occipital (O1 and O2) electrodes, across which the presented data was averaged. E,F. Violin plots demonstrate the E. aperiodic intercept and F. aperiodic slope across conditions for CC and SC individuals, with individual subjects connected by colored lines, and solid/dashed black lines showing mean/median respectively. Figure and caption reproduced from Pant et al. (Under Review) (Appendix I).

However, the aperiodic fit to the 1-20 Hz range suggested a lowered rather than increased E/I ratio in the visual cortex of CC vs SC individuals (**Pant et al., Under Review**; Ossandon et al., 2023), across occipital channels. The aperiodic slope was steeper in CC vs SC individuals, regardless of eye opening or eye closure at rest (**Pant et al., Under Review**; Ossandon et al., 2023), or flickering stimulation **(Pant et al., Under Review)** (Figure 1.1). Crucially, MRS findings in CC individuals suggested a lowered E/I ratio in the visual cortex. The concentration of excitatory (Glx) and inhibitory (GABA+) neurotransmitters in the visual cortex was quantified using the MEGA-PRESS sequence, i.e. an MRS spectral-editing technique targeted towards quantification of Glx/GABA+ (Mescher et al., 1998; Mullins et al., 2014). While the concentrations of Glx and GABA+ did not significantly differ between groups in the visual cortex, the ratio of Glx/GABA+ concentration was reduced in CC vs SC individuals at rest, regardless of eye closure (Figure 1.1).

One hypothesis proposed to reconcile seemingly contradictory correlates of E/I ratios across different measures was that adult homeostatic plasticity (L. Chen et al., 2022; Keck et al., 2017; Turrigiano & Nelson, 2004; Whitt et al., 2013) might compensate for increased excitation following sight restoration **(Pant et al., Under Review) (Appendix I).** It was speculated that the visual cortex developed adaptations to congenital blindness, including a lower threshold for excitation, in the absence of visual experience-dependent inhibitory circuitry. Following sight restoration, newly available visual excitation might therefore have resulted in significant circuit instability in blindness-adapted circuits, which would require commensurate downregulation. Supporting this argument, a

lower Glx/GABA+ concentration in the visual cortex of CC individuals correlated with better visual outcomes (logMAR visual acuity), consistent with the notion that the lowered Glx/GABA+ concentration might be reflective of compensatory effects following sight restoration. A need for such homeostatic compensation was further supported by the signs of increased activity (indicated by the aperiodic intercept **(Pant et al., Under Review)**; BOLD activity (Raczy et al., 2023)) in CC individuals, which might require downregulation across different spatiotemporal scales to prevent runaway excitation (Isaacson & Scanziani, 2011). Under such an interpretation, the more spatially restricted fMRI and 20-40 Hz aperiodic slope[11] might reflect increased local neural firing following sight restoration in CC individuals; while the more spatially extensive measures of Glx/GABA+ concentration and the 1-20 Hz aperiodic slope[12] might reflect the commensurate decrease in E/I drive. Such homeostatic regulation of the E/I ratio might be useful when an animal's environment changes compared to the developmental environment (see Section 2.1). Non-human animal work has provided previous evidence for regulation of the E/I ratio by multiple mechanisms of neuroplasticity during and following development; periods of *decreased* excitatory signals via monocular deprivation in the adult mouse visual cortex resulted in an *increased* E/I drive to the deprived eye (Barnes et al., 2015). In fact, a recent model of homeostatic plasticity mechanisms predicted that periods of increased excitation might result in commensurate downregulation of the E/I ratio (Keck et al., 2017).

Interestingly, in CC individuals, visual cortex Glx concentration predicted a high amount of the variance in the aperiodic intercept in occipital channels during ambient and flickering visual stimulation (Figure 2.3) **(Pant et al., Under Review) (Appendix I).** No such correlation was documented in SC individuals. Such a qualitative difference in the relationship between the aperiodic intercept and Glx concentration in CC vs SC individuals, together with quantitatively increased aperiodic intercept, might reflect a more "immature" response of the visual cortex of CC individuals to incoming visual input. On the physiological level, it was shown in non-human animals that large amounts of spontaneous, noisy cortical activity at birth undergoes decorrelation/sparsification (Chini et al., 2022; Rochefort et al., 2009; Trägenap et al., 2023; Vinje & Gallant, 2000). Developmental "decorrelation" between neuronal responses was proposed to be driven by inhibitory development. It might be that in CC individuals, the absence of such developmental "decorrelation" is reflected by the qualitative and quantitative differences in the aperiodic offset from SC individuals.

[11] Higher frequencies have been associated with local, feedforward processing (Bastos et al., 2015; Maier et al., 2010; Van Kerkoerle et al., 2014).
[12] Lower frequences have been associated with processing in feedback, long-range networks (Clayton et al., 2018; Van Kerkoerle et al., 2014).

Nevertheless, aspects of visual cortex development appeared to be preserved in CC individuals: despite the overall increased aperiodic offset, the developmental decrease of the offset with chronological age, previously observed in SC individuals, was preserved in the visual cortex of CC individuals (Appendix I). This finding might suggest that the visual cortex of CC individuals underwent "typical" developmental processes, including the development of inhibitory circuity, but in an "atypical" environment. In this context, non-human animal models of lid suture, which maintain diffuse visual input but deprive animals of patterned vision, might be particularly applicable to the cataract model. Lid suture has been shown to result in sufficient permissive light activation to allow cortical maturation[13], but resulted in reduced neural selectivity, which did not improve after eye opening (Antonini & Stryker, 1998; White et al., 2001).

While these initial results from CB and CC individuals align with the hypothesis that the E/I ratio plays a role in human sensitive period plasticity, a longitudinal assessment of CC individuals' Glx/GABA+ ratios and EEG aperiodic slope, pre- and post-surgery, would be necessary to reconcile the differing metrics of E/I ratios. Additionally, testing individuals who became permanently blind in adulthood might provide further insight into whether the effects on visual cortex E/I ratio result from differing developmental vs. adult (visual) environments.

2.4.2 Anatomical evidence consistent with interrupted synaptic pruning linked to congenital visual deprivation.

It was repeatedly demonstrated that the visual cortex of CC individuals showed an increased cortical thickness compared to normally sighted controls (Feng et al., 2021; Guerreiro, Erfort, et al., 2015; Hölig et al., 2023). Increased cortical thickness in visual regions has previously been documented in permanently congenitally blind (CB) individuals (Aguirre et al., 2016; Bridge et al., 2009; Hasson et al., 2016; Jiang et al., 2009), suggesting that this structural change resulted from patterned visual deprivation at birth and did not reverse after sight restoration. The thicker visual cortex of CC and CB individuals was proposed to indicate an interruption of synaptic pruning in visual circuits (Jiang et al., 2009)[14]. Indeed, one of the documented effects of congenital visual deprivation in non-human

[13] By contrast, dark rearing has been proposed to result in the delayed or "arrested" maturational processes in the visual cortex which proceed following restoration but never reach the level of controls, as evidenced by prolonged sensitivity to visual input, e.g. monocular deprivation (Cynader, 1983; Mower et al., 1985; White et al., 2001).

[14] Note, however, that other mechanisms might also explain increased cortical thickness in CC and CB individuals; a decrease in myelination rather than an interruption of synaptic pruning might lead to the border between cortical and subcortical regions being altered on MRI T1 scans (Hölig et al., 2023; Natu et al., 2019). A recent study at 7T MRI did not find increased cortical thickness in CB individuals, instead reporting a decrease in both grey and white matter in the

primates was such interruption of synaptic pruning in the visual cortex (Bourgeois, 1996; Bourgeois et al., 2000). Crucial evidence from Hölig et al., (2023) suggested that increased visual cortical thickness correlated with worse visual acuity outcomes in CC individuals. Further, Pant et al demonstrated that poor visual acuity outcomes correlated with increased Glx/GABA+ ratios in the visual cortex of 10 CC individuals **(Pant et al., Under Review) (Appendix I),** suggesting a link between an altered E/I ratio in the visual cortex and reduced visual acuity. Together with the finding of a similar correlation between higher visual cortex Glx/GABA+ and worse visual acuity **(Pant et al., Under Review) (Appendix I),** this might indicate that increased physiological compensation (reflected by a lower Glx/GABA+ ratio) and reduced structural changes (reflected by a thinner visual cortex) correspond to better visual outcomes following congenital cataract removal surgery. It might be that in the absence of vision within a sensitive period, aberrant inhibitory transmission prevents the activity-guided synapse elimination, which typically takes place with age. In Section 3.4, the possible effects of such structural deficits on the functional level, particularly in corticocortical pathways, are further discussed.

2.4.3 Behavioral evidence consistent with altered inhibitory tuning in the visual cortex following congenital visual deprivation.

A consistent finding following the removal of dense congenital cataracts has been that if surgery is not performed within a few weeks from birth, patients suffered from a permanent reduction of visual acuity. In late (> 6 months of age) treated patients, although visual acuity and contrast sensitivity (Kalia et al., 2014; Maurer et al., 2006) improved after cataract removal surgery, it did not reach the level of age-matched controls. **Pant et al., (Under Review) (Appendix I)** linked deficits in visual acuity to E/I ratios in the visual cortex (see Section 2.4.2). Retinotopic mapping with 7 T fMRI has further shown that the deficits underlying poor visual acuity in CC individuals might be cortical; the population receptive field (pRF) and cortical magnification factor (CMF) in the visual cortex of 9 CC individuals correlated with the visual acuity (Heitmann et al., 2023). In non-human animal models, the proportion of inhibitory neurotransmission has been directly linked to neural response properties of the early visual cortex; for example, developmental increase in inhibition was

occipital cortex (Kupers et al., 2022). White the cortical thickness data might result from either or both effects, T1/T2 and T2* weighted imaging in high-field MRI might better distinguish the source of the structural changes by quantifying myelination in the visual cortex (see Section 4.3).

shown to modulate receptive field narrowing[15] with age (Fang et al., 2021; Tao & Poo, 2005), while increased GABAergic transmission via diazepam was shown to widen ocular dominance columns (Hensch & Stryker, 2004; Sale et al., 2010).

Among low-level visual functions, higher MRS quantified GABA+ has also been related to lower contrast detection thresholds in normally sighted individuals (Hammett et al., 2020; Ip et al., 2019). These authors suggested that GABAergic inhibition allowed for lower detection thresholds by noise suppression. Further, GABA concentrations have been linked to eye dominance in typically sighted adults (Ip et al., 2021). Given that binocular vision (Banks et al., 1975; Birch et al., 2009; Harwerth et al., 1990; Lewis & Maurer, 2009) and contrast sensitivity (Ellemberg et al., 1999) have been shown to be impaired in CC individuals, possible links to GABA+ concentration might be investigated in such patients. Further, concurrent investigation of behavioral/electrophysiological metrics of cortical inhibition, such as the effects of surround suppression (Angelucci & Bressloff, 2006), would allow further insight into whether deficient visual behavior might link with impaired cortical inhibition in CC individuals.

[15] Note that narrow receptive fields correspond to better visual acuity.

3. Recurrent processing in the human visual cortex following congenital visual deprivation

3.1 Background

In the visual pathway, light signals are transformed via photoreceptor cells and transmitted via the optic nerve to the lateral geniculate nucleus, and onward to the visual cortex. This direction of transmission is commonly referred to as "feedforward processing." Feedforward processing relies sequentially on the retinogeniculate and thalamocortical pathway. However, accurate visual perception requires the integration of multiple visual signals (eg: binding individual visual features into objects, faces, places) across space and time, as well as modulations from higher-order signals such as prior knowledge, expectations, and attention (Emberson, 2017; Gilbert & Li, 2013). Referred to as "feedback processing", such signaling has been shown to be reliant on intricate corticocortical and corticothalamic connectivity (Gilbert & Li, 2013) in primates (Felleman & Van Essen, 1991). Decades of neuroanatomical and physiological work has demonstrated the necessity of "top-down" or feedback signals for typical vision, even at the level of basic visual functions. The interaction between feedforward and feedback signals has been referred to as recurrent processing (Angelucci & Bressloff, 2006; Isaacson & Scanziani, 2011).

3.2 Experience-dependent development of corticocortical projections

The framework of activity-dependent molding of cortical circuits based on the environmental statistics been proposed several times (Buzsáki, 2006; Guidotti et al., 2015; Herrmann et al., 2016; Li et al., 2020; Pezzulo et al., 2021; Toyoizumi et al., 2013). Therefore, activity-directed development of corticocortical connectivity was proposed to be a structural process underlying sensitive period plasticity (Röder et al., 2021).

In studies of prospective development, corticocortical connectivity in visual regions has been shown to demonstrate a long trajectory, reliant on weeks of post-natal vision in ferrets (Khalil & Levitt, 2014) and months of post-natal vision in macaques (Barone et al., 1995; Batardière et al., 2002; Distler et al., 1996). Retrospective studies provided primary evidence for the dependence of visual corticocortical elaboration on visual experience. Prenatal enucleation resulted in an alteration of the hierarchical organization within the macaque visual cortex (Magrou et al., 2018), based on the

proportion of supragranular to infragranular neurons.[16] Additionally, as opposed to the regular "band-like" callosal pattern at the border of area 17/18 and extra striate cortex of the ferret, ill-defined patches of callosal cells were found after enucleation at postnatal day 7, but not 20 (Bock et al., 2012; Bock & Olavarria, 2011). The authors interpreted this finding as indicative of reduced precision of ferret callosal patterns due to postnatal visual deprivation within a sensitive period. As opposed to enucleation, postnatal lid suture in kittens allowed for the initial development of axonal arbors, but resulted in stunted growth and a lack of differentiation into columns in striate and extrastriate regions (Zufferey et al., 1999). Finally, dark rearing and lid suture both impacted the clustering and extent of horizontal connectivity in the ferret visual cortex (White et al., 2001). As corticocortical projections appeared to rely on visual experience for typical development, it was proposed that their altered structure and function might underlie persistent deficits following atypical development.

While (V1-V2) corticocortical connectivity in humans has directly been shown to become refined with age in retrograde tracer studies (Burkhalter, 1993; Burkhalter et al., 1993), most investigations of the development of corticocortical visual pathways in humans are indirect. Studies of prospective development have demonstrated that from early childhood to adulthood, perception and learning appeared to be more reliant on feedback, top-down than feedforward, bottom-up cues (Röder & Kekunnaya, 2021; Rohlf et al., 2017). It was suggested that with age and visual experience, increasing higher-order (corticocortical) influences on lower-level neural responses might result in such changes (Dehaene et al., 2010; Dekker et al., 2019; Emberson, 2017), predicting later development of corresponding physiological correlates. In normally sighted individuals, one such physiological correlate of feedback processing in the visual cortex is the alpha range (8-14 Hz) of the human EEG (Jensen & Mazaheri, 2010; Klimesch et al., 2007; Sauseng et al., 2011; Worden et al., 2000). Alpha oscillations have been repeatedly reported to increase in power with age, from 3 months to 21 years of age (Cellier et al., 2021a; Marshall et al., 2002), consistent with a predicted long developmental trajectory of the underlying neural assemblies. Additionally, the latency of the P1 visual event-related potential shifted from 260 ms in neonates to about 100 ms within the first six months of life (McCulloch et al., 1999). This shift has been thought to indicate the development of the visual cortex pathway, as the P1 has been associated with extrastriate neural generators (Clark et al., 1994). Finally, population receptive field (pRF) mapping between the ages of 5-26 years has shown that while

[16] The percentage of Supragranular Labeled Neurons (SLN) provided an index of hierarchical distance based on the principle that supragranular neurons predominantly terminate in Layer IV and project feedforward, while infragranular neurons terminate outside of layer IV and project feedback (Markov et al., 2014; Vezoli et al., 2021).

retinotopic maps in early visual regions were defined by the age of 5 (Dekker et al., 2019; Gomez et al., 2018, 2019), "higher" visual regions along the ventral and lateral stream increased their representation of foveal eccentricities with age (Gomez et al., 2018, 2019).

3.3 Altered correlates of recurrent processing following congenital visual deprivation

It was hypothesized that correlates of feedback processes, which rely on intact corticocortical circuits, might be more affected by aberrant visual experience than correlates of processes which are more reliant on feedforward, thalamocortical circuits (Kral et al., 2017; Röder et al., 2021). A repeatedly documented finding from CC individuals was a reduction in alpha (8-14 Hz) oscillatory power (Bottari et al., 2016, 2018; Ossandón et al., 2023; **Pant et al., 2023**). Alpha power was found to be lower in a larger group of CC individuals compared to individuals treated for developmental cataracts (DC) and SC individuals at rest (Ossandón et al., 2023), as well as during biological (Bottari et al., 2015) and global motion tasks (Bottari et al., 2016). Reduction in alpha power was found in congenitally blind individuals at rest as well (Novikova, 1974; Ossandón et al., 2023) and during somatosensory tasks (Kriegseis et al., 2006). Given the previously evidenced link between alpha oscillations and feedback processing (Klimesch et al., 2007; Sauseng et al., 2011; Worden et al., 2000), reduced alpha power following transient congenital visual deprivation was interpreted as an indication of reduced integrity of the underlying corticocortical feedback pathways in the visual cortex (Bottari et al., 2016; Ossandón et al., 2023; Pant et al., 2023).

A recent **(Pant et al., 2023) (Appendix II)** study tested the prediction that impaired feedback processing resulting from a phase of congenital blindness result in an impaired interaction of feedback and restored feedforward signals (Kral et al., 2017; Röder & Kekunnaya, 2021; Yusuf et al., 2022). The characteristic evoked alpha "resonance" effect has been used as an indirect measure to assess the interaction between feedforward and feedback processing in the alpha range of typically sighted individuals; wherein it was found that on stimulation with visual white noise, there was a selective increase in alpha power in the occipital channels (Herrmann, 2001; Vanrullen & MacDonald, 2012). **Pant et al., (2023) (Appendix II)** adapted the paradigm from VanRullen and MacDonald (2012) and tested 13 CC individuals and 13 age-matched SC individuals who observed visual "white-noise" (1-30 Hz). CC individuals showed a lower likelihood of demonstrating significant stimulus-evoked alpha activity. On average, stimulus-evoked alpha oscillations were found to be reduced in amplitude in CC vs SC individuals' occipital channels **(Pant et al., 2023)** (Figure 2.1). Resting-state alpha oscillations were also found to be reduced in these CC compared to SC individuals, regardless of eye closure.

Further, CC individuals with lower resting-state alpha amplitude were more likely to demonstrate a lower stimulus-evoked alpha amplitude, indicating a link between the two phenomena. Crucially, 8/13 CC individuals who demonstrated above-threshold stimulus-evoked alpha activity also demonstrated better visual acuity outcomes than 5/13 CC individuals who did not demonstrate such activity **(Pant et al., 2023)** (Figure 2.1).

Together, this linked reduction in stimulus-evoked and resting-state alpha power results suggest altered feedback signaling in the visual cortex corresponding to congenital visual deprivation, which does not reverse after sight restoration. Therefore, both prospective (i.e. increase in alpha power with postnatal visual experience (Cellier et al., 2021b; Marshall et al., 2002)) and retrospective evidence (i.e. impairment of alpha oscillations in the absence of typical vision), strongly suggest that the neural assemblies underlying alpha oscillations develop within a sensitive period. However, it was noted that deficits in alpha oscillations appeared to be worse in some CC individuals than others, uncorrelated to duration of blindness or time since surgery, necessitating an account of what factors might result in the partial or task-specific recovery.

The predicted consequences of altered corticocortical circuitry include greater deficits downstream in the visual pathway (Röder & Kekunnaya, 2021). Findings from neuroimaging correlates of hierarchical visual processing indeed suggested such a pattern of deficits in CC individuals (Pitchaimuthu et al., 2021; Sourav et al., 2018). The first of these studies investigated the C1 event-related potential, i.e. the earliest visual event- event related potential, which has been linked to striate processing in humans (Sourav et al., 2018, 2020). The C1 potential did not differ in amplitude between SC and CC individuals, suggesting that striate processing in humans might not be altered by congenital patterned visual deprivation. However, the P1, which is the event potential associated with extrastriate processing, was reduced in CC compared to SC individuals (Sourav et al., 2018, 2020). Similarly, the first harmonic of the steady-state visual-evoked response (SSVEP), associate with early visual processing, was of equal amplitude in CC, DC and SC individuals (Pitchaimuthu et al., 2021). By contrast, the amplitude of the second harmonic of the SSVEP, which has been linked to higher-order visual processing, was lower in CC individuals (Pitchaimuthu et al., 2021). Crucially, the intermodulation frequency response, which was proposed to arise from the visual system integrating flickering and lateral motion, was impaired in CC individuals. Given that such integration of multiple visual signals requires corticocortical communication, lower intermodulation responses might correspond to deficits in integration across multiple visual circuits in CC individuals.

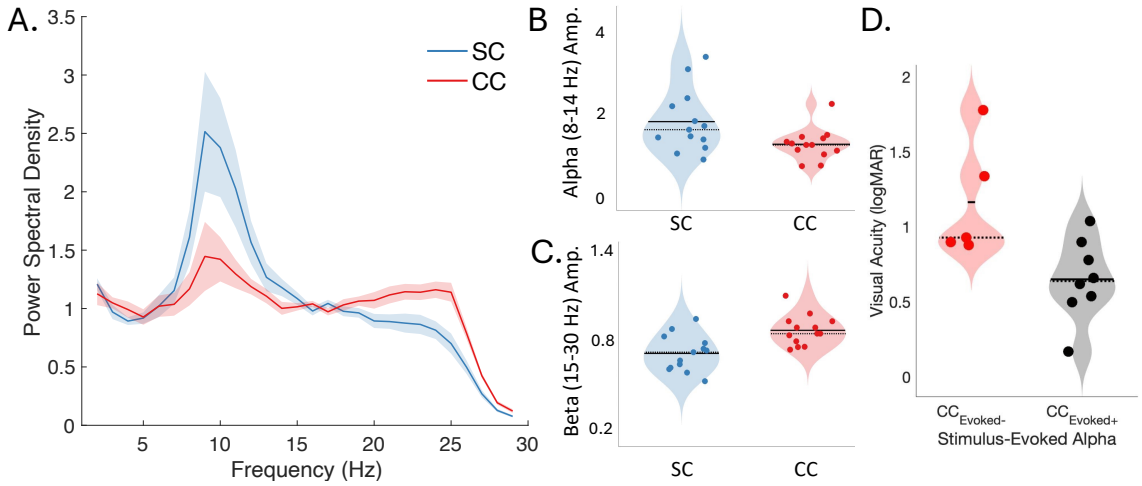


Figure 3.1. Stimulus-evoked oscillatory activity in congenital cataract-reversal individuals. A. The average spectrum of cross-correlation functions between presented white-noise luminance sequences and occipital EEG activity across all congenital cataract-reversal (CC, red) and normally sighted control (SC, blue) participants. The shaded region represents standard error of the mean. B,C. Violin plots displaying the average evoked alpha (B) and beta (C) amplitude in SC (blue) and CC (red) individuals. Solid lines indicate the mean values and dotted lines indicate median values in each group. D. Violin plots depict the visual acuity in logMAR units in the CC group divided into subgroups with (black) and without (red) an above-threshold stimulus-evoked alpha peak ($CC_{Evoked+}$, $CC_{Evoked-}$). Figure and caption reproduced from Pant et al., 2023 (Appendix II).

A strong line of evidence suggesting corticocortical reorganization in the absence of early visual experience comes from studies of resting state functional connectivity (RSFC).[17] Multiple studies showed that long-range functional connectivity between the visual and frontal/parietal cortex was increased in CB compared to SC individuals (Bedny et al., 2010; Burton et al., 2014; Deen et al., 2015; Hirsch et al., 2015; Kanjlia et al., 2016, 2018), while RSFC between visual and non-visual sensory cortices was decreased in CB vs SC individuals (Burton et al., 2014; Liu et al., 2007). However, a reduction of RSFC between visual and non-visual sensory cortices in CB vs SC individuals seems to only exist if SC individuals are measured with eyes closed (Guerreiro et al., 2021). Simultaneously, one study measuring RSFC between MT/MST and other retinotopic visual areas found that such within-visual cortex functional connectivity was decreased in CB vs SC individuals (Bedny et al., 2010), which was replicated independent of eye closure (Guerreiro et al., 2021). Recent RSFC evidence from CB individuals has suggested that their secondary visual cortices were more similar to normally sighted infants than sighted adults, i.e. strongly connected to frontoparietal regions rather than other

[17] Via correlated fluctuations of BOLD activity between seed regions and target regions during rest, inferences of frequent co-activation, and therefore connectivity, are made between the two regions.

sensory/motor cortices (Tian et al., 2024). These findings were used to argue that the establishment of top-down connectivity between the frontal and visual cortex requires visual experience in infants, likely within a sensitive period (Tian et al., 2024). Crucially, the increased RSFC between frontal/temporal and visual regions was also documented in one study investigating CC individuals operated upon within the first year of life (Feng et al., 2021), albeit to a lower extent than shown in CB individuals.

Another line of evidence consistent with corticocortical alterations in the visual cortex of CC individuals comes from investigations of category selectivity in the ventral visual cortex. Category selectivity in the ventral visual cortex of normally sighted individuals is thought to arise from corticocortical connectivity (Dehaene & Dehaene-Lambertz, 2016; Osher et al., 2016; Saygin et al., 2016). Such corticocortical connectivity was directly shown to be refined via experience in non-human primates (Arcaro & Livingstone, 2021) and indirectly in CC individuals (Feng et al., 2021). Further, an EEG study investigating the N170 response, a negative event-related potential, showed face-specific enhancement in SC and DC but not CC individuals, suggesting underlying impairments in face processing in CC individuals (Röder et al., 2013). These physiological data have been further supported by reduced behavioral performance in CC individuals' face processing behavior (reviewed in Section 2.4.3). Notably, despite three years of visual experience, one sight-recovered individual who became blind at the age of three years[18] did not show category selectivity in the ventral visual cortex in an fMRI study, despite preserved object selectivity in the lateral occipital complex (Huber et al., 2015). Reduced stimulus-selectivity might suggest a lack of the visual-experience dependent refinement of underlying corticocortical connections that allow such responses in SC individuals (Feng et al., 2021).

In parallel, corticocortical reorganization is thought to underlie the widely-documented cross-modal plasticity in congenital blindness (Bedny, 2017; Collignon et al., 2013; Hirsch et al., 2015; Klinge et al., 2010; Noppeney, 2007) (see Section 3.4.2 on structural changes in blindness). Under this assumption, persistent cross-modal influences in CC individuals might suggest that corticocortical reorganization attributable to the absence of visual experience does not reverse when thalamocortical visual signals are restored. Indeed, responses to auditory motion stimuli in visual-motion-responsive regions MT/MST, which have been demonstrated in congenitally blind individuals (Bedny et al.,

[18] Participant M.M., who was not congenitally blind prior to sight recovery, as his blindness followed a chemical accident at 3 years of age. His vision was restored via a stem-cell procedure after 40 years of blindness.

2010), were reported in one sight recovery participant (Saenz et al., 2008)[19]. Further, an fMRI study using auditory, visual and audio-visual speech stimuli demonstrated a lack of typical cortical signatures of multisensory integration in CC individuals: an enhanced response to audio-visual compared to auditory or visual stimulation was not seen in the STS, and an atypical suppression of audio-visual compared to visual responses was observed in the visual cortex, in the same study (Guerreiro, Putzar, et al., 2015). The authors suggested that restored visual input might interfere with auditory (presumably cross-modal) signals in the visual cortex (de Heering et al., 2016; Guerreiro, Putzar, et al., 2015; Putzar, Goerendt, et al., 2007) (see Section 3.4.3).

However, an account of alterations in correlates of corticocortical processing following congenital visual deprivation requires reconciliation with findings of partial recovery. Concomitant with the evidence for altered corticocortical processing following congenital visual deprivation, certain aspects appeared to be preserved in the CC visual cortex. In Pant et al. (2023, Appendix II), while 5/13 CC individuals did not show above-threshold stimulus-evoked alpha oscillations, the other 8/13 individuals did demonstrate recovery of stimulus-evoked alpha activity, consistent with preservation or recovery of the underlying circuits. Given that the presence vs. absence of above-threshold stimulus-evoked alpha oscillations additionally predicted better visual acuity, it might be inferred that greater alteration of underlying feedback circuits corresponds to worse visual outcomes when sight is restored. One previous fMRI study directly investigated feedback processing by measuring the effect of task relevance in CC individuals' responses to moving face stimuli (Guerreiro et al., 2022). They found that face-selective FFA responses and motion-selective hMT+ responses in CC individuals increased to the level of SC individuals when the stimuli were task relevant. However, FFA and hMT+ responses were lowered in CC compared to SC individuals when stimuli were task irrelevant. Therefore, this study concluded that top-down modulation of neural activity at least partly in these areas seemed to have recovered in CC individuals (Guerreiro et al., 2022). Finally, EEG responses to biological motion processing (along with behavioral responses, see Section 3.4.3) appeared to be intact in CC individuals (Bottari et al., 2015). Longitudinal assessment of resting-state alpha activity in CC individuals pre- and post- surgery might help disentangle whether such findings are the result of preservation despite the absence of patterned vision, or recovery following sight restoration. The

[19] Saenz et al (2008) tested one participant (M.S.) who was congenitally blind prior to cataract removal in one eye at age 43 (acuity 20/400), and diagnosed with retinopathy of prematurity in the other eye. This study also tested participant M.M. (see footnote 18).

principles governing which aspects of feedback processing remain intact and which aspects suffer permanent impairment from congenital visual deprivation remain an area of active enquiry.

One hypothesis on the representational level suggested that top-down, generative "priors" might be carried by spontaneous activity in the brain (Alamia & VanRullen, 2019; Buzsáki, 2006; Fiser et al., 2010; Friston, 2005; Trägenap et al., 2023), providing a "scaffold" for stimulus-evoked processing. Several researchers have speculated that experience refines such priors (Guidotti et al., 2015; C. M. Lewis et al., 2009). In this context, partial recovery of resting-state (Ossandón et al., 2023; Pant et al., 2023; Raczy et al., 2022) and stimulus-evoked activity in CC individuals might reflect that in the absence of visual experience, specific "priors" which rely on the visual modality are disrupted.

3.4 Anatomical evidence for altered corticocortical circuitry due to congenital visual deprivation.

A recent study directly tested corticocortical connectivity after congenital visual deprivation by investigating white-matter tracts in CC children[20] (Pedersini et al., 2023). No changes in white matter integrity in the optic radiation and the optic tract were found following cataract surgery. This absence of structural changes following sight restoration was interpreted as resulting from the closure of the sensitive period for the early visual cortex. By contrast, three white matter pathways which project to the visual cortex (superior longitudinal fasciculus (SLF)[21], inferior fronto-occipital fasciculus (IFOF)[22], and inferior longitudinal fasciculus (ILF)[23]) demonstrated significantly increased fractional anisotropy following cataract removal surgery. Further, the posterior callosum forceps[24] showed a significantly lower mean diffusivity as a function of time since surgery. As increased fractional anisotropy and reduced mean diffusivity are thought to indicate increased structural integrity of these tracts, Pedersini et al. interpreted their findings to result from plasticity following sight restoration.

These results from CC individuals conform to some structural changes observed in the corticocortical pathways of CB individuals. Ptito et al reported increased white matter volume in the SLF and IFOF, i.e. between frontal and occipital cortex; and simultaneously, white matter atrophy in the ILF, splenium of the corpus callosum, optic tract and optic radiations (Ptito et al., 2008). One other study additionally reported reduced integrity of the splenium (Tomaiuolo et al., 2014), suggesting

[20] Participants aged 6-16 years were tested pre- and post- operatively, with data from 4-11 visits per participant.
[21] White matter tract which connects the frontal, occipital, parietal, and temporal lobes
[22] White matter tract which passes backward from the frontal lobe into the occipital and temporal lobe
[23] White matter tract which connects the occipital and temporal lobe
[24] Callosal white matter bundle that connects the occipital lobes across hemispheres

that inter-hemispheric communication in the occipital cortex is reduced in CB individuals. Crucially, as several studies have documented atrophy of thalamocortical tracts in CB individuals (Noppeney, 2007; Ptito et al., 2008; Shimony et al., 2006), these data support the argument that corticocortical projections (particularly from the frontal cortex) might be the source of cross-modal changes during blindness (Bedny, 2017).[25] In the context of sight recovery and Pedersini et al's findings, along with the physiological findings outlined in Section 3.4.1, the extent of reversal of these structural differences might determine the extent of visual recovery, or conversely, persistent cross-modal influences in behavior (Section 3.4.1).

However, it is yet to be directly assessed whether alterations in tracts would be seen to the same extent in a large sample of pre-surgery CC adults, as in the aforementioned studies with CB individuals with diverse aetiology, including Retinopathy of Prematurity or Anophthalmia.[26] Individuals born blind due to dense congenital cataracts retain spontaneous activity, retinal waves and diffuse light perception during their phase of blindness. It is relevant to note that non-human animal work suggested a permissive role for patterned vision to allow for the elaboration of corticocortical pathways; light perception was sufficient for the initial growth of axonal arbors in the visual cortex (White et al., 2001; Zufferey et al., 1999), nevertheless, the specificity and extent of these connections was reduced.

3.5 Low- and high-level perceptual deficits following congenital visual deprivation

3.5.1 Visual perception following congenital visual deprivation.

It was proposed that the visual functions with longer developmental trajectories might be the most susceptible to damage due to congenital visual deprivation (Maurer & Hensch, 2012; Röder & Kekunnaya, 2021, 2022). Given the evidence for greater deficits in feedback than feedforward pathways in CC individuals (see Section 3.4.1), such a hypothesis would predict that more complex, "top-down" reliant visual behaviors might be more likely to be impaired in CC individuals. Below, selected behavioral findings are briefly reviewed in the context of this hypothesis.

[25] Note, however, that fMRI and TMS findings have also implicated corticocortical connections between other primary sensory cortices and visual cortex as the source of cross-modal plasticity in congenital blindness (Klinge et al., 2010; Wittenberg et al., 2004), see (Bedny, 2017).

[26] Ptito et al (2008) tested 1/11 and Tomaiuolo et al (2014) tested 3/28 participants born with dense congenital cataracts in their sample.

Along with reduced logMAR visual acuity following surgery (Section 2.4.3), behavioral deficits in CC individuals appeared for high (> 2 cpd)[27] spatial and low (5 and 10 Hz) temporal frequencies (Ellemberg et al., 1999). Even years after surgery, CC patients treated during infancy could not see spatial frequencies of 10-20 cpd (Maurer et al., 2007). Nevertheless, despite such low-level visual deficits, CC individuals appeared to be able to complete tasks such as 2-D shape recognition (McKyton et al., 2015), object recognition (Ossandón et al., 2022) or face identification (Maurer et al., 2007). These findings suggest at least a partial recovery of visual behavior post-surgery in CC individuals, which has been established as a benefit of undergoing surgery, even late in life.

However, results from CC individuals suggest that while their visual system seems able to detect independent visual signals, the ability to integrate multiple visual signals into a single percept remains impaired (Putzar, Hötting, et al., 2007). CC individuals showed reduced performance compared to SC individuals on tasks involving the incorporation of mid- to high-level visual features, such as 3-D depth perception from shading (McKyton et al., 2015), perception of illusory contours (McKyton et al., 2015; Putzar, Hötting, et al., 2007), and perception of global motion amongst moving random dots (Bottari et al., 2018; Rajendran et al., 2020). Further, studies of face processing found that while CC individuals performed the same as controls at identifying the same person in forward facing face images (Maurer et al., 2007), they were significantly worse than controls when detecting the same face after manipulations of viewing angle (Heering et al., 2016; Putzar, Hötting, et al., 2010), lighting conditions (Putzar, Hötting, et al., 2010), and feature configuration (eg: altered spacing between the nose and mouth) (Le Grand et al., 2001). Such deficits cannot be explained solely from lower visual acuity. Indeed, CC individuals showed worse performance on coherent motion detection tasks than SC individuals (Bottari et al., 2018; Hadad et al., 2012), even when SC individuals' acuity was artificially reduced using Bangerter filters (Rajendran et al., 2020).

An exception in this pattern of increasing behavioral deficits with stimulus complexity is biological motion perception. When controlled for visual acuity, CC individuals were able to identify biological actions to the same behavioral performance levels as SC individuals (Rajendran et al., 2020). In stark contrast to face processing, CC individuals' performance level in biological motion perception stayed the same even when stimuli were viewed from different angles. This lack of experience-

[27] Cycles per degree (CPD) measures the spatial frequency resolution of the visual system in terms of the number of cycles (black-white pairs) that can be distinguished in one degree of visual angle, while logMAR measures the smallest discernible detail using character/symbol tests, expressed as the logarithm of the angle subtended by the character/symbol. While both are related to visual acuity, they quantify different aspects of vision and are not directly interchangeable.

dependence specific to biological motion perception was proposed to result from the privileged status of such perception with regards to an organism's survival (Bottari et al., 2015; Rajendran et al., 2020; Troje & Westhoff, 2006).

3.5.2 Multisensory behavior following congenital visual deprivation.

Peripheral input from the visual system has been shown to play a crucial role in the development of multisensory regions, and therefore, multisensory behavior (Lewkowicz & Röder, 2015). As detailed in Section 3.4.3, visual behavior deficits following sight recovery in CC individuals were shown to go beyond those expected from low visual acuity and extend to higher visual functions. Below, multisensory findings in CC individuals are briefly discussed to assess whether they might show a pattern of deficits along the processing hierarchy.

First, multisensory integration of simultaneous cues in the visuo-haptic as well as audio-visual modalities appeared preserved in CC individuals. In a simple audio-visual detection task, CC individuals showed multisensory facilitation to the same extent as SC individuals (de Heering et al., 2016; Putzar et al., 2012). Additionally, a robust illusion that result from integration of simultaneous visuo-haptic cues, the size-weight illusion, appeared to be identical between CC, DC and SC individuals **(Pant et al., 2021) (Appendix III, Figure 3.2)**. Pant et al (2021) further confirmed that CC individuals indeed made use of visual cues for size estimation; the SWI was identical between CC and SC individuals even when handling the weights with an attached a string, thereby eliminating haptic cues of size (Figure 3.2). This finding was replicated in a separate sample of CC individuals (Piller et al., 2023), and it was longitudinally observed that while CC participants did not optimally integrate visuo-haptic size cues immediately after surgery, they developed the ability to do so within 4-12 months of surgery (Senna et al., 2021). On one hand, this finding might be unsurprising considering congenitally blind individuals tested in Pant et al (2021, Appendix III) as well as earlier work (Ellis & Lederman, 1993) showed a full-sized SWI, and that visuo-haptic transfer appeared to recover soon after sight restoration (J. Chen et al., 2016; Held et al., 2011). On the other hand, given prospective evidence that visuo-haptic development follows a long developmental trajectory (Gori et al., 2008), it might be considered surprising that the absence or degradation of visual input within this period did not impair the SWI. Finally, the ventriloquism effect, a robust illusion resulting from integration of simultaneous audio-visual cues, was also preserved in both CC and DC individuals (Bruns et al., 2022).

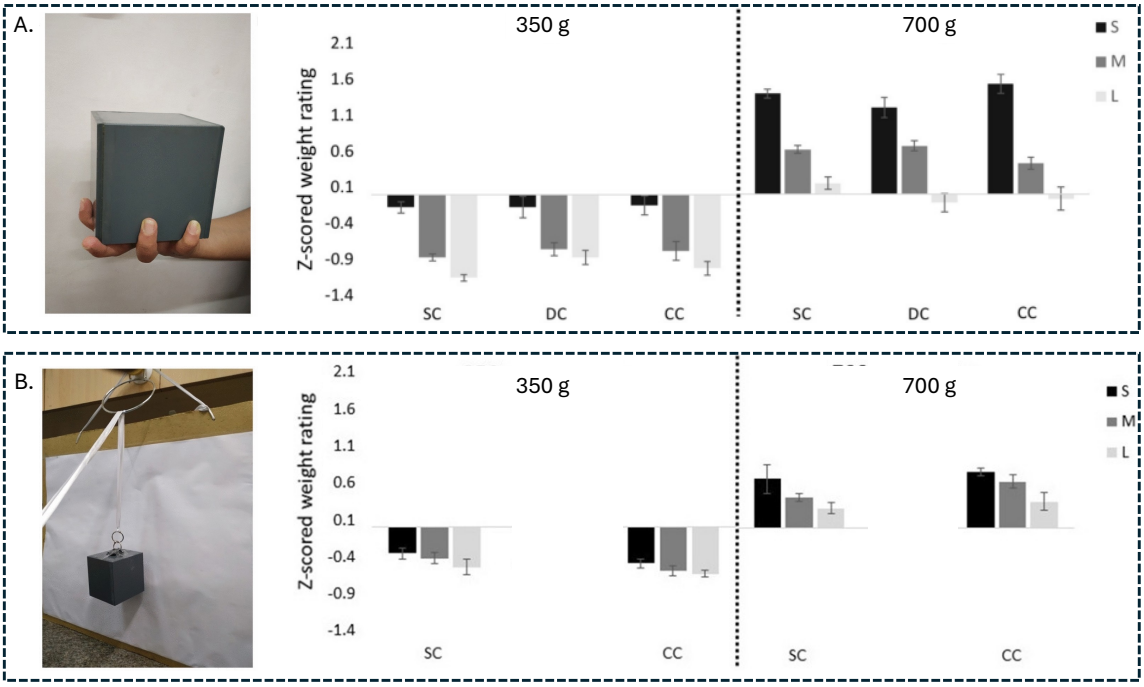


Figure 3.2. The size-weight illusion following transient visual deprivation. A. (Left) Set-up and (right) average z-scored weight ratings from the visuo-haptic condition of the experiment testing the Size-Weight-Illusion are displayed. Z-scored weight ratings were averaged for the Small (S), Medium (M) and Large (L) cubes across the typically sighted Control (SC), developmental cataract reversal (DC) and congenital cataract reversal (CC) groups, separately for the 350 g and 700 g weights. Error bars depict standard error of mean (SEM). B. (Left) Experimental setup and (right) average z-scored weight ratings for the visual-only condition of experiment testing the Size-Weight Illusion are displayed. Z-scored weight ratings were averaged for the Small (S), Medium (M) and Large (L) cubes across the typically sighted Control (SC) and congenital cataract reversal (CC) groups, separately for the 350 g and 700 g weights. Error bars depict SEM. Figure and caption reproduced from **Pant et al. (2021), (Appendix III).**

However, the integration of cross-modal cues further separated in space and time appeared to be altered in CC individuals. One study tested the audio-visual capture effect, wherein auditory and visual stimuli are presented with a short temporal offset with respect to each other, causing the visual stimulus to be perceived as temporally shifted towards the sound (Putzar, Goerendt, et al., 2007). CC individuals showed a reduced auditory capture effect, which was surprising considering their reduced vision might have caused them to rely more on auditory cues. The authors interpreted this finding as evidence of impaired multisensory binding processes in CC individuals. Indeed, despite exhibiting an intact spatial ventriloquism effect, CC individuals tested by Bruns et al. (2022) recalibrated visual localization based on exposure to consistently spaced audiovisual stimuli (ventriloquism after-effect) to a greater extent than DC and SC individuals (Bruns et al., 2022).

In addition to integrating stimuli, sequential multisensory interactions that did not require binding differed between SC and CC individuals. A greater attentional reliance on audition in CC than SC individuals was found while task switching: CC individuals were slower than SC individuals at switching from auditory to visual tasks, but not from visual to auditory tasks (de Heering et al., 2016). Second, when tested on temporal order judgement (TOJ, described in Section 3.2), CC individuals demonstrated a reversal of the typical audio-visual or visuo-tactile TOJ biases observed in SC individuals (Badde et al., 2020). CC individuals perceived visual stimuli as occurring earlier than tactile or auditory stimuli and demonstrated a lower accuracy in the visual and cross-modal TOJ tasks than DC or SC groups. These deficits were specific to visual cues, as CC individuals performed indistinguishably from DC and SC individuals on tactile and auditory (but not visual) TOJ.

Based on these findings, it was proposed that deficits with more complex multisensory stimuli, i.e. integrated based on features other than stimulus onset, might be impaired in CC individuals (Badde et al., 2020), due to their longer developmental trajectory (Lewkowicz & Röder, 2015). In line with this proposal, CC individuals showed worse performance than SC individuals even on concurrently presented audio-visual integration tasks when they included higher cognitive components, such in the context of speech. First, CC individuals demonstrated a reduced susceptibility to the McGurk effect, which could not be explained by reduced lip reading abilities (Putzar, Hötting, et al., 2010). Second, CC individuals demonstrated no multisensory facilitation in speech perception compared to SC individuals (Putzar, Goerendt, et al., 2007).

3.5.2 Neural underpinnings of multisensory behavior following sight recovery.

An absence of evidence of differences between CC and SC individuals on certain multisensory behaviors is not unequivocal evidence of an absence of differences in, for example, visuo-haptic integration **(Pant et al., 2021)**, particularly on a neural level. David Marr proposed that on an implementational level, differing routes might be taken to achieve the same computation (Marr, 1982). Oculomotor control in CC individuals might be considered an example of an implementational difference. Eye movements differ between CC and SC individuals, to the extent that nystagmus has been a diagnostic criterion for congenital cataracts. It nevertheless appeared that CC individuals employed identical visual exploration strategies to nystagmus controls, DC and SC individuals while performing an object detection task (Ossandón et al., 2022; Zerr et al., 2020). CC individuals accounted for nystagmus jerks, and appeared to make use of working memory information for task completion to the same extent as control groups (Ossandón et al., 2022).

Such findings add a further caveat to an interpretation of identical responses in cross-sectional studies of CC and SC individuals: rather than recovery of the "same" underlying processing as SC individuals, indistinguishable behavioral outcomes in CC individuals following surgery might be a result of alternate pathways or strategies adopted during a phase of blindness (Röder, 2001). Neuroimaging work investigating multisensory integration in CC individuals would be necessary to shed light on such pathways (Putzar, Goerendt, et al., 2010; Sourav et al., 2024).

2.6 Linking excitatory/inhibitory neurotransmission and neuronal oscillations following sight recovery in humans.

Studies of rodent development have linked the development of corticocortical connectivity to the increase in inhibition (Toyoizumi et al., 2013; Vogels et al., 2011) and proposed a modulatory role for the E/I balance in the formation of neural networks (Isaacson & Scanziani, 2011; Sadeh & Clopath, 2021). Accounts of the functioning of typical neuronal assemblies have proposed that feedforward and feedback inhibition within a population of neurons "paces" characteristic oscillatory activity (Buzsáki, 2006; Isaacson & Scanziani, 2011). The high and low excitatory phases of oscillations have been thought to accordingly align or modify incoming signals (Jensen et al., 2012). Specifically, the transmission of excitatory signals have been linked to higher frequency oscillations (Bastos et al., 2015; Van Kerkoerle et al., 2014). It was noted that the beta (15-30 Hz) range of the stimulus-evoked EEG spectrum was increased in power in CC vs SC individuals (Figure 2.1)[28]. Together with the reduction in stimulus-evoked alpha power **(Pant et al., 2023) (Appendix II),** this finding suggests that in CC individuals' EEG spectra, power is increased in the higher and decreased in lower frequencies during visual stimulation. In conjunction with the findings detailed in Section 2.4.1, the shift in power towards higher frequencies in CC individuals might be consistent with increased feedforward excitation.

As detailed in Section 3.2, EEG findings of increased alpha power corresponding to unattended stimuli have suggested that functional (feedback) inhibition might be reflected in alpha oscillations (Banerjee et al., 2011; Händel et al., 2011; Jensen & Mazaheri, 2010; Worden et al., 2000). In typically sighted humans, a negative relationship between MEG assessed alpha oscillatory power and pharmacologically upregulated[29] GABAergic function has been demonstrated (Lozano-Soldevilla et al., 2014), with a simultaneous increase in gamma power. Given that alpha power was reduced in

[28] The stimulation range (1-30 Hz) in Pant et al., 2023 did not allow for investigation of gamma frequencies
[29] Via administration of Lorazepam, a benzodiazepine known to enhance GABA conductance

CC individuals across conditions (Bottari et al., 2016; Ossandón et al., 2023; Pant et al., 2023), and that CC individuals were found to show lower Glx/GABA+ concentrations in the visual cortex **(Pant et al., Under Review),** the correlational link between inhibitory/excitatory neurotransmission and oscillatory dynamics was exploratorily assessed in 10 CC individuals. After correcting for the aperiodic component of CC individuals' EEG response, alpha power measured during visual stimulation correlated positively with Glx concentration during eye opening (Figure 3.3). Further, alpha power during eye closure was predicted by GABA+ concentration measured while CC individuals' eyes were closed (Figure 3.3). No such correlation was found for normally sighted individuals **(Pant et al., Under Review).**

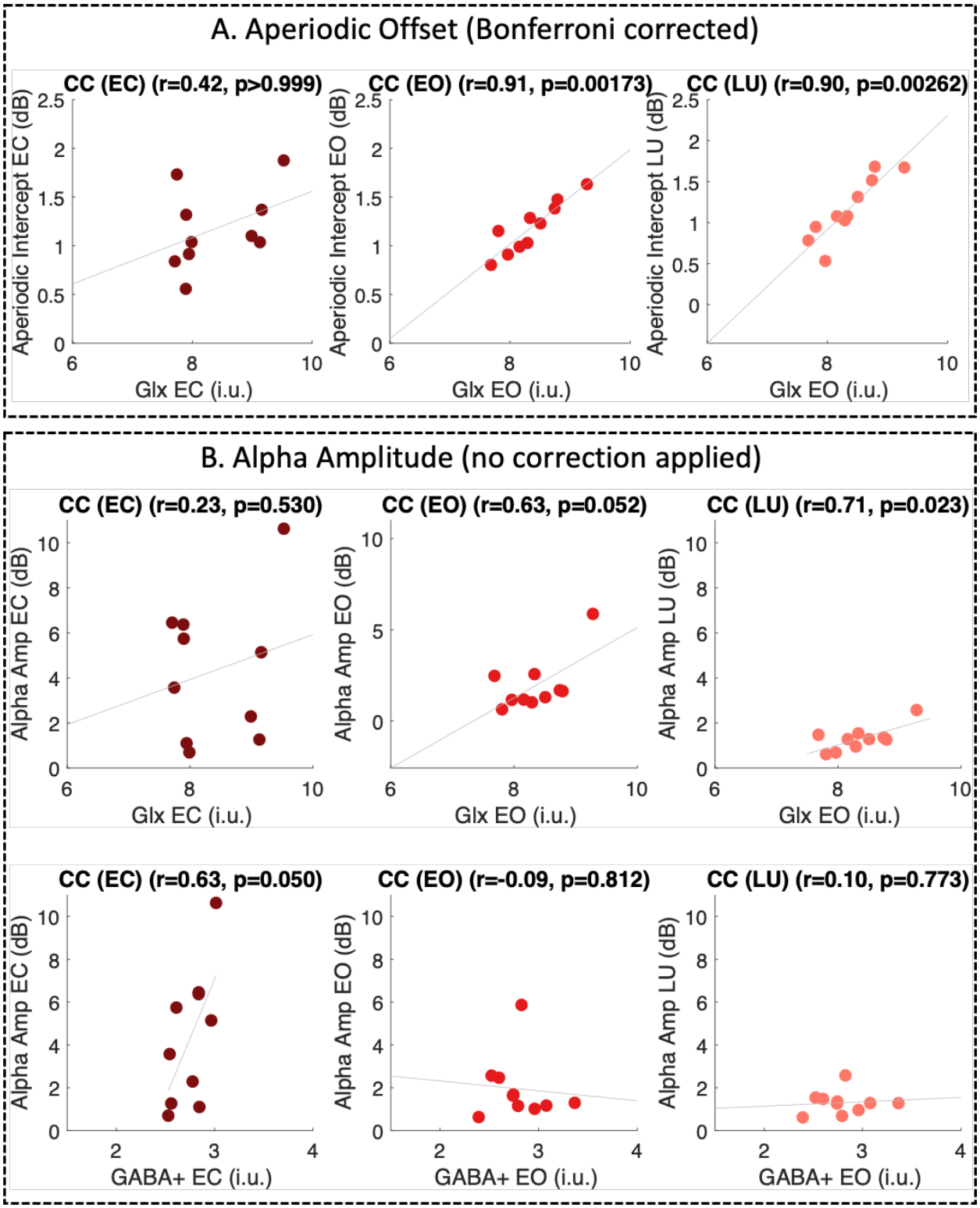


Figure 3.3. Correlation between neurotransmitter concentrations and electroencephalography (EEG) measures in congenital cataract-reversal individuals. A. Correlations for the CC group are displayed between aperiodic intercept measured across occipital electrodes in the eyes closed (EC, left), eyes open (EO, middle) and visual stimulation (LU, right) conditions, and the visual cortex Glutamate/Glutamine (Glx) concentration measured in the eyes closed (right) and eyes open (middle,

left) conditions respectively. Displayed p-values are Bonferroni corrected as described in Appendix I. B. (Top Row) Correlations for the CC group are displayed between alpha amplitude measured across occipital electrodes in the eyes closed (EC, left), eyes open (EO, middle) and visual stimulation (LU, right) conditions, and the visual cortex Glx concentration measured in the eyes closed (right) and eyes open (middle, left) conditions respectively. (Bottom Row) Correlations for the CC group are displayed between aperiodic intercept measured across occipital electrodes in the eyes closed (EC, left), eyes open (EO, middle) and visual stimulation (LU, right) conditions, and the visual cortex Gamma Aminobutyric Acid (GABA+) concentration measured in the eyes closed (right) and eyes open (middle, left) conditions respectively. All correlation p-values are exploratorily presented without correction for multiple comparisons. Figure and caption reproduced from Pant et al. (Under Review) (Appendix I).

As these effects were not corrected for multiple comparisons applied in Study I, and were not previously hypothesized, they undeniably require further assessment in a larger group. Nevertheless, the direction of the correlation between alpha power with GABA+/Glx concentration is reminiscent of the positive relationship between Glx and the aperiodic offset during passive and active stimulation (Figure 3.3, Section 2.4.1, **Appendix I**), in that it showed a correlation in CC but not SC individuals. Further, the correlation between alpha amplitude measured during active visual stimulation with Glx at eye opening, and GABA+ at eye closure, i.e., in the absence of visual stimulation, is in the direction expected from the excitatory and inhibitory role of Glx and GABA+ respectively. This effect, if replicated in a larger sample, might suggest that disrupted feedback signaling correlated with an alteration in the E/I dynamics of the visual cortex of CC individuals. Therefore, when vision is restored, not only do the measured alpha oscillations remain quantitatively lowered (Bottari et al., 2016; Ossandón et al., 2023; Pant et al., 2023), but neuronal firing might remain qualitatively "unsynchronized" to incoming visual stimulation (Jensen & Mazaheri, 2010; Zoefel & VanRullen, 2017). Note that while models based on non-human animal have proposed mechanisms by which the link between E/I dynamics and the elaboration of recurrent circuitry might be causal, correlations in neuroimaging work do not provide causal evidence.

4. Implications of findings from the congenital cataract-reversal model

4.1 Implications for visual rehabilitation

The observed changes in neurotransmitter concentrations, resting-state, and task-based aperiodic EEG activity suggested an alteration of the visual cortex E/I ratio attributable to a phase of congenital blindness. Several non-human animal models (Baroncelli et al., 2012; Sale et al., 2010), and initial work with humans used disinhibition/reduction of GABAergic transmission, to restore (ocular dominance) plasticity in amblyopic adults. Mechanisms of disinhibition include fluoxetine administration (Vetencourt et al., 2008), environmental enrichment (Baroncelli et al., 2012; Bartoletti et al., 2004), exercise (Baroncelli et al., 2012), and perceptual learning (Baroncelli et al., 2011; Levi, 2005). Our findings suggesting that deficient cortical E/I dynamics might underlie the deficits in visual behavior in CC individuals would be of relevance for extending such disinhibition paradigms to pharmacological disinhibition or motor training paradigms following delayed surgery.

4.2 Insights from sensitive periods beyond the visual system

Across sensory, motor and higher cognitive domains, the sensitive period has been understood as a cascade of events (Hensch & Fagiolini, 2004; Larsen et al., 2023; Toyoizumi et al., 2013). A recent review suggested that sensitive periods might follow a sequence of similar neural processes along the sensory-motor-higher cognitive axis (Larsen et al., 2023). Therefore, isolating maturational changes in the visual system offers insight into what might be general principles of neuroplasticity in the human brain.

In the auditory domain, the age-dependence of successful cochlear implantation in individuals born with sensorineural hearing loss has been established (Geren & Snedeker, 2009; Gilley et al., 2010; Kral & Eggermont, 2007; Nicholas & Geers, 2007), analogous to early cataract removal in the visual domain (Birch et al., 1993, 2009). No age-dependent outcome differences were reported in adult groups implanted from the age of 20 years onwards (Schwab et al., 2015). This phenomenon is thought to reflect sensitive periods in auditory development. The development of corticocortical interareal interactions in the auditory cortex as an underlying maturational process of sensitive period plasticity was directly demonstrated in congenitally deaf and cochlear implanted cats (Kral et al., 2017; Yusuf et

al., 2022), and indirectly in humans via an increased latency of the P1 evoked potential[30] with increased age at cochlear implantation (Sharma et al., 2002; Silva et al., 2017). On a representational level, it was proposed that the feature space gradient typically represented in the cortex undergoes refinement within the sensitive period (Kral, 2013). In atypical development, this feature space was described as "smeared," therefore making it harder for the animal to use incorrectly represented features in learning and higher-order tasks. The present work from congenital cataract-reversal individuals supports such an interpretation and extends it to the visual domain in humans.

4.3 Limitations of the sight recovery approach

While this cumulus discussed patterns across non-human and human studies, generalization across various species and methods requires caution. As non-invasive measures used in cognitive neuroscience do not allow for "direct" measurement, correlational signals do not indicate the same level of evidence that is seen with invasive animal models, and vice versa. Post-mortem histological studies with congenital cataract-reversal and permanently congenitally blind individuals would help shed light on cytoarchitectonic and tract changes corresponding to visual deprivation.

Further, we focused on two specific processes underlying sensitive periods. Given that in biological systems several processes interact, the interpretation of the effects seen in these studies is incomplete. Other key mechanisms of sensitive period plasticity, namely, acetylcholine transmission (Bear & Singer, 1986; Liu et al., 1994; Morishita, 2012) and myelination (Innocenti, 2022; Larsen et al., 2023), have not been investigated. Further studies are necessary to shed light on acetylcholine transmission in permanent and transient visual deprivation, via MRS quantification of Choline[31] during visual processing. Additionally, the characterization of myelin sheath integrity via T2 imaging (van der Weijden et al., 2021) might provide insight into whether myelination in the visual cortex relies on patterned visual input.

Not all the studies discussed tested a developmental cataract group to control for a period of patterned visual deprivation later in life, or a nystagmus control group to control for effects of involuntary eye movements. Despite findings consistent with the hypothesized sensitive period and prior literature, the extension of these paradigms to developmental cataract-reversal individuals, and

[30] Analogous to the visual domain, the P1 ERP has been linked to higher auditory processing in the auditory cortex, see Sourav et al., 2018.

[31] Choline is the metabolic stage of the acetylcholine-choline cycle which is "visible" with Magnetic Resonance Spectroscopy (Lindner et al., 2017; Rae, 2014)

individuals with nystagmus, is necessary to assess the specificity of the observed effects to disruption of patterned visual experience at birth.

Finally, the sample sizes in almost all the studies in this dissertation are small, given that the population of CC individuals is rare. Nevertheless, replications and larger sample studies over longer time periods are necessary before generalizing such findings.

4.4 Conclusions

Recent neuroimaging and electrophysiological work in individuals with reversed congenital cataracts is consistent with an alteration of the E/I ratio, and a disruption of processing reliant on corticocortical circuits. . This body of evidence, together with prior work implicating these processes in non-human animal models, suggests that the establishment of an E/I balance and the elaboration of corticocortical networks in the visual cortex might be two processes which underlie sensitive periods in the human visual cortex.

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Appendices

Appendix I

Pant et al. (Under Review). Altered visual cortex excitatory/inhibitory ratio following transient congenital visual deprivation in humans. eLife.

Altered visual cortex excitatory/inhibitory ratio following transient congenital visual deprivation in humans

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ABSTRACT

Non-human animal models have indicated that the ratio of excitation to inhibition (E/I) in neural circuits is experience dependent, and changes across development. Here, we assessed 3T Magnetic Resonance Spectroscopy (MRS) and electroencephalography (EEG) markers of cortical E/I ratio in ten individuals who had been treated for dense bilateral congenital cataracts, after an average of 12 years of blindness, to test for dependence on early visual experience. First, participants underwent MRS scanning at rest with their eyes opened and eyes closed, to obtain visual cortex Gamma-Aminobutyric Acid (GABA+) concentration, Glutamate/Glutamine (Glx) concentration, and the concentration ratio of Glx/GABA+, as measures of inhibition, excitation, and E/I ratio respectively. Subsequently, EEG was recorded to assess aperiodic activity (1-20 Hz) as a neurophysiological measure of the cortical E/I ratio, during rest with eyes open and eyes closed, and during flickering stimulation. Across conditions, sight recovery individuals demonstrated a significantly lower visual cortex Glx/GABA+ ratio, and a higher intercept and steeper aperiodic slope at occipital electrodes, compared to age-matched sighted controls. In the sight recovery group, a lower Glx/GABA+ ratio was associated with better visual acuity, and Glx concentration correlated positively with the aperiodic intercept in the conditions with visual input. We interpret these findings as resulting from an increased E/I ratio of the visual cortex as a consequence of congenital blindness, which required commensurately increased inhibition after restored visual input provided additional excitation.

INTRODUCTION

Sensitive periods are epochs during the lifespan within which effects of experience on the brain are particularly strong (Knudsen, 2004). Non-human animal work has established that structural remodelling (Bourgeois, 1997) and the development of local inhibitory neural circuits strongly links to the timing of sensitive periods (Gianfranceschi et al., 2003; Hensch et al., 1998; Hensch & Bilimoria, 2012; Hensch & Fagiolini, 2004; Takesian & Hensch, 2013). Early visual experience has been shown to fine-tune local inhibitory circuits (Benevento et al., 1992; Chattopadhyaya et al., 2004; Gandhi et al., 2008; Toyoizumi et al., 2013), which dynamically control feedforward excitation (Tao & Poo, 2005; Wu et al., 2022). The end of the sensitive period has been proposed to coincide with the maturation of inhibitory neural circuits (Hensch, 2005; Wong-Riley, 2021; H. Zhang et al., 2018). Within this framework, neural circuit stability following the sensitive period is maintained via a balance between excitatory and inhibitory transmission across multiple spatiotemporal scales (Froemke, 2015; Haider et al., 2006; Maffei et al., 2004; Takesian & Hensch, 2013; Wu et al., 2022). Such an excitatory/inhibitory (E/I) ratio has been studied at different organizational levels, including the synaptic and neuronal levels, as well as for neural circuits (Van Vreeswijk & Sompolinsky, 1996; Wu et al., 2022).

The early experience-dependence of local inhibitory circuit tuning is supported by a large body of work in non-human animals. In particular, studies of the mouse visual cortex has demonstrated a disrupted tuning of local inhibitory circuits as a consequence of lacking visual experience at birth (Hensch & Fagiolini, 2004; Levelt & Hübener, 2012). In addition, dark-reared mice have been shown to have spontaneous neural firing in adulthood (Benevento et al., 1992) and a reduced magnitude of inhibition, particularly in layers II/III of the visual cortex (Morales et al., 2002), suggesting an overall higher level of excitation.

Human neuroimaging studies have similarly demonstrated that visual experience during the first weeks and months of life is crucial for the development of visual circuits (Baroncelli et al., 2011; Lewis & Maurer, 2005; Maurer & Hensch, 2012; Röder et al., 2021; Röder & Kekunnaya, 2021; Singh et al., 2018). As studies manipulating visual experience are impossible in human research, much of our understanding of the experience-dependence of visual circuit development comes from patients who underwent a transient period of congenital blindness due to dense bilateral congenital cataracts. If human infants born with dense bilateral cataracts are treated later than a few weeks from birth, they suffer from a permanent reduction of not only visual acuity (Birch et al., 1998; Khanna et al., 2013) and stereovision (Birch et al., 1993; Tytla et al., 1993) but additionally from impairments in higher-level visual functions

such as face perception (Le Grand et al., 2001; Putzar et al., 2010; Röder et al., 2013), coherent motion detection (Bottari et al., 2018; Hadad et al., 2012; Maurer & Lewis, 2017), visual temporal processing (Badde et al., 2020) and visual feature binding (McKyton et al., 2015; Putzar et al., 2007). These visual deficits in congenital cataract-reversal individuals have been attributed to altered neural development due to the absence of vision, as individuals who suffered from developmental cataracts do not typically display a comparable severity of impairments (Lewis & Maurer, 2009; Sourav et al., 2020). While extant literature reported correlations between structural changes and behavioral outcomes in congenital cataract-reversal individuals (Feng et al., 2021; Guerreiro et al., 2015; Hölig et al., 2023; Pedersini et al., 2023), functional brain imaging (Heitmann et al., 2023; Raczy et al., 2022) and electrophysiological research (Bottari et al., 2016; Ossandón et al., 2023; Pant et al., 2023; Pitchaimuthu et al., 2021) have started to unravel the neural mechanisms which rely on visual experience during sensitive periods for development.

Resting-state activity measured via fMRI suggested an increased E/I ratio in the visual cortex of congenital cataract-reversal individuals (Raczy et al., 2022): The amplitude of low frequency (<1 Hz) (blood oxygen level-dependent) fluctuations (ALFF) in visual cortex was increased in congenital cataract-reversal individuals compared to normally-sighted controls when they were scanned with their eyes open. Since similar changes were observed in permanently congenitally blind humans, the authors speculated that congenital visual deprivation resulted in increased E/I ratio of neural circuits due to impaired neural tuning, which was not reinstated after sight restoration (Raczy et al., 2022). Other studies measured resting-state electroencephalogram (EEG) activity and analyzed periodic (alpha oscillations) (Bottari et al., 2016; Ossandón et al., 2023; Pant et al., 2023) as well as aperiodic activity (Ossandón et al., 2023). Both measures pointed towards an higher E/I ratio of visual cortex in congenital cataract-reversal individuals (Ossandón et al., 2023). In recent research, authors have interpreted the slope of the aperiodic component of EEG power spectral density as an indication of the relative level of excitation; the flatter the slope, the higher the assumed E/I ratio (Gao et al., 2017; Lombardi et al., 2017; Medel et al., 2020; Muthukumaraswamy & Liley, 2018; Nanda et al., 2023). In fact, an increasing number of prospective studies in children have reported a flattening of this slope that was interpreted as higher levels of excitation with increasing age (Favaro et al., 2023; Hill et al., 2022). Ossandón et al. (2023), however, observed that in addition to the flatter slope of the aperiodic power spectrum in the high frequency range (20-40 Hz), the slope of the low frequency range (1-19 Hz) was steeper in both, congenital cataract-reversal individuals, as well as in permanently congenitally blind humans. The low frequency range has often been associated with inhibition (Jensen & Mazaheri, 2010; Lozano-Soldevilla,

2018; Lozano-Soldevilla et al., 2014). However, it remains unclear how to reconcile EEG resting-state findings for lower and higher frequency ranges.

Two studies with permanently congenitally blind humans employed Magnetic Resonance Spectroscopy (MRS) to investigate the concentration of both, the inhibitory neurotransmitter Gamma-Aminobutyric Acid (GABA), and the excitatory neurotransmitters Glutamate/Glutamine (Glx) as proxy measures of visual cortex inhibition and excitation, respectively (Coullon et al., 2015; Weaver et al., 2013). Glutamate/Glutamine concentration was significantly increased in the visual cortex of anophthalmic compared to normally-sighted individuals, suggesting increased excitability (Coullon et al., 2015). Preliminary evidence in congenitally permanently blind individuals suggested a decreased GABA concentration in the visual cortex compared to normally-sighted individuals (Weaver et al., 2013). Thus, these MRS studies corroborated the hypothesis that a lack of visual input at birth enhances relative excitation in visual cortex. However, the degree to which neurotransmitter levels recover following sight restoration after a phase of congenital blindness, and how they related to electrophysiological activity, remained unclear.

Here, we filled this gap: we assessed Glutamate/Glutamine (Glx) and Gamma Aminobutyric Acid (GABA+) concentrations using the MEGA-PRESS sequence (Mescher et al., 1998) in individuals whose sight had been restored, on average, after 12 years of congenital blindness. The ratio of Glx/GABA+ concentration was used as a proxy for the ratio of excitatory to inhibitory neurotransmission (Grent-'t-Jong et al., 2022; Liu et al., 2015; Steel et al., 2020; Takei et al., 2016; L. Zhang et al., 2020). Ten congenital cataract-reversal individuals were compared to age-matched, normally sighted controls at rest, both with eyes open and with eyes closed. To link MRS and EEG markers of cortical excitation/inhibition, we subsequently assessed the aperiodic slope of the EEG spectrum in the same subjects across three conditions: at rest with eyes closed, at rest with eyes open, and while viewing visual stimuli which changed in luminance at frequencies ranging from 1 to 30 Hz (Pant et al., 2023). Additionally we calculated the aperiodic intercept, which has previously been linked to broadband neuronal firing (Manning et al., 2009; Musall et al., 2014; Winawer et al., 2013). We predicted an altered visual cortex Glx/GABA+ concentration ratio in the edited MRS signal in congenital cataract-reversal individuals, and a higher intercept as well as altered slope of the EEG aperiodic component. We further hypothesized that neurotransmitter changes would relate to changes in the slope and intercept of the EEG aperiodic activity in the same subjects.

METHODS

Participants

We tested two groups of participants. The first group consisted of 10 individuals with a history of dense bilateral congenital cataracts (CC, 1 female, Mean Age = 25.8 years, Range = 11 – 43.5). Participants in this group were all recruited at the LV Prasad Eye Institute (Hyderabad, India) and the presence of dense bilateral cataracts at birth was confirmed by ophthalmologists and optometrists based on a combination of the following criteria: clinical diagnosis of bilateral congenital cataract, drawing of the pre-surgery cataract, occlusion of the fundus, nystagmus, a family history of bilateral congenital cataracts, and a visual acuity of fixating and following light (FFL+) or less prior to surgery, barring cases of absorbed lenses. Absorbed lenses occur specifically in individuals with dense congenital cataracts(Ehrlich, 1948) and were diagnosed based on the morphology of the lens, anterior capsule wrinkling, and plaque or thickness of stroma.

Duration of deprivation was calculated as the age of the participant when cataract removal surgery was performed on the first eye. Two participants were operated within the first year of life (at 3 months and 9 months of age), all other participants underwent cataract removal surgery after the age of 6 years (Mean Age at Surgery = 11.8 years, SD = 9.7, Range = 0.2 – 31.4). All participants were tested at least 1 year after surgery (Mean Time since Surgery = 14 years, SD = 9.1, Range = 1.8 - 30.9) (Table 1).

	COMORBIDITIES			**GENDER**	**VISUAL ACUITY PRE SURGERY**		**DURATION OF VISUAL DEPRIVATION (YEARS)**	**TIME SINCE SURGERY (YEARS)**	**VISUAL ACUITY ON DATE TESTED (LOGMAR)**	**FAMILY HISTORY**
	ABSORBED LENSES	**STRABISMUS**	**NYSTAGMUS**		**OD**	**OS**				
1	*No*	*Yes*	*Yes*	*Male*	*FFL -*	*FFL +*	*0.2*	*16.8*	*0.17*	*No*
2	*Yes*	*Yes*	*Yes*	*Male*	*1.18*	*1*	*20.8*	*22.7*	*0.9*	*Yes*
3	*Yes*	*Yes*	*Yes*	*Male*	*1.48*	*1.77*	*15.6*	*3.1*	*0.9*	*No*
4	*Yes*	*NA*	*Yes*	*Male*	*CF at 1.5 m*	*CF at 3 m*	*7.0*	*8.2*	*0.62*	*No*
5	*No*	*Yes*	*Yes*	*Male*	*NA*	*NA*	*14.0*	*18.4*	*0.88*	*Yes*
6	*No*	*Yes*	*Yes*	*Male*	*NA*	*NA*	*6.0*	*17.9*	*0.78*	*Yes*
7	*No*	*Yes*	*Yes*	*Male*	*PL+*	*PL+*	*0.7*	*12.4*	*0.54*	*No*
8	*Yes*	*No*	*Yes*	*Male*	*1.2*	*1.3*	*16.4*	*1.8*	*0.66*	*Yes*

9	*No*	*NA*	*Yes*	*Male*	*NA*	*NA*	*6.0*	*30.9*	*1.34*	*Yes*
10	*Yes*	*Yes*	*Yes*	*Female*	*1.48*	*1.48*	*31.4*	*7.4*	*1.04*	*Yes*

Table 1: Clinical and demographic information of the participants with a history of dense bilateral congenital cataracts (CC). NA indicates that patient's data for the field were not available. FFL: Fixating and Following Light; CF: Counting Fingers; PL: Perceiving Light. Duration of visual deprivation was calculated by subtracting the date of birth from the date of surgery on the first eye. Time since surgery was calculated by subtracting the date of surgery on the first eye from the date of testing. Visual acuity on the date of testing was measured with the Freiburg Vision Test (FrACT) (Bach 1996).

The second group comprised of 10 normally sighted individuals (SC, 8 males, Mean Age = 26.3 years, Range = 12 – 41.8). Participants across the two groups were individually age matched (± 2 years, $t_{(9)} = -0.12$, $p = 0.91$). One additional individual was tested in each group, however, they were excluded from data analysis as their data files were corrupted due to inappropriate file transfer from the scanner. All participants (as well as legal guardians for minors) gave written and informed consent. This study was conducted after approval from the Local Ethical Commission of the LV Prasad Eye Institute (Hyderabad, India) as well as of the Faculty of Psychology and Human Movement, University of Hamburg (Germany).

Data Collection and Analysis

The present study consisted of three data acquisition parts: Magnetic Resonance Spectroscopy (MRS), Electroencephalography (EEG), and visual acuity assessment.

Magnetic Resonance Spectroscopy

Participants underwent MRI and MRS scanning at LUCID Diagnostics in Hyderabad (India) with a 3T GE SIGNA Pioneer MRI machine employing a 24-channel head coil. An attendant was present in the scanning room for the duration of the scan to ensure that participants were comfortable and followed the instructions.

A T1 weighted whole brain image was collected for each participant (Repetition Time (TR) = 14.97 ms, Echo Time (TE) = 6.74 ms, Matrix size = 512 × 512, In-plane resolution = 0.43 × 0.43 mm, Slice thickness = 1.6 mm, Axial slices = 188, Interslice interval= -0.8 mm, Inversion time = 500 ms, Flip angle = 15°). This structural scan enabled registration of every MRS scan to the participants' anatomical

landmarks (Figure 1). For this scan, participants were instructed to keep their eyes closed and stay as still as possible.

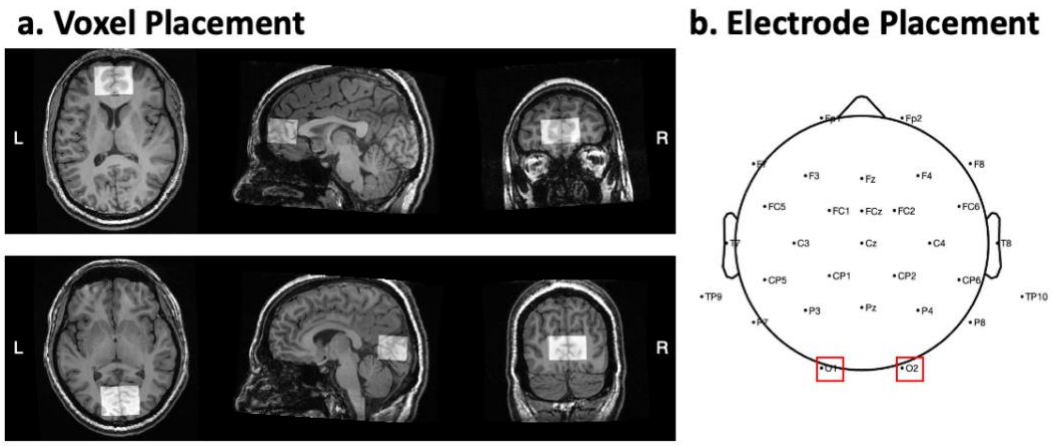

Figure 1: Voxel placement for Magnetic Resonance Spectroscopy and electrode placement for Electroencephalography. *a. Position of the frontal cortex (top) and visual cortex (bottom) voxels in a single subject. Figures output from GannetCoRegister. b. Electrode montage according to the 10/20 electrode system with marked occipital electrodes (red) preselected for analysis.*

The MRS scans consisted of single-voxel spectroscopy data that were collected using the MEGA-PRESS sequence, which allows for in-vivo quantification of the low-concentration metabolites GABA and glutamate+glutamine (Glu+Gln) (Mescher et al., 1998; Mullins et al., 2014). Due to the spectral overlap of GABA (3.0 ppm) and Glu/Gln (3.75 ppm) with the higher concentration peaks of N-Acetyl Aspartate (NAA) and Creatine (Cr), accurate quantification of GABA and Glu/Gln is challenging. MEGA-PRESS uses spectral editing to obtain these measurements. Spectroscopy data consist of an edit-ON and an edit-OFF spectrum for each voxel, wherein the "ON" and "OFF" refer to whether the frequency of the editing pulse applied is on- or off-resonance with the signal coupled to the GABA complex (applied at approximately 1.9 ppm). Therefore, subtracting repeated acquisitions of the edit-ON and edit-OFF spectra allows for measurement of the magnitude of signals differing in their response to the editing pulse (e.g. GABA), while cancelling out signals that do not (e.g. Cr) (Mescher et al., 1998). Each MEGA-PRESS scan lasted for 8 minutes and was acquired with the following specifications: TR = 2000 ms, TE = 68 ms, Voxel size = 40 mm x 30 mm x 25mm, 192 averages (each consists of two TRs). Additionally, 8 unsuppressed water averages were acquired, allowing all metabolites to be referenced to the tissue water concentration. Concentrations of GABA and Glu/Gln quantified from these acquisitions are

respectively referred to as GABA+, due to the presence of macromolecular contaminants in the signal (Mullins et al., 2014), and Glx, due to the combined quantification of the Glu, Gln and Glutathione peaks.

Two MRS scans were collected from the visual cortex, centered on the calcarine sulcus of every participant (Figure 1). The scans were recorded with the participants' eyes open (EO condition) and eyes closed (EC condition), respectively. During the scans, participants were instructed to lie as still as possible.

To ensure that we were identifying neurochemical changes specific to visual regions, we selected the frontal cortex as a control region (Figure 1) and collected two scans (EO and EC) from the frontal cortex too. The order of the MRS scans was counterbalanced across individuals for both locations and conditions. Two SC subjects did not complete the frontal cortex scan for the EO condition and were excluded from the statistical comparisons of frontal cortex neurotransmitter concentrations.

MRS Data Analysis

All data analyses were performed in MATLAB (R2018b, The MathWorks Inc.). For MRS data analyses we used Gannet 3.0, a MATLAB based toolbox specialized for the quantification of GABA+ and Glx from edited spectrum data (Edden et al., 2014).

GABA+ and edited Glx concentration values were obtained and corrected using the *GannetFit, GannetCoRegister,* G*annetSegment* and *GannetQuantify* functions (Edden et al., 2014). Briefly, reported concentration values were corrected for the differences in GABA concentration and relaxation times between different kinds of tissue in the voxel (grey matter, white matter and cerebrospinal fluid) (Harris et al., 2015). Gannet uses SPM12 to determine the proportion of grey matter, white matter and cerebrospinal fluid in each individual participant's voxel (Penny et al., 2007). Note that the tissue fraction values did not differ between groups or conditions (all p's > 0.19, see Supplementary Material S2). GABA+, Glx and Glx/GABA+ values were compared across groups as proxy measures of inhibition, excitation and E/I ratio respectively. The use of Glx/GABA+ as a proxy measure of E/I neurotransmission is supported by a study that observed a regional balance between Glx and GABA+ at 3T (Steel et al., 2020). Further, the Glx/GABA+ ratio has been employed in prior studies of visual (Takei et al., 2016; L. Zhang et al., 2020), cingulate (Bezalel et al., 2019), frontal (Liu et al., 2015) and auditory cortex (Grent-'t-Jong et al., 2022).

To control for potential unspecified visual cortex changes due to eye pathology, as opposed to genuine changes in neurotransmitter ratio, we compared N-Acetyl Aspartate (NAA) concentrations in the visual cortex of CC vs SC individuals. NAA forms one of the most prominent peaks in the MR

spectrum (2.0 ppm chemical shift). NAA has been quantified with high reproducibility in the visual cortex(Brooks et al., 1999) and medial-temporal cortex (Träber et al., 2006) of neuro-typical individuals as well as in various pathologies across visual, frontal and temporal cortex (Paslakis et al., 2014), for example, schizophrenia (Mullins et al., 2003). We did not expect to find differences in NAA concentration between CC and SC individuals as it has not been demonstrated to vary in anophthalmia (Coullon et al., 2015) or permanent early blindness (Weaver et al., 2013) in humans. TARQUIN 4.3.11 was employed to analyze the OFF-spectrum data (Wilson et al., 2011) to assess NAA concentration. FID-A toolbox was used to correct the data for phase errors across acquisitions arising from temporal changes in the magnetic field strength or participant motion (Simpson et al., 2017).

Mean Signal-to-Noise Ratio values for GABA+ and Glx in all groups and conditions were above 19 in the visual cortex and above 8 in the frontal cortex (Supplementary Material S3). A recent study has suggested that an SNR value above 3.8 allows for reliable quantification of GABA+ (Zöllner et al., 2021), in conjunction with considering a given study's sample size (Mikkelsen et al., 2018). Cramer-Rao Lower Bound (CRLB) values, that is, the theoretical lower limit of estimated error, were 30% or lower for NAA quantification in both groups and conditions (Cavassila et al., 2001). Note that CRLB values above 50% are considered unreliable (Wilson et al., 2019). We confirmed the within-subject stability of metabolite quantification by testing a subset of the sighted controls (n=6) 2-4 weeks apart (Supplementary Material S5).

All reported values are water-normalized.

Prior to in-vivo scanning, we confirmed the GABA+ and GABA+/Glx quantification quality with phantom testing (Henry et al., 2011; Jenkins et al., 2019). Imaging sequences were robust in identifying differences of 0.02 mM in GABA concentration. This 0.02 mM difference was documented by Weaver et al (2013) between the occipital cortices of early blind and sighted individuals. The known vs. measured concentrations of both GABA ($r = 0.81$, $p = 0.004$) and GABA/Glx ($r = 0.71$, $p = 0.019$) showed significant agreement. The detailed procedure and results are described in the Supplementary Material (Supplementary Material S4). The spectra from all individual subjects are shown in Supplementary Material S10.

MRS Statistical Analysis

All statistical analyses were performed using MATLAB R2018b.

We compared the visual cortex concentrations of 3 neurochemicals (GABA+ and Glx from the DIFF spectrum, NAA from the edit-OFF spectrum) between the two groups. For each metabolite we

submitted the concentration values from the visual cortices of CC and SC individuals to a group (2 Levels: CC, SC)-by-condition (2 Levels: EO, EC) ANOVA model. To compare the Glx/GABA+ ratio between groups, we additionally submitted this ratio value to a group-by-condition ANOVA. Identical analyses were performed for the corresponding frontal cortex neurotransmitter values. Wherever necessary, post-hoc comparisons were performed using t-tests.

Electrophysiological recordings

EEG data were collected to investigate aperiodic activity in the same participants and on the same day. Data were acquired in three conditions: at rest with eyes open (EO, 3 minutes), at rest with eyes closed (EC, 3 minutes) and during visual stimulation with stimuli that changed in luminance (LU) (Pant et al., 2023). We used the slope of the aperiodic (1/f) component of the EEG spectrum as an estimate of E/I ratio (Gao et al., 2017; Medel et al., 2020; Muthukumaraswamy & Liley, 2018). Further, we compared the intercept of the aperiodic component in the human EEG between groups, as an estimate of broadband neuronal firing activity (Haller et al., 2018; Manning et al., 2009; Miller, 2010).

The EEG was recorded using Ag/AgCl electrodes attached according the 10/20 system(Homan et al., 1987) to an elastic cap (EASYCAP GmbH, Herrsching, Germany) (Figure 1). We recorded 32 channel EEG using the BrainAmp amplifier, with a bandwidth of 0.01–200 Hz, sampling rate of 5 kHz and a time constant of 0.016 Hz /(10 s) (http://www.brainproducts.com/). All scalp recordings were performed against a left ear lobe reference.

Participants were asked to sit as still as possible while EEG was being recorded. First, resting-state EEG data were collected. During the EO condition, participants were asked to fixate on a blank screen. During the EC condition, participants were instructed to keep their eyes closed. The order of conditions was randomized across participants. The EEG data sets reported here were part of data published earlier (Ossandón et al., 2023; Pant et al., 2023).

Subsequently, EEG data were recorded during 100 trials of a target detection task with stimuli that changed in luminance (LU). Stimuli were presented with a Dell laptop, on a Dell 22 inch LCD monitor with a refresh rate of 60 Hz. They were created with MATLAB r2018b (The MathWorks, Inc., Natick, MA) and the Psychtoolbox 3 toolbox (Brainard, 1997; Kleiner et al., 2007). On each trial, participants observed a circle at the center of a black screen, subtending a visual angle of 17 degrees. The circle appeared for 6.25 s and changed in luminance with equal power at all frequencies (0-30 Hz). At the end of every trial, participants had to indicate whether a target square, subtending a visual angle of 6

degrees, appeared on that trial. The experiment was performed in a darkened room (for further details, see (Pant et al., 2023)).

EEG Data Analysis

Data analysis was performed using the EEGLab toolbox on MATLAB 2018b(Delorme & Makeig, 2004). All EEG datasets were filtered using a Hamming windowed sinc FIR filter, with a high-pass cutoff at 1 Hz and a low-pass cutoff at 45 Hz. Eye movement artifacts were detected in the EEG datasets via independent component analysis using the *runica.m* function's *Infomax* algorithm in EEGLab. Components corresponding to horizontal or vertical eye movements were identified via visual inspection and removed (Plöchl et al., 2012).

The two 3 minutes long resting-state recordings (EC, EO) were divided into epochs of 1 s. Epochs with signals exceeding ±120 µV were rejected for all electrodes. We then calculated the power spectral density of the EO and EC resting-state data using the *pwelch* function (window length = 1000, overlap = 0).

Datasets collected while participants viewed visual stimuli that changed in luminance (LU) were down-sampled to 60 Hz (antialiasing filtering performed by EEGLab's *pop_resample* function) to match the stimulation rate. The datasets were divided into 6.25 s long epochs corresponding to each trial. Subsequently, baseline removal was conducted by subtracting the mean activity across the length of an epoch from every data point. After baseline removal, epochs with signals exceeding a threshold of ±120 µV were rejected in order to exclude potential artifacts. Finally, we calculated the power spectral density of the LU data using the *pwelch* function (window length = 60 samples, overlap = 0).

We calculated the aperiodic (1/f) component of the power spectrum for the EO, EC and LU conditions (Donoghue, Haller, et al., 2020; Schaworonkow & Voytek, 2021). First, we fit the 1/f distribution function to the frequency spectrum of each participant, separately for each electrode. The 1/f distribution was fit to the normalized spectrum converted to log-log scale (range = 1-20 Hz) (Donoghue, Dominguez, et al., 2020; Gyurkovics et al., 2021; Schaworonkow & Voytek, 2021). We excluded the alpha range (8-14 Hz) for this fit to avoid biasing the results due to documented differences in alpha activity between CC and SC individuals (Bottari et al., 2016; Ossandón et al., 2023; Pant et al., 2023). This 1/f fit resulted in a value of the aperiodic slope, an aperiodic intercept value corresponding to the broadband power of 1-20 Hz, and a fit error value for the spectrum of every participant, individually for all electrodes. The visual cortex aperiodic slope and intercept values were obtained by

averaging across pre-selected occipital electrodes O1 and O2, giving one value of broadband slope and intercept per participant for the EO, EC and LU conditions (Figure 1).

EEG Statistical Analysis

We compared the average visual cortex aperiodic slope and intercept in separate group (2 Levels: CC, SC) by condition (3 levels: EC, EO, LU) ANOVA models.

Visual acuity

Visual acuity was measured for every participant on the date of testing, using the Freiburg Visual Acuity Test (FrACT) (Bach 1996, Bach 2007, https://michaelbach.de/fract/). Visual acuity is reported as the logarithm of the mean angle of resolution (logMAR, Table 1), wherein higher values indicate worse vision(Elliott, 2016). As in previous studies, we ran a number of exploratory correlation analyses between GABA+, Glx and Glx/GABA+ concentrations, and visual acuity at the date of testing, duration of visual deprivation, and time since surgery respectively in the CC group (Birch et al., 2009; Guerreiro et al., 2015; Kalia et al., 2014; Rajendran et al., 2020). We additionally tested the correlation between the aforementioned metrics and chronological age across the CC and SC groups.

Correlation analyses between MRS and EEG measures

Exploratory correlation analyses between EEG and MRS measures were run separately for CC and SC individuals. We calculated correlations between the aperiodic intercept and GABA+, Glx and Glx/GABA+ concentrations. Further, correlations between aperiodic slope, and the concentrations of GABA+, Glx and Glx/GABA+ were assessed. MRS measures collected at rest with eyes open (EO) and eyes closed (EC) were correlated with the corresponding resting-state EEG conditions (EO, EC). The correlation between EEG data collected while participants viewed flickering stimuli (LU) calculated with GABA+, Glx and Glx/GABA+ concentration measured while participants' eyes were open at rest. We did not have prior hypotheses as to the best of our knowledge no extant literature has tested the correlation between aperiodic EEG activity and MRS measures of GABA+,Glx and Glx/GABA+. Therefore, we corrected for multiple comparisons using the Bonferroni correction (6 comparisons).

RESULTS

Transient visual deprivation lowered Glx/GABA+ concentration in the visual cortex.

The water-normalized Glx/GABA+ concentration ratio was significantly lower in the visual cortex of congenital cataract-reversal (CC) than age-matched, normally sighted control (SC) individuals (main effect of group: $F(1,39) = 5.80$, $p = 0.021$) (Figure 2). This effect did not vary with eye closure (main effect of condition: $F(1,39) = 2.29$, $p = 0.139$, group-by-condition interaction: $F(1,39) = 1.15$, $p = 0.290$). As a control for unspecified effects of surgery or visual deprivation on neurochemistry, the frontal cortex Glx/GABA+ concentration was compared between groups. There was no difference between CC and SC individuals in their frontal cortex Glx/GABA+ concentration (main effect of group: $F(1,37) = 0.05$, $p = 0.82$, main effect of condition: $F(1,37) = 2.98$, $p = 0.093$, group-by-condition interaction: $F(1,37) = 0.09$, $p = 0.76$) (Figure 2).

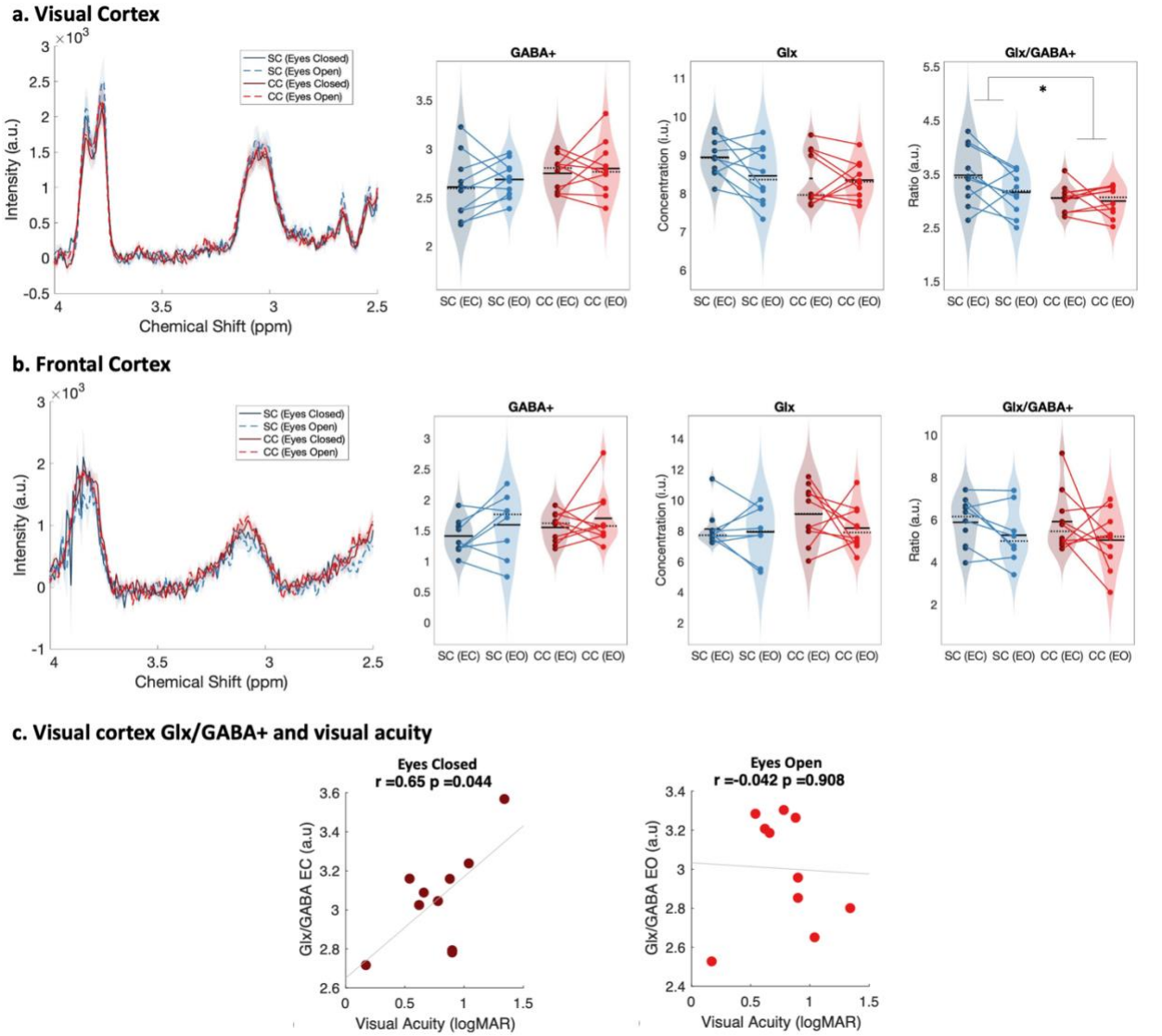

Figure 2: Edited spectra obtained from Magnetic Resonance Spectroscopy (MRS). *a. Average edited spectra showing GABA+ and edited Glx peaks in the visual cortices of normally sighted individuals (SC, green) and individuals with reversed congenital cataracts (CC, red) are shown. Edited MRS DIFF spectra are separately displayed for the eyes open (EO) and eyes closed (EC) conditions using dashed and solid lines respectively. The standard error of the mean is shaded. Water-normalized GABA+, Glx and Glx/GABA+ concentration distributions for each group and condition are depicted as violin plots on the right. The solid black lines indicate mean values and dotted lines indicate median values. The coloured lines connect values of individual participants across conditions. b. Corresponding average edited MRS spectra and water-normalized GABA+, Glx and Glx/GABA+ concentration distributions measured from the frontal cortex are displayed. c. Correlations between visual cortex Glx/GABA+ concentrations in the visual cortex of CC individuals and visual acuity in logMAR units are depicted for the eyes closed (EC, left) and eyes open (EO, right) conditions.*

When separately comparing CC and SC individuals' GABA+ and Glx concentrations in the visual cortex, we did not find any group difference (GABA+ main effect of group: $F(1,39) = 2.5$, $p = 0.12$, main effect of condition: $F(1,39) = 0.6$, $p = 0.43$, group-by-condition interaction: $F(1,39) = 0.03$, $p = 0.86$; Glx main effect of group: $F(1,39) = 2.8$, $p = 0.103$, main effect of condition: $F(1,39) = 1.8$, $p = 0.19$, group-by-condition interaction: $F(1,39) = 1.27$, $p = 0.27$) (Figure 2). In the frontal cortex, GABA+ and Glx concentrations did not vary either with group or condition (all p values > 0.19) (Figure 2).

Glx/GABA+ concentration measured when CC individuals' eyes were closed correlated positively with visual acuity on the logMAR scale ($r = 0.65$, $p = 0.044$), indicating that CC individuals with higher Glx/GABA+ values had worse visual acuity (Figure 2C, Supplementary Material S5). The same correlation was not significant for the eyes opened condition ($r = -0.042$, $p = 0.908$) (Figure 2C). Duration of deprivation and time since surgery did not significantly predict Glx/GABA+, GABA+ or Glx concentrations in the CC group (all p values > 0.088, Supplementary Material S6).

No difference in NAA concentration between CC and SC individuals' visual cortices.

As a control measure to ensure that between-group differences were specific to hypothesized changes in Glx and GABA+ concentrations, we compared the NAA concentration between CC and SC individuals. The NAA concentration did not significantly differ between groups, neither in their visual (main effect of group: $F(1,39) = 0.03$, $p = 0.87$, main effect of condition: $F(1,39) = 0.31$, $p = 0.58$, group-by-condition interaction: $F(1,39) = 0.09$, $p = 0.76$) nor their frontal cortices (main effect of group: $F(1,37)$

= 1.1, p = 0.297, main effect of condition: F(1,37) = 0.14, p = 0.71, group-by-condition interaction: F(1,37) = 0.03, p = 0.86) (Supplementary Material S1, Figure S1).

Transient visual deprivation resulted in a steeper aperiodic slope and higher aperiodic intercept at occipital sites.

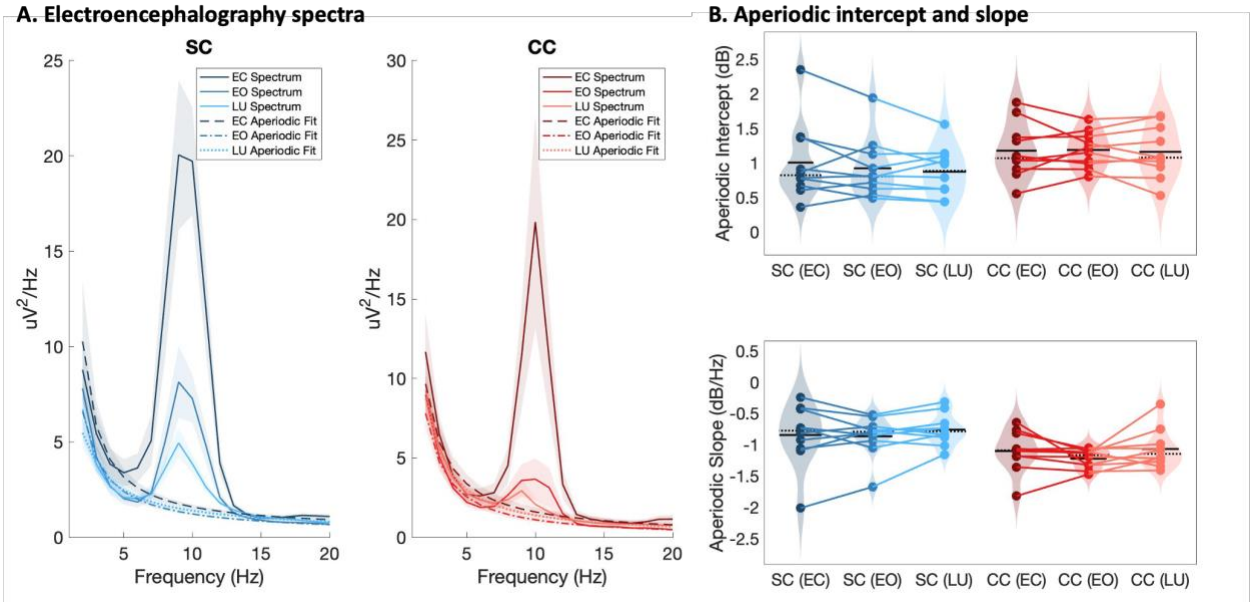

Figure 3: Full spectrum and aperiodic activity of the electroencephalogram (EEG). *a. EEG spectra across O1 and O2 with the corresponding aperiodic (1/f) fits for normally sighted individuals (SC, blue, left) and individuals with reversed congenital cataracts (CC, red, right). Spectra of EEG recordings are displayed for the eyes closed (EC) and eyes opened (EO) conditions, as well as while viewing stimuli that changed in luminance (LU). Shaded regions represent the standard error of the mean. b. Aperiodic intercept (top) and slope (bottom) value distributions for each group and condition are displayed as violin plots. Solid black lines indicate mean values, dotted black lines indicate median values. Coloured lines connect values of individual participants across conditions.*

The aperiodic slope (1-20 Hz), measured via EEG as an electrophysiological estimate of the E/I ratio(Gao et al., 2017; Muthukumaraswamy & Liley, 2018), was compared between CC and SC individuals. The aperiodic slope was significantly steeper i.e. more negative, at occipital electrodes in CC than in SC individuals (F(1,59) = 13.1, p < 0.001) (Figure 3). Eye closure and visual stimulation did not affect the steepness of the aperiodic slope (F(2,59) = 0.78, p = 0.465, group-by-condition interaction: F(2,59) = 0.12, p = 0.885).

The aperiodic intercept (1-20 Hz) was compared between CC and SC individual to estimate group differences in broadband neural activity(Manning et al., 2009; Musall et al., 2014; Winawer et al., 2013) and was found to be significantly larger at occipital electrodes in CC than SC individuals (main effect of group: $F(1,59) = 5.2$, $p = 0.026$) (Figure 3). Eye closure did not affect the magnitude of the aperiodic intercept in either group(main effect of condition: $F(2,59) = 0.16$, $p = 0.848$, group-by-condition interaction: $F(2,59) = 0.11$, $p = 0.892$).

Within the CC group, visual acuity, time since surgery and duration of blindness did not significantly correlate with the aperiodic slope or the intercept (all p's > 0.083, Supplementary Material S7). Age negatively correlated with the aperiodic intercept across CC and SC individuals, that is, a flattening of the intercept was observed with age. Similar effects of chronological age have been previously observed (Hill et al., 2022; Voytek et al., 2015) (Supplementary Material S6, Supplementary Material S9).

Glx concentration predicted the aperiodic intercept in CC individuals' visual cortices during ambient and flickering visual stimulation.

We exploratorily tested the relationship between Glx, GABA+ and Glx/GABA+ measured at rest and the EEG aperiodic intercept measured at rest and during flickering visual stimulation, separately for the CC and the SC group.

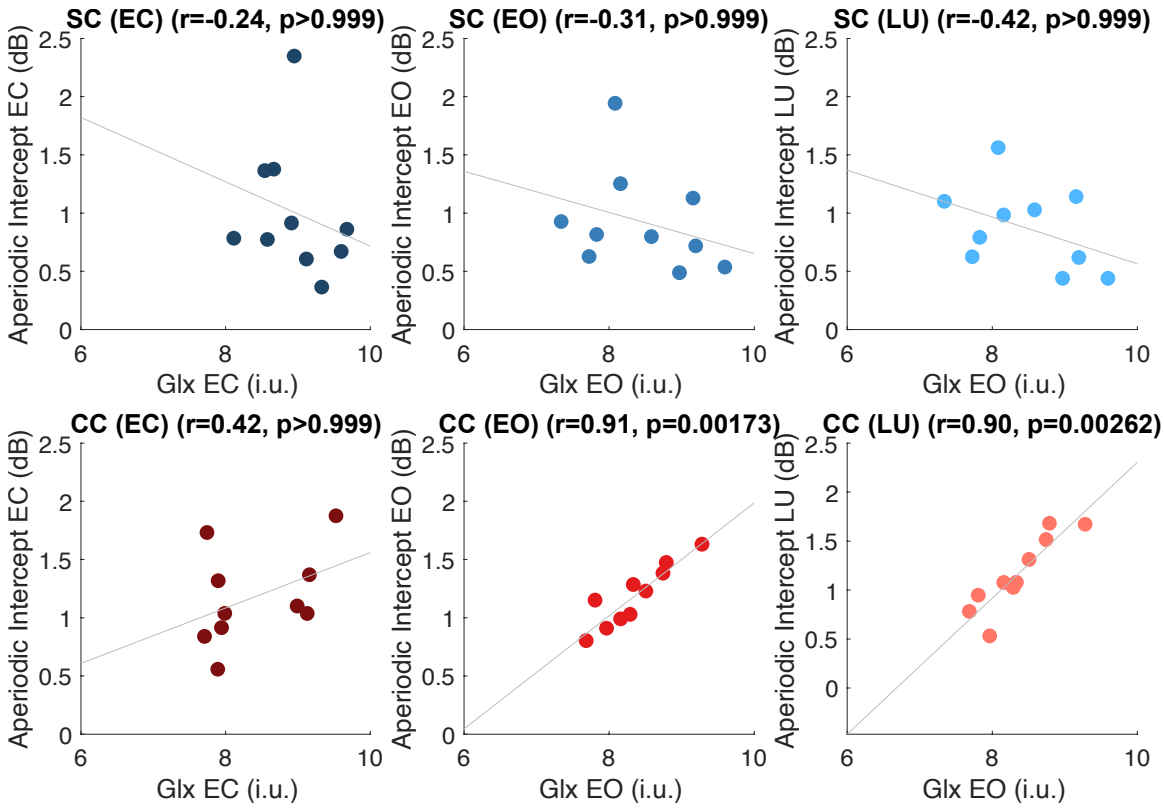

Figure 4: Exploratory correlation analyses between the aperiodic intercept (1-20 Hz) and glutamate/glutamine (Glx) concentration in the visual cortex. *Correlations between water-normalized Glx concentration and aperiodic intercept are shown for the eyes closed (EC, left), eyes open (EO, middle) and visual stimulation (LU, right) conditions for sighted controls (SC, green, top) and individuals with reversed congenital cataracts (CC, red, bottom). Displayed p values are Bonferroni corrected for multiple comparisons.*

Visual cortex Glx concentration in CC individuals was positively correlated with the aperiodic intercept either when participants had their eyes open during rest ($r = 0.91$, $p = 0.001$, Bonferroni corrected) or when they viewed flickering stimuli ($r = 0.90$, $p < 0.001$, Bonferroni corrected). Corresponding correlations were not significant for Glx concentrations in the eyes closed condition ($r = 0.341$, $p > 0.99$, Bonferroni corrected). By contrast, in SC individuals no significant correlation was observed between visual cortex Glx concentration and aperiodic intercept in any condition (all p's > 0.99, Bonferroni corrected) (Figure 4).

A negative correlation between the aperiodic slope and Glx concentration in CC individuals (i.e., steeper slopes with increasing Glx concentration) was observed during visual stimulation, but did not

survive correction for multiple comparisons (Supplementary Material S8). No such correlation was observed between Glx concentration and aperiodic slope in the eyes open or closed conditions. Visual cortex GABA+ concentration and Glx/GABA+ concentration ratios did not significantly correlate with the aperiodic intercept or slope in either CC or SC individuals, during any experimental condition (Supplementary Material S8).

DISCUSSION

Research in non-human animals has provided convincing evidence that the ratio of excitation to inhibition (E/I) in visual cortex is reliant on early visual experience (Froemke, 2015; Haider et al., 2006; Hensch et al., 1998; Takesian & Hensch, 2013; Wu et al., 2022). In parallel, research in humans who were born blind due to dense bilateral cataracts, and received delayed sight restoration surgery in childhood or as adults, has found limited recovery of both basic visual and higher order visual functions (Birch et al., 2009; Röder & Kekunnaya, 2021). The present study tested whether neurotransmitter concentrations and electrophysiological markers of cortical E/I ratio depend on early visual experience in humans, and how possible changes in visual cortex E/I ratio relate to visual recovery. First, we employed Magnetic Resonance Spectroscopy (MRS) and assessed Glutamate/Glutamine (Glx) and Gamma-Aminobutyric Acid (GABA+) concentrations, as well as their ratio, in the visual cortex (Shibata et al., 2017; Steel et al., 2020; Takei et al., 2016). Second, the slope and intercept of the aperiodic spectrum of EEG resting-state activity during eye opening and eye closure (Gao et al., 2017; Muthukumaraswamy & Liley, 2018; Ossandón et al., 2023), as well as during flickering stimulation (Pant et al., 2023), were measured over the occipital cortex in the same individuals. The EEG measures allowed us to relate neurotransmitter changes to neural activity changes in congenital cataract-reversal individuals.

We found a lower Glx/GABA+ concentration ratio in the visual cortex of congenital cataract-reversal (CC) individuals as compared to normally sighted controls (SC). Additionally, the slope of the aperiodic EEG power spectrum was steeper for the low frequency range (1-20 Hz), and its intercept was higher in CC than SC individuals. In the CC group, Glx concentration correlated with the intercept of the aperiodic component during ambient and flickering stimulation. Glx/GABA+ concentration ratio during eye closure predicted visual acuity of CC individuals. Together, the present results provide strong evidence for experience-dependent development of the E/I ratio in the human visual cortex, with consequences for behavior.

Altered Glx/GABA+ ratio after sight restoration in congenitally blind humans

Previous MRS studies in the visual cortex of permanently congenitally blind humans reported higher Glx concentrations (Coullon et al., 2015) in five anophthalmic humans, and numerically lower GABA concentrations in congenitally blind humans (Weaver et al., 2013) (n = 9), as compared to normally sighted individuals. These results were interpreted as suggesting a higher E/I ratio in the visual cortex of permanently congenitally blind humans, which would be consistent with the extant literature on higher BOLD activity in the visual cortices of the same population (Bedny, 2017; Röder & Kekunnaya, 2022). We observed a lower Glx/GABA+ ratio in CC individuals, which suggests a lower rather than higher E/I ratio. Our results imply a change in neurotransmitter concentrations as a consequence of *restoring* vision following congenital blindness. Here, we speculate that due to limited structural plasticity after a phase of congenital blindness, the neural circuits of CC individuals, which had adapted to blindness after birth, employ available, likely predominantly physiological plasticity mechanisms (Knudsen, 1998; Mower et al., 1985; Röder et al., 2021), in order to re-adapt to the newly available visual excitation following sight restoration.

Structural remodeling for typical E/I balance requires visual experience following birth (Hensch & Fagiolini, 2005; Takesian & Hensch, 2013; H. Zhang et al., 2018) and is linked to a sensitive period (Desai et al., 2002; Hensch & Fagiolini, 2005). A repeatedly documented finding in permanently congenitally blind humans is the increased thickness of visual cortex (Andelin et al., 2019; Guerreiro et al., 2015; Hölig et al., 2023; Jiang et al., 2009), which was not observed in late-blind humans (Andelin et al., 2019). These structural changes in permanently congenitally blind individuals were interpreted as a lack of experience dependent pruning of exuberant synapses and/or reduced myelination typically shifting of the grey-white matter boundary (Natu et al., 2019). In parallel, it was observed that the overproduction of synapses during the initial phase of brain development in non-human primates was independent of experience, but that synaptic pruning, predominantly of excitatory synapses, depended on visual experience (Bourgeois, 1996; Bourgeois et al., 1989). This lack of excitatory pruning has been though to underlie the observed higher excitability of visual cortex due to congenital visual deprivation (Benevento et al., 1992; Huang et al., 2015; Morales et al., 2002), which was interpreted as a homeostatic adjustment of the E/I ratio resulting from the lack of visual feedforward excitation (Huang et al., 2015; Turrigiano & Nelson, 2004). Indeed, sight restoration in non-human primates after several months of congenital bilateral lid suture resulted in higher spontaneous firing in visual association cortex (Hyvärinen et al., 1981). Further, neuronal spiking was increased in dark reared mice when exposed to ambient light (Benevento et al., 1992). Crucially, increased visual cortex thickness (Feng et al., 2021; Guerreiro et al., 2015; Hölig et al., 2023) and higher BOLD activity during rest with the eyes open (Raczy

et al., 2022) have been observed for CC individuals as well, suggesting incomplete recovery of cortical structure and function after sight restoration in humans. Thus, the restored feedforward drive to visual cortex after surgery might reach a visual cortex with a lower threshold for excitation, possible due to a relatively higher number of excitatory synapses (Bourgeois, 1996; Morales et al., 2002).

Studies in non-human animals have demonstrated that excitation and inhibition appear to go hand-in-hand (Froemke, 2015; Haider et al., 2006; Isaacson & Scanziani, 2011; Tao & Poo, 2005). Outside of the sensitive period, the visual cortices of CC individuals to maintain neural circuit stability (Lee & Kirkwood, 2019; Turrigiano & Nelson, 2004). An overall reduction in Glx/GABA ratio would counteract the aforementioned adaptations to congenital blindness, e.g. a lower threshold for excitation, which might come with the risk of runaway excitation in the presence of restored visually-elicited excitation. Previous MRS studies have observed a reduction of GABA concentrations in visual cortex (Lunghi et al., 2015) and an increase in the BOLD response (Binda et al., 2018) following monocular blindfolding in adulthood, which was interpreted as indicative of adult homeostatic plasticity. Further, studies in adult mice have provided support for a homeostatic adjustment of the E/I ratio following prolonged changes in neural activity (Chen et al., 2022; Goel & Lee, 2007; Keck et al., 2017; Whitt et al., 2013). For example, a long period of decreased activity following enucleation in adult mice commensurately decreased inhibitory drive (Keck et al., 2011), primarily onto excitatory neurons (Barnes et al., 2015). In line with the lowered Glx/GABA+ ratio being a compensatory measure, the observed correlation of the Glx/GABA+ ratio during eye closure and visual acuity suggests that the more successful this downregulation of the E/I ratio, the better the visual recovery.

The correlation of a lower Glx/GABA+ ratio with better visual acuity is reminiscent of a previously identified correlation in a larger group of CC individuals between decreased visual cortex thickness and better visual acuity (Hölig et al., 2023). Hence, CC individuals with more advanced structural normalization appear to have a better starting point for functional recovery mediated by physiological plasticity.

Glx correlated with the aperiodic intercept of EEG resting-state activity during visual stimulation in congenital cataract-reversal individuals.

An increased intercept of the aperiodic component of EEG activity was observed in the same CC individuals who underwent MRS assessment, irrespective of eye opening or eye closure, as well as during flickering stimulation. The intercept of the aperiodic component has been linked to overall

neuronal spiking activity (Manning et al., 2009; Musall et al., 2014) and fMRI BOLD activity (Winawer et al., 2013).

Moreover, the slope of the aperiodic component for the low frequency range (1-20 Hz) was steeper in CC individuals. By contrast, the slope of the higher (20-40 Hz) frequency range was flatter in CC than SC individuals (Ossandón et al., 2023). Higher frequencies (such as 20-40 Hz) have been predominantly associated with local circuit activity and feedforward signaling (Bastos et al., 2018; Van Kerkoerle et al., 2014); the increased 20-40 Hz slope may therefore signal increased spontaneous spiking activity in local networks. We speculate that the steeper slope of the aperiodic activity for the lower frequency range (1-20 Hz) in CC individuals reflects the concomitant increase in inhibition.

Interestingly, in CC individuals, the intercept of the aperiodic activity was highly correlated with the Glx concentration during rest with eyes open, and during flickering stimulation (also see Supplementary Material S11). Based on the assumption that the aperiodic intercept reflects broadband firing (Manning et al., 2009; Winawer et al., 2013), this suggests that the Glx concentration might be related to broadband firing in CC individuals during active and passive visual stimulation. As this is the first study testing a relationship between aperiodic EEG parameters and MRS parameters in humans, we interpret this finding based on results from non-human animals. In typically developed adults, sparse neuronal coding (Toyoizumi et al., 2013) after synaptic pruning reflected decorrelated activity (Chini et al., 2022; Sompolinsky et al., 2001; Trägenap et al., 2023; Vinje & Gallant, 2000). Given that visual deprivation resulted in interrupted pruning of predominantly excitatory synapses in monkeys' visual cortices (Bourgeois, 1996, 1997), we speculate that in the absence of adequate inhibitory tuning for incoming visual input, restored feedforward drive might result in more correlated spiking activity in CC individuals. Indeed, poorly tuned visual responses were evidenced in prior work with CC individuals, including larger (population) receptive fields (Heitmann et al., 2023) and a broader scalp topography of the first cortical visual event related potential (Sourav et al., 2018), as well as higher gamma band activity (Ossandón et al., 2023), which has been linked to firing in feedforward circuits (Van Kerkoerle et al., 2014). Electrophysiological studies with CC individuals have additionally demonstrated a reduced stimulus-selectivity of visual association cortex (Le Grand et al., 2001; Röder et al., 2013; Segalowitz et al., 2017), consistent with imprecise neural representations in this population.

Why might an enhanced inhibitory drive, as indicated by the lower Glx/GABA ratio and, possibly, the 1-20 Hz range of aperiodic EEG activity, not allow for complete recovery of neural tuning? As mentioned above, E/I balance is reflective of multiple interacting mechanisms, and typically maintained

by both feedforward inhibition and feedback-mediated inhibition (Froemke, 2015; Isaacson & Scanziani, 2011; Keck et al., 2017; Wu et al., 2022). Feedback connectivity typically emerges later than feedforward connectivity (Batardière et al., 2002; Burkhalter, 1993), and thus is likely more susceptible to damage from early sensory deprivation (Magrou et al., 2018; Yusuf et al., 2022). The markedly reduced alpha oscillatory activity during rest (Ossandón et al., 2023) and in response to white-noise stimulation (Pant et al., 2023) has been interpreted as indirect evidence for deficits in recurrent connectivity within the visual system of CC individuals. Moreover, deficits in the higher harmonic responses and intermodulation frequency responses in steady state visual-evoked responses (Pitchaimuthu et al., 2021), both indicative of bidirectional processing in visual cortex (Kim et al., 2011), have been reported as additional evidence for altered recurrent circuitry in CC individuals. Therefore, the downregulated E/I ratio in CC individuals reflected in the present study likely differs from fine-tuned inhibition within recurrent networks necessary for typical visual processing.

Aperiodic EEG activity correlated with chronological age in sight recovery individuals and normally sighted controls

In both the CC and SC group, the intercept of the aperiodic component of EEG activity decreased with chronological age, irrespective of condition. This chronological age effect replicates corresponding earlier reports in healthy populations (Hill et al., 2022; Voytek et al., 2015). The effect of chronological age in the present study is, again, similar to a correspondingly preserved effect of chronological age on the cortical thickness in CC individuals in cross-sectionally assessed MRI data (Hölig et al., 2023). The reduction of visual cortex thickness during childhood, after an initial increase, is a well-documented trend in brain development (Gilmore et al., 2020; Natu et al., 2019). Thus, we speculate that some typical developmental changes emerge despite aberrant visual experience.

Limitations

To the best of our knowledge, the present study is the first assessment of neurotransmitter concentrations within the visual cortex of sight recovery individuals with a history of congenital blindness by employing non-invasive MRS.

We are aware that MRS has a low spatial specificity. Moreover, MRS measures do not allow us to distinguish between presynaptic, postsynaptic and vesicular neurotransmitter concentrations. However, previous work has validated the link between MRS measures of GABA and Glutamate and the activity of inhibitory and excitatory neuronal assemblies, respectively, both in rodents and non-human

primates (Bielicki et al., 2004; Takado et al., 2022). Further, our phantom testing showed high correlations between the experimentally varied metabolite concentrations and the extracted GABA and Glx concentrations, validating the employed assessment and analysis pipelines (Figure S3). Finally, all reported group differences in MRS parameters were specific to visual cortex, and were not found for the frontal control voxel.

The sample size of the present study is relatively high for the rare population , but undoubtedly, overall, rather small. We nevertheless think that our results are valid. Our findings neurochemically (Glx andGABA+ concentration), and anatomically (visual cortex) specific. The MRS parameters varied with parameters of the aperiodic EEG activity and visual acuity. The group differences for the EEG assessments corresponded to those of a larger sample of CC individuals (n=38) (Ossandón et al., 2023), and effects of chronological age were as expected from the literature.

Conclusion

The present study in sight recovery individuals with a history of congenital blindness indicates that E/I balance is a result of early experience, and crucial for human behavior. We provide evidence that E/I balance in sight recovery individuals is altered even years after surgery, which might result from the previous adaptation to congenital blindness.

CONFLICT OF INTEREST

Dr. Sunitha Lingareddy is the Managing Director Radiology at Lucid Medical Diagnostics, Hyderabad, India. All other authors have no conflicts to declare.

AUTHOR CONTRIBUTIONS

RP, KP, JO, JF and BR conceptualized the study. RP, KP, IS and PR collected the data. IS, PR and RK diagnosed, recruited and provided clinical assessments of participants. RP, JO and KP analyzed the data. BR and JF supervised data analysis and methodological decisions. BR, RK and SL provided infrastructure, resources and funding. RP and BR wrote the original draft of the manuscript, and all authors provided edits and reviews on the final draft of the manuscript.

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KEYWORDS

Brain development, Sensitive periods, Visual Cortex, congenital cataracts, sight recovery, Excitatory-Inhibitory balance.

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Supplementary Material

S1. Magnetic Resonance Spectroscopy OFF-Spectra

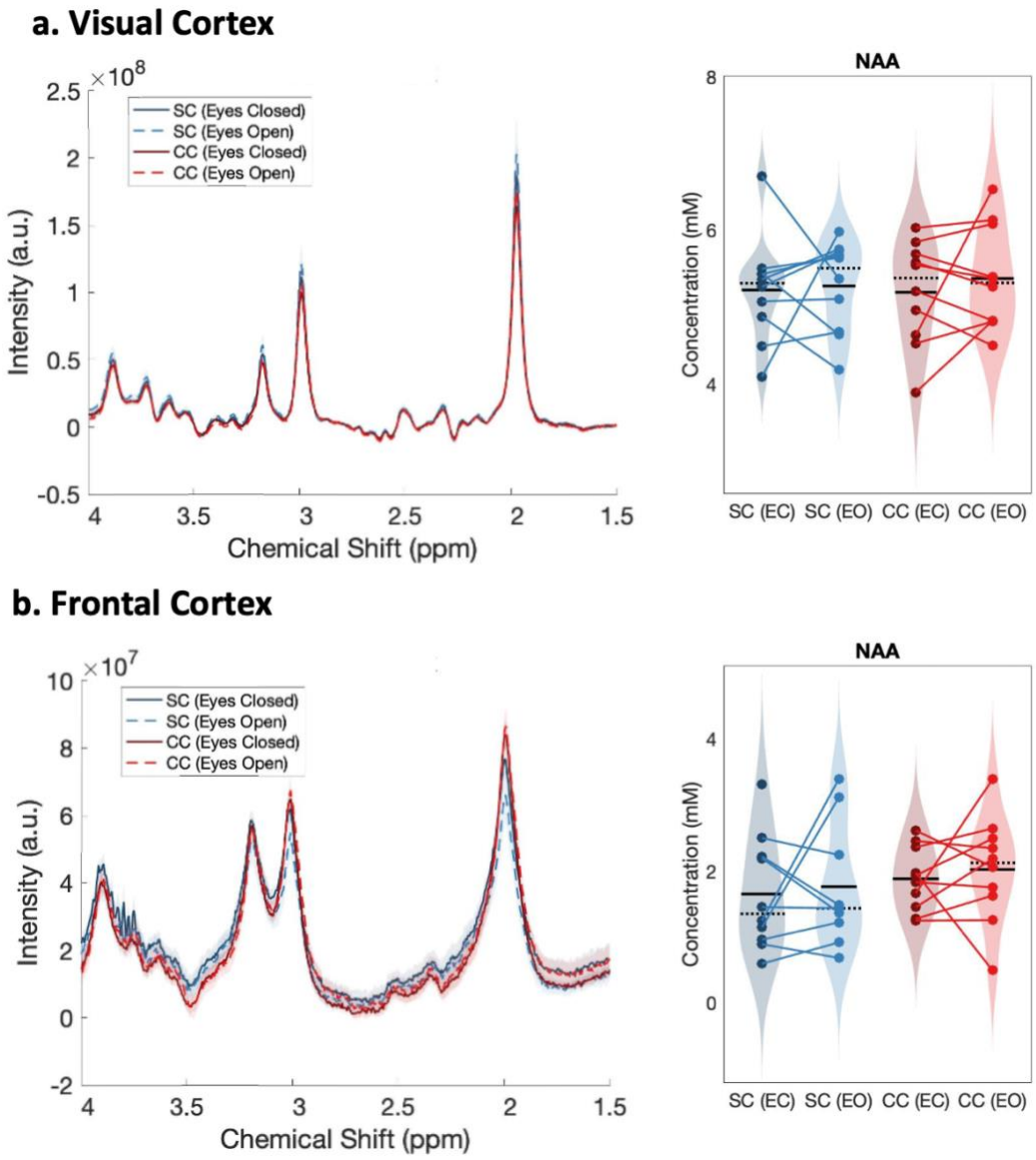

***Figure S1*: OFF spectra obtained from Magnetic Resonance Spectroscopy (MRS).** *a. Average spectra showing NAA peaks in the visual cortices of normally sighted individuals (SC, green) and individuals with reversed congenital cataracts (CC, red) are shown. Spectra are displayed for the eyes open (EO) and eyes closed (EC) conditions. The standard error of the mean is shaded. NAA concentration distributions for each group and condition are demonstrated as violin plots on the right. The solid black lines indicate mean values and dotted lines indicate median values. The coloured lines connect values of individual*

participants across conditions. b. Corresponding average MRS spectra and NAA concentration distributions measured from the frontal cortex are displayed.

S2. Tissue Fractions

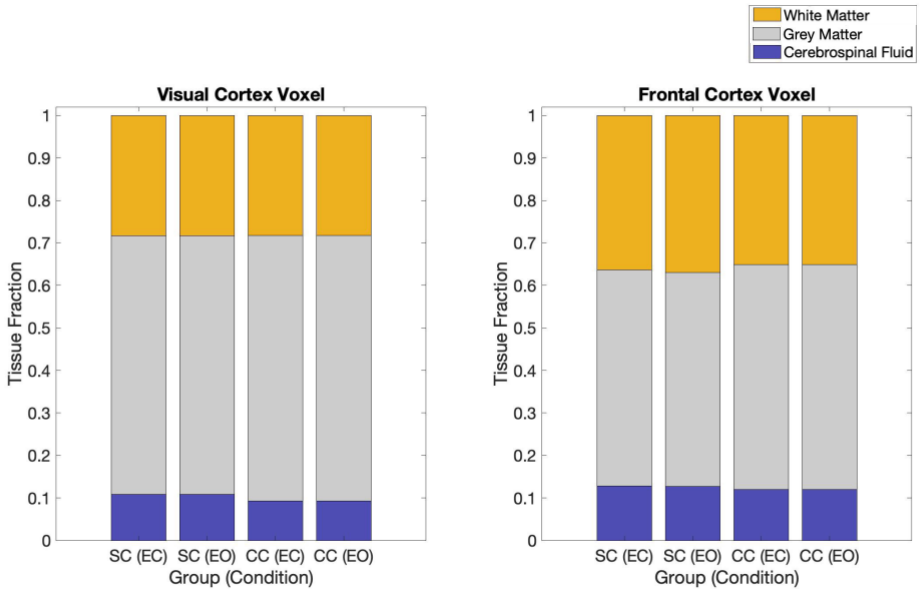

Figure S2: Tissue fractions for Magnetic Resonance Spectroscopy (MRS) voxels. *The fractions of white matter (yellow), grey matter (grey) and cerebrospinal fluid (blue) are displayed for the eyes open (EO), and eyes closed (EC) conditions in the congenital cataract-reversal group (CC) and the normally sighted control group (SC). Tissue fractions were separately calculated for the visual (left) and frontal (right) cortex voxels.*

S3. MRS Data Quality Metrics

Signal-to-Noise Ratio			
		CC	SC
Visual Cortex	GABA+	21.53 (3.66)	19.08 (3.99)
	Glx	23.75 (3.75)	22.18 (5.26)
Frontal Cortex	GABA+	10.311 (2.20)	8.30 (1.93)
	Glx	15.82 (4.85)	13.58 (3.86)
Full-Width-Half Maxima			
		CC	SC
Visual Cortex	GABA+	19.84 (1.13)	19.10 (0.71)

Frontal Cortex	Glx	16.62 (1.63)	16.46 (1.63)
	GABA+	21.69 (3.15)	23.23 (3.41)
	Glx	27.54 (8.70)	30.63 (12.64)
Fit Error			
		CC	SC
Visual Cortex	GABA+	3.42 (0.63)	3.68 (0.63)
	Glx	3.10 (0.58)	3.18 (0.47)
Frontal Cortex	GABA+	6.57 (2.20)	8.31 (3.65)
	Glx	4.44 (1.54)	5.15 (1.90)

Table S3: Quality metrics for edited Magnetic Resonance Spectroscopy data obtained from Gannet 3.0. *The mean quality metric reported across participants with the standard deviation in parentheses.* The *displayed quality metrics are those output from Gannet 3.0: Signal-to-noise-ratio (SNR), calculated in GannetFit.m by estimating the noise in the GABA+/Glx signal across acquisitions and dividing the absolute peak height of the GABA+/Glx signal by the estimated noise; Full-width-half-maxima (FWHM), defined as the width of the GABA+ peak in Hertz (Hz); and Fit Error, defined as the standard deviation of the residual of the GABA+/Glx peak fit, expressed as a percentage of the GABA+/Glx peak height.*

S4. Phantom Testing

Phantom testing was conducted to confirm the quality of the MRS data and analysis pipeline. GABA concentration was varied from 0 to 2mM in a 1L, 7.2 pH phantom with fixed metabolite concentrations of Cr (8 mM), NAA (15 mM), Glutamate (12 mM) and Glutamine (3 mM) (Jenkins et al., 2019). Phosphate Buffer Saline (PBS) was used to maintain the pH at room temperature. The base solution of several metabolites was included to gauge the quality of the overall signal as well as ensuring the similarity of the phantom to metabolites present in-vivo (Jenkins et al., 2019). The range of used GABA concentrations included the previously reported GABA concentration in the visual cortex of congenitally blind individuals (Weaver et al., 2013).

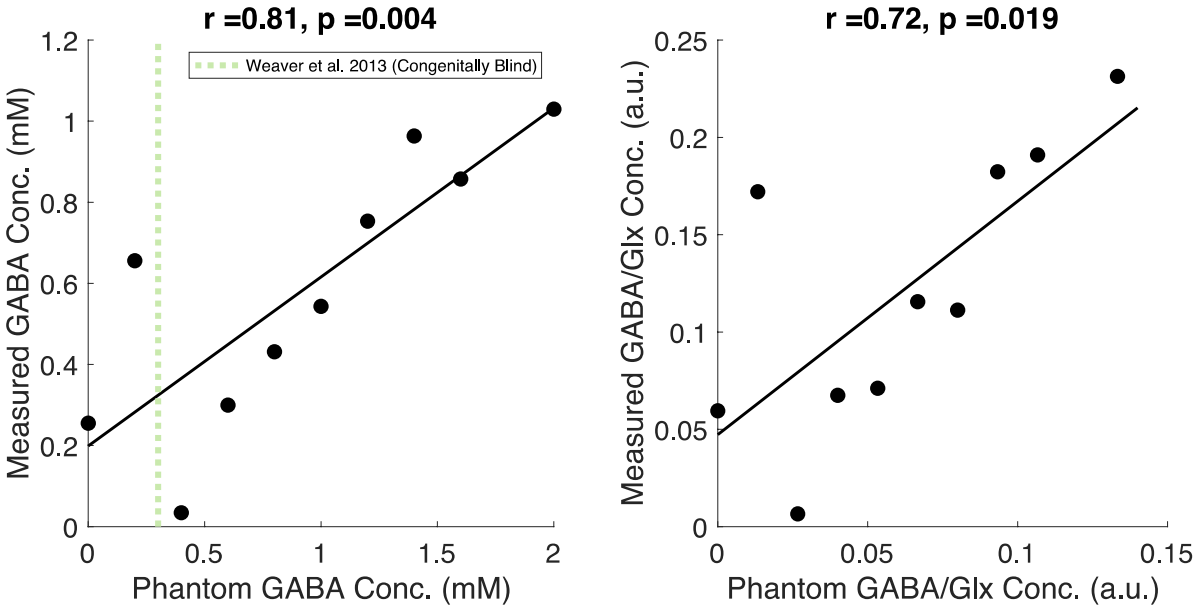

Figure S4: Phantom testing of GABA concentrations*. Plots depicting the correlation between known and measured concentrations from phantom scans of (left) Gamma-Aminobutyric Acid (GABA) and (right) ratio of GABA to Glutamate/Glutamine (Glx) concentration. In the left panel, previously reported GABA concentration from the visual cortex of congenitally blind individuals* (Weaver et al., 2013) *is marked with a vertical dotted line.*

Eleven phantom scans were obtained varying the known concentration of GABA in steps of 0.2 mM (corresponding to 0.0206 g) (Figure S4), the reported difference in visual cortex GABA concentration between early blind (mean = 0.3 mM) and normally sighted (mean = 0.5 mM) individuals' visual cortex (Weaver et al., 2013). Note that the authors reported that this group difference did not survive the Bonferroni-Holm correction. Nevertheless, to the best of our knowledge, no other study has reported significant GABA concentration differences between permanently congenitally blind humans and sighted controls based on MRS assessments in humans.

For both GABA+ and the concentration ratio of GABA+/Glx (calculated instead of Glx/GABA+ due to the 0-GABA concentration solution), our measured values showed significant agreement with the known phantom concentration values (Figure S4). These results demonstrate that our data acquisition and analysis pipeline were adequate to identify differences between CC and SC individuals' visual cortices within previously reported concentration ranges.

S5. Metabolite ratios

As a test of stability of within-participant MRS measurements, the visual cortex Glx/GABA+ ratio as well NAA/Cr, Cho/NAA and Cho/Cr ratios were compared within the same subjects tested at different time-points. Six normally sighted participants were scanned 2-4 weeks apart. The concentration ratios from the first and second scan were compared with t-tests were separately for the eyes closed (EC) and eyes open (EO) conditions (Figure S4). We did not find a significant difference in any of the four tested ratios across individuals (all p's > 0.271, all t's < 1.23).

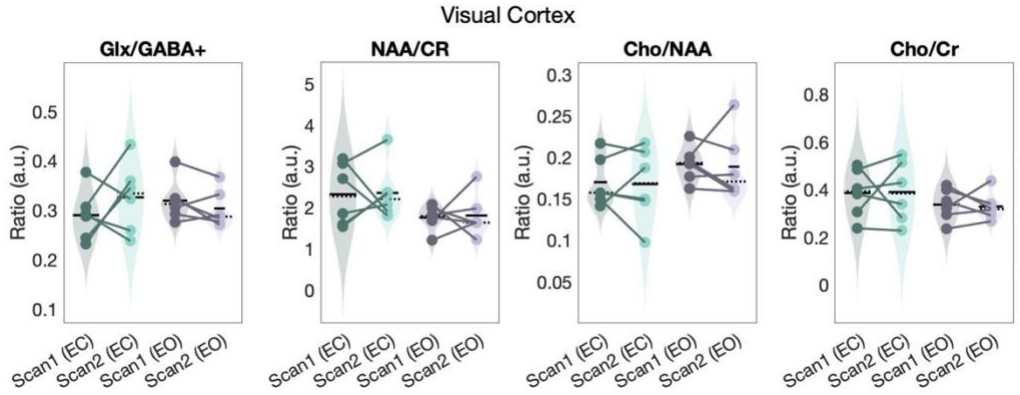

Figure S5: Within-subject metabolite ratio stability. *From left to right, violin plots depict the ratio of Glutamate/Glutamine (Glx) to Gamma-Aminobutyric acid complex (GABA+), N-Acetyl Aspartate (NAA) to Creatine (Cr), Choline (Cho) to NAA and Cho to Cr across two scans with the eyes opened (EO) and eyes closed (EC). Scans were conducted 2-4 weeks apart. Line segments indicate individual subjects across scans.*

S6. Exploratory correlation analysis between Magnetic Resonance Spectroscopy measures and visual deprivation history

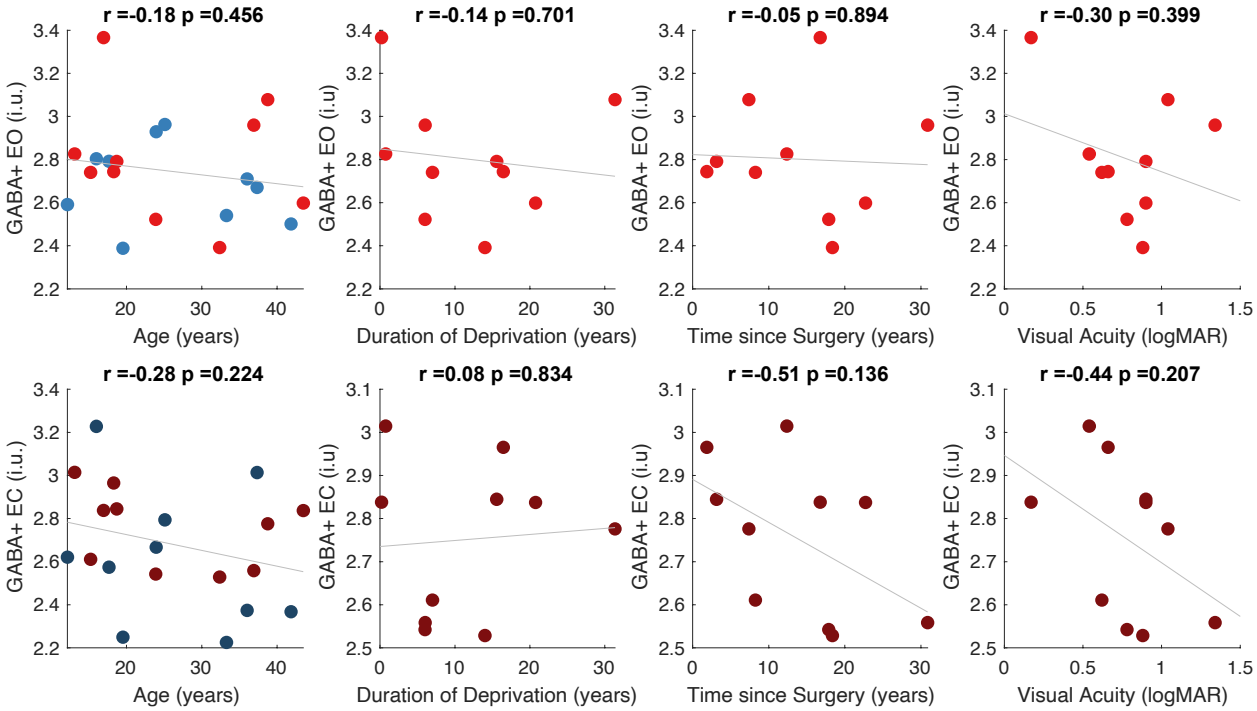

Figure S6.1. Effect of visual deprivation history on GABA+ concentration: *Correlations between visual cortex GABA concentration and (left to right) chronological age of the congenital cataract-reversal (CC, red) and normally sighted individuals (SC, blue), and duration of visual deprivation, time since surgery and visual acuity in the CC individuals, are depicted. Correlations were separately calculated for the eyes open (EO, top row) and eyes closed (EC, bottom row) conditions.*

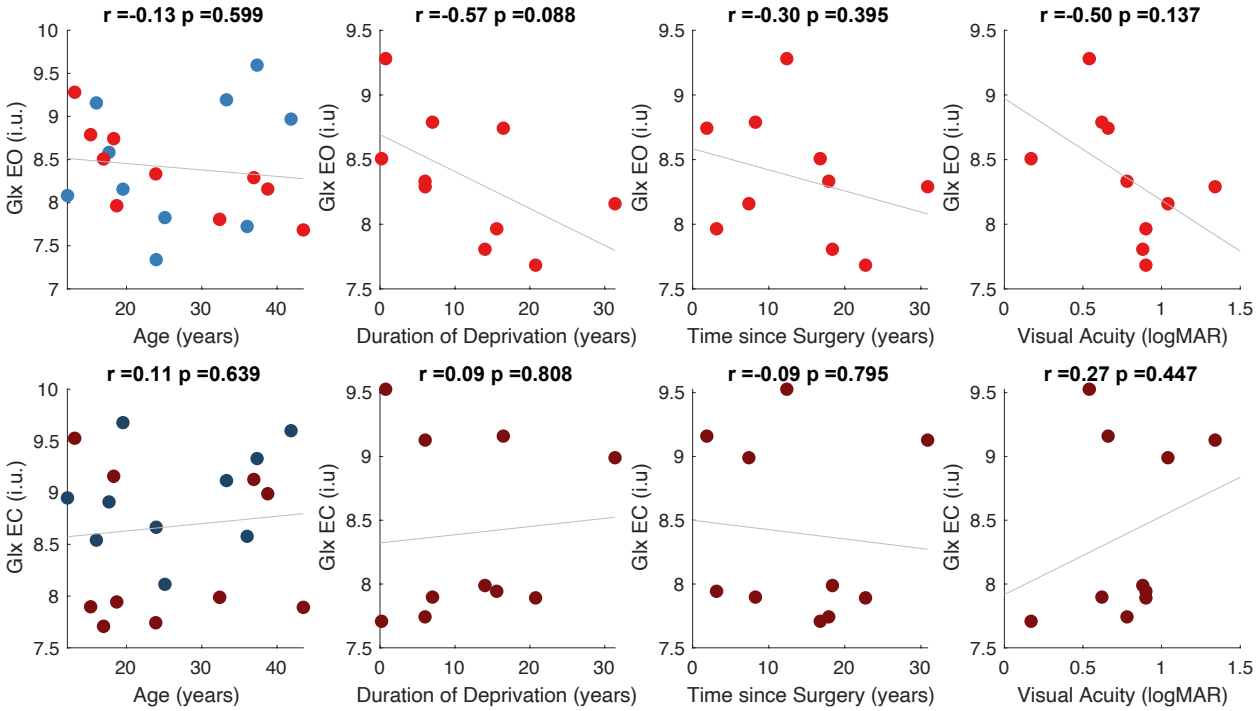

Figure S6.2. Effect of visual deprivation history on Glx concentration: *Correlations between visual cortex Glutamate/Glutamine (Glx) concentration and (left to right) age in the congenital cataract-reversal (CC, red) and normally sighted control (SC, blue) groups, and duration of visual deprivation, time since surgery and visual acuity in the CC group, are depicted. Correlations were separately calculated for the eyes open (EO, top row) and eyes closed (EC, bottom row) conditions.*

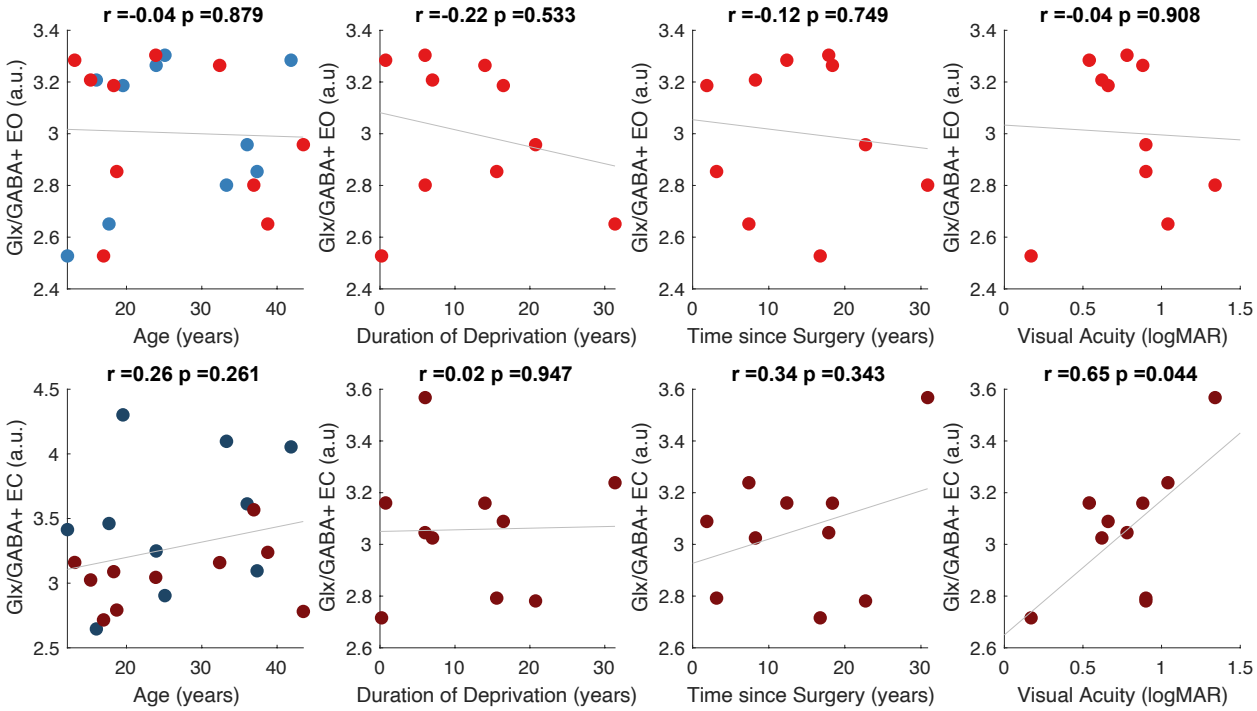

Figure S6.3. Effect of visual deprivation history on Glx/GABA concentration: *Correlations between visual cortex Glx/GABA concentration and (left to right) age in the congenital cataract-reversal (CC, red) and normally sighted control (SC, blue) groups, and duration of visual deprivation, time since surgery and visual acuity in the CC group, are depicted. Correlations were separately calculated for the eyes open (EO, top row) and eyes closed (EC, bottom row) conditions.*

S7. Exploratory correlation analysis between the aperiodic slope and intercept of the EEG power spectrum and visual deprivation history

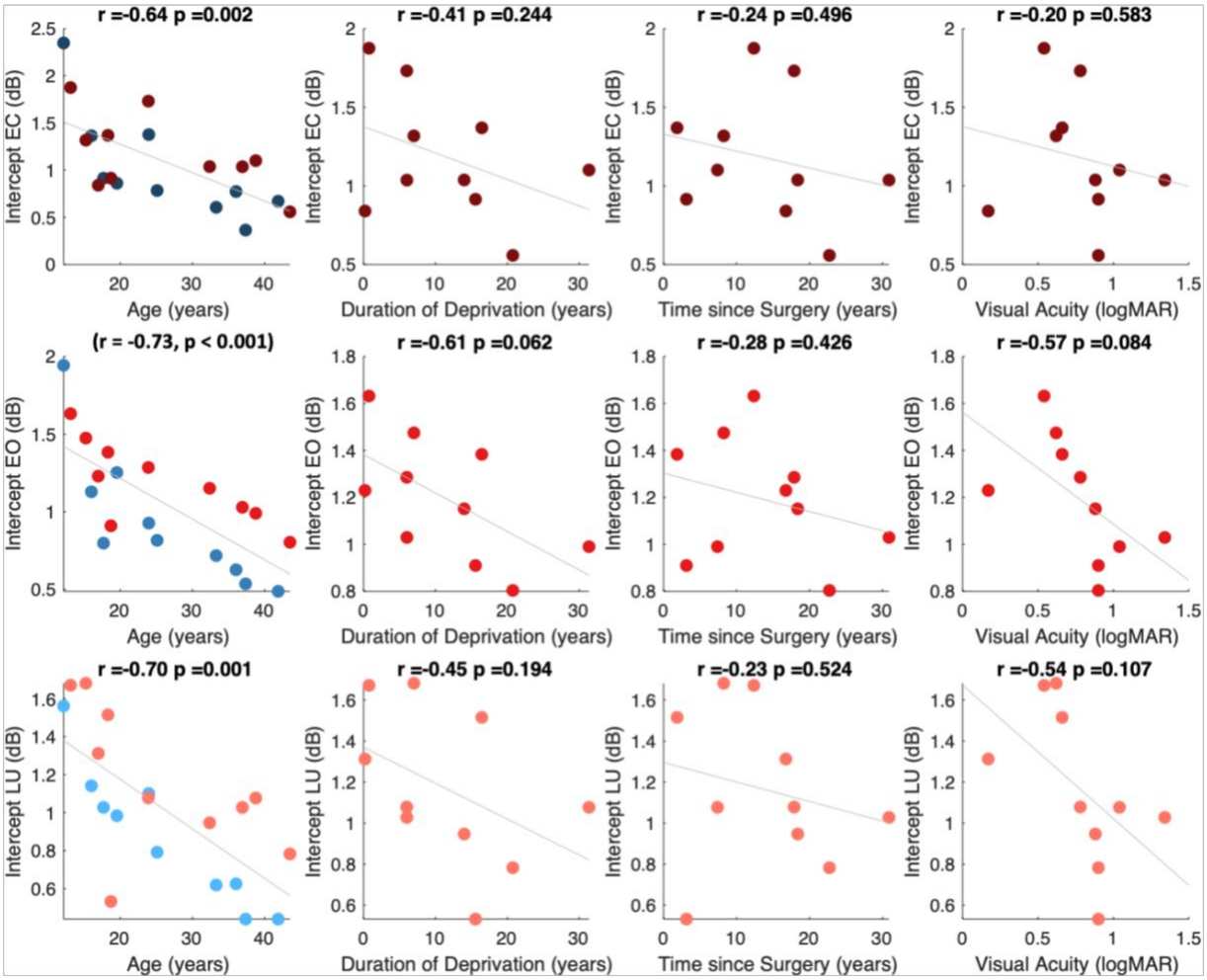

Figure S7.1: Effect of visual deprivation history on aperiodic intercept: *Correlations between aperiodic intercept and (left to right) age in the congenital cataract-reversal (CC, red) and normally sighted control (SC, blue) groups, and duration of visual deprivation, time since surgery and visual acuity in the CC group, are depicted. Correlations were separately calculated for the aperiodic intercept while participants viewed stimuli that changed in luminance (LU, top row) and the eyes open (EO, middle row) and eyes closed (EC, bottom row) conditions.*

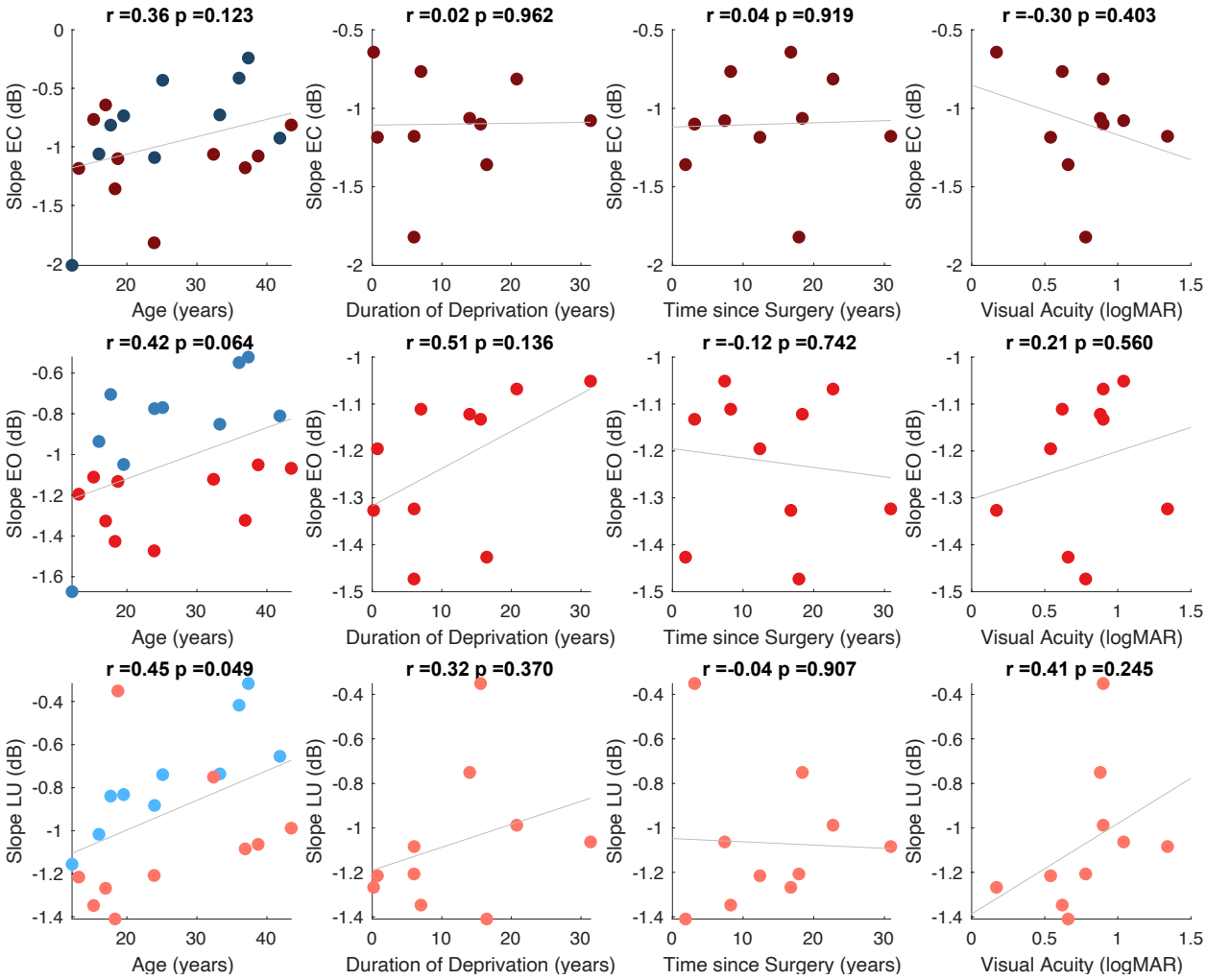

Figure S7.2: Effect of visual deprivation history on aperiodic slope: *Correlations between aperiodic slope and (left to right) age in the congenital cataract-reversal (CC) and normally sighted control (SC) groups, duration of visual deprivation, time since surgery and visual acuity in the CC group. Correlations separately calculated for the aperiodic slope while participants viewed flickering stimuli (LU, top row) and the eyes open (EO, middle row) and eyes closed (EC, bottom row) conditions.*

S8. Exploratory correlation analysis between Electroencephalography and Magnetic Resonance Spectroscopy measures

We tested the correlations between Glx, GABA+ and Glx/GABA+ measured at rest, and EEG aperiodic broadband intercept as well as slope in CC and SC individuals, measured at rest and while participants observed a flickering visual stimulus. Below, we report the exploratory correlations prior to Bonferroni correction for 6 comparisons (Figures S7.1 - S7.5). Note that the correlation found between

the aperiodic slope (1-20 Hz) and Glx concentration was not significant (all p's > 0.219) after correcting for multiple comparisons.

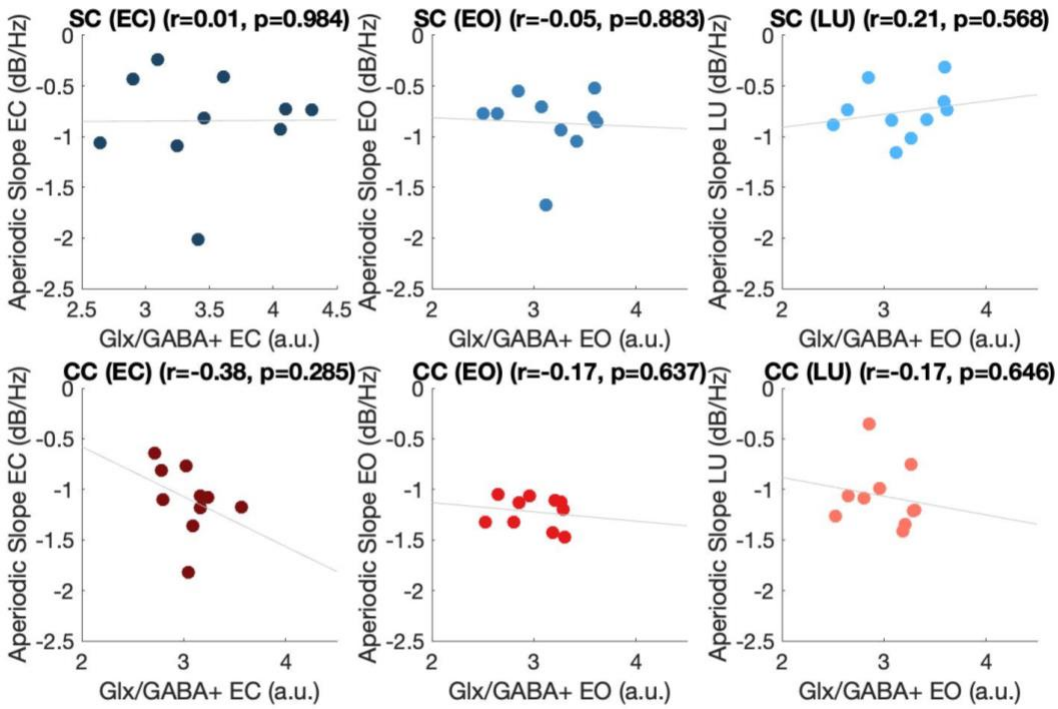

Figure S8.1: Correlation between aperiodic slope and Glx/GABA+ concentration. *Correlations between the aperiodic slope and visual cortex Glx/GABA+ concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between aperiodic slope measured while subjects viewed flickering stimuli (LU) and visual cortex Glx/GABA+ concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

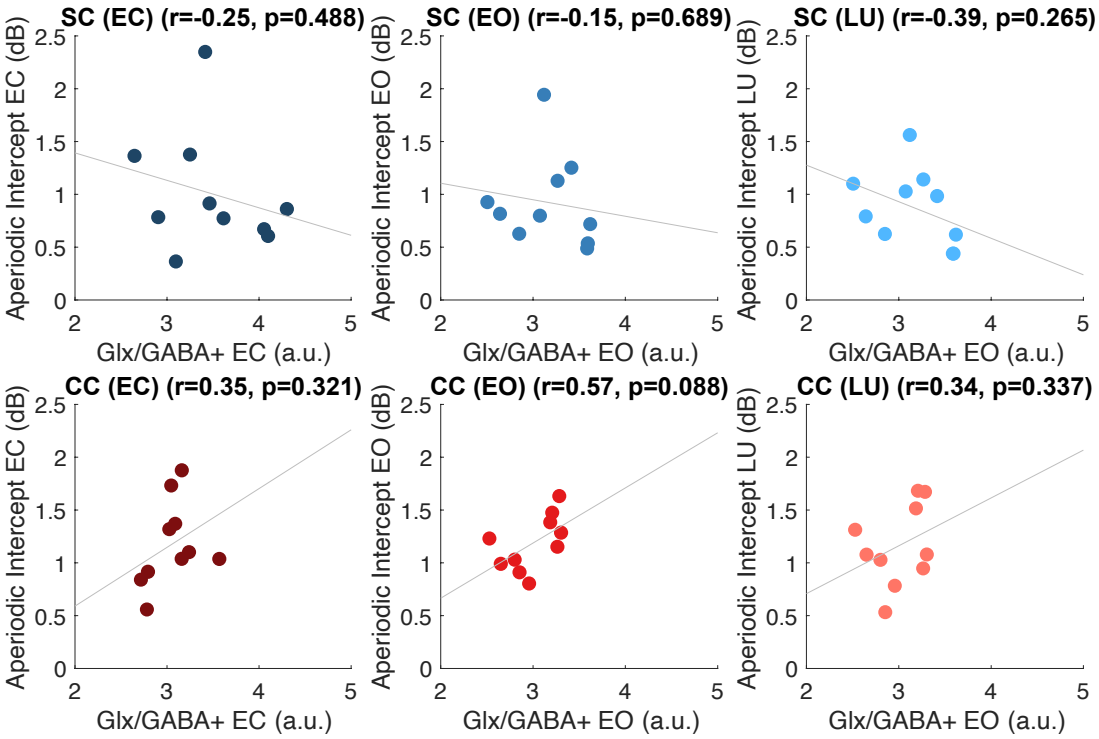

Figure S8.2: Correlation between aperiodic intercept and Glx/GABA+ concentration. *Correlations between the aperiodic intercept and visual cortex Glx/GABA+ concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between aperiodic intercept measured while subjects viewed flickering stimuli (LU) and visual cortex Glx/GABA+ concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

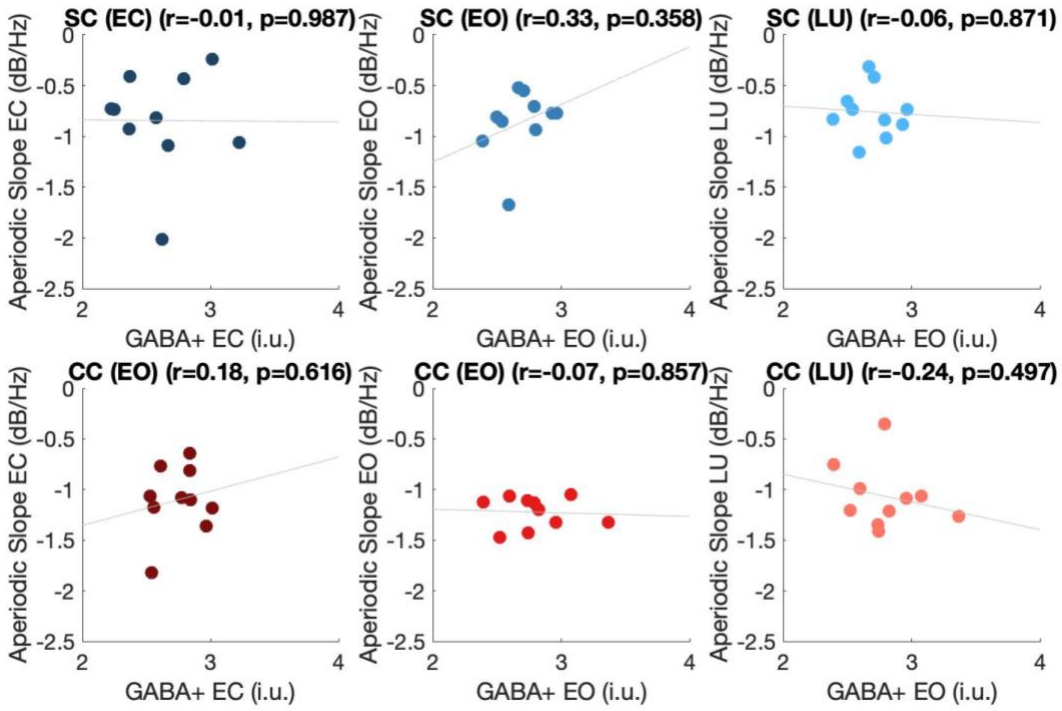

Figure S8.3: Correlation between aperiodic slope and GABA+ concentration. *Correlations between the aperiodic slope and visual cortex GABA+ concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between aperiodic slope measured while subjects viewed flickering stimuli (LU) and visual cortex GABA+ concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

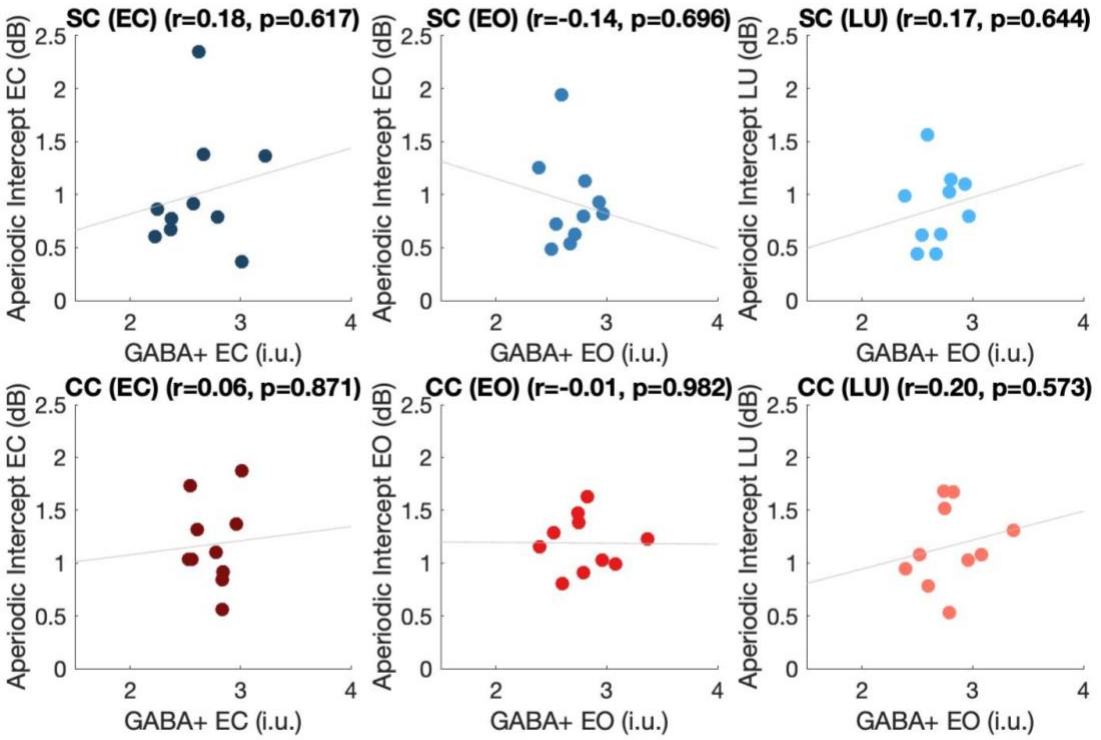

Figure S8.4: Correlation between aperiodic intercept and GABA+ concentration. *Correlations between the aperiodic intercept and visual cortex GABA+ concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between aperiodic intercept measured while subjects viewed flickering stimuli (LU) and visual cortex GABA+ concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

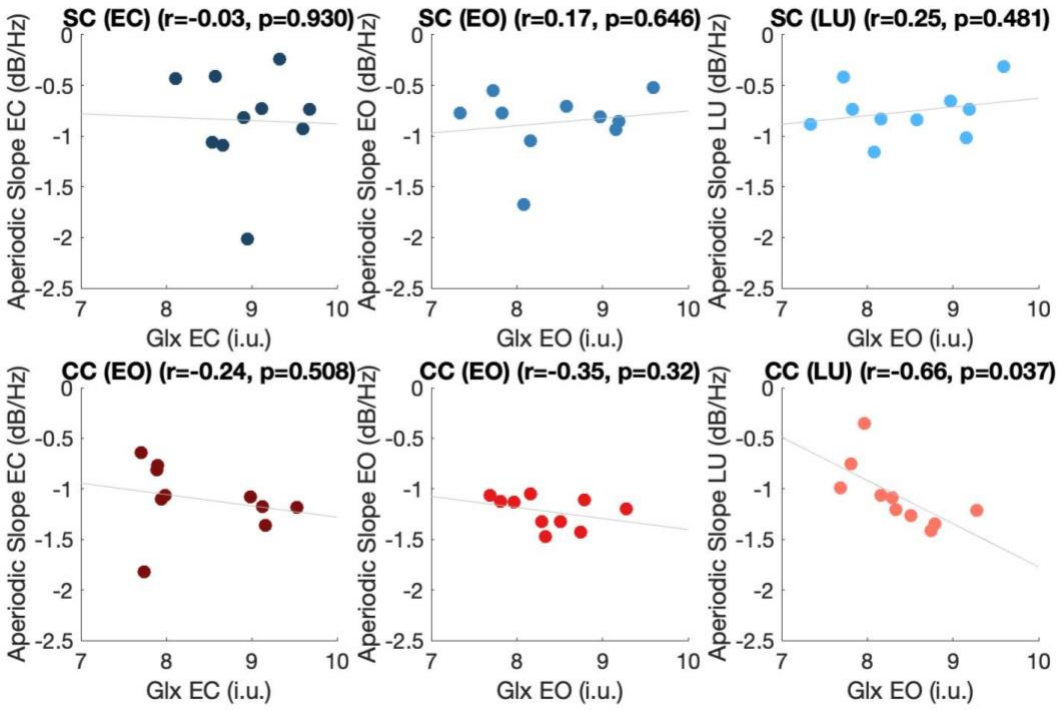

Figure S8.5: Correlation between aperiodic slope and Glx concentration. *Correlations between the aperiodic slope and visual cortex Glx concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between aperiodic slope measured while subjects viewed flickering stimuli (LU) and visual cortex Glx concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

S9: Correlation analysis between aperiodic slope and intercept

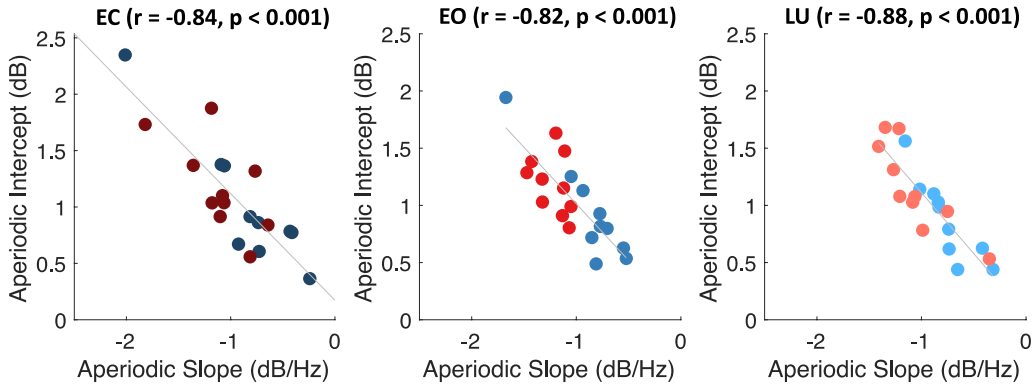

Figure S9: Correlations between aperiodic slope and aperiodic intercept. *Correlation between aperiodic slope and aperiodic intercept measured at rest with eyes closed (EC, left panel), eyes open (EO, middle*

panel), and while participants viewed flickering stimuli (LU, right panel). Correlations are shown across normally sighted control (SC, blue) and congenital cataract-reversal (CC, red) individuals.

S10. Individual subjects' MRS edited spectra (Visual Cortex)

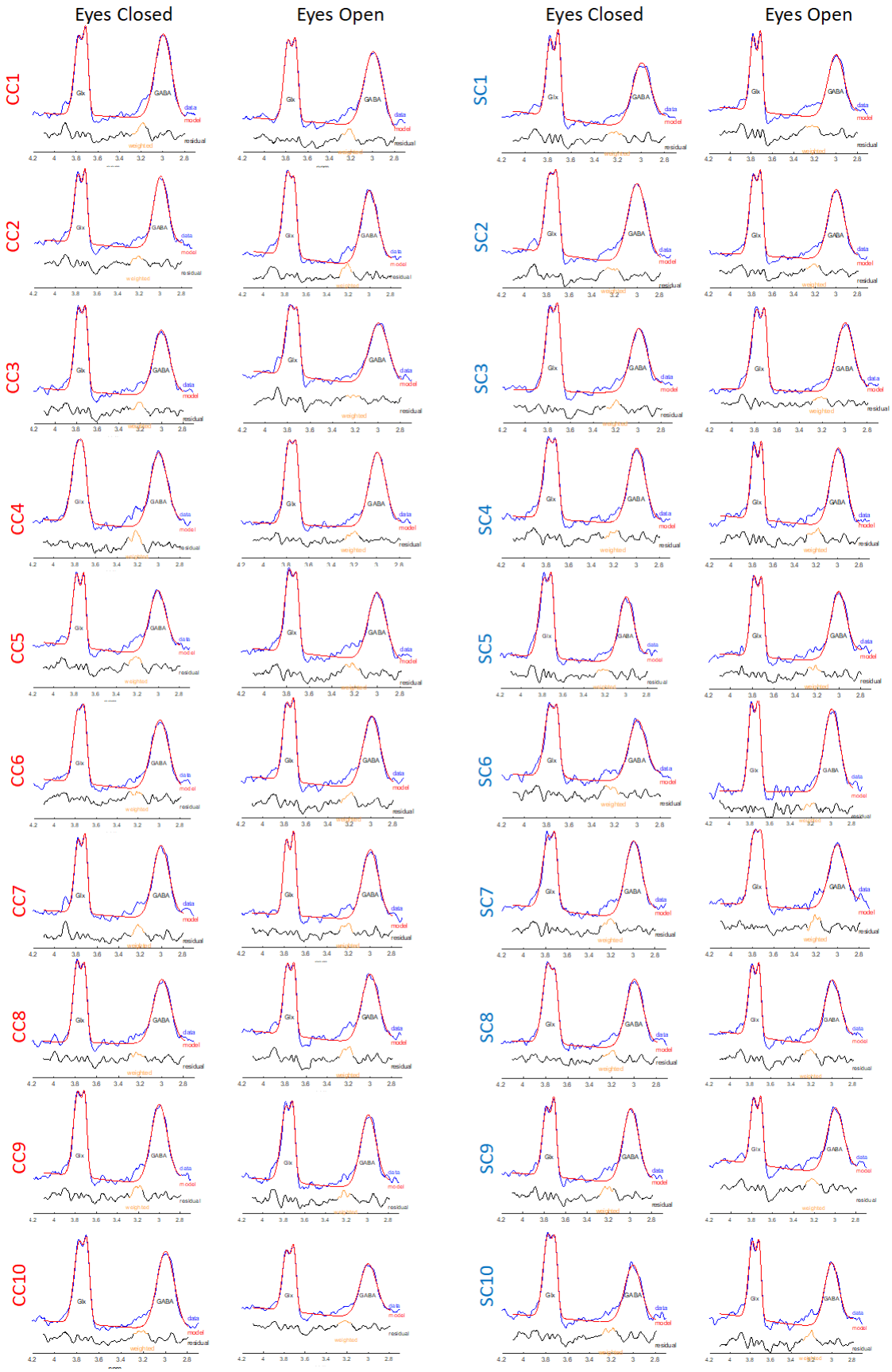
Eyes Closed
Eyes Open
Eyes Closed
Eyes Open
CC1
CC2
CC3
CC4
CC5
CC6
CC7
CC8
CC9
CC10
SC1
SC2
SC3
SC4
SC5
SC6
SC7
SC8
SC9
SC10
Glx
GABA
data
model
residual
weighted

Figure S10: Edited spectra of participants showing GABA+ and Glx peaks. *Individual participants' edited spectra and the respective model fits for congenital cataract-reversal (CC, left) and normally sighted control (SC, right) individuals. Spectra are shown as output by GannetFit.m for the eyes closed and eyes open conditions for each subject.*

S11. Exploratory correlation analysis between high frequency (20-40 Hz) aperiodic slope and Glutamate/Glutamine (Glx) concentrations

Given the surprisingly high correlation we observed between Glutamate/Glutamine (Glx) concentration in the visual cortex and the EEG aperiodic intercept in the 1-20 Hz range, we exploratorily tested the correlation between Glx and the aperiodic slope and intercept in the 20-40 Hz range. These data were available for the eyes open (EO) and eyes closed (EC) resting state conditions for every participant. Correlations were not calculated for the flickering stimulation (LU) condition as stimulation frequencies ranged from 1-30 Hz. Congenital cataract-reversal (CC) individuals showed a similarly high correlation between Glx concentration and the 20-40 Hz aperiodic intercept ($r = 0.77$, $p = 0.009$) as with the 1-20 Hz aperiodic intercept while watching ambient visual stimulation at rest (Figure 5). No such correlation was found while CC individuals' eyes were closed or in the normally sighted control (SC) group (Figure S10.1, S10.2). The relationship between Glx and aperiodic slope was in the same direction for the 1-20 Hz and 20-40 Hz slope values across CC individuals (Figure S7.5). Glx concentration was inversely correlated with the steepness of slope ($r = -0.74$, $p = 0.0149$), that is, the higher the Glx concentration, the steeper was the slope of the aperiodic component. This correlation of the steepness of the aperiodic slope with higher Glx concentration in CC individuals was the same as in the lower (1-20 Hz) frequency range (see S7.5). Note that this correlation is reported exploratorily and has not been corrected for multiple comparisons. No such correlations were found between the aperiodic slope or intercept and GABA+ or Glx/GABA+ concentrations.

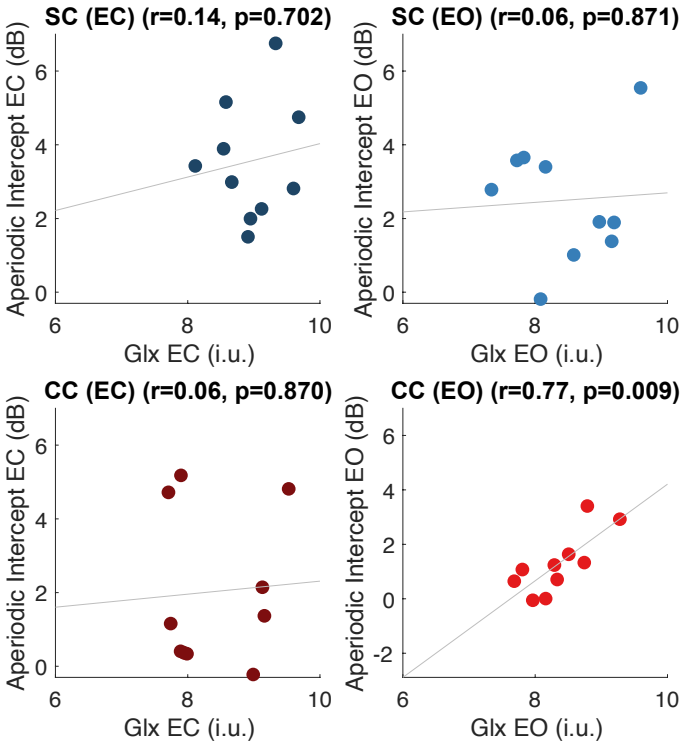

Figure S11.1: Correlation between aperiodic intercept (20-40 Hz) and Glx concentration. *Correlations between the aperiodic intercept (20-40 Hz) and visual cortex Glx concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (right panels) are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

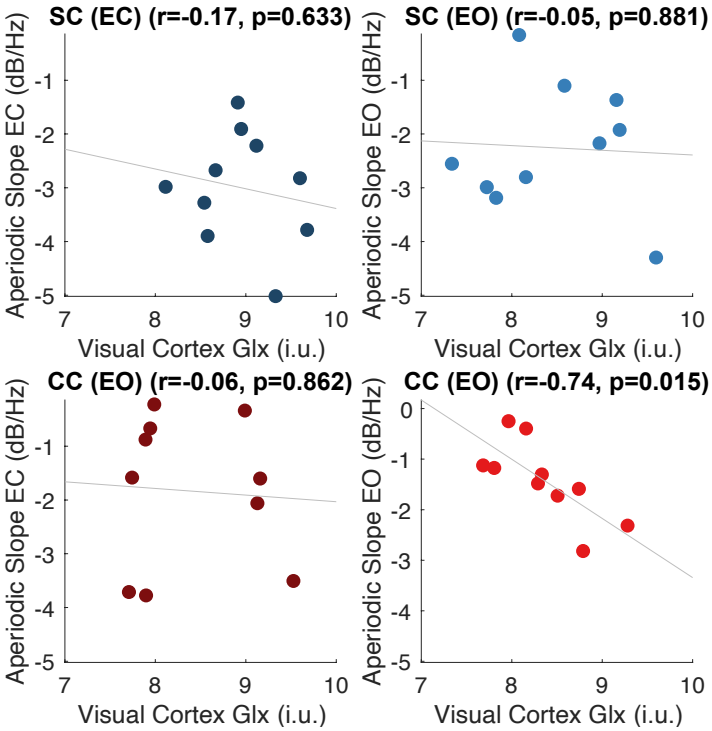

Figure S11.2: Correlation between aperiodic (20-40 Hz) slope and Glx concentration. *Correlations between the higher (20-40 Hz) aperiodic slope and visual cortex Glx concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (right panels) are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

S12. Exploratory correlation between alpha power and neurotransmitter concentration

Previous literature has repeatedly suggested that a transient period of congenital visual deprivation permanently lowers the amplitude of EEG alpha activity at occipital electrodes (Bottari et al., 2016; Ossandón et al., 2023; Pant et al., 2023). Additionally, one study applied lorazepam, a GABA agonist, and reported that the alpha amplitude was related to GABAergic transmission (Lozano-Soldevilla et al., 2014). We exploratorily assessed the correlation between alpha power and neurotransmitter concentrations to test whether they might be related to lowered alpha power during eyes opening (EO) or closure (EC) at rest, or while viewing flickering stimuli (LU). In the CC group but not in normally sighted control (SC) individuals, Glx concentration in the visual cortex was significantly correlated with alpha power while participants viewed flickering stimuli (LU condition: r = 0.71, p = 0.023); a trending correlation of Glx concentration and alpha power in the EO condition was additionally observed (r=0.62, p=0.052; Figure S11.2). Correspondingly, a trending correlation was found between CC but not SC

individuals' alpha amplitude and GABA+ concentration while their eyes were closed (r = 0.63, p = 0.0503) (Figure S11.1). No correlations between Glx/GABA+ ratios and alpha amplitude were found in either group (Figure S11.3). Note that these correlations are exploratorily reported here without correction for multiple comparisons.

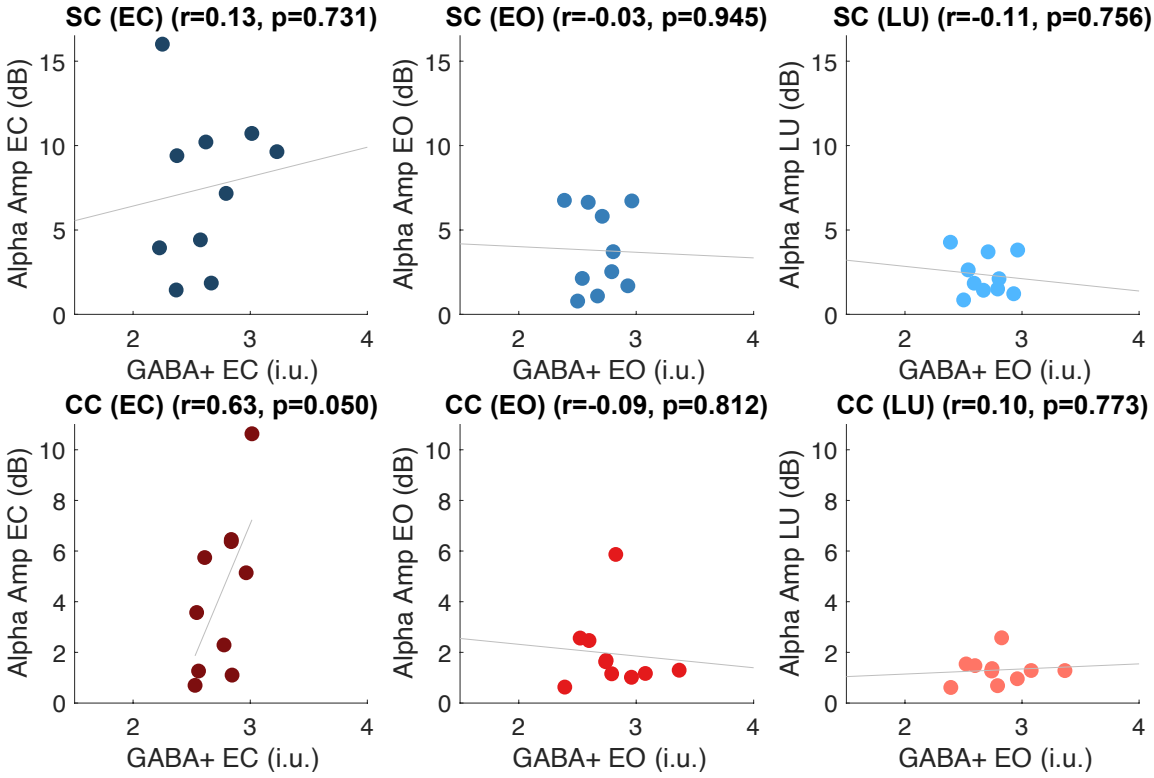

Figure S12.1: Correlation between alpha amplitude (8-14 Hz) and GABA+ concentration. *Correlations between the alpha amplitude and visual cortex GABA+ concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between alpha amplitude measured while subjects viewed flickering stimuli (LU) and visual cortex GABA+ concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for normally sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

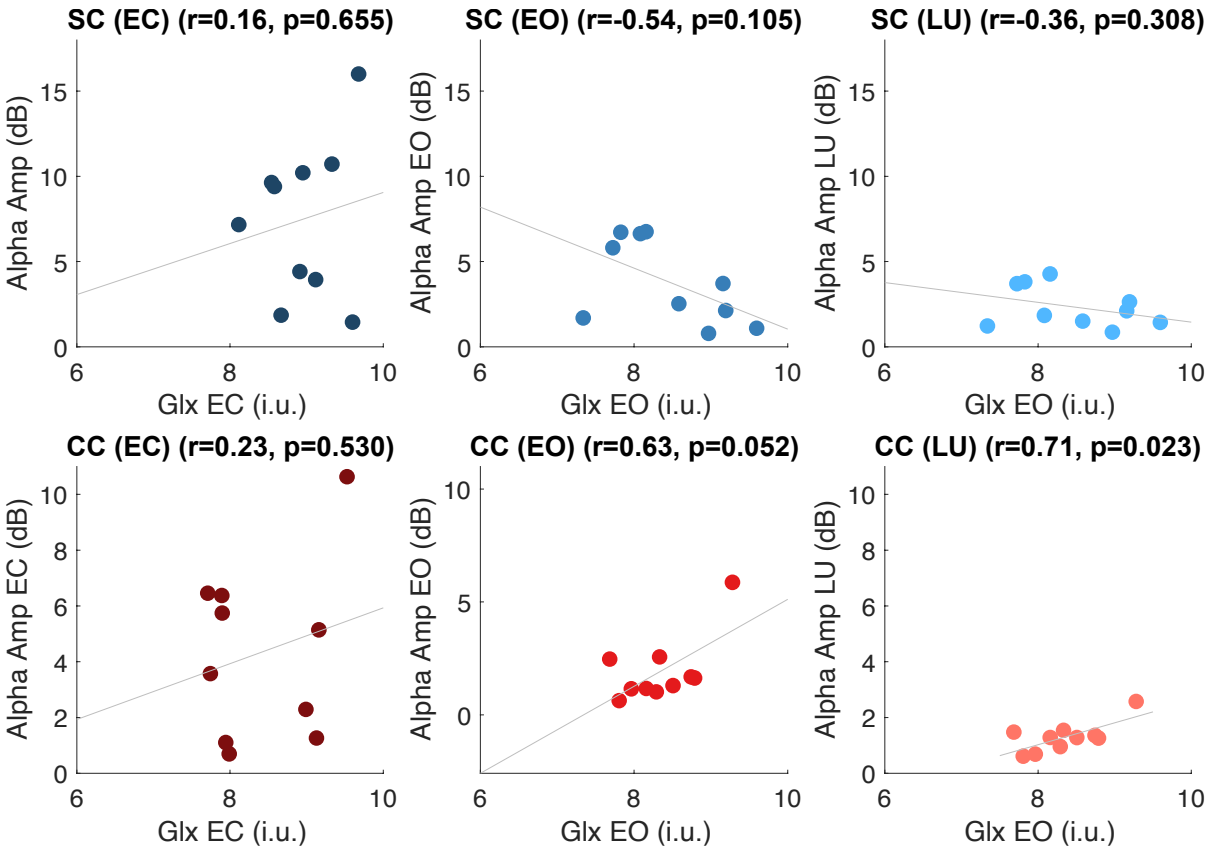

Figure S12.2: Correlation between alpha amplitude (8-14 Hz) and Glx concentration. *Correlations between the alpha amplitude and visual cortex Glx concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between alpha amplitude measured while subjects viewed flickering stimuli (LU) and visual cortex Glx concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

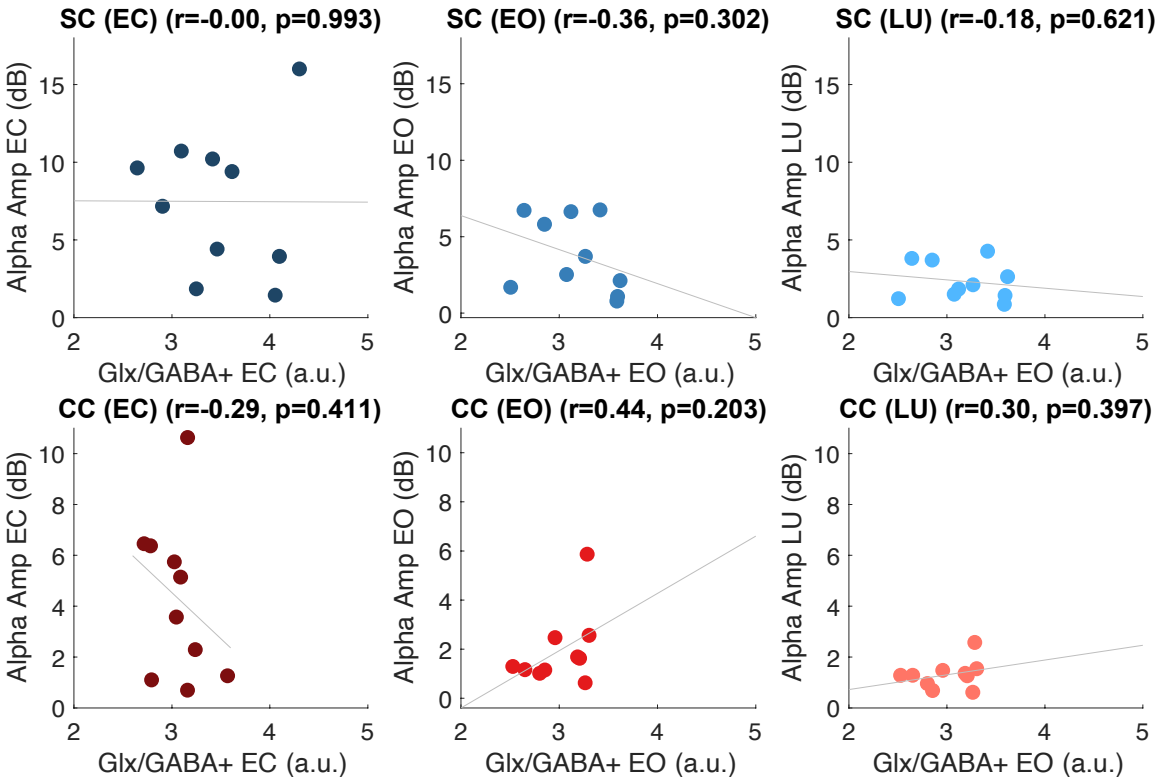

Figure S12.3: Correlation between alpha amplitude (8-14 Hz) and Glx/GABA+ concentration. *Correlations between the alpha amplitude and visual cortex Glx/GABA+ concentration measured at rest with eyes closed (EC) (left panels) and eyes open (EO) (middle panels), and the correlation between alpha amplitude measured while subjects viewed flickering stimuli (LU) and visual cortex Glx/GABA+ concentration measured in the EO condition (right panels), are depicted. Correlations were calculated separately for sighted control (SC, blue, top row) and congenital cataract-reversal (CC, red, bottom row) individuals.*

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Pant, R., Ossandón, J., Stange, L., Shareef, I., Kekunnaya, R., & Röder, B. (2023). Stimulus-evoked and resting-state alpha oscillations show a linked dependence on patterned visual experience for development. *NeuroImage: Clinical*, 103375. https://doi.org/10.1016/J.NICL.2023.103375

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Appendix II

Pant et al., (2023). Stimulus-evoked and resting-state alpha oscillations show a linked dependence on patterned visual experience for development. NeuroImage:Clinical, Vol. 38, 103375.

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Stimulus-evoked and resting-state alpha oscillations show a linked dependence on patterned visual experience for development

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ABSTRACT

Persistent visual impairments after congenital blindness due to dense bilateral cataracts have been attributed to altered visual cortex development within a sensitive period. Occipital alpha (8–14 Hz) oscillations were found to be reduced after congenital cataract reversal, while participants performed visual motion tasks. However, it has been unclear whether reduced alpha oscillations were task-specific, or linked to impaired visual behavior in cataract-reversed individuals. Here, we compared resting-state and stimulus-evoked alpha activity between individuals who had been treated for dense bilateral congenital cataracts (CC, n = 13, mean duration of blindness = 11.0 years) and age-matched, normally sighted individuals (SC, n = 13). We employed the visual impulse response function, adapted from VanRullen and MacDonald (2012), to test for the characteristic alpha response to visual white noise. Participants observed white noise stimuli changing in luminance with equal power at frequencies between 0 and 30 Hz. Compared to SC individuals, CC individuals demonstrated a reduced likelihood of exhibiting an evoked alpha response. Moreover, stimulus-evoked alpha power was reduced and correlated with a corresponding reduction of resting-state alpha power in the same CC individuals. Finally, CC individuals with an above-threshold evoked alpha peak had better visual acuity than CC individual without an evoked alpha peak. Since alpha oscillations have been linked to feedback communication, we suggest that the concurrent impairment in resting-state and stimulus-evoked alpha oscillations indicates an altered interaction of top-down and bottom-up processing in the visual hierarchy, which likely contributes to incomplete behavioral recovery in individuals who experienced transient congenital blindness.

1. Introduction

Dense bilateral congenital cataracts can cause complete patterned visual deprivation in humans (Birch et al., 2009). Delayed treatment results in increasingly severe visual impairment the later patients undergo surgery, which has been attributed to altered neural development instead of predominantly peripheral eye abnormalities (Maurer & Hensch, 2012; Röder & Kekunnaya, 2021). Based on invasive electrophysiological recordings in cochlear-implanted deaf cats (Yusuf et al., 2021, 2022), it was hypothesized that delayed sensory experience following birth particularly affects the elaboration of top-down processing (Röder & Kekunnaya, 2021), which is crucial for modulation of bottom-up signals. This hypothesis is consistent with feedback processing relying on corticocortical pathways, which showed a longer developmental trajectory than feedforward pathways in the mammalian visual cortex (Burkhalter, 1993; Ibrahim et al., 2021; Batardière et al., 2002).

Consistent with impaired feedback processing in the absence of visual experience, electroencephalography (EEG) studies in individuals treated for congenital cataracts reported reduced alpha (8–14 Hz) oscillations during visual motion tasks (Bottari et al., 2016; Bottari et al., 2018). Multiple lines of evidence have linked alpha oscillations in the human EEG to feedback control of neural excitation in the visual cortex (Jensen & Mazaheri, 2010; Klimesch et al., 2007). Similar to findings from cataract-reversed individuals, permanently congenitally blind individuals also demonstrated lower alpha activity during non-visual tasks (Kriegseis et al., 2006) and at rest (Kriegseis et al., 2006; Novikova, 1974).

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Available online 13 March 2023

A special role of alpha oscillations in vision has been suggested by two widely-observed phenomena: first, the human EEG features prominent alpha oscillations at rest, which are enhanced with eye closure (Adrian & Matthews, 1934). Second, visual stimulation in the alpha range caused greater entrainment (Thut et al., 2011) of neural oscillations than at any other frequencies (Başar et al., 1997; Herrmann, 2001). Alpha oscillations were interpreted as the "natural frequency" at which an internal oscillator can be entrained by stimulation, resulting in an enhanced response (Notbohm et al., 2016; VanRullen, 2016). Preferred neural responses in the alpha range were further observed in the impulse response function of the visual system to unbiased visual white-noise (Childers & Perry, 1971; Lalor et al., 2007). VanRullen and MacDonald (2012) employed white-noise stimulation, which changed in luminance with equal power between 0 and 80 Hz. Occipital EEG responses were cross-correlated with the presented luminance values, revealing a peak in the alpha range of the cross-correlation spectrum. This phenomenon purportedly reflected an increased response of the visual system, typically oscillating at rest in the alpha range, to the alpha frequencies in the stimuli (Notbohm et al., 2016; Vanrullen & MacDonald, 2012). A correlation was observed between the amplitudes and frequencies of the resting-state and evoked alpha peaks, suggesting that both phenomena were linked. Based on such a relationship, and given the reduction of alpha oscillations in congenital blindness at rest (Novikova, 1974), we expected to find a reduction of both stimulus-evoked and resting-state alpha oscillations in cataract-reversed individuals.

Alternate accounts, however, interpreted evoked alpha oscillations as the linear addition of bottom-up activity from each stimulus, without reliance on resting-state alpha oscillations (Capilla et al., 2011; Keitel et al., 2019). Under this account, alpha reduction in cataract-reversed individuals might be specifically linked to visual processing, possibly as a consequence of impaired extrastriate processing (Sourav et al., 2018).

We adapted the EEG paradigm from VanRullen and MacDonald (2012) to elicit stimulus-evoked oscillations and unbiasedly determine the response properties of the visual cortex in sight-recovery individuals who underwent transient congenital blindness. Further, resting-state EEG was recorded with both eyes opened and eyes closed. Thirteen cataract-reversed individuals, who had been born blind due to bilateral dense cataracts, were compared to 13 age-matched, normally-sighted controls. We observed reduced alpha activity in the stimulus-evoked impulse response in cataract-reversed individuals, which was linked to lower visual acuity. The same individuals demonstrated reduced resting-state alpha oscillations. We interpreted these findings as evidence of compromised development of recurrent processing of the visual environment, resulting in poor vision.

2. Methods

2.1. Participants

We tested two groups of participants.

The first group consisted of individuals who had been deprived of patterned vision at birth due to delayed treatment for dense bilateral congenital cataracts (CC individuals; n = 13, 3 female, Mean Age = 23.1 years, SD = 10.9 years, Range = 10.9 – 43.5 years) (Table 1). This group was recruited at the LV Prasad Eye Institute (LVPEI) by ophthalmologists and optometrists. Diagnosis of these patients was based on the following combination of criteria: the presence of dense bilateral congenital cataracts at birth, occlusion of the fundus, nystagmus, a diagnosis of dense bilateral congenital cataracts in immediate family members, and a visual acuity of counting fingers at 1 m or less prior to surgery, barring cases of absorbed lenses. Absorbed lenses occur specifically in individuals with dense congenital cataracts (Ehrlich, 1948). Participants with absorbed lenses were diagnosed based on the morphology of the lens, anterior capsule wrinkling, and plaque or thickness of stroma. All 13 participants lacked stereovision, and 9 of 13 participants were implanted with intraocular lenses (Mean Visual Acuity = 0.85, SD = 0.40, Range = 0.17–1.78, all measured in logMAR units). Participants wore their optical corrections for the duration of the experiment. Maternal rubella was excluded as a cause of congenital cataracts in this group; explicitly excluded in the medical files of 11 participants, and not noted in the medical records of 2 participants (Supplementary Table S9).

All but two participants in this group were operated on after at least 1 year of patterned visual deprivation prior to surgery (Mean duration of blindness = 11 years, Range = 0.2 – 31.4 years). One participant received cataract removal surgery at the age of 3 months (Table 1). All participants were tested at least 11 months after receiving cataract removal surgery (Mean time since surgery = 12 years, Range = 0.9 – 30.9 years) to exclude acute effects, and to allow for extensive post-surgical visual experience.

The second group was recruited from the local area of the city of Hyderabad, and consisted of normally sighted individuals (SC, n = 13, 2

Table 1
Demographic and clinical information of the participants with a history of dense bilateral congenital cataracts (CC). NA indicates patient's data for the field were not available. FFL: Fixating and Following Light; CF: Counting Fingers; PL: Perceiving Light. Duration of visual deprivation was calculated by subtracting the date of birth from the date of surgery on the first eye. Time since surgery was calculated by subtracting the date of surgery in the first eye from the date of testing. Visual acuity reported was on the date of testing and measured using the Freiburg Vision Test (FrACT) (Bach, 2007).

	COMORBIDITIES			GENDER	VISUAL ACUITY PRE-SURGERY		DURATION OF VISUAL DEPRIVATION (YEARS)	TIME SINCE SURGERY (YEARS)	VISUAL ACUITY ON DATE TESTED (LOGMAR)	FAMILY HISTORY	INTRA-OCULAR LENS
	ABSORBED LENSES	STRABISMUS	NYSTAGMUS		OD	OS					
1	No	Yes	Yes	Male	FFL -	FFL +	0.2	16.8	0.17	No	Yes
2	Yes	Yes	Yes	Male	1.18	1	20.8	22.7	0.9	Yes	Yes
3	Yes	Yes	Yes	Male	1.48	1.77	15.6	3.1	0.9	No	No
4	Yes	NA	Yes	Male	CF at 1.5 *m*	CF at 3 *m*	7.0	8.2	0.62	No	Yes
5	No	Yes	Yes	Male	NA	NA	14.0	18.4	0.88	Yes	Yes
6	No	Yes	Yes	Male	NA	NA	6.0	17.9	0.78	Yes	Yes
7	No	Yes	Yes	Male	PL+	PL+	0.8	12.4	0.54	No	No
8	Yes	Yes	Yes	Male	1.2	1.3	16.4	1.9	0.66	Yes	Yes
9	No	Yes	Yes	Male	NA	NA	5.0	5.9	0.93	Yes	No
10	No	Yes	Yes	Female	NA	NA	5.0	11.0	0.5	Yes	Yes
11	Yes	Yes	Yes	Female	1.77	1.77	15.0	0.9	1.78	Yes	Yes
12	No	NA	Yes	Male	NA	NA	6.0	30.9	1.34	Yes	No
13	Yes	Yes	Yes	Female	1.48	1.48	31.4	7.4	1.04	Yes	Yes

female, Mean Age = 25.2 years, SD = 9.4 years, Range = 12.1 – 41.8 years). The two groups did not differ in mean age (t(24) = 0.52, p = 0.606).

All participants were tested at the LVPEI in English, Hindi or Telugu. None had a history of genetic, neurological or cognitive disorders. All participants (and their parents or legal guardians in case of minors) gave written informed consent. The study was approved by the Local Ethics Commission of the LVPEI, Hyderabad, India, as well as the ethics board of the Faculty of Psychology and Human Movement, University of Hamburg (UHH, Hamburg, Germany). Participants were compensated for costs associated with participation in this study including travel and accommodation. Children were additionally given a small gift.

2.2. Procedure

Our experiment was adapted from VanRullen & MacDonald (2012) and modified for visually impaired individuals and children.

Stimuli were presented with a Dell laptop on a Dell 22-inch LCD monitor with a refresh rate of 60 Hz. Stimuli were created with MATLAB r2018b (The MathWorks, Inc., Natick, MA) and Psychtoolbox 3 (Brainard, 1997; Kleiner et al., 2007).

A session started with the recoding of resting-state EEG. Participants were asked to sit as still as possible during the recording, and either to fixate on a blank, dark screen (eyes open condition, EO) or to keep their eyes closed (eyes closed condition, EC). The order of these two conditions was randomized across participants, and each condition lasted for at least 3 min.

During the task, data were collected in a darkened room. In consecutive experimental trials, participants watched a circle at the center of a black screen. The visual angle subtended by the circle was 17 degrees. This circle changed in luminance between values ranging from 0 to 1. Luminance values changed with equal power at all temporal frequencies between 0 and 30 Hz, thus rendering each trial a white-noise luminance sequence (Fig. 1, Supplementary Material S1) (Luo et al., 2021; Vanrullen & MacDonald, 2012). Unique, randomly generated white-noise sequences were presented for every trial and participant. Luminance values were gamma corrected to ensure a linear luminance output (monitor gamma value = 2.041). Participants were asked to perform 100 trials of a duration of 6.25 s each, divided into blocks of 10 trials.

In 10% of trials, a single square subtending a visual angle of 6 degrees appeared at the circle's center. The luminance of this square was scaled to 0.9 times the luminance value of the circle. The target square would appear at the circle's center for a randomly selected time, excluding the first 50 and last 50 frames. For the duration of its appearance, this square changed luminance at the same frequency as the circle. Participants were instructed to watch for the target square. At the end of every trial, participants verbally indicated whether or not they saw a square on that trial (Fig. 1). The experimenter recorded the response (maximum response time = 10 s) (Supplementary Material S6). No feedback was provided on accuracy during the time of testing. At the end of every block, participants were asked whether they would like to take a break or continue with the task. Some participants terminated the experiment early; four participants (2 CC, 2 SC) performed 80 trials, and 1 CC participant performed 70 trials.

Prior to the beginning of the experiment, all participants performed 10 practice trials with a target appearing on 30% of them.

The EEG was recorded using Ag/AgCl electrodes attached according to the 10/20 system (Homan, Herman, & Purdy, 1987) to an elastic cap (EASYCAP GmbH, Herrsching, Germany). We recorded 32 channel EEG using a BrainAmp amplifier, with a bandwidth of 0.01–200 Hz and sampling rate of 5 kHz (https://www.brainproducts.com/). All scalp recordings were performed against a left ear lobe reference.

After the EEG recording, visual acuity was measured binocularly for every participant on the day of testing using the Freiburg Vision Test or FrACT (https://michaelbach.de/fract/, Bach, 2007). Visual acuity is reported as the logarithmic of the mean angle of resolution (logMAR), wherein higher values indicate worse vision (Elliott, 2016).

2.3. Data analysis

2.3.1. Visual stimulation EEG analysis

The EEGLab toolbox in MATLAB 2018b was used for data analyses (Delorme & Makeig, 2004). First, datasets were filtered using a Hamming windowed sinc FIR filter, with a high-pass cutoff of 1 Hz and a low-pass cutoff of 45 Hz. The resulting data were down-sampled to 60 Hz (antialiasing filtering performed by EEGLab's *pop_resample* function) to match the luminance stimulation rate. The data were divided into 6.25 s long epochs corresponding to each trial. Subsequently, baseline removal was conducted by subtracting the mean activity across the length of an epoch from every data point. After baseline removal, epochs with signals exceeding a threshold of ± 120 μV were rejected in order to exclude artifacts.

Based on the existing literature (Lozano-Soldevilla & VanRullen, 2016, 2019; VanRullen, 2016; VanRullen & MacDonald, 2012) and pilot testing with 73 electrodes at University of Hamburg (see Supplementary Material S2), we analyzed data exclusively from the two occipital electrodes, O1 and O2. Recordings were referenced to the left earlobe. For each trial, the luminance values presented from 0.5 s to 5.75 s after trial onset were cross-correlated with the corresponding EEG time points

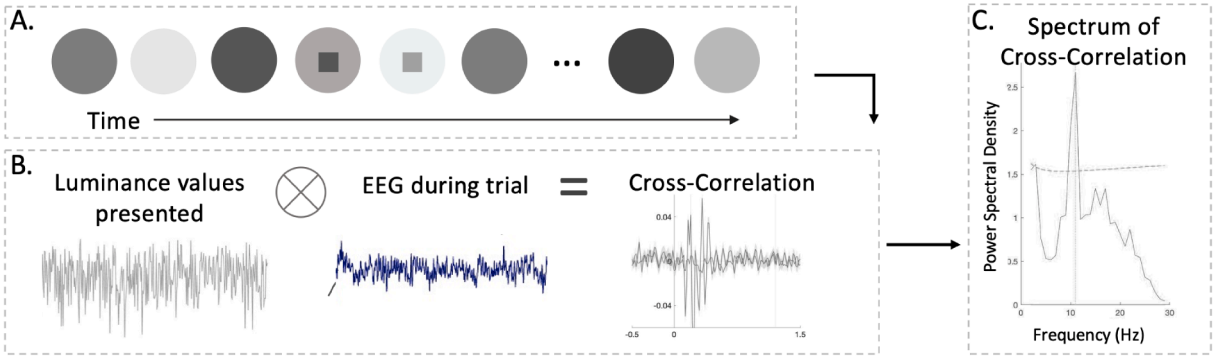

Fig. 1. **A**. Schematic representation of the stimuli during a trial, and subsequent data analysis. Participants watched a circle that randomly changed in luminance. **B**. For each trial the EEG response was cross-correlated with the luminance value presented on that trial. **C**. The frequency spectrum of this cross-correlation analysis was calculated across all the trials. The peak frequency and amplitude of the cross-correlation spectrum was determined and used as a dependent variable.

during that trial. The initial and final portions were excluded from the analysis in order to eliminate the transients due to stimulus onset and offset (VanRullen & MacDonald, 2012). The average cross-correlation value across trials was computed across all visual stimulation epochs for every participant. As a control, we additionally calculated the cross-correlation of each EEG epoch with a luminance sequence that was presented on a different, randomly selected trial. This control analysis was carried out to ensure that the evoked alpha response was specific to the stimuli presented and not an artifact of any kind of flickering stimulation (VanRullen & MacDonald, 2012).

Next, the amplitude spectrum of each participant's cross-correlation function was calculated both for O1 and O2, for the delays between 0.2 s and 1.2 s. These delays were chosen as in VanRullen and MacDonald (2012). Using the *pwelch* function in MATLAB, we obtained the power spectral density of the cross-correlation (window length = 60 samples, overlap = 0, spectrum resolution = 1 Hz) (VanRullen & MacDonald, 2012).

Prior to identifying peaks in the spectrum of the cross-correlation function, we removed the aperiodic (1/f) component of this spectrum for each subject. Note that this analysis was not performed by VanRullen and MacDonald (2012). However, as has been suggested in several recent studies, we applied this correction to ensure that potential between-group differences in oscillations were not driven by differences in aperiodic activity (Donoghue et al., 2020b; Schaworonkow & Voytek, 2021). First, we fit the 1/f distribution function to the frequency spectrum of each participant. The 1/f distribution was fit to the normalized spectrum converted to logarithmic scale (range = 1–20 Hz) (Donoghue et al., 2020a; Gyurkovics et al., 2021; Schaworonkow & Voytek, 2021). We excluded the alpha range (8 – 14 Hz) for this fit, to avoid biasing the results (Donoghue et al., 2021; Schaworonkow & Voytek, 2021; Voytek et al., 2015; Waschke et al., 2017). This 1/f fit gave us a value of the slope, an overall intercept value corresponding to the broadband power of all frequencies, and a fit error for the cross-correlation spectrum of every participant. On subtracting the fitted 1/f spectrum from the original spectrum in logarithmic scale, we obtained the corrected cross-correlation spectrum for each subject between 1 and 20 Hz.

We used MATLAB's *findpeaks* function to identify peaks between 7 and 14 Hz. Two criteria were used to define above-threshold peaks, in order to set quantitative criteria for whether an evoked alpha peak existed at all. First, the peak had to be higher than one standard deviation of the fit error, obtained from the 1/f fit of the cross-correlation spectrum. Second, peaks had to be at least 1 Hz (i.e. equal to the resolution of the spectrum) in width. Peak identification was performed individually for O1 and O2. Subsequently, for every subject, the peak frequency and amplitude were averaged across O1 and O2.

Finally, 1/f corrected spectra were averaged across O1 and O2 in order to obtain a mean cross-correlation spectrum for each subject.

2.3.2. Resting-State EEG analysis

Resting-state data were preprocessed identically to the visual stimulation EEG data. We filtered the 3-minute-long resting-state recordings using a Hamming windowed sinc FIR filter (High and Low Cutoffs: 1–45 Hz). Next, we divided the recording into epochs of 1 s, and rejected epochs with signals exceeding ± 120 μV. Finally, we calculated the power spectral density of the preprocessed EEG data using the *pwelch* function (window length = 1000 samples, overlap = 0).

We followed an identical procedure as the one described above for the cross-correlation spectrum to obtain peaks in the alpha range of the resting-state spectrum.

2.3.3. Statistical analysis

We hypothesized that stimulus-evoked occipital alpha activity in CC individuals was reduced compared to SC individuals. To test this hypothesis, first, the mean amplitude of the cross-correlation spectrum in the alpha range (8–14 Hz, averaged across O1 and O2) was compared between the two groups with a *t*-test. Second, a chi-square test was employed to test the likelihood that CC vs SC individuals presented an evoked alpha response. Third, for the subgroups of individuals who demonstrated above-threshold evoked alpha responses in their cross-correlation spectra, t-tests were conducted in order to compare the peak frequency and peak amplitude between CC and SC individuals.

Mean resting-state alpha activity was compared between groups. The average amplitude of the resting-state spectrum between 8 and 14 Hz for every subject (averaged across O1 and O2) was derived, and a group (2 levels: CC, SC) by condition (2 levels: EO, EC) ANOVA was performed on these average alpha amplitude values. Additionally, the likelihood of presenting an above-threshold resting-state alpha peak was compared between the two groups using Chi-squared tests. This was done separately for the EO and EC conditions. Finally, for the subgroup of individuals with above-threshold resting-state alpha peaks in the SC and CC groups, group-by-condition ANOVAs were performed in order to compare the peak frequency and peak amplitude values between these subgroups of CC and matched SC individuals.

As in VanRullen and MacDonald (2012), we tested for the presence of a correlation between the peak alpha frequency and amplitude values of the cross-correlation spectra, and the peak alpha frequency and amplitude in the resting-state (EC) spectra, respectively. These correlations were tested for the individuals who demonstrated an above-threshold alpha peak in the cross-correlation and resting-state (EC) spectra across both the CC and SC groups.

To determine whether vision loss history might predict the presence vs absence of alpha activity, CC participants were categorized based on whether or not they presented an above-threshold peak in the evoked alpha response, and compared on visual acuity, time since surgery, duration of blindness and age. Identical analyses were conducted comparing CC individuals categorized based on whether they presented above-threshold resting-state alpha activity, separately for the eyes closed and eyes opened conditions. Due to differing and small sizes of the subgroups of CC individuals, non-parametric testing was used to compare the subgroups via the Wilcoxon Rank Sum Test.

Anonymized data and materials will be made available upon reasonable request to the corresponding author, under stipulations of applicable law including, but not limited to the General Data Protection Regulation (EU 2016/679). This experiment was not pre-registered.

3. Results

3.1. Reduced amplitude of stimulus-evoked alpha activity in congenital cataract-reversed individuals

First, we tested the cross-correlation of the EEG response with the corresponding white-noise luminance sequence (the average cross-correlation from each group is depicted in Fig. 2A,B). As seen in Fig. 2C, the average spectral density of this cross-correlation showed a peak in the alpha range for both the SC and the CC group. However, the mean power in the alpha range (8–14 Hz) was significantly reduced in the CC compared to the SC group ($t(24) = -2.3$, $p = 0.028$) (Fig. 2C, 2D). While all SC participants displayed an above-threshold (see Methods) peak in the alpha range, only 8 of 13 CC participants did; the likelihood of an individual demonstrating an evoked alpha peak was significantly higher in the SC than in the CC group (Chi squared test: $\chi^2 = 6.2$, $p = 0.013$) (Fig. 2C):

For the subgroup of 8 CC individuals with an above-threshold evoked alpha peak (henceforth referred to as $CC_{Evoked+}$), peak frequency values did not differ from those observed for the SC group ($t(19) = 0.3$, $p = 0.73$) (Fig. 2E). Moreover, the peak evoked alpha amplitude did not significantly differ between the $CC_{Evoked+}$ subgroup and the SC group ($t(19) = 1.35$, $p = 0.19$) (Supplementary Material S3).

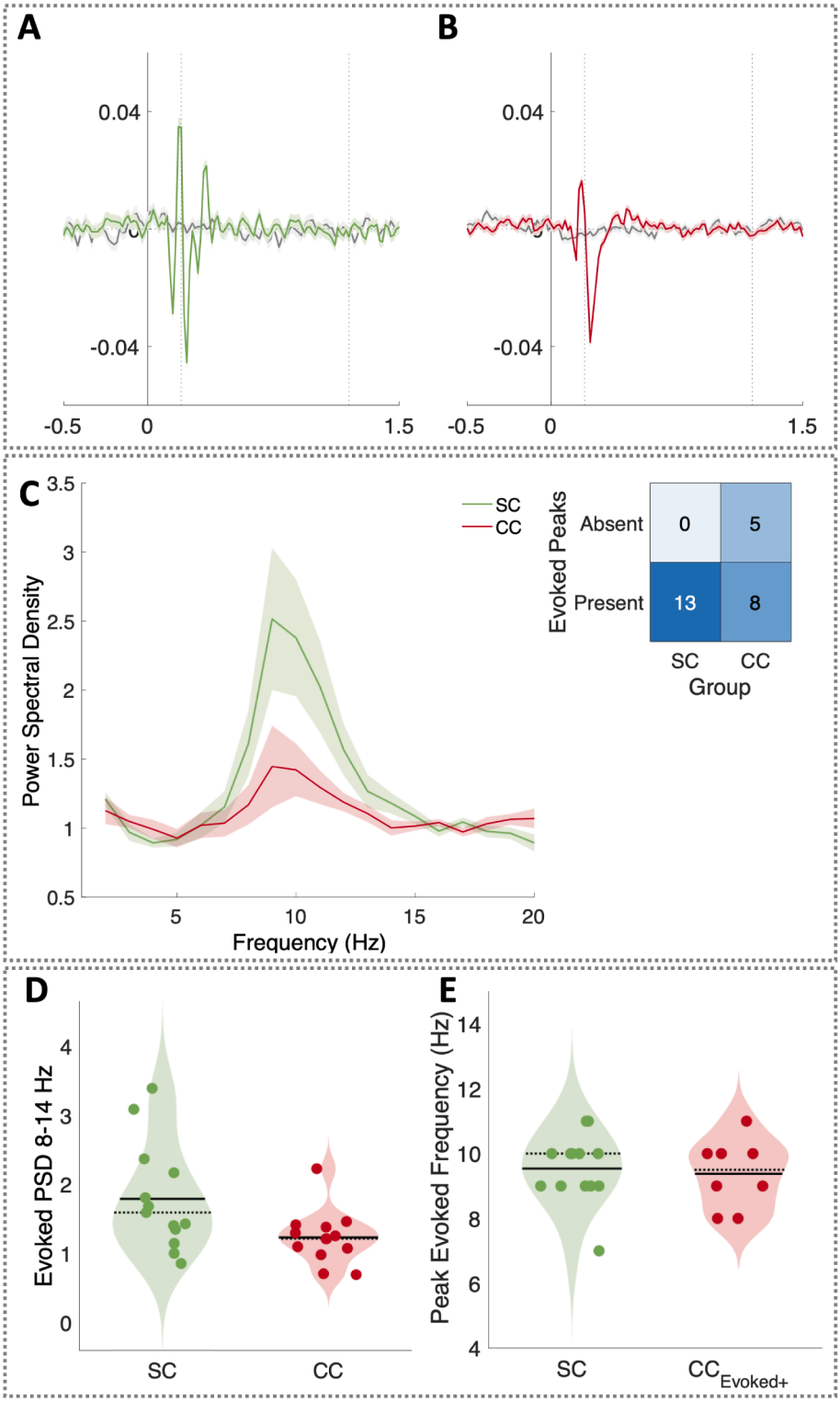

Fig. 2. Stimulus-evoked alpha activity in congenital cataract-reversed (CC) and normally sighted (SC) individuals. **A,B.** The cross-correlation of the EEG response with the corresponding luminance values presented. Average cross-correlation response from participants of the A. SC (green) and the B. CC (red) group, respectively. The average cross-correlation across all trials is plotted in colour. The grey line represents the average cross-correlation of the EEG response on every trial with a randomly selected, mismatched luminance sequence. The shaded region represents the standard error of mean. The dotted lines mark the section of the cross-correlation used to calculate the spectrum. **C.** The average spectrum of cross-correlation functions across all CC (red) and SC (green) subjects. The shaded region represents standard error of the mean. Inset table listing the number of individuals in each group with and without an above-threshold evoked alpha peak. **D.** Violin plots displaying the average evoked alpha amplitude (averaged between 8 and 14 Hz) in SC (green) and CC (red) individuals. Solid lines indicate the mean values and dotted lines indicate median values of the average evoked alpha amplitude in the SC and CC group. Individual subjects have been horizontally jittered for a better view of overlapping data points. **E.** Violin plots displaying the peak frequency distributions of SC and $CC_{Evoked+}$ individuals, the subgroup of CC individuals who presented an above-threshold evoked alpha peak. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Reduced amplitude of resting-state alpha activity in congenital cataract-reversed individuals

To test the effects of transient early visual deprivation on resting-state alpha oscillations, we compared the alpha range of the resting-state spectra between CC and SC individuals. CC individuals showed an overall reduction of the average alpha power (8–14 Hz) compared to SC individuals, in both the eyes open (EO) and the eyes closed (EC) conditions (main effect of group: $F(1,48) = 9.6$, $p = 0.003$) (Fig. 3A,C). Across groups, alpha amplitude was significantly lower in the eyes open (EO) than in the eyes closed (EC) condition (main effect of condition: $F(1,48) = 11.5$, $p = 0.001$). The reduction of alpha power from the EC to

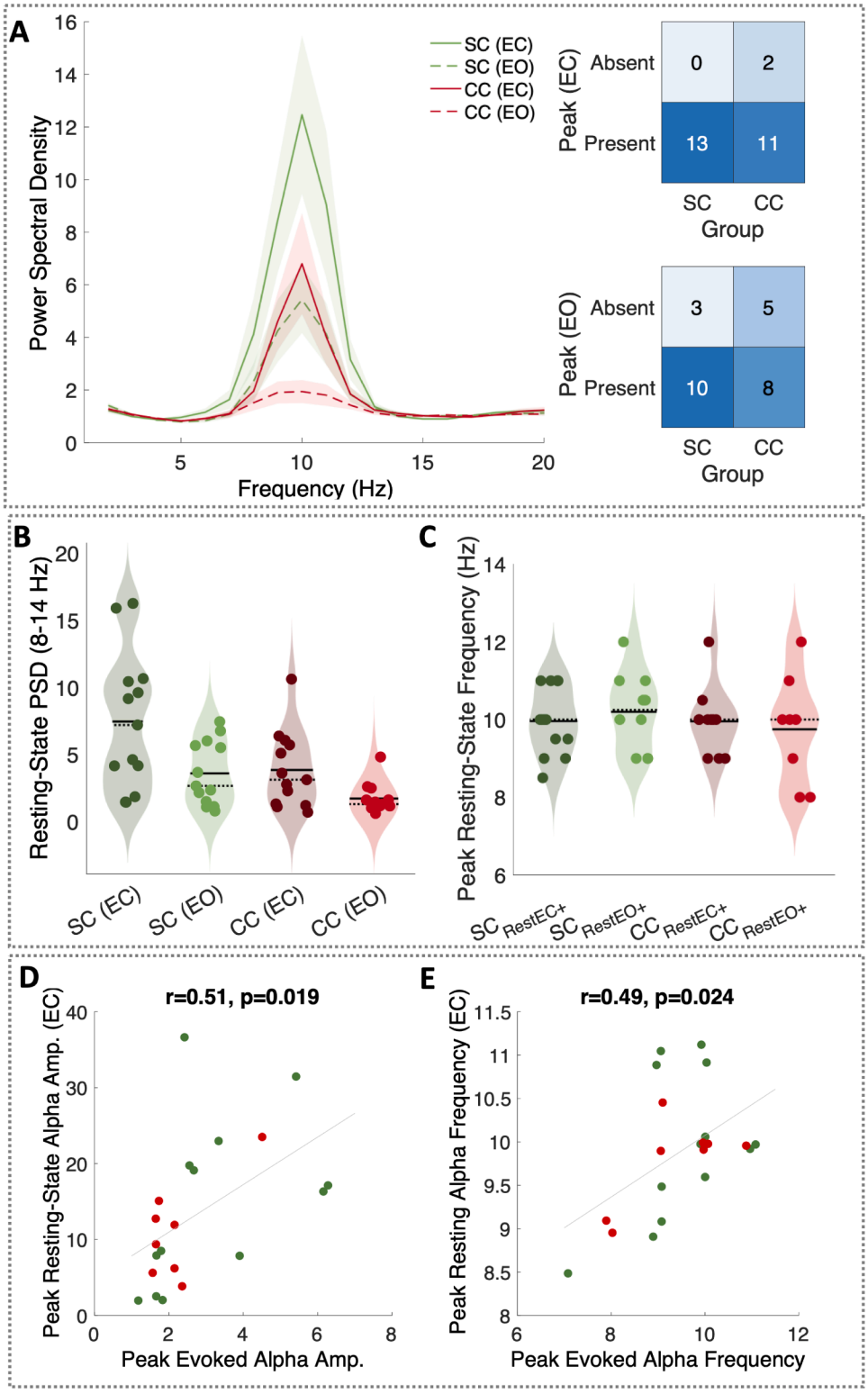

Fig. 3. Resting-state alpha oscillations of congenital cataract-reversed (CC) and normally sighted control (SC) individuals. **A.** Mean resting-state spectra with eyes opened and eyes closed, averaged across all SC (green) and all CC (red) individuals. Shaded regions represent the standard error of the mean. Inset tables listing the number of individuals in each group with and without an above threshold alpha peak, for the eyes open and the eyes closed condition. **B.** Violin plots illustrate the average (8–14 Hz) resting-state alpha amplitude distributions for SC and CC individuals. Solid lines indicate the mean values and dotted line indicate median values of the average evoked alpha amplitude in the SC and CC group. **C.** Violin plots illustrate the peak alpha frequency distributions for the subgroup of SC and CC individuals with an above-threshold resting-state alpha peak in either the eyes open ($SC_{RestEO+}$, $CC_{RestEO+}$) or eyes closed ($SC_{RestEC+}$, $CC_{RestEC+}$) condition. **D,E.** Pearson correlation between stimulus-evoked and resting-state alpha oscillations. Correlations between values of D. amplitude and E. frequency of the resting-state and evoked alpha peaks across $CC_{Evoked+}$ (red) and SC (green) individuals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the EO condition was indistinguishable between the CC and SC group (group-by-condition interaction $F(1,48) = 0.96$, $p = 0.333$) (Fig. 3A,C).

The likelihood of demonstrating an above-threshold (see Methods) peak in the alpha range of the resting-state spectrum did not differ between the SC and CC groups, neither in the EO (Chi squared test: $\chi^2 = 0.72$, $p = 0.395$) nor in the EC condition (Chi squared test: $\chi^2 = 2.17$, $p = 0.141$) (Fig. 3B).

Within the subgroups of CC and SC individuals with above-threshold resting-state alpha peaks (SC group: $n = 13$ in the EC condition, 10 in the EO condition, henceforth referred to as $SC_{RestEC+}$ and $SC_{RestEO+}$ respectively; CC group: $n = 11$ in the EC condition, 8 in the EO condition, henceforth referred to as $CC_{RestEC+}$ and $CC_{RestEO+}$ respectively), the peak

frequency value did not differ between the EO and EC conditions (main effect of condition: $F(1,34) = 0.06$, $p = 0.81$). Moreover, the subgroups of $SC_{RestEO+}$, $SC_{RestEC+}$, $CC_{RestEC+}$ and $CC_{RestEO+}$ individuals did not differ in peak frequency (main effect of group: $F(1,34) = 2.3$, $p = 0.13$, group-by-condition interaction: $F(1,34) = 1.08$, $p = 0.31$) (Fig. 3D).

Finally, there was a marginal reduction of the peak resting-state alpha amplitude in the $CC_{RestEC+}$ and $CC_{RestEO+}$ subgroups compared to the $SC_{RestEO+}$ and $SC_{RestEC+}$ subgroups (main effect of group: $F(1,34) = 3.07$, $p = 0.089$), and the expected increase of peak alpha amplitude with eye closure across subgroups (main effect of condition: $F(1,34) = 8.17$, $p = 0.007$, group-by-condition interaction: $F(1,34) = 0.05$, $p = 0.821$) (Supplementary Material S4).

Across the $SC_{Evoked+}$ and $CC_{Evoked+}$ subgroups ($n = 21$), there was a significant positive correlation between the peak resting-state alpha frequency and the peak evoked alpha frequency ($r = 0.49$, $p = 0.024$) and between the peak resting-state alpha amplitude and the peak evoked alpha amplitude ($r = 0.51$, $p = 0.019$) (Fig. 3E,F).

3.3. Concurrent reduction of stimulus-evoked and resting-state alpha power in congenital cataract-reversed individuals

As expected from the mechanistic account described in VanRullen and MacDonald (2012), the subgroup of $CC_{Evoked-}$ individuals, with no stimulus-evoked alpha peak ($N = 5$), had a significantly lower resting-state alpha amplitude than $CC_{Evoked+}$ individuals, who demonstrated such a peak ($N = 8$) (main effect of subgroup: $F(1,22) = 14.3$, $p = 0.001$) (Fig. 4A). Resting-state alpha power increased with eye closure in both subgroups (main effect of condition: $F(1,22) = 7.3$, $p = 0.013$). However, the magnitude of this effect was larger in $CC_{Evoked+}$ than in $CC_{Evoked-}$ individuals (subgroup-by-condition interaction $F(1,22) = 4.61$, $p = 0.043$; Fig. 4B).

Post-hoc testing revealed lower alpha power in the EC condition in $CC_{Evoked-}$ than $CC_{Evoked+}$ individuals ($t(11) = 3.3$, $p = 0.007$), while this difference was marginally significant for the EO condition ($t(11) = 1.96$, $p = 0.076$).

3.4. Lower visual acuity in cataract-reversed individuals without an above-threshold evoked alpha response

Visual acuity was significantly better, that is, logMAR values were lower, in $CC_{Evoked+}$ ($n = 8$) than $CC_{Evoked-}$ ($n = 5$) individuals (Wilcoxon rank-sum test: $z = 2.2$, $p = 0.0286$) (Fig. 5). When we compared visual acuity in CC individuals with vs without an above-threshold resting state peak, there was no difference in visual acuity between $CC_{RestEC+}$ ($n = 11$) vs $CC_{RestEC-}$ individuals ($n = 2$) in the eyes closed condition (Wilcoxon rank-sum test: $z = 1.09$, $p = 0.277$), or between $CC_{RestEO+}$ ($n = 7$) vs $CC_{RestEO-}$ individuals ($n = 6$) in the eyes open condition (Wilcoxon rank-sum test: $z = 0.14$, $p = 0.886$) (Fig. 5). There was no subgroup difference in chronological age, time since surgery or duration of blindness between $CC_{Evoked+}$ and $CC_{Evoked-}$ individuals (Supplementary Material Fig. S7).

4. Discussion

The present study investigated stimulus-evoked and resting-state alpha (8–14 Hz) oscillations in individuals who had experienced congenital blindness for an average of 11 years, due to delayed surgery for dense bilateral congenital cataracts. We used the association between stimulus-evoked and resting-state alpha as a proxy to assess bottom-up and top-down processing in the visual system and how it depends on early visual experience in humans (see Yusuf et al., 2022, for a non-human model of auditory deprivation). Stimulus-evoked oscillations were assessed with the visual impulse response to white noise. In normally sighted individuals (SC) we replicated the main results from VanRullen and MacDonald (2012): we observed the characteristic prominent stimulus-evoked alpha response (Başar et al., 1997; Childers & Perry, 1971; Lalor et al., 2007; Vanrullen & MacDonald, 2012). Individuals treated for congenital cataracts (CC) demonstrated a lower amplitude of both stimulus-evoked and resting-state alpha oscillations, as compared to the SC group. Stimulus-evoked and resting-state alpha oscillations were correlated in amplitude and peak frequency across CC and SC individuals. Finally, visual acuity was worse in CC individuals who did not demonstrate an above-threshold evoked alpha peak. The present study provides electrophysiological evidence for the crucial role of early visual experience in the joint emergence of stimulus-evoked and

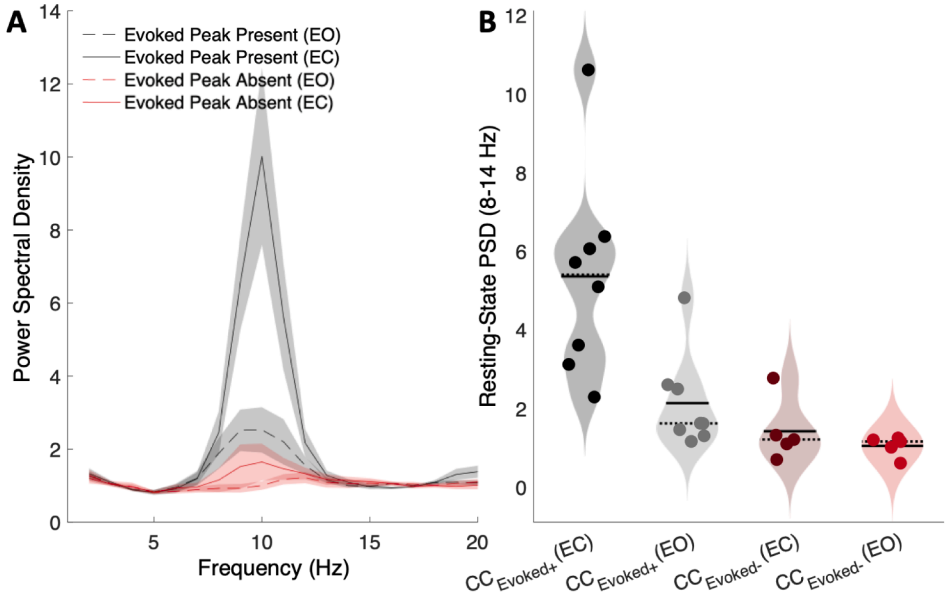

Fig. 4. A. Mean resting-state spectra plotted for the eyes opened and eyes closed conditions in the subgroup of cataract-reversed individuals with ($CC_{Evoked+}$, $n = 8$, black) and without ($CC_{Evoked-}$, $n = 5$, red) an above-threshold evoked alpha peak. Shaded region represents the standard error of mean. **B.** Violin plots depict the mean resting-state alpha amplitude of $CC_{Evoked+}$ and $CC_{Evoked-}$ individuals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

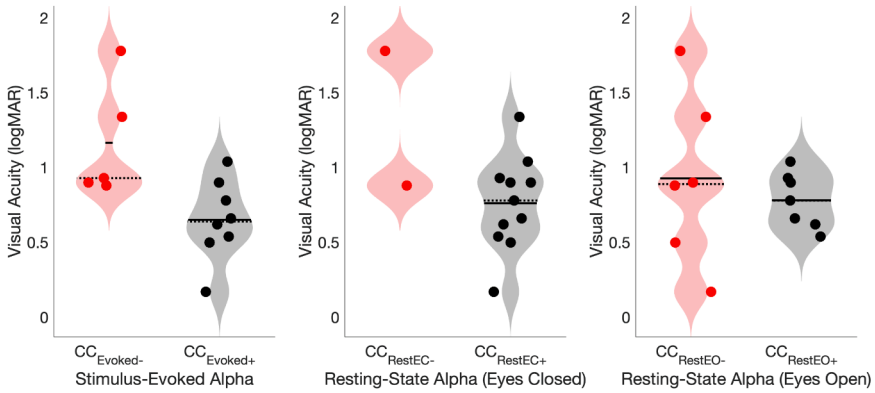

Fig. 5. Violin plots depict the visual acuity in logMAR units in the CC group divided into subgroups with (black) and without (red) an above-threshold peak in the stimulus-evoked ($CC_{Evoked+}$, $CC_{Evoked-}$), resting-state ($CC_{RestEC+}$, $CC_{RestEC-}$, eyes closed) and resting-state ($CC_{RestEO+}$, $CC_{RestEO-}$, eyes open) conditions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

resting-state alpha oscillations. These findings are compatible with the idea that the elaboration of top-down pathways, which functionally shape upstream sensory areas to process the visual environment, is experience-dependent; and likely linked to a sensitive period in human brain development.

Multiple lines of evidence have linked alpha oscillations to feedback communication in the visual system, including results from non-human animal studies (Maier et al., 2010; Van Kerkoerle et al., 2014) invasive recordings from humans at rest (Halgren et al., 2019), non-invasive EEG recordings (Händel et al., 2011; Jensen & Mazaheri, 2010; Klimesch et al., 2007; Worden et al., 2000) and transcranial magnetic stimulation studies in humans (Riddle et al., 2020; Sauseng et al., 2011; Zanto et al., 2011). Stimulus-evoked alpha activity has been proposed to result from entrainment of the cortical generators of resting-state oscillations (Başar et al., 1997; Herrmann, 2001; Herrmann et al., 2016; Notbohm et al., 2016; Zoefel et al., 2018) and thus, likely reflects an interaction of top-down and bottom-up signals. Evidence for an enhanced propensity of the visual cortex to generate alpha oscillations was demonstrated by assessing the impulse response to visual white noise (Vanrullen & MacDonald, 2012). Visual white noise comprises equal stimulation at all frequencies; nevertheless, visual circuits entrain predominantly in the alpha range. The correlation between the peak frequency and amplitude of stimulus-evoked and resting-state alpha oscillations, also observed in the present study, is compatible with a link between stimulus-evoked and resting state alpha oscillations (Vanrullen & MacDonald, 2012; Zoefel et al., 2018).

Within the entrainment account of stimulus-evoked alpha oscillations, we speculate that jointly reduced stimulus-evoked and resting-state alpha oscillations might reflect an altered interaction of top-down and bottom-up processing streams, or recurrent processing (Yusuf et al., 2022), in the visual cortex. Non-human animal models have provided three lines of evidence for this idea. First, the lack of visual experience caused a flattening of the cortical hierarchy in macaque visual cortex (Magrou et al., 2018). In sighted macaques, the laminar ratio, i.e. the ratio of supragranular neurons to the sum of supragranular and infragranular neurons, decreases from lower to higher visual regions, and is considered a quantitative measure of interareal distance in the cortical hierarchy (Markov et al., 2014). In enucleated macaques, this laminar ratio was altered, which might imply impaired interareal communication in the visual cortex (Magrou et al., 2018). Second, feedback interareal projections in the visual cortex have been shown to be the subject of experience-dependent shaping to a greater extent than feedforward projections in macaques (Batardière et al., 2002), humans (Burkhalter et al., 1993) and rodents (Ibrahim et al., 2021). Thus, the connectivity necessary to iteratively adjust resting-state activity to optimize visual processing might be particularly vulnerable to the effects of early visual deprivation (Pezzulo et al., 2021). Third, analogous observations of altered feedback processing after sensory restitution were made in electrophysiological recordings from the auditory cortex of congenitally deaf cats, stimulated via cochlear implants. Feedback coupling from secondary to primary auditory cortex, measured by phase consistency, was particularly lowered by congenital auditory deprivation (Yusuf et al., 2021). Functional coupling between infragranular and supragranular layers in A1 was reduced in cochlear-implanted compared to normally hearing cats (Yusuf et al., 2022) suggesting an impairment of the interaction of feedback and feedforward processing streams after sensory restitution. Similar to the present work, the authors suggested that the lack of sensory experience at birth interrupts the sculpturing of feedback connectivity in sensory cortex, resulting in impaired orchestration of bottom-up and top-down processing pathways (Kral et al., 2017; Yusuf et al., 2021, 2022).

Reduced alpha entrainment would be consistent with lower visual capabilities in CC individuals. Previous studies have found that an alpha entrainment improves sub-threshold detection (Spaak et al., 2014) and distractor suppression (Wiesman & Wilson, 2019). Accordingly, in our study the individuals with reversed congenital cataract who featured a significant stimulus-evoked alpha peak were those with better visual acuity outcomes. Interestingly, a study which optogenetically inactivated top-down signals from marmoset V2 to V1 found increased receptive field sizes in V1 (Nurminen et al., 2018), which implies lower visual acuity. Assuming that lower alpha activity is associated with impaired feedback tuning of early visual cortex, it would be justified to conclude that a deficit of this mechanism contributes to the lower visual acuity as found in the present study and repeatedly documented in CC individuals. Further, our interpretation of impaired recurrent processing would be consistent with other visual deficits reported in CC individuals, including visual feature binding (McKyton et al., 2015; Putzar et al., 2007), coherent motion processing (Hadad et al., 2012; Rajendran et al., 2020) and face identity processing (Le Grand et al., 2001; Putzar et al., 2010). Higher visual functions require the integration of outputs of multiple neural circuits within and across visual areas, and thus, functional interareal connectivity. For example, deactivating top-down connectivity from the mouse homologous area V2 to V1 resulted in a reduced firing to illusory contours (Pak et al., 2020), reminiscent of a similar deficit in CC individuals (McKyton et al., 2015; Putzar et al., 2007). In addition to the present results, another electrophysiological study in CC individuals found evidence for impaired interareal communication. Pitchaimuthu et al. (2021) recorded steady-state visual evoked potentials to visual stimuli simultaneously changing two features - flickering and moving horizontally. Such combined stimulation typically results in intermodulation frequency responses in the EEG,

indicating the integration of input across multiple visual areas (Kim et al., 2011). Intermodulation frequency responses were absent in CC individuals, interpreted as evidence for impaired integration across visual regions (Pitchaimuthu et al., 2021).

The present findings are compatible with prospective developmental results from ferrets and humans. Invasive recordings in the ferret visual cortex demonstrated that the similarity between stimulus-driven and resting-state activity increased during early development (Berkes et al., 2011). Moreover, studies in humans have documented a protracted developmental trajectory for resting-state alpha oscillations into adolescence (Cellier et al., 2021; Marshall et al., 2002). Rare results on stimulus-evoked alpha responses in children suggested maturation beyond early childhood (Kolev et al., 1994). Therefore, we hypothesize that congenital blindness prevented the development of characteristic resting-state activity, which might prepare visual circuits to efficiently response to visual input. As a consequence, stimulus-evoked processing might be less efficient, resulting in worse visual behavior.

Testing the integrity of visual circuits in humans who were treated for bilateral dense cataracts could be considered analogous to the prevalent approach in non-human animals, wherein experimentally manipulated visual deprivation is used to study the effects of experience on brain development. Limitations of the human model have been discussed (Röder & Kekunnaya, 2021), and here we acknowledge some challenges for the present study. Humans who had experienced a period of visual deprivation longer than about 8 weeks following birth typically suffer from nystagmus (Supplementary Table S9), and therefore differences in involuntary eye movements between the CC and SC groups are confounded with our measurements. However, nystagmus might not explain the present results, as all CC participants suffered from nystagmus, but eight out of thirteen showed a stimulus-evoked alpha peak. Moreover, differences in resting-state EEG are unlikely to be linked to fixation abilities.

Further, non-invasively recorded alpha oscillations cannot unambiguously be equated with top-down activity. Testing for the modulation of alpha power with top-down cues in CC individuals would be necessary to further investigate whether top-down modulation of restored bottom-up input is affected by congenital visual deprivation in humans. Initial evidence suggested that despite an overall reduction of activity in CC compared to SC individuals in visual motion areas (hMT), CC individuals displayed increased hMT activity if the motion was task relevant (Guerreiro et al., 2022). In agreement with the present findings, these results suggest that top-down control of upstream visual areas is less stimulus-specific and precise, but not entirely absent in individuals who recovered vision after congenital blindness.

CRediT authorship contribution statement

Rashi Pant: Conceptualization, Formal analysis, Writing – original draft, Visualization. **José Ossandón:** Conceptualization, Software, Writing – review & editing. **Liesa Stange:** Software, Writing – review & editing. **Idris Shareef:** . **Ramesh Kekunnaya:** Supervision. **Brigitte Röder:** Supervision, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103375.

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Supplementary Material

S1. Schematic of white-noise luminance spectrum generation

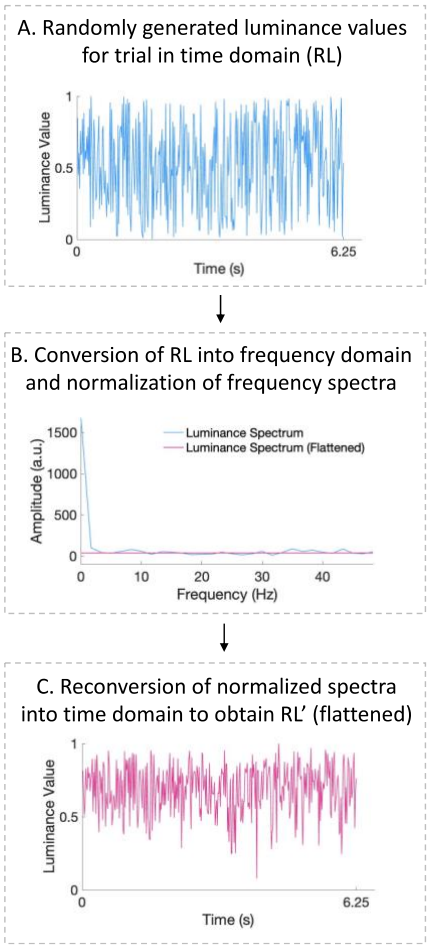

Figure S1. Schematic of generating white-noise sequences of luminance values. A. An example of the random luminance sequence initially generated (blue). B. Original frequency decomposition of randomly generated sequence (blue) and the normalized flattened spectrum of the same sequence (pink). C. Reconversion of flattened spectrum from the previous step into luminance values corresponding to it. These luminance values are presented to the participant.

S2. Pilot testing

Pilot testing of the visual task described in Methods was conducted with two normally sighted participants (Ages: 26 years, 21 years) in a darkened, electrically and acoustically shielded room at the University of Hamburg, (Germany). We used a 73 electrode EEG setup and a monitor with a refresh rate of 120 Hz. Using the same data analysis procedure as described in Methods, we replicated results from VanRullen and MacDonald (2012). Both pilot participants demonstrated a

peak in the alpha range of the cross-correlation response spectra. Like in VanRullen and MacDonald (2012), this response was most expressed at the occipital electrodes (O1 and O2).

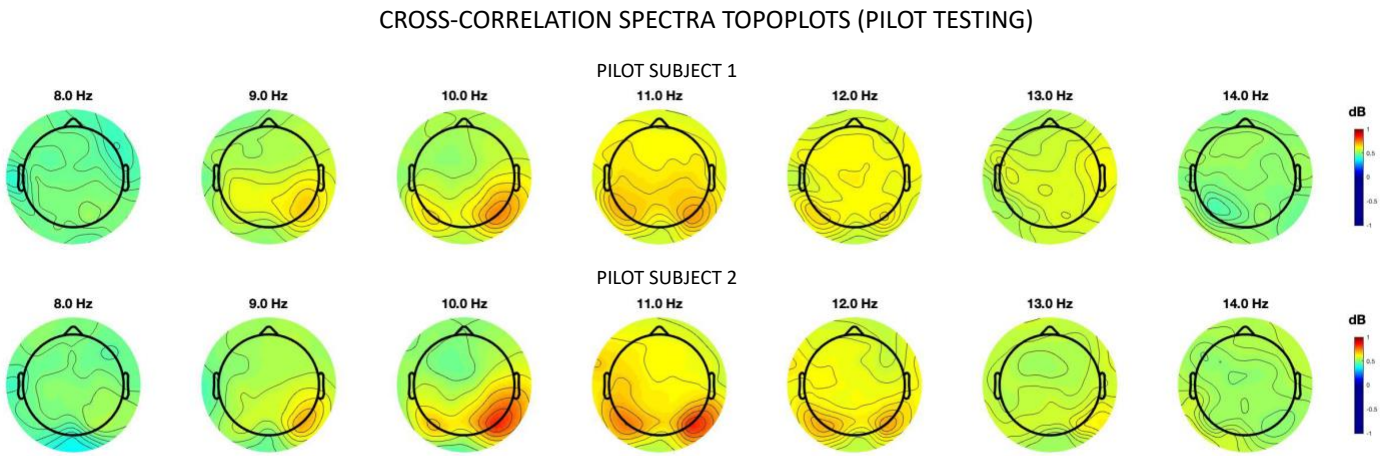

Figure S2: Topographic representation displaying the power (dB) of the cross-correlation spectra of the EEG response and the luminance changes. Cross-correlation spectra from two normally sighted pilot participants are represented as a heatmap on the scalp, with higher values (red) corresponding to higher power at frequencies between 8-14 Hz.

S3. Peak amplitude of the stimulus-evoked spectrum

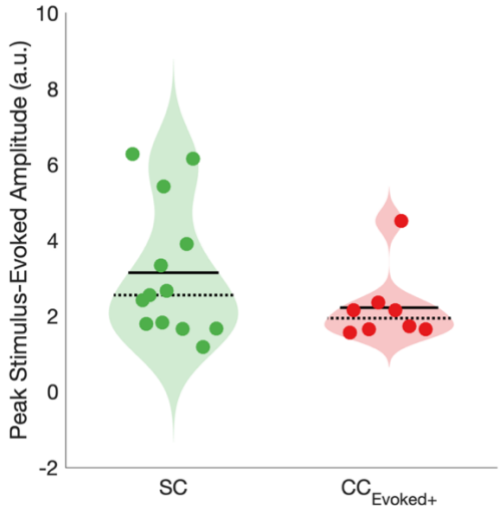

Figure S3: Violin plot showing the distribution of the stimulus-evoked alpha amplitude at the peak frequency of normally sighted (SC) individuals and cataract-reversed individuals who presented above-threshold evoked alpha peaks ($CC_{Evoked+}$).

S4. Peak alpha amplitude of the resting-state spectrum

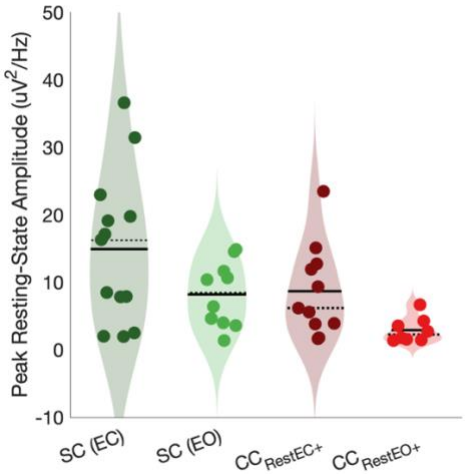

Figure S4: Violin plot showing the distribution of the peak resting-state alpha amplitude in normally sighted (SC) and cataract-reversed (CC) individuals who presented above-threshold resting-state alpha peaks in the eyes open (RestEO+) and eyes closed (RestEC+) conditions.

S5. Correlation analysis of demographic data with peak stimulus-evoked alpha frequency and amplitude

The effect of chronological age on peak evoked alpha frequency and average evoked alpha amplitude across both the CC and SC groups was tested. Chronological age predicted neither frequency nor amplitude of evoked alpha activity across groups (Figure S5). Next, within the CC group, we tested whether duration of visual deprivation, time since surgery and visual acuity affected the peak evoked alpha frequency and average evoked alpha amplitude. None of these demographic and clinical factors were correlated with average amplitude or peak frequency of the evoked alpha oscillations (Figure S5).

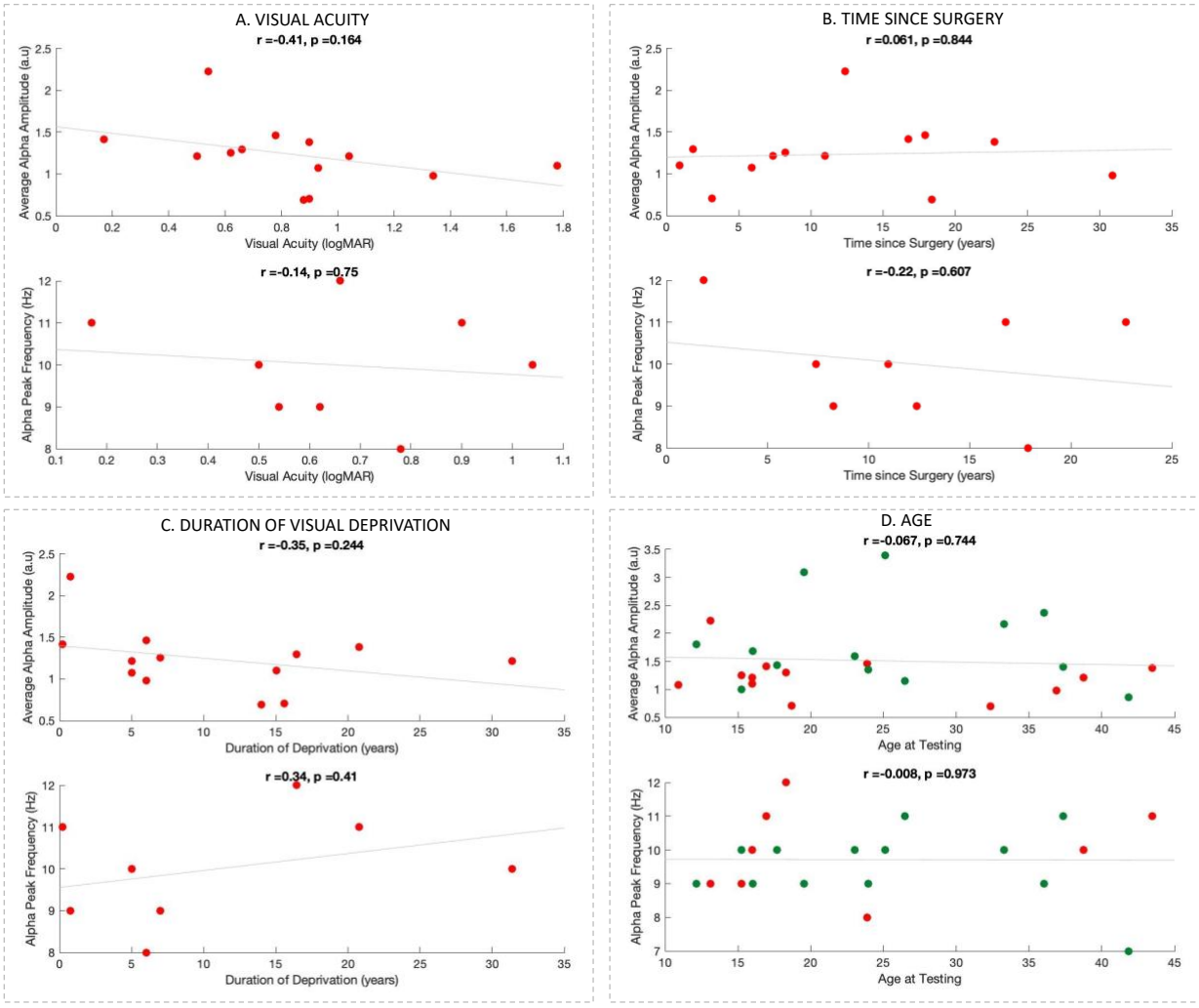

Figure S5: Correlations between the average stimulus-evoked alpha amplitude and peak evoked alpha frequency and demographic factors within the CC and SC groups. Correlations of the average alpha amplitude (top panel) and the alpha peak frequency (lower panel) with A. visual acuity in the CC group (measured using FrACT on the date of testing), B. time since surgery in the CC group (calculated by subtracting the date of surgery in the first eye from the date of testing), C. duration of visual deprivation (calculated by subtracting date of birth from date of surgery in the first eye) in the CC group and D. chronological age at testing in the CC (red) and SC (green) group

S6. Behavioral data

We tested behavioral performance on the target detection task across all trials. Participants were asked to indicate at the end of trial whether or not they saw a target on that trial. Accuracy was

defined as the ratio of correctly indicated rejections and hits to the total number of trials performed by the participants. Accuracy did not differ between groups (t(12) = -1.012, p = 0.331).

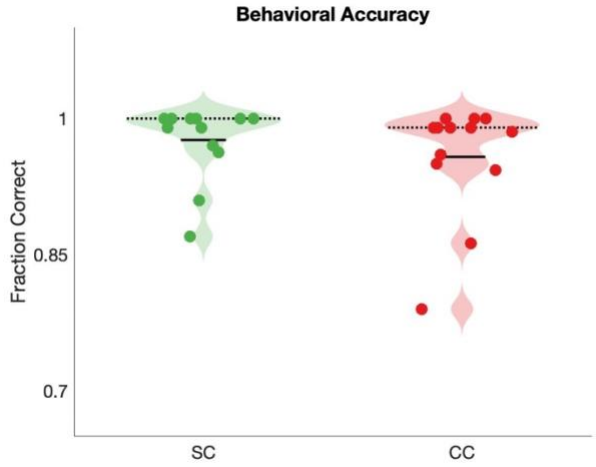

Figure S6: Violin plot showing the distribution of the accuracy on target detection in cataract-reversed (CC) and age-matched sighted control (SC) individuals.

S7. Demographic data of cataract-reversed individuals with an above-threshold evoked alpha response present vs absent

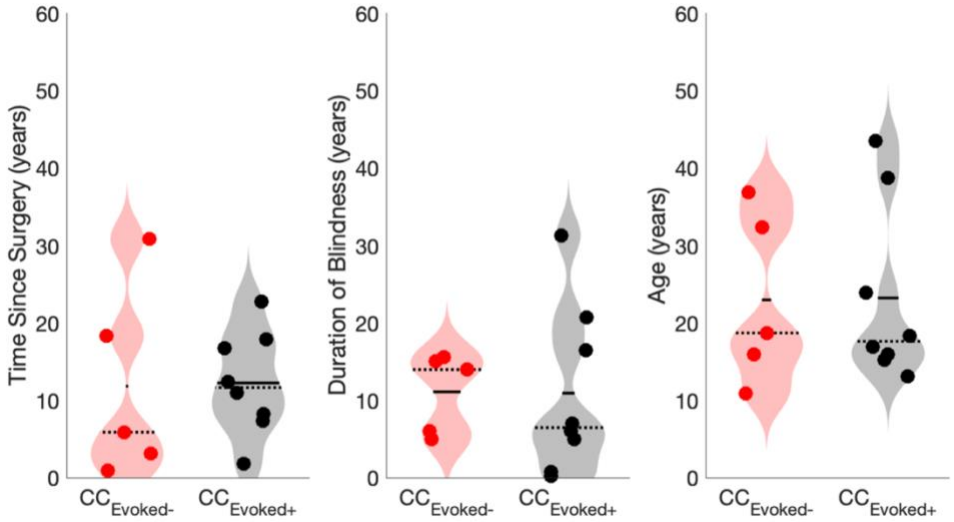

Figure S7 Violin plots showing time since surgery, duration of blindness and chronological age of cataract-reversed individuals with ($CC_{Evoked+}$ black, present) and without ($CC_{Evoked-}$, red, absent) an above-threshold stimulus-evoked alpha peak.

S8. Topoplots of stimulus-evoked alpha activity in SC and CC individuals

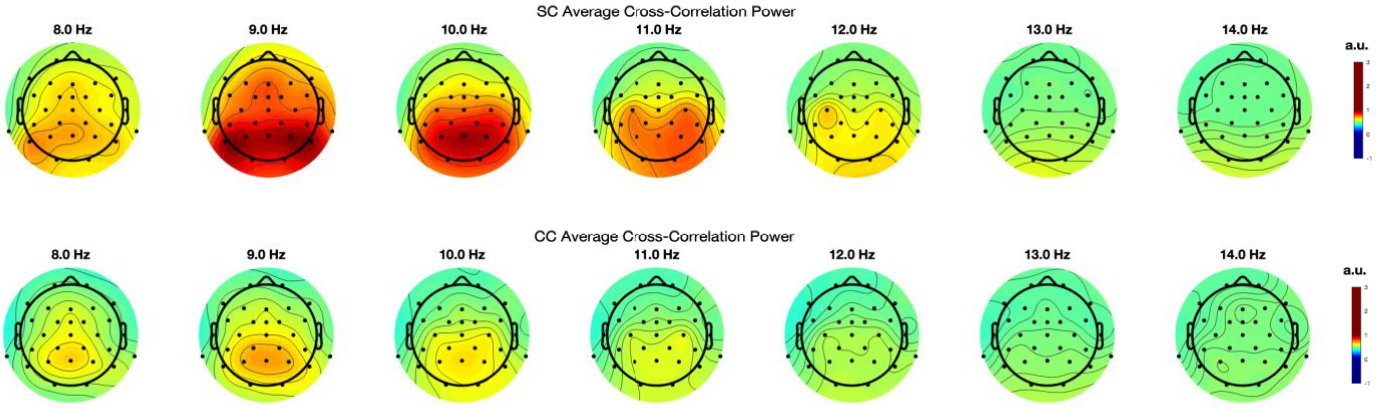

Figure S8. Topographic representation displaying the average power (a.u.) of the cross-correlation spectra of the EEG response and the luminance changes normally sighted (SC) participants (top) and cataract-reversed individuals (CC). Power is represented as a heatmap on the scalp, with higher values (red) corresponding to higher power of the cross-correlation at frequencies between 8-14 Hz.

S9. Extended participant aetiology

(Excel Spreadsheet)

Table S9: Extended clinical information of the participants with a history of dense bilateral congenital cataracts (CC). NA indicates patient's data for the field were not available. FFL: Fixating and Following Light; CF: Counting Fingers; PL: Perceiving Light. Duration of visual deprivation was calculated by subtracting the date of birth from the date of surgery on the first eye. Time since surgery was calculated by subtracting the date of surgery in the first eye from the date of testing. Visual acuity reported was on the date of testing and measured using the Freiburg Vision Test (FrACT) (Bach, 2007). *Fundus photography was conducted for participant numbers 8,9 and 13.*

S10. Relationship between visual acuity improvement and alpha oscillations

In order to assess whether CC patients' stimulus-evoked alpha power showed a clear benefit of surgery with significantly improved visual acuity values, we tested the correlation between the difference in logMAR values Post-Pre surgery and stimulus-evoked alpha power in the 8-14 Hz

range. Note that negative Post-Pre surgery logMAR values indicate greater improvement in vision. Further, for participants with Pre-Sx visual acuities in the CF range, we used plausible extensions to the FrACT scale in logMAR units as described by the authors (Lange et al., 2009; Schulze-Bonsel et al., 2006). Improvement in visual acuity did not significantly predict the amplitude of stimulus-evoked alpha activity (r = -0.62, p = 0.103).

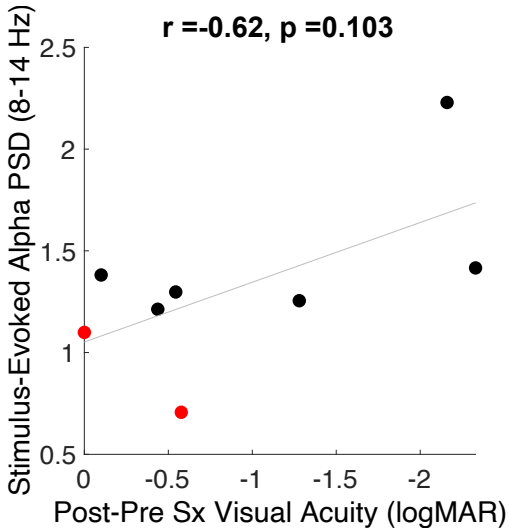

Figure S10. Correlation between stimulus-evoked alpha power and change/improvement in visual acuity after cataract removal. Note that the x-axis is inverted in direction to indicate greater improvement in vision.

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	NYSTAGMUS	DESCRIPTION OF NYSTAGMUS IN MEDICAL REPORT	STRABISMUS	AMBLYOPIA WORSE IN STRABISMIC EYE*	ABSORBED LENSES	INTRA-OCULAR LENS	GENDER	PRE-SURGERY VISUAL ACUITY (logMAR)		DURATION OF VISUAL DEPRIVATION (YEARS)	TIME SINCE SURGERY (YEARS)	BINOCULAR VISUAL ACUITY ON DATE TESTED (logMAR)	FAMILY HISTORY	OPTICAL CORRECTION (CLOSEST TO DATE TESTED)
								OD	OS					
1	Yes	Horizontal, jerky nystagmus with moderate amplitude and low frequency	Yes	No	No	Yes	Male	FFL -	FFL +	0.2	16.8	0.17	No††	OD: plano, OS: -0.50 DS/-0.75 DC x 90, add: OU- +3.00 DS
2	Yes	Multiplanar, jerky nystagmus with moderate frequency and moderate amplitude	Yes	No	Yes	Yes	Male	1.18	1	20.8	22.7	0.9	Yes††	OD: -0.75 DS/-0.75 DC x 90, OS: +1.50 DS, add: OU- +3.00 DS
3	Yes	Horizontal, jerky nystagmus with moderate amplitude and fast frequency	Yes	Yes	Yes	No	Male	1.48	1.77	15.6	3.1	0.9	No††	OD: +9.75 DS/-2.00 DC x 165, OS: +10.50 DS/-1.50 DC x 95
4	Yes	Rotational, jerky nystagmus with moderate frequency and low amplitude	NA	No	Yes	Yes	Male	CF at 1.5 m	CF at 3m	7.0	8.2	0.62	No††	OD: 0.0 DS/-0.75 DC x 40, OS: -1.50 DS/-0.75 DC x 40, add: OU- +3.00 DS
5	Yes	Multiplanar, jerky nystagmus	Yes	Yes	No	Yes	Male	NA	NA	14.0	18.4	0.88	Yes†	OD: -2.25 DS/-2.00 DC x 90, OS: -2.50 DS/-2.25 DC x 50, add: OU- +3.00 DS
6	Yes	Horizontal, left beating jerky nystagmus with low amplitude and high frequency	Yes	No	No	Yes	Male	NA	NA	6.0	17.9	0.78	Yes††	OD: +4.50 DS/-3.00 DC x 70, OS: +10.00 DS/-4.50 DC x 90, add: OU- +3.00 DS
7	Yes	Horizontal, jerky nystagmus with high amplitude and high frequency	Yes	Yes	No	No	Male	PL+	PL+	0.8	12.4	0.54	No††	OD: +15.00 DS/-1.00 DC x 180, OS: +13.00 DS/-1.00 DC x 180
8	Yes	Horizontal, jerky nystagmus with moderate frequency and amplitude	Yes	Yes	Yes	Yes	Male	1.2	1.3	16.4	1.9	0.66	Yes††	OD: +0.75 DS/-2.00 DC x 180, OS: +0.75 DS/-2.00 DC x 180, add: OU- +3.00 DS
9	Yes	Horizontal, jerky nystagmus of small amplitude and high frequency	Yes	Yes	No	No	Male	NA	NA	5.0	5.9	0.93	Yes††	OD: +14.00 DS, OS: +14.00 DS, add: OU- +3.50 DS
10	Yes	Horizontal, jerky nystagmus with moderate frequency and mild amplitude	Yes	No[1]	No	Yes	Female	NA	NA	5.0	11.0	0.5	Yes††	OD: +4.00 DS/-2.00 DC x 95, OS: +2.75 DS/-1.50 DC x 85, add: OU- +2.75 DS
11	Yes	Horizontal nystagmus which later changed to multiplanar nystagmus	Yes	No	Yes	Yes	Female	1.77	1.77	15.0	0.9	1.78	Yes††	OD: -1.00 DS, OS: 0.0 DS/-2.00 DC x 160, add: OU- +3.00 DS
12	Yes	Horizontal, jerky nysagmus	NA	No[2]	No	No	Male	NA	NA	6.0	30.9	1.34	Yes†	OD: +11.00 DS, OS: +12.00 DS, add: OU- +4.00 DS
13	Yes	Multiplanar nystagmus	Yes	No	Yes	Yes	Female	1.48	1.48	31.4	7.4	1.04	Yes††	OD: 0.00 DS, OS: 0.00 DS, add: OU- +3.00 DS

* All participants lacked stereovision and presented with developmental amblyopia due to patterned visual deprivation. †No record of maternal rubella ††Maternal rubella explicitly excluded

[1] *Bilateral amblyopia, equal impairment in both the eyes* [2] *Deprivational amblyopia presesnt but no strabismus recorded*

Appendix III

Pant et al., (2021). The size-weight illusion is unimpaired in individuals with a history of congenital visual deprivation. Scientific Reports, Vol. 11, 1-13.

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The size-weight illusion is unimpaired in individuals with a history of congenital visual deprivation

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Visual deprivation in childhood can lead to lifelong impairments in multisensory processing. Here, the Size-Weight Illusion (SWI) was used to test whether visuo-haptic integration recovers after early visual deprivation. Normally sighted individuals perceive larger objects to be lighter than smaller objects of the same weight. In Experiment 1, individuals treated for dense bilateral congenital cataracts (who had no patterned visual experience at birth), individuals treated for developmental cataracts (who had patterned visual experience at birth, but were visually impaired), congenitally blind individuals and normally sighted individuals had to rate the weight of manually explored cubes that differed in size (Small, Medium, Large) across two possible weights (350 g, 700 g). In Experiment 2, individuals treated for dense bilateral congenital cataracts were compared to sighted individuals in a similar task using a string set-up, which removed haptic size cues. In both experiments, indistinguishable SWI effects were observed across all groups. These results provide evidence that early aberrant vision does not interfere with the development of the SWI, and suggest a recovery of the integration of size and weight cues provided by the visual and haptic modality.

Infants born with dense bilateral cataracts lack patterned vision until their sight is restored by cataract removal surgery. When surgery is performed late, i.e. beyond the first few weeks from birth, these individuals have been reported to suffer from permanent visual and multisensory impairments[1–5]. These impairments are hypothesized to be a behavioral consequence of neural system changes, resulting from aberrant sensory input within a sensitive period of development[6,7]. One way to assess visual and multisensory functional recovery in cataract reversal individuals is to test their susceptibility to well-known perceptual illusions. Perceptual illusions are typically extremely robust, suggesting that they arise from automatic processing principles[8]. Thus, the lack (or reduced likelihood) of perceiving a visual or multisensory illusion is indicative of impaired visual or multisensory processing, respectively.

Putzar et al.[9] tested the automatic detection of illusory contours in congenital cataract reversal individuals who had undergone cataract surgery between 1 and 17 months of age. They observed deficits in individuals who experienced more than 5–6 months of visual deprivation, and interpreted this result as evidence for impairments in the automatic binding of visual features—i.e. visual feature binding. This finding was extended by McKyton et al.[10] to a population of cataract reversal individuals who had undergone surgery only after the age of 5 years. These results suggested that early visual experience is required to acquire the neural circuits necessary for visual feature binding, providing evidence in favor of the sensitive period hypothesis. While this conclusion is compatible with the long developmental trajectory of illusory contour perception[11], other studies replicated this finding for individuals treated for monocular[12] (but not binocular) congenital cataracts.

Gandhi et al. tested the Ponzo and Müller-Lyer illusions, wherein equally long lines are perceived to be of different lengths depending on their surroundings[13]. Forty-eight hours after cataract surgery, they found a full recovery of this illusion[13], despite the fact that sight was partially restored only at 8 years of age or later. Since both these illusions were thought to arise from the interpretation of two-dimensional perspective cues as three-dimensional depth, they concluded that this process did not depend on early childhood vision.

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Illusions have additionally been used to investigate the extent of multisensory recovery following cataract surgery. In an initial study, Putzar et al.[14] employed an audio-visual temporal capture effect, characterized as follows: if an auditory stimulus is presented with a short temporal offset with respect to a visual stimulus, the visual stimulus is often perceived as temporally shifted towards the time point when the sound was presented. This effect was significantly reduced in congenital cataract reversal individuals[14]. The residual visual impairments would have, according to the inverse efficiency rule of multisensory integration, predicted a larger capture in this group, suggesting that the multisensory binding process was impaired[15]. Similarly, cataract reversal individuals had a significantly reduced likelihood of showing the McGurk effect[16]. In this illusion, auditory speech, presented concurrently with an incongruent visual lip movement, produces a percept that matches neither the auditory nor the visual input. The absence of the McGurk effect in congenital cataract reversal individuals was subsequently shown to be related to a lack of multisensory enhancement in superior temporal brain regions, known to be essential for audio-visual speech perception[17–19]. Finally, visual motion after-effects (perception of stationary stimuli as moving in the direction opposite to previously presented moving stimuli) were found after auditory motion adaptation in cataract-reversal individuals[20], i.e., a cross-modal after-effect which has not been found in normally sighted individuals. These results converge to the conclusion that multisensory binding processes do not fully recover after sight restoration in individuals with a history of congenital cataracts. Although recent studies with cataract reversal individuals have demonstrated recovery of multisensory redundancy effects[2,21] and partial recovery for auditory-visual simultaneity judgements[22], multisensory binding based on more complex features, such as speech[14], seems to depend on early visual input.

It is currently unclear to what degree visuo-haptic and visuo-motor processing recovers after a transient phase of congenital visual deprivation. A developmental study with children found that visuo-haptic integration reaches adult-like performance only by 10 years of age[23]. Prior to that, children show signs of either vision or touch dominating visuo-tactile perception. Evidence from studies in a small number of individuals who had dense (but not necessarily congenital) bilateral cataracts suggested a quick emergence of visuo-haptic interactions after surgery, when these individuals were tested in vision-to-touch object matching tasks (n = 1[24]; n = 5[25]). However, later single case studies pointed towards impaired spatial representations for visuo-tactile localization after at least two years of visual deprivation[26,27]. Further, a study testing sight recovery individuals on an automatic imitation task, which mapped vision to motoric performance, found performance deficits even two years after surgery[28].

A phenomenon observed in typical visuo-haptic development is the perception of the size-weight illusion (henceforth referred to as the SWI), which has been described as "immutable"[29]. The SWI is an illusion perceived when two unequally sized objects of the same weight are compared—the smaller object is perceived as being heavier than the larger one.

The "classical" SWI is assumed to require the integration of visual and haptic input (for review, see Dijker)[30]. Though the SWI has been documented for a long time, there is still a debate on whether it occurs due to conflicting sensorimotor input, or is a purely cognitive effect due to a mismatch in expectations[31]. At present, the contribution of early visual experience to the occurrence of the illusion is unclear.

Several lines of evidence have suggested a crucial role of ongoing visual input in the perception of the SWI. First, the SWI was reported to disappear when visual cues were not presented to normally sighted participants, even if they were allowed to access them beforehand, suggesting a crucial role of continued visual perception for the illusion, and providing a strong argument that the SWI reflects visuo-haptic integration[32]. Additionally, the SWI was observed to increase with an increase in visual disparity between sizes; if two objects of the same weight had a greater difference between their visually perceived sizes, the illusion perceived was stronger[33]. This was found to be true even in the absence of haptically perceived size differences, when visually perceived size was varied using objects with adjustable heights but constant surface area[34]. Finally, in a rapid adaptation study using functional MRI with an SWI task, the ventral premotor area (PMv) responded more when the SWI was perceived, i.e. when participants compared the weights of two objects of different sizes and the same weight, than when participants compared objects of the same size and weight[35]. Importantly, the PMv did not show an independent adaptation to size and weight properties, but adapted to the combination of these properties, therefore providing neural evidence for the integration of concurrent but separate sensory input. These results suggest that early visual deprivation might affect the SWI, if the ability to integrate visual and haptic cues does not recover.

The SWI was observed to occur when size information was perceived exclusively visually (i.e. using a string set-up to weigh objects, preventing individuals from using haptic cues to estimate size) or exclusively haptically (i.e. blindfolding individuals to prevent them from accessing visual estimates of size)[36,37]. However, both these studies reported that the SWI was smaller when the task presented sighted individuals with size cues that were exclusively visual, as compared to when the task was haptic or visuo-haptic. Moreover, congenitally blind individuals have been reported to experience the SWI as well[37,38]. These results would lead us to hypothesize that the SWI emerges independent of visual input, and thus, should manifest unimpaired in sight-recovery individuals too—at least if the objects are perceived exclusively haptically. However, there might be some competition between belatedly available visual input and other sensory modalities[39,40], which might worsen visual performance[14,20]. Consistent with this assumption, a reduced visuo-haptic SWI was reported in visually impaired individuals with some residual visual capabilities[41]. Therefore, it could be hypothesized that the visuo-haptic SWI, both with and without haptic size information, is reduced in individuals who recover from transient congenital or developmental visual deprivation.

The second account for the occurrence of the SWI has proposed that this illusion is a result of violated expectations, and originates from top-down rather than bottom up processes[42–45]. If the SWI is a result of exclusively visual statistics gathered over the lifespan—i.e. an increased amount of force on the larger object because of the belief that smaller objects should weigh less—then individuals who have not had access to vision early in life, when tested with and without haptic size information, should either not manifest the illusion, or perceive it to a lower degree.

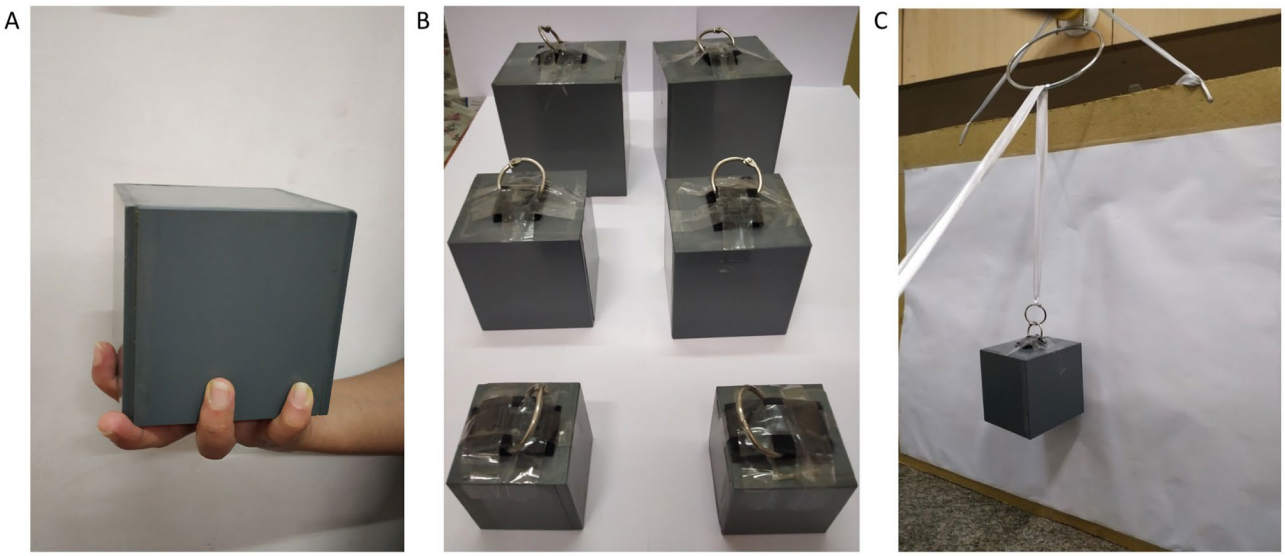

Figure 1. (**A**) Large-sized cube stimulus placed in the dominant hand, demonstrating the procedure for Experiment 1. (**B**) The six stimuli used in the study (front to back: Small, Medium, Large, 350 g and 700 g respectively), with attachments for Experiment 2. (**C**) String set-up of Experiment 2. A smooth ribbon is used to lift the cube during each trial, ensuring that only visual size cues are available to the participant.

In order to test for the dependence of visuo-haptic interactions on early visual input, we performed two experiments using an SWI paradigm employed by Buckingham and Goodale, wherein subjects were asked to rate cubes across three sizes (Small, Medium, Large) and two weights (350 g, 700 g) on how heavy they thought they were[42]. The first experiment tested the "classic" visuo-haptic SWI, that is the SWI when simultaneously receiving visual and haptic size information. A group of dense bilateral congenital cataract reversal individuals (CC) as well as a group of individuals who had suffered developmental cataracts (DC) were tested, and compared to a group of normally sighted controls (SC). We additionally ran and separately analyzed data from two congenitally blind (CB) individuals to pilot whether we would replicate the findings from Ellis and Lederman[37]. Such an illusion would necessarily be based on exclusively haptic estimates of size. The second experiment used a string set-up to ensure only visual size cues were available to participants, in order to isolate the visual contribution to the SWI[36,37,46]. A group of congenital cataract reversal individuals (CC) and a group of normally sighted controls (SC) were compared. We hypothesized that in Experiment 1, the SWI would be impaired in CC compared to SC and DC individuals, due to aberrant visual experience interfering with multisensory integration[39,40], and that in Experiment 2, CC individuals would not experience the SWI when deprived of haptic size information[37,46].

Results

Sight-recovery individuals show an intact visuo-haptic SWI (Experiment 1). Experiment 1 allowed participants to access both visual and haptic estimates of size (Fig. 1A). When z-scored weight ratings were assessed in a size-by-weight-by-group analysis of variance (ANOVA with repeated measures), all groups performed the task in a principled manner, as indicated by a main effect of weight, wherein the 700 g weight was rated as heavier than the 350 g weight ($F(1,23) = 639.15$, $p < 0.001$, $\eta_g^2 = 0.85$).

There was a main effect of size, demonstrating the presence of the SWI ($F(2,46) = 147.11$, $p < 0.001$, $\eta_g^2 = 0.74$), i.e. participants perceived smaller sized objects of the same weight to be heavier. Crucially, the group-by-size ($F(4,46) = 0.96$, $p = 0.419$, $\eta_g^2 = 0.03$), group-by-weight ($F(2,23) = 2.63$, $p = 0.094$, $\eta_g^2 = 0.04$), and size-by-weight-by-group interactions ($F(4,46) = 1.64$, $p = 0.181$, $\eta_g^2 = 0.05$) were all not significant. Therefore, CC individuals displayed an indistinguishable SWI from DC and SC individuals (Fig. 2).

We found a size-by-weight interaction, indicating that the illusion was stronger for the 700 g than the 350 g weight ($F(2,46) = 11.82$, $p = 0.001$, $\eta_g^2 = 0.15$). In order to follow up on this effect, two post-hoc 3 (size) × 3 (group) repeated measures ANOVAs were conducted, separated by the weight condition. There was a main effect of size for both the 350 g ($F(2,46) = 59.08$, $p < 0.001$, $\eta_g^2 = 0.66$) and the 700 g ($F(2,46) = 108.24$, $p < 0.001$, $\eta_g^2 = 0.79$) weights, demonstrating that the SWI was highly significant for both weights in all groups. Again, we found no group-by-size interaction (350 g: $F(4,46) = 0.57$, $p = 0.63$, $\eta_g^2 = 0.04$; 700 g: $F(4,46) = 1.74$, $p = 0.179$, $\eta_g^2 = 0.11$), indicating that the degree to which the three groups experienced the SWI was indistinguishable (Fig. 3).

Paired t-tests across the three groups confirmed that participants experienced the smaller cube as heavier than the medium (350 g: $t(24) = 8.28$, $p < 0.001$; 700 g: $t(24) = 7.64$, $p < 0.001$) and large cube (350 g: $t(24) = 9.95$, $p < 0.001$; 700 g: $t(24) = 11.52$, $p < 0.001$) of the same weight, and the medium sized cube as heavier than the large cube of the same weight (350 g: $t(24) = 5.97$, $p < 0.001$; 700 g: $t(24) = 8.49$, $p < 0.001$).

Both CB individuals tested showed an impressively clear SWI (Fig. 2). We found that their z-scores (Fig. 2) fell within the core range of the remaining groups. Thus, these two participants replicated prior results[37,46].

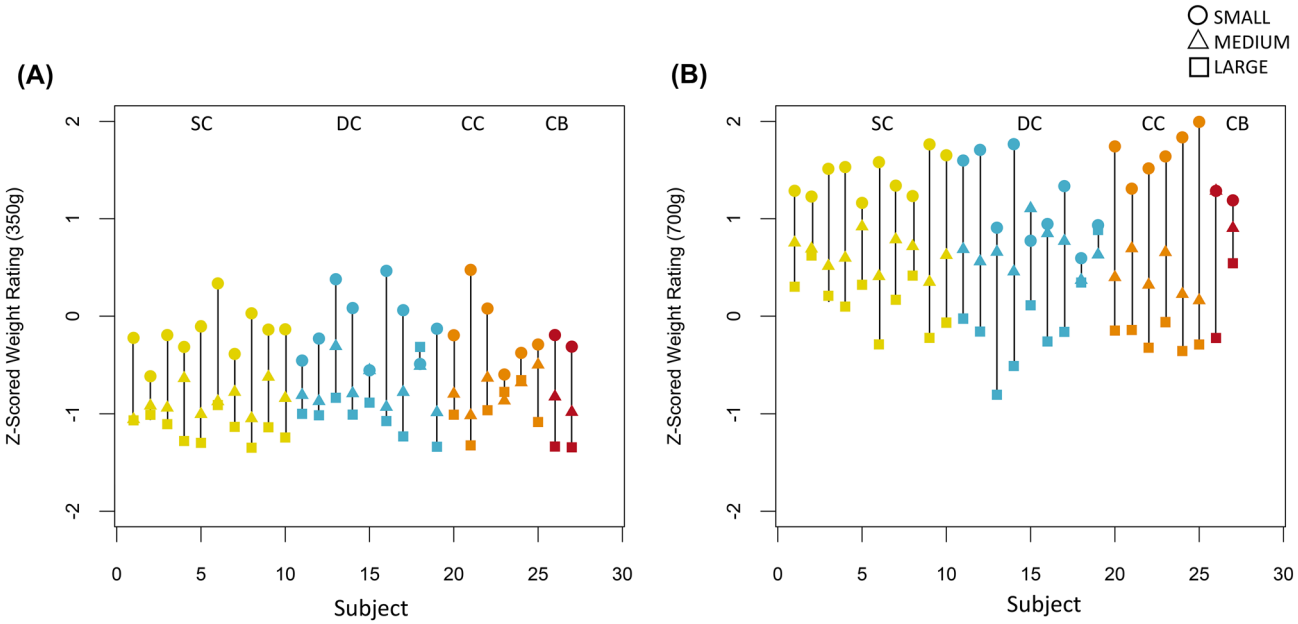

Figure 2. Experiment 1 (with visual and haptic size information); z-scored weight ratings of all individuals in the Sighted Control (SC, yellow), the Developmental Cataract group (DC, blue), the Congenital Cataract group (CC, orange), and two Congenitally Blind (CB, red) individuals, t (**A**) for the 350 g and (**B**) for 700 g weights (Experiment 1).

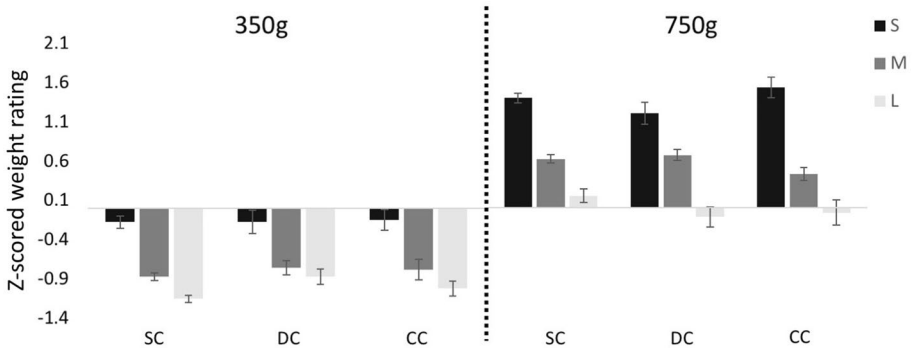

Figure 3. Experiment 1 (with visual and haptic size information); average z-scored weight ratings for the Small (S), Medium (M) and Large (L) cubes across the Sighted Control (SC), Developmental Cataract (DC) and Congenital Cataract (CC) groups, for the 350 g and 700 g weights (Experiment 1). Error bars depict standard error of mean (SEM).

SWI Index. In order to obtain a measure of illusion strength for each individual, we calculated an SWI Index by subtracting the mean z-scored weight judgment of the largest cube from that of the smallest cube, separately for each weight.

We conducted separate one way ANOVAs for the 350 g and 700 g weights to assess the effect of group on the calculated SWI Index. The CC, DC, and SC groups did not differ in the strength of the illusion—neither for the 350 g ($F(2,23) = 0.72$, $p = 0.497$, $\eta_g^2 = 0.06$) nor the 700 g weights ($F(2,23) = 0.74$, $p = 0.487$, $\eta_g^2 = 0.06$) (Fig. 3). We further tested these null findings against effect sizes obtained from studies in the literature. Based on a comparable study and task found for the 700 g weight, we used equivalence analyses[47] to confirm that the SWI index was equivalent in the CC, DC and SC groups—i.e. the SWI indices were within the bounds obtained by Buckingham and Goodale[42] (the presence of any meaningful effect of group was rejected with all p's < 0.024, see Supporting Information S1).

The two CB individuals tested showed SWI indices within the range of the other groups (350 g: − 1.145 and − 1.034; 700 g: − 1.507 and − 0.646), demonstrating a full strength SWI.

Sight recovery individuals show an SWI with exclusively visual size estimates (Experiment 2). Experiment 2 was performed as a follow up to the results from Experiment 1, in order to assess the occurrence of the SWI in the absence of haptic size cues (Fig. 1B,C). Since we found no group differences in Experi-

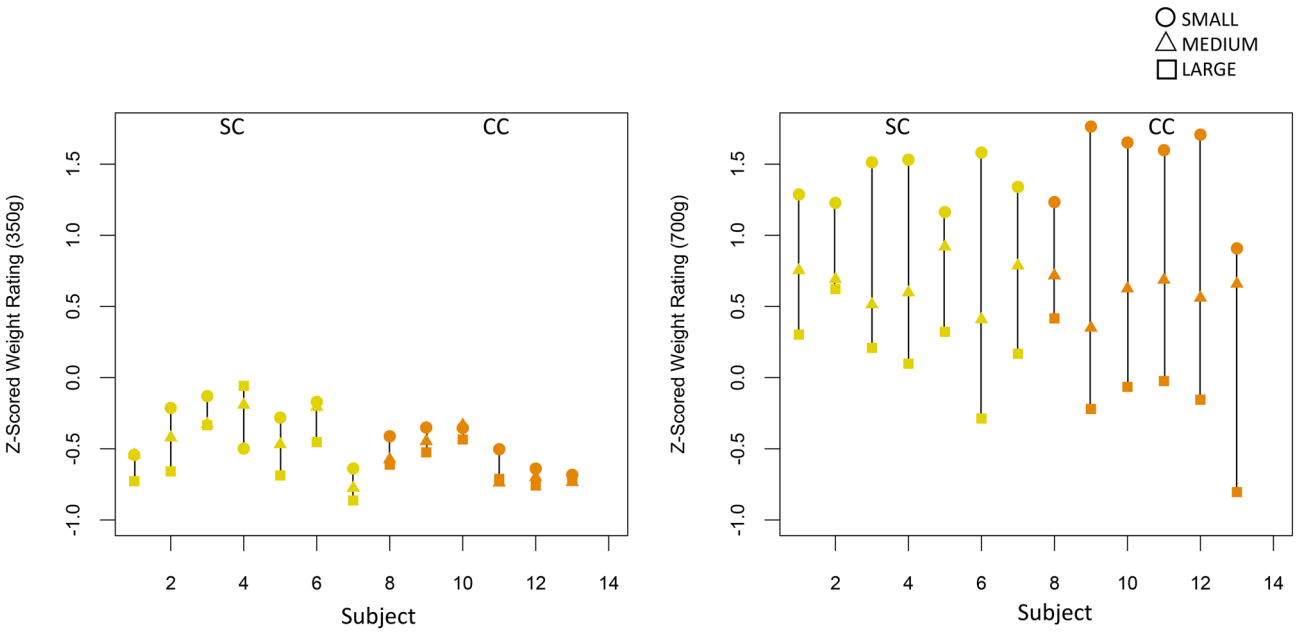

Figure 4. Experiment 2 (with only visual size information); z-scored weight ratings of all individuals in the Sighted Control group (SC, yellow) and Congenital Cataract group (CC, orange) groups (A) for the 350 g and (B) for 700 g weights (Experiment 2).

ment 1, and our a priori hypothesis was restricted to the effects of transient congenital patterned visual deprivation on the development of the SWI, we ran two groups: CC and SC individuals. Further, given the limitations on recruitment of special populations, as our goal with this experiment was to isolate the visual contribution to the full-sized SWI observed in CC individuals, DC individuals were not tested. In light of the occurrence of a full-sized SWI with (necessarily) exclusively haptic size cues in CB individuals in Experiment 1 and prior studies[37,46], we did not repeat an additional haptics-only condition.

In a group-by-weight-by-size ANOVA performed for Experiment 2, we obtained a main effect of weight ($F(1,11) = 110.80$, $p < 0.001$, $\eta_g^2 = 0.833$), indicating that participants performed the task in a principled manner. Additionally, the main effect of size was significant ($F(2,22) = 8.82$, $p = 0.009$, $\eta_g^2 = 0.203$), confirming an SWI with this task across groups (Fig. 4). The CC participants did not differ from the SC group in their performance on this task, as evidenced by the lack of a significant main effect of group ($F(1,11) = 0.158$, $p = 0.999$, $\eta_g^2 < 0.001$), and of significant group-level interactions (group-by-size: $F(2,22) = 0.048$, $p = 0.861$, $\eta_g^2 = 0.002$; group-by-weight: $F(1,11) = 1.866$, $p = 0.199$, $\eta_g^2 = 0.077$; group-by-size-by-weight: $F(2,22) = 0.556$, $p = 0.509$, $\eta_g^2 = 0.009$).

Across groups, participants experienced the smaller cube as heavier than the medium cube (350 g: $t(12) = 2.03$, $p = 0.056$; 700 g: $t(12) = 2.02$, $p = 0.066$) as well as the large cube (350 g: $t(12) = 2.74$, $p = 0.018$; 700 g: $t(12) = 2.86$, $p = 0.014$) of the same weight, and the medium sized cube as heavier than the large cube of the same weight (350 g: $t(12) = 2.62$, $p = 0.023$; 700 g: $t(12) = 3.03$, $p = 0.010$), confirming the presence of the SWI with this paradigm (Fig. 5).

SWI Index. The CC and SC groups did not differ in the strength of the illusion for either the 350 g ($F(1,11) = 0.169$, $p = 0.688$, $\eta_g^2 = 0.015$), or the 700 g weights ($F(1,11) = 0.001$, $p = 0.971$, $\eta_g^2 < 0.001$) (Fig. 5). When compared using equivalence testing for the 700 g weight, conducted based on available effect sizes in the literature, we found the SWI indices to be equivalent, significantly rejecting any effect of group (both p's < 0.006, see Supporting Information S1).

The visual contribution to the SWI is identical in sight recovery and sighted individuals. We compared the SC and CC groups of Experiment 1 and 2 in a group-by-weight-by-experimental task ANOVA, in order to assess whether the groups differed between how they performed when both visual and haptic size estimates were available, compared to when only visual size information was available. We confirmed that the SWI was significantly stronger in Experiment 1 compared to Experiment 2 (main effect of Experimental Task: $F(1,26) = 56.396$, $p < 0.001$, $\eta_g^2 = 0.511$), and stronger for the 700 g than the 350 g weight (main effect of Weight: $F(1,26) = 9.089$, $p = 0.006$, $\eta_g^2 = 0.153$) (Fig. 6). The group-by-experiment interaction ($F(1,26) = 0.357$, $p = 0.555$, $\eta_g^2 = 0.006$), group-by-weight interaction ($F(1,26) = 1.083$, $p = 0.307$, $\eta_g^2 = 0.021$), and group-by-weight-by-experiment interaction were all non-significant ($F(1,26) = 0.631$, $p = 0.424$, $\eta_g^2 = 0.012$), confirming that in both experiments CC individuals perceived an indistinguishably strong SWI from SC individuals, suggesting that the "visual" contribution to the SWI did not differ in the two groups.

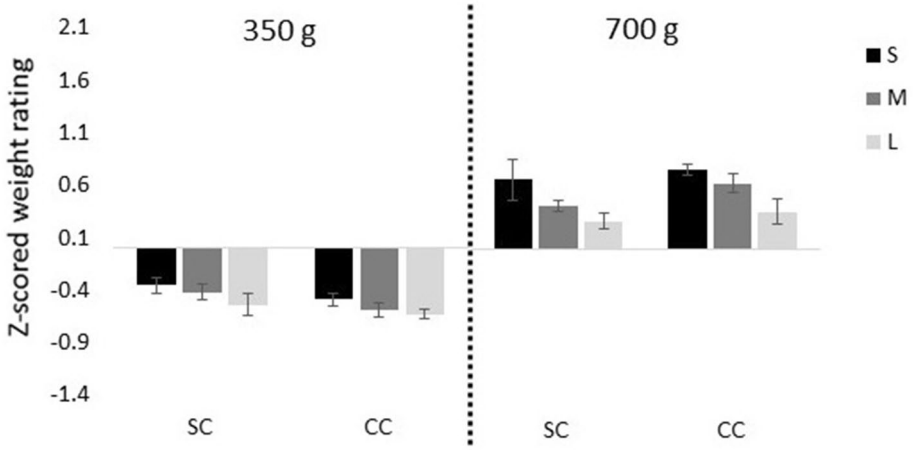

Figure 5. Experiment 2 (with only visual size information); average z-scored weight ratings for the Small (S), Medium (M) and Large (L) cubes for the Sighted Control group (SC) and Congenital Cataract group (CC), for the 350 g and 700 g weights. Error bars depict standard error of mean (SEM).

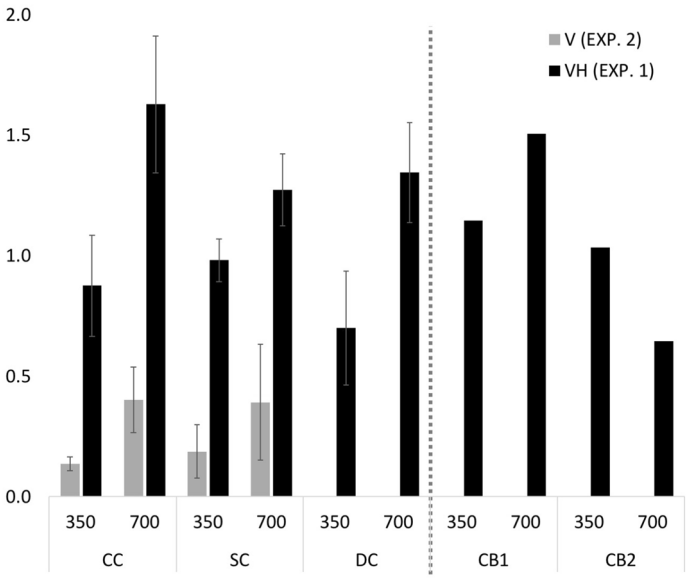

Figure 6. Size-Weight Illusion Indices across groups and for the two CB individuals for Experiment 1 (with visual and haptic size information, black bars, labelled VH) and Experiment 2 (with only visual size information, gray bars, labelled V), for the 350 g and 700 g weights. The y-Axis depicts the difference in z-scores between the large and small cubes of each weight, averaged for each group (CC, DC, and SC). Error bars depict the SEM.

Relationship between strength of the SWI and the duration of visual deprivation. To test for a possible effect of duration of patterned visual deprivation on the strength of the SWI, we calculated the correlation between age at surgery and the average SWI Index (across 350 g and 700 g) for CC individuals. This correlation was not significant neither for Experiment 1 ($r = 0.05$, $t(4) = 0.10$, $p = 0.463$), nor did the correlation reach significance for Experiment 2 ($r = -0.76$, $t(4) = -2.357$, $p = 0.078$). Additionally, no correlation was observed between illusion size and age at time tested in either group (see Supporting Information S4.3).

Discussion

The present study investigated whether the manifestation of the size-weight illusion (SWI) depends on patterned visual experience after birth. We tested sight recovery individuals with a history of dense bilateral congenital cataracts, and compared this group to sight recovery individuals with a history of developmental cataracts, as well as a group of normally sighted controls. Our results demonstrated a significant "classical" SWI (with visual and haptic size information available) in all groups; indeed, the size of the SWI was indistinguishable between the three groups. Furthermore, we replicated previous results from Ellis and Lederman[37] and showed that two

permanently congenitally blind individuals experienced the SWI to a degree that fell within the range of all the other participants.

We additionally used a string set-up in Experiment 2 to test whether the CC group used visual size cues, rather than relying only on haptic size cues in Experiment 1[46]. As in Experiment 1, the SWI experienced with exclusively visual size information was equivalent across sight recovery individuals with a history of congenital cataracts, and sighted controls. Together, these results suggest that the visuo-haptic SWI is resilient to atypical visual experience after birth.

No sensitive period effects for visuo-haptic integration as tested by the SWI. A previous study of individuals who were operated upon for dense bilateral congenital cataracts reported that in an object matching task conducted two days-post-surgery, while unimodal tactile and visual performance was observed to be at ceiling, tactile to visual mapping was found to be severely impaired (Held et al., n = 5)[48]. However, the authors observed that this ability rapidly improved over the next five days. A subsequent case study of sight recovery suggested that visuo-tactile processing recovers in object recognition and object matching tasks within three days of sight restoration, despite a lack of visual experience after birth (Chen et al., n = 1)[24]. As these studies tested participants closer to the date of surgery, and given that the sight recovery individuals in the present study were all tested one year from surgery (in order to exclude acute but transient effects of surgery) our findings are consistent with these existing studies on visuo-haptic object recognition. However, both Held et al. and Chen et al. tested visuo-haptic transfer through object matching tasks. By contrast, we provide evidence for the recovery of visuo-haptic *integration* (i.e. a unified percept by fusing input from both sensory modalities) despite early patterned visual deprivation, therefore extending these studies[40,49]. Our findings might be considered surprising in light of two prospective studies, which suggested a protracted developmental pathway for the SWI. The first study observed that the SWI increased in size after the age of 5 years[43]. They related this increase to the development of abstract reasoning skills. However, abstract reasoning explained no more than about 10% of the effect, and the SWI existed even in the youngest group. A second study showed that typically developing children did not optimally integrate visuo-haptic input in an adult-like manner until the age of 10 years[23]. However, optimal integration is typically defined as optimal cue integration as predicted by forced fusion models. These models weight individual cues according to their relative reliability, to derive a multisensory outcome. It has more recently been demonstrated that in situations where it is ambiguous whether or not to integrate sensory information, the data from children as young as 5 years of age, like those of adults, are better explained by causal inference models[50]. Given that some (n = 4) of our CC participants had been older than 10 years of age at the time of surgery, our results suggest that patterned vision during this period of multisensory development was not crucial for the typical manifestation of the SWI, with either visuo-haptic or only visual size information.

These results showing an indistinguishable SWI in sight recovery individuals, both with a congenital as well as a developmental history of transient blindness, provide evidence that the multisensory processes underlying the SWI are resilient to atypical visual experience. First, participants of both cataract groups still suffered visual impairments at the time of testing. Nevertheless, the SWI was not smaller in magnitude in either group, compared to normally sighted individuals. A smaller SWI in sight recovery individuals would have been expected from the aforementioned reliability-based optimal integration account[51]. Second, neither years of blindness nor the timing of the transient phase of blindness (developmental vs. congenital) had a significant influence on the size of the SWI. Finally, the extent of the "visual" contribution to the SWI was indistinguishable between sight recovery and sighted individuals. This identical behavioral performance, regardless of atypical visual history across groups and tasks, provides strong evidence that visuo-haptic processing, as assessed with the SWI, does not rely on sensitive period plasticity to develop normally.

It is possible that different underlying neural mechanisms support the identically sized SWI in sight recovery individuals[52]. As sensitive periods are properties of neural circuits, further neuroimaging studies need to confirm whether visuo-haptic processing develops normally in the absence of typical visual experience[6,53]. Additionally, the absence of sensitive period effects in one tested behavior does not contradict the general role of sensitive period plasticity[5,53–56]. Disengaging functions which do and do not develop within sensitive periods will, in the long run, be essential to uncovering the general principles of functional brain development.

To the best of our knowledge, the present study is the first to conclusively show the manifestation of a full-strength SWI in sight recovery individuals, both for the condition with visual and haptic size information, as well as the condition with only visual size information. Further, strict criteria were used for the inclusion of sight recovery participants, in order to ensure high homogeneity of etiology within the CC and DC group. We chose a retrospective, developmental approach with individuals who underwent cataract reversal surgery before the age of 23 years, and were older than 8 years of age at the time of testing. After the age of 8 years, no further increase in the SWI had been observed in prospective studies[43]. The present study did not find any difference in the size of the SWI, neither for the visuo-haptic nor for the visual experiment. A significant, equivalent SWI was consistently perceived by individual participants across all groups, despite the fact that in the cataract groups, age at surgery, time since surgery and visual acuity at time of testing varied, potentially increasing between group differences. Our stringent inclusion criteria restricted the sample size within a special population, however, all individual subjects showed the SWI with established paradigms in a consistent pattern (Figs. 2,3), allowing us to interpret the lack of group differences and confirming them with equivalence testing. We consider these results to be highly robust evidence against the dependence of the SWI on early visual input, therefore suggesting the lack of a sensitive period for the development of the SWI.

Mechanisms of the SWI. What are the possible mechanisms by which the SWI could manifest in CC individuals? While our study does not allow us to disentangle the models explaining the occurrence of the SWI,

interpreting our results in light of these hypotheses can shed light on the mechanisms of the SWI. Below, we engage with the dominant models of the SWI.

On one hand, it could be assumed that the SWI is a purely haptic process, as was consistent with earlier reports of the SWI manifesting in congenitally blind adults, and replicated in two congenitally bind adults in the present study[37,38]. However, a purely haptic account of the SWI would have predicted the absence of the SWI when haptic size cues are unavailable to sight recovery individuals. In fact, prior studies employing a string set-up in congenitally blind individuals, as expected, did not observe an SWI[37,46]. Instead, in the present study, sight recovery individuals perceived an SWI even when only visual size cues were available. Additionally, a recent study observed that congenitally blind individuals experience the SWI without haptic size cues, but when size estimates were obtained through echolocation[46]. Together, this evidence strongly argues against an exclusively haptic account of the SWI.

On the other hand, it has been suggested that the SWI is a multisensory phenomenon occurring due to a conflict between concurrent visual (size) and haptic (weight) sensory input[30,33,57]. Within this framework, our data suggest that while the SWI can develop through haptic input alone, it might nevertheless be modulated by visual input, due to the recovery of visuo-haptic processing despite atypical visual experience[22,24,25]. Indeed, full or partial recovery of visuo-tactile functions has been reported, depending on the task. While prior studies have shown that in a simultaneity judgement task designed to test a unified multisensory percept, visuo-tactile performance was unimpaired despite a lack of early visual experience[21,22], sight recovery individuals did not show normal visuo-tactile temporal order biases[27,58]. Additionally, our findings of a larger SWI when both visual and haptic size information was available than when only a visual size estimate was possible, in both sight recovery and sighted individuals, fit with a multisensory framework for the occurrence of the SWI[36,37].

Conclusions

The occurrence of the Size-Weight Illusion (SWI), both when visual and haptic size information was available, as well as when only visual size information was assessable, was resilient to atypical visual experience within the first months and years of life. These results provide strong evidence that the visuo-haptic processes underlying the SWI do not require typical visual experience within a sensitive period for normal development. Further studies are needed to explore whether the SWI is supported by the same neural mechanisms in typical and atypical development, by employing neuroscience techniques[35].

Methods

Ethical approval. All participants, as well as their legal guardians in case of minors, provided written and informed consent. Testing was conducted after obtaining ethical approval from the German Psychological Society (DGP) and the local ethics board of the Hyderabad Eye Research Foundation. All methods and tests were performed in accordance with the relevant guidelines and regulations of both collaborating institutions.

Experiment 1. *Participants.* We tested three groups of individuals. The first group consisted of seven individuals born with dense bilateral cataracts, who subsequently underwent cataract removal surgery (referred to as CC individuals: 3 females, 4 males; Age = 8–35 years, M = 21.2 years, SD = 9.8, Table 1). The CC individuals were diagnosed by ophthalmologists and optometrists at the LV Prasad Eye Institute (LVPEI) in Hyderabad (India). They were tested by the some of the authors, partially with the help of a translator, in English, Hindi or Telugu. The data from four additional CC individuals were excluded due to unwillingness to cooperate (n = 2) or a documented developmental delay (n = 2). Individuals were categorized as part of this group based on the presence of dense bilateral cataracts at birth, a pre-surgery visual acuity of counting fingers at 1 m or less (barring absorption of lenses), presence of nystagmus, occlusion of fundus/retina, and immediate family members who had also been diagnosed with dense bilateral congenital cataracts. Duration of blindness was calculated by subtracting the date of birth from the date of the first eye surgery (M = 13.21 years, SD = 8.24, Range = 2–23.05 years). One individual did not have his precise date of surgery information available (operated after 6 months of age), and was excluded from duration calculations. Visual acuity pre-surgery in the better eye ranged from a minimum of light perception (PL +) to a maximum of counting fingers close to the face (CFCF). One participant had been able to count fingers at a distance of 3 m pre-surgery. We included this participant due to clearly partially absorbed lenses (OD Visual Acuity: counting fingers at 1.5 m, OS Visual Acuity: counting fingers at 3 m). All other criteria such as nystagmus and family history pointed towards the presence of dense bilateral cataracts at birth. Visual acuity post-surgery in the better eye in this group ranged from a minimum of counting fingers at a distance of 1 m to a maximum of 20/40. All individuals included in this group lacked patterned vision at birth, in accordance with the criteria set by the WHO[59].

The second group consisted of nine individuals who had either partial congenital cataracts or developmental cataracts, and were subsequently operated upon to remove the cataracts (referred to as DC individuals: 2 females, 7 males; Age = 8–37 years, M = 14.8 years, SD = 9.2, Table 1). The testing procedure was the same as that of the CC group. Comparing this group with the CC individuals allowed us to isolate effects caused by transient patterned visual deprivation at birth from effects due to general visual impairments caused by a changed periphery. Visual acuity pre-surgery in the better eye ranged from following light to a maximum of 20/80. Visual acuity post-surgery in the better eye ranged from 20/1200 to 20/20. All individuals included in this group did not lack patterned vision at birth, but suffered from degraded visual input for some or all of their early childhood, therefore providing a control group for the possibility that any observed impairments of the CC group were not specific to visual input at birth, but due to degraded visual input at any stage of life.

Sub	Age (years)	Group	Gender	Absorbed lenses	Presence of nystagmus	Pre-surgery visual acuity		Post-surgery visual acuity		Duration of blindness (years)	Time since surgery (years)
						Right	Left	Right	Left		
Experiment 1											
1	23.25	CC	Male	No	Yes	Unknown	Unknown	CF (close to face)	20/126	Unknown	
2	35.54	CC	Male	No	Yes	Unknown	Unknown	20/120	20/40	2.00	33.54
3	21.78	CC	Female	Yes	Yes	Unknown	Unknown	20/317	20/252	21.02	0.76
4	16.97	CC	Female	No	Yes	PL + PR +	CF (Close to Face)	PL + PR +	CF at 1 m	16.05	0.92
5	30.76	CC	Male	No	Yes	Unknown	Unknown	20/400	20/800	23.05	7.72
6	11.24	CC	Female	No	Yes	PL +	PL +	20/125	CF at 0.5 m	10.16	1.08
7	8.62	CC	Male	Yes	Yes	CF at 1.5 m	CF at 3 m	20/500	20/126	7.00	1.62
8	18.34	DC	Female		No	FL +	FL +	20/60	20/30	–	–
9	37.02	DC	Male		Yes	20/200	20/300	20/200	20/200	–	–
10	10.05	DC	Male		Yes	PL + PR inaccurate	PL + PR inaccurate	20/1200	20/1200	–	–
11	8.62	DC	Male		No	20/100	20/100	20/20	20/20	–	–
12	8.01	DC	Male		No	20/80	20/100	20/40	20/40	–	–
13	10.15	DC	Female		No	PL + PR +	CF at 2 m	20/170	20/16	–	–
14	17.71	DC	Male		No	6/60	CF at 1 m	20/63	CF at 0.5 m	–	–
15	14.24	DC	Male		Yes	FL +	Poor fixation	20/40	CF at 0.5 m	–	–
Experiment 2											
1	33.09	CC	Male	No	Yes	Unknown	Unknown	CF at 1 m	20/200	14.00	19.10
2	15.24	CC	Male	Yes	Yes	CF at 1.5 m	CF at 3 m	20/500	20/126	7.00	8.24
3	18.30	CC	Male	Yes	Yes	20/500	20/800	20/125	20/500	16.45	1.85
4	17.28	CC	Female	Yes	Yes	20/600	CF at 1 m	20/250	20/500	15.42	1.85
5	37.39	CC	Male	No	Yes	Unknown	Unknown	20/400	20/800	23.05	14.34
6	44.74	CC	Male	Yes	Yes	20/300	Unknown	20/125	20/200	22.02	22.72

Table 1. Participant characteristics for all sight recovery participants in Experiments 1 and 2. Age was calculated on the day of testing, and duration of blindness was calculated by subtracting date of birth from date of first surgery. Time since surgery was calculated by subtracting date of first surgery from date of testing. Visual acuity is reported separately for each eye (*CF* counting fingers, *PL* perception of light, *PR* projection of rays in all quadrants, *FL* fixate and follow light).

The third group consisted of 10 individuals with normal or corrected-to-normal vision and who had no history of visual deficits or eye injuries (referred to as SC group: 7 females 3 males; Age = 19–36 years, M = 25.8 years, SD = 5.3). SC individuals were tested at the University of Hamburg, Hamburg, Germany, in German.

In addition to these three groups, we ran two congenitally blind individuals who had no more than light perception since birth and at the time of the study (referred to as CB individuals: 1 female, 1 male; Ages = 33 and 44 years). They were tested at the University of Hamburg, Germany, using German. Their data were analyzed separately due to the small group size. The purpose of including these two participants was to replicate the presence of the SWI in individuals who totally lack vision since birth, but not for statistical comparisons between groups[37,46].

All individuals included in the data analysis reported no history of neurological or cognitive impairments. All participants were right handed, and used that hand to perform the task.

Stimuli and apparatus. Participants were tested using a free-rating, absolute-magnitude-estimation procedure: they freely chose a rating scale of their preference and estimated how much an object weighed on that scale[42]. This scale was adjustable during the course of the experiment.

Participants rated one of 6 gray plastic cubes that were placed on their palms. The cubes were small (5 cm side length), medium (7.5 cm side length) or large (10 cm side length), and had one of two different weights (either 350 g or 700 g) (Fig. 1). The weight was invisibly fixed in one corner, with the rest of the inside being hollow to ensure the same distribution of weight in each cube. Participants were instructed to hold the dominant arm bent at 90 degrees, and for each trial, the cube was placed on the palm of their dominant hand such that it was clearly visible. Participants were required to lift each cube for approximately 15 s, and to judge its weight. Upon the rating response, the experimenter removed the cube from the participants' hand.

We used random orders, and in one run, each cube was lifted 5 times. We repeated this across two runs, leading to a total of 60 trials. For participants who did not complete 60 trials, we used only the completed run of 30 trials (CC: n = 1; DC: n = 3). Participants were instructed not to rotate the arm for additional sensory cues, and not to throw the cube in the air and catch it again. This procedure took around 30 minutes in total.

Data analysis. In order to compare subjective judgements across participants, rating scores were z-transformed within each participant. This was done by subtracting the individual's mean weight judgement from each weight judgement, and dividing by the standard deviation[42]. Due to this z-scoring, all weight judgements reflect deviations from the same mean (zero), with higher z values indicating heavier weight judgements. In order to be included in the data analysis, participants had to consistently rate the 350 g cubes as lighter than the 700 g cubes, to exclude the possibility of a response bias as opposed to a principled difference in perceived weight due to size. This was true of all participants in Experiment 1.

We used frequentist statistics to analyze the data. Z-scores across participants were submitted to a mixed ANOVA. Our model considered two within-group factors—namely, weight (2 levels: 350 g, 700 g) and size (3 levels: small, medium, large), and one between-group factor—group (3 levels: CC, DC, and SC) in a repeated measures ANOVA. Levene's test for Homogeneity of Variance was performed on the z-score data to ensure that the scores do not violate the assumption of equal variance for parametric testing, due to unequal sample sizes between groups ($F(2,23) = 0.27$, $p = 0.764$). Post-hoc ANOVAs and t-tests were performed according to the resulting interactions, and post-hoc equivalence testing was conducted to confirm the results (Supplementary Information S1).

All analyses were conducted in R (version 3.3.2), using the ez-package (https://github.com/mike-lawrence/ez). This package corrects for violations of sphericity when there are more 2 levels in the within subject variable (size) via the Greenhouse–Geisser correction. All effect sizes reported are generalized eta squared (η_g^2) values.

This study was not pre-registered, and sample sizes were limited by strict inclusion criteria within a special population.

Experiment 2. Data for this experiment was collected at LVPEI, Hyderabad, India, by the some of the authors, partially with the help of a translator, in English, Hindi or Telugu.

Participants. The CC group consisted of six individuals defined and classified the same way as in Experiment 1 (1 female, 5 males; Age = 17–44.7 years, M = 27.67 years, SD = 12.37; Duration of blindness = 2–22.01 years, M = 12.98 years, SD = 7.28, Table 1). An additional CC participant was excluded as they did not consistently rate the 350 g cubes as less heavy than the 700 g cubes, indicating that they were not performing the task in a principled manner, possibly due to translation issues (see Supporting Information S2). For four out of six included participants, visual acuity pre-surgery in the better eye ranged from a minimum of counting fingers at 1 m to a maximum of 20/300, with a history of partially absorbed lenses in all four of them. All other criteria, such as presence of nystagmus and family history, pointed towards the presence of dense bilateral cataracts at birth. For the remaining two participants, visual acuity pre-surgery was unknown, but based on the combination of a family history of dense congenital cataracts, very poor visual acuity post-surgery, nystagmus and esotropia, these participants were classified as having dense bilateral congenital cataracts. Visual acuity post-surgery in the better eye in this group ranged from a minimum of 20/400 to a maximum of 20/125.

The SC group consisted of seven individuals with normal or corrected-to-normal vision, with no history of eye injuries or abnormalities (5 females, 2 males; Age = 21–29 years, M = 24.13, SD = 3.08).

Stimuli and apparatus. Participants used a white, smooth ribbon to hold and lift one of the same six cubes used in Experiment 1, by pulling it with their dominant hand. The ribbon was wrapped around a metal ring fixed to a wall, in order to minimize friction that could possibly affect weight judgements, and allow participants to estimate the weight of the cube while it was suspended at eye level (Fig. 1). An important experimental consideration for the use of a string/handle set-up to test the SWI in sight recovery individuals was to control for the precision of the visual cues provided, due to residual visual impairments in visually impaired individuals[5]. Therefore, viewing distance was determined by each CC and SC participant based on how comfortable they were seeing the cube. However, viewing distance was not significantly different between groups ($t(4) = 1.656$, $p = 0.137$; CC: Mean = 58 cm, SD = 8.69 cm, Range = 50–70 cm; SC: Mean = 64.71 cm, SD = 5.19 cm, Range = 60–73 cm). This was done to minimize the possibility of potential differences in illusion size being confounded with differences in visual acuity, due to viewing at a fixed distance. Participants were instructed identically to Experiment 1 described above, and the experimenter placed and removed the cubes from the apparatus for each trial to prevent the participant from having any haptic contact with the stimuli.

Participants were not permitted to haptically handle the cubes at any time, before or during the course of the task, and were naïve to how many sizes and weights were presented. A post-study questionnaire recorded their estimates for how many weights and sizes were presented (see Supporting Information S3).

The same random trial orders used in Experiment 1 were used for Experiment 2, and 60 trials were completed per participant.

Data analysis. Z-scores were calculated using a procedure identical to the one described for Experiment 1 above.

The ANOVA model comprised two within-group factors (Size: 3 levels, Weight: 2 levels) and one between-group factor with 2 levels (CC, SC). Post-hoc ANOVAs and t-tests were performed according to the resulting interactions.

Additionally, a cross-experiment ANOVA with group and experimental task as between- subject factors and weight as a within- subject factor (group: 2 levels for SC and CC; task: 2 levels for Experiment 1 and 2) was performed.

Data availability

The datasets generated/analyzed during this study are available from the corresponding author upon reasonable request.

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Author contributions

R.P. designed and collected data for Experiment 2, analyzed the data for both experiments, made the figures and tables and wrote the paper. M.G., P.L. and D.B. designed and collected data for Experiment 1, M.G. analyzed the data for both experiments and wrote the paper. I.S. recruited, counselled and diagnosed sight recovery individuals and assisted in data collection for Experiment 2. R.K. counselled and diagnosed sight recovery individuals for all experiments and supervised the work. B.R. designed the study, collected the data for Experiment 1 and wrote the paper. All authors edited the manuscript.

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The Size-Weight Illusion is unimpaired in individuals with a history of congenital visual deprivation

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Supporting Information

S1. Equivalence Testing

S1.1 Experiment 1.

In order to clarify the non-significant group effects (i.e. the SWI being equally strong in individuals with atypical visual experience as in normally sighted controls), we used post-hoc equivalence testing to compare the SWI indices between the CC, DC and SC groups[1,2]. For this purpose, we chose to define the upper and lower bounds of interest based on published values obtained by Buckingham and Goodale[3], i.e. the study we had used as a model for the present experimental procedure. They had tested a relatively large sample size of healthy individuals (n=39), calculated the SWI index ("effect size") similar to our method, and reported z-scored values in their Figure 1[3]. In an additional literature search, we were not able to detect any additional study analyzing and reporting group differences in the SWI, as assessed via a comparable paradigm to the one we had implemented. Further, we report only the values we obtained for the 700g weight as the selected paper used an identical weight (exploratory equivalence testing with the 350g condition produced, however, identical results). We used WebPlotDigitizer (v 3.9) in order to select conservative values[4,5]. The lowest possible value for the small cube and the highest possible value for the large cube were selected for the 700g weight condition, which reflects the smallest possible effect size. We used these values to calculate an approximate mean

SWI index (M = -1.782, SD = 1.134), and an upper and lower bound corresponding to a 98% confidence interval (CI) of this normal distribution (0.859, -4.424).

Equivalence testing was performed using the TOSTER package (https://github.com/Lakens/TOSTER) in R (Version: 3.3.2). We compared the average SWI index between the SC and CC, SC and DC and CC and DC groups to determine the presence of an effect outside of the bounds obtained, for the 700g weight (Table S1). Equivalence testing assumes the presence of such an effect between the compared means of the compared groups, and therefore equivalence is defined as the significant rejection of the null hypothesis[2]. We found that the SWI effect measured by the SWI index was equivalent between all groups compared – i.e. the presence of an effect of group that lies outside the described upper or lower bounds was rejected with p's < 0.024 (Table S1).

Bound	**CC | SC**		**DC | SC**		**CC | DC**	
	t(15)	***p***	***t(17)***	***p***	***t(14)***	***p***
Lower	13.74	< 0.001	17.16	< 0.001	14.79	<0.001
Upper	-4.09	< 0.001	-3.66	0.001	-2.19	0.023

Table S1: Equivalence test results comparing mean SWI Indices (effect sizes) between the SC, the CC and the DC groups for the 700g weight. Results of equivalence testing determine the likelihood of rejecting the null hypothesis (i.e. the presence of an effect size difference between the tested groups, outside of the specified bounds). T and p values reported are for the one-sided t-test against each of the two bounds.

S1.2 Experiment 2.

Using an identical procedure to Experiment 1, when we compared CC and SC individuals on their illusion strength for the 700g weight, the effect size was found to be equivalent (Lower Bound: t(11) = 2.99, p = 0.006; Upper Bound: t(11) = -15.22, p < 0.001, Table S1).

S2. Excluded participant (Experiment 2)

One CC participant (36, Female) was excluded from data analysis on account of not cooperating, and the experiment was aborted after 30 trials. During the experiment, it was observed that she was seemingly randomly giving objects one of four possible numerical weights, even when it was reiterated that she

should try to focus on the perceived weight of the object and could freely use any scale. She failed to rate the 700g medium cube as heavier than the 350g medium cube, confirming that she was not assigning principled weight ratings. Based on this, her data was excluded from the final analysis.

S3. Post-Study Questionnaire (Experiment 2)

After the experiment was complete, we asked participants how many distinct weights and sizes they perceived across the 60 trials.

The estimate for the number of cube sizes presented ranged from 3-10 (Mean = 5.8, Median = 3) in the CC and 3-7 (Mean = 4.29, Median = 4) in the SC group. Participants of both groups were subjectively asked to answer how well they could see during the task, and all participants across both groups stated that they could see the stimuli adequately well.

The estimate for the number of weights presented ranged from 5-20 (Mean = 12.33, Median = 9.5) in the CC group and 5-8 (Mean = 6.28, Median = 6) in the SC group, confirming that none of the participants perceived only two weights during the task, and demonstrating the robustness of the SWI perceived by both groups with this paradigm.

S4. Correlations

S4.1 Duration of Blindness (Experiments 1 and 2).

For Experiment 2, to disambiguate the trending correlation between duration of visual deprivation and SWI Index in CC individuals, we further tested a multiple regression with duration of visual deprivation as well as visual acuity as predictor variables (no autocorrelation between variables, $r = -0.125$, $t(4) = -0.253$, $p = 0.813$). No significant effect of duration of deprivation ($t(4) = -2.326$, $p = -0.102$) or visual acuity ($t(4) = 1.224$, $p = 0.308$) was observed, indicating that the variance in the SWI Index was not significantly explained by duration of visual deprivation (Figure S1).

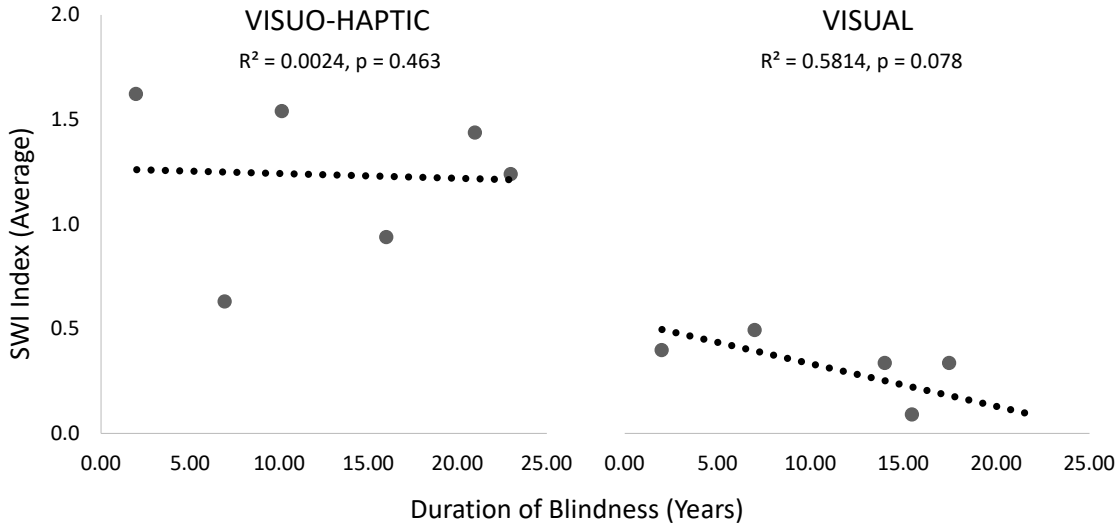

Fig S1: Correlation between duration of blindness at the time of testing and the calculated SWI Index for the CC group in Experiment 1 (left) and Experiment 2 (right).

S4.2 Pre-surgery visual acuity (Experiment 2)

In Experiment 2, to ensure that better vision as a result of absorbed lenses prior to surgery did not have an impact on the SWI, we tested for a relationship between SWI Index and pre-surgery visual acuity. Of the 4 participants with a known pre-surgery visual acuity, 3 participants had a quantifiable value (i.e. better than CF), based on which there was no significant correlation between pre-surgery acuity and SWI size ($r = -0.580$, $t = -0.711$, $p = 0.303$).

S4.3 Age (Experiment 2)

To ensure that we did not miss potential differences in SWI size due to age differences between our groups, we tested for any effect of age on SWI size in our sample. We observed no significant correlation between age and SWI index in either group (Figure S2).

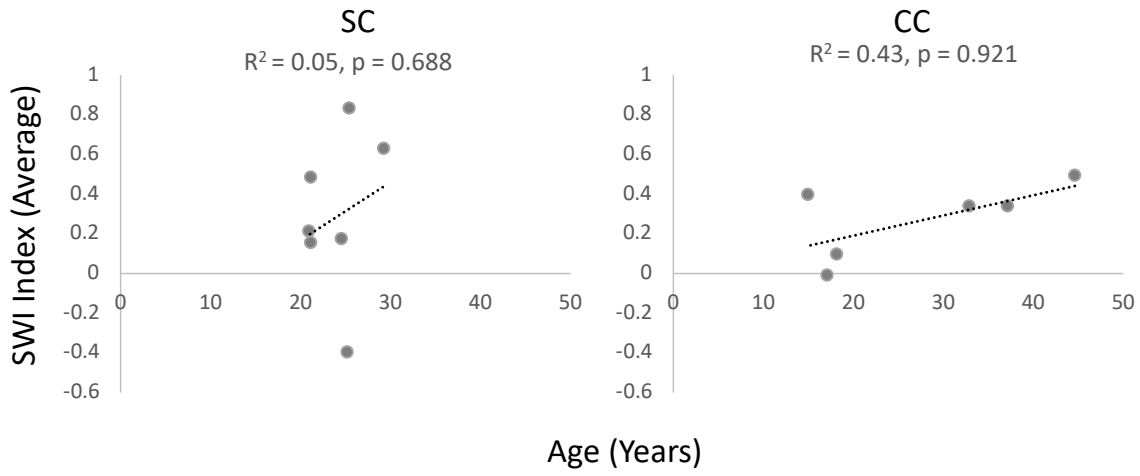

Figure S2: Correlation between age in years and SWI Index for Experiment 2.

S4.4 Time since surgery (Experiments 1 and 2)

Additionally, we also tested for any effect of time since surgery on SWI size in our sample. This was calculated by subtracting the age at first surgery from the age on date tested, for every CC participant, and correlated with the mean SWI index. We observed no significant correlation between time since surgery and SWI index in Experiment 1 or 2 (Figure S3).

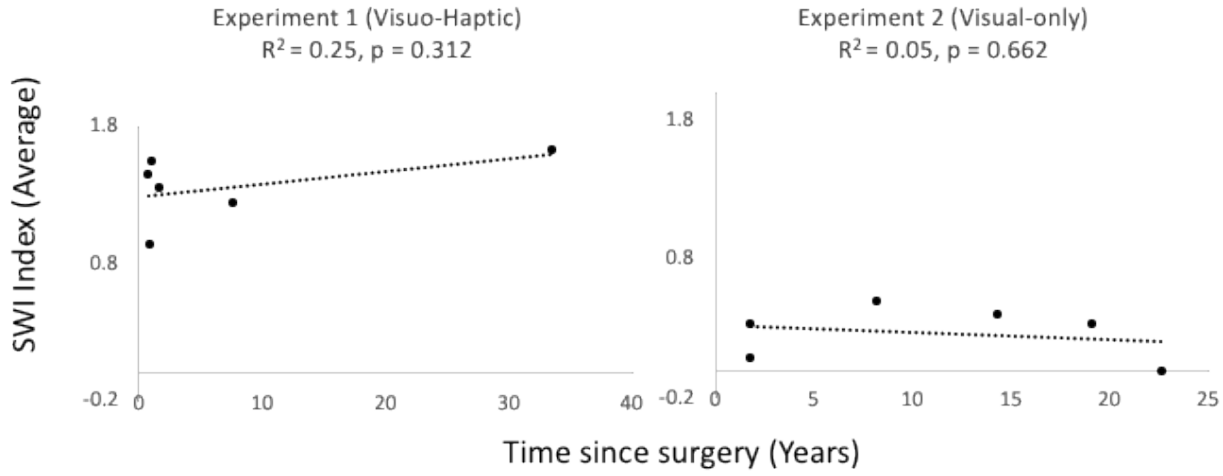

Figure S3: Correlation between time since surgery in years and SWI Index for Experiments 1 and 2.

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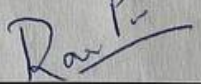
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