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The development of oscillatory and aperiodic resting state activity is linked to a sensitive period in humans

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ABSTRACT

Congenital blindness leads to profound changes in electroencephalographic (EEG) resting state activity. A well-known consequence of congenital blindness in humans is the reduction of alpha activity which seems to go together with increased gamma activity during rest. These results have been interpreted as indicating a higher excitatory/inhibitory (E/I) ratio in visual cortex compared to normally sighted controls. Yet it is unknown whether the spectral profile of EEG during rest would recover if sight were restored. To test this question, the present study evaluated periodic and aperiodic components of the EEG resting state power spectrum. Previous research has linked the aperiodic components, which exhibit a power-law distribution and are operationalized as a linear fit of the spectrum in log-log space, to cortical E/I ratio. Moreover, by correcting for the aperiodic components from the power spectrum, a more valid estimate of the periodic activity is possible. Here we analyzed resting state EEG activity from two studies involving (1) 27 permanently congenitally blind adults (CB) and 27 age-matched normally sighted controls (MCB); (2) 38 individuals with reversed blindness due to bilateral, dense, congenital cataracts (CC) and 77 age-matched sighted controls (MCC). Based on a data driven approach, aperiodic components of the spectra were extracted for the low frequency (Lf-Slope 1.5 to 19.5 Hz) and high frequency (Hf-Slope 20 to 45 Hz) range. The Lf-Slope of the aperiodic component was significantly steeper (more negative slope), and the Hf-Slope of the aperiodic component was significantly flatter (less negative slope) in CB and CC participants compared to the typically sighted controls. Alpha power was significantly reduced, and gamma power was higher in the CB and the CC groups. These results suggest a sensitive period for the typical development of the spectral profile during rest and thus likely an irreversible change in the E/I ratio in visual cortex due to congenital blindness. We speculate that these changes are a consequence of impaired inhibitory circuits and imbalanced feedforward and feedback processing in early visual areas of individuals with a history of congenital blindness.

1. Introduction

Sensitive periods are epochs in life during which the effects of experience on brain organization are particularly strong (Knudsen, 2004). In non-human animal research sensitive periods have been investigated by systematically manipulating sensory, often visual, experience during early development (Hubel and Wiesel, 1970; Levelt and Hübener, 2012). If sensory capacities do not fully recover after reinstalling typical input, it is concluded that the development of the associated neural mechanisms is linked to receiving adequate input during a sensitive period. In the case of human vision, the mechanisms of developmental neuroplasticity have been mainly investigated in permanently congenitally blind humans (Pavani and Röder, 2012; Renier et al., 2014; Bedny, 2017; Röder and Kekunnaya, 2022) and more recently in humans who regained sight late in life after a transient period of congenital blindness, most often due to bilateral cataracts. The study of "sight-recovery" individuals is essential to assess whether and to which degree adaptations of neural circuits to congenital blindness are reversible and thus for assessing sensitive periods in human brain development (Maurer et al., 1989; Röder and Kekunnaya, 2021). Sight-recovery

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individuals have been found to show considerable improvements in some visual functions including the perception of simple visual features such as color (McKyton et al., 2015; Pitchaimuthu et al., 2019) and shape (Maurer et al., 1989; McKyton et al., 2015), and the control of eye movements (Zerr et al., 2020; Ossandón et al., 2022). By contrast, other functions such as visual acuity (Lewis and Maurer, 2005), stereovision (Tytla et al., 1993) and the perception of face identity (Le Grand et al., 2001; Putzar et al., 2010) seem to recover less well. Therefore, the research of individuals with reversed congenital cataracts suggests sensitive phases in human sensory development but their neural mechanisms in humans have hardly been investigated.

Congenital blindness is known to lead to profound changes in resting-state electroencephalographic (EEG) activity: Most prominent is the reduction or abolishment of alpha oscillatory activity (Cohen et al., 1961; Jeavons, 1964; Birbaumer, 1971; Novikova, 1974; Noebels et al., 1978; Kriegseis et al., 2006). Additionally, recent MEG studies have reported an increase in oscillatory activity in the gamma range (Schepers et al., 2012; Lubinus et al., 2021). As alpha and gamma activity have been linked to interareal feedback and feedforward processing, respectively (van Kerkoerle et al., 2014; Bastos et al., 2015; Michalareas et al., 2016; Vezoli et al., 2021), lower alpha activity accompanied by higher gamma activity might indicate an altered excitatory/inhibitory (E/I) balance in visual cortex, which some authors attributed to impaired feedback control (Lubinus et al., 2021; Röder et al., 2021). The idea of an increased E/I ratio in visual cortex in congenitally blind individuals is consistent with resting state neuroimaging data showing higher cortical activation in permanently congenitally blind humans (Wanet-Defalque et al., 1988; Veraart et al., 1990; Jiang et al., 2015; Rączy et al., 2022). Changes in E/I balance due to congenital visual deprivation are compatible with a large body of research in non-human animal models demonstrating that the timing of sensitive periods is controlled by the maturation of inhibitory circuits (Hensch, 2005; Froemke, 2015). When adequate sensory experience is lacking, sensitive periods can persist for longer durations but finally terminate and leave neural circuits in an immature state which is characterized by unfinished inhibitory networks (Singer and Tretter, 1976; Gabbott and Stewart, 1987; Benevento et al., 1992, 1995; Morales et al., 2002; Kotak, 2005; Jiao, 2006; Sanes and Kotak, 2011; Kaneko and Stryker, 2014).

Currently it is unclear whether the documented changes in the EEG resting state profile are reversible if sight were restored. In order to postulate a sensitive period an incomplete reversibility of neural network functioning must be demonstrated (Knudsen, 2004). Recent reports of task-related EEG activity in sight recovery individuals with a history of congenital cataracts have found a similarly reduced alpha activity during visual processing (Bottari et al., 2016, 2018). However, it could be argued that the observed alpha reduction during a visual task in congenital cataract reversal individuals might be due to more extensive ongoing desynchronization since visual processing could be more “effortful” in these individuals. Thus, it is crucial to evaluate alpha activity in sight recovery individuals in a task-free setting such as during rest. Analyzing resting state EEG provided the additional opportunity to address the reversibility of enhanced gamma band activity observed in congenital blindness.

Recently, it has been recognized that periodic and aperiodic components of the power spectrum carry partially distinct information and that changes in aperiodic aspects might look like changes in the periodic activity (He, 2014; Wen and Liu, 2016; Donoghue et al., 2020). Thus, it is nowadays considered as essential to remove the aperiodic components of the power spectrum to identify oscillatory activity in distinct narrow frequency bands (Pesaran, 2018; Donoghue et al., 2021). The aperiodic component reflects what has often been considered as ‘background’ activity. It approximately follows a $1/f^x$ distribution (Pritchard, 1992), which can be characterized by the intercept and slope (the x exponent in $1/f^x$) of a linear fit of the spectrum in log-log coordinates. In addition to being used to derive a more valid estimate of periodic activity, the aperiodic component itself has been proposed as an indicator of distinct neurophysiological mechanisms (Buzsáki et al., 2012). For example, the slope of the aperiodic component has been considered as an estimate of E/I balance in neural circuits: the less negative the slope, that is the flatter the fit, the higher the excitability of the underlying neural circuits (Gao et al., 2017; Lombardi et al., 2017; Medel et al., 2020).

The present study assessed resting state periodic and aperiodic EEG activity of a large group of both congenitally permanently blind individuals (CB, $n = 27$) and sight recovery individuals with a history of congenital blindness due to bilateral dense total cataracts (CC, $n = 38$). The CB and the CC groups were compared to age-matched normally sighted controls (MCB and MCC, respectively). Based on previous results we hypothesized that alpha oscillatory activity is reduced, and gamma band activity is increased in CB participants compared to MCB participants. Additionally, we hypothesize that CB individuals would show a flatter power spectrum, indicated by a less negative aperiodic slope, and thus, together with the expected alpha and gamma results, suggesting an increased E/I ratio. Based on the previously reported reduced alpha activity during visual processing, we predicted a similar combination of degraded alpha but enhanced gamma activity in the CC group and a flatter aperiodic slope indicative of a higher E/I ratio. Additionally, in CC individuals we assessed the difference in resting state activity between an eyes open (EO) and an eyes closed (EC) conditions. Based on a recent assessment of slow blood oxygenation level-dependent (BOLD) fluctuations during rest in a similar sample of individuals with reversed congenital cataracts (Rączy et al., 2022), we expected a desynchronization of alpha and increase of gamma band activity for the eyes open vs. the eyes closed condition in the CC group, similar to what is typically observed in normally sighted individuals.

2. Material and methods

2.1. Participants

2.1.1. Congenitally permanently blind individuals and matched controls

A group of 27 congenitally blind adults (CB group; 12 females, mean age: 37 years, SD: 11, range: 21 – 55; see Suppl. Table 1) were recruited in Germany. The cause of blindness was attributed to pre- or perinatal anomalies in the eyes, which resulted in a congenital, bilateral, total blindness from birth. Some of the participants had residual light perception ($n = 18$). Twenty-seven sighted participants from the local community of the city of Hamburg (Germany), matched in gender and age with the congenitally blind participants served as controls (MCB group; 12 females, mean age: 38 years, SD: 10, range: 22 – 55). All sighted participants had normal or corrected-to-normal vision. These data were recorded during an extensive study comparing CB and MCB individuals in working memory (Gudi-Mindermann et al., 2018; Rimmele et al., 2019); MEG resting state results from the same participants have recently been reported (Lubinus et al., 2021).

2.1.2. Congenital cataract reversal and control groups

This section contains standard phrasing describing participants characteristics that were recycled from our prior publications for consistency (Zerr et al., 2020; Ossandón et al., 2022). Congenital cataract reversal individuals (CC group) were selected from a large number of patients treated at the LV Prasad Eye Institute with the diagnosis of congenital cataracts. Based on medical records, a clinical history of bilateral congenital cataracts and a history of patterned visual deprivation were confirmed. A lack of fundus view and an absence of retinal glow were taken as evidence for the absence of patterned light reaching the retina prior to cataract surgery. In the case of partially absorbed lenses or missing presurgery information, CC participants were considered to have suffered from profound bilateral visual deprivation when they presented a limited recover of visual acuity, suffered from nystagmus, exhibited sensory strabismus, and had a positive family history of congenital cataracts. These classification criteria have recently been validated by an electrophysiological biomarker (Sourav et al., 2020).

The CC group consisted of 38 individuals (11 females; mean age: 18.8 years, SD: 9.8, range: 6.4 – 41.7) who had their cataracts removed at a mean age of 9.7 years (SD: 9.3, range: 3 months – 36.1 years), and were tested on average 9 years after cataract removal surgery (SD: 8.8, range: 5 months – 35.6 years). Of the 38 participants, 29 had a documented history of strabismus (17 esotropia and 12 exotropia) and 25 had implanted intraocular lenses. Seventeen participants had a known family history of congenital cataracts and 9 individuals had partially absorbed lenses. Absorbed lenses regularly emerge in individuals born with congenital cataracts and can be clinically unambiguously differentiated from non-dense or partial cataracts based on their morphology (Amaya et al., 2003). Absorbed cataracts strongly imply dense cataracts at birth; absorption typically starts in mid childhood. Pre-surgical visual acuity measurements revealed that 36 out of 38 CC participants were clinically blind (i.e. had an visual acuity of less than 3/60) (World Health Organization, 2019). The remaining 2 CC individuals had partially absorbed lenses pre-surgery and a pre-surgery vision corresponding to severe visual impairment. All CC participants suffered from nystagmus which is strong evidence for the absence of pattern vision at birth. After surgery, two participants remained with very low vision and their visual acuity could only be assessed qualitatively. The other 36 CC participants' post-surgical visual acuity of the best eye ranged from 0.02 to 0.5 decimal units (geometric mean: 0.14; logMAR: 0.3 – 1.8, logMAR mean: 0.85). A detailed description of CC participants is presented in Suppl. Table 2.

The sighted control group consisted of 75 individuals with normal or corrected-to-normal vision (MCC group); 32 participants were tested in Hyderabad (6 females, mean age: 22.2 years, SD: 10.2, range: 9 – 42) and 43 were tested in Hamburg (13 females, mean age: 16.7 years, SD: 7.0, range: 7 – 37) with an identical setup. After checking that these two groups did not differ in the EEG measures reported here, we combined them into a single MCC group (mean age: 19.1 years, SD: 8.9). The combined group was age-matched to the CC group both in terms of mean age (two-sample *t*-test, $t_{(111)} = -0.19$, $p = 0.85$) and age variance (two-sample F-test $F_{(37,74)} = 1.2$, $p = 0.47$).

None of the participants had any other known sensory system deficit or a known neurological disorder. Expenses associated with taking part in the study were reimbursed. Minors received a small present. Participants, and if applicable, their legal guardians, were informed about the study and received the instructions in one of the languages they were able to understand (in most cases Telugu, Hindi or English in India, and German in Germany). All participants gave written informed consent before participating in the study; in case of minors, legal guardians additionally provided written informed consent. The study was approved by the ethics board of the Faculty of Psychology and Human Movement Science of the University of Hamburg (Germany) and by the ethics board of the LV Prasad Eye Institute (Hyderabad, India).

2.2. EEG acquisition

2.2.1. Congenitally permanently blind (CB) and matched control (MCB) groups (recorded at the University of Hamburg, Germany)

The EEG was continuously recorded, referenced to the left ear lobe with 96 Ag/AgCl scalp electrodes (EasyCap GmbH, Herrsching, Germany), mounted in a cap according to the 10–10 system (Oostenveld and Praamstra, 2001). Electrode AFz was used as ground. The EEG signal was amplified with BrainAmp DC amplifiers (BrainAmp, http://www.brainproducts.com/) and digitized using the BrainVision Recorder software (Brain Products GmbH). The analog EEG signal was sampled at 5000 Hz and hardware-filtered with a band pass between 0.0159 to 1000 Hz. The recording software applied an online low-pass filter with an upper cut off at 225 Hz (antialiasing filter Butterworth 24 dB/Oct). The final signal was downsampled to 500 Hz before saved to disk. Impedances were generally kept below 10 kΩ. The participants were asked to relax and avoid any specific mental operations. EEG was acquired for about 4–5 min while participants were blindfolded.

2.2.2. Congenital cataract reversal group (CC) (recorded at the LV Prasad Eye Institute) and matched controls (MCC) (recorded at the LV Prasad Eye Institute and at the University of Hamburg, Germany)

The EEG was acquired with identical recording setups, that is, from 32 Ag/AgCl electrodes positioned according to the 10–20 system (Acharya et al., 2016), with AFz serving as ground and the left earlobe as reference. The EEG signal was recorded at a sampling rate of 1000 Hz with a BrainAmp DC amplifier (Brain Products GmbH, Gilching, Germany). A hardware bandpass filter with a passband of 0.016 to 250 Hz was employed for the recording. The electrode impedances were generally kept below 10 kΩ. The EEG was acquired in two consecutive runs of about 3–4 min each, one with the eyes open and one with the eyes closed. During the eyes open condition, participants were asked to keep their eyes open and to look straight ahead.

2.3. Data analysis and statistics

2.3.1. EEG preprocessing

EEG data were preprocessed in MATLAB (version R2015a and R2019b, MathWorks Inc., Natick, MA, USA) using the EEGLAB toolbox (Delorme and Makeig, 2004), the Fieldtrip toolbox (Oostenveld et al., 2011), and custom scripts. First, data were filtered with a sinc FIR filter with a high-pass frequency at 0.1 Hz (6 dB cut off at 0.05 Hz, 0.1 Hz transition bandwidth, using EEGLAB's *pop_eegfiltnew* function). Line noise was reduced by Spectrum Interpolation (Leske and Dalal, 2019) in which frequencies between 45.5 and 54.5 Hz were interpolated using fieldtrip's *ft_preproc_dftfilter* function. Each frequency in this range was substituted by an interpolation from adjacent frequencies (i.e., frequencies between 45.5 to 54.5 Hz were interpolated with the average amplitude of frequencies between 43 and 45 and between 55 and 57 Hz). Electrodes which flatlined for more than 5 s were removed. Next all recordings were average referenced. To remove typical biological artefacts (blink, eye movement, muscle, heart) the Independent Component Analysis was employed (EEGLAB's *pop_runica* function, using *Infomax* algorithm). Components representing artifacts were identified by employing the ICLabel classifier (Pion-Tonachini et al., 2019). Components were considered as representing an artefact and thus removed if the classifier probability for the artifact categories muscle, eye, and heart exceeded 0.8 (on average 5.4 components were disregarded per subject, SD = 4.1). After the removal of artefactual components, previously rejected channels were interpolated using spherical interpolation (EEGLAB's *pop_interp* function, on average 0.8 channels were interpolated per participant, SD: 0.9). For the analysis of alpha activity, data were low-pass filtered with an upper cut-off at 40 Hz (6 dB cut off at 59.64 Hz, 39.29 Hz transition bandwidth). For the analysis of gamma activity and aperiodic components this filtering procedure was not applied. Finally, data were epoched into 2 s segments; epochs with values exceeding +/- 100 μV were removed.

Only participants who had at least 10 artefact free epochs for a given analysis were included; this threshold resulted in the exclusion of 3 CC participants for the gamma activity analysis in the eyes open condition, and 1 CC participant for the analysis of gamma activity in the eyes closed condition. For the analysis of alpha activity, on average, 102 epochs (SD: 21.6, range: 54 – 163) per participant were retained for the eyes open condition, and 119.2 epochs (SD: 32.6, range: 26 – 197) for the eyes closed condition. For the analysis of gamma activity and aperiodic slope, on average, 89.9 epochs (SD: 26.9, range: 13 – 154) per participant were retained for the eyes open condition, and 106.4 epochs (SD: 38.9, range: 10 – 221) for the eyes closed condition. There was no significant difference between the number of trials entering the analyses between groups except for the analysis of gamma activity in the eyes open condition, in which CC participants ended with less epochs than MCC participants but the average number was still high (CC group: 82.3 epochs ~164 s, MCC group: 93.5 epochs ~187 s, $t_{(108)} = -2.05$, $p = 0.04$).

2.3.2. EEG spectral analysis

Power spectral densities (PSD) were estimated per participant, condition, and electrode using MATLAB's *pwelch* function (2 s segments, no overlap, Hamming window, frequency resolution 0.5 Hz).

Participants' PSDs were fit in the log-log space in order to identify its aperiodic and periodic (alpha) components. Although there are numerous studies in recent years which have investigated aperiodic activity, the parameters for fitting the aperiodic component have wildly varied: Different frequency ranges have been used and some authors divided the spectrum in low and high frequency ranges and fitted two slopes. Here we only considered the range 1 – 45 Hz due to the fact that not all recordings were done in an electrically shielded room and in agreement with recent EEG studies (Fransson et al., 2013; Voytek et al., 2015; Waschke et al., 2017; Dave et al., 2018; Colombo et al., 2019; Stock et al., 2020; Tran et al., 2020; Cellier et al., 2021; Racz et al., 2021; Hill et al., 2022).

Not all previous studies have found a clear single linear trend of the aperiodic activity across all frequencies of the spectrum. Both, empirical and theoretical models of EEG/MEG activity have reported a 'knee' separating different linear regions of the spectra (Bédard et al., 2006; Miller et al., 2009; Muthukumaraswamy and Liley, 2018; Racz et al., 2021). Thus, we first compared a single linear fit with a data-driven piecewise fit of two regression lines. The piecewise fit divided the spectrum in two frequency ranges separated by the location of the fit 'breakpoint'. The grand average log-log spectra across all electrodes, conditions and participants (CB-MCB groups CC-MCC groups were separately analyzed) was fitted both with a single linear fit and with a piecewise fit that allowed the free placement of one breakpoint. These fits were performed using the Shape Language Modeling toolbox (D'Errico, 2021) for the frequencies between 1.5 to 45 Hz, excluding frequencies from 7 to 13 Hz (to avoid a bias by the expected prominent periodic alpha component, see Voytek et al., 2015; Waschke et al., 2017)). Model comparison was done by evaluating the fits' coefficient of determination (R^2) and Bayesian information criterion (BIC), which was modified to penalize multiple fits (Hall et al., 2013; Han and Taamouti, 2017). **Suppl. Figs. 1a-b** shows for CB and MCB groups (Study 1) that a piecewise model better fitted the data: R^2 was higher and the Bayesian Information Criterion (BIC) was lower (R^2 linear fit: 0.933 vs. piecewise fit: 0.995; BIC linear fit: 17.2 vs. piecewise fit: −32.8). The optimal breakpoint for the piecewise fit was at 19 Hz. The superiority of a piecewise fit was further confirmed by comparing R^2 and BIC values between the single linear fit and a two-component fit for each participant, now with a fixed breakpoint at 19.5 Hz (see **Suppl. Figs. 1c-d** and **Suppl. Fig. 2** for each participant fit). According to R^2 and BIC values, in 94,4% and 70.4% of all participants the piecewise fit was better, respectively. The same analyses for CC and MCC participants revealed highly similar results (see **Suppl. Figs. 1g-j** and **Suppl. Fig. 3**): The piecewise fit was superior to the single linear fit, with the freely placed breakpoint found at 19.94 Hz (grand average comparison between piecewise and single fit: R^2: 0.998 vs 0.973 and BIC: −45.1 vs. 7.4). According to R^2 and BIC values, in 95.5% and 61.6% of all participants the piecewise fit with a fixed breakpoint at 19.5 Hz was better, respectively.

In addition, we compared the piecewise fit with fits generated by the "fitting oscillations & one-over F" (FOOOF) algorithm (Donoghue et al., 2020) implemented in the MATLAB toolbox Brainstorm (Tadel et al., 2011). The analyses included FOOOF fits with and without a knee (parameters: frequency range:1.5 – 45; peak model: gaussian; peak width limit: 0.5 – 12 Hz; max. number peaks: 3; min. peak height: 3 dB; proximity threshold: 2 SD). The piecewise fit outperformed both of these FOOOF fits, at the groups and subjects' level (see **suppl. Figs. 1e,f,k,l**). While the FOOOF fits did uncover beta components in a subset of participants (see **suppl. Figs. 2,3**), they did not provide a better fit of aperiodic activity, confirming that the breakpoint of the piece-wise fit found at ~19 Hz was not an artifact of possible beta components.

In summary, the analyses of both studies (CB/MCB and CC/MCC) indicated that the spectra between 1 and 45 Hz were best modelled with two regression lines and a breakpoint around 19 – 20 Hz. Therefore, the final analysis of the aperiodic spectra was based on two linear fits of the log-log spectrum: (1) a low-frequency aperiodic slope (Lf-Slope) derived from the linear fit of the PSD between 1.5 and 19.5 Hz; (2) a high-frequency aperiodic slope (Hf-Slope) derived of a linear fit of the PSD between 20 and 45 Hz.

The low frequency aperiodic estimation was additionally used to correct the spectra for a more valid assessment of oscillatory alpha activity (periodic activity). The corrected spectrum between 1.5 and 19.5 Hz was calculated by dividing the untransformed PSD by the corresponding low frequency fit estimates (transformed back to non-log scale) at each frequency (PSD/fit). In other words, the corrected spectra values indicating the periodic activity were defined as the ratio between the PSD and the estimated background aperiodic activity.

To identify whether a participant presented an alpha periodic component, the PSD, corrected for aperiodic activity, was averaged for electrodes O1 and O2. The presence of a peak was defined by employing the MATLAB's *findpeaks* function searching for a peak in the PSD between 4 and 14 Hz with the following parameters: peak minimum width of 2 Hz and peak value above 2 times the estimate of the standard deviation of the fit's error. Alpha power was calculated as the average power of the log-transformed (in decibels, dB) values between 7 and 13 Hz. For deriving gamma power, the original PSD was used, that is, the PSD not corrected for the aperiodic component. Distinct gamma peaks do typically not arise in resting state electrophysiological recordings (e.g., Goncharova et al., 2003; Groppe et al., 2013; de la Salle et al., 2016; Frauscher et al., 2018; Muthukumaraswamy and Liley, 2018); the same held for the present datasets (see Suppl. Figs. 1–3 show grand averages of and each individual's PSD). Gamma activity was defined as the average power of the log-transformed (decibels, dB) values between 30 and 45 Hz.

Groups (CB vs. MCB groups and CC vs. MCC groups) were compared separately for the periodic activity (alpha and gamma power) and the slopes of the aperiodic components at each electrode. CC and MCC groups were compared separately for the eyes open and eyes closed conditions. For CC and MCC participants additional within-group contrast analyses were performed comparing the eyes open and eyes closed conditions. Finally, the difference between the eyes closed vs. eyes open condition was compared between the CC and MCC group. All condition and group differences were evaluated with either paired or unpaired two-sample t-tests for the within-group and between group contrasts, respectively. The false discovery rate (FDR) (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001) was used to correct for multiple comparisons across electrodes. In all analyses the FDR bound (or "q") was set at 0.05. The result of the FDR correction is described in the text as "x/32, $p < threshold$", meaning that we rejected the null-hypothesis for x channels that had a p-value smaller than the FDR calculated *threshold*.

2.4. Data and material availability

The code for the statistical analyses, figures, and the anonymized, pre-processed data are available at the Research Data Repository of the University of Hamburg (http://doi.org/10.25592/uhhfdm.12047). Original EEG datasets are available upon reasonable request from the corresponding author.

3. Results

3.1. Alpha power is reduced in congenitally blind (CB) and cataract reversal (CC) individuals

CB participants showed a reduction of alpha power compared to the MCB group (see Figs. 1**a-c**, in all analyses alpha power was corrected from aperiodic background activity, see methods section *EEG spectral analysis* and Suppl. Figs. 1–3). The group difference was significant at

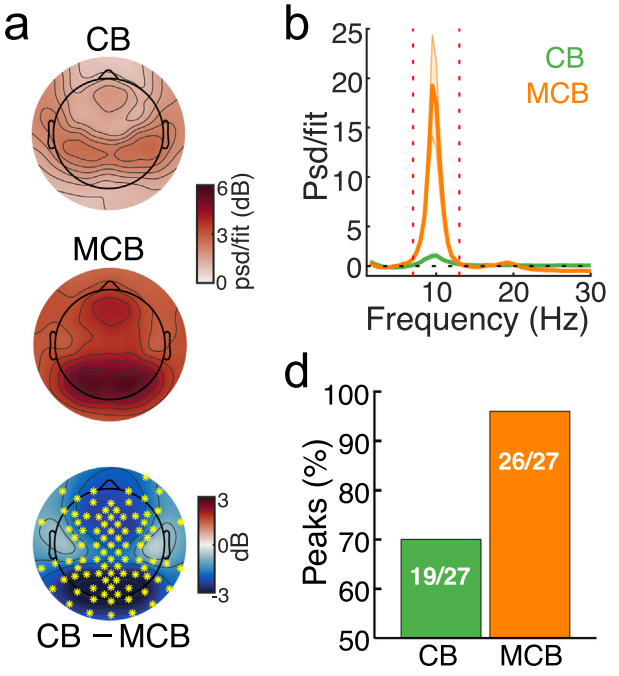

Fig. 1. Alpha activity in congenitally blind individuals (CB) and in age-matched normally sighted controls (MCB). (a) Topoplots of alpha power (7 –13 Hz) for each group as well as the group difference. In all figures, yellow stars indicate electrodes with a significant difference between groups (*t*-test contrasts, FDR corrected). **(b)** Average power spectra for the CB (green) and MCB (orange) group at occipital electrodes (O1/O2). **(c)** Average alpha power at O1/O2 for individual participants together with the group mean and the standard error of the mean. An * indicates that at least one of the electrodes used in the plot average was significantly different, as shown in the respective topoplots. **(d)** Percentage of participants with a detectable peak between 4 – 14 Hz at O1/O2. **(e)** Peak frequency of alpha activity of individuals with an alpha peak together with the group mean and the standard error of the mean.

most electrodes, except for a few centro-temporal electrodes (80/96 $p < 0.036$). Despite the overall reduced alpha activity in CB individuals, more than half of them featured an alpha peak at occipital electrodes (19/27 participants, see **Fig. 1d** and **Suppl. Figs. 4a-b**). The presence of an alpha peak was not related to whether CB participants had residual light perception (6/8 individuals without an alpha peak had residual light perception compared to 12/19 with a peak; one of the two anophthalmic participants had an alpha peak). All but one MCB participants displayed an alpha peak (26/27) which represented a significantly higher proportion compared to the CB group ($\chi^2 = 4.8$, $p = 0.03$). The peak frequencies did not differ between the CB individuals and MCB individuals (CB group: 10.02 Hz, SD:0.99; MCB group: 9.8 Hz, SD: 0.98, see Fig. 1**e**). In sum, after controlling for aperiodic activity we were able to replicate the earlier reported reduction of alpha activity in permanently congenitally blind individuals and, additionally, demonstrated that the subjects who featured an alpha peak did so at the same frequency as sighted controls.

CC participants showed a reduction of alpha power compared to the MCC group (see Figs. 2**a-c,e**). This reduction was more pronounced in the eyes closed condition for which the group difference was significant for almost all electrodes, expect for a few centro-temporal electrodes (26/32, $p < 0.038$). For the eyes open condition the group difference was restricted to occipito-parietal electrodes (11/32, $p < 0.012$). All groups showed a significant reduction in alpha power in the eyes open compared to eyes closed condition (CC group: 31/32, $p < 0.007$; MCC group: 32/32, $p < 0.001$). The condition effect did not differ between groups.

Most of the participants of both groups (>90%) featured a detectable alpha peak at occipital electrodes in the eyes closed condition (see Fig. 2**d** and **Suppl. Figs. 4c-f**, CC: 35/38; MCC: 74/75). In contrast, in the eyes open condition less CC participants (29/38) had a detectable alpha peak compared to MCC participants (70/75). Thus, the likelihood of an alpha peak in the eyes open condition was lower in the CC group than in the MCC group (eyes open: CC vs MCC groups, $\chi^2 = 5.25$, $p = 0.02$). Mean alpha peak frequency did not differ between groups (eyes closed CC group: 9.5 Hz SD: 0.85, MCC group: 9.9 Hz SD: 0.82; eyes open CC group: 9.6 Hz SD: 1.06, MCC group: 9.9 Hz SD: 1.06, see Fig. 2**f**).

Alpha power was not correlated with chronological age, neither when considering all participants nor in separate group analyses (see **Suppl. Fig. 5a**). For the CC group alpha power was neither correlated with visual acuity (see **Suppl. Fig. 5b**), nor with age at surgery (see **Suppl. Fig. 5c**), nor with the time elapsed between surgery and testing (see **Suppl. Fig. 5d**).

CB and CC groups differed in their age range and were investigated in different labs Therefore, a direct comparison of both groups must be considered as preliminary. Since alpha power did not vary with chronological age, we performed an additional exploratory analysis comparing the alpha activity of CB and CC groups. As seen in **supplementary figure 6**, CC participants exhibited higher alpha power at occipital electrodes in the eyes closed condition compared to CB participant ($p < 0.0004$).

In sum, CB and CC participants showed a significant reduction of alpha power compared to normally sighted controls. However, a large proportion of participants of these groups featured a detectable alpha peak. This was so in the CC group particularly in the eyes closed condition. CC individuals showed the typical alpha reduction for the eyes open vs. eyes closed condition.

3.2. CB and CC participants differ in aperiodic activity from normally sighted adults

The aperiodic component of the spectrum was studied by fitting the log-log spectra with a piecewise fit with a breakpoint at 19.5 Hz (see Method section *EEG spectral analysis* and Suppl. Figs. 1–3). Participants' log-log spectra were thus fitted by two regression lines, one for the low frequency range (1.5 – 19.5 Hz) and one for the high frequency range (20 – 45 Hz). For each of these regression lines the slope was derived to which we refer as Lf-Slope and Hf-Slope, respectively.

CB individuals showed a steeper (more negative) Lf-Slope (1.5 – 19.5 Hz fit) than MCB individuals at occipito-parietal electrodes (4/96 $p < 0.001$, see Figs. 3**a-c**). In contrast, the Hf-Slope (20 – 45 Hz fit) was flatter (less negative) in the CB than in the MCB group at occipito-parietal electrodes (13/96 $p < 0.008$, see Figs. 3**d-f**). At a few fronto-temporal electrodes, the Hf-Slope was steeper in the CB group (4/96 $p < 0.008$).

As shown in Figs. 3e, a flatter Hf-slope was associated with increased power in the low gamma range. This relationship was confirmed by analyzing gamma power between 30 – 45 Hz. CB individuals exhibited higher gamma power compared to the MCB group (see suppl. material section *Analysis of gamma power* and **suppl. Figs. 9a-c**). In addition,

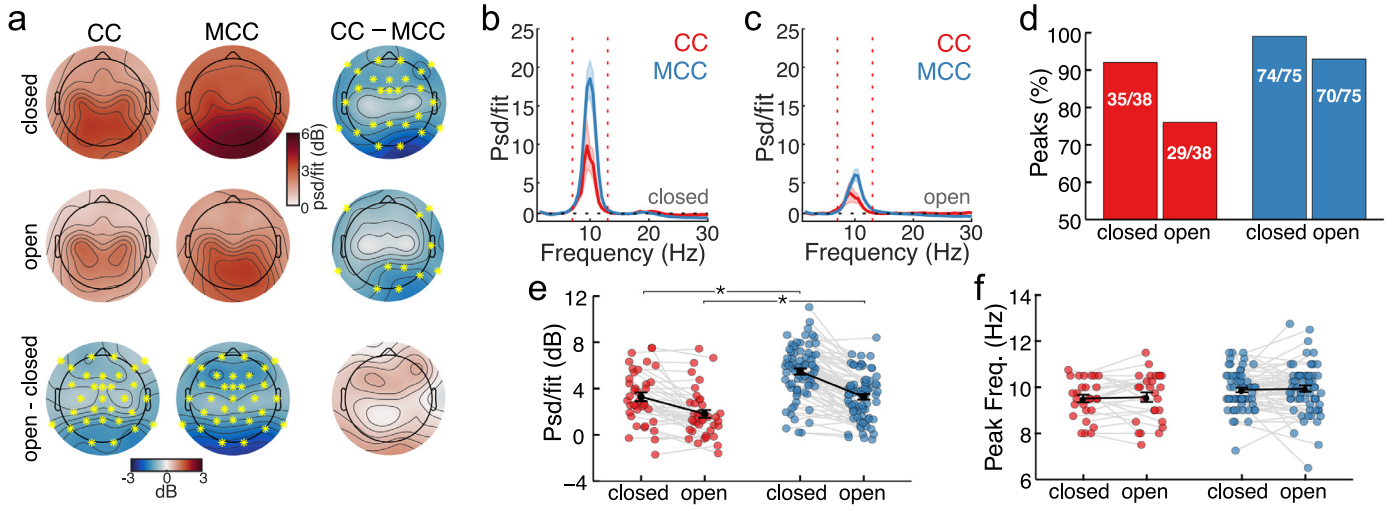

Fig. 2. Alpha activity in congenital cataract reversal (CC) and age-matched normally sighted (MCC) individuals. (a) Topoplots of alpha power (7–13 Hz) for each group, as well as the condition and group differences. **(b)** Group average corrected spectra at O1/O2 eyes closed condition. **(c)** Group average corrected spectra at O1/O2 eyes open condition. **(d)** Number and percentage of participants with a detectable peak between 4 – 14 Hz at O1/O2. **(e)** Average corrected alpha power at O1/O2 for each participant, condition, and group. **(f)** Peak frequency of alpha activity for each participant, condition, and group.

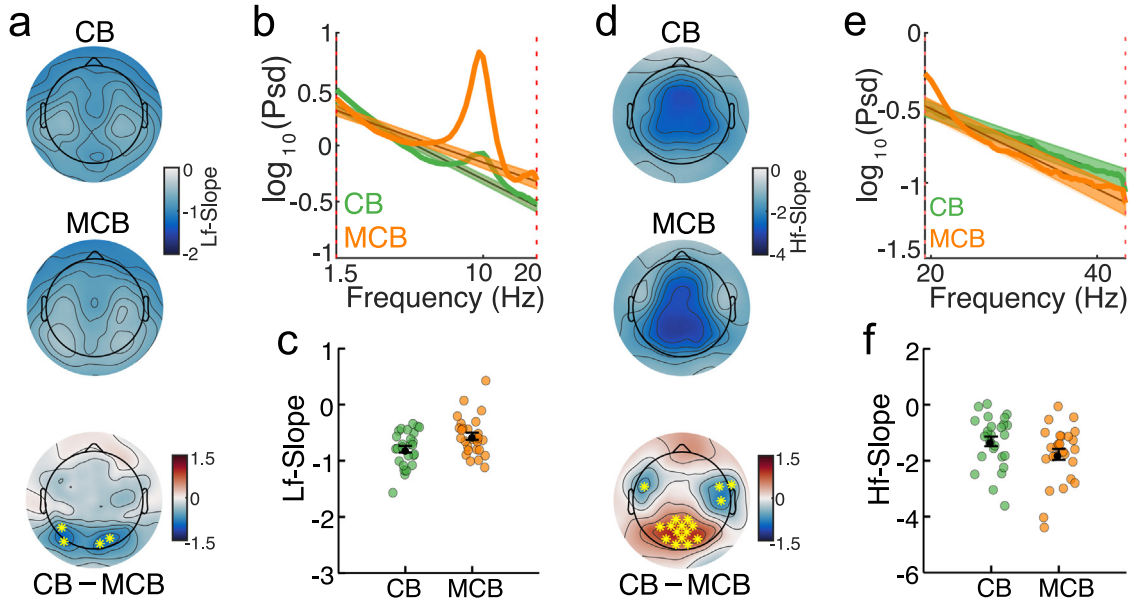

Fig. 3. Aperiodic activity in congenitally blind individuals (CB) and in age-matched normally sighted controls (MCB). (a) Topoplots of Lf-Slope for each group as well as the group difference. **(b)** Group average log-log spectra between 1.5 – 19.5 Hz at O1/O2. Straight lines indicate a linear fit and the shaded area shows the fit error **(c)** Average Lf-Slope at O1/O2 for each participant and group. **(d)** Topoplots of Hf-Slope for each group as well as the group difference. **(e)** Group average log-log spectra between 20 – 45 Hz at O1/O2. **(f)** Average Hf-Slope at O1/O2 per participant and group.

gamma power was positively correlated with the Hf-slope in both groups (see **suppl. Fig. 9d**). Neither the Hf-slope nor the Lf-slope was correlated with alpha power in either group (see **suppl. Figs. 11a,b**).

CC participants featured a steeper (more negative) Lf-Slope than the MCC group at all electrodes and for both the eyes open and the eyes closed conditions (see Figs. 4**a-d**, CC eyes closed: 32/32 $p < 0.04$, eyes open: 32/32 $p < 0.04$). The Lf-Slope was steeper for the eyes open than the eyes closed condition in the MCC but not in the CC group at centro-parietal electrodes (8/32 $p < 0.001$). However, the condition effect for the Lf-Slope was not significantly different between groups.

The Hf-Slope was flatter (less negative) in the CC than in the MCC group at occipito-parietal electrodes (see Figs. 4**e-h**). This group difference was significant only in the eyes closed condition (7/32 $p < 0.01$). The Hf-Slope was flatter (less negative) in the eyes open compared to the eyes closed condition in both groups (**see** Fig. 4**e,** CC: 6/32 $p < 0.001$; MCC: 27/32 $p < 0.007$) and the condition effect was indistinguishable between groups.

CC individuals exhibited higher gamma power compared to MCC individuals (see suppl. material section *Analysis of gamma power* and **suppl. Fig. 10**). In addition, gamma power was positively correlated with the Hf-slope across the CC and MCC groups (see **suppl. Figs. 10e,f**). In contrast to what was observed for the CB and MCB group, the Hf-slope was significantly correlated with alpha power in both the CC and MCC groups (see **suppl. Figs. 11c-f**).

The Lf-Slope was positively correlated with chronological age when considering all participants and each group separately (see **Suppl. Fig. 7a**). For the CC group, the Lf-Slope was neither correlated with visual acuity (see **Suppl. Fig. 7b**), nor with age at surgery (see **Suppl.**

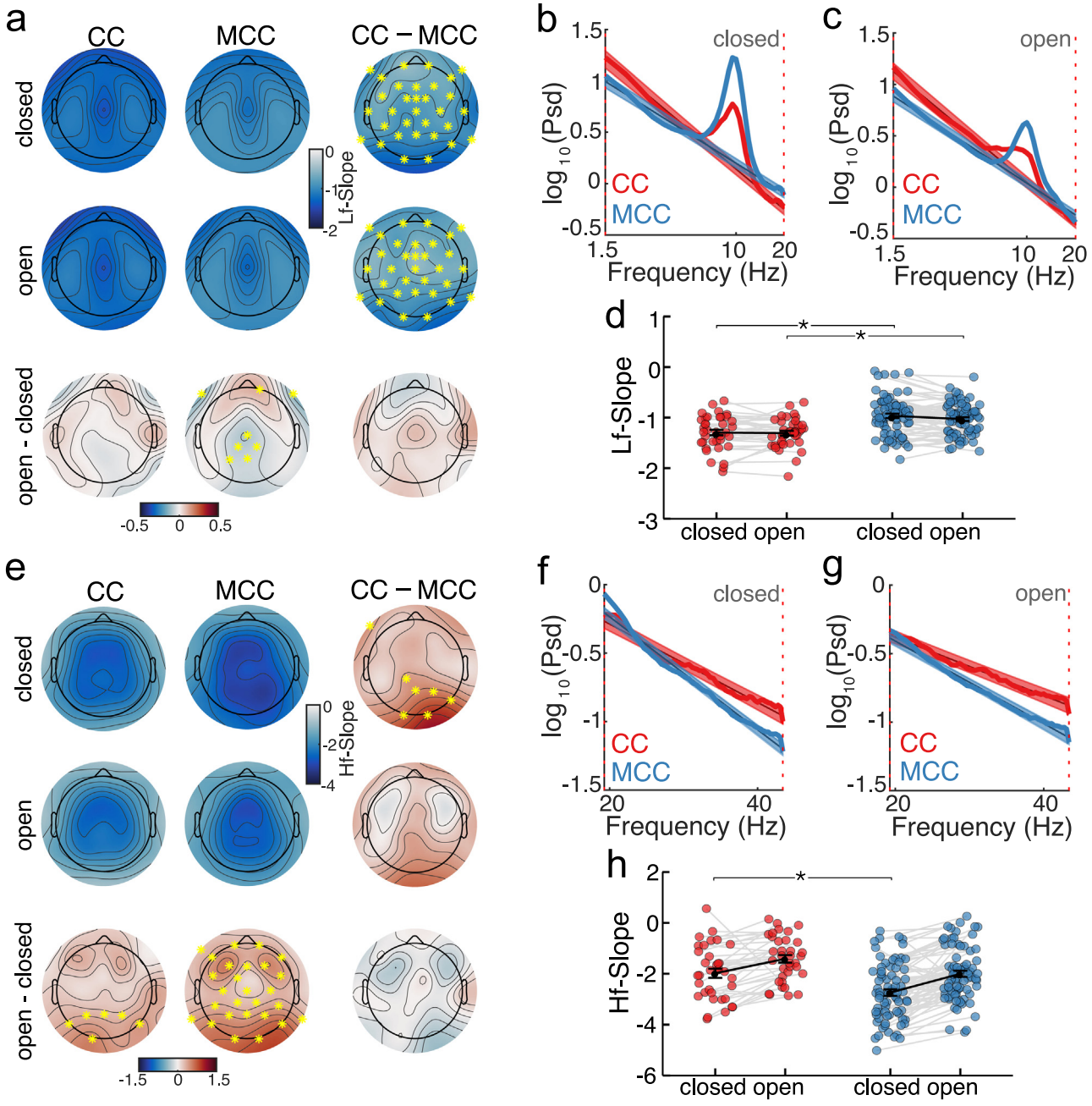

Fig. 4. Aperiodic activity congenital cataract reversal (CC) and age-matched normally sighted (MCC) individuals. (a) Topoplots of Lf-Slope for each group, condition, and group/condition differences. **(b)** Group average log-log spectra between 1.5 – 19.5 Hz for the eyes closed condition at O1/O2. **(c)** Group average log-log spectra between 1.5 – 19.5 Hz for the eyes open condition at O1/O2. **(d)** Average Lf-Slope at O1/O2 for each participant, condition, and group. **(e)** Topoplots of Hf-Slope for each group, condition, and group/condition differences. **(f)** Group average log-log spectra between 20 – 45 Hz for the eyes closed condition at O1/O2. **(g)** Group average log-log spectra between 20 – 45 Hz for the eyes open condition at O1/O2. **(h)** Average Hf-Slope at O1/O2 for each participant, condition, and group. .

Fig. 7c), but there was a weak positive correlation with the time elapsed between surgery and testing in the eyes open condition (see **Suppl. Fig. 7d**). The Hf-Slope was not correlated with chronological age, neither when considering all participants nor in separate group analyses (see **Suppl. Fig. 8a**). For the CC group the Hf-Slope was neither correlated with visual acuity (see **Suppl. Fig. 8b**), nor with age at surgery (but showed a trend both in Eyes closed and open conditions, see **Suppl. Fig. 8c**), nor with the time elapsed between surgery and testing (see **Suppl. Fig. 8d**).

In summary, the present results revealed similar changes in both the Lf-Slope and Hf-Slope characterizing aperiodic EEG activity in both the CB and CC groups compared to their controls: The Lf-Slope (1.5–19.5 Hz fit) was steeper (more negative) and Hf-Slope (20–45 Hz fit) was flatter (less negative). These group differences were localized to posterior, mostly occipital, electrodes in the CB group but were broadly distributed in the CC group.

4. Discussion

Electrophysiological resting state activity has been known to be altered in congenitally blind humans and thus the typical spectral profile of the EEG at rest was concluded to be experience dependent. However,

it was untested whether differences between permanently congenitally blind humans and normally sighted controls were due to altered periodic and/or aperiodic activity. In addition, whether EEG resting state activity would normalize if sight were restored was unknown. To investigate these questions, we first analyzed resting state EEG activity in 27 permanently congenitally blind adults and compared their data to age and gender matched normally sighted controls. Permanently congenitally blind individuals displayed lower periodic alpha activity but higher gamma activity. For the aperiodic activity we found a steeper (more negative) Lf-Slope (1–19.5 Hz) and a flatter (less negative) Hf-Slope (20–45 Hz). Crucially, the results of 38 sight-recovery individuals with a history of transient congenital blindness due to cataracts by and large resembled those of the permanently congenitally blind group. Periodic alpha activity was reduced, and gamma activity was increased compared to matched normally sighted controls. Moreover, the Lf-Slope of the aperiodic activity was steeper (more negative) both during eyes open and eyes closed, and the Hf-Slope was flatter (less negative) with eyes closed in this group. This pattern of results provides strong evidence for prevailing changes of the mechanisms involved in the generation of resting state activity after experiencing congenital blindness. The observed changes in both the permanently congenital blind group and in the group of sight recovery individuals with a history of congenital blindness suggest a higher E/I ratio in visual cortex. Nevertheless, the CC group did displayed differences between the eyes open and eyes closed conditions for periodic activity in the alpha range and the Hf-Slope of aperiodic activity, suggesting some recovery too.

4.1. *Effects of permanent congenital visual deprivation on alpha and gamma activity*

The present finding of lower alpha oscillatory activity in permanently congenitally blind individuals replicates earlier resting state EEG studies (Cohen et al., 1961; Jeavons, 1964; Birbaumer, 1971; Novikova, 1974; Noebels et al., 1978; Campus et al., 2021). However, previous studies did not distinguish between periodic and aperiodic components of the power spectrum. In fact, aperiodic activity can mask or simulate changes in periodic activity (He, 2014; Wen and Liu, 2016; Donoghue et al., 2020). By estimating and consecutively controlling for the aperiodic component of the power spectrum, here we were able to unambiguously demonstrate that the reduced alpha power in permanently congenital blind humans is due to a reduction of genuine oscillatory activity in the alpha range. The more rigorous estimate of periodic alpha activity indicated, however, that posterior alpha oscillatory activity is not fully abolished in permanently congenitally blind humans. In fact, the majority of the permanently congenitally blind individuals displayed a peak in the alpha range and, moreover, this peak emerged at the same frequency as in normally sighted controls (Novikova, 1974; Red'ka and Mayorov, 2014; Campus et al., 2021). Congenitally blind individuals featured an alpha peak independent of whether they reported residual light perception. In contrast to the marked reduction of alpha activity, gamma activity was enhanced in the congenitally blind group. Unsurprisingly, we did not observe a narrowband peak in the gamma range and higher gamma activity corresponded to the observed flatter Hf-Slope in the CB group. Higher gamma activity in CB individuals corroborates recent MEG reports of enhanced gamma activity in this group both during a non-visual task (Schepers et al., 2012) and during rest (Lubinus et al., 2021).

Several resting state studies have shown that alpha power correlates negatively, and gamma power positively with fMRI BOLD activity in visual areas (Goldman et al., 2002; Moosmann et al., 2003; Schölvinck et al., 2010; Liu et al., 2012; Feige et al., 2017; Huang et al., 2019). Thus, lower alpha activity and higher gamma activity in congenitally blind humans suggest a higher level of cortical excitation (Kriegseis et al., 2006; Röder et al., 2021; Rączy et al., 2022), which is consistent with the result of several previous PET and fMRI studies (Wanet-Defalque et al., 1988; Veraart et al., 1990; Jiang et al., 2015; Rączy et al., 2022). Therefore, we interpret the altered oscillatory profile in congenitally blind humans as evidence for a higher E/I ratio in visual cortex.

We additionally argue that the altered spectral profile is compatible with effects of congenital deprivation on the developmental trajectories of feedforward and feedback connectivity. Previous studies have demonstrated that feedback pathways develop later than feedforward pathways (Burkhalter, 1993; Dong et al., 2004; Markov et al., 2013; Dehaene-Lambertz and Spelke, 2015). At birth, connectivity from lower to higher visual areas is mostly adult like, whereas projections from higher to lower visual areas are considerably remodeled towards a stronger role for feedback connectivity (Barone et al., 1995; Batardiere, 2002). Studies in monkeys have suggested that this shaping is guided by visual experience: Enucleation before birth resulted in a replacement of parts of primary and secondary visual cortices by a so called "hybrid" cortex (Rakic et al., 1991; Dehay et al., 1996) which received predominantly feedforward connections from other, normally hierarchically higher, cortical areas (Magrou et al., 2018). Indirect evidence from humans suggests a similar experience dependence of structural remodeling: Congenitally blind humans typically feature a higher thickness of occipital cortical areas (Bridge et al., 2009; Jiang et al., 2009; Park et al., 2009; Hölig et al., 2022), which has been attributed to a lack of pruning (Jiang et al., 2009; Park et al., 2009). This higher visual cortical thickness has been linked to the lack of pruning of predominantly excitatory synapse, as demonstrated in visually deprived monkeys (Bourgeois and Rakic, 1996). Structural changes in early sensory areas have been observed in deaf cats too (Berger et al., 2017) and recent studies similarly proposed that deafness affects top-down connectivity to a larger degree than bottom up connectivity (Yusuf et al., 2022).

A recent behavioral report in human infants adds further evidence to the idea of feedback communication maturing later than feedforward communication: infants did not demonstrate visual backward-masking prior to the age of seven months, suggesting a functional feedforward connectivity but immature feedback communication in visual cortex (Nakashima et al., 2021).

The altered spectral profile of alpha and gamma activity reported here suggests experience dependent effects on the development of feedforward and feedback communication in the human brain. Alpha oscillations have been associated with feedback communication and gamma oscillations have been proposed to mediate feedforward processing (van Kerkoerle et al., 2014; Bastos et al., 2015; Michalareas et al., 2016; Vezoli et al., 2021; Yusuf et al., 2021). Although these associations have not yet been demonstrated during resting state or in the absence of a narrowband gamma peak, we hypothesize that the changes in the oscillatory activity profile during rest reflect an experience dependent development of the orchestration between feedforward and feedback communication in humans, as it has been suggested earlier for deaf cats (Kral et al., 2017; Yusuf et al., 2022)

4.2. *The congenital blindness induced reduction of alpha and increase of gamma activity persisted after sight restoration*

Although studies in permanent blindness allow investigating whether the development of neural circuits require experience, whether this experience must be available at an early age, that is, during a sensitive period, must be investigated in individuals whose sight was restored after a transient phase of congenital blindness (Knudsen, 2004; Röder et al., 2021; Röder and Kekunnaya, 2022). Two previous EEG studies reported reduced alpha activity, and alpha desynchronization, during a visual task in individuals with reversed congenital cataracts (Bottari et al., 2016, 2018). Yet it was unclear whether this observed reduction in alpha activity was predominantly a task related deficit (exaggerated ongoing desynchronization during visual stimulation) or even an artifact of aperiodic activity mimicking a reduction in periodic alpha activity. The present study overcame these limitations by acquiring EEG during resting state and moreover by including a much larger number

of well-characterized individuals with a history of bilateral dense congenital cataract. The sight recovery group featured the same pattern of changes in alpha, and gamma, activity as we found for the permanently congenitally blind group.

Our results suggest that visual experience following birth is necessary for the development of the underlying neural circuits. However, we are not able to delineate the precise timing of a proposed sensitive period. In fact, there is extensive evidence for the existence of multiple sensitive periods in human visual development which might all contribute to the resting state spectral profile. Moreover, Maurer et al. (2007) proposed "sleeper effects" that is, visual deprivation during the first months might cause effects on neural circuits that mature much later. Sleeper effects are a challenge for the retrospective identification of the timing of sensitive periods. Nevertheless, the present study unambiguously demonstrates that visual experience is a prerequisite for the full development of typical resting state activity.

A sensitive period for the development of the cortical circuits underlying oscillatory processes is consistent with additional observations in individual with reversed congenital cataracts. They have been shown to have higher visual cortical thickness similar to permanently congenitally blind individuals (Guerreiro et al., 2015; Feng et al., 2021; Hölig et al., 2022) and to display enhanced resting state BOLD responses in visual cortex (Rączy et al., 2022). Thus, similar as in permanently congenitally blind individuals, visual brain areas of individuals with reversed congenital cataracts seem to be characterized by a higher E/I ratio during rest.

An altered pattern of feedforward and feedback communication in visual cortex would predict that visual tasks relying on the binding of visual features would be particularly affected in individuals with reversed congenital cataracts. In fact, previous studies have revealed, in addition to visual acuity deficits, impairments in higher order visual processes. The latter were larger, for instance for coherent motion (Hadad et al., 2012; Rajendran et al., 2020) and face identity processing (Le Grand et al., 2001; Putzar et al., 2010), than what was expected from the visual acuity deficits. Thus, it was hypothesized that functions which require the integration of information across multiple hierarchical levels of the visual system, and thus relying on recurrent processing, recover least (McKyton et al., 2015; Röder et al., 2021). Two recent neurophysiological studies have provided direct evidence for this assumption: Pitchaimuthu et al. (2021) recorded steady state visual evoked potentials (SSVEPs) to visual stimuli that changed in luminance at a rate of 6.1 Hz and which simultaneously moved laterally at a slower rate (Pitchaimuthu et al., 2021). Individuals with reversed congenital cataracts displayed a typical first harmonic response while higher harmonics and intermodulation frequency responses were reduced or absent, respectively. Higher harmonic responses have been associated with visual processing in extrastriate brain regions and intermodulation frequency responses with visual feature binding across visual regions (Gundlach and Müller, 2013; Alp et al., 2016). Pant et al. (2023) has recently observed, in a subset of the participants of the present study, a lower EEG alpha resonance to white noise stimulation in individuals with reversed congenital cataracts and provided evidence for an impact of altered resting state activity on visual processing. These and the present findings converge to the hypothesis that unbalanced feedforward and feedback communication might contribute to prevailing visual impairments observed after sight restoration in CC individuals.

4.3. Effects of congenital visual deprivation on aperiodic activity

A recently introduced neurophysiological estimate of E/I balance of neural circuits are the aperiodic components of the PSD. Yet, studies have largely differed in the frequency range which was used to calculate the linear fit of the PSD or whether one or two fits for different ranges of the spectrum were calculated. Since standards are still missing, we decided for a data driven solution and found that the best fit was achieved with two rather than one linear regression line with a cut-off point between 19 and 20 Hz. This value well matched descriptive observations of previous studies (Pritchard, 1992; Bédard et al., 2006; Gao, 2016; Colombo et al., 2019; Racz et al., 2021). Moreover, the validity of our approach was confirmed by the replication of serval pervious results such as the finding of a flatter Hf-Slope for the eyes open vs. the eyes closed condition (Hill et al., 2022), a flatter Lf-Slope than Hf-Slope (Bédard et al., 2006; Colombo et al., 2019), a more central/anterior topography for low frequency aperiodic activity compared to the more occipital topography of high frequency aperiodic activity (Racz et al., 2021), and the negative correlation between corrected alpha power and the hf-Slope slope (Podvalny et al., 2015; Muthukumaraswamy and Liley, 2018; Hill et al., 2022).

Based on a simulation of excitatory and inhibitory post-synaptic currents, Gao et al. (2017) proposed that the slope of the aperiodic activity reflects cortical E/I balance. In their study, flatter slopes in the frequency range between 30 and 60 Hz (Gao et al., 2017) were associated with an increased E/I ratio. Other modeling studies have reported similar associations for fits including the 1 – 40 Hz (Medel et al., 2020) and 30 – 100 Hz range (Trakoshis et al., 2020; Chini et al., 2022). Additionally, Podvalny et al. (2015) provided evidence that a flattening of the aperiodic slope in the 10 – 100 Hz range relates strongly to task-induced neural activation in human visual cortex. In the present study, we found a flatter Hf-Slope in both permanently and transiently congenitally blind participants. Moreover, the Hf-slope values but not the Lf-Slope negatively correlated to alpha activity in the CC and MCC group, a finding that was reminiscent of results reported by Podvalny et al. (2015) despite the broader frequency range included in the latter study. Thus, the flatter Hf-slopes in the CC and CB group might be indicative of a higher excitability of their visual cortices.

Understanding the reason for the steeper Lf-Slope within the groups of individuals with either permanent or transient congenital blindness is less straightforward. One previous modeling study indicated that a flatter slope in both low-frequency fit (1 – 30 Hz) and in high-frequency fits (30 – 100 Hz) of simulated LFP was associated with higher E/I ratio (Trakoshis et al., 2020). Although the frequency ranges these authors employed were slightly different to those we used, this modeling data seem incompatible with our results. In contrast, two studies that evaluated the effects of ketamine, a noncompetitive NMDA antagonist, on human EEG activity, reported opposite changes of the Lf- and Hf-slope of the PSD, which were remarkably similar to the results we observed in the present study for the CC and the CB group. Specifically, ketamine resulted in a steeper aperiodic Lf-Slope (1 – 20 Hz range in Colombo et al., 2019, and 1 – 2.5 Hz in Muthukumaraswamy and Liley, 2018) and a flatter Hf-Slope (20 – 40 Hz in Colombo et al., 2019 and 5 – 100 Hz in Muthukumaraswamy and Liley, 2018). Moreover, previous neurophysiological studies have shown that ketamine decreases alpha and increases gamma resting state power (Muthukumaraswamy et al., 2015; Rivolta et al., 2015; de la Salle et al., 2016; Vlisides et al., 2017; Nugent et al., 2019).

Pharmacologically blocking NMDA receptors causes a reduction in the firing rate of fast-spiking GABAergic interneurons while the firing rate of pyramidal neurons remains unchanged or increases (Homayoun and Moghaddam, 2007; Quirk, 2009). This seemingly paradoxical effect of NMDA receptor blocking has been attributed to a stronger effect on the GABAergic interneurons than on the pyramidal neurons which results in a net disinhibition of pyramidal neurons (Seamans, 2008; Miller et al., 2016). Consistent with this view, neuroimaging studies in humans have shown that ketamine increases brain activity (Långsjö et al., 2003, 2004; De Simoni et al., 2013; Doyle et al., 2013). In addition to these direct effects, ketamine has been observed to selectively reduce the GABAergic function of fast-spiking parvalbumin-positive interneurons (Kinney et al., 2006; Behrens et al., 2007). Interestingly, an essential role of parvalbumin-positive interneurons in sensitive period plasticity is well accepted (Hensch, 2005; Levelt and Hübener, 2012) and sensory deprivation is known to particularly affect parvalbumin-positive interneurons (Gabbott and Stewart, 1987;

Benevento et al., 1992; Morales et al., 2002; Jiao, 2006; Sanes and Kotak, 2011; Kaneko and Stryker, 2014).

The similarity between the effects of ketamine and congenital blindness (see summary of results in Supplementary Table 3) on the aperiodic component of the EEG is compatible with the idea that the altered aperiodic EEG activity in permanent congenital blindness and after a transient phase of congenital blindness, might indicate a special deficit in the functioning of inhibitory interneurons. Sight restoration does not seem to fully remediate these deficits.

Our preliminary exploratory correlation analyses suggested that the aperiodic components were the more similar to normal the more time had passed since surgery (Lf-Slope, see Suppl. Fig. 7d) and, possibly, the shorter the congenital visual deprivation had lasted in individuals with reversed congenital cataracts (Hf-Slope, see Suppl. Fig. 8c). Future work needs to demonstrate how variations in resting state activity or certain aspects thereof are related to individual differences in visual recovery after congenital blindness.

4.4. Modulation of periodic oscillatory activity with eyes open vs eyes closed

Despite the alterations in periodic and aperiodic brain activity, congenitally cataract reversal individuals do show a modulation of alpha oscillations and the Hf-Slope of the aperiodic component in response to opening their eyes. These modulations were in the same direction and of a similar relative magnitude as in normally sighted controls. We thus conclude that the reduced alpha desynchronization observed in cataract reversal individuals during visual tasks (Bottari et al., 2016, 2018) might be a consequence of an additional reduction of ongoing activity.

Two thirds of the congenital cataract reversal individuals had an above threshold alpha peak. Although not matched by age and sex and tested with slightly different EEG settings, an exploratory direct comparison of CB and CC individuals revealed higher alpha power in CC individuals at occipital electrodes. This result points towards some recovery too. Despite the high reliance of alpha on early visual experience, our findings indicate that some alpha activity emerges without early visual experience. First, half of the CB individuals featured an alpha peak. Second, group differences in alpha power were not observed (CC vs. MCC) or less strong (CB vs. MCB) over the temporal, central, and centro-parietal scalp. The latter likely emerges from sensorimotor areas (Salmelin and Hari, 1994) and has been termed the rolandic rhythm. In fact, a tactile attention effect on this rhythm (van Ede et al., 2011; Bauer et al., 2012; Ossandón et al., 2020) was preserved in permanently congenitally blind humans (Schubert et al., 2015). Based on the literature it is highly unlikely that alpha activity at occipital channels arises from the sensorimotor area (van Ede et al., 2011; Bauer et al., 2012; Ossandón et al., 2020). Thus, even permanently congenitally blind humans feature some alpha activity which was uncovered after removing the aperiodic component.

Whether this occipital alpha activity in CB individuals reflects some predefined neural network properties or the consequence of input of the intact modalities cannot be decided based on the present data. Alpha activity seems to be an almost ubiquitous phenomenon in the cortex (Jasper and Penfield, 1949; Groppe et al., 2013; Frauscher et al., 2018) and its full expression seems to depend on adequate experience not only in the visual but also in the auditory system (Yusuf et al., 2017). Thus, we speculate that alpha activity is part of an overarching neural network regulating mechanism which in combination with aperiodic activity, guarantees a certain E/I balance. The latter is set based on experience after birth and likely comprises a scaffold for future processing of the expected environmental input (e.g. Pezzulo et al., 2021).

In conclusion, the present study adds to the emerging view that the refinement rather than the setup of neural circuits is experience dependent (Röder, 2013; Röder et al., 2021). Our results demonstrate this developmental principle for resting state activity, which is considered a prerequisite for efficient task related processing (Pezzulo et al., 2021).

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Data and code availability

The code for the statistical analyses, figures, and the anonymized, pre-processed data are available at the Research Data Repository of the University of Hamburg (http://doi.org/10.25592/uhhfdm.12047). Original EEG datasets are available upon reasonable request from the corresponding author.

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.

Credit authorship contribution statement

José P. Ossandón: Methodology, Formal analysis, Writing – original draft. **Liesa Stange:** Formal analysis, Writing – review & editing. **Helene Gudi-Mindermann:** Investigation, Writing – review & editing. **Johanna M. Rimmele:** Investigation, Writing – review & editing. **Suddha Sourav:** Methodology, Investigation, Writing – review & editing. **Davide Bottari:** Conceptualization, Writing – review & editing. **Ramesh Kekunnaya:** Resources, Writing – review & editing. **Brigitte Röder:** Conceptualization, Funding acquisition, Writing – original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2023.120171.

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