Sensitive period for the plasticity of alpha activity in humans

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\textbf{A B S T R A C T}

Visual experience is crucial for the development of neural processing. For example, alpha activity development is a vision-dependent mechanism. Indeed, studies report no alpha activity is present in blind adults. Nevertheless, studies have not investigated the developmental trajectory of this activity in infants and children with blindness. Here, we hypothesize that the difference in neural activity of blind compared to sighted subjects is: absent at birth, progressive with age, specifically occipital and linked to a gradual motor impairment. Therefore, we consider spectral power of resting-state EEG and its association with motor impairment indices, in blind subjects and in sighted controls between 0 and 11 years of age. Blind subjects show posterior alpha activity during the first three years of life, although weaker and slower maturing compared to sighted subjects. The first great differentiation between blind and sighted subjects occurs between 3 and 6 years of age. Starting in this period, reduced alpha activity increases the probability of motor impairment in blind subjects, likely because of impaired perception/interaction. These results show that visual experience mediates the neural mechanisms generating alpha oscillations during the first years of life, suggesting that it is a sensitive period for the plasticity of this process.

\textbf{1. Introduction}

Alpha rhythm (8–12 Hz) dominates occipital EEG activity in adults (Bazanova and Vernon, 2014; Lopes Da Silva, 1995; Steriade et al., 1990). It is associated with a large number of perceptual and cognitive tasks (Klimesch, 2012) and plays an important role in controlling attention (Foxe and Snyder, 2011; Kelly et al., 2006; MacLean et al., 2012; Mathewson et al., 2011) and working memory (Wianda and Ross, 2019). Moreover, it is strictly linked to visual input (Callaway and Yeager, 1960; Dewan and Muhlhauser, 1969; Dustman and Beck, 1965; Lesevre and Remond, 1967; Robinson, 1966; Shaw, 2003; Walsh, 1953).

Alpha waves are reduced or missing in blind individuals (Adrian and Matthews, 1934; Akiyama et al., 1964; Birbaumer, 1971; Cohen et al., 1961; Enge et al., 1973; Jan and Wong, 1988; Kriegseis et al., 2006; Noebs et al., 1976; Novikova, 1974).

In sighted people, posterior alpha activity increases during development until late childhood (8–12 years) (Anderson and Perone, 2018; Eisermann et al., 2013; Gasser et al., 1988; Klimesch et al., 1998; Mistovic et al., 2015). Previous literature has proposed two main perspectives to evaluate the development of EEG activity. The first considers the evolution of activity in standard frequency bands called delta1 = [0.5–2] Hz, delta2 = [2–4] Hz, theta = [4–8] Hz, alpha1 = [8–10] Hz and alpha2 = [10–13] Hz that reflect specific functional processes in adults. This perspective follows from the hypothesis that activity in those bands has, to some extent, the same functional role from the earliest stages of human life (i.e., the fixed bands hypothesis (Red'ka and Mayorov, 2014)). Evidence shows that the alpha1 and alpha2 bands are linked to different perceptual-cognitive functions (Petsche et al., 1997). Alpha2 is associated with memory and semantics (Doppelmayr et al., 2002; Klimesch, 1997; Klimesch et al., 1994), while alpha1 is more related to attention, expectation and encoding (Doppelmayr et al., 2002; Klimesch, 1997; Klimesch et al., 1993). Alpha becomes suppressed in response to a variety of tasks, such as selective attention and control, memory and visuo-spatial tasks (Foxe and Snyder, 2011; Kelly et al., 2006; Klimesch, 2012; MacLean et al., 2012; Mathewson et al., 2011). Theta is a band that is linked to sensory and cognitive processing in many tasks (Klimesch, 1999), while delta oscillations reflect inhibition (John et al., 1980; Matousek and Petrenč, 1973). Moreover, overrepresentation of delta activity occurs in blind subjects during late childhood (8–12 years) (Red'ka and Mayorov, 2014).

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The second perspective arises from the hypothesis that function is mediated by a band shifting toward a higher frequency as age increases (i.e., the shifting bands hypothesis). Convincing evidence exists in the literature that frequency boundaries of alpha rhythm in infancy and toddlerhood (6–9 Hz) do not coincide with conventional alpha1 and alpha2 bands in adults (Marshall et al., 2002; Stroganova et al., 1999). Previous studies have demonstrated shifts in the frequency boundaries with maturation between delta and theta and between theta and alpha toward higher frequency ranges (Orehkova et al., 2006). The spectral composition of EEG varies with age and this variation is pronounced during the first years of development (Anderson and Perone, 2018; Eisermann et al., 2013; Gasser et al., 1988; Miskovic et al., 2015; Orekhova et al., 2006). During the first weeks of life, low-amplitude, poorly defined activity is observable and composed of random-frequency waves in the delta, theta, and alpha ranges. The dominant activity in children’s resting state is 4–6 Hz in 6-month-olds and 5–7 Hz by 1 year of age. At 4 years of age, 7–8 Hz waves predominate, and by 8 years-old, most children exhibit alpha-band activity within the adult frequency range (Nelson and Collins, 2008). As resting-state activity continues to develop during childhood and adolescence, the amplitude of slow-wave (delta and theta) rhythms recedes, while faster rhythms (alpha, beta, and gamma) increase (John et al., 1980; Matousek and Petersén, 1973). This dynamic is a sign of central nervous system (CSN) maturation (Clarke et al., 2001; Kaynyzev, 2012).

It remains unclear whether and how alpha activity develops in blind children, including whether it is present from birth and whether its development is attenuated or delayed compared to sighted children. Reduced occipital alpha power in blind children may result from attenuated inhibitory circuits (Sherman and Spear, 1982) and/or from the atrophy of structures crucially involved in the rhythm’s generation. Alpha waves may originate from the thalamus (Andersen and Anderson, 1968; Andersson and Manson, 1971). Further, the lateral geniculate nuclei (LGN) are known to be atrophied following blindness in animals (Berman, 1991; Rakic et al., 1991) and humans (Breitenseher et al., 1998). Alternatively, the alpha rhythms of the visual cortex might arise from cortex layers IV and V, from where the activity spreads via cortico-cortical connections (Plutscheller and Lopes Da Silva, 1999). Accordingly, pyramidal cells of cortex layer V exhibit intrinsic rhythm-generating properties capable of producing synchronous alpha waves. These structures change with early visual deprivation (Sherman and Spear, 1982). Interestingly, the pyramidal cells in layer V of the primary visual cortex maintain strong connections to the superior colliculi (SC), which plays an essential role in controlling eye movements (Wenzhi and Yang, 2009). In animals, direct visual input to the SC decreases significantly after total visual deprivation from birth. Moreover, in blindness, corticocollicular connectivity completely fails (Sherman and Spear, 1982). Indeed, visual responses in the SC decrease markedly in the wake of congenital visual deprivation (Vidyasagar, 1978).

Two questions remain unanswered. When does the differentiation of alpha activity between sighted and visually impaired individuals emerge during development? What cortical mechanisms are associated with the generation of the activity? Visual input mediates this mechanism; development and blindness are two ideal models to answer these questions. Our study investigates the developmental trajectory of the EEG spectral composition, and specifically the occipital alpha activity in congenital blind/severely impaired children and sighted controls.

Specifically, we test four hypotheses. First, we hypothesize that a difference exists between blind and sighted children in activation of the occipital area that is strictly related to visual processes, and that this difference is absent or weak at birth and increases with age. Second, we hypothesize that this difference is due to activity in the visual areas of the brain. When considering the whole scalp, we expect that differences between groups originate predominantly in the posterior areas and not in other areas, e.g., motor areas. Third, two subbands exist within the alpha band, namely alpha1 and alpha2, and they have different functional roles (perception-attention vs. memory-semantic). Moreover, the whole EEG spectrum evolves with age, and the peak of alpha activity shifts towards higher frequencies. With this in mind, we hypothesized that lack of vision affects all EEG activity, not only at the level of the alpha band. Specifically, that at a finer level, blindness affects alpha subbands differently according to their specific functional roles. Moreover, blindness affects the spectrum at a global level, affecting the shift of the alpha peak and activity at lower frequencies. Fourth, we hypothesize that, eventually, the perceptual impairment resulting from a lack of vision reduces a person’s capacity to interact with their external environment, producing motor dysfunctions. Moreover, we propose a specific association of these deficits with activity in visual areas of the brain will indicate a true perceptual, not merely motor, origin for such deficits.

This study measures alpha activity at rest in 60 completely blind or severely impaired subjects (BSI, for details, see Methods and Supplementary Table 1) and 66 sighted infants/children (S) ranging in age from 20 days to 10 years and 11 months. We show that in the first 3 years of life, posterior alpha activity is present in blind/severely impaired and sighted subjects alike. Indeed, despite it is weaker in the first years of life of the former, the first great differentiation in alpha activity between blind and sighted subjects emerges between 3 and 6 years of age. Such results suggest that the first three years of life can constitute the sensitive period for the plasticity of this process in humans.

2. Materials and methods

2.1. Subjects involved

Several EEG studies have examined the frequency content of spontaneous EEG during development among people who are blind, showing that alpha waves are generally reduced or even predominantly missing over posterior recording sites (Adrian and Matthews, 1934; Akiyama et al., 1964; Birbaumer, 1971; Cohen et al., 1961; Enge et al., 1973; Jan and Wong, 1988; Noebels et al., 1978; Novikova, 1974). Several limitations appear in previous studies. In fact, some studies considered age intervals within late childhood, i.e., 8–12 years (Cohen et al., 1961; Red’ka and Mayorow, 2014). Other studies consider mixed subjects in wide age intervals, e.g., 2.5 years - 7 years (Jeavons, 1964), 8 years – 12 years (Red’ka and Mayorow, 2014), 5 years – 14 years (Cohen et al., 1961), 4 months – 16 years (Akiyama et al., 1964) or even 2.5 months – 22 years (Jan and Wong, 1988). Moreover, previous studies generally provided only qualitative evidence of an overall alpha reduction in blind youngsters (Akiyama et al., 1964; Cohen et al., 1961; Jan and Wong, 1988; Jeavons, 1964). Finally, some studies did not consider age-matched sighted control groups (Cohen et al., 1961; Jan and Wong, 1988; Jeavons, 1964). Only one study quantitatively investigated the EEG in blind and visually impaired subjects (using spectral analysis) and it focused exclusively on late childhood (8–12 years) (Red’ka and Mayorow, 2014). In this study, we considered EEG recordings at rest for 60 blind/severely impaired (BSI) individuals (36 individuals were completely blind from birth, 24 individuals had severely impaired vision from birth) and 66 sighted (S) individuals aged 20 days to 10 years and 11 months. We divided subjects into three age bins based on previous literature (Gori et al., 2014; Vercillo et al., 2016) that identified different sensory integrations characterizing different age stages: from 0 to less than 3 years with 19 BSI subjects (9 Females) and 17 S subjects (9 F); from 3 to less than 6 years with 19 BSI (10 F) and 22 S (8 F); and finally, from 6 to less than 11 years with 22 BSI (11 F) and 27 S (13 F). Supplementary Table 1 presents details about the BSI group. None of the subjects had a history of prenatal infections, distress during delivery, genetic syndromes or metabolic disorders. In agreement with institutional ethics, study data are available upon request.

A total of 14 patients (five BSI) in our sample were born preterm; two were extreme preterm (<32 weeks gestational age (GA)) and the rest were late preterm (33–36 weeks GA). None of these children presented CNS anoxic-ischemic-haemorrhagic injury. Developmental and
cognitive assessment was based on the most commonly used standardized tests, which we chose according to the age and cooperation of the child (i.e., Griffiths Mental Development Scales (Luiz et al., 2006), Leiter-R (Leiter, 1980), Wechsler scales (Wechsler, 2003, 2002) or Raven matrices test (Raven et al., 1996)). BSI children were assessed with Reynell-Zinkin Scale (Reynell, 1978) and the verbal subscales of the Wechsler scales. In 38 children, we evaluated a normal or altered psychomotor development level based on clinical evaluation and information on the child’s adaptive behaviour and school functioning provided by parents and teachers. The mean age of the subjects born preterm was 3.7 years for BSI and 5.3 years for S groups. To the best of our knowledge, there have been no studies demonstrating differences in resting state EEG between pre-school children who were born at term and healthy children who were born preterm, especially late preterm as in most preterm subjects in our sample.

All the subjects in this study presented with good general health status; some of them had slight developmental delay, especially in the motor domain, motor coordination impairment, and/or hypotonia, as is often described in visually impaired children (Dale et al., 2017; Dale and Sonksen, 2002; Fazzi et al., 2005; Jan et al., 1975). None were epileptic or cognitively impaired. However, since previous studies (Akiyama et al., 1964; Cohen et al., 1961; Jan and Wong, 1988; Jeavons, 1964) have found that BSI children sometimes present epileptic EEG patterns (e.g., spikes and/or polyspikes in occipital areas) we considered only segments of EEG recording without such abnormal patterns. Furthermore, all BSI subjects were exclusively affected by congenital disorders and/or cognitive impairment ascribed to visual areas, while in the earliest stages of life the activity of other areas is not significantly affected. We therefore compared spectral activity for delta1 [0.5–2] Hz, delta2 [2–6] Hz, theta [4–8] Hz, alpha1 [8–10] Hz and alpha2 [10–13] Hz spectral bands. To make the spectral activity comparable among subjects, we normalized it by computing the relative spectral power, which measures the ratio of the total power in the band (i.e., absolute spectral power) to the total power in the signal.

2.2. EEG data acquisition and pre-processing

EEG data were collected with a 512 Hz sampling frequency using a Nicolet vEEG 5.94 system; missing or artifacts electrodes were interpolated to obtain a complete montage of 72 derivations placed according to the International 10/20 System for all subjects.

While a resting-state with closed eyes maximally elicits alpha rhythm, studies report (Ben-Simon et al., 2013; Boytsova and Danko, 2010; Kelly et al., 2006; Miskovic et al., 2019) it is also active during a resting state with opened eyes in a dark, quiet room (i.e., in conditions of reduced attention to the external environment and sensory deprivation). We thus considered resting periods (Barry et al., 2009) of subjects (blind or sighted) placed in sensory deprivation conditions with opened eyes in a dark, silent and comfortable room. We made this decision because it is very difficult to record awake EEG in infants and toddlers (0–3 years) while their eyes are closed; however, this condition is not generally appropriate for studying alpha rhythm in such subjects (Stroganova et al., 1999). Children of this age are unable to follow verbal instruction (De Haan et al., 2003; Singer and de Haan, 2007), whereas spontaneous closure of one’s eyes usually indicates that they are falling asleep. This functional state is not optimal for measuring alpha rhythm, which is reduced in infant EEG during drowsiness. Indeed, it is replaced by “hypnagogic hypersynchrony” which is a specific EEG pattern containing rhythmic theta (3–5 Hz) bursts (Stroganova et al., 1999). Furthermore, alpha activity is strongly elicited during rest in conditions of sensory deprivation such as with open eyes in a dark quiet room (Boytsova and Danko, 2010; Miskovic et al., 2019). These conditions are reportedly the best for recording resting state in infants/children (Stroganova et al., 1999). An operator continuously monitored the state of subjects using EEG and infra-red camera recordings. In a later scoring phase, based on the EEG and video recording, we excluded periods in which subjects were moving or falling asleep from the analysis.

EEG recordings were filtered to those between 0.1 and 100 Hz. Transient high-amplitude artifacts were removed using artifact subspace reconstruction (ASR), which is an automated artifact rejection method available as a plug-in for EEGLAB software (Delorme and Makeig, 2004; Mullen et al., 2015). ASR uses a sliding window technique whereby each window of EEG data is decomposed via principal component analysis and compared with data from a clean baseline EEG recording. Within each sliding window, the ASR algorithm identifies principal subspaces that deviate from the baseline; it then reconstructs these subspaces using a mixing matrix computed from the baseline EEG recording. In the current study, we used a sliding window of 500 ms and a threshold of 3 standard deviations to identify corrupted subspaces. In addition, channels were removed if their correlation with other channels was below 0.85 or if the line noise to signal ratio exceeded 4 standard deviations from the channel population mean. Time windows were removed after the application of the previously described criteria — that is, when the fraction of contaminated channels exceeded the threshold of 0.25. We kept other parameters default. We used ASR instead of independent component analysis (ICA) because the latter requires a high number of samples for convergence, which makes running ICA problematic with the relatively short recordings that this study has available. For the same reason, statistical analyses and inferences were based on electrodes rather than conducting an ICA decomposition on the data to isolate the visual-occipital alpha rhythm from the central-motor one, etc., and then running statistical tests specifically on the component(s) corresponding to visual alpha.

Using the cleaned data of each subject (mean segment duration = 333 s, 95% CI = [195, 638] s), we computed the power spectral density (PSD) expressed in µV²/Hz. To do this, we applied the spectopo function of EEGLAB, which returns a PSD estimate via Welch’s method. The signal was divided into sections with a duration of 1 s and a 50% overlap. Each section was windowed with a Hamming window, whereby we computed and averaged the modified periodograms. We then considered spectral activity for delta1 (0.5–2) Hz, delta2 (2–4) Hz, theta (4–8) Hz, alpha1 (8–10) Hz and alpha2 (10–13) Hz spectral bands. To make the spectral activity comparable among subjects, we normalized it by computing the relative spectral power, which measures the ratio of the total power in the band (i.e., absolute spectral power) to the total power in the signal.

2.3. Statistical analysis

Based on our first hypothesis, we tested that a difference could exist between blind and sighted infants/children with regard to the activation of visual areas, but also that this difference could increase and become significant with age even if it were initially absent or weak at birth. Therefore, in a first analysis, we focused on the effect of age and visual impairment on spectral activity in the occipital area, which plays a crucial role in visuo-attentional processes, measured as the average spectral activities in O1, Oz and O2 electrodes. These are the standard electrodes to check activity of visual cortex (Kriegseis et al., 2006; for a review see Lenassi et al., 2008). For each spectral band, we performed an independent ANOVA with relative band power as the dependent variable and group (BSI or S) and age bin ([0–3], [3–6] or [6–11]Y) as between subject factors. We performed post-hoc comparisons using unpaired two-tailed t-tests retaining as significant comparisons with p < 0.05 after Bonferroni correction.

Based on our second hypothesis, we tested that the difference of spectral activity between blind and sighted subjects that is specifically ascribed to visual areas, while in the earliest stages of life the activity of other areas is not significantly affected. We therefore compared spectral activity between groups (BSI and S) over the entire scalp for each spectral band and age bin. For each electrode, we used unpaired two-tailed t-tests for comparison, retaining as significant those with p < 0.05 after false discovery rate (FDR) correction with consideration to all electrodes.

Based on our third hypothesis, we tested whether lack of vision could
impact the spectrum other than the alpha band level. We checked if blindness could also impact EEG spectrum at a finer level to see if blindness might affect alpha subbands differently depending on their specific functional roles. We also investigated this a global level, affecting the shift of the alpha peak and the activity of lower frequency. This involved evaluating how age and blindness modulated the whole spectrum and especially the peak frequency of the background EEG activity for each subject. We considered the whole EEG spectrum. To reliably estimate peak frequency of background activity, we adopted a three-stage approach. First, we searched for the peak in the raw spectrum. Second, we searched for the peak in the spectrum after it was detrended using an exponential decay function. Toward this purpose, we considered the logarithm of the power spectral density (PSD) at different frequencies and fitted a linear regression model: log(PSD) = A + B*Frequency. In this way, we computed the PSD using coefficients A and B estimated by the regression, PSDest = exp(A) * exp(B*Frequency) and we searched for the peak in the detrended PSD PSDdetrend = PSD - PSDest. Both in the raw and in the detrended spectrum, we used the findpeaks function of the pracma package (Borchers, 2019) for R (R Core Team, 2020) to automatically identify peaks in the background. Third, we compared automatic peak estimates from stages one and two and where they differed (most times they matched), we selected the most reliable peak position by means of visual inspection. We assessed changes in peak frequency using an ANOVA with peak frequency as the dependent variable and group (BSI and S) and age bin ([0–3]Y, [3–6]Y and [6–11]Y) as between-subject factors. We performed post-hoc comparisons using unpaired two-tailed t-tests retaining as significant only those comparison with $p < 0.05$ after a Bonferroni correction.

Finally, to test our fourth hypothesis, that perceptual impairment (Gori et al., 2014; Vercillo et al., 2016) from lack of vision eventually reduces capacity to interact with the external environment and produces motor dysfunctions measurable with specific clinical indices. Moreover, we checked if a specific association of these dysfunctions with the activity of visual areas exists, which would indicate that they have a genuinely perceptual and not a merely motor origin. Therefore, we related EEG spectral activities with specific clinical scores that reflect motor dysfunction – namely motor coordination impairment (MCI) and hypotonia. For all parameters, two clinicians evaluated each subject; in the analysis, we kept only those subjects for which clinician evaluations agreed. To test the association between spectral activities in different bands and clinical findings, for each score and age bin of the BSI group we applied logistic regression models (LRM) which allowed us to predict MCI and hypotonia probability as a function of the relative power in each EEG band. Specifically, we expect that decreased alpha and bands and clinical findings, for each score and age bin of the BSI group differences increases with age. We computed the Power Spectral Density (PSD). Then, we considered the relative spectral activity for the delta1 (0.5–2) Hz, delta2 (2–4) Hz, theta (4–8) Hz, alpha1 (8–10) Hz and alpha2 (10–13) Hz spectral bands. We also computed the whole EEG spectrum for each subject to determine a reliable estimation of the peak frequency of the background activity (see Methods section for more details).

Top Fig. 1 shows the average percentage of alpha1 activity for the occipital area compared to the whole EEG PSD (relative power) at different ages. A significant interaction occurred between group and age bin ($F(2,120) = 3.94$, $P = 0.02$, $\eta^2_p = 0.13$). Specifically, S infants/children had stronger alpha1 activity at all ages relative to BSI children, and the gap between groups increased with age ([0–3]Y: $t(34) = 3.22$, $P = 0.008$, (Cohen’s) $d = 1.08$; [3–6]Y: $t(39) = 2.9$, $P = 0.02$, $d = 0.91$; [6–11]Y: $t(47) = 4.76$, $P = 0.0006$, $d = 1.37$). Moreover, BSI infants/children alpha1 activity increased from the youngest to the middle age bin, ($t(36) = 3.15$, $P = 0.01$, $d = 1.02$) but not from the middle to the oldest age bin ($t(39) = 0.52$, $P = 0.5$, $d = 0.16$). As expected, alpha1 of S infants/children increased both from the youngest to the middle ($t(37) = 3.45$, $P = 0.004$, $d = 1.12$) and from the middle to the oldest age bin ($t(47) = 2.50$, $P = 0.04$, $d = 0.72$).

Fig. 1 also shows occipital alpha2 relative power for each age bin. Much as with occipital alpha1, occipital alpha2 exhibits a significant interaction between group and age bin ($F(2,120) = 3.65$, $P = 0.03$, $\eta^2_p = 0.47$). Here, BSI and S groups had similar alpha2 activity in the youngest ($t(34) = 2.23$, $P = 0.1$, $d = 0.74$) and middle ($t(39) = 0.5$, $P = 1$, $d = 0.16$) age bins, but in the oldest age bin, sighted children had higher alpha2 compared to BSI subjects ($t(47) = 2.82$, $P = 0.02$, $d = 0.81$). Within the BSI group, alpha2 behaved similarly to alpha1, increasing

![Fig. 1. Top. Relative power of alpha1 activity [8-10] Hz in Occipital area (O1, O2 electrodes) of blind/severely impaired (BSI) compared with sighted (S) subjects. Bars represent means and error bars represent standard error of means (SEM). Different colors represent different age bins. Bottom. Average relative power of alpha2 activity [10-13] Hz in Occipital area of BSI compared with S subjects. Different colors represent different age bins.](image-url)
from the youngest to the middle ($t_{36} = 2.91, P = 0.02, d = 0.94$), but not from the middle to the oldest age bins ($t_{39} = 0.72, P = 0.5, d = 0.23$). Conversely, alpha2 of sighted subjects increased both from the youngest to the middle ($t_{37} = 2.82, P = 0.02, d = 0.91$) and from the middle to the oldest age bins ($t_{47} = 2.92, P = 0.02, d = 0.84$). Thus, within the alpha band, the first subband showing differences between BSI and S subjects is alpha1 starting from the first year of life, while alpha2 diverges between groups significantly later at 6–11 years of age.

What about the other bands? For occipital delta1 (Fig. 2) we did not observe a significant interaction between group and age bin ($F(2,120) = 1.29, P = 0.28, \eta^2_p = 0.01$); rather, we saw only a main effect of group, with higher delta1 power for BSI than for S subjects ($F(1,120) = 21.4, P = 0.00001, \eta^2_p = 0.15$). Similarly, for the occipital theta (Fig. 3) no interaction between group and age bin was present ($F(2,120) = 0.60, P = 0.55, \eta^2_p = 0.03$), but a main effect of age bin occurred, with decreasing theta power from the youngest to the oldest age bin ($t_{83} = 3.21, P = 0.002, d = 0.70$). An opposite effect to the alpha band occurred for the occipital delta2 relative power at different ages (Fig. 4). A significant interaction between group and age bin was present ($F(2,120) = 0.83; [6,11]-Y: t(34) = 0.50, P = 1, d = 0.17$), while at older ages sighted subjects had lower delta2 activity compared to BSI subjects; much like with alpha1, the difference between groups increased with age ($t(3-6)Y: t(39) = 2.64, P = 0.03, d = 0.83; [6-11]-Y: t(47) = 5.46, P = 0.000005, d = 1.57$). However, delta2 did not change with age in BSI subjects, from the youngest to the middle age bin ($t_{36} = 1.88, P = 0.2, d = 0.61$), or from the middle to the oldest age bin ($t_{39} = 0.18, P = 0.5, d = 0.06$). Instead, the delta2 power of sighted subjects decreased both from the youngest to the middle ($t_{37} = 2.90, P = 0.02, d = 0.94$) and from the middle to the oldest age bins ($t_{47} = 3.03, P = 0.01, d = 0.87$).

Our second analysis indicated that the difference of EEG spectral activity between blind and sighted subjects is specifically ascribable to the activity of visual areas, while activity in other areas is not significantly affected during the earliest stages of life. We compared spectral activity between groups over the entire scalp for each spectral band and age bin. For each electrode, we compared using unpaired two-tails t-tests, retaining tests with $P < 0.05$ as significant after FDR correction considering all electrodes. Fig. 5 presents the significant comparisons (non-significant differences in green) using a topographic map for each age bin (columns), for different bands (alpha1, alpha2 and delta2, see rows) and for BSI and S children. Differences are mostly located in the occipital areas. They specifically involve the alpha1 band for the middle age bin, while in the oldest age bin, differences are stronger and tend to involve a larger scalp area and different bands.

Our third analysis showed that lack of vision impacts the EEG spectrum beyond just the alpha band level. Results indicates that, at a finer level, blindness differentially affects alpha subbands. Moreover, blindness impacts the EEG spectrum at a global level, affecting the shift of the alpha peak and the activity at lower frequencies. The spectral composition of the EEG varies with age and it is particularly marked during development (Anderson and Perone, 2018; Eisermann et al., 2013; Gasser et al., 1988; Miskovic et al., 2015). To evaluate whether the differentiation we observed between S and BSI subjects was associated with a different spectral composition of the EEG spectrum, we calculated its change during development for both groups. Fig. 6 provides an overview of how the whole spectrum of EEG resting-state
activity evolves with age in both groups. In sighted individuals, as ages increase, background activity shifts towards higher frequencies and becomes more evident (with sharper and more pronounced peaks). In the youngest age bin, background activity has two components: one at around 4.5 Hz and the other at 8.5 Hz. As age increases, the power at lower frequencies (0–4 Hz) progressively decreases. In BSI individuals, background activity shows both a slower shift and a reduced power. Moreover, compared with S subjects, BSI subjects present with a strong over-representation of low frequencies while maintaining similar power for all age bins. In both groups, while in the [0–3] age bin the two alpha components separate, they merge in the [3–6] age bin and overlap in the [6–11] age bin, creating a single pronounced peak within the standard alpha band reported in adults.

As Fig. 7 demonstrates, an ANOVA on peak frequencies of background activity revealed a significant interaction between group and age bin ($F(2,113) = 7.37, P = 0.001, \eta_p^2 = 0.12$). Specifically, sighted subjects showed peak frequencies that increased from the youngest to the middle ($t(38) = 5.63, P < 0.001, d = 1.71$) and from the middle to the oldest age bins ($t(47) = 2.55, P = 0.04, d = 0.93$), as expected. In contrast, BSI individuals kept the same peak frequencies from the youngest to the middle ($t(32) = 0.10, P = 0.5, d = 0.05$) to the oldest age bin ($t(33) = 1.11, P = 0.05, d = 0.36$). Accordingly, compared with BSI individuals, the peak frequencies of sighted individuals were lower in the youngest age bin ($t(33) = -2.23, P = 0.048, d = 0.69$) and higher in the middle ($t(37) = 2.77, P = 0.01, d = 0.97$) and for the oldest age bins ($t(43) = 2.30, P = 0.04, d = 0.79$).

This study’s previous results indicated a specific joint effect of age and blindness on alpha and delta activities. Our final analysis revealed a specific association between motor dysfunctions and brain activity in visual areas. In the second analysis we found that differences between groups were present mostly in the posterior areas and not in other areas, e.g., motor areas, therefore the results of this last analysis support a
specific association of motor dysfunction indices with spectral activity in occipital areas. Logistic Regression Models pointed to strong associations of alpha activities with specific clinical examination scores. As Fig. 8 displays, a decrease in relative alpha1 activity increased the probability of both motor coordination impairment (MCI, $\chi^2(1) = 12.99$, $P = 0.0003$, Accuracy = 0.91), and hypotonia ($\chi^2(1) = 8.96$, $P = 0.003$, Accuracy = 0.88) for the [3–6)Y age bin. Furthermore, for the [6–11)Y age bin, decreasing alpha1 and alpha2 activity increases the probability of motor coordination impairment (alpha1: $\chi^2(1) = 8.38$, $P = 0.004$, Accuracy = 0.83; alpha2: $\chi^2(1) = 12.79$, $P = 0.0004$, Accuracy = 0.90) and hypotonia (alpha1: $\chi^2(1) = 10.89$, $P = 0.001$, Accuracy = 0.88; alpha2: $\chi^2(1) = 17.62$, $P = 0.00003$, Accuracy = 0.95) (Fig. 9). Alpha2 was the best predictor of the clinical scores. None of the models using age as a predictor variable showed significant results.

In summary, the BSI group showed lower alpha activity and higher delta activity than the S group—a difference that was mainly located in posterior scalp areas. Moreover, when comparing the BSI to S groups, the BSI group showed a slower shift in background activity peak as a function of age. Finally, in the BSI group, lower alpha activity increased the probability of motor coordination impairment (alpha1: $\chi^2(1) = 8.38$, $P = 0.004$, Accuracy = 0.83; alpha2: $\chi^2(1) = 12.79$, $P = 0.0004$, Accuracy = 0.90) and hypotonia (alpha1: $\chi^2(1) = 10.89$, $P = 0.001$, Accuracy = 0.88; alpha2: $\chi^2(1) = 17.62$, $P = 0.00003$, Accuracy = 0.95) (Fig. 9). Alpha2 was the best predictor of the clinical scores. None of the models using age as a predictor variable showed significant results.

4. Discussion

Alpha rhythm is a rhythmic activity in the range of 8–12 Hz, likely generated in thalamo-cortical feedback loops and in the cortex (Lopes Da Silva, 1995; Steriade et al., 1990). The current study investigated alpha activity development in sighted and BSI infants and children to shed light on the cortical mechanisms associated with alpha activity generation in human brains.

We present four main findings reflecting our initial four hypotheses. First, there is a difference between blind and sighted subjects in the activation of occipital area, which is crucially related to visual processes. This difference is weak at birth and increases with age, starting at 3–6 years of age. Second, when the whole scalp is considered to check the possible involvement of other areas this difference is specifically ascribed to the activity of visual areas, and other areas are not affected in the earliest stages of life. Third, the lack of vision affects the spectrum at the alpha band level, but also at other levels. In fact, blindness affects the spectrum at a global level, producing slower shifts of the alpha peak and slower decay of activity at a lower frequency. Additionally, at a finer level, blindness differentially affects alpha subbands depending on their specific functional roles: earlier alpha1 activity reflects low level perceptual processes, and later alpha2 activity reflects cognitive processes. Fourth, motor dysfunctions are specifically associated with the activity of visual areas in blind children, indicating a possible genuinely perceptual origin of motor impairments; this supports the hypothesis that over time, a perceptual deficit resulting from a lack of vision can reduce a person’s capacity to interact with their external environment, with potential negative consequences for motor development.

To uncover the effects of reduced visual experience on EEG spectra from a developmental perspective, we considered two complementary approaches, trying to integrate the fixed bands and shifting bands hypotheses. On one hand, our first, second and fourth analyses investigated the association between developmental changes and motor dysfunction indices of relative spectral power within the conventional frequency bands: delta1 (0.5–2 Hz), delta2 (2–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz) and alpha2 (10–13 Hz). Indeed, the fixed bands hypothesis affirms that activity in those bands assumes, to some extent, identical functional roles from the earliest stages of life. On the other hand, our third analysis evaluated how vision as a function of age modulates the whole EEG spectrum, and in particular, the peak of background activity. Indeed, the shifting bands hypothesis affirms that a band shifting towards higher frequency with increasing age mediates a certain functional role. Importantly, even in the presence of these frequency shifts, the comparison of BSI subjects with sighted subjects based on conventional spectral bands keeps all its strength, because it is based on age-matched bins.

4.1. The difference in neural activity of blind compared to sighted subjects is weakest at birth, increases with age and is specifically occipital

Our first and second analyses are based on fixed bands. The first analysis, specifically considering spectral power in occipital electrodes, showed that posterior alpha activity is present in both blind and sighted subjects during the first stages of life, contrary to the findings of some previous researchers (Akiyama et al., 1964; Cohen et al., 1961; Jan and Wong, 1988; Jeavons, 1964; Red’ka and Mayorov, 2014). Although the posterior alpha activity of blind subjects diverges from sighted subjects within the first three years of life, the major difference appears in the age range between 3 and 6 years. Indeed, alpha activity is more than twice as strong in sighted compared to BSI children who are between 3 and 6 years of age, and about four times greater in sighted children who are between 6 and 11 years of age (Fig. 1). The second analysis of topographical distribution of spectral power over the whole scalp, showed
that the difference between blind and sighted subjects is attributable to activity of visual areas, since the occipital region is mainly involved.

Our results suggest that visual experiences mediate the neural mechanisms that generate alpha oscillations during the first three years of one’s life and to a greater extent between 3 and 6 years, which correspond to the preschool period. This period is extremely important, as it is fundamental for children’s development. During this time, children start kindergarten, expand their language skills, and begin a social life among peers. Enrichment of social and perceptual stimulation define the preschool years as a critical period for the development of visual acuity and maturation of visual evoked potentials (VEPs) (Lenassi et al., 2008), multisensory integration in complex tasks (Mix et al., 1996) and visuo-spatial and visuo-motor processes (Freier et al., 2017; James and Kersey, 2018; Maffongelli et al., 2019; Moll et al., 2013; Schipke et al., 2012). Importantly, the first alpha subband showing differences between blind and sighted subjects is alpha1 starting from the first year of life (Fig. 1A), while only later does alpha2 diverges between groups (Fig. 1B), suggesting that neural processes related to attention are the first that visual deprivation affects, followed by alteration of the processes related to semantics and memory.

4.2. Lack of vision affects the whole spectrum and especially the alpha1 and alpha2 subbands

Our third analysis, based on the shifting band hypothesis, revealed that blindness also affects the spectrum at a global level. Specifically, it showed that background activity has two peaks in younger sighted subjects, one at around 4.5 Hz and the other at 8.5 Hz, which progressively merge during development. These two peaks could be the early representation of alpha1 and alpha2 subbands. Moreover, the power within lower frequencies (0–4 Hz) gradually reduces and the higher frequencies become more defined as with age. Similar to sighted subjects, blind subjects show two peaks of background activity in the youngest age bin. However, with respect to sighted individuals, BSI subjects present an over-representation of activity at lower frequencies and a slower shift toward higher frequencies. According to our interpretation, the slower shift seems to produce a first difference in the alpha1 frequency and a later one in the alpha 2 subband.

This divergence from sighted children may result from the synaptic density and total number of synapses in the human visual cortex reaching a maximum in the earliest phases of life, then gradually decreasing to adult values (Huttenlocher, 1994). Moreover, a large body of evidence supports the crucial role of visual stimulation in the development of the structure and function of the visual cortex (Wiesel, 1982). The onset of visual stimulation influences the development of the electrical activity of the visual cortex in human children (Stroganova et al., 1999). The lack of visual input therefore alters these mechanisms.

4.3. The difference in neural activity of BSI compared to S subjects is linked to a gradual motor dysfunction

Our fourth analysis, based on the fixed band hypothesis and using logistic regression models, not only confirms the role of conventional bands according to their association with our clinical findings, but also supports the speculation on alpha1 and alpha2 subbands.

In fact, we found that a reduced amount of alpha activity (i.e., a stronger difference from sighted subjects) in blind subjects increases the probability of having both motor coordination impairment and
hypotonia. These findings indicate that reduced alpha development generates a general impairment, most likely because of reduced capability to perceive and interact with the surrounding space, leading to hypotonia. Specifically, in agreement with the results of our second analysis, this association firstly emerges in the [3–6]Y age bin involving only the alpha1 band, while later, in the [6–11]Y age bin, it also involves alpha2. When replacing alpha activity with age in the regression models, they were never significant: the observed association with clinical findings specifically reflects that the development of EEG activity is not generically driven by age.

4.4. Reconciling the fixed and shifting bands hypotheses

4.4.1. Alpha activity evolution

Our third analysis, based on the whole spectrum, revealed for the first time that the two perspectives of fixed and shifting hypotheses coexist. In fact, there are two distinct peaks in the youngest age bin when examining the EEG spectra of blind and sighted subjects. One peak occurs in the standard alpha band for all age bins, even for the youngest one, supporting the fixed band hypothesis. The other peak, which is stronger, shifts towards higher frequencies with increasing age and merges more with the first peak as age increases, supporting and extending classical shifting band hypothesis (Marshall et al., 2002; Orskova et al., 2006; Stroganova et al., 1999).

The activity we observed suggests that while slower and weaker, alpha rhythm generation mechanisms do develop in the first years of life in BSI children just as they do in sighted children. However, when visual input is unavailable, alpha activity is partially suppressed or altered later in childhood. This result matches previous work on individuals with a cataract removed (Stroganova et al., 1999) where the immediate appearance of alpha rhythm in EEG followed pattern vision recovery.

4.4.2. Slow activity evolution

Our results reveal that the difference between BSI and sighted children affects not only the alpha band and its subbands but reflects a more general reorganization of the whole spectrum, including lower frequencies.

While the theta band is generally linked to sensory and cognitive processing in a number of different tasks (Klimesch, 1999), our results indicate an absence of modulation from blindness. This agrees with the known shift of the EEG spectrum towards higher frequencies as a function of age: slower delta2 seems to play a role of faster theta activity during the earliest stages of human life. Two of our results support this interpretation. First, we observed more delta activity (Figs. 2 and 4) but not theta activity (Fig. 3) in BSI compared to S children at all ages. In fact, in the oldest age bin, delta2 was more pronounced in blind/–severely impaired subjects than in sighted subjects, which reveals a specular pattern with respect to alpha2. This is also linked to high level cognitive functions. Such results suggest that delta2 may be a proxy of theta activity during the earliest stages of life and that, in the [6–11]Y age bin, cognitive impairments could originate following an attentive deficit already present in the [3–6]Y age bin and related to alpha1 activity. In agreement with this interpretation, researchers have documented increases of delta power in resting EEG for a wide array of developmental disorders and pathological conditions. The lack of specificity of this effect indicates that increases in slow waves and/or decreases in alpha are near-universal responses to any brain damage or pathology. Our results show that increased delta waves of blind subjects start even earlier in life. Indeed, the first differences in occipital areas occur in the [3–6] year age bin, while stronger differences appear in the [6–11] years age bin and confirm the direct link of this pattern with blindness when considering the excluded comorbidities and abnormal pattern from our sample.

Importantly, over-representation of slow frequency activity in BSI individuals, like other spectral differences between groups seems to be directly linked to blindness and to lower overall levels of functioning. In fact, the two groups presented similar general characteristics, such as normal birth weight, overall normal health (checked by general objective examination), and no psychomotor delay (assessed by global clinical examination).

4.5. Final considerations

In summary, our results first clarify the pattern of evolution of the spectral composition of EEG activity as a function of age and reconcile the fixed and shifting band hypotheses. The age bins adopted in this study are based on EEG activity development related to the sensory and cognitive functions investigated herein. In fact, there is evidence that relevant EEG developmental stages are new-born (up to 4 months, though none of our subjects were that young), infant (up to 12 months), child (1–3 years), pre-school (3–5 years), and school age (6–12) with strong changes in the EEG patterns; for a review, see (Eisermann et al., 2013). In the current study, we merged the infant and child stages to ensure both a sufficient statistical power in each group and a better balance between experimental groups. This made our analyses more robust. Importantly, as Fig. 1 shows, the variability of our youngest age bin is much lower than the variability in other age bins (compare the error bars of red bars vs. other bars). This indicates that development of alpha activity among subjects in the youngest age bin is homogeneous. Furthermore, the middle and oldest age bins reflect pre-school and school-age stages; these stages vary among countries and for Italy are (3–6) and (6–11) years old, respectively.

Second, our results showed how blindness has an impact on the development of EEG activity. Our results do not seem weakened by the fact that we considered both blind and severely impaired people. First, our visually impaired subjects presented with a level of severity that was sufficient to show significantly decreased alpha activity (Jan and Wong, 1988). Second, the severity of visual impairment was homogeneous among participants. Third, visually impaired people generally show a weaker alpha reduction compared with blind people (Jan and Wong, 1988). We can therefore reliably expect that having all blind subjects would only increase the differences seen with respect to sighted people.

5. Conclusions

Functional brain development is characterized by sensitive periods during which experience is required for the full development of neural circuits and associated behaviour. However, researchers only know a few neural markers of sensitive period plasticity in humans. Our data document brain mechanisms reflecting plastic reorganization due to visual impairment during the earliest stages of life. They indicate, for the first time, a sensitive period for the development of alpha oscillatory activity in humans. There is a need for further examination whether these results reflect a cross-modal plasticity, and/or if they are due to atrophy of the alpha-generating brain structures.

Data availability

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

Author contributions

M.G., C.C. and S.S. conceived the study; V.D.G., G.P., F.M., and H.V. acquired the data; C.C. and H.V. analysed data. M.G., C.C. and S.S. wrote the manuscript. C.C prepared figures. All authors reviewed the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.
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Appendix A. Supplementary data
Supplementary material related to this article can be found, in the online version, at doi.org/10.1016/j.dcn.2021.100965.

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