Review

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Congenital visual pathway abnormalities: a window onto cortical stability and plasticity

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Sensory systems project information in a highly organized manner to the brain, where it is preserved in maps of the sensory structures. These sensory projections are altered in congenital abnormalities, such as anophthalmia, albinism, achiasma, and hemihydranencephaly. Consequently, these abnormalities, profoundly affect the organization of the visual system. Surprisingly, visual perception remains largely intact, except for anophthalmia. Recent brain imaging advances shed light on the mechanisms that underlie this phenomenon. In contrast to animal models, in humans the plasticity of thalamocortical connections appears limited, thus demonstrating the importance of cortical adaptations. We suggest that congenital visual pathway abnormalities provide a valuable model to investigate the principles of plasticity that make visual representations available for perception and behavior in humans.

Sensory structures and their cerebral representations

All primary senses are organized topographically in our brain. These topographic maps reflect the layout of the sensory organs, such as the retina, cochlea, olfactory epithelium, or skin surface. Beyond the sensory cortex, topographic maps exist in the motor cortex as well, reflecting the layout of our musculature. Recently, we also revealed a topographic map for numerosity (or 'number sense' [1,2]), suggesting that the topographic organization common to primary cortices is also present in the association cortex [3]. Such consistent topographic organizations suggest that the computational benefits of topographic representations, such as local wiring efficiency [4,5], applies to sensory, motor, and cognitive functions alike. Clearly, topographic maps are a fundamental organizational principle of our brain. In our visual system, the spatial layout of the retina and consequently the visual scene is preserved, giving rise to visual field maps (also known as retinotopic maps [6,7]; see Glossary). We do not have one but rather multiple visual field maps. These cover the occipital lobe and parts of both the parietal and temporal lobes. Each hemisphere encodes the opposite visual hemifield, that is, the right hemisphere encodes the left visual field and vice versa (Figure 1). Nowadays, experiments lasting under an hour

Glossary

Contiguous Representation (formerly Boston Pattern): V1 comprises a contiguous map spanning both the contralateral and ipsilateral visual field. In contrast to the 'Interleaved (Suppressed) Representation', this pattern requires altered geniculostriate connections and demonstrates precortical plasticity.
Contralateral: representing the opposite side of the body or visual field.
Extrastriate cortex: visual cortex beyond V1 and contains many more maps of the visual field.
Interleaved Representation (formerly True Albino Pattern): V1 receives input from opposing visual hemifields, which is organized as interleaved maps from the contralateral and ipsilateral visual hemifield. This pattern is expected, if the LGN projects, despite abnormal input due to enhanced or reduced optic nerve crossing at the chiasm, in an unaltered manner to V1. It therefore indicates conservative geniculostriate connections. Intracortical plasticity is required to resolve a potential sensory conflict, that is, crosstalk of information across opposing hemifields.
Interleaved Suppressed Representation (formerly Midwestern Pattern): geniculostriate projection as for the 'Interleaved Representation', but the ipsilateral visual field fails to activate V1. In conclusion, conservative geniculostriate connections appear complemented by a suppression of the abnormal additional V1 input. As a consequence, hemianopia for the ipsilateral visual hemifield is expected.
Ipsilateral: representing the same side of the body or visual field.
Lateral geniculate nucleus (LGN): a thalamic nucleus that receives retinal ganglion cell (RGC) input from both eyes and projects predominantly to V1.
Optic chiasm: X-shaped connection between the eye and brain where the axons from the nasal but not temporal retina cross.
Plasticity and reorganization: the terms plasticity and reorganization are ubiquitous in studies of visual disorders, but these terms are ill-defined. The most basic definition is signals not observed in control subjects. The neural basis of these terms is likewise vague and the interpretation ranges from changes in synaptic strength to growing new connections, to growing new neurons. These neural changes also vary, in the same order, from being generally accepted to unresolved. The ability for plasticity and reorganization is thought to be different in development versus adults, and hence changes during lifespan.
Retinal ganglion cells (RGCs): are the final stage of retinal processing and their axons project predominantly to the LGN.
Stability: opposite of plasticity and reorganization, features or visual organization and function that remain unaltered in the face of disorders.
Temporal and nasal retina: the retina is vertically divided into two parts: the nasal (nearer to the nose with respect to the location of the fovea) and temporal (nearer to the temple with respect to the location of the fovea) retinae. Temporal and nasal retinae are normally processed in different hemispheres.
V1: the primary visual cortex (also known as striate cortex and area 17) receives LGN input from both eyes, which is organized as interleaved maps of the contralateral visual field.
Visual field map: visual field maps (or retinotopic maps) preserve the spatial layout of the visual field, that is, neighboring locations in the brain process neighboring locations in the visual field. Although the visual field layout is preserved, sizable distortions are present, in particular, more neural resources are devoted to the center of the visual field. Visual information is organized in visual field maps in the retina, LGN, V1, and large parts of the extrastriate cortex.

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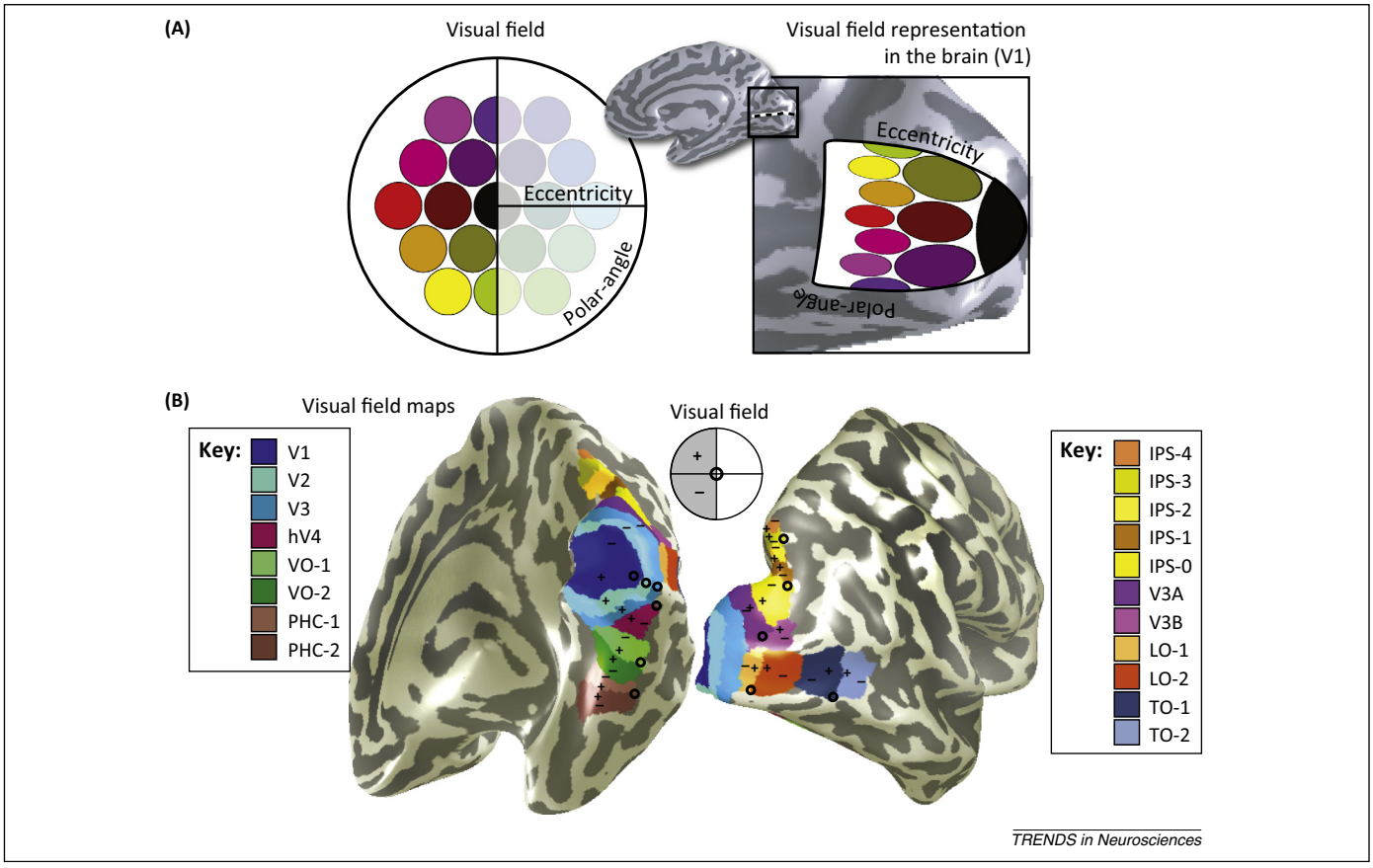

Figure 1. Visual field maps. **(A)** Schematic illustration of the visual field representation in V1. The visual field is shown in the left panel; the center of the visual field is at the black circle and the polar coordinate axes – eccentricity and polar angle – are identified. V1 lies within and around the calcarine sulcus (inset, broken line). The left visual field (left panel) is represented on the right cortical surface (unfolded cortical surface, inset and right panel). This representation uses a mathematical transformation proposed by Schwartz [64] that captures biological measurements. The visual field is inverted, corresponding to the inverted image on the retina. The representation of the central part of the visual field is enlarged compared with more peripheral regions, a phenomenon commonly referred to as cortical magnification. **(B)** A schematic overview is shown of several visual field maps on an unfolded representation of the right hemisphere from a medial–ventral (left) and dorsal–lateral (right) perspective. The right visual field maps represent the left visual field (inset), the upper and lower visual field representations are indicated with a '+' and '−', respectively. This schematic overview is only one interpretation of the visual field mapping data. Others also exist. Only V1, V2, V3, and V3A are firmly established. Abbreviations: V1–4, visual areas 1–4; V3a/b, visual areas 3a and 3b; IPS1–4, visual areas 1–4 in the intraparietal sulcus; LO1/2, lateral occipital areas 1 and 2; TO1/2, temporal occipital areas 1 and 2; VO1/2, ventral occipital areas 1 and 2; PHC1/2, parahippocampal cortex areas 1 and 2.

can reconstruct these visual field maps *in vivo* in humans [8–10].

Even though topographic maps can emerge without a sensory organ, the connections between the sensory organs and the brain are critical in preserving topographic maps. The connection between the eyes and brain are X-shaped ('Chi' in the Greek alphabet), and hence the intersection is known as the optic chiasm. Newton correctly deduced that this connection structure allows information from the two eyes to be combined. At the optic chiasm the fate of axons from the eyes is decided such that axons from both the left and the right eye, which carry information from the right visual hemifield, are guided to the left hemisphere and vice versa. As a result of this partial crossing of the optic nerves at the human chiasm, contralateral visual field maps are found in each hemisphere. Thus, the optic chiasm is a key connection between the eye and brain and essential for the preservation of visual field maps. Acquired damage to the optic chiasm results in blindness in specific parts of the visual field, that is, visual field defects, that are predicted based on the visual field map representation of the connections. Congenital visual pathway abnormalities affecting the optic chiasm, by contrast, do not lead to visual field defects even though normal visual field maps are not preserved.

Here, we discuss the impact of substantial congenital visual pathway abnormalities on visual system organization and perception to highlight the underlying plastic processes. We will focus on specific congenital abnormalities that affect the visual pathways from the eye to the visual cortex. We consider their consequences on the cortical organization and behavior. Finally, we link these human observations to animal literature, models of cortical organization, and our thoughts for future research directions.

Visual pathway abnormalities in humans

Topographic representations of the visual field are a dominant feature of the visual system, which result from the delicate interplay of preprogrammed mechanisms, for example, chemoaffinity gradients, molecular midline markers, spontaneous neural activity waves, and experience-dependent mechanisms during early development [11–15]. Changes to the input of the visual system will therefore challenge, depending on the time of the change, adult or developmental plasticity operating within a

framework of stability and plasticity. Acquired retinal or post-retinal damage of the adult human visual system can cause the loss of the input to the primary visual cortex. This cortical deafferentation initiates processes of adult plasticity of the visual system. The scope of the resulting reorganization in the adult visual system has been much debated [16]. Sizable reorganizations of the visual field maps [17–19] have been called into question [20–22] and it appears that fine-scale changes of the response properties of the primary visual cortex, that is, limited changes in receptive field positions and size and in response amplitudes, are neuronal adaptive mechanisms induced by acquired visual field defects [23,24].

The scope of plasticity triggered by congenital or early developmental visual pathway abnormalities appears different from adult plasticity. This is exemplified by the comparison of the cortical organization in individuals with acquired and congenital foveal dysfunction. The latter is found in individuals with rod achromatopsia. Their vision is, due to congenitally dysfunctional cones, purely rod driven. As the fovea is rod free, the primary visual cortex does not receive foveal input in this condition. In contrast to acquired foveal dysfunction in adults [20], the deafferented cortical foveal representation in rod achromatopsia is not silent, but driven by parafoveal input [25]. In essence, the visual field maps are preserved, but only represent retina covered with functional photoreceptors, that is, rods. This is taken as evidence for sizable cortical remapping of the primary visual cortex in this congenital visual pathway abnormality. The investigation of the organization of the visual system in even more severe congenital visual pathway abnormalities is expected to reveal critical information on the interplay of stability and plasticity during the development of the human visual system, with consequences for both basic research and clinical applications. Such congenitally altered visual pathways are encountered in the absence of functioning eyes (anophthalmia), for sizable misrouting of the optic nerves at the optic chiasm (albinism and achiasma), or for the absence of one of the hemispheres (hemihydranencephaly; Box 1). The respective investigations in these conditions will be detailed in the following sections.

Anophthalmia

A striking congenital visual system malformation is bilateral anophthalmia, that is, the lack of functionally intact eyes, allowing the fate of structure and function of the visual system in the absence of input from the eyes to be studied (Box 1). Functional magnetic resonance imaging (fMRI) investigations, for example, of the cortical language network in anophthalmia, both stimulation related and resting state, demonstrate the integration of the visual cortex into the underlying auditory processing and highlight the scope of functional plasticity, in particular, of the extrastriate cortex [26,27]. Remarkably, at the macroscopic scale posterior interhemispheric connections, that is, comprising the corpus callosum at the splenium, are unaltered [28]. Accordingly, resting state blood–oxygen-level-dependent (BOLD) is highly correlated for the primary visual cortex of both hemispheres [26]. Even the detailed arrangement of callosal connections of the primary visual cortex, that is, the relative positioning of interhemispheric V1 connections for anterior versus posterior and dorsal versus ventral V1 in the splenium, is preserved in anophthalmia [29]. This is reminiscent of the typical visuotopic organization of the interhemispheric V1 connections in healthy individuals, that is, neighboring regions within each V1 are connected to the corresponding regions of the contralateral V1 via neighboring fibers in the splenium [30,31]. This similarity to the normal splenial structure indicates a critical degree of stability of the corticocortical wiring of the early visual system in anophthalmia, which is remarkable in the face of substantial crossmodal plasticity of the occipital cortex in affected individuals. While this degree of stability refers to the interhemispheric connections via the corpus callosum, it is not known whether the intrahemispheric connections, for example, between V1 and V2, also resemble those in healthy individuals. In the case of stable corticocortical connections, it would be expected that, for example, posterior and anterior portions of V1, normally driven by fovea and periphery, respectively, are connected to posterior and anterior portions of V2. Detailed investigations are needed to assess the interplay of stability and plasticity of corticocortical connections in this condition of most severe congenital visual deprivation. As visually driven responses cannot be assessed in these cases, other approaches need to be applied for this purpose. Resting state BOLD connectivity and the reconstruction of visual field maps from these data [32,33] appear to be a viable option for this purpose.

Misrouting of the optic nerves

Conditions with input from the eyes to the visual system that is mediated by substantially altered congenital connections allow for a more direct assessment of the self-organization of the visual cortex and of the scope of plasticity in the visual system. Here, in contrast to anophthalmia, visual stimulation can be used to determine the properties of the visual field maps. Such alterations are found in congenital malformations of the optic chiasm caused by misrouting of the optic nerves. The partial crossing of the optic nerves typical for the human visual system is enhanced in albinism and virtually absent in achiasma (Box 1). As a result, the visual cortex receives, in either case, input not only from the contralateral but also from the ipsilateral visual field. In albinism, this is due to an abnormal crossing of the fibers from the temporal retina (Box 2). In achiasma, this is due to absent crossing of the fibers from the nasal retina. Although the cause of the abnormal input to the visual cortex differs in both conditions, being due to either enhanced or reduced crossing at the optic chiasm, the challenge to the visual cortex is very similar, that is, the accommodation of information from the ipsilateral visual field in addition to the normal input from the contralateral visual field.

The macroscopic cortical visual field representations in albinism and achiasma were recently reconstructed using fMRI [34–38]. In all cases maps of the visual field were found, which deviated significantly from those of controls (Figure 2). Opposing hemifields are not represented in opposite hemispheres, but as maps that are superimposed onto each other. In this cortical overlay of maps, the

Box 1. Congenital visual pathway abnormalities in humans

(i) **Anophthalmia**/microphthalmia is a rare condition (combined birth prevalence: up to 30 per 100 000 cases) associated with an absence and reduction of eye size in the orbit, respectively, while some normal adnexal elements and eyelids are usually present [65]. Both genetic and environmental causes have been identified and in one-third of the cases it is part of a syndrome [66]. Several genes were identified in relation to anophthalmia, most prominently SOX2 [67]. In monocular anophthalmia/severe microphthalmia, the lateralization of the optic nerve projections of the fellow eye was reported to be normal [68], which confirms a partial decussation at the optic chiasm in these cases.

(ii) **Albinism** is an inherited (18 genes identified [69]), rare (1:17 000), and variable hypopigmentation of the eyes (ocular albinism) or eyes, skin, and hair (oculocutaneous albinism) associated with various ocular symptoms of variable extent, that is, fundus and iris hypopigmentation, foveal hypoplasia, enhanced optic nerve crossing, strabismus, nystagmus, reduced visual acuity, and reduced binocular vision [Creel, D.J. (2014) Visual and auditory anomalies associated with albinism. *Webvision* (http://webvision.med.utah.edu/book/electrophysiology/visual-and-auditory-anomalies-associated-with-albinism/)]. Here retinal ganglion cell axons that erroneously cross at the optic chiasm extend, depending on the pigmentation deficit [70], between 2 degrees and 15 degrees (mean of 8 degrees [71,72]) into the temporal retina. This projection abnormality is considered to be a pathognomonic sign of albinism and its detection with visual evoked potentials (VEPs) has been established as a reliable tool to aid the diagnosis of albinism, especially for mild hypopigmentation (Figure I). Studies confirming the absence of misrouting in carriers of ocular albinism (OA) and of oculocutaneous albinism type IA (OCA1A) [73,74], and in primary ciliary dyskinesia with and without inverted body symmetry (situs inversus) [75], demonstrate the high specificity of the detection of albinism with the misrouting VEP paradigm. However, two exceptions with misrouting in the absence of any pigment deficit must be noted: (i) congenital stationary night blindness (CSNB) can be associated with optic nerve misrouting [76,77]; and (ii) foveal hypoplasia, optic nerve decussation defects, and anterior segment dysgenesis (FHONDA) has recently been attributed to mutations of a glutamate channel coding gene (SLC38A8) [78–80]. The signaling pathway that leads to optic nerve misrouting in these cases and its relation to the mechanisms underlying misrouting in albinism remains to be elucidated [81].

(iii) **Achiasma** (non-decussating retinal-fugal fiber syndrome [45,46]) is a very rare syndrome (<50 cases published since its initial description in [36,37,39,42,45,47,82–91]) with, often isolated, congenital absence or hypoplasia of the optic chiasm leading to absent or reduced crossing of the axons from the nasal retina. It is typically characterized by the combination of see-saw nystagmus, positive misrouting VEP or fMRI indicating ipsilateral projection, and MRI evidence of chiasm hypoplasia. Other typical ocular symptoms are strabismus, reduced visual acuity, and reduced binocular and stereo vision. A genetic cause is suspected from reports in animal models [92,93] and the underlying mechanisms are unknown.

(iv) **Hemihydranencephaly** is a very rare syndrome (<15 cases published) characterized by a complete or near-complete unilateral loss of the cerebral cortex. The hemispheric loss occurs during prenatal development, presumably after neural migration and before synaptogenesis. The underlying mechanisms are unknown but vascular insult is a primary suspect [94]. Motor, cognitive, and language functions are often preserved with good or partially good performances. Vision can extend ipsilateral relative to the remaining hemisphere. The bilateral visual field, although restricted, indicates a rewiring of the visual pathways [42–44].

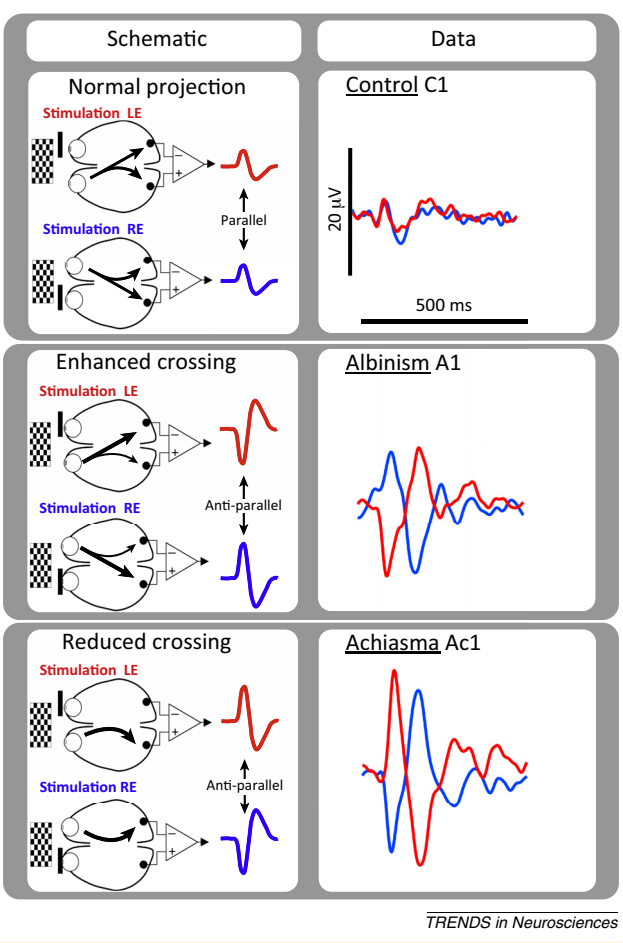

Figure I. Misrouting visual evoked potential (VEP) paradigm (after [45,95]; cross-validated with functional magnetic resonance imaging (fMRI) [36,37,96,97]). Left panels: Schematic. Upon left or right eye stimulation interhemispheric VEP differences are determined (schematically depicted by differential amplifier symbol). While the difference traces for left and right eye stimulation are similar in controls, they are inverted in their polarity in albinism and achiasma. Albinism and achiasma can be differentiated due to VEP dominance on the hemisphere contralateral and ipsilateral to the stimulated eye, respectively. Right panels: Examples of interhemispheric activation differences. Upon stimulation of either eye, parallel difference traces were obtained for a control (C1) and anti-parallel traces for an individual with albinism (A1) and another with achiasma (Ac1).

responses in the same cortical region are elicited by stimulation in the contralateral and ipsilateral visual hemifield. The overlaid representations are evident both in albinism (nine subjects [34,35]) and in achiasma (five subjects [36–39]). Furthermore, we demonstrated for achiasma that, consistent with the superimposed representation of the hemifields, each cortical location has two population receptive fields in each hemifield that are mirrored across the vertical meridian [36]. The population receptive field sizes within each hemifield are within the normal range. Currently, there are no comparable measurements for albinism, although we assume similar population receptive field characteristics due to the superimposed maps. In both albinism and achiasma, visual field maps can be detected similarly to healthy subjects leading to the identification of a number of visual areas (V1, V2, V3, hV4, V3ab, VO1, VO2, PHC1, PHC2 [35]; Figure 1). These investigations demonstrated that the overlaid representation of opposing visual

Box 2. Developmental mechanisms underlying chiasm malformations

Different molecular mechanisms shape the development of the optic chiasm. They promote (i) crossed or (ii) uncrossed projections, or (iii) the general patterning of the optic chiasm. While the mechanisms underlying the reduced optic nerve crossing in human achiasma are unclear, animal studies suggest mechanisms that lead to enhanced crossing in albinism. These studies demonstrated the relevance of EphB1 expression, regulated by the transcription factor Zic2 [98,99], for the ipsilateral projection at the optic chiasm. Growth cones of retinal axons that are expressing EphB1 are repelled by ephrin-B2 expressing glia at the optic chiasm midline, as demonstrated in EphB1$^{-/-}$ mice [100]. Accordingly, during human embryogenesis EphB1 is expressed in the ganglion cells of the temporal retina, which is projecting ipsilaterally [101]. In animal models of albinism, the expression of the transcription factor Zic2 [102] and consequently EphB1 [103] is reduced which corresponds to the enhanced crossing of the optic nerves at the chiasm in albinism. The relation of these changes to the pigmentation defect in albinism, that is, the reduction of ocular or oculocutaneous melanin levels, is currently under investigation. The delayed neurogenesis in albinism might lead to a reduction of Zic2 expressing ganglion cells in the temporal retina [104,105]. The delaying effect of hypopigmentation on retinal neurogenesis is likely to be mediated through the reduction of retinal levels of the early melanin precursor L-DOPA in albinism [106,107]. Finally, it should be noted that it is at present uncertain, to which extent the above mechanisms actually translate to the development of the human optic chiasm, as it differs distinctly in its architecture from that of the relevant animal models [67].

hemifields in V1 is propagated into the extrastriate cortex even as far as to the visual field map clusters of the ventral occipital (VO) and the parahippocampal cortex (PHC) [35,37], that is, areas involved in high level processing of colors, scenes, and objects.

The macroscopic geniculocortical and corticocortical connections were reconstructed using diffusion tensor imaging (DTI) and tractography in achiasma [36,37]. Measurements of the diffusion properties and sizes of the fiber bundles are within the normal range. Thus, there is no evidence at the macroscopic scale for a reorganization of the visual pathways beyond the optic chiasm. No comparable measurements are available for albinism, although we hypothesize that there too the macroscopic connectivity of the visual pathways beyond the optic chiasm is preserved. The MRI-based assessment of the cortical morphometry in albinism in large subject cohorts (no comparable analyses are available for achiasma) revealed subtle changes of the thickness and convolution of the visual cortex. These changes are more likely to be related to the foveal hypoplasia and visual acuity reduction in albinism [40,41] than to the misrouting of the optic nerves. This again suggests that the abnormal representation of the visual fields does not induce gross structural changes in the visual cortex.

Hemihydranencephaly

Hemihydranencephaly is an extremely unusual disorder characterized by a complete or near-complete unilateral absence of the cerebral cortex (Box 1). Behaviorally, there is a variable degree by which the visual field extends ipsilateral to the affected hemisphere, indicating a rewiring of the visual pathways [42–44]. Visual field maps were reconstructed for an individual who lost large parts of the right hemisphere during embryonic development. She therefore lacked an optic chiasm, but still retained largely bilateral visual fields [42]. This condition was associated with microphthalmia of the right eye and thus resembled the condition achiasma described earlier, as the left optic nerve projects entirely ipsilateral, that is, to the left hemisphere. Remarkably, the visual field mapping in the dorsal portions of the early visual cortex largely corresponds to that described earlier for achiasma, that is, overlaid representations. By contrast, for ventral portions of the early visual cortex, islands of non-overlapping maps of the upper portions of the opposing hemifields were observed, which might be related to circumscribed defects in the upper visual hemifield field of that individual, as discussed later.

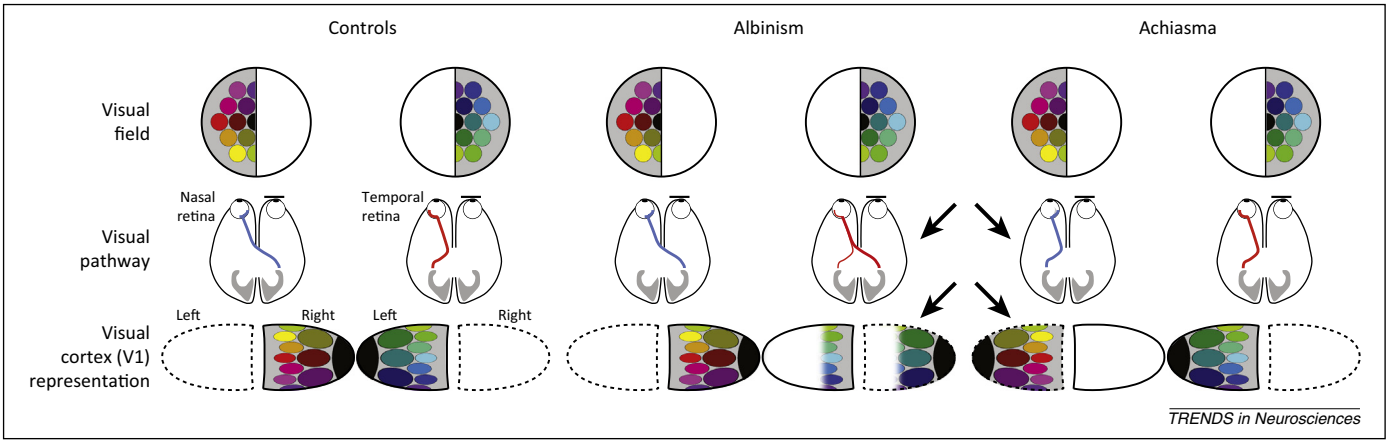

Figure 2. Schematic V1 visual pathways and visual field maps in controls, albinism (enhanced optic nerve crossing at the optic chiasm), and achiasma (reduced optic nerve crossing at the optic chiasm). The top row depicts the left and right visual fields, respectively. The middle row depicts the retina–geniculate–V1 visual pathways for the left eye only. In controls, the nasal retina (blue) projects to the contralateral hemisphere, whereas the temporal retina (red) projects to the ipsilateral hemisphere. The atypical pathways in albinism and achiasma are indicated with an arrow. In albinism, parts of the temporal retina (red) project to the contralateral hemisphere, whereas in achiasma the nasal retina (blue) projects to the ipsilateral hemisphere. The bottom row depicts the visual field maps for left and right V1. In controls, the left and right visual fields are represented in right and left V1, respectively. In albinism, central parts of the right visual field are represented in the right hemisphere, and in achiasma the left visual field is represented in the left hemisphere. Macroscopic imaging with functional magnetic resonance imaging (fMRI) demonstrated that these abnormal cortical representations of the ipsilateral visual hemifield (arrows) are arranged as an overlay of mirror symmetrical visual field positions onto the normal representations of the contralateral visual hemifield.

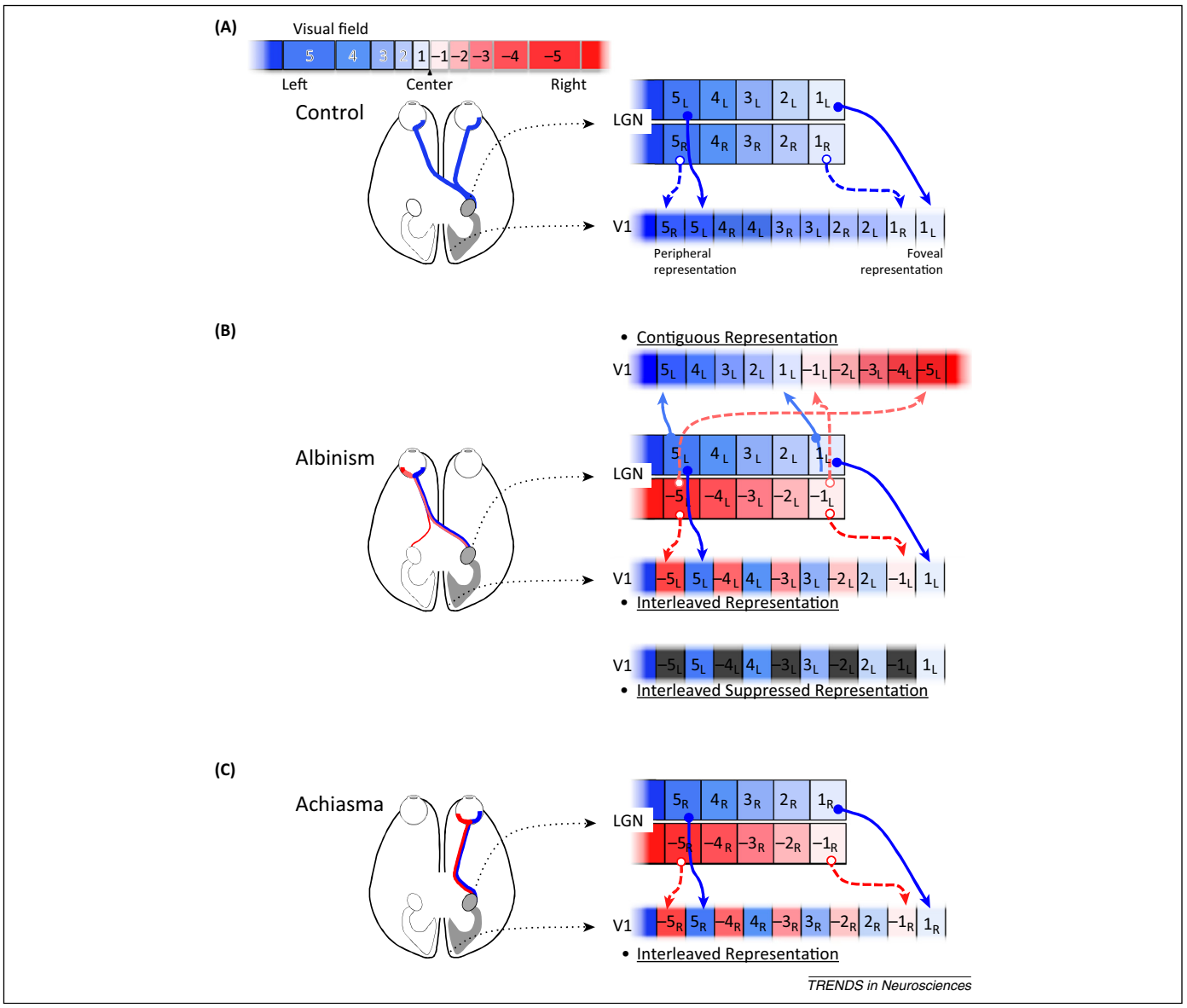

Figure 3. Schematic of visual field representations in the visual cortex in **(A)** control, **(B)** albinism, and **(C)** achiasma as inferred from investigations at the mesoscopic and microscopic scale. (A) Control. The binocular input to the right lateral geniculate nucleus (LGN) is organized in retinotopic maps of the left visual field (color coded blue; positive numbers) that are separate for each eye (fields with positive numbers, subscript indicates L – left, R – right eye input; the LGN is schematized as only two LGN layers with input from either eye). The geniculostriate projection (unbroken lines for left, broken lines for right eye input) results in interleaved registered retinotopic representations of the two eyes in V1. (B) Albinism. For the central visual field, the right LGN receives monocular input from the nasal (i.e., left hemifield, color coded blue) and the temporal hemiretina (i.e., right hemifield, color coded red) of the contralateral, that is, left, eye (indicated by the subscript L). Consequently, there is in addition to the normal input from the contralateral visual field (positive numbers) input from the ipsilateral visual field (negative numbers). Three different projections from the LGN to V1 were inferred from animal models of albinism: **'Contiguous Representation'** (former 'Boston Pattern'; geniculostriate projection depicted superior to the LGN schematic) requires a reordering of the geniculostriate projection (note the inversion of the geniculostriate projection for the additional input of the ipsilateral hemifield, i.e., broken light red lines; unbroken blue lines indicate the projection of the normal input of the contralateral hemifield). **'Interleaved Representation'** (former 'True Albino Pattern'; geniculostriate projection depicted below the LGN schematic) indicates geniculostriate projections that are equivalent to those found in controls, although they operate on partially abnormal input, that is, the representation of the ipsilateral visual field (broken red lines). This cortical organization therefore indicates the conservation of the normal geniculostriate projection scheme despite abnormal LGN input. It is supported by the cortical data obtained in non-human and human primates with albinism. The same conservative geniculostriate projection is inferred for the **'Interleaved Suppressed Representation'** (former 'Midwestern Pattern'; cortical organization depicted below Interleaved Representation), except that the abnormal representation of the ipsilateral visual field is suppressed (indicated by dark gray fields with negative numbers). A consequence is hemianopia for the ipsilateral visual hemifield. (C) Achiasma. The right LGN receives monocular input from the nasal and from the temporal hemiretina of the ipsilateral, that is, right, eye (indicated by the subscript R). Consequently, there is in addition to the normal input from the contralateral visual field (blue fields with positive numbers) input from the ipsilateral visual field (red fields with negative numbers). Data on the resulting V1 representation are only available for achiasma in humans; these macroscopic imaging data support the 'Interleaved Representation' in V1, which is also found in primates with albinism. Color coding of visual field/visual field representations: blue and red shading indicate left and right hemifields, respectively, bright and dark indicate center and periphery, respectively.

Behavioral consequences of congenital malformations of the optic chiasm

Because maps are ubiquitous in the human brain, they appear as a requirement for normal perception and behavior. Yet, the conditions albinism and achiasma, with disrupted normal visual field maps, are associated only with some degree of visual impairment. Specifically, visual acuity and steady fixation are compromised to variable degrees and binocular visual function, including binocular alignment and stereo vision, is largely absent. Some of these impairments are related to altered ocular development, in particular in albinism, where foveal hypoplasia

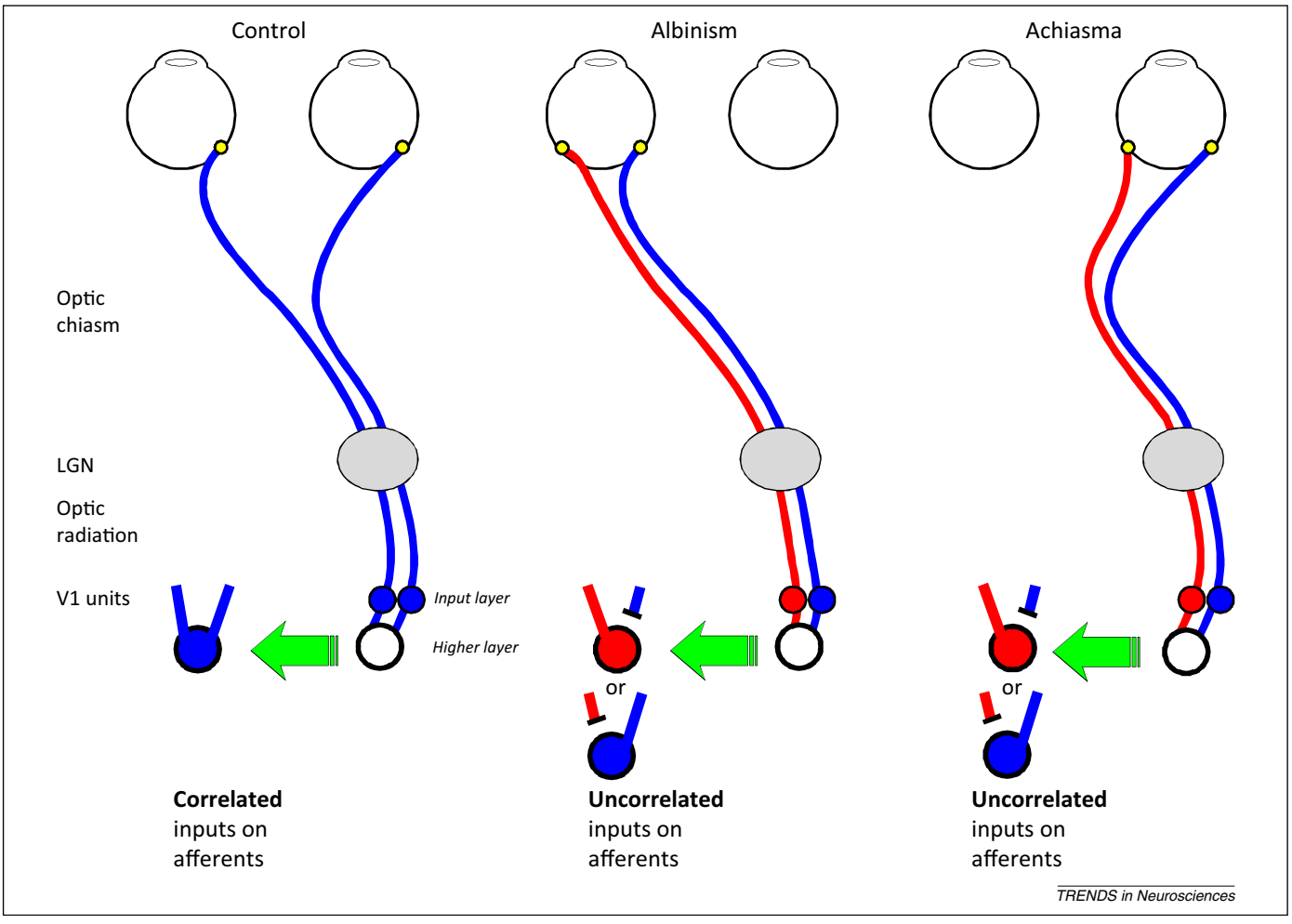

Figure 4. Illustration of hypothetical changes to the cortical microcircuitry in V1 in albinism and achiasma. The schematic of the retinogeniculostriate projection demonstrates the convergence of information from both eyes or hemiretinae onto V1 units of the right hemisphere. In the control, these units receive binocular information from corresponding locations in the contralateral, that is, left, visual field (color coded blue), which results in highly temporally correlated input. By contrast, in albinism and achiasma they receive monocular information from the contralateral, that is, left, and ipsilateral, that is, right (color coded red), visual field. The much higher temporal correlation of inputs in the first case is expected, via classical Hebb-like learning mechanisms, to yield binocular V1 units in the control, but not in albinism or achiasma. This way, experience-driven plasticity would serve to resolve the potential sensory conflict in V1 (extended after [108]).

and iris translucency are expected to cause reduced visual acuity. Others, such as stereoblindness, are a likely consequence of disturbed communication between the eyes due to the misrouting of the optic nerves. Remarkably, it appears that the disruption of the normal visual field maps by misrouting in human albinism and achiasma does leave major aspects of visual processing virtually intact. Qualitatively, this is evident from the observation that affected individuals make effective use of their vision in daily life, including sport activities and reading. This applies particularly to achiasma, while some restrictions apply to albinism, but these are more likely due to photophobia and retinal maldevelopment than to the visual pathway abnormalities [36,38,42,45–48]. For hemihydranencephaly, few reports detail the visual consequences. The most striking findings concern diverse observations of the eye ipsilateral to the lesioned hemisphere, which was microphthalmic [42], amblyopic [43], or relatively normal, as assessed by visual evoked potentials (VEPs) [44]. The cause and timing of the injury leading to hemihydranencephaly may be more diverse than albinism and achiasma, thus behavioral consequences may likewise vary. However, the reports available suggest relatively normal visual perception for the abnormal representation with slightly decreased to normal acuity but with visual field restrictions [42–44].

Recent investigations in albinism and achiasma give a quantitative account of the integrity of visual function in the face of abnormal input to the visual cortex. They focused on two fundamental questions. First, whether visual perception for the abnormal representation, that is, of the ipsilateral visual field is equivalent to that for the normal representation, that is, of the contralateral visual field. This was addressed by comparing the detection thresholds for light spots in the two visual hemifields using standardized perimetric procedures for ophthalmological diagnostics. This way, similar visual field sensitivities were demonstrated for both hemifields (albinism [49], achiasma [36]). These measurements highlight that both the representation of the contralateral and of the ipsilateral hemifield are made available for visual perception, which contrasts with reports of hemianopia for the ipsilateral visual hemifield in some animal models of albinism [50,51] (Figure 3). Furthermore, more specific measurements of visual function in humans indicate that major characteristics of pattern vision are intact for both representations (albinism [52], achiasma [38]), including

adaptive mechanisms as demonstrated by the presence of the tilt after-effect (albinism, psychophysics [53]; achiasma, fMRI [54]).

The second fundamental question addresses whether in albinism and achiasma perception is independent in opposing hemifields. Because the representations of the hemifields are cortically overlaid, information from mirror symmetrical visual field positions with respect to the vertical meridian is represented in close cortical vicinity (Figure 2B,C). As detailed above, at the fMRI resolution each cortical location has two receptive fields, one in each hemifield, mirrored across the vertical meridian. Such bilateral receptive fields in fMRI, that is, responses due to summed neural activity, could arise either from spatially intermixed neurons with either ipsilateral or contralateral receptive fields or from single neurons with bilateral receptive fields [55] due to communication normally occurring between neighboring neural populations. Such bilateral receptive field neurons would lead to crosstalk of information between hemifields, aspects of which may cause apparent interferences with perceptual tasks. This was investigated by determining the transfer of adaptation to oriented lines (tilt after-effect) from one hemifield to the other. Remarkably, no such adaptation transfer was found neither in behavioral nor fMRI paradigms (albinism, psychophysics [53]; achiasma, fMRI [54]). This suggests at the mesoscopic scale independent interleaved representation of both hemifields. Such independent representations are fundamental for independent visual processing and for the absence of a confusion of left and right in the visual perception of affected individuals (albinism [53], achiasma [36,38]).

Animal models, cortical fine structure, and classification schemes

In humans with congenital chiasmatic abnormalities, the cortical visual field maps from opposing hemifields macroscopically appear to be arranged as overlays. This prompts the question of the developmental mechanisms that cause this specific pattern. Knowledge about the fine-grain structure of the visual cortex is expected to shed light onto this question. Mesoscopic imaging is required for this purpose. While high-resolution fMRI investigations of the visual cortex are currently pioneered in human achiasma [56], previous investigations in animal models of albinism applied invasive electrophysiological and histological techniques that allowed for a detailed description of the visual cortex. Remarkably, they revealed that in the presence of enhanced crossing of the optic nerves at the chiasm, the visual cortex can be organized not only in one, but in three different ways (reviewed in [34,57]). Historically, these three critically different cortical mapping schemes in V1 were termed 'Boston Pattern', 'Midwestern Pattern', and 'True Albino Pattern', but a more descriptive naming scheme is appropriate. This is, for better generalizability, required to be independent of the disease underlying the projection abnormality as albinism is not the only cause of chiasmatic abnormalities. Therefore, we here propose a novel nomenclature intended for future use, that is, 'Contiguous Representation', 'Interleaved Suppressed Representation', and 'Interleaved Representation' in V1, respectively, as detailed in the Glossary and schematized in Figure 3.

If the normal geniculostriate projection (Figure 3A) is preserved in the presence of abnormal lateral geniculate nucleus (LGN) input in albinism (Figure 3B) or achiasma (Figure 3C), an 'Interleaved Representation' in V1 is expected, as detailed in Figure 3. This has in fact been demonstrated directly via single cell recordings from V1 of cats [58,59] and a non-human primate with albinism [60]. These investigations showed that representations of mirror symmetrical locations in opposing hemifields alternate and thus reflect the presence of hemifield dominance columns [60], instead of ocular dominance columns (Figure 3A). As this V1 organization is the natural consequence of unaltered geniculostriate projections in the presence of the altered input to the LGN, an 'Interleaved Representation' in V1 is taken as evidence for a lack of large-scale developmental plasticity in the geniculostriate projection. It appears therefore that conventional developmental mechanisms using chemoaffinity gradients for map formation [61,62] shape the geniculostriate projection even in the presence of abnormal input to the LGN. Decisively, for mapping procedures with a resolution that does not allow the differentiation of the columnar organization, that is, with common fMRI providing macroscopic imaging, the above mapping will appear as overlaid maps of opposing hemifields, as described for human albinism and achiasma. Consequently, it is expected that the overlays that were observed in human albinism and achiasma will separate when inspected at higher resolution to form interleaved hemifield dominance domains, as has previously been observed in the respective non-human primate counterpart [60]. This is currently being investigated with high-resolution fMRI as reflected by a recent conference contribution, which suggests the existence of hemifield dominance columns in human achiasma [56]. Current evidence therefore suggests that the 'Interleaved Representation' is established in V1 in human albinism and achiasma. This cortical organization scheme points to a lack of large-scale developmental plasticity of the human geniculostriate connections. It should be noted that these results are also in agreement, although partial, with those of the unusual case of an individual with only one hemisphere and monocular microphthalmia [42], as described earlier. Even here overlaid representations dominated V1, which is indicative of the 'Interleaved Representation'. In addition, in ventral portions of the visual cortex islands of non-overlapping maps were observed. These might be related to circumscribed visual field defects in the upper hemifield of that individual or indicate the 'Contiguous Representation' in this part of the visual cortex. It should be noted that hemihydranencephaly may theoretically differ from both achiasma and albinism because both eyes and hemifields can converge onto one hemisphere [43]. In this case, therefore, developmental mechanisms should be challenged to accommodate information for the entire visual field from both eyes within a single hemisphere.

In conclusion, while in non-primate animal models of chiasmatic abnormalities several organization schemes are available, in human and non-human primates the

Box 3. Outstanding questions

- **What is the microscopic and mesoscopic organization structure of striate and extrastriate projection targets?**
  The knowledge of the fine structure of topographic maps in congenital visual pathway abnormalities will provide profound insights into the mechanisms of human visual system development and plasticity. Currently, it is presumed that in congenital malformations of the human chiasm, V1 ocular dominance columns are reassigned to hemifield dominance columns to incorporate the additional information from the ipsilateral visual field. This mechanism may not suffice in hemihydranencephaly where both eyes and hemifields may converge to one hemisphere. Furthermore, this mechanism is not available in the extrastriate visual cortex due to the absence of ocular dominance columns, which prompts the plasticity of extrastriate visual areas. These questions also extend to anophthalmia: if the macroscopic organization is preserved, will the microscopic and mesoscopic organization structure also survive?
- **What are the consequences of congenital visual pathway abnormalities on perception?**
  The abnormal mapping in albinism, achiasma, and hemihydranencephaly leaves a number of basic aspects of visual function unaffected. However, specifically, perceptual processes requiring the interaction of separated neural networks might be apt to side effects of abnormal visual field representations. Detailed combined physiological and psychophysical investigations are expected to further our understanding of the origin, plasticity, and functionality of such interactions. One focus is the organization of feed-forward, horizontal, and feedback circuits within the visual system, which can be addressed by assessing the effects of lateral interactions, adaptation, and attention on visual processing in the presence of visual pathway abnormalities. Another focus is the nature of sensory integration, which can be addressed by assessing potential conflicts during crossmodal and visuomotor integration as this requires the interaction of normal nonvisual and abnormal visual mappings.
- **Therapy and clinical relevance**
  Congenital visual pathway abnormalities are a valuable general model of the scope and the dynamics of developmental plasticity in the human visual system. Their investigation is therefore expected to be of general assistance for the optimization of recent rehabilitation and vision restoration strategies in congenital and acquired blindness [109–112]. More specifically, the relation of visual pathway abnormalities and the clinical symptoms might open therapeutic initiatives directly in the affected individuals. A potentially rewarding target is the question of the origin of nystagmus. While congenital foveal dysfunction is commonly believed to be a cause of the infantile nystagmus syndrome, this might not be the exclusive cause in chiasmatic abnormalities. For example, nystagmus is evident in achiasma in the absence of foveal maldevelopment and in animal models of albinism without a fovea. The miswiring of the visual system might result in nystagmus [113]. Consequently, the investigation of subcortical components of the visual system in chiasmatic abnormalities might shed light on this question.

'Interleaved Representation' in V1 appears to be prevailing and might even be the sole organization pattern. This suggests a lack of plasticity at the level of the geniculostriate projections in primates and the question is prompted whether developmental plasticity at the level of the visual cortex provides sufficient scope to support visual processing of the extra input from the ipsilateral visual field. Changes in the development of the intracortical circuitry that normally subserves the integration of binocular information [15,63] are required to eliminate crosstalk of information from one visual hemifield to the other, as proposed in Figure 4. Further, the finding that the abnormal representation is propagated to advanced stages of the ventral processing stream in both albinism and achiasma [35], again as superimposed maps, indicates largely preserved corticocortical connections. In addition, the abnormal input from the ipsilateral visual field is, in albinism, propagated to the dorsal processing stream, although its exact mapping is not clear yet [52]. This puts a particular challenge to integrative processing, such as sensory and visuomotor integration, in individuals with chiasmic malformations.

Concluding remarks

Congenital visual pathway abnormalities, such as malformations of the optic chiasm, have profound effects on the structure and function of the visual system. They provide unique insight into the interplay of stability and plasticity in the human visual system and are therefore a powerful model both for furthering basic understanding of developmental mechanisms in the human brain and for estimating the efficacy of therapeutic interventions. Most of the relevant research to date has focused on the primary visual cortex, where changes to the intracortical circuitry appear to be of vital importance to making abnormal visual field representations available for visual perception. In the future, the organization of subcortical and higher cortical projection targets in the visual pathway and their relation to visual function will be rewarding targets for research (Box 3). The former might help to understand the origin of oculomotor disorders, the latter to understand the mechanisms of development and plasticity in sensory and visuomotor integration.

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