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Disentangling How the Brain is "Wired" in Cortical (Cerebral) Visual Impairment

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Cortical (cerebral) visual impairment (CVI) results from perinatal injury to visual processing structures and pathways of the brain and is the most common cause of severe visual impairment or blindness in children in developed countries. Children with CVI display a wide range of visual deficits including decreased visual acuity, impaired visual field function, as well as impairments in higher-order visual processing and attention. Together, these visual impairments can dramatically influence a child's development and well-being. Given the complex neurologic underpinnings of this condition, CVI is often undiagnosed by eye care practitioners. Furthermore, the neurophysiological basis of CVI in relation to observed visual processing deficits remains poorly understood. Here, we present some of the challenges associated with the clinical assessment and management of individuals with CVI. We discuss how advances in brain imaging are likely to help uncover the underlying neurophysiology of this condition. In particular, we demonstrate how structural and functional neuroimaging approaches can help gain insight into abnormalities of white matter connectivity and cortical activation patterns, respectively. Establishing a connection between how changes within the brain relate to visual impairments in CVI will be important for developing effective rehabilitative and education strategies for individuals living with this condition.
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Introduction

Brain-related visual impairment remains a highly challenging condition to assess and manage. In a fully developed brain, acquired bilateral injury to visual processing areas (primarily the occipital lobes) results in a condition referred to as "cortical blindness."[1] It was historically described in soldiers who exhibited profound vision loss after suffering traumatic gunshot wounds to posterior portions of the head, despite having normal eye function.[2]

More recently, there has been a growing concern regarding children born with profound visual impairment because of brain damage occurring in early development. The visual deficits observed are much more heterogeneous and difficult to characterize than in adults with acquired brain injury. Moreover, because these children tend to have a complex underlying neurologic history, their visual impairments are often incorrectly characterized, or even remained undiagnosed by eye care providers.[3]

To differentiate early-onset damage to the developing visual system (as compared to acquired brain injury in the adult brain), the term "cortical visual impairment" was coined because these children were rarely profoundly blind.[4] Nevertheless, as the diversity of children with brain-based visual impairment was more carefully assessed and appreciated, it became evident that many deficits associated with higher-order visual processing and visually guided motor impairments were also present. Thus, the term "cerebral" was substituted in place of "cortical" to more globally encompass these higher-order

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visual processing deficits and their presumed association with damaged areas of the visual processing pathway (eg, subcortical structures including the thalamus, optic radiations, and other white matter pathways, as well as higher-order associative processing areas of the cortex) (see also Refs. 5 and 6 for further discussion). Currently, the definition of cortical or cerebral visual impairment (CVI) has evolved to encompass a significant deficit in visual function associated with damage to retrochiasmatic visual pathways and cerebral structures in the absence of major ocular disease, oculomotor disorder, or uncorrected refractive error. In other words, it is a condition characterized by visual deficits that cannot be explained by ocular abnormalities alone.[7–11]

It should also be noted that the diagnosis of CVI is different to that of "delayed visual maturation." In this latter condition, an infant will typically have a normal perinatal history and developmental milestones with no ophthalmologic disorders, yet appear visually unresponsive in early infancy. Visual acuity may be markedly reduced when first tested, but rapidly improves to normal, or near-normal levels within weeks or months.[12,13]

Depending on the location and extent of the damage, children with CVI often present with a broad range and combination of visual dysfunctions such as decreased visual acuity, visual field deficits, and also impairments in oculomotor, visuomotor, and cognitive visual processing.[7,14–16] The variability in the location and extent of brain injury across individuals makes the prediction of visual functional outcomes and recovery in patients with CVI particularly challenging.[17] Furthermore, because of widespread neuronal damage, other sensory deficits (eg, hearing) may often be present in addition to cognitive delays, motor disabilities (such as cerebral palsy), and neurologic conditions (such as seizures).[10,18] In clinical institution-based and population-based studies of CVI, cerebral palsy is frequently reported as an associated comorbidity (26%,[10] 59%,[19] and 73%[20]). Cerebral palsy in the presence of cognitive impairment has also been reported in conjunction with CVI (37%[11] and 97%[21]). Taken together, these associated comorbidities make the diagnosis and characterization of the underlying visual impairment even more challenging.

Although children with CVI typically have some degree of residual visual function, the effect of CVI is often very detrimental on a child's development, learning, mobility, and overall quality of life.[22,23] In some cases, visual function may improve during early development owing to either delayed maturation of less damaged pathways or from neuroplastic changes in the brain's "re-wiring."[9-11,24] Nonetheless, the relationship between observed visual deficits and the underlying structural and functional brain changes resulting from damage to the visual processing system remains poorly understood in CVI.[25] Specifically, it remains unknown how the maldevelopment of key visual pathways relates to the organization of the visual system as a whole, and further, how structural and functional brain changes relate to visual impairments observed within the clinical setting and in daily activities. A key advancement needed in this arena is gaining a greater understanding of these alterations in brain connectivity and function in CVI to enhance visual function and capabilities, and even possibly predict developmental trajectories.

Epidemiology of CVI

It is striking to realize that the primary cause of profound visual impairment in children in developed countries is the result of damage and maldevelopment of the brain rather than the eye itself. CVI is a rising significant public health concern and currently the most common cause of severe visual impairment or blindness in the pediatric population.[26,27] For example, a population-based study in the United Kingdom of newly diagnosed children with severe vision loss or blindness found that CVI (48%) was the most common causal disorder compared to damage to the retina (29%) or optic nerve (28%).[28] A similar prevalence of CVI has been reported from other studies of childhood visual impairment or blindness from the Netherlands (25%[21]), New Zealand (30%[19]), and Ireland (45%[29]). In the United States, a study by Kong and coworkers (2012) surveyed schools for the blind and reported that from a total of 3,070 students, the leading cause of blindness was CVI (18%), followed by optic nerve hypoplasia (15%) and retinopathy of prematurity (14%).[30] According to the American Foundation of the Blind, 30%-40% of observed cases of visual impairment in children are associated with CVI.[31] Moreover, current trends suggest that the incidence of CVI is continuing to rise, in large part due to advancements in the delivery of neonatal intensive care. The improved care in turn contributes to greater infant survival from neurologic damage and complications occurring during pregnancy and perinatal period.[27,32]

Causes of CVI in Children

The causes of CVI are numerous although perinatal hypoxic ischemia is the most common culprit, leading to impaired maturation of key visual pathways and structures (a general condition referred to as white matter damage of immaturity). As a result, cell death (ie, necrosis) of myelinated and premyelinated fibers occurs obstructing the normal development of white matter pathways that communicate along the visual processing stream (including the optic radiations) as well as between sensory and motor areas of the brain. At the same time, cortical gray matter and subcortical structures (including the thalamus) are also often affected.[33] Apart from hypoxic injury, other important causes of CVI include infection, metabolic disorders, trauma, and epilepsy (see also Ref. 9 for further discussion).

It is now understood that gestational age at birth (and associated birth weight) is important in determining the consequences of perinatal hypoxia. Thus, in characterizing the nature of the resulting brain injury, it is useful to distinguish between infants who are born prematurely vs those born at term. Indeed, children born prematurely with low birth weight represent a higher risk for developing visual impairment including CVI.[34]

In preterm infants, brain maldevelopment is often associated with periventricular leukomalacia (PVL).[35] This typically involves hemorrhagic necrosis in the periventricular white matter just dorsal and lateral to the external angle of the lateral ventricles.[36] There is characteristic enlargement of the lateral ventricles and focal gliosis of surrounding white matter pathways coursing on to the visual cortex.[16,27] The main factors commonly associated with PVL are an underdeveloped vasculature of the surrounding white matter and impairment of cerebral blood flow regulation, both of which can predispose white matter to ischemic injury in the preterm infant. Crucially, as the tracts of the optic radiations and connections to visual association cortex travel within the periventricular white matter, PVL is often associated with impaired visual processing.[16,27] In infants born at term, perinatal hypoxic ischemia results in hypoxic ischemic encephalopathy (HIE) and is the primary cause leading to CVI in term infants.[19,37] In HIE, areas that are most commonly damaged are deep gray matter, hippocampus, brainstem, and thalamic regions.[38]

Characterization of Visual Deficits

Children with CVI often present with decreased visual acuity ranging from mild to moderate impairment or low vision and even (though more rarely) profound blindness.[14] Visual field defects are frequently present (typically in the lower hemifield),[27,32] and contrast sensitivity may also be reduced.[14] Oculomotor abnormalities are similarly common in children with CVI.[9-11] In a study of 121 children with CVI, oculomotor abnormalities were prevalent including limited fixation (48%), abnormal smooth pursuit (89%), and abnormal saccadic eye movements (44%). Strabismus was present in 73%, along with impaired ocular motility (85%) and nystagmus (54%).[14] However, as noted earlier, these deficits are not sufficient to explain the broad range of visual dysfunctions observed in CVI.

Behavioral characteristics and visual dysfunctions in CVI (first described by Jan and colleagues) are markedly different from children with ocular causes of blindness and visual impairment.[39,40] The profile of behaviors described include variable visual attention and inattention (particularly in unfamiliar or complex environments), supplementing vision with touch, looking away while reaching for objects, close viewing in the absence of refractive errors, objects that are moving are attended better than when static, attraction to colored objects, and light gazing as well as photophobia. There are also observed difficulties in higher-order visuospatial processing leading to substantial functional limitations that affect a child's learning, mobility, and development.[22,23] This broad spectrum of visual deficits makes testing not only difficult but also challenging in terms of developing appropriate and individualized rehabilitative strategies.[8,17]

A practical and useful conceptual framework in characterizing observed deficits in CVI is to incorporate the two-stream hypothesis of visual processing. This hypothesis proposes a functional division of labor between the processing of spatial properties compared with object-related information as a way to describe how the visual system analyzes attributes within a visual scene.[41] Briefly, the dorsal stream projects from the occipital cortex to posterior parietal cortical areas and is responsible for spatial processing and visuomotor control for action. In contrast, the ventral stream projects from occipital cortex to the temporal lobe and is responsible for the identification of objects and their attributes. Based on clinical observations and psychophysical evidence regarding the nature of the visual dysfunctions in CVI, certain investigators have proposed that CVI may be a condition best characterized as a dorsal stream "dysfunction" or "vulnerability" consistent with an impairment in the functioning of the dorsal or spatial visual processing pathway.[42-44] In this view, impairment of dorsal visual stream processing would influence upon an individual's ability to process and interact with complex visual scenes in two-dimensional and three-dimensional space.[7,45] Dorsal pathway dysfunction has been presumed to be the consequence of white matter damage surrounding the lateral ventricles and affecting occipital-parietal brain areas. It is worth noting, however, that despite strong clinical observations and psychophysical evidence, neurophysiological support for this concept remains lacking.

It is important to note that spatial processing deficits are not always observed in individuals with CVI, nor do they occur in isolation from other nonspatial visual processing deficits. At the same time, it remains unclear if there is indeed a strong predilection for spatial processing impairments in CVI, or if there is a bias related to testing methodologies and deficits that are more associated with the nature of assessment or cognitive delays (ie, cognitive issues such as imagery, language, and memory; see Ref. 46 for further discussion) or both. Younger and more visually impaired children typically cannot participate in higher "cognitive" visual tests and thus, ventral pathway functions may be underrepresented in many studies. Indeed, many individuals with CVI also exhibit visual dysfunctions related to object identification including recognizing faces and object shapes.[6,14,46,47] Impairments in object identification would be consistent with the notion of dysfunction along the ventral visual processing pathway. Lastly, as concomitant oculomotor and attentional issues are also often present in individuals with CVI, damage to other areas implicated with ocular movements and attention (eg, frontal areas) may also be involved. Therefore, although damage along key visual processing streams may be associated with observed perceptual deficits, it is important to recognize that the underlying maldevelopment of the brain in CVI appears to be more extensive and complex than previously assumed.

Assessment

Just as it is critical to provide early intervention services for an individual with delayed milestones, it is important to provide vision services early in life for individuals with CVI to maximize the development of visual functioning. If parents are concerned that their child is not responding visually or is not developing typical visual motor skills (such as reaching for an object of interest), then CVI should be part of the differential diagnosis along with more commonly considered ocular causes of visual impairment (eg, uncorrected refractive error, visual field loss,

and ocular health issues) and oculomotor dysfunction (eg, strabismus and nystagmus). This issue is particularly relevant in the cases where the child has a known history of neurologic complications or cognitive delay.

When seeing a patient for a comprehensive functional low-vision evaluation, the eye care practitioner often needs to review reports from many health care providers and specialties (eg, neurology, radiology, occupational and physical therapy, and speech and language) while maintaining coordinated communication with education services. This information has to be synthesized to help guide the examination as well as provide a framework for considering appropriate interventions (eg, corrective glasses, vision therapy, and training strategies), and advocating for vision educator services as part of the individualized family service plan or the individualized educational plan.

The approach to assessing visual function in individuals with CVI often requires significant adaptation to collect reliable data. In this context, no individual is "untestable" or considered too "uncooperative" to be examined.[48] The purpose of the modified vision examination by an appropriately trained pediatric ophthalmologist or optometrist is to assess both *visual function* and *functional vision*. Visual function findings relate to performance measures such visual acuity (detection vs recognition), contrast sensitivity, visual field, color vision, ocular movements, and an assessment of ocular health. Functional vision is an assessment of how an individual uses their vision in daily activities. For example, "is the child visually curious? Will the child only look at someone only after they speak? Does the child respond better to a novel stimulus or to a familiar one?."

Because many of the children seen for evaluation are developmentally delayed and may have numerous behavioral particularities, it is up to the doctor and his or her staff to create an environment in which the patient will be successful. Crucially, the clinician must perform the right test, at the right time, and in the right manner. For example, assessing eye movement function may be performed with a favorite toy before testing visual acuity (for further details regarding examination see Refs. 31, 49, and 50)

The findings of the evaluation, in conjunction with the previously reviewed information and history, should provide the basis upon which the eye care provider can educate the family and participating caregivers. Additional evaluations by these professionals may include community-based functional vision assessment, orientation and mobility assessment, and a learning media assessment with a sensory channel component.[31,51]

The Role of Brain Imaging in CVI

One of the greatest challenges in characterizing the neurophysiological substrate underlying visual dysfunction in CVI is that damage to cerebral structures is highly heterogeneous across individuals in terms of location, as well as timing, extent, and cause. As mentioned previously, early developmental damage to the brain may implicate retrogeniculate visual structures and pathways including the thalamus, optic radiations and other white mater connections, and cortical gray matter. Given this heterogeneity, it has been suggested that developing a subclassification based on anatomic damage could be helpful with regard to diagnostic specificity.[52] In this regard, brain imaging methodologies may be of particular utility to better understand the relationship between brain maldevelopment and visual impairment.[27,53-55] A number of studies have attempted to associate visual impairments observed in individuals with CVI with alterations in brain structure using standard clinical neuroimaging modalities such as ultrasound, computerized tomography (CT), and more recently, magnetic resonance imaging (MRI) and other MRI-based modalities. In this regard, neuroimaging studies can help in 2 important directions. First, brain imaging can accurately define important parameters regarding the nature of the cerebral injury (such as location and extent). Second, there is the possibility of identifying characteristic features that may have prognostic value regarding neurodevelopmental outcome.[54] Again, the relationship between visual dysfunction and cerebral damage in CVI is complex and remains poorly understood.[25] However, as new imaging approaches continue to develop, and with higher sensitivity to detect subtle changes in brain structure and function, we may be in a better position to understand the relationship between the effect of injury and the trajectory of brain development.

A number of studies have attempted to relate functional visual impairments to perinatal brain injury, but with mixed results.[37,56-59] For example, Schenk-Rootlieb et al[60] reviewed the CT scans of 36 individuals with CVI (from a cohort of 49 patients diagnosed with cerebral palsy). Abnormalities of the white matter were detected adjacent to the posterior horns of the lateral ventricles, white matter under the visual cortex, as well as to the visual cortex itself.[60]

Further attempts to characterize structural damage have been carried out with more advanced imaging modalities such as MRI. In contrast to ultrasound and CT, MRI offers greater sensitivity to structural changes in the brain. In a study, Guzzetta et al[57] reviewed findings regarding visual disorders in children with neonatal brain lesions and reported that visual impairment was more consistent with the site and severity of lesions in the case of individuals born premature with PVL than in term born children with HIE. The presence and severity of visual impairment was not always consistent with the severity of HIE. These results suggest that the presence and degree of PVL are important factors in relation to the extent of functional impairment of the individual.[57,61] Serdaroglu et al[62] used structural MRI and reported that the severity of PVL correlated with neurodevelopmental outcomes. Specifically, children with mild PVL had minor motor problems or mild-to-normal functional outcomes, whereas the presence of cortical atrophy and thinning of the corpus callosum were associated with more developmental delays.[62] Cioni et al,[63] also using MRI, attempted to correlate visual functional with neurodevelopmental outcomes in children with PVL aged between 1 and 3 years. Visual outcome measures included acuity, visual field function, and optokinetic nystagmus. Using a multivariate analysis approach, these investigators found that there was a

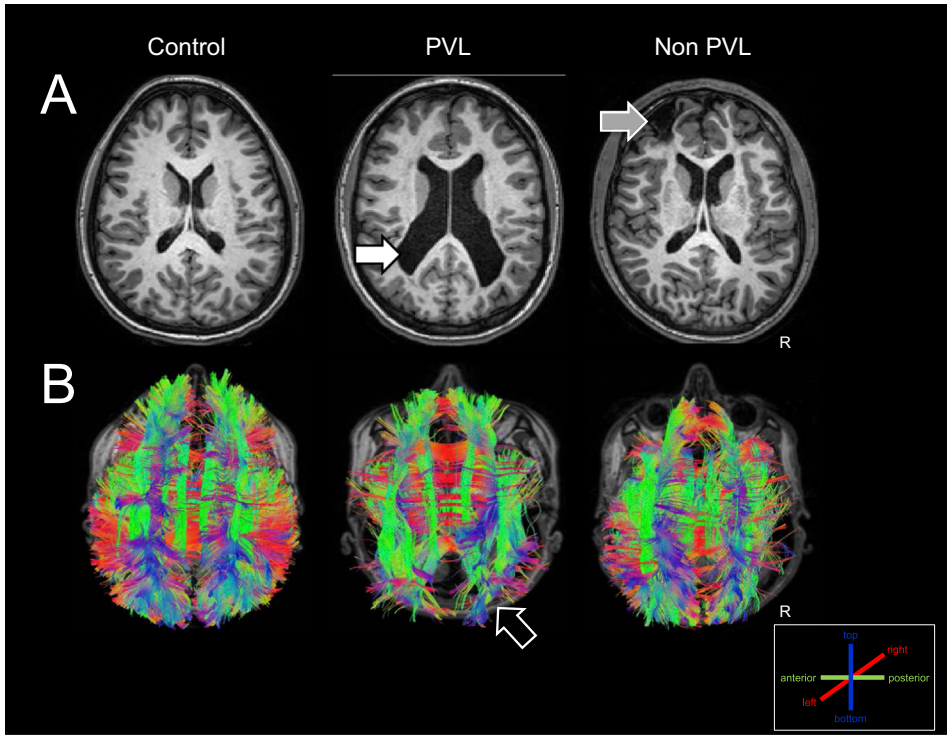

Figure 1 (A) Axial T1-weighted MRI images in a normally sighted control (19-year-old girl; no history of visual dysfunction; left panel) and an individual with CVI born prematurely (16-year-old girl; 20/60 is standard Snellen clinical notation visual acuity; middle panel) and another individual with CVI born at term (19-year-old boy; 20/100 is standard Snellen clinical notation visual acuity; right panel). Note the presence of enlarged lateral ventricles characteristic of periventricular leukomalacia (PVL) (white arrow, middle panel) compared to the control individual. In contrast, the lateral ventricles appear normal in the individual with CVI born at term (right panel). However, areas of focal cortical and white matter damage are apparent (gray arrow). With standard MRI imaging, no further information is provided beyond gross anatomic changes. (B) Corresponding axial view of whole-brain white matter tractography reconstruction in the same individuals revealed with diffusion MRI (HARDI). Note the robust arborization present throughout the brain in the control individual. In contrast, evidence of decreased white matter connections (including the occipital pole; black arrow) is evident in the individual born premature with CVI due to PVL (middle panel). In the individual with CVI born at term (right panel), white matter connectivity appears reduced, but not as dramatic as in the individual with PVL. Color scheme corresponds to fiber orientation plane (green: anterior to posterior, red: left to right, blue: head to feet). White matter fiber tracking and reconstruction was performed using DSI Studio software (http://dsi-studio.labsolver.org/). Both T1-weighted and HARDI images were acquired in the same scanning session. HARDI images were acquired with an 18-min scan time. (Modified with permissiom from Hirsch et al.[77]) (Color version of figure is available online.)

strong association between the degree of visual impairment and the damage observed to optic radiations (as indexed by structural MRI).[63]

These early studies using standard clinical neuroimaging techniques have helped characterize gross changes in cerebral structure in relation to CVI. Additionally, the finer resolution afforded by MRI has allowed for the generation of images with greater detail. However, the underlying microarchitecture of key white matter pathways (such as the optic radiations and cortical-cortical connections) cannot be fully ascertained with standard structural imaging techniques. For this purpose, advances in diffusion-based imaging modalities (ie, diffusion MRI) such as diffusion tensor imaging (DTI) and high angular resolution diffusion-based imaging (HARDI) combined with tractography analysis techniques can be used to reveal the organization and integrity of specific white matter projections. In turn, this analysis can reveal important information as to how the brain is interconnected.[64,65] Briefly, diffusion MRI tracks the movement of water molecules in the brain. The constrained motion of water in association with the orientation of axonal fibers allows for the overall organization of white matter projections to be inferred.[64,65] By employing tractography techniques, the brain can be "virtually dissected" so that key pathways of interest can be reconstructed and individually examined.[66]

In a recent study by Lennartsson et al,[67] diffusion-weighted MRI was performed in a group of individuals with documented visual dysfunction who had white matter damage predominantly in the superior posterior periventricular white matter. It was found that early injury to the optic radiations was associated with characteristic patterns of visual field deficits. The authors of this review have also investigated white matter structure in CVI using HARDI. Although both DTI and HARDI techniques provide information regarding white matter organization, it is becoming increasingly established that HARDI is superior in its ability to delineate the organization of crossing

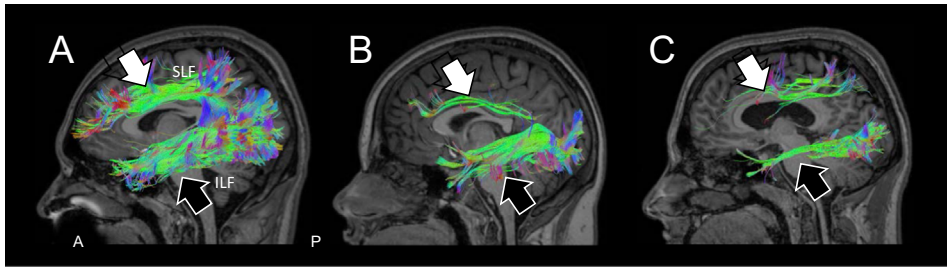

Figure 2 Sagittal view of white matter tractography of the dorsal and ventral visual processing streams is revealed with diffusion MRI (HARDI). "Virtual dissection" allows for the reconstruction of the superior longitudinal (SLF) and inferior longitudinal (ILF) fasciculi (corresponding to the neuroanatomical correlates of the dorsal or spatial and ventral or object visual processing streams, respectively). The fasciculi were reconstructed by seeding the occipital pole. Similar patterns of white matter tractography emerged from both hemispheres in each individual, so reconstruction in only the left hemisphere is shown for simplicity. (A) Reconstruction of the 2 fasciculi in a normally sighted control (18-year-old boy; no history of visual dysfunction). Note the robust appearance of the SLF (white arrow) and ILF (black arrow). (B) Reconstruction of the same 2 fasciculi in an individual with CVI with spatial processing deficits (14-year-old boy; 20/25 is standard Snellen clinical notation visual acuity). Note the dramatic reduction in the structural integrity of the SLF consistent with spatial processing deficits. (C) Reconstruction in a second individual CVI (20-year-old boy; 20/25 is standard Snellen clinical notation visual acuity) with observed deficits in both spatial processing and object recognition. Note the corresponding reduction in structural integrity of both the SLF and the ILF, respectively. Color scheme same as presented in Figure 1. (Modified with permission from Bauer et al.[73]) (Color version of figure is available online.)

fibers, and ultimately the overall microarchitecture of the brain.[65,68,69] In a preliminary study, white matter whole-brain connectivity was characterized using HARDI in individuals with CVI associated with PVL and individuals with CVI born at term (ie, non-PVL). Compared to age-matched and normal controls, it was noted that individuals with CVI and PVL showed a marked reduction in the degree of overall white matter arborization. In comparison, whole-brain connectivity in individuals with CVI but born at term (ie, non-PVL) did not appear as impaired (Fig. 1). These preliminary observations are in line with clinical observations regarding the effect of PVL compared to HIE on visual dysfunctions and other associated sensorimotor and cognitive delays in CVI.[57]

As mentioned previously, clinical observations have suggested that CVI may represent a condition of dorsal stream "dysfunction" or "vulnerability" consistent with maldevelopment and impaired function of the dorsal or spatial visual processing pathway.[42-44] It would be reasonable to surmise that individuals with dramatic spatial processing deficits would also show evidence of associated structural deficits in the white matter connections subserving the dorsal or spatial processing pathway. Again, diffusion-based imaging can prove useful in helping to associate changes in the structure and integrity of the dorsal stream with observed deficits in spatial visual processing. Specifically, previous work has identified the superior longitudinal fasciculus (SLF) as the neuroanatomical correlate to the dorsal visual processing pathway. The SLF can be accurately characterized using white matter tractography reconstruction techniques.[66] For its part, the inferior longitudinal fasciculus (ILF) has been identified as the neuroanatomical correlate to the ventral visual processing pathway and similarly it can be accurately reconstructed.[70]

In the case of CVI, a number of recent studies have investigated the individual pathways implicated in the processing of visual information between cortical areas of the brain with the aim of establishing a possible association between the structural integrity of these pathways and visual dysfunction in CVI. In a study by Ortibus et al,[71] the integrity of the ILF (measured by fractional anisotropy) was examined using DTI in association with impairments in object identification observed in a cohort of individuals with CVI. Specifically, it was shown that the structural integrity of the ILF was significantly decreased in CVI compared to normally developed controls.[71] In a case series study by some of the coauthors of this review (C.M.B. and L.B.M.), HARDI imaging was used to reconstruct the SLF and ILF in 2 individuals with CVI with clinically assessed visual dysfunctions characterized as impairments in visual guided attention and visuospatial processing.[72,73] Compared to a sighted control subject, both CVI cases revealed a striking reduction in the structural integrity of the SLF (defined as a reduction in the number of fibers present in the fasciculus, see Fig. 2). Interestingly, commensurate reductions in the ILF were also observed in the individual with CVI that also exhibited object-related visual deficits (Fig. 2C). The observed reductions in the structural integrity associated with the key extrageniculo-striate visual pathways implicated in visual processing help provide for a neuroanatomical basis for the visual dysfunctions observed in individuals with CVI.[73]

Findings using diffusion-based MRI techniques such as DTI and HARDI appear to support the view that white matter changes are dramatically altered in the case of CVI. It is also possible to investigate the activation of cortical areas in correspondence to visual stimulation using functional MRI (fMRI). In contrast to diffusion-based imaging, fMRI measures task-related changes in blood flow and oxygenation levels to infer activity within localized regions of the brain.[74] In a recent case study using a combined HARDI and fMRI approach, Merabet et al[75] demonstrated in an individual with CVI and clinically documented inferior visual field deficit (assessed by

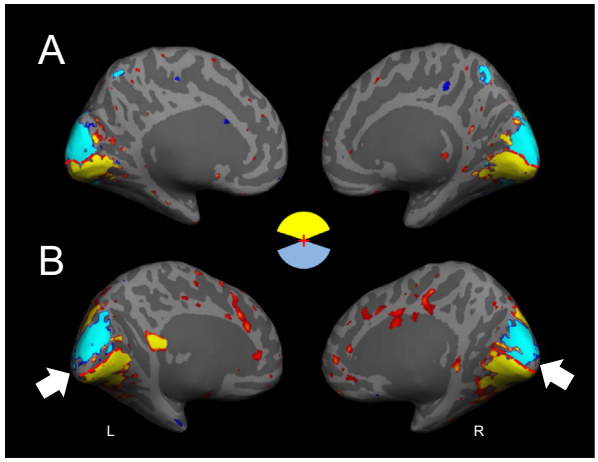

Figure 3 Activation of early retinotopic areas of the occipital cortex using fMRI (inflated projection of the brain showing the posterior poles of the right and left hemisphere). (A) Selective stimulation of the upper and lower visual fields leads to robust and corresponding activation within the lower (yellow) and upper (blue) banks of the calcarine sulcus (red dotted line). (B) Activation of corresponding retinotopic areas in an individual with CVI using the same upper and lower visual field stimuli. This individual has a documented bilateral inferior visual field defect (as measured by formal perimetry testing). Note that activation within the lower visual field appears reduced (gaps in activation indicated by arrows) compared to the sighted control (for further details regarding this clinical case report, see Ref. 75). (Color version of figure is available online.)

formal perimetric testing) that there was a correspondence between the location and extent of damage (as revealed by combined structural and functional imaging) and the location of the visual field deficit observed. Specifically, damage to superior branches of the optic radiations (characterized by HARDI) were associated with reduced retinotopic activation of corresponding early visual cortical areas (as indexed by fMRI) responsible for the representation of the inferior visual field (Fig. 3). This relationship is in accordance to the known anatomical and functional organization of visual pathways and geniculocortical representation of visual field space[76] and demonstrates the advantage of combining a clinical and multimodal neuroimaging approach to help characterize the underlying neurophysiology of visual deficits.

Guzzetta et al[57] notably reported that structural MRI–defined areas of brain damage were not always predictive of visual field defects in children as expected in adults with the same lesions. In a review by the same investigators,[24] it was found that many individuals diagnosed with CVI and with early periventricular damage to the optic radiations often showed normal development of visual field function. The authors suggested that the preservation of such visual function they reported may be the result of compensatory neuroplastic reorganization.[24] This observation certainly has important rehabilitative implications that merit further careful study. Furthermore, it also speaks to the value of advanced imaging techniques (such as diffusion MRI and fMRI) to characterize anatomical-functional-behavioral relationships at the individual level.

Conclusions

Taken together, it is becoming clearer that visual dysfunctions observed in CVI are likely associated with a vulnerability and maldevelopment of numerous key pathways supporting the developing visual system. Neuroplastic changes within the developing brain (such as the "re-wiring" of main geniculocortical or corticocortical connections) may support the sparing of visual function in certain individuals. It is important that future work focus on establishing a neurophysiological basis for CVI to associate structural and functional impairments of visual processing pathways with a broad range of measured outcomes of visual processing deficits at the individual level.

The use of advanced neuroimaging modalities such as diffusion MRI and fMRI are still in their infancy in terms of their application in CVI, but early studies suggest that much can be learned regarding the underlying neurophysiology of this condition beyond standard structural imaging alone. Uncovering associated links between brain connectivity (ie, "wiring"), brain activation (as indexed by fMRI), and the visual dysfunction observed in the clinical setting may help provide clues for the development of novel education and rehabilitation strategies for individuals living with CVI.

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