# Neural and socio-cognitive sequelae of congenital disorders of the peripheral visual system during mid-childhood

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# Abstract

Previous studies identified cognitive difficulties in individuals with congenital visual impairment that significantly impacted on wellbeing and educational attainment. However, factors leading to adverse outcome remained unclear. The current study aimed to identify associations and mechanisms of specific cognitive deficits associated with visual impairment from a neurodevelopmental perspective. Based on recent theoretical advances (Johnson, 2011), it was assumed that visual impairment leads to differences in cognition by influencing experience-driven brain maturational processes, which support the integration between cortical areas to support cognitive processes. In order to explore this hypothesis, children with visual impairment due to disorders that were thought to only affect peripheral sensory parts of the visual system were assessed on neuropsychological instruments covering a range of functional domains. Further, structural and functional neurophysiological methods were employed to establish the impact of visual impairment on brain organisation. The results of the present work confirm earlier reports of specific deficits in spatial memory, social understanding, and aspects of executive function, despite typical performance in other domains. In addition, the current study is the first study to indicate dosage-dependence with some aspects of social communication being even impaired in children with only mild to moderate visual impairment, while aspects of executive function and spatial memory were only found to be deficient in children with more severe forms of visual impairment. Further, neurophysiological investigations indicated differences in structural and functional brain organisation in children with VI that related to differences in behavioural performance. In general, the results of the present study suggest that visual sensory impairment impacts on brain and cognitive development with important implications for education and clinical treatment of children with visual impairment.

# Declaration

I, Johannes Michael Christian Bathelt, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Johannes Bathelt

# List of figures and tables

## Figures

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It may be that when we no longer know what to do
we have come to our real work,

and that when we no longer know which way to go
we have come to our real journey.

The mind that is not baffled is not employed.
The impeded stream is the one that sings.

by Wendell Berry, Standing By Words, 2011

# Acknowledgements

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# Thesis Overview

The main purpose of the current study is to investigate the impact of congenital visual impairment on the development of cognitive function via differences in experience-driven brain maturation. The following section will give a brief description of the main content of subsequent chapters to provide an overview of the structure of the whole thesis.

Chapter 1: General Introduction - On the background of typical function of the visual system and its relationship to visual perception, the nature of visual impairment and its impact on cognitive and neural development are discussed based on the existing literature.  The extended dorsal stream model is introduced, which frames the structure of the rest of the thesis. The model suggests that three main connections of the extended dorsal stream are involved in different aspects of cognitive function. These connections may be altered as a consequence of visual impairment, which may affect the associated cognitive functions.

Chapter 2: General Methodology - This chapter describes the methodological approach and investigative instruments employed throughout the study highlighting benefits and limitations of the methods with respect to the research questions.

Chapter 3: Background Characteristics - This chapter is intended to characterise the study sample of school-age children with visual impairment. The main conclusion of the chapter is that no significant differences were found between children with visual impairment and typically-sighted controls for verbal ability or parental factors. However, differences in quality of life and adjustment were found that justify a detailed investigation of factors contributing to these adverse effects.

Chapter 4: Parieto-prefrontal pathway: Executive function – The extended dorsal stream model poses that connections between parietal and frontal regions are involved in executive function. This chapter reports results of direct assessments of auditory attention and verbal fluency, and results of a parent questionnaire assessing everyday executive abilities. Further, findings of an electrophysiological study of selective auditory attention are presented. While performance on direct assessments of executive abilities fell in the same range as the control group, the parent questionnaire and electrophysiological experiment indicated differences in executive function.

Chapter 6: Parieto-motor cortex pathway: Social cognition & communication- The extended dorsal stream model suggested that connections between the parietal and motor cortex are involved in social cognition via self-other mapping. Therefore, communicative profiles, mentalizing ability and response to basic auditory social stimuli was assessed. The results indicated high prevalence of autism-like traits, deficits in mentalizing, and differences in the neural substrates mediating responses to own-name stimuli.

Chapter 4: Parieto-medial temporal pathway: Spatial memory function- The extended dorsal stream model contained indirect connections between the parietal lobe and the medial temporal lobe. These connections are thought to be involved in the transfer of visual information for spatial memory. This chapter reports the results of assessments of spatial memory. In addition, short-term memory was assessed to control for general differences in memory performance. While performance on short-term memory fell in the same range as the typically-sighted control group, significantly lower performance was found for spatial memory in children with severe to profound visual impairment.

Chapter 7: Structural Brain Organisation – In order to directly assess differences in the integration of visual areas, structural differences in brain organisation were investigated. Following reports of structural brain differences in adults with visual impairment, this chapter reports results of investigations of cortical thickness, integrity of key white matter pathways, and whole-brain white matter connectome differences relating variation on these measures to differences on behavioural and cognitive measures. The main findings include a direct relationship between visual function and integrity of the optic radiations as well as thickness of the pericalcarine cortex.

Chapter 8: Functional Brain Organisation – In addition to structural differences, functional differences were evaluated using resting-state EEG for differences frequency composition and network relationships between cortical sources. The results were suggestive of reorganisation in cortical networks with increased local connectivity and decreases in some long-range connections.

Chapter 9: Discussion and Conclusion - This chapter summarises the main findings of the previous chapters and discusses the implications of these results in relation to the extended dorsal stream model and the interactive specialisation framework. Implications for educational and clinical practice, limitations, and suggestions for further studies are also discussed.

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# Chapter 1: General Introduction

## 1.1. Chapter Introduction

### *1.* General Introduction

*"I do not see how the dreamer can cease to see unless the dreamer ceases to know. Perhaps it is significant that I cannot remember having dreamed about people's faces for a long time."*

John M. Hull, *Touching the Rock - An Experience of Blindness*

In the book "Touching the Rock" emeritus professor John M. Hull describes his personal experience of losing his sight in his mid-forties. The description of the extreme struggle even with simple tasks, like making a cup of tea, illustrate how much we rely on vision in our everyday life. He also describes how visual memories and concepts gradually fade away. This demonstrates how intricately vision is linked to our experience of the world in past and present. On the neurological level, this is reflected in the finding that 55% of the cortex is involved in visual processing compared to only 3% for auditory processing and 11% for somatosensory processing (Felleman & Van Essen, 1991). Further, the complexity of visual function is evident in the complex networks that are required for visual processing, which involve large numbers of forward and backward connections between cortical as well as subcortical structures. The study of deficits in the visual system provides a unique opportunity to see how the visual system develops when visual input is largely degraded or completely absent. Specifically, the development of cortical networks that are driven by the processing of vision-related information in typically-sighted individuals is a highly important area of investigation, which will help to elucidate the cognitive sequelae of changes in visual experience over development.

The first section of this chapter will provide a general overview of the anatomy, physiology and postnatal development of the visual system. Building on this description, the next section will review how visual function is measured in humans and how alterations on different levels of the visual system influence visual function. The third section of the chapter will discuss definitions and epidemiology of visual impairment in children and provide an overview of the characteristics, aetiology and genetics of the VI disorders that are relevant to the rest of this discussion. The fourth section will review the literature on cognitive alterations in visual impairment. Finally, the last section will review the literature about structural and functional differences in brain organisation in individuals with visual impairment with a focus on reorganisation that may mediate differences in cognitive processes.

## 1.2. The Visual System

### 1.2.1. Anatomy

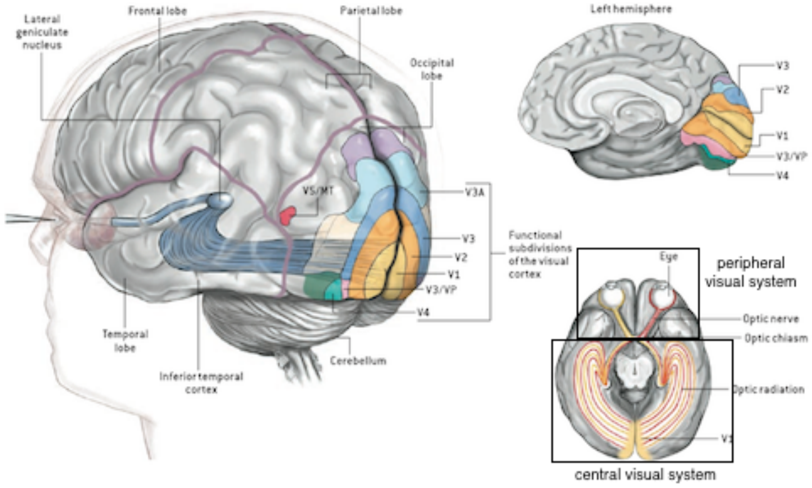


**Figure 1: Illustration of the visual system in humans** Light information is transformed into electrochemical signal in the retina of the eye. Ganglion cells project from the eye to the thalamus forming the optic nerve. Projections from the thalamus reach the primary visual cortex via the optic radiations. Visual information is processed in a hierarchy of visual areas in the occipital cortex. Representations are successively more specific in higher-order areas. However, extensive feedback connections exists between cortical areas. The bottom right illustration highlights the anatomical distinction between peripheral and central visual system. Figure adapted from (Logothetis, 1999).

The visual system can be roughly divided into a peripheral and a central part: The peripheral part comprises the globe of the eye with all its structures and the optic nerve up to the optic chiasm. The central part of the visual system consists of the optic nerve from the optic chiasm, the visual nuclei of the thalamus (most notably the lateral geniculate nucleus), the optic radiations and areas of the visual cortex (see Figure 1).

### 1.2.1.1. Structure of the eye

The most important structures of the eye for vision are the cornea, pupil, lens, glass body, retina and retinal pigment epithelium. Most of the refractive power of the eye is determined by the cornea (Prasad & Galetta, 2011) and cannot be changed. The role of the pupil is to adjust the eye to different brightness levels through constriction or dilation, which allows for vision under a large range of light conditions. The lens of the eye is located behind the pupil and is attached to the ciliary muscles on both sides. The refractive properties of the lens are adjusted through constriction of the ciliary muscles, which leads to elongation of the lens. Accommodation of the eye to different points of focus is achieved by these means. The glass body is the large chamber of the eye, which is filled with vitreous liquid. The glass body contributes to the passive optic properties of the eye.

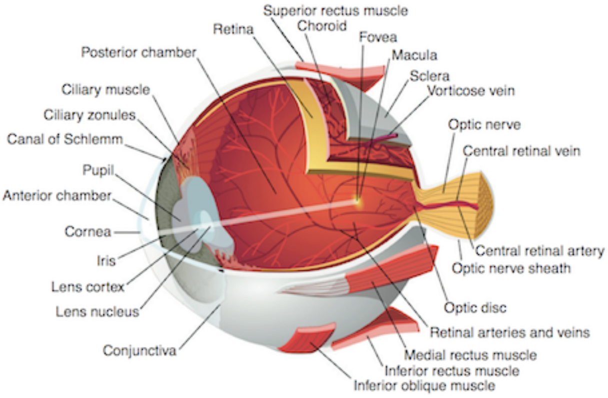


**Figure 2: Structures of the eye and anatomy of the retina.** The most important structures of visual function are the cornea, pupil, lens and glass body filled with vitreous liquid. The retinal pigment epithelium metabolically supports the retina and absorbs scattered light. Figure taken from Prasad & Galetta, 2011.

### 1.2.1.2. Retina

The retina contains photoreceptors that react to photic stimulation with membrane potential changes. This process is mediated by the protein "retinal" which changes from 11-cis to all-trans configuration under the influence of light energy. The conformational change is transduced into electrochemical signals by the transmembrane protein opsin and an associated complex of proteins. Ultimately, the conformational changes lead to the activation of sodium channels through the metabolic action of phosphodiesterase (Wassle, 2004). Consequently, sodium flows into the cell and leads to depolarisation.

Humans possess four different types of photoreceptors that are relevant for vision: three types of cones that are most responsive to different parts of the wavelength spectrum and rods that have a broad tuning curve[1]. Rods are saturated under normal light conditions and are mostly important for scotopic vision, e.g. at night (Adelson, 1982). Each type of cone photoreceptor responds maximally to a different wavelength with maxima in the red, green or blue light spectrum. The distribution of the rod and cone receptors on the retina is highly skewed: the highest density of cone receptors is found in the fovea; more ex-central locations show lower densities of cones, but higher densities of rod receptors.

Photoreceptors project onto retinal ganglion cells via bipolar cells. There are lateral connections between bipolar cells and retinal ganglion cells via horizontal cells and amakrine cells. The lateral connections mediate early processing stages via lateral inhibition, which support contrast enhancement and boundary detection (Kandel, Schwartz, & Jessell, 2000). Different types of retinal ganglion cells can be distinguished that give rise to parallel pathways to the lateral geniculate nucleus (LGN) or the thalamus and further. Midget ganglion cells constitute the majority of retinal ganglion cells and give rise to the parvocellular pathway (Nassi & Callaway, 2009). These cells have small receptive fields and show response with high spatial and low temporal frequency. On the other hand, parasol ganglion cells give rise to the magnocellular pathway and show complementary response properties with large receptive fields, high temporal and low spatial resolution (Schiller & Logothetis, 1990). Konicellular cells are another ganglion cell type that contributes to both the magno- as well as parvocellular pathway. However, their functional role is less well understood (Nassi & Callaway, 2009).

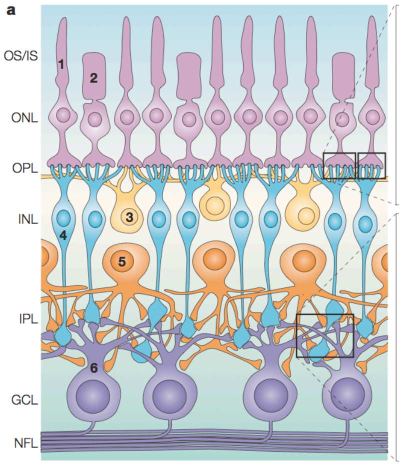


**Figure 3: Layer organisation of the mammalian retina** The retina is organised in different layers. The first layer contains the photoreceptor cells rods (1) and cones (2). These cells respond to light stimulation with electrochemical changes. Photoreceptors project to bipolar cells (4). Bipolar cells project to ganglion cells (6), whose axons form the optic nerve. Other cell types like horizontal cells (3) and amakrine cells (5) are important for early processing via lateral inhibition. Figure modified from (Wassle, 2004).

### 1.2.1.3. Optic tract

The axons of the ganglion cells leave the eye and form the optic nerve. The optic chiasm is an important decussation point for the fibres of the optic nerve. Fibres that convey information from the same part of the visual field project to the same hemisphere. The optic nerve projects onto two main nuclei in the thalamus: the lateral geniculate nucleus (LGN) and nuclei of the pulvinar. Fibres that synapse in the LGN give rise to large projections to the primary visual cortex. This pathway is referred to as the optic radiations. It projects laterally and then bends in a characteristic shape, called Meyer's loop, posteriorly and terminates in the inferior occipital cortex (Benjamin, Singh, Prabhu, & Warfield, 2014; Gonzalez & Smith, 2012).

Other projections arise from the pulvinar and are relayed to brainstem nuclei within the superior colliculi and pretectum. These nuclei are important for the coordination of eye movements, saccade generation and pupil dilation (Trepel & Dalkowski, 2008).

#### 1.2.1.4. Visual cortex

The primary visual cortex (V1) is located on the posterior pole of the occipital cortex. V1 receives retinotopically organised input from the lateral geniculate nucleus of the thalamus via the optic radiation. The segregation of the parallel magno- and parvocellular pathways is also maintained. Neurons of the magnocellular pathway synapse to neurons in layer 4Cα of V1, whereas neurons of the magnocellular pathway synapse onto neurons in layer 4Cβ (Prasad & Galetta, 2011). Nasal aspects of the visual fields terminate in the central parts of the posterior pole of the occipital cortex in the left and right hemisphere. Lateral parts of the visual fields are represented on more ex-centric locations of the V1. The visual field is not linearly represented, but is transformed due to the higher density of photoreceptors in the fovea. Neurons within V1 respond to basic visual properties like luminance, contrast or colour.

The secondary visual cortex (V2) receives input from V1. A large number of feedback connections to V2 is also found. V2 shows a similar retinotopic organisation to V1, but neurons within V2 respond to slightly higher-order aspects of visual stimuli, like orientation and spatial frequency (Hedgé & Van Essen, 2005).

#### 1.2.1.5. Dorsal and ventral stream

Beyond V1 and V2, the visual system is thought to be divided along two main streams. Mishkin and Ungerleider originally proposed the two stream hypothesis of visual function in a landmark paper in 1982 (Mishkin & Ungerleider, 1982). Based on lesion studies in macaques, they proposed that visual information is conveyed from the primary visual cortex (V1) to ventral areas (V2, ventral V4, rostral inferior temporal cortex, posterior inferior temporal cortex) for object or identity-related tasks (ventral stream) and to dorsal areas for location-related tasks (V1, dorsal V4, posterior parietal cortex) ("What" and "Where" stream)[2]. The two stream hypothesis was later revised by Goodale and Milner that emphasised that the dorsal stream is closely linked to action (Goodale & Milner, 1992). They propose that the ventral stream is concerned with identification, whereas the dorsal stream is engaged in computations relating to the manipulation of objects ("What" and "How" stream). Electrophysiological and neuroimaging studies in humans using delayed matching of either category or use of tools support this distinction (Chao and Martin 2000; Oberman, Hubbard et al. 2005).

### 1.2.1.6. Summary

In summary, the optical system may be divided into a peripheral part comprising the globe of the eye, retina, and anterior optic nerve and a central part arising at the level of the optic chiasm, where fibres segregate according to visual hemifields. The peripheral part of the visual system is mostly involved in the sensory transduction of light energy into electro-chemical signals. These signals are further processed in the central part of the visual system, which ultimately leads to visual perception.

Specialised cell types are already present on the retina that respond to specific features in the environment. This segregation of function is also present in the central visual system with specialised processing streams for different stimulus aspects, e.g. a ventral stream for object recognition and a dorsal stream that processes vision for action.

## 1.2.2. Development of visual function

### 1.2.2.1. Development of visual acuity

Although humans are born with a fully developed visual system, the development of visual function undergoes substantial postnatal changes. Metabolic activity of the occipital cortex was found to respond to visual stimulation in newborns (Taga, Asakawa, Hirasawa, & Konishi, 2003), but VEP studies suggest very limited visual acuity that develops from 1.6 LogMar in the first postnatal month to 1 LogMAR at 6 months (Dobson & Teller, 1978; Lenassi, Likar, Stirn-Kranjc, & Brecelj, 2008). Visual acuity continues to improve in the second year of life from 1.6 at 12 months to 0.6 at 24 months (Courage & Adams, 1990; Kohl & Samek, 1988). Typical adult levels of vision are reached around 4 years of age (Sonksen, Wade, Proffitt, Heavens, & Salt, 2008). However, VA continues to improve up to the mid-20s surpassing typical adult vision followed by a decrease in visual function in the late twenties. VA in 10 year old children was found to be -0.1 logMAR (Frisén, 1981) and the peak performance in 25 year olds -0.15 logMAR (Elliott, Yang, & Whitaker, 1995) and -0.2 (Frisén, 1981).

Sonksen and colleagues investigated the development of VA in a normative preschool to mid-childhood sample representative of the UK population for gender, ethnicity and socioeconomic status (Sonksen et al., 2008). Importantly, the study by Sonksen et al. did not exclude children with vision difficulties and therefore provided representative norms for the whole range of visual function in the population within this age range. A steep increase of visual function was found between about 3 years and 5 years of age. Changes in VA later in child development (5-8 years) were three times smaller than during the early period of rapid development (see Figure 6) (also see Leat, Yadav, & Irving, 2009).

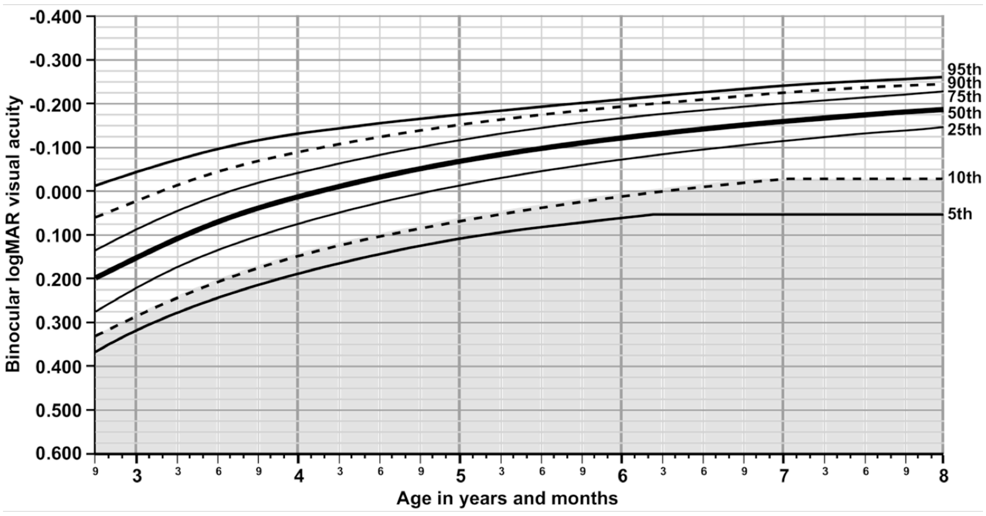


**Figure 4: Visual acuity at different ages determined by the Sonksen LogMAR test of visual acuity for children between 2year 9months and 8years.** Visual acuity changes rapidly between 3 and 5 years of age. Subsequent changes are less pronounced.

Although visual acuity is the most common characteristic to describe the development of visual function, it is not the only aspect of vision. Importantly for this discussion, other aspects of vision may show a different developmental pattern to VA. For instance, contrast sensitivity (CS) shows a more prolonged period of development (Adams & Courage, 2002; Leat et al., 2009). Further, several studies find differences in the development of contrast sensitivity for stimuli with high and low spatial frequencies (Adams & Courage, 2002; Benedek, Benedek, Kéri, & Janáky, 2003) and between static and dynamic stimuli (Benedek et al., 2003). VEP studies of infants suggest more gradual development of CS compared to VA (Atkinson, Braddick, & Braddick, 1974; Norcia, Tyler, & Hamer, 1990). Adult-like performance on behavioural CS tasks are not reached until 7 to 12 years (Leat & Wegmann, 2004). CS for low spatial frequency stimuli reaches adult-like levels earlier showing rapid development within the first three years of life. High spatial frequency CS shows a more gradual development reaching adult-levels in late childhood (Adams & Courage, 2002; Ellemberg, Lewis, Liu, & Maurer, 1999). Benedek and colleagues further reported earlier maturation of CS for static compared to dynamic stimuli (Benedek et al., 2003). Most studies used luminance defined gratings. Chromatic CS shows a different developmental pattern with much more rapid development during infancy and plateau performance close to adult level by early childhood. Because of the different response properties of the magnocellular (M) and parvocellular (P) pathways, luminance contrast sensitivity is associated with the M and colour CS with the P pathway. Therefore, several authors conclude that the difference in the maturation of colour and luminance CS suggests more prolonged development of the M compared to the P pathway (Nassi & Callaway, 2009; Wassle, 2004). Further, Hammarrenger and colleagues compared visually evoked potential (VEP) responses between very low birth weight children for varying in spatial frequency and contrast (Hammarrenger et al., 2007). The authors reported significant differences in responses related to the M pathway in the low-birth weight children, whereas P responses were not significantly different to the control group. Based on this finding, the authors concluded that the M pathway is more sensitive to developmental insult compared to the P pathway.

In summary, studies about visual development in typically-sighted children show that vision displays substantial postnatal development. The precise developmental progression depends on the visual function with visual acuity maturing earlier than higher-level aspects of vision, like motion processing.

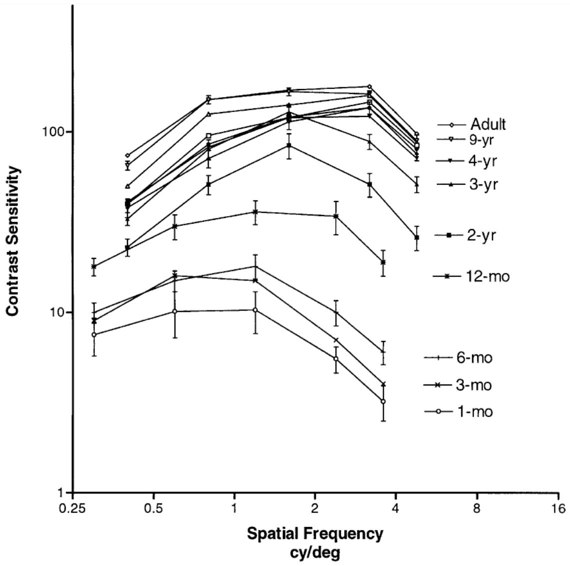


**Figure 5: Contrast sensitivity between infancy and adulthood.** Lower spatial frequency show rapid development during the first three years of life reaching levels close to adult performance at 4 years of age. Higher spatial frequency contrast sensitivity shows a more gradual development with adult-like levels in mid-childhood. Figure reproduced from Adams et al. 2002

### 1.2.2.2. Development of depth perception

While basic visual information is available from birth in human infants, higher visual functions like depth perception show a protracted development that depends on visual experience (Adolph, 2000). A classic paradigm tested if infants would crawl over a visual cliff that was covered by glass (Gibson & Walk, 1960). The results suggested that depth perception develops in the second year of life. However, later studies found that crawling experience predicted visual cliff behaviour above chronological age (Richards & Rader, 1983). Learned associations between visual perception and sensory-motor consequences are therefore more likely to explain the visual cliff responses rather than vision alone (Adolph, 2000; Richards & Rader, 1983).

**Figure 6: Illustration of the classic visual cliff paradigm referenced in many textbooks of developmental psychology.** The infant is placed on a table with a cliff on the other side covered by a transparent plexiglass sheet. The infant has to traverse the visual cliff to reach the his/her mother on the other side of the table (image taken from Gibson & Walk, 1960).

Studies of grasping behaviour provide a different picture. A study by Yonas and colleagues presented 4 to 5 month old infants with toys that were either within or out of their reach (Yonas & Hartman, 1993). While 4 month olds reached for the toy without adjusting their posture, 5 month olds leant forward to grasp objects that were just out of their reach. The authors interpreted this behaviour to reflect understanding of spatial depth in 5 month olds. Performance on this paradigm depends on binocular integration and visuomotor integration rather than isolated depth perception (Nawrot, Mayo, & Nawrot, 2009). However, depth information may also be accessed through monocular cues based on motion parallax, i.e. difference in relative motion between objects in near-compared to far- space. Nawrot and colleagues investigated preferential looking of infants between 8 and 29 weeks in response to display with depth information through motion parallax compared to random dot displays. The results indicated that infants are already sensitive to monocular depth information from motion parallax by 4 months of age.

#### 1.2.2.3. Development of face processing

Faces are a highly salient source of social information for the infant. This is reflected in the finding that responses to face-like patterns are already present from birth with newborn infants preferring to look at high-contrast face patterns compared to other similar stimuli (Fantz, 1963; Goren, Sarty, & Wu, 1975; Johnson, Dziurawiec, Ellis, & Morton, 1991). However, face processing undergoes major refinements and prolonged postnatal development between birth and adolescence. Early in postnatal development, face processing becomes increasingly attuned to upright human faces. Pascalis and colleagues reported a event-related potentials study that shows that adults and 9-month old infants showed differences between the identities of human faces, but not monkey faces (Pascalis & Nelson, 2002). However, the response of 6 month old infants show differences for the identity of both human and monkey faces. The authors interpreted these findings to reflect perceptual narrowing that accompanies the fine-tuning of perceptual processing towards salient visual stimuli (de Haan, Humphreys, & Johnson, 2002).

Face processing continues in mid-childhood and adolescence. Studies using fMRI found that activations associated with processing faces become more focal and more specifically activated by face stimuli between childhood and adolescence (Cohen Kadosh, Henson, Cohen Kadosh, Johnson, & Dick, 2010; Cohen Kadosh, Johnson, Henson, Dick, & Blakemore, 2013). The specificity of the activation in response to faces seems to be explained by expertise acquired through exposure these stimuli. This is supported by studies that show similar activations in response to different car models in car experts (Gauthier & Curby, 2005). These findings highlight that exposure to visual stimuli is in parts driving the development of stimulus-specific processing networks (Gauthier & Nelson, 2001). These developmental processes are likely to be severely disrupted when visual information is either not available or degraded (Maurer, Lewis, & Mondloch, 2005).

In addition to rather coarse information that is necessary to recognise faces, face stimuli provide more fine-grained information that are important for interactions between the infant and the caregiver. One of the most important aspects for cognitive and social development is the ability to pick-up eye gaze. The ability to shift the focus of visual attention with reference to the gaze direction of another person was found to be present between the ages of 3 to 4 months (Hood, Douglas Willen, & Driver, 1998; Willen, Hood, & Driver, 1997). The ability to follow the gaze of a caregiver is thought to be important for establishing joint attention and providing communicative context (Murray, 2014). These behaviours have found to be important for language acquisition (Hirotani, Stets, Striano, & Friederici, 2009) and social development (Jaffe, Stern, & Peery, 1973). However, for infants with severe to profound VI, Dale and colleagues found that joint attention behaviours are severely disrupted (Dale, Tadić, & Sonksen, 2014; Dale & Salt, 2008).

In summary, the last sections illustrate that visual function undergoes substantial postnatal development. The time course of development depends on the particular aspect of visual function with relatively basic visual function maturing earlier, e.g. visual acuity, compared to higher-level aspects of vision, like motion processing and face recognition. The literature also suggests that experience plays a role in the postnatal development of higher-order aspects of vision, i.e. face processing, which may have important implications for the development of children with congenital VI. The next section will examine differences in structural and functional brain differences in individuals with congenital VI.

### 1.2.3. Psychophysics of Vision

This section will provide a background about the measurement of visual acuity and how different parts of the anterior optic system affect visual acuity. Visual acuity describes the ability of the visual system to resolve two points that are separate in space as being separate. Visual acuity is generally assessed in recognition tasks in which participants have to recognise and name visual targets. The most common test of visual acuity in adults is the Snellen Visual Acuity Chart, which consists of lines of letter of decreasing sizes. The acuity of the participant is equated as the smallest line that the participant is still able to read. The letter size is designed so that the smallest critical detail (gap between strokes or outward strokes) subtends 1/5$^{th}$ of the height. At a standard viewing distance, the smallest critical element subtends one minute of an arc on the eye of the observer. Snellen visual acuity is described as:

$$VA = \frac{D}{D'} \qquad (1)$$

VA: visual acuity

D': standard viewing distance (6m or 20feet)

D: distance at which each letter subtends 5 minutes of an arc (1min for each critical stroke)

Visual acuity can also be described as the angle which the stroke of the letter subtends at the person's eye at a given distance. This is called the minimum angle of resolution (MAR). The MAR is commonly given in log10 format (logMAR). Table 1 presents conversions between different ways of expressing visual acuity in Snellen acuity and logMAR. The scientific standard for reporting visual acuity is the logMAR unit.

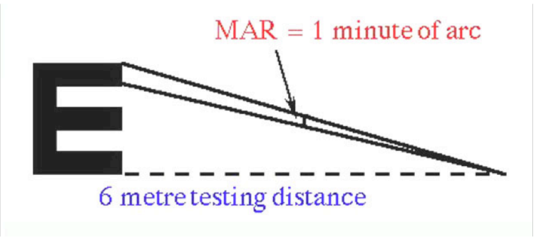


**Figure 7: Illustration of visual acuity calculation** For 6/6 vision, the participant has to be able to recognise a letter from a distance of 6 metres. The letter is designed in a way that the critical stroked subtend an angle of 1 minute of an arc from that distance.

**Table 1: Conversion between visual acuity expressed as Snellen visual acuity, MAR and logMAR**

| **Snellen VA** | | **MAR** | **logMAR** |
|---|---|---|---|
| Metres | Feet | | |
| 6/60 | 20/200 | 10.00 | 1 |
| 6/48 | 20/160 | 8.00 | 0.9 |
| 6/38 | 20/125 | 6.30 | 0.8 |
| 6/30 | 20/100 | 5.00 | 0.7 |
| 6/24 | 20/80 | 4.00 | 0.6 |
| 6/19 | 20/60 | 3.20 | 0.5 |
| 6/15 | 20/50 | 2.50 | 0.4 |
| 6/12 | 20/40 | 2.00 | 0.3 |
| 6/9 | 20/30 | 1.60 | 0.2 |
| 6/7.5 | 20/25 | 1.25 | 0.1 |
| 6/6 | 20/20 | 1.00 | 0.0 |
| 6/4.8 | 20/16 | 0.80 | -0.1 |
| 6/3.8 | 20/12.5 | 0.63 | -0.2 |
| 6/3 | 20/10 | 0.50 | -0.3 |

Visual acuity depends on the integrity of the optical system (mostly cornea, pupil and lens) and the spacing of the photoreceptors on the retina. Because of the optics of the eye, a point in space is projected as a point spread function. According to Raleigh's criterion, two points can be separated, if the peaks of their PSFs fall at least in the minimum of each other (Figure 5) (Campbell & Green, 1965). Neurophysiologically, it has been suggested that this criterion is fulfilled when an "on-off-on" response in the photoreceptors is possible (Lorenz & Brodsky, 2009).

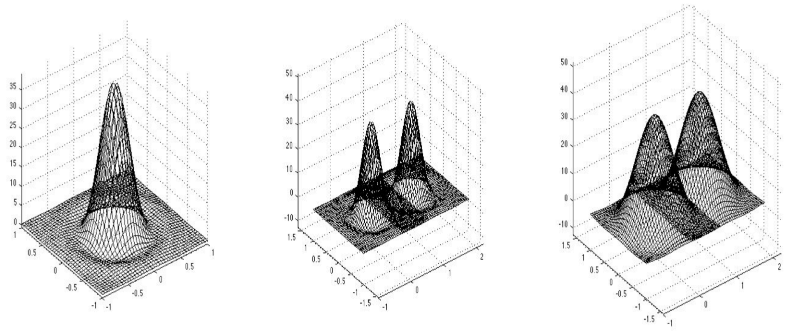


**Figure 8: Point spread function of a single- and two-point light sources on the retina.** Because of the optics of the eye, a point light source is projected onto the retina as a point spread function (left). Two point can be resolved as being separate when the maximum of one PSF has a minimum distance of the minimum of the second PSF according to Raleigh's criterion (middle). If the projection of the image onto the retina is blurred due to refractive error or if the grid of photoreceptors is coarser, the PSF is broader and the two-point light sources can no longer be resolved (right).

Several factors influence visual acuity:

a) Refractive error

Refractive error leads to a blurred image on the retina. Therefore, the point spread function (PSF) of points are broader and harder to separate. Refractive error can be caused by myopia (optics are too powerful for the length of the eyeball), hyperopia (optics are too weak for the length of the eyeball), astigmatism (uneven projection along different axes due to uneven curvature of the cornea) and presbyopia (decreased flexibility of the lens). Some degrees of refractive error are common in the typically-sighted population and can be treated through glasses or contact lenses.

b) Pupil size

A pupil diameter of 3 to 5mm is optimal for maximum visual acuity. Larger diameters limit visual acuity due to refraction.

c) Illumination

Visual acuity depends on the light conditions: under low light conditions (scotopic vision), the rod receptors limit the maximum visual acuity. Under scotopic conditions, the density of type II amakrine cells is critical for visual acuity and is highest at 5-15$^{a}$ eccentricity (Wassle, 2004). Under normal light conditions (photopic), the density of cone receptors is the most important factor. The highest density of cone receptors is found in the fovea.

d) Area of the retina that is being stimulated

Because the density of photoreceptors and interneurons varies between different regions of the retina, there are large variations in visual acuity depending on the point of projection onto the retina. Different light conditions are also processed optimally at different locations (see above).

e) Contrast sensitivity

Visual acuity charts that are used to determine visual acuity for assessment purposes use maximum contrast (black letters on white background). However, contrast is an important factor in everyday vision. Gratings with varying transitions can be used to assess contrast sensitivity. Gratings may either be defined by luminance differences or by colour transitions.

In summary, visual acuity indicates the resolution that the visual system can provide. It is measured by the ability to distinguish details of a given size from a standard distance. Differences in visual acuity may arise from a number of variables including changeable factors, e.g. contrast, light conditions, fixation point, and factors that are not easily changed, e.g. shape of the eye, density of photoreceptors, refractive properties of the lens. In developed countries, visual impairment is mostly caused by factors that cannot be remediated through corrective lenses (refractive error, astigmatism) or surgical intervention (glaucoma) (Rahi, Cable, BCVISG, 2003).

## 1.2.4. Congenital Visual Impairment

Whereas the first part of this chapter described the typically functioning visual system, the second part will focus on visual impairment. First, the categorisation of VI disorders according to the part of the visual system that is affected will be introduced. These definitions will be used throughout the subsequent chapters. Next, studies about the epidemiology of VI disorders in developed countries will be summarised to highlight the scope of VI problems in the context of the general population. Finally, different congenital disorders that lead to VI are described to illustrate the heterogeneity of this group.

### 1.2.4.1. Definitions

Congenital visual impairment is used as an umbrella term to describe a very heterogeneous group of disorders that is associated with reduced visual function from birth. Individuals with visual impairment may be described in terms of the severity of their visual impairment or in terms of the parts of the visual system that are likely to be affected and therefore causing the visual impairment. Reduction in visual function may arise from failure of parts of the visual system to develop fully or may be caused by damage to parts of the visual system through early insult (Dale & Sonksen, 2002). Further, disorder can either affect central or peripheral parts of the visual system. Congenital disorders of the peripheral visual system (CDPVS) can affect the retina, globe of the eye, or optic nerve up to the optic chiasm. They can either be simple, if there is no other brain involvement (e.g. colomboma, optic nerve hypoplasia), or complex, if other brain areas are affected (e.g. septo-optic dysplasia) (Parr, Dale, Shaffer, & Salt, 2010). Central disorders affect areas of the brain that are involved in visual processing, i.e. cerebral VI (Dutton & Jacobson, 2001), and potentially other areas of the brain. This investigation focusses on 'simple' peripheral disorders of congenital origin that are likely to be caused by genetic and embryonic developmental abnormalities.

In addition, congenital VI can be described in terms of the degree or level of available visual function or degree of vision loss. Clinically, visual acuity is the most commonly used measure to describe visual function. Visual acuity is used to determine if individuals are able to read printed materials for the classification of legal blindness. However, many individuals with low visual acuity are not able to read printed materials from a standard distance, but are still able to perceive forms and shapes (Sonksen, Petrie, & Drew, 1991). The following definitions were used to describe different groups of visual function in this investigation according to LogMar Acuity (Sonksen LogMar Scale) and Near Detection Scale:

**Table 2: Vision group definitions used in the present study**

| Group | Snellen Acuity | LogMar Acuity | Functional vision |
|---|---|---|---|
| Mild/moderate VI | 6/36 - 6/24 | 0.6-0.8 | Able to read large print |
| Severe VI | worse than 6/36 | >0.8 | Form perception |
| Profound VI | not measurable | not measurable | Potentially light perception |

### 1.2.4.2. Epidemiology

Congenital visual impairment is a rare disorder with an incidence of 4-6 cases in every 10,000 children (Rahi et al., 2003). A large epidemiological study conducted by Bunce and Wormald surveyed 328 certificates of blindness from England and Wales between April 1999 and March 2000 about causes of blindness and partial blindness in the age group of 0 to 15 years of age (Bunce and Wormald 2008). The most common cause for blindness in this age group was cortical visual impairment and disorders of the optic nerve, which accounted for 41.2% of all cases. A second study by the same authors analysed additional data for the time between April 2007 and March 2008 (Bunce, Xing, & Wormald, 2010). The authors found that the overall incidence of blindness decreased in most age groups, but increased in the under 17 years age group. Rahi and Cable analysed reports from 439 children in the UK under 16 years of age that were newly diagnosed with severe visual impairment or blindness in 2000 (Rahi et al., 2003). Cortical visual impairment or visual pathway damage was the most common cause of blindness or severe visual impairment in 47.8% of cases, followed by optic nerve damage (28.7%) and retinal damage (28%).

Hatton and colleagues collected data from a sample of 2,155 children in 29 US states between 0 and 39 months of age who entered specialised treatment for visual conditions (Hatton, Schwietz, Boyer, & Rychwalski, 2007). They identified cortical visual impairment as the most common cause for visual impairment in this group (23.6%), followed by retinopathy of prematurity (16.2%) and optic nerve hypoplasia (9.7%). These reports are largely consistent with reports from other populations in developed countries (Alagaratnam, Sharma, Lim, & Fleck, 2002; Bamashmus, Matlhaga, & Dutton, 2004; Blohmé & Tornqvist, 1997): Despite varying criteria for the classification of blind or visually impaired children, all surveyed studies identify cortical visual impairment and damage to the optic nerve as the most common causes of impaired vision in children.

For 'simple' congenital disorders of the peripheral visual system, Sonksen et al (2002) estimated that there are around 350 children born with conditions in this category in the UK. The epidemiological studies show the rarity of isolated disorders of the visual system. Because of the rarity of these cases, the sample that could be recruited to the current study was limited.

### 1.2.4.3. VI disorders

Previous sections of this chapter introduced visual impairment due to potentially simple congenital disorders of the peripheral visual system ('simple' CDPVS). This term describes disorders leading to reduced visual acuity associated with alterations in the globe of the eye, retina, or anterior optic nerve up to the optic chiasm. Other brain involvement is not indicated in this group of disorders (potentially simple). The diagnostic group of potentially simple disorders of the peripheral visual system is a heterogeneous group of disorder with maximal effects in different parts of the anterior visual system and varying genetic background. The following sections will summarise the most common diagnostic groups within the 'simple' CDPVS category to illustrate this heterogeneity.

### 1.2.4.3.1. Disorders of the globe of the eye

Ocular Coloboma

Isolated ocular coloboma results from a failure of the fissure of the optic cup to close during early development (Pagon, 1981). The inheritance pattern is mostly autosomal recessive, but autosomal dominant in some families (Lorenz & Brodsky, 2009). Isolated ocular coloboma may result in variable vision levels from no visual impairment to profound VI in the affected eye depending on the extent and location of the coloboma.

### 1.2.4.3.2. Retinal disorders

Cone-rod dystrophies (CRDs)

CRDs are characterised by decreased visual acuity, dyschromatopsia, photoaversion (Hamel, 2007). The disease progresses from an early stage with primary cone dystrophy that leads to decreased acuity and loss of sensitivity in the central visual fields to rod and cone dystrophy in later stages. At the later stage, sensitivity in the peripheral field also decreases and night blindness occurs. The vision level at the later stages is between logMAR 1.3 to profound visual impairment (Hamel, 2007). Genetically, CRDs are very heterogeneous with both autosomal recessive and dominant inheritance. Currently, 13 genes have been identified that account for non-syndromic CRDs. Notably, mutations in genes for rod and cone differentiation and survival, e.g. *CRX* (Freund et al., 1997), are linked to autosomal dominant inheritance, whereas mutations in genes coding proteins for retinoid metabolism, e.g. *ABCA4*, are associated with autosomal recessive forms (Maugeri et al., 2000).

Retinitis pigmentosa

Retinitis pigmentosa is a form of retinal dystrophy with a characteristic pattern of progressive vision loss. The onset of vision loss may occur between childhood and mid-adulthood, but the first vision problems usually become apparent during early adolescence (Hartong, Berson, & Dryja, 2006). The vision loss progresses from night blindness to loss of the peripheral fields. Finally, central vision degenerates leading to complete loss of vision typically at around 60 years of age. (Hartong et al., 2006). The inheritance pattern of retinitis pigmentosa is varied: most cases are inherited in autosomal dominant (50-60%) or autosomal recessive (30-40%) fashion, but X-linked inheritance patterns are also known (5-15%) (Grøndahl, 1987; Hartong et al., 2006). Therefore, it is reasonable to assume that retinitis pigmentosa reflects a multitude of genetic disorders with similar symptoms. Most mutations affect the rhodopsin or opsin genes (Farrar, Kenna, & Humphries, 2002).

Leber's congenital amaurosis (LCA)

LCA is characterised by dystrophy of the rods and cones from birth (Lorenz & Brodsky, 2009). Vision ranges from logMAR 1 in rare cases to severe or profound visual impairment in most cases (Lambert, Kriss, Taylor, Coffey, & Pembrey, 1989). Vision loss is not progressive (Lorenz & Brodsky, 2009). Clinically, patients present with nystagmus, slow or absent pupillary response and vision loss (Grieshaber & Niemeyer, 1998). LCA is a hereditary disorder with complex genetics. Mutations are mostly recessive, but can occasionally be autosomal dominant (Hamel, 2007). Mutations in 11 genes account for 70% of LCA cases. These genes code for proteins that are involved in a wide range of cellular functions including phototransduction, cell polarity, protein chaperoning and others (Fazzi et al., 2007). Therefore, it is assumed that LCA is a summary term for different genetic disorders with similar presentation (Fazzi et al., 2007). However, the presentation of different disorders is slightly different in progression.

#### 1.2.4.3.3. Disorders affecting the optic nerve

Optic Nerve Hypoplasia (ONH)

ONH is a marked decrease in the number of axons and associated tissue (mesoderm, glial cells) in the optic nerve (Lorenz & Brodsky, 2009). It can be unilateral or bilateral. The thinning of the optic disc can be evaluated through ophthalmoscopy, but MRI offers a better insight into the thinning of the optic nerve. Visual acuity ranges from logMAR 0 to profound visual impairment. The vision loss is mostly stable, unless amblyopia develops in one of the eyes. Sleep disturbance due to melatonin deficiency may also be present (Wee & Van Gelder, 2004). ONH may result from excessive apoptosis of neurons during prenatal development. OHN has been linked to several risk factors during pregnancy including young maternal age, primaparity, low maternal weight and drug/alcohol consume during pregnancy (Patel, McNally, Harrison, Lloyd, & Clayton, 2006). There is currently little known about genetic factors that contribute to ONH (Garcia-Filion & Borchert, 2013).

### 1.2.4.3.4. Syndromic disorders

Albinism

Albinism is an inherited autosomal recessive trait that results in the reduction or loss of melanin. Ocular albinism affects the eye only, whereas oculocutaneous albinism leads to loss of pigment in the eyes and skin (Lorexn & Brodsky, 2009). Both forms of albinism are associated with vision problems. Abnormal decussation, optic nerve hypoplasia, astigmatism and amblyopia are common. Further, the retinal pigment epithelium may degenerate in the absence of melanin, which leads to increase scattering of light and reduced visual acuity. Further, the loss of pigment in the iris reduces the efficacy of light adaptation to bright conditions (Bridge et al., 2014).

## 1.3. Plastic Brain Reorganisation

The last section described how differences in structures of the anterior visual system can lead to visual impairment. The next section will focus on how differences in visual input influence central brain organisation. Visual processing in the brain is subserved by extensive networks that are intricately linked with other brain areas to provide information for perceptual and cognitive processing. If visual information is not provided through the anterior visual system, central networks that are typically involved in the processing of visual information may be reorganised. The following section will review the literature on structural and functional differences in brain organisation in individuals with visual impairment to highlight potential mechanisms that may contribute to differences in cognition. The first part will focus on structural differences in grey and white matter, while the second section will review functional differences, mostly concerning the recruitment of typically visual areas for processing of other information. The final section will discuss findings from a brain network viewpoint and will introduce the main neurophysiological hypotheses of the current work.

### 1.3.1. Structural Differences

A third of the brain surface is devoted to processing visual information in sighted humans. The functional literature reports compensatory adaptation in the other modalities in individuals with visual impairment. However, the intrinsic organisation of the brain might limit the ability of cortical areas to serve other functions. Further, the time and severity of visual impairment during development also has a profound impact on structural and functional plasticity (Dale & Sonksen, 2002). Based on human and non-human animal studies, there are two main routes that allow for the reorganisation of the visual brain (Amedi et al. 2003; Bavelier & Neville, 2002): i) Subcortical: studies about enucleation in different rodent and non-human primate species suggest that other modalities can enter the visual cortex through connections on the level of the thalamus (lateral geniculate nucleus, pulvinar) (Bavelier & Neville, 2002). For instance, the primary visual cortex that received input from the cochlea in enucleated hamsters displayed a tonotopical organisation highly similar to the primary auditory cortex rather than the typical retinotopical organisation of V1 (Izraeli et al., 2002). The increased cortical area devoted to processing of other senses like audition or somatosensation can lead to better-than-typical perceptual abilities in these modalities (Bavelier & Neville, 2002) ii) Cortico-cortical: Cortical areas usually involved in processing visual information can receive input from other cortical areas that process information from other modalities. Cortico-cortical reorganisation can further be distinguished by a) long-range connections between primary sensory areas, e.g. primary auditory cortex (A1) and primary visual cortex (V1), and b) short-range connections through multimodal convergence zones (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). These possibilities are not mutually exclusive.

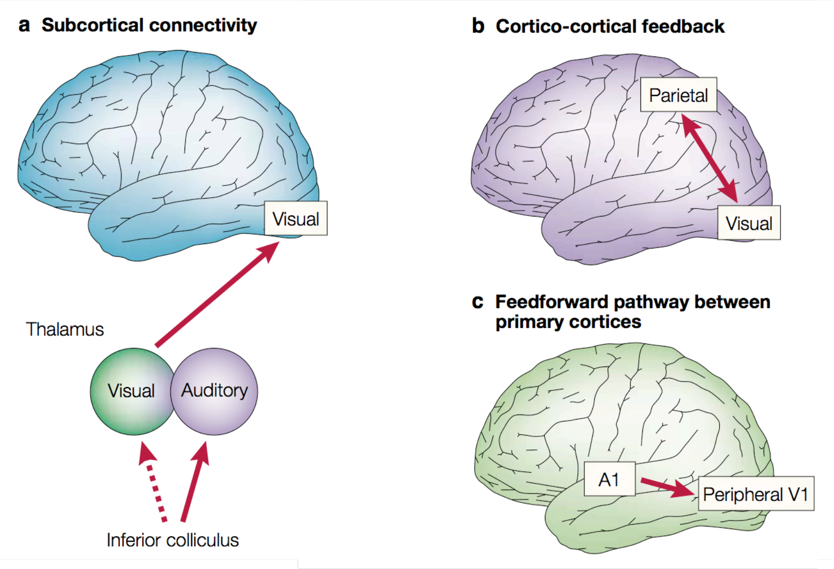


**Figure 9: Possible routes for reorganisation in response to early visual deprivation** Information can cross over from other modalities to primary visual cortical areas through a) subcortical rewiring on the level of the lateral geniculate nucleus (LGN) of the thalamus b) cortico-cortical connection through multimodal convergence zones c) long-range connections between primary sensory areas. Graphic reproduced from Bavelier and Neville 2002

A study by Kauffman and colleagues found that V1 responds to tactile information in a Braille reading test after a few days of blindfolding in sighted volunteers (Kauffman, Théoret, & Pascual-Leone, 2002). Based on these observations, the meta-modal theory of brain specialisation and development suggest that cortical regions are not primarily linked to a specific modality, but are devoted to carrying out specific computations. Therefore, cortical areas mediate specific computations regardless of the input modality. In addition, modalities are assumed to compete for the cortical processing resources (Merabet, Rizzo, Amedi, Somers, & Pascual-Leone, 2005; Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Therefore, tactile information can be processed in V1, but is usually suppressed, because V1 is occupied with visual processing. Investigations of brain structure provide some indication if sub-cortical or cortical plasticity is a more likely mechanism for brain adaptation in visually impaired humans and can offer important insight into the likely balance of impairment and compensatory plasticity. The following sections will review the relevant structural neuroimaging literature with a focus on more recent quantitative studies and on evidence for cortical and subcortical reorganisation in visual impairment.

Early neuroimaging studies investigated structural differences between visually impaired and sighted groups qualitatively. A study by Breitenseher and colleagues notes that the visual tracts comprising the optic nerve, optic chiasm and optic radiations are atrophied in 7 out of 12 congenitally blind adults that were analysed. In contrast, the lateral geniculate nucleus of the thalamus and the visual cortex appeared intact in all participants (Breitenseher et al., 1998). A study by Waugh and colleagues analysed MRI and CT scans of children with visual impairment from a clinical database (Waugh, Chong, & Sonksen, 1998). The authors reported more brain abnormalities in scans in children with profound VI than in children with severe VI. Notably, the site of lesion was variable and did not emerge as a significant factor. There was also a higher incidence of brain abnormalities in children who displayed regressive or plateauing developmental setback even when controlled for visual level. These findings seem to indicate that a) higher visual areas do not show gross anatomical abnormalities in congenitally blind people b) children with worse visual impairment or intellectual disability have additional brain abnormalities beyond what would be predicted from visual impairment alone, i.e. only atrophy of the anterior visual system.

However, newer studies show that there are additional, more subtle differences between early blind and sighted groups. More advances in quantitative imaging methods made it possible to assess structural brain difference between participant groups in more detail. Voxel-based morphometry (VBM) uses the content of the MR signal indicative of grey matter (GM), white matter (WM) and cerebro-spinal fluid (CSF). The values of these signals are transformed from the native space of the participant's MR scan to a common reference frame, e.g. MNI space (Ashburner & Friston, 2000). The content of grey matter, white matter and CSF in the common reference frame can then be compared between groups. Another method uses diffusion weighted imaging (DWI) together with tractography. DWI measures the diffusion of water molecules (Jones, 2008). In highly structured tissues, like white matter, the diffusion is limited in certain directions (anisotropy), i.e. water can diffuse relatively freely along the fibres, but not perpendicular to them (Jones, 2008). The anisotropy is expressed as a tensor for each voxel of the MR scan. Anisotropy can be directly compared between groups through measures like fractional anisotropy (FA) or the tensors can be used to reconstruct the white matter pathways. The integrity of reconstructed white matter pathways can be compared through similar measures, i.e. FA within the pathway. This technique is used to assess differences in white matter in VI, which is indicative of the quality of information transfer between brain areas (Mori & van Zijl, 2002).

A number of groups used VBM to compare early blind adult participants to sighted comparison groups. A consistent finding in the VBM literature is that the anterior visual pathway (optic nerve, optic chiasm, optic radiations) shows a decrease in WM (Noppeney, Friston, Ashburner, Frackowiak, & Price, 2005; Pan et al., 2007; Ptito, Schneider, Paulson, & Kupers, 2008; Shu, Li, Li, Yu, & Jiang, 2009). Studies using DWI show similar findings, i.e. reduced FA in the optic tract (Schoth & Krings, 2004; Shimony et al., 2006). A study by Schoth and colleagues investigated the integrity of white matter tracts in acquired human blindness (Schoth, Burgel, Dorsch, & Krings, 2006) with DWI and tractography. The participants in this study had conditions that affected their eye sight after their first year of life. Importantly, there were no significant differences in WM integrity in the anterior visual pathways nor any other pathway under investigation (forceps major and minor, corpus callosum) (Jiang et al., 2009; Schoth et al., 2006, see Figure 10). There was also no correlation between time of blindness and FA in these white matter structures when corrected for age. These results indicate that early visual experience interacts with the development of white matter structures. During an early critical period visual input is required to maintain the anterior visual pathway. Any brain differences reported in the literature are therefore likely to be an effect of visual deprivation interacting with ongoing brain maturation (Noppeney, 2007).

Anatomical differences between individuals with visual impairment and sighted controls beyond the anterior visual pathway are more inconsistent between studies, which is in part explained by the varying definition of early blindness (onset between 1 and 6 years of age), differing levels of remaining sight (light perception included or excluded) and different methodologies (VBM, cortical thickness analysis, DTI). One of the most consistent findings is a reduction in the volume and white matter content of the posterior corpus callosum (cc) (Ptito et al., 2008; Shimony et al., 2006). The posterior cc allows visual information from the primary visual cortex (V1) to cross between the hemispheres. A reduction of this white matter pathway indicates that visual areas are less well integrated in visually impaired individuals. This may imposes constraints on the functional reorganisation.

In addition, a reduction in white matter of the inferior longitudinal fasciculus (IFL) was found (Shu, Li, Li, Yu, & Jiang, 2009). The ILF connects occipital areas with temporal areas. Two studies used DTI scans to contrast white matter structural networks between early blind and sighted individuals (Liu et al., 2007; Shu, Liu, Li, Li, Yu, & Jiang, 2009). The authors reported a general reduction in network efficiency (longer mean path length, reduced global network efficiency) in the blind participants. Most differences were found in the connection of occipital, temporal and frontal nodes. Global structural network efficiency correlated with years of learning Braille (Li et al., 2013). Notably, while global efficiency was reduced, local efficiency was not significantly different between early blind and controls (Liu et al., 2007). These results indicate that while primary visual areas might take up functions that are not related to vision in congenitally blind individuals, the integration of these areas is altered in the absence of vision. A reduction in the efficiency of integration of occipital areas might limit the functions that these areas can mediate and constrain maximal network efficiency. Unfortunately, both studies did not analyse the integrity of network modules. It is conceivable that only modules that are linked to occipital nodes are different in the congenitally blind group, whereas other modules show a similar organisation to network modules of sighted participants. In turn, differences in many modules would imply that the development of occipital areas through visual input has important and far-reaching influences on general brain development and structural organisation. If other modules were unaffected, this would imply that the general organisation of the brain network is conserved and only networks directly involved in visual processing are affected by the VI.

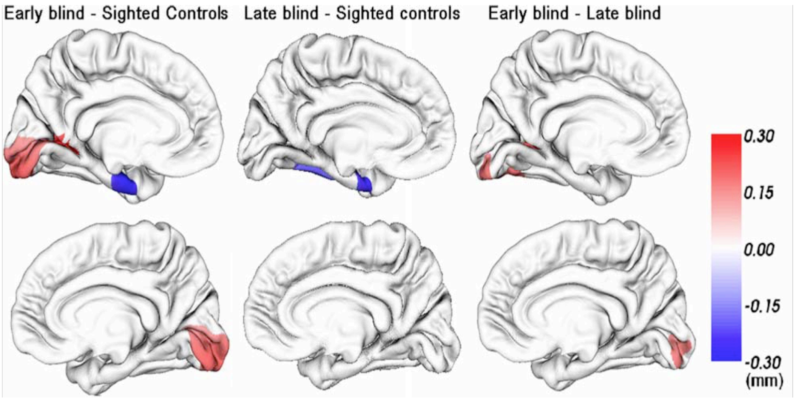


**Figure 10: Differences in cortical thickness between early blind (onset before 1 year after birth), late blind (onset between 7 and 24years of age) and matched sighted participants**. Early blind participants show an increase in cortical thickness in occipital areas. A decrease in left enthorhinal and inferior temporal cortex can be seen in both early and late blind participants. Reproduced from Jiang et al. 2009 Journal of Neuroscience

The primary visual cortex itself also displays alterations in visual impairment. Cortical thickness analysis shows that the overall V1 volume is increased in early blind individuals (Jiang et al., 2009; Noppeney et al., 2005). In contrast, GM content and surface area of V1 are reduced in blind groups (Leporé et al., 2010; Park et al., 2009). Importantly, a study comparing early and late blind individuals reported differences in cortical volumes between early and late blind groups (Jiang et al., 2009, also see Leporé et al. 2010). The differences in cortical thickness are best explained by a reduction in synaptic pruning. Synaptic pruning is an important process to fine-tune cortical processing to environmental input. Consequently, the increase in cortical thickness together with a reduction in GM content can be attributed to reduced synaptic pruning in profound visual impairment. The reduction in surface area in V1 might be explained by adjacent areas taking over cortical space. Cortical modularity is thought to be moulded by a competitive process, in which cortical micro-columns receive different inputs and specialise through structural adaptation conducive of the computations that the input requires (Rakic, 1988). In the visually deprived brain, visual columns at the periphery can receive inputs from adjacent areas. Their adaptation makes them structurally and functionally indistinguishable from the adjacent cortex (Bavelier and Neville 2002). However, adaptation of the whole areas is limited, because inputs might not reach deeper within visual cortical areas. Further, core areas are likely to be intrinsically more specialised even in the absence of input, because any morphogenic gradients that govern the cell types and composition of columns have had a stronger effect in the core area (Rakic, Ayoub, Breunig, & Dominguez, 2009).

### 1.3.2. Functional Differences

Visual areas of the cortex mediate non-visual functions in blind individuals. The findings in the literature fall into two general categories: i) visual cortical areas mediate basic processing of input from other modalities ii) visual cortical areas serves as higher-order multimodal association areas that support cognitive function. Processing of information from other modalities can be achieved through subcortical rewiring or through long-range connections between primary sensory areas. Alternatively, more processed input can reach visual areas through short-range connections with multisensory convergence zones (Hamilton, Keenan, Catala, & Pascual-Leone, 2000; Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

A study by Sadato and colleagues from 1996 first described cerebral blood flow increases in the visual cortex for early blind participants while reading Braille words compared to non-words (Sadato et al., 1996). In contrast, late blind and control participants showed suppression in V1 activation suggesting that the activation seen in the early blind participants is functionally meaningful. Hamilton and coworkers reported the case of a professional Braille reader with congenital blindness that suffered a stroke to the medial occipital cortex in her late 50s and permanently lost the ability to read Braille (Hamilton et al., 2000). This case study supports the view that areas of the visual cortex play a crucial role in Braille reading in proficient users. In addition, two studies by Burton et al. further investigated the specific function that is mediated by visual areas during Braille reading (Burton, 2002; Burton et al., 2002). Participants had to generate words in response to learned random Braille patterns or sound stimuli (Burton et al., 2002). The fMRI results demonstrated that visual areas become active for both language tasks, i.e. Braille and verbal. Another study compared fMRI responses between discrimination of random Braille dots, finger tapping and finger stimulation (Gizewski, Gasser, de Greiff, Boehm, & Forsting, 2003). Areas of the visual cortex were only active during the Braille discrimination task. These findings indicate that the visual cortex is required for higher-order processing rather than basic tactile discrimination during Braille reading. This hypothesis is confirmed by an experiment carried out by Amedi et al. that demonstrated that rTMS to occipital areas disrupts word generation in early blind participants, but not in late blind or sighted control participants in a Braille reading task (Amedi et al., 2004).

Visual areas of the cortex are also implicated in lower-order processing of stimuli in other modalities in congenitally blind people. A repetitive transcranial stimulation (rTMS) study that stimulated the occipital cortex in resting state found that early blind participants experienced tactile sensations in response to the stimulation, whereas control participants saw phosphenes (Ptito et al., 2008). Notably, the locus of the sensations for rTMS to different regions of the posterior head indicated a somatotopic organisation. Further, an fMRI study that required participants to discriminate frequency of vibration found activation of the visual cortex in early blind participants, but not in late blind participants or sighted controls (Burton et al., 2004). In addition, a study of two Braille-naive participants with late onset blindness found that visual areas were active in a Braille discrimination task even though the participants' did not understand the meaning of the patterns.

In summary, the current evidence suggests that visual areas mediate functions that are relevant to Braille reading. These functions include tactile discrimination as well as higher-order language processing. The imaging data suggests that visual areas are not subdivided into areas that take over specific functions. Conversely, the activation of similar brain areas in different tasks is more consistent with the meta-modal theory that predicts that areas are recruited for specific computations dynamically according to task demand (Pascual-Leone and Hamilton 2001).

Further, functional imaging studies that used tasks that require either lower-level or higher-level processing in other modalities indicate that areas of the visual cortex can also be recruited for processing in these tasks. For instance, sound localisation tasks were associated with activation in visual brain areas in congenitally blind participants (Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005; Weeks et al., 2000). Tasks involving either verbal working memory, long-term episodic memory or semantic language processing were also associated with activation of visual cortical areas (Raz, Amedi, & Zohary, 2005).

However, it is important to evaluate if these activations are mere by-products of processing in other areas or if their activation is indicative of compensatory superior abilities in other modalities in blind people. Some studies found correlations between task performance and activation in visual areas in blind people. A study by Raz and colleagues that investigated long-term episodic memory retrieval in early blind participants found that activation in primary visual areas correlated positively with task performance (Raz et al., 2005). In addition, a study that contained a task that required verbal working memory also found a positive linear relationship between visual cortex activation and task performance in early blind participants (Amedi et al., 2003). The performance of the early blind participants on the verbal working memory task was also significantly better than the performance of the sighted control group (Amedi et al., 2003). Equally, higher performance for early blind participants in locating sounds in a mono-aural listening condition that was associated with activation of visual cortex areas, was reported (Gougoux et al., 2005). However, a more rigorous psychophysic investigation of three dimensional sound localisation that made use of moveable loudspeakers instead of virtual sound locations found that congenitally blind participants are significantly less accurate when locating sounds in the vertical plane (Zwiers, Van Opstal, & Cruysberg, 2001). Yet, congenitally blind and sighted participants performed on a similar level in horizontal localisation. Animal studies with blinded barn owls found that especially the calibration of vertical sound localisation depends on visual input. Sound localisation on the horizontal axis relies on time differences between the ears. In contrast, vertical localisation requires the assessment of differences in sound envelope caused by deformation of the pinna (Knudsen & Knudsen, 1989) These differences give no intrinsic indication of the location of the sound source and therefore need to be calibrated. Taken together, these studies show that typically visual areas of the cortex can be recruited for processing information from other sensory modalities in congenitally blind individuals. This recruitment may be associated with higher task performance.

Another important question is what anatomical connections are most likely to allow the information transfer between different brain areas for the various functions that are mediated by the visual cortex in blind adults. Several studies investigated functional connectivity with different methodologies and conditions. An investigation by Liu and colleagues derived whole brain functional connectivity from resting state fMRI (Liu, Yu et al. 2007). Due to the prolonged duration of the resting state, the findings reported by Liu are likely to reflect anatomical underpinnings of functional connectivity. The authors report decreased connectivity between occipital regions of interest (ROIs) and all other areas. An exception was increased connections between occipital and frontal language areas. The connection strength in these vertices was associated with early experience in Braille. These findings indicate that connections that are functionally relevant can be reorganised. Further, the absence of other pronounced differences in network architecture suggests that other aspects are not changed after early visual deprivation. A case in point is a study by Burton et al. that contrasted resting periods with activation during an auditory discrimination task to evaluate the task-independent Default Mode Network (DMN) (Burton, Snyder et al. 2004). No significant differences in the nodes and vertices of the DMN were found between congenitally blind and sighted control participants. This indicates that the development of the DMN does not depend on specific sensory input. Therefore, aspects of brain organisation that are not directly involved in processing visual information (primary and secondary visual areas) do not necessarily change their interaction with other brain areas after early visual deprivation.

Two studies used Dynamic Causal Modelling on fMRI data to shed light on the regions that provide input to visual areas in early blind brains. Based on the anatomical considerations three principle inputs are possible: i) subcortical through the LGN of the thalamus ii) long-range cortico-cortical, i.e. direct connections between primary sensory areas iii) short-range cortico-cortical connections, i.e. information is relayed through multimodal convergence zones. A study by Klinge and colleagues investigated the relationships between primary auditory and visual areas as well as thalamic nuclei in an auditory discrimination task in congenitally blind and sighted participants (Klinge, Eippert et al. 2010). Model selection favoured a strongly interconnected model for both participant groups. Further, the authors reported stronger direct connections between A1 and V1. Another line of evidence based on ERP experiment by Roder and coworkers further suggests direct cortical connections between auditory and visual areas. Roder et al. found more negativity over occipital channels in congenitally blind participants in an auditory oddball detection task (Roder et al., 1996). The negative deflection occurred in the N2 window (200-350ms after stimulus onset). Notably, no differences in earlier components, e.g. N1, were found. The latency of the difference between blind and sighed suggests that cortico-cortical connections mediate the difference in brain response, because subcortical rewiring would lead to earlier ERP differences. The latency range is most consistent with a direct connection between primary areas as opposed to relays via multimodal convergence zones that would also lead to differences in later components. Therefore, both ERP and DCM findings suggest that auditory information reaches primary visual areas through direct long-range connections between A1 and V1.

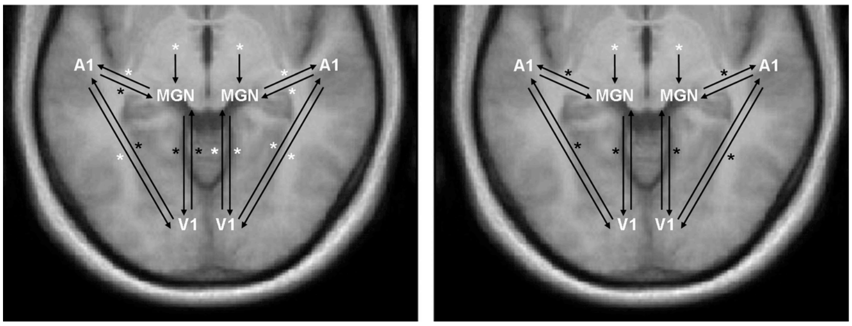


**Figure 11: Model of connections between primary auditory (A1), visual (V1) cortex and medial geniculate nucleus (MGN) of the thalamus in an auditory discrimination task suggested by DCM** The model for the congenitally blind group are shown on the left, sighted controls on the right; White asterisk: p<.05 corrected; black asterisk: p<.05 uncorrected. The model suggests direct feedforward and feedback connections between A1 and V1. Direct connections from MGN to V1 were present in both groups, but were not significantly different between blind and sighted. Image reproduced from Klinge et al., 2010, Journal of Neuroscience

In contrast, the direct connections between primary sensory areas with visual areas that were found in the auditory domain do not generalise to other modalities. A DCM fMRI study by Fujii and colleagues found no evidence for a direct connection between primary somatosensory cortex (S1) and V1 in a Braille discrimination task (Fujii, Tanabe et al. 2009). The model favoured by Bayesian model selection contained relays through multimodal areas of the dorsal stream between S1 and V1.

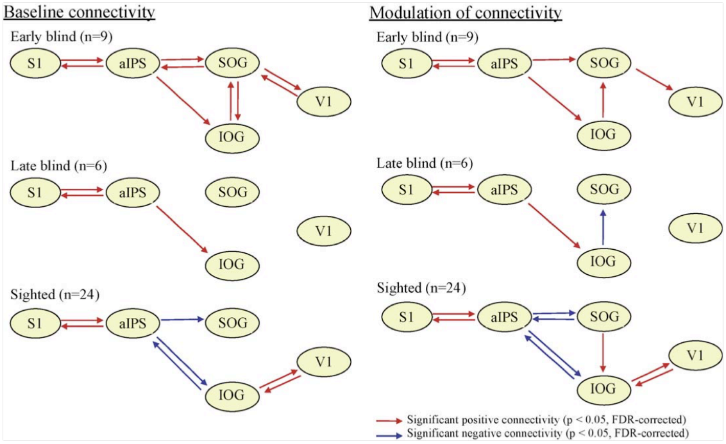


**Figure 12: Model of connection between S1 and V1 favoured by DCM in a Braille discrimination task in early blind (<16 years), late blind (>16 years) and sighted control participants.** S1: primary somatosensory cortex, aIPS: anterior parietal sulcus, SOG: superior occipital gyrus, IOG: inferior occipital gyrus, V1: primary visual cortex. Direct connections between S1 and V1 are not implicated by the Bayesian model selection. The areas are connected through multimodal areas of the dorsal stream. Notably, positive connections between aIPS, SOG and IOG appear negative in sighted controls. This is most likely to reflect competitive suppression of these areas in sighted participants. Graphic reproduced from Fujii et al., 2009, Neuroscience Research

In summary, functional imaging studies suggest that visual cortical areas are recruited for processing stimuli in other modalities. Visual areas are active during both low-level processing of sensory input and higher-level processing. The recruitment of visual areas is associated with higher-than-typical performance in early blind participants in most tasks. Information is transferred from primary non-visual sensory areas to visual areas through direct long-range connections or via multimodal convergence zones. The functional imaging literature does not support a strong contribution of subcortical rewiring.

### 1.3.3. Brain organisation in cognitive networks

Based on lesion studies in macaques, Mishkin and Ungerleider proposed that higher visual processing occurs along two largely separate streams (Mishkin & Ungerleider, 1982): a dorsal stream that is involved in the processing of spatial information and vision for action, and a ventral stream that is involved in the processing of the identity of objects. The general concept of the two stream theory haven been supported by later neuropsychological (Goodale & Milner, 1992) and imaging studies (Culham, He, Dukelow, & Verstraten, 2001). Further, developmental studies found that dorsal stream functions are particularly affected in a range of neurodevelopmental disorders and children at risk for adverse developmental outcomes, including William's syndrome (Atkinson et al., 1997), autism (Spencer et al., 2000), hemiplegia (Gunn et al., 2002), dyslexia (Cornelissen, Richardson, Mason, Fowler, & Stein, 1995), and children with very low birth weight (Atkinson et al., 2002).

More recent accounts that describe dorsal connectivity in more detail provide predictions about possible cognitive consequences of altered dorsal stream function. Based on a comprehensive review of the animal and human literature, Kravitz and colleagues proposed a revised view of dorsal stream anatomy (Kravitz, Saleem, Baker, & Mishkin, 2011). Initially, dorsal stream pathways follow a shared origin of connections arising from higher level visual areas of the occipital lobe (V2, V3, V3A) to area V6 at the junction between occipital and parietal lobe. From there, three main pathways can be distinguished:

A) a parietal-prefrontal pathway involved in the top-down control of eye movement for spatial working memory and attention (Courtney, Petit, Haxby, & Ungerleider, 1998; Curtis, 2006)

B) a parieto-motor cortex pathway important for grasping and general integration between vision and action (Gamberini et al., 2009). In addition to the role of the parieto-motor cortex pathway for vision of action, there is also evidence to suggest that the integration of these areas is important for action understanding through coupling of action observation and motor execution (Cook, Dickinson, & Heyes, 2012; C. Heyes, 2010).

C) an indirect parietal-mediotemporal pathway implicated in visuospatial memory and spatial representation (Kravitz et al., 2011; Margulies et al., 2009; Vincent, Kahn, Van Essen, & Buckner, 2010). Even though anatomical and functional evidence exists that suggest a connection between these areas, the connections are assumed to involve several intermediaries and the functional consequences of selective disconnection are not clear. Therefore, evidence for the parieto-mediotemporal pathway seems the less conclusive than for the other pathways.

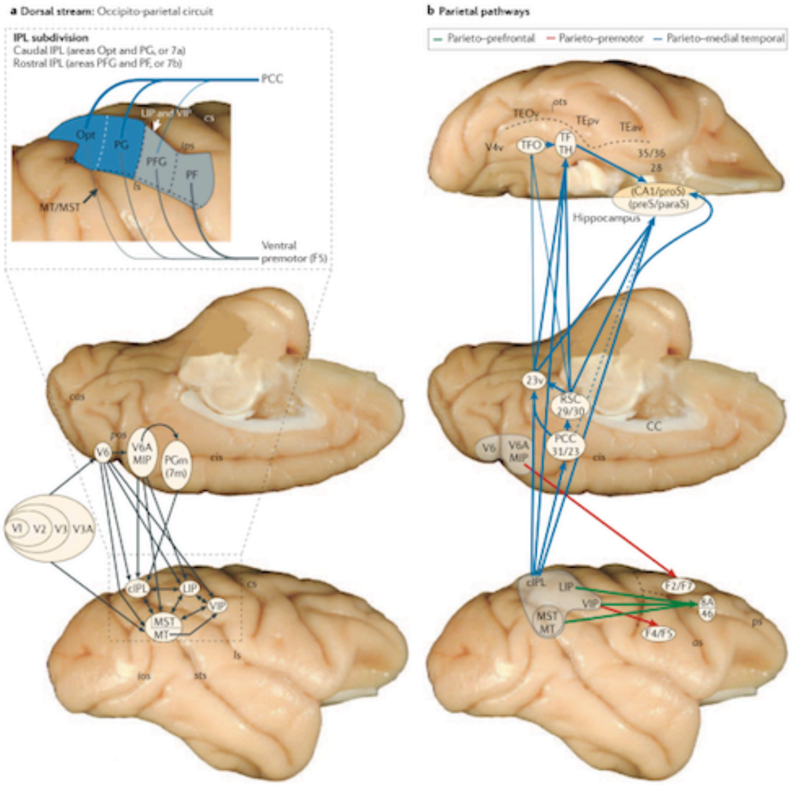


**Figure 13: Main pathways of the extended dorsal stream displayed on macaque anatomy.** Figure reproduced from Kravitz et al. 2011

This account of dorsal stream integration across the brain is also in line with network descriptions of brain functions, but places a slightly different emphasis on the specificity of dorsal stream visual input. The connections of parietal regions that are extensively discussed in Kravitz et al. 2011 overlap with parietal hub regions that have been identified in network analyses of structural and functional neuroimaging data in human participants (Ball et al., 2014; Huang et al., 2013; Stam, 2014; van den Heuvel & Sporns, 2011). For instance, a study by van den Heuvel and Sporns in 2011 identified left and right superior parietal lobes to be parts of the so-called rich club based on white matter connectome analysis. Nodes within the rich club are nodes with high number of connections that are central for network organisation . The importance of rich club nodes is further exemplified by a meta-analytic study that found that changes in rich club nodes are implicated across a range of acquired and developmental brain disorders (Crossley et al., 2014). Further, computational modelling confirmed that changes to rich club organisation have a disproportioned effect on overall brain organisation compared to simulated changes to other nodes (Crossley et al., 2014).

Given the central role of superior parietal connections suggested by recent network analyses, it is not surprising that connections through these nodes are implicated in a range of cognitive functions. Further, the dense connectivity of these nodes also suggests resilience - similarly efficient network structure may be achieved through re-routing. Further, superior parietal nodes are part of a cluster of nodes that undergoes significant changes between childhood and adulthood (Grayson et al., 2014) indicating an effect of intrinsic or experience-driven reorganisation in the integration of these nodes with possible implication for developmental patterns observed in VI.

Based on the anatomical model of the extended dorsal stream and previous neurophysiological and anatomical studies, we expected differences in the integration of occipital regions via superior parietal hubs in children with VI. Therefore, the current study focusses on cognitive functions that are predicted to be impaired by the extended dorsal stream model and previous behavioural studies in children with VI. Based on the predictions of the model, differences in executive abilities were hypothesised to be related to the integration of occipital areas with prefrontal areas. Differences in social function were thought to arise from differences in the integration of the parieto-motor cortex pathway with areas of the social brain network. Further, direct connections between the parietal and medial temporal lobe are thought to be associated with the transfer of visual information for spatial memory and spatial navigation.

## 1.4. Sensory experience, brain maturation, and cognitive development

The previous sections reviewed the anatomy of the visual system, visual development, and disorders of vision in congenital disorders of the peripheral visual system. Further, differences in brain organisation of adults with congenital visual disorders were discussed. Potential influences of differences in brain organisation were highlighted on the basis of the extended dorsal stream model. The next section expands on these predictions by discussing the impact that sensory experience and brain maturation may have on cognitive development within the wider theoretical framework of interactive specialisation (Johnson, 2001; 2010; Johnson & de Haan, 2010; Karmiloff-Smith, Scerif, & Thomas, 2002; Mareschal et al., 2007).

Early theories of cognitive development put minor importance on sensory experience for cognitive development. Piaget suggested that sensory experience is related to early cognitive development in infants (sensorimotor stage), but is superseded by more abstract representational thinking in older children (Piaget, 1972). Vygotsky's theories also highlight the importance of abstract representations, particularly language and social interaction (Vygotsky, 1978 – English translation). Cognitive science theorists in the middle of the 20th century compared the mind to a computer's software that is largely independent of the body's hardware (Marr, 1982). However, the advent of human *in vivo* imaging technologies and the accessibility of large-scale genetic screening techniques revealed that biological factors play an important role in cognition and cognitive development (Johnson, 2010; Johnson, Munakata, & Gilmore, 2002; Mareschal et al., 2007; Nelson, de Haan, & Gunnar, 2006). From a reductionist perspective, changes on lower levels of the system may cause higher-level differences. For instance, differences in a certain gene may cause cognitive differences. However, recent evidence suggests that the transcription of genes may be modulated through epigenetic mechanisms depending on the environmental context of the organism, which will influence phenotypic traits (Holliday, 1990). Therefore, multi-directional interactions between different levels of organism are assumed (Gottlieb, 1992). For instance, gene may be up- or down-regulated depending on the demands of the environment on the organism. This view was later extended to incorporate brain and cognitive development in the interactive specialisation (IS) framework (Johnson, 2001; 2010; Johnson & de

Haan, 2010; Karmiloff-Smith et al., 2002). According to IS, genes, brain, and behaviour act as multiple, interacting constraints on development.

Congenital visual impairment may be caused by genetic factors, e.g. SOX mutations, e.g. retinitis pigmentosa (Koenekoop et al., 2003), or by early insult, e.g. hypoxia. These differences may be seen as a first constraint on development: In the absence of vision, the development of brain areas and cognitive functions that depend on vision is likely to follow a different trajectory compared to typically-sighted individuals. Further constraints are imposed because information that is important for the development of a particular cognitive function may be less accessible through other sensory modalities. Therefore, within the IS one might assume primary effects arising from the absence of vision and secondary effects that arise from constraints imposed on developmental processes. Based on this view, the current investigation assessed effects of congenital VI on cognitive processes that do not require online access to visual information, but may have been influenced by the absence of vision over development.

## 1.5. Visual Impairment & Cognitive Development

In line with Interactive Specialisation framework, differences in behaviour have been reported for children with visual impairment beyond differences that are directly linked to vision. A high level of learning difficulties (up to 50 or 60%) have been identified in many different cohorts of children with VI (Absoud, Parr, Salt, & Dale, 2011; Alimovic, 2013; Parr et al., 2010). Even in samples selected for normal intelligence, a recent study of children with potentially 'simple' CDPVS group and normal verbal intelligence identified an uneven cognitive profile with relative strengths in structural language skills and relative weaknesses in social understanding (Tadić, Pring, & Dale, 2009). Other studies have also identified significant weakness in the social domain (Brambring & Asbrock, 2010; Minter, Hobson, & Bishop, 1998; Peterson, Peterson, & Webb, 2000), executive function (Tadić, Pring, & Dale, 2009), and spatial representation (Gaunet et al., 2006; Ittyerah, Gaunet, & Rossetti, 2007; Pasqualotto, Spiller, Jansari, & Proulx, 2013; Schmidt, Tinti, Fantino, Mammarella, & Cornoldi, 2013). The following section will review the literature on behavioural and cognitive difference in these domains.

### 1.5.1. Attention

The extended dorsal stream model suggested that differences in the integration of parietal areas with prefrontal areas may lead to differences in executive abilities. One aspect of executive function that has previously been studied in VI is attention. Attention refers to the selective processing of stimuli. Attention helps to prioritise information that is relevant to the current goals or the demands of a task (Johnson & de Haan, 2010). Attention may either be understood as a supra-modal mechanism that processes information from different sensory modalities or as separate, yet similar processes for each sensory modality. Different lines of evidence support a supra-modal view.

From an experimental perspective, one would assume that if attentional processes were separate, there would be little interference when simultaneously attending to stimuli in different modalities. Contrary to this assumption, diminished performance has been reported when participants attended to a task-irrelevant modality for a number of modality pairings (Lloyd, Merat, McGlone, & Spence, 2003; Spence, Lloyd, McGlone, Nicholls, & Driver, 2000; Spence, Nicholls, & Driver, 2001). However, this effect seemed to depend on the task demands: for low-level modality-specific discrimination, little interference of task-irrelevant information in another modality was found. On the other hand, higher level (cognitive) tasks produced interference (Alais, Morrone, & Burr, 2006). The following discussion refers to attention that is engaged in higher-level tasks based on the paradigms reported in the literature.

From a psychometric perspective, both auditory and visual tasks of the Test of Everyday Attention for Children (TEACh) were associated with a common sustained attention factor with similar factor loadings with auditory and visual tasks (~0.5) (Manly, Nimmo-Smith, Turner, Watson, & Robertson, 2001).

From a developmental perspective, theoretical accounts suggest that cross-modal attention effects arise from the constructions of a spatial representation in which information from different modalities is integrated (Driver & Spence, 1998). This account is supported by single-unit recordings in monkeys that show that the activity of multi-sensory neurons in different areas (superior temporal lobe, superior parietal lobe, frontal lobe) is modulated by the location of the stimulus in space. Vision is thought to play an important role in the construction of a common spatial representation across modalities (Bremner, Holmes, & Spence, 2008). Indeed, some authors argue that subcortical mechanisms of visual orienting are precursors for cortically mediated attention (Johnson & de Haan, 2010). Differences in early visual experience may therefore lead to differences in attention development that is apparent in other sensory modalities. A study by Tadić and colleagues identified higher variability in responses to adult directed attention bids during a structured play situation in toddlers and pre-schoolers with visual impairment (Tadić, Pring, & Dale, 2009). The strongest effects were seen in the profoundly visually impaired children compared to children with SVI who were rated similar to the comparison group of typically-sighted. However, attention in older children with VI has not been widely researched, which is possibly explained by the general rarity of developmental cognitive investigations in this area.

The limited available literature indicates that attention is altered in children with VI. For instance, an epidemiological study that assessed the prevalence of ADHD diagnosis by parental report in 264 children attending specialist schools for the visually impaired between 4 and 17 years of age found an elevated prevalence of ADHD in children with low vision. Further, lower prevalence of ADHD diagnoses was found for children with PVI compared to the typically-sighted general population (Decarlo et al., 2014). Further, an experimental study by Cavézian and colleagues found attentional deficits in a group of 7 year old children with mild to moderate visual disorders (refractive error, strabismus, nystagmus, amblyopia) (Cavézian et al., 2013; Leat & Lovie-Kitchin, 2008). In contrast, other aspects of attention were found to be superior in visually impaired groups when assessed with appropriate, non-visual materials. For instance, a study that assessed performance on verbal tasks of the original version of the Wechsler Intelligence Scale for Children found that children with visual impairment performed significantly higher than the control group on sustained auditory attention (Witkin, Birnbaum, Lomonaco, Lehr, & Herman, 1968).

In conclusion, attention may be affected in school age children with VI, particularly in children with low vision.

## 1.5.2. Social Development

The extended dorsal stream model suggested that alterations in the integration between parietal and premotor areas may influence social understanding via disruptions of self-other mapping. Indeed, congenital visual impairment has also been linked to differences in cognitive and social development. Investigations about social cognition in children with visual impairment fall into two broad categories: studies investigating the development of specific skills, e.g. ability to pass Theory of Mind tasks and studies comparing the behavioural features of children with VI to autism spectrum disorder (ASD) in sighted children.

### 1.5.2.1. Theory of Mind Development

Theory of Mind (ToM) describes the ability to make inferences and reason about the mental states of other agents. Different accounts further divide ToM into subprocesses, like the ability to processes the beliefs of others as measured in false belief tasks and the ability to reason about the goals and actions of others (Gunnar & de Haan, 2006). False belief tasks predominantly incorporate object transfer questions that create a conflict between the participant's knowledge about the location of an object and the belief of an agent in the task (Wimmer & Perner, 1983). The ability to pass such first-order false belief tasks is typically established between 3 and 4 years of age (Gunnar & de Haan, 2006), although there is evidence for precursors in infancy (Baillargeon, Scott, & He, 2010; Kovács, Téglás, & Endress, 2010).

Different theoretical accounts about ToM and its development exist that generate different predictions about ToM in visual impairment. Briefly, domain-specific accounts assume a specific module subserving ToM abilities (Leslie, Friedman, & German, 2004), whereas domain-general accounts propose that ToM relies either on a system that holds general principles about mental states (theory-theory account) or on a system that is based on perceptual-motor mapping (simulation account) (Mahy, Moses, & Pfeifer, 2014). It has been suggested that these accounts are not necessarily mutually exclusive, but instead represent different aspect of a ToM system (Apperly, 2008).

One might assume that simulation aspects of ToM are particularly impaired in children with visual impairment, because a large amount of information like eye gaze, facial expression and body posture may not be available to them. This might disrupt the self-other mapping to is thought to mediate social understanding according to the simulation view. Indeed, several studies report delays in the ability of children with severe to profound VI to pass false belief tasks (Brambring & Asbrock, 2010; Minter et al., 1998; Peterson et al., 2000). However, a study by Pijnacker and colleagues investigating advanced ToM abilities in school-age children found that test scores were predicted by verbal IQ rather than by vision level. Brambring & Ashbrock further highlight that the delays seen in the development of first-order false belief tests in preschool children with VI are comparable to delays in other domains, e.g. language (Brambring & Asbrock, 2010). Indeed, Dunn & Brophy identified language as the most predictive factor for ToM scores in children with ASD and moderate learning difficulties (Fisher, Happé, &

Dunn, 2005) and deaf children of non-signing parents were found to show delays in ToM acquisition (Peterson & Siegal, 1995). Further, a study by Brown and colleagues in Peter Hobson's research group that split a group of children with PVI according to verbal IQ and employed control groups of typically developing as well as autistic children. They report that the VI group with higher verbal IQ obtained similar scores for social communication abilities to the typically developing group, whereas the subgroup with lower verbal IQ rated similarly to the group of sighted autistic children (Brown, Hobson, Lee, & Stevenson, 1997).

In summary, evidence from the literature suggests delays in the development of ToM abilities in children with visual impairment. However, the developmental impact seems to be mediated by verbal ability.

#### 1.5.2.2. Behavioural similarities with autism spectrum disorder

Several studies investigated parallels between ASD in typically-sighted children and behaviour observed in children with severe or profound VI. A large sample was presented in a study by Mukkades and colleagues that assessed the prevalence of ASD in 257 children from specialist school for the visually impaired in Turkey (Mukkades, Kilincaslan, Kucukaltun-Yildirim, Sevketoglu, & Tuncer, 2007). The study reports that 22% of the sample met criteria for ASD based on questionnaire measures and psychiatric evaluation. Further, in line with Brown et al., higher ASD scores were associated with lower vision level, lower verbal IQ and higher incidence of additional neurological impairments (Brown et al., 1997; Mukkades et al., 2007). A number of small case series suggests that a large proportion of children VI meet criteria for ASD: 9 out of 18 children (Absoud et al., 2011), 5 out of 9 (Williams, Fink, Zamora, & Borchert, 2013), 5 out of 5 (Rogers & Newhart-larson, 1989). Several factors have been identified that may contribute to this apparently high incidence and the considerable within-sample variation: a) Verbal IQ (Brown et al., 1997) b) ASD is more prevalent in certain diagnostic categories, and c) depends on the age of the group under investigation (Brown et al., 1997).

### 1.5.3. Spatial Representation & Procedural Intelligence

The extended dorsal stream model suggested that indirect connections between the parietal cortex and the medial temporal lobe are involved in the transfer of information for spatial cognition. Spatial cognition describes the acquisition, updating, manipulation and utilisation of knowledge about the environment. These abilities are important for navigation, spatial memory and, object use in everyday life. Vision is usually the most salient sense for spatial cognition, because a large amount of information can be acquired in parallel about objects in near space as well as objects further away (Cattaneo & Vecchi, 2011). In contrast, tactile information can only be obtained serially and is limited to objects within reach. Audition provides more spatial information, but with limited accuracy. In addition, objects do not necessarily produce sounds all the time. Further, some authors argue that vision binds together and calibrates information from other sensory modalities within a spatial reference frame (Abel, Figueiredo, Consoli, Birt, & Papsin, 2002; Cattaneo & Vecchi, 2011). Spatial representation in individuals with visual impairment has been an area of intense research with many conflicting reports in the literature. The most researched questions include the type of spatial reference frame used, i.e. egocentric vs allocentric representation, memory for object locations and, mental representation of space.

#### 1.5.3.1. Spatial Reference Frame

Space may be represented relative to the viewer (egocentric) or to an external reference (allocentric, viewpoint-independent). Vision has been found to play an important role in the development of spatial representation (Ali, Cowie, & Bremner, 2014). Developmental studies investigating representation of near space with congenitally blind children and blind-folded sighted controls between 6 and 12 years found that both groups used an allocentric reference frame in a pointing task in near space (Gaunet et al., 2006; Ittyerah et al., 2007). However, another study reports that children with congenital PVI between 6 and 8 years used an egocentric reference frame in a similar pointing task (Iossifova & Marmolejo-Ramos, 2013). The differences in the results may be explained by differences in onset and degree of visual impairment between the studies.

Further, Rieser and colleagues studied the influence of congenital PVI compared to later onset PVI on the ability to judge Euclidean distance in a novel environment

(Rieser, Lockman, & Pick, 1980). The best performance was found in the blindfolded sighted controls followed closely by the late blind group and the worst performance was observed in the congenitally blind participants. These findings suggest that vision during early parts of development is necessary to form accurate spatial representations. Further, a study comparing the performance of individuals with monocular SVI and binocular moderate VI on three-dimensional visual memory task found that participants with moderate VI perform on a similar level as sighted controls, whereas individuals with monocular SVI performed on the same level as PVI participants (Vecchi et al., 2006). These findings suggest that binocular vision rather than visual acuity per se is important for the development of spatial cognition.

### 1.5.3.2. Spatial Memory

In addition to the reference frame used for spatial representation in individuals with VI, spatial memory and mnemonic strategies are highly important for individuals with visual impairment. Specifically, the question of whether individuals with severe to profound visual impairment prefer route-based or survey-based mental representation of memorised spatial layouts has been researched. Route descriptions provide information from the view point of a person mapping the environment, while survey descriptions take an outside perspective and provide information about the relative locations of landmarks (Loomis et al., 1993). A study by Afonso compared the ability of adults with PVI and blindfolded matched controls to provide a description of a novel environment based on verbal description, haptic learning with a tactile map, or active locomotor exploration (Afonso et al., 2010). The results indicated no significant difference in the verbal and haptic condition, but significantly higher performance in the locomotor condition for the PVI group. This suggests that this group benefitted from an active route-based acquisition. However, another study highlights that route-based representations are hard to maintain when the path length increases (Cornoldi, Tinti, Mammarella, Re, & Varotto, 2009): for shorter path lengths, the performance of blindfolded sighted participants and congenitally blind adults reached similar performance, but congenitally blind adults scored significantly lower when the path length was increased. These results show that congenitally blind adults used a serial, route-based representation.

The only developmental study that investigated strategies used by children with visual impairment on a spatial learning task required children with PVI and a matched blindfolded comparison group to learn a tactile map (Ungar, Blades, & Spencer, 1995).

Children with PVI were less able to provide an accurate description of the map and used strategies that were less appropriate, e.g. verbal rehearsal. In addition, children in the VI group were less able to estimate the relative distance between landmarks on the tactile map. On the individual level, children with VI that reached higher performance used strategies that were more similar to the strategies used by blindfolded controls, i.e. spatial imagery. These findings are in line with a recent study by Schmidt and colleagues (Schmidt et al., 2013): Profoundly visually impaired individuals that used an imagery strategy obtained scores similar to typically-sighted participants. Further, a correlation between mobility skills and the use of imagery strategies was found indicating that experience and training of mobility skills in individuals with PVI is associated with better spatial representation.

#### 1.5.3.3. Mental manipulation of objects and spatial layouts

Studies about mental manipulation of spatial representations have mostly focused on the ability to recognise objects (or arrays of objects) after rotation. Similar to other topics of spatial cognition, reports in the literature about the ability of congenitally and late blind adults to pass rotate tasks is often contradictory: one of the first investigations reported no performance differences between congenitally blind adults and blindfolded control participants on a haptic recognition task after rotation (Carpenter & Eisenberg, 1978). However, a study by Millar and colleagues that matched blind and sighted participants on haptic recognition abilities found that blind participants' performance was significantly worse when mental rotation or perspective taking is required (Millar, 1976; Pasqualotto & Newell, 2007). The finding that there is considerable variation in spatial skills within adults with congenital severe and profound visual impairment in a recent study by Koustriava and colleagues (Koustriava & Papadopoulos, 2012) might explain the difference in results. Specifically, Koustriava et al. found that body knowledge and directionality scores are predictive of near space encoding scores.

#### 1.5.3.4. Spatial Cognition Summary

In summary, in line with the predictions of the extended dorsal stream model individuals, the existing literature shows differences in spatial memory and spatial cognition in VI compared to typically-sighted controls. Individuals with severe to profound visual impairment are more likely to use an egocentric spatial reference frame and memorise spatial configuration in route-based form. These strategies are not optimal to represent complex spatial layouts and provide a disadvantage when spatial representation have to be manipulated, e.g. rotation or Euclidean distance judgment. However, discrepancies in research findings as well as investigations that compared inter-individual differences indicate that a proportion of individuals with VI is able to solve these tasks and uses strategies and representation similar to typically-sighted participants. Mobility, use of sensory substitution, and mobility training are likely factors that contribute to the variability.

### 1.5.4. Vision & Cognitive Development Summary

In summary, a review of the existing literature on cognitive differences in individuals with VI suggested areas of cognitive deficits that are consistent with the three streams of the extended dorsal stream model: a) questionnaire measures and epidemiological studies suggested difficulties in executive abilities in children with VI b) weakness were found in mentalizing abilities with delays in the development of theory of mind and high rates of behavioural characteristics associated with autism spectrum disorder, and c) spatial memory and spatial representation were also found to be affected with preferences for egocentric spatial representation and decreased spatial memory capacity.

## 1.6. Chapter Discussion

The present chapter provided the general background of visual impairment during childhood and introduced the overarching hypotheses of the current work. The first part of the chapter introduced mechanisms of visual perception and the development of visual function in typically-sighted individuals. Based on this background, the concept of congenital disorders of the peripheral visual system (CDPVS) was introduced. This term refers to a number of disorders affecting the globe of the eye, retina, and anterior optic nerve. A detailed description of CDPVS disorders highlighted the heterogeneity of disorders even within diagnostic categories and the overriding communality of decreased visual function in this group.

Following on from anatomical differences in the periphery of the visual system, the possible impact of visual impairment on central brain organisation was discussed based on reports from the literature. This discussion showed structural and functional re-organisation that arises as a secondary consequence of congenital visual impairment. The published literature suggests that this reorganisation is not only linked to perceptual differences, but also extends to cognitive processes. The extended dorsal stream model was introduced. According to this model, projections of the dorsal stream to target areas in the prefrontal, premotor, and medial temporal cortex are involved in specific cognitive functions. Parieto-prefrontal connections are implicated in executive function and spatial working memory. Parieto-motor cortex functions are thought to contribute to the integration of space and motor control, and by extension to social understanding via self-other mapping. Indirect connections between the parietal and medial temporal lobe are hypothesised to play a role in spatial memory and spatial navigation.

Based on these predictions, the existing literature on cognitive differences in VI was reviewed. In line with predictions of the model, the literature review identified deficits in aspects of attention, social understanding, and spatial memory.

The organisation of subsequent chapters follows this general line of argument by describing dissociations of performance within functional domains that are then related to extended dorsal stream model.

The first data chapter will describe general background characteristics, including results of questionnaire measure of adaptive behaviour, strengths and difficulties, quality of life, and parental factors.

The second chapter focusses on functions associated with parieto-prefrontal of the extended dorsal stream model. The chapter contains findings based on neuropsychological and electrophysiological investigations of executive functions, including sustained and divided attention, semantic and phonemic verbal fluency, parent questionnaires of everyday executive ability, and neural correlates of binaural listening. It was expected that particular executive functions are affected by VI: higher performance was hypothesised for sustained auditory attention and lower performance on divided auditory attention tasks. On the other hand, verbal fluency was expected to be similar to the typically-sighted group. Parent ratings were expected to show higher degrees of executive function difficulties in everyday life as reported in a previous study.

The third chapter discusses investigations of functions related to parieto-motor cortex connections of the extended dorsal stream model. The prevalence of autistic features, communicative profiles, mentalizing abilities, and neural responses to basic auditory social stimuli are evalulated. Based on previous reports, a high prevalence of autistic behaviours and communication profiles was predicted. Further, lower scores were expected on assessments of mentalizing abilities. A dissociation between children with mild/moderate and children with severe/profound VI was expected based on studies that identified residual vision as a protective factor during early social development.

The fourth chapter will report results relating to parieto-medial temporal connections of the extended dorsal stream model related spatial memory. Findings on spatial memory performance are reported and contrasted with results of a verbal short-term memory assessment.

The fifth chapter reports investigations of structural brain organisation including integrity of key white matter pathways that are implicated in the transfer of visual information throughout the brain and a white matter connectome analysis. Differences in measures of structural properties were related to differences on the cognitive level discussed in preceding chapters.

The sixth chapter describes results of quantitative analysis of resting-state functional EEG data that is aimed to characterise differences in the functional relationship of cortical areas. Alterations in the integration of typically visual areas of the occipital cortex were expected.

# Chapter 2: General Methodology

Before describing the results in the main body of this thesis, the current chapter will describe the methodological background of the study. First, recruitment details will be described, including inclusion criteria and recruitment sources. Next, methods employed in the study will be introduced alongside general analytic approaches that were employed throughout the study, e.g. data processing of MRI and EEG data, and general analysis procedures.

## 2.1. Participant Recruitment

### 2.1.1. Recruitment criteria

The current investigation aimed to assess the cognitive and social development of school-age children with congenital disorders of the peripheral visual system. Based on this goal the following inclusion and exclusion criteria were defined:

Inclusion criteria:

- congenital visual impairment in the moderate to profound range
- primary diagnosis of paediatric disorders affecting the globe of the eye, the retina, or the anterior optic nerve up to the optic chiasm (potentially 'simple' congenital disorders of the peripheral visual system, CDPVS – Sonksen and Dale 2002)
- age between 8 years and 13 years (mid-childhood)
- good verbal functioning:
  - verbal IQ at the last assessment above 75 or if vIQ not available, attending mainstream school at age-appropriate level
  - English as a first language or being taught in an English-speaking mainstream school

Exclusion criteria:

- comorbid neurological disorders
- indications of other brain involvement based on paediatric report, e.g. involvement of midline structures or pituitary (as in septo-optic dysplasia), i.e. potentially 'complex' congenital disorders of the peripheral visual system or cortical visual impairment; Sonksen and Dale 2002).
- indication of endocrine abnormalities on paediatric report

The current investigation focussed on the mid-childhood range as previous studies suggested the most pronounced effects on the cognitive domains of interest (executive function, social understanding) in this age range (see Chapter 1 for a detailed discussion of the literature). Mid-childhood is also the age range during which these functions undergo rapid development in typically-sighted children.

Only children with disorders affecting anterior parts of the visual system with no involvement of central parts were included. Through this inclusion criterion, the study aimed to obtain a picture of the most selective visual impairment. So that any effects that are observed on the behavioural and neural level as likely to be secondary consequences of the visual deprivation. If cases with central brain abnormalities were included, any observed effect may have arisen as a primary result of central brain damage.

Further, the current investigation focussed on higher functioning children with visual impairment. The majority of school-age children on the database at the primary recruitment site (Developmental Vision Service) did not meet inclusion criteria, because their verbal ability was below expectation for their chronological age. This is in line with prevalence estimates of up to 50-60% of children with visual impairment having additional learning difficulties (Rahi et al 2002). Therefore, the current sample is not thought to be representative of children with visual impairment as a whole. Instead, the study is designed to focus on cognitive differences that are specific to VI, i.e. functions that are affected even when general verbal ability is in the normal range. The limitations for clinical interpretation of findings from the current study are discussed in further detail in the General Discussion chapter.

Children in the typically-sighted control group were recruited to fit in the same age range, attend mainstream school at age-appropriate level, have no known neurological or psychiatric conditions, have either normal or corrected-to-normal vision, and have English as a first language or attend mainstream school in the UK at age-appropriate level. Due to variation in assessment methods and incomplete data, matching could not be based on stringent one-to-one matching of participants on previous test scores.

### 2.1.2. Recruitment sources

Children with visual impairment were recruited through the Developmental Vision Clinic (DVC) at Great Ormond Street Hospital for Children NHS Foundation Trust, Moorfield's Eye Hospital NHS Foundation Trust and through self-referral. The DVC is a tertiary clinical service that specialises in the assessment of vision and cognitive ability of infants, children, and adolescents with visual impairment. The clinic consists of multi-disciplinary teams of paediatricians, ophthalmologists, psychologists, and occupational therapists. Secondary or tertiary health care providers may refer patients to this service. Due to the highly specialised nature of the DVC, extremely rare disorders or patients with greater behavioural or cognitive difficulties are likely to be seen at this clinic. However, during infancy to school-entry age, young children and parents are routinely referred for specialised ongoing assessment and guidance. Potential participants for this study were identified through the clinic database which includes children who were referred during their early years and were not receiving ongoing treatment at the time of their participation in the study.

Moorfield's Eye Hospital served as an additional recruitment centre. Moorfield’s specialises in the assessment and treatment of ophthalmological conditions and also offers paediatric ophthalmological services. Both patients with common or rare eye disorders and varying degrees of visual impairment may be seen at this hospital.

Collaborating clinicians at the two main recruitment sites approached families with children that met the recruitment criteria. Interested families that signed an initial contact form were approached with further information about the study. In addition to recruitment through the hospital, specialist teachers for children with VI were informed through letters and emails as well as general newsletters distributed by charities (Royal National Institute for the Blind RNIB. Mary Kitzinger Trust). In addition, the study was advertised online (Great Ormond Street Hospital Children's Charity website) and through leaflets at the Department of Ophthalmology at GOSH. Families that were informed about the study through these means were recruited via self-referral.

Children in the typically-sighted control group were recruited locally through emails and leaflets. In two cases, typically-sighted siblings of children with visual impairment were included in the control group.

### 2.1.3. Research Ethics

This study was reviewed by the Bloomsbury Research Ethics Committee following a detailed assessment of ethical procedures and codes of practice. Formal approval for the project was granted in November 2012 (Reference: 12/LO/0939).

The recruitment process was carried out as follows: Families in the VI group were initially approached by a member of their clinical care team either as part of their ongoing treatment or because they had been treated at one of the clinics involved in recruitment for this study. If participants had signed an expression of interest form, they were sent study information sheets for parents and children by the researcher. The letter was followed up by a phone conversation to answer potential questions and determine eligibility and availability. Testing sessions were arranged to accommodate the needs of participants as much as possible with the majority of testing being carried out on weekends or during school holidays. Travel expenses and subsistence during the day were covered to lessen the financial burden on families. Children received a gift voucher for the participation. All parents provided written informed consent on the testing day. Children completed a Child Assent form with assistance of the parents. When children were too tired or distressed, testing was aborted and additional testing sessions were arranged when appropriate.

Following standard procedure, all MRI scans were monitored by a clinical radiologist at Great Ormond Street Hospital for Children NHS Foundation Trust. In the case of incidental findings, the clinical care professional of the families would have been contacted to discuss indications for medical intervention with the family.

All scores of neuropsychological tests and questionnaires were monitored by a clinical psychologist with expertise in visual impairment. All parents were sent a descriptive report with the offer to discuss potential questions with a clinician on the phone. In the case of test scores within the clinical range, additional materials were enclosed by the clinical team pertaining to follow-up procedures. For confidentially reasons, any further clinical advice was not disclosed to the researcher.

## 2.2. Sample Characteristics

The participant sample consisted of 18 children with visual impairment (9 female) between 8 and 13 years of age (mean age: 10.76, age SD: 1.39, age range: 8.27-13.32) and a control group of 18 typically-sighted children (8 female, mean age: 10.62, age SD: 1.44, age range: 8.73-12.92). In the VI group, 8 children had visual acuity levels in the mild/moderate range (MVI) and 8 children in the severe range (SVI). One child with unilateral involvement had mild visual impairment in the better side and profound visual impairment on the other. One child had only light perception (PVI).

**Table 3 Overview of sample characteristics in the VI group.** Genetic diagnostics are listed in the comments in the cases, in which this information was available from the paediatric reports.

| ID | Gender | Age [y] | WISC Verbal Comprehension | Sonksen LogMar | Near Detection | Vision Group | Visual Disorder | Comments |
|---|---|---|---|---|---|---|---|---|
| MVI 1 | female | 9.19 | 114 | 0.1 | - | MVI | congenital nystagmus | |
| MVI 2 | female | 13.32 | 95 | 0.4 | - | | Ocular fibrosis | |
| MVI 3 | female | 11.91 | 104 | 0.5 | - | MVI | Bilateral optic nerve hypoplasia | |
| MVI 4 | male | 12.34 | N/A | 0.54 | - | MVI | Rod-cone dystrophy | |
| MVI 5 | female | 8.27 | 104 | 0.6 | - | MVI | oculocutaneous albinisim | |
| MVI 6 | male | 12.06 | 104 | 0.6 | - | MVI | congenital nystagmus | |
| MVI 7 | male | 10.64 | 116 | 0.6 | - | MVI | congenital nystagmus | |
| MVI 8 | male | 9.82 | 93 | 0.7 | - | MVI | ocular albinism, congenital nystagmus | |
| MVI 9 | female | 12.26 | 96 | left: 0.23, right: light perception | - | MVI/ PVI | unilateral optic nerve hypoplasia | |
| SVI 1 | female | 10.98 | 87 | 0.9 | - | SVI | hereditary progressive cone dystrophy | |
| SVI 2 | male | 11.69 | 148 | 0.9 | - | SVI | oculocutaneous albinisim | |
| SVI 3 | female | 10.98 | 78 | 1.1 | - | SVI | Familial exudative vitreoretinopathy (FEVR) | LRP5 mutation |
| SVI 4 | male | 9.57 | 119 | 1.2 | - | SVI | Leber's congenital amaurosis | |
| SVI 5 | male | 9.01 | | 1.225 | - | SVI | ocular albinism, nystagmus | |
| SVI 6 | male | 9.91 | 96 | 1.225 | - | SVI | Norrie's disease | |
| SVI 7 | female | 11.04 | 75 | N/A | yellow smartie | SVI | Leber's congenital amaurosis | |
| SVI 8 | female | 9.86 | 95 | N/A | wooly ball 50cm | SVI | bilateral micro-ophthalmia, retinal coloboma, right eye removed | SOX6 mutation |
| PVI 1 | male | 10.36 | 134 | N/A | light perception only | PVI | Leber's congenital amaurosis | |

**Table 4: Overview of sample characteristics of the control group.** Where known from the paediatric reports, genetic diagnosis is listed in the Comments column.

| ID | Gender | Age [y] | WISC Verbal Comprehension | Sonksen LogMar |
|---|---|---|---|---|
| C 1 | female | 8.56 | 98 | -0.3 |
| C 2 | female | 8.73 | 110 | 0.1 |
| C 3 | male | 8.90 | 116 | -0.3 |
| C 4 | male | 9.08 | 102 | 0.1 |
| C 5 | female | 9.12 | 98 | -0.1 |
| C 6 | male | 9.34 | 108 | -0.2 |
| C 7 | male | 10.07 | 96 | 0.1 |
| C 8 | male | 10.16 | 134 | 0.0 |
| C 9 | male | 10.37 | 106 | 0.0 |
| C 10 | male | 10.74 | 102 | -0.2 |
| C 11 | female | 10.78 | 134 | 0.1 |
| C 12 | female | 10.82 | 116 | -0.2 |
| C 13 | female | 10.89 | 83 | 0.0 |
| C 14 | female | 11.09 | 130 | -0.3 |
| C 15 | female | 11.78 | 144 | 0.1 |
| C 16 | male | 12.70 | 106 | -0.2 |
| C 17 | male | 12.77 | 130 | -0.2 |
| C 18 | male | 12.92 | 124 | -0.3 |

## 2.2.1. Verbal IQ

### 2.2.1.1. Introduction

Previous studies reported a high prevalence of additional learning disabilities in children with VI (Alimovic, 2013). In order to exclude the confounding effect of additional learning disability and to assess the specific influence of visual impairment on cognitive development, only children with visual impairment with verbal abilities in the typical range were recruited to the study. The following section reports on the assessment of verbal abilities in the study sample that were carried out to ascertain if this recruitment goal was met.

Verbal intelligence is the ability to analyse information and solve problems using verbal concepts. Similar to other measures of "intelligence", vIQ is typically derived as a composite of results on a range of tasks that focus on particular aspects of verbal reasoning (Nisbett et al., 2012). On the Wechsler Intelligence Scale for Children 4th edition (WISC-IV), verbal comprehension (vIQ) is a composite score derived from scale scores in three tests (Wechsler, 2004):

- Vocabulary, which assess the ability of the participant to accurately define the meaning of presented words, e.g. "What is a bicycle?"
- Similarities, which requires the participant to identify similarities between two concepts, e.g. "How are a cat and a mouse alike?"
- Comprehension, which consists of questions concerning understanding of social constructs or common knowledge, e.g. "Why do cars have seat belts?"

Two classic studies investigated measures of the performance of "blind" children on the original version of the Wechsler intelligence scale for children. Tillman and Bashaw 1968 reported lower performance of the blind group on the Similarities subtest (Tillman, 1973), while Witkin et al. 1968 reported no significant difference between blind children and controls on any verbal comprehension subtest (Witkin et al., 1968). A possible reason for the discrepancy in findings may lie in the inclusion of children with some visual function in the Tillman and Bashaw study. However, scores of visual acuity are not disclosed in either study.

### 2.2.1.2. Materials & Methods

General ability was assessed using verbal subtests of the Wechsler Intelligence Scale for Children 4th edition (WISC-IV) (Wechsler, 2004). The WISC-IV is a widely used psychometric battery, which assess general ability including verbal intelligence, working memory, processing speed and perceptual reasoning. Verbal subtests of the WISC have also been used with children with VI (Dekker, 1993; Tadić, Pring, & Dale, 2009; Tillman, 1973; Tillman & Bashaw, 1968; Witkin et al., 1968)

The administered subtests included all items of the verbal comprehension composite score (Vocabulary, Similarities, Comprehension). Two items were altered that made direct reference to visual experience:

- The first practice item on the Similarities subtest "How are RED and BLUE alike?" was not administered. Instead, the second practice item and the first test item were used as practice items. The total raw score was adjusted accordingly.
- The wording in the Comprehension item "What are you supposed to do if you see thick smoke coming from your neighbour's house?" was altered to "What are you supposed to do if you **smell** smoke coming from your neighbour's house"?

These alterations were used for the whole sample, including the typically-sighted control group. All other items were administered verbatim according to the WISC-IV administration manual (Wechsler, 2004).

Assessment scores were transferred to scaled scores with reference to the test norms. Subtest scores are scaled to a mean of 10 and a standard deviation of 3. Composites scores are normed to have a mean of 100 and a standard deviation of 15.

### 2.2.1.3. Results

All participants in the study completed the verbal comprehension assessment. The verbal comprehension tests Vocabulary, Similarities and Comprehension, of the WISC-IV were administered. Group-level analysis did not indicate a significant difference in WISC Verbal Comprehension (vIQ) between the VI and the control group (Independent sample t-test: VI: mean=101.94, SE=4.81, Range=75-148; control: mean=113.17, SE=3.87, Range=83-144; t(31.125)=-1.8193, p=0.079). Analysis of verbal comprehension by vision group did not indicate significant differences between the groups (One-way ANOVA: MVI: mean=103.25, SE=3, Range=93-116; S/PVI: mean=100.78, SE=8.94, Range=75-148, F(2,32)=1.665, p=0.205). Two children in the VI group reached scores more than 1 standard deviation below the mean of the norm (scaled score < 85). Eight children in the control group and four children in the VI group reached scores more than one standard deviation above the mean of the norms (vIQ > 115).

Next, differences in scores on subtests that make up the Verbal Comprehension Composite were analysed. Statistical comparison indicated a trend-level interaction between participant group and subtest (rmANOVA: F(2,66)=3.61, p=0.066). Post-hoc simple contrasts showed significant differences between the groups on Vocabulary (VI:

mean=9.88, SE=0.93, Range=4-17; control: mean=12.39, SE=0.65, Range=8-18, t(29.065)=-2.211, p=0.035, Bonferroni-corrected p=0.105) with lower mean scores in the VI group. However, this difference did not survive correction for multiple comparisons. Differences on other subtest did not reach significance level.

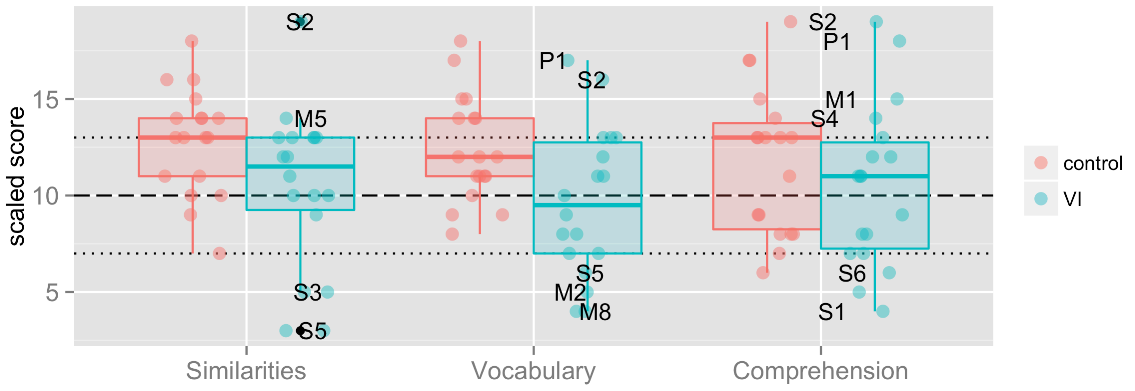


**Figure 14: Scores on individual subtests that make up the Verbal Comprehension composite**. Scaled scores adjusted for participant age with reference to the WISC-IV norms are presented. The control group appears in red and the VI group in blue. The dashed line indicates the norm mean score and the dotted lines indicate one standard deviation variation from the mean. There were significant differences between the groups on Vocabulary with lower scores in the VI group that did not survive stringent correction for multiple comparisons. Labels for cases of scores below or above one standard deviation refer to the identifiers presented in Table 4.

Limited statistical power associated with moderate sample size in the current study may have limited the effects that could be detected with the statistical tests. A post-hoc power calculation was conducted to assess the effect size that could be detected given the sample size for each statistical test. For the two-sided t-test comparison of scores, a large effect sizes of Cohen's d > 0.94 could be detected with a power of 0.80 and at a significance level of 0.05.

### 2.2.1.4. Discussion

The verbal comprehension composite was assessed to determine underlying differences in general verbal cognitive ability between the visually impaired and typically-sighted control group that might influence further domain-specific investigations of cognitive performance. Importantly, children with visual impairment in the current investigation were recruited to have verbal reasoning abilities in the typical range in order to avoid confounding effects of comorbid general intellectual disability. However, because of challenges of initial identification and recruitment (i.e. reliance on previous clinic records of younger age or parent reported attendance of age appropriate mainstream school) some children were included whose verbal IQ was slightly below the lower cut-off at 80. Nevertheless, there was no significant difference between the groups on the verbal comprehension composite score. However, a trend-level difference was found. Follow-up contrasts indicated that this trend-level difference was driven by significantly lower performance on the vocabulary subtests in the VI group that did not survive correction for multiple comparison. However, most children in the VI group fell within the expected range for typically developing children based on the norms of the tests, while the scores of children in the control group were skewed towards higher test scores. This skew may be explained by a combination of influences of recruitment method as well as general biases in the participation in research studies towards families with higher education and socio-economic status (Williams & Cottle, 2011).

## 2.3. General analysis approach

Originally, the study was designed to investigate the effect of different vision levels on outcome measures, including scores on neuropsychological assessments and neuroimaging measures. In contrast to previous studies, vision level was intended to be treated as a continuous variable rather than comparing arbitrarily defined vision groups. However, it was not possible to recruit a sufficient number of participants across the range of visual acuity scores in children with VI due to the rarity of the disorders and various practical constraints (geographical, financial, temporal). For instance, only one child with profound visual impairment could be recruited to the study. Because the sample was not sufficient to investigate the effect of vision level, the study focussed on group comparisons between children with VI and controls for primary analyses. As a second step, vision groups were compared (S/PVI vs MVI vs control) to highlight possible differences between groups with different levels of visual acuity.

Further, the effect of individual diagnostic groups could not be addressed in the current study. Diagnostic categories under the umbrella of 'simple' CDPVS are rare with an incidence of less than 1 in 10,000 births even in the most common categories (Rahi et al., 2003). In addition, diagnostic categories often consist of multiple genetic disorders that share common symptoms. For instance, Leber's congenital amaurosis is associated with mutations in at least 11 different genes linked to different cellular functions and various modes of inheritance from autosomal dominant to recessive (Fazzi et al., 2007). In turn, even groups of a specific diagnostic category represent a heterogeneous sample with differing underlying biology. In addition to practical limitations in recruiting a sufficiently large homogeneous sample, previous studies based on clinical databases found vision level to be the most predictive factor for developmental outcome in infants with VI (Dale et al., 2014) above visual disorder diagnosis. Future studies may address differences between rare genetically defined groups with VI. The current studies focussed on the impact of vision on cognitive and brain development across 'simple' CDPVS diagnostic groups.

## 2.4. Neuropsychology

One of the central aims of the current investigation was to establish the neuropsychological profile of school-age children with visual impairment in order to relate differences in behavioural performance to likely underlying cognitive and neural mechanisms. Neuropsychology is a summary term for approaches that try to relate brain structure and function to psychological constructs. Often rigorous tests are applied that are known to be related to the function of specific neural substrates based on the studies involving patients with focal lesions or other known neurological deficits. The benefit of using neuropsychological tests is that test results can be used to formulate hypotheses about the involvement of these neural substrates.

Based on previous reports in the literature, a protocol was selected to focus on aspects of cognition that were indicated to be affected (executive function, social understanding, spatial reasoning) (Dekker, 1993; Hobson, 2011; Tadić, Pring, & Dale, 2009), while also assessing the overall cognitive profile. Where possible, tests that have been validated in samples of children with VI were used (Dekker, 1993). These tests provide the advantage that test scores can be compared to a normative sample of children with VI. Further, the effect of vision level could be statistically adjusted with reference to a large normative sample of children with varying level of VI. However, only very few tests provide norms for children with sensory impairments, let alone isolated visual impairment. The validity of typically-sighted norms is substantially limited according to reports that find large differences in test scores when simulating visual differences with refractive glasses in typical adults (Kempen, Krichevsky, & Feldman, 1994). Therefore, only auditory and verbal tests were used for all children in the sample. Some items were adapted to match the experience of children with severe visual impairment and avoid biasing test results towards children with better vision.

## 2.5. Electrophysiology

### 2.5.1. Channel-level EEG & ERP

One of the central aims of the current study is to investigate functional reorganisation of cortical networks as indicated by adult neuroimaging studies of congenitally blind and early blind adults (Burton et al., 2002; Ptito et al., 2008; Sadato et al., 1996; Weeks et al., 2000). Specifically, the adult literature indicates that occipital cortical areas act as higher-order association areas (Klinge, Eippert, Roder, & Buchel, 2010). This reorganisation may be adaptive and support compensatory skills in children with visual impairment (Maurer et al., 2005). EEG is often the method of choice for paediatric functional imaging investigations (Bathelt, O'Reilly, & de Haan, 2014). In addition, the high temporal resolution of the EEG is especially suited to track the hierarchy of cortical activations that may indicate difference in functional organisation in the current investigation (Roder, Rosler, & Neville, 2000; Roder, Rosler, Hennighausen, & Nacker, 1996; Roder et al., 1999).

Electroencephalography is a commonly used neuroimaging tool in paediatric populations that offers high temporal resolution, which is directly related to neurophysiological processes (Michel & Murray, 2012). Briefly, EEG measures the electrical activity that is mostly generated by cortical neurons through electrodes placed on the head (Luck, 2005). The signal is amplified so that it can be digitally recorded in real time. Modern EEG recording systems can be applied with short preparation times (~15min). Further, the recording environment is less restrictive than MRI or MEG, which is particularly important in paediatric populations that often do not tolerate these situations well (de Haan, 2007). The EEG signal is a rich source of neurophysiological information and different analysis methods exist that exploit different properties of the signal depending on the research questions. A widely used method is the event-related potential (ERP) method. For ERP analysis, the EEG is averaged over repeated presentations of the same stimulus in order to isolate the EEG signal that is time-locked to the stimulus processing from ongoing brain activity (Luck, 2005). Different components can be distinguished in the ERP waveform that are thought to be related to different processing stages depending on the eliciting stimulus and experimental paradigm. ERP components are commonly characterised through measures like mean or peak amplitude, onset latency and peak latency. These measures are also used to describe difference in ERP components between participant groups or experimental manipulations. ERPs give a millisecond-by-millisecond account of cortical processing, but are limited in spatial resolution.

### 2.5.2. Source-level analysis

Electrical currents generated in the brain pass through different tissues between their generator and the EEG electrodes on the surface of the scalp.[3] This leads to mixing and spatial smearing of source activity known as the volume conduction effect. Therefore, activity measured by the electrodes on the surface of the scalp reflects activity from multiple sources that might be distant to the position of the electrode on the head (Michel & Murray, 2012). Spatial information provided by structural MRI to take account of the volume conduction effect through biophysical modelling. The use of structural information for source reconstruction of EEG recordings is particularly useful for studies involving a paediatric population.

A prevailing assumption in channel level ERP analysis comparing different age groups is that the same neural substrates respond, but that the timing or response amplitude varies across ages (Nelson et al., 2008). Similar scalp topography is often used as an indicator of similar underlying neural activity. However, many different source configurations can lead to similar scalp topographies (Michel et al., 2004). By applying source estimation, this uncertainty can be reduced and quantified. The independence of observations is critical for network accounts of brain function: if the sources are mixed, correlations will be biased towards higher local connectivity. Source reconstruction can be applied to reduce this bias (Bathelt, O'Reilly, Clayden, Cross, & de Haan, 2013). Alternatively, differences in timing and phase can be used for connectivity analysis, but these mathematical models require assumptions that are hard to evaluate in non simulated data (David, Cosmelli, & Friston, 2004). In summary, source estimation provides additional information to channel level EEG and ERP analysis based on knowledge about anatomy and biophysical properties of tissue.

Different algorithms have been devised to find solutions to the inverse problem. These algorithms fall broadly into two categories: parametric

and non parametric (Grech et al., 2008). Parametric models assume one or multiple dipoles that may vary in location, orientation and strength. In contrast, non parametric models contain a large number of dipoles with fixed location and orientation. In these models, the scalp electrical activity is explained as a combination of activations in the fixed dipoles (Grech et al., 2008; Michel et al., 2004; Wendel et al., 2009). Non parametric, distributed source models can be based on knowledge about anatomy and conductivity in different media. Boundary Element Models incorporate conductivity values for the main tissues of the head with different shells for the brain, cerebro-spinal fluid, and skull. This is based on the assumption that conductivity is mostly constant within each compartment, but that marked changes occur at the boundary of different compartments. Finite element models are based on further segmentation of MR scans into grey and white matter so that conductivity values can be assigned to each voxel (Richards, 2005).

In practical terms, non-parametric models are particularly useful for source reconstruction in complex cognitive tasks, in which the number

of areas involved may not be known (Michel et al., 2004). Boundary element models are most widely used in the current literature, probably because the more accurate Finite Element Models pose comparably high computational demands. Further, there is considerable inter-individual variability in grey and white matter so that FEMs should be based on individual MRI scans.

Non parametric models require a second step for matching the scalp measured activity to the predictions of the forward model. Again, different approaches with different advantages and drawbacks have been discussed in the literature (see Michel et al. 2004 for an overview). The most widely used algorithms are based on minimum norm estimation (MNE), which matches the scalp measured activity to a current distribution in the forward model with the lowest overall intensity (Hauk, 2004). MNE is biased towards weak and superficial sources. Depth weighted MNE algorithms try to reduce the surface bias by introducing weighting matrices based on mathematical assumptions (Michel et al., 2004).

In summary, source reconstruction through modelling methods has been limited for children until recently. This is because most EEG analysis software relies on head models based on adult anatomy that substantially limits the accuracy of source solutions in children (Brodbeck et al., 2011). The cheap access to computational power and the provision of user friendly software for source reconstruction make it possible to overcome these limitations. Applying source estimation to the EEG provides two important advantages over analysis based on channel level observations alone: improved spatial resolution and independence of observations.

Source estimation may not be informative in some cases: good coverage of the head is required to distinguish sources. High density systems with 128 or more electrodes are recommended (Hauk, 2004; Michel et al., 2004) ; a sparser coverage will act as a spatial filter leading to more wide-spread source activation or false negative results (Michel et al., 2004). Spatial filtering techniques may also be used to improve the spatial resolution of the EEG signal by reducing spatial mixing on the scalp level. Alternative methods to reduce the influence of volume conduction effects without head modelling are used, e.g., Laplacian filtering (Tandonnet, Burle, Hasbroucq, & Vidal, 2005) or Current Source Density analysis (Tenke & Kayser, 2012). However, these methods do not provide more information about neural generators as volume conduction effects are not only restricted to sensors in close spatial proximity (Michel & Murray, 2012). An additional limitations concerns the conductivity values used for biophysical modelling. Unfortunately, there are currently no detailed studies of conductivity of different head tissue types for adult or developing humans as these studies can only be carried out post-mortem. Conductivity values are therefore based on small and not necessarily representative samples. However, empirical studies that investigated the effect of different conductivity values on source reconstruction results reported little effects over a wide range of conductivity values (Stenroos & Hauk, 2013). Further, comparison of source solutions with MEG, which is not influenced by volume conduction, show high correspondence to EEG-derived solution (Sharon, Hamalainen, Tootell, Halgren, & Belliveau, 2007).

There are additional tentative limitations to employing source analysis compared to traditional channel level analysis. Source reconstruction has only been widely used for the last decade, whereas channel-level EEG analysis has been employed for neuroscience investigations for over 50 years. Therefore, there are many established analysis procedure and best practice guidelines for channel-level analysis that are widely accepted. in contrast, for source analysis, many different algorithms and implementations exists without a generally accepted standard. Further, the interpretation of channel-level results is aided by a large literature describing different components and their relationship to cognitive measures. This literature may help in the interpretation of source results, but the relationship between channel-level observation and source signal is complex as outlined above. In order to benefit from both traditional channel-level analysis and advanced source imaging, both analyses were carried out. Channel-level analyses were performed based on previous reports in the literature to compare results to published findings. In a next step, the source solution of these differences was analysed to gain additional information about neural substrates that are most likely to contribute to the channel level difference.

## 2.5.3. General methods

### 2.5.3.1. EEG recording

The EEG was recorded using a GES 200 high-density, high impedance recording system with a NetAmps 200 amplifier and HydroCel Geodesic Sensor Nets with 128 channels with suitable sizes for all participants (Electrical Geodesics Inc., OR). Saline solution was used as the conductivity medium for recording according to the instructions of the technical manual of the recording system.

Recordings were obtained using NetStation software V4.1.2 (Elecrtical Geodesics Inc., OR) on an Apple Macintosh PowerPC G4 running Mac OS 10.3.9. The EEG was recorded with a hardware low-pass filter at 400Hz and a hard-ware high-pass filter at 0.01Hz. The sample frequency was set to 250Hz. A vertex reference was used for recording. Display filters between 0.1Hz and 40Hz were used during the recording for better online visualisation of the recording.

The amplifier was calibrated and impedances were measured for each recording. Channels with impedance higher than 50kΩ were checked for good contact with the scalp and adjusted where necessary following procedures described in the Geodesic Sensor Net Technical Manual (Electrical Geodesic Inc., OR). An electrooculogram (EOG) was also recorded through the EEG system using a pair of electrodes positioned above and below both eyes for the detection of eye-related artefacts in the EEG.

### 2.5.3.2. Recording environment

The EEG was recorded in a quiet room at the Wolfson Assessment Centre, which is the child cognitive neuroscience research laboratory of the UCL Institute of Child Health. Parents could accompany the child, if so desired. The participant sat behind an opaque divider to avoid distraction. Participants faced a screen with fixation crosses that changed the background colour between experimental trials. The large fixation cross was presented to make it easier for participants to minimise eye movement. Participants who were not able to fixate on the cross because of very low vision were instructed to look ahead and minimise their eye movements as much as possible. The screen was switched off for the resting-state EEG recording. Bright fluorescent strip lights were switched off during the recording to further minimise eye blinks. Instead, a dim clip-on desk lamp was used as a light source. The participant was monitored through a webcam to monitor participant wellbeing, alertness, and wellbeing.

### 2.5.3.3. Stimulus presentation

Stimuli were presented through Creative Labs EP-660 in-ear headphones (Creative Labs Inc., Singapore). The headphones were electrically shielded by the manufacturer. Our own tests did not indicate that the headphones induced electrical artefacts above background noise in empty room recordings.

The experimental paradigms were implemented in MATLAB R2012b (The MathWorks, MA) using Psychtoolbox V3 functions (Kleiner, Brainard, Pelli, Ingling, & Murray, 2007). Stimuli were presented on a Dell Optiplex (Dell Inc., TX) running Windows XP Service Pack 3 (Microsoft Inc., NW). Sound stimuli were presented through a Creative Sound Blaster X-Fi PCI Express sound card with a low latency driver (Creative Labs Inc., Singapore). The offset latency for auditory stimuli as employed in the ERP paradigms using this setup was measured to be 17ms with a standard deviation of 2ms using an EGI latency testing device.

### 2.5.3.4. Processing for event-related potentials

The EEG recordings were exported to EEGLAB format for processing and analysis. The pre-processing pipeline was based on routines as previously reported (Bathelt et al., 2014). Unless otherwise stated, the following pre-processing was applied to recordings for all experiments: First, the EEG was digitally filtered with finite impulse response (FIR) filters at a high-pass frequency of 0.1Hz and a low-pass frequency of 30Hz in EEGLAB 11.0.3 (Delorme & Makeig, 2004; Delorme et al., 2011). Second, the continuous EEG signal was segmented according to stimulus codes set during the recording. Third, trials with absolute amplitudes higher than 150µV in several channels were rejected. Channels with amplitudes above the rejection threshold in a set percentage of trials were also rejected (the details of the channel and trial rejection algorithm are presented in Figure 15). Activity in the rejected channels was interpolated from surrounding channels using spherical interpolation in datasets with sufficient remaining data (less than 12 channels marked as bad, i.e. <10% of EEG channels).

After artefact rejection, the EEG was submitted to independent component analysis (ICA). Briefly, ICA is a blind source separation algorithm that sorts signals into statistically maximally independent components (Delorme, Sejnowski, & Makeig, 2007). Independent components are described as matrix that when multiplied with the data yields independent component waveforms. It is assumed that the scalp-recorded EEG is a mixture of EEG and artefacts that are statistically independent (Choi, Cichocki, & Park, 2005; Jung et al., 2000; Vorobyov & Cichocki, 2002)[4]. Components containing non-EEG data may be identified through supervised or non-supervised approaches. For supervised rejection, components are identified based on the waveform and spatial characteristic. Similarity measures are then used to reject components with similar components from either the same dataset or all datasets within a study (Jung et al., 2000; Nolan, Whelan, & Reilly, 2010; Vorobyov & Cichocki, 2002). However, artefact characteristic may vary widely both within and between participants. Alternatively, data-driven approaches may be used. The fully-automatic artefact statistical thresholding for EEG artefact rejection (FASTER) algorithm uses characteristics such as spatial kurtosis, amplitude range and slop to characterise each component. Components with a z-score on these measured are removed and the remaining data is recombined (Nolan et al., 2010). This approach was found to perform with higher sensitivity and specificity than a supervised correction approach or manual artefact identification with simulated data. For real-world data, FASTER processing was found to lead to smaller variance in the baseline period in a visual oddball paradigm compared to the other methods, which likely indicates better removal of non-time locked activity (Nolan et al., 2010). The FASTER approach was taken to retain a maximum number of trials and obtain higher signal-to-noise ratio (SNR) compared to artefact rejection with stricter amplitude thresholds.

In order to further improve SNR, several channels were combined for channel-level analyses. The channel selection for each analysis was based on reported topographies of experimental effects in the available literature and are discussed for each experiment in subsequent chapters.

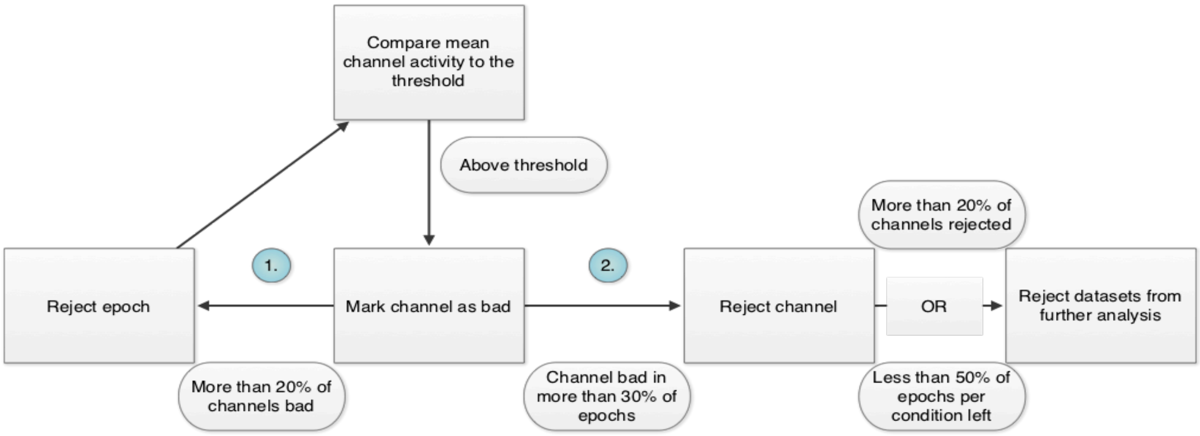


**Figure 15. Flow-diagram illustrating the artefact rejection algorithm used for pre-processing of EEG data for ERP analysis.** Reproduced from Bathelt et al. 2014.

### 2.5.3.5. Cortical source analysis

Cortical sources of the scalp-measured EEG were estimated based on boundary element models (BEM) of age-appropriate MRI templates taken from the Neurodevelopmental MRI database (NRD) (Sanchez, Richards, & Almli, 2012). The NRD contains average templates of infants, children, and adolescents. In the 8-years-to-13-year age range, templates are available in half-year steps. Each template is based on scans of 30 to 70 individuals with roughly equal gender contribution (please see Sanchez et al. 2012 for a detailed description of the database). The individual scans were co-registered and averaged using an iterative non-linear registration procedure to create age-specific templates (Sanchez, Richards, & Almli, 2011).

Surfaces and cortical parcellations of the average templates were obtained using FreeSurfer software (Fischl, 2012). Head models consisted of four shells comprising skin, skull, CSF, and cortex that were associated with default conductivity values.

A distributed source model constrained to the surface of the cortex was used as implemented in OpenMEEG (Gramfort, Papadopoulo, Olivi, & Clerc, 2010). In this type of model, the surface representation of the cortex is populated with dipoles oriented perpendicular to the surface analogous to the orientation of pyramidal cells in the cortex layers (Michel et al., 2004). Finally, the sLORETA algorithm was used to match scalp-measures voltage distributions to the predictions of the forward model. Please refer to the appendix for a more detailed description of the cortical source analysis approach and discussion of alternative methods etc. (see Bathelt et al. 2014).

## 2.5.4. Brief description of paradigms

### 2.5.4.1. Resting-state connectivity

Eyes-closed resting state EEG was recorded over two minutes. Participants were instructed to close their eyes, avoid movement, let their mind wander and think of nothing in particular. A sound stimulus signalled the start and end of the two minute interval. The recording was segmented into 1s epochs and filtered in three frequency bands (alpha, beta, gamma) as previously reported (Bathelt et al., 2013). The likely generators in each epochs were estimated based on sLORETA (Hauk, 2004) using age-appropriate average MRI templates (Sanchez et al., 2012). The source signals was derived for 34 regions of interest in each hemisphere based on cortical parcellation according to the Desikan-Killany atlas using Freesurfer software (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). Subsequently, the Pearson correlation coefficient between each pair of time series was derived to characterise linear coupling between the source signals. The correlation coefficients were averaged for all epochs for each participant to estimate individual connectivity patterns. Graph theory measures were then applied to characterise the network properties. A pilot investigation in a sample of typically developing children between 2 and 5 years indicated that this method replicated key findings about network development in children based on resting-state functional MRI (Bathelt et al., 2013) - due to the scope of this thesis and spatial constraints, the findings in the typically developing group will not be presented in detail in this dissertation (the publication is included in the Appendix).

### 2.5.4.2. Binaural listening

Previous reports based on parental reports of everyday executive skills had indicated attention deficits in school-age children with visual impairment (Tadić, Pring, & Dale, 2009). An electrophysiological paradigm was employed to further elucidate underlying mechanisms of attention difficulties. In the current study, the binaural listening paradigm required participants to selectively attend to a story presented in one ear while ignoring a story that was presented in the other ear (Coch, Sanders, & Neville, 2005; Sanders, Stevens, Coch, & Neville, 2006). Sound probes were inserted randomly in the left and right audiostream as onset markers for the event-related response. Previous studies had identified modulation of the auditory N1 component by attention (Coch et al., 2005; Lackner, Santesso, Dywan, Wade, & Segalowitz, 2013; Sanders et al., 2006; Strait, Slater, Abecassis, & Kraus, 2014). Further, by comparing modulation of the auditory N1 component on the attended and unattended side between groups that are expected to show impairments in selective attention and typical control groups, the likely underlying deficit can be investigated. Differences in amplitude on the attended side suggest deficit in selectively attending to a stimulus, whereas differences on the unattended side are suggestive of deficits in the suppression of irrelevant stimuli (see Stevens et al. 2012 for a review).

#### 2.5.4.3. Subject's own name

Previous behavioural studies had indicated problems in social understanding in children with visual impairment (Hobson, 2011). Therefore, the current study aimed to investigate possible neural correlates of deficits in the processing of social stimuli in school-age children with visual impairment.  An auditory event-related potentials paradigm for basic social processing was selected. In this paradigm, participants listen to recordings of their own name. These responses are contrasted with responses to a control name that is matched for the number of syllables. This paradigm is known as the subjects' own name paradigm in ERP research (Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006; Ofek & Pratt, 2005; Perrin, García-Larrea, Mauguière, & Bastuji, 1999). Similar paradigms have also been used in fMRI investigations of social cognition (Kampe, Frith, & Frith, 2003).

## 2.6. Magnetic Resonance Imaging

### 2.6.1. Structural MRI

Magnetic resonance imaging (MRI) is a non-invasive imaging technique that allows one to reconstruct the composition of tissues inside the body using strong magnetic fields and pulses of electromagnetic waves. For imaging, the participant is placed in a large coil that generates a homogenous magnetic field around the body. Protons within body tissues align to the orientation of the magnetic fields. Electromagnetic wave pulses in the radiofrequency band are applied to perturb the alignment of the protons. The energy that protons emit when returning to the resting orientation is measured. Emission of electromagnetic energy is via two process, so called longitudinal relaxation, also known as T1 relaxation and spin-spin relaxation also known as T2 relaxation. Depending on the timing of the applied radiofrequency pulses different contrasts can be obtained that are sensitive to different T1 and T2 relaxation rates of tissues resulting in T1 and T2-weighted images. Differences in the proton density of different tissue types provide sufficient difference in the signal to image the composition of body tissues. Magnetic resonance images can be used to investigate the topology and composition of tissues using quantitative methods.

In the current investigation, structural T1-weighted images were obtained with comparatively high resolution (1mm isometric resolution) for two main purposes:

a) Reconstruction of cortical surfaces

The contrasts between grey and white matter can be used to derived three dimensional models of the cortex (Dale et al., 1999; Fischl et al., 1999). Based on these models, parameters like cortical thickness and surface area can be quantified and compared between groups. Previous reports about differences in these measures in congenitally blind adults indicated that this method is sensitive to changes in brain anatomy associated with visual impairment (Jiang et al., 2009).

b) Anatomical reference

In addition to direct analysis of anatomical T1-weighted images, high-resolution images are also important as an anatomical reference for other imaging modalities like analysis of diffusion-weighted or functional imaging data that provide less spatial resolution. In the present study T1-weighted images were co-registered to diffusion-weighted data in order to identify anatomical landmarks like the lateral geniculate nucleus that are much easier to identify with higher spatial resolution and T1-weighted contrast (Soares, Marques, Alves, & Sousa, 2013).

### 2.6.2. Diffusion-weighted imaging

Differences in white matter are of particular interest as these changes may indicate differences in the integration between different brain areas that may provide adaptive advantages (Fornito & Bullmore, 2014; Johansen-Berg & Behrens, 2006; Le Bihan, 2003). Diffusion-weighted imaging (DWI) allows one to quantitatively assess the integrity of major white matter structure in vivo. DWI is a variant of MRI that measures the diffusion of water molecules in tissues. In contrast to conventional MRI, a pair of sharp magnetic field gradient pulses is applied: the first pulse magnetically labels the protons, while the second pulse is used to read out the spatial displacement through diffusion (Le Bihan, 2003). In the absence of boundaries, water diffuses freely in all directions due to Brownian motion. However, free diffusion is hindered in biological tissues to varying degrees depending on the type, integrity, architecture of tissue structures (Basser & Jones, 2002; Soares et al., 2013). For instance, diffusion is unconstrained in cerebrospinal fluid, but diffuses more freely along white matter fibres than perpendicular to them (Le Bihan, 2003).

Different models have been used to characterise diffusion in each voxel of an MRI. The diffusion tensor that describes the main direction of diffusion in a three dimensional matrix representation has been used widely (Wedeen, Hagmann, Tseng, Reese, & Weisskoff, 2005). However, to accurately model the high prevalence of multiple diffusion directions in large parts of the white matter, alternative models, such as Q-ball, ball-and-stick, or constrained spherical deconvolution models, have gained in popularity in recent years (Tournier, Calamante, & Connelly, 2012).

Maps of diffusion parameters may be compared on a voxel by voxel basis across the whole brain volume or within regions of interest using approaches like voxel-based morphometry or tract-based spatial statistics (Smith et al., 2006). Alternatively, streamline approaches can be used to reconstruct particular white matter structures (tractography). For tractography, a seed region is selected based on anatomical knowledge. A tracking algorithm reconstructs a streamline by connecting the principal diffusion direction between voxels. Tracking parameters like maximum angle, minimum diffusion parameter value, exclusion regions etc. may be defined to optimise the reconstruction of the tract (Dell'Acqua & Catani, 2012; Soares et al., 2013). Alternatively, connections can be reconstructed from seed regions throughout the whole brain volume and streamlines of interest can be selected from the reconstruction (Catani & Thiebaut de Schotten, 2008). Probabilistic tracking algorithms are commonly used that select the statistically most likely path of a streamline based on a large number of repetitions (Behrens et al., 2003). Ultimately, the segmented pathways are used to identify voxels within a particular white matter structure of interest and to extract diffusion parameters for that tract for quantitative comparison.

## 2.7. Network analysis

### 2.7.1. Graph Theory

Changes in the visual experience that accompany visual impairment have been found to lead to the reorganisation of structural and functional brain networks (Jiajia Li et al., 2013; Liu et al., 2007; Shu, Liu, Li, Li, Yu, & Jiang, 2009). One of the main aims of the current investigation was to assess these changes in network organisation in school-age children with congenital VI. Graph theory provides a mathematical framework for this purpose to describe and quantify the properties of networks (Rubinov & Sporns, 2010). One of the advantages of using graph theory as an abstract description is that network properties can be directly compared between different imaging modalities. Further, properties of empirically obtained graphs can be compared to models with known or fixed properties to investigate factors that may have contributed to network organisation (Deco et al., 2014).

The basic premise of graph theory is that networks can be described as a combination of nodes and their connections (edges) (Fornito & Bullmore, 2014; Hagmann, Grant, & Fair, 2012; Sporns, 2013). Nodes may be voxels in MRI, channels in M/EEG, or cortical regions spanning a number of voxels. Edges can be based on different properties depending on the imaging modality including the correlation or coherence between time series (Sporns, 2013), correlation in cortical thickness between areas (Sporns, 2013), or number of fibres that connect areas based on diffusion tractography (Tymofiyeva, Hess, Xu, & Barkovich, 2014).

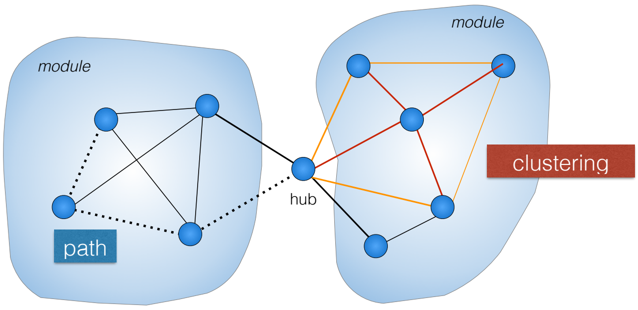


**Figure 16: Illustration of graph theory concepts.** Figure adapted from Bullmore et al. 2009.

### 2.7.2. Network-based statistics

In addition to the general description of network architecture, differences in the presence or weight of specific connections within the network are of interest. However, a comparison of all edges within the network would lead to inflation of type I errors even in networks with relatively few nodes. Correction for multiple comparison for each contrast would lead to very conservative control and would increase the chance of type II error. Further, strict control of error rates assumes independence of observations, which does not take the structure of nodes in a network into account. Zalesky and colleagues introduced so-called network-based statistics (NBS) for comparisons of networks between groups (Lang, Tomé, Keck, Górriz-Sáez, & Puntonet, 2012; Zalesky, Cocchi, Fornito, Murray, & Bullmore, 2012; Zalesky, Fornito, & Bullmore, 2010). NBS is based on permutation t-tests, which allows for comparison across the network and does not depend on assumptions of similar weight distributions in each comparison group. Further, a cluster-wise correction for multiple comparisons is applied so that differences between the groups in co-dependent subnetworks can be identified. Comparisons of simulated neuroimaging data found high sensitivity and specificity using NBS compared to strong multiple comparison correction (Zalesky et al., 2010). NBS is commonly used in network-focus studies across imaging modalities in adult and paediatric studies, e.g. (Finn et al., 2014; Wang et al., 2013b)

## 2.8. General statistical approach

Comparisons between groups were based on repeated-measures analysis of variance models (rmANOVA). These models are based on assumptions of normality and sphericity. Normality assumptions were evaluated using the Shapiro-Wilk test (Shapiro & Wilk, 1965) with a significance cut-off at 0.1 as recommended in the original publication. The built-in implementation of the Shapiro-Wilk test in R 3.1 was used (Royston, 1991).

Sphericity assumptions were tested using Mauchly's test (Mauchly, 1940) for comparisons with more than two variables - sphericity is not an issue in two group comparisons (Mauchly, 1940), e.g. VI vs control analyses. In the case of violated sphericity assumptions, the Greenhouse-Geisser correction was applied (Greenhouse & Geisser, 1959). Implementations of these algorithms in Frank E. Harrell's R package (Hmisc 3.14) were used (Harrell, 2001).

Follow-up contrasts or simple comparisons between means were based on Student's t-tests using in-built R 3.1 implementation. Welch correction was applied to account for difference in variance between the groups (Welch, 1947). Bonferroni corrections was applied to correct for multiple comparisons. Both uncorrected and Bonferroni-corrected pvalues are reported to offer the reader a better insight into statistical trends.

Correlation analyses were based on bivariate correlations (A. Field, Miles, & Field, 2012). When controlling for additional variables partial correlations were used. The Hmisc 3.14 implementation of both algorithms was used (Harrell, 2001).

Post-hoc power calculations are included in the analysis chapter to indicate the effect sizes that could be detected at a significance level of 0.05 at a power of 0.80 (Cohen, 1965) given the number of participants available for each measure. Power calculations were performed using G*Power v3.1 for Mac (Erdfelder, Faul, & Buchner, 1996; Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007).

## 2.9. *A priori* considerations of statistical power

The required sample size was assessed *a priori* for behavioural measures and for correlations between neuroimaging and behavioural measures based on clinically significant differences and published results. Power calculations were reviewed by the

Statistical Support Service at the UCL Institute of Child Health and were submitted with other background materials to the Research Ethics Committee.

First, the number of children that would be eligible for the study was estimated based on clinical records at the main recruitment site. Clinical records indicated that 30-40 children with severe to profound visual impairment would be eligible to the study (children with mild to moderate VI were not considered here, because milder forms of VI are much more common and would therefore not create a bottleneck for recruitment).

Next, power calculations were carried out and compared to the groups size that could potentially be recruited. For power calculations, results of the Children's Communication Checklist-2 were selected as the primary outcomes measure, because scores of clinical comparison groups and previous results in an independent sample of children with VI were available. First power calculations were based on scores reported for the normative sample of the CCC-2 (Bishop, 2003). According to the CCC-2 norms, children with clinically relevant communication disorders are unlikely to obtain a General Communication Composite (GCC) above the 10th percentile. This translates to a score of 50 or below. In the normative sample of the CCC-2, 11 of 72 children reached scores 45 and 54. Power calculations were based on the minimum distance in scores between children who met criteria for communication deficits and those who did not in the normative sample (see Bishop 2003 for the scores). Using these scores, the power of a two-sided t-test is in excess of 95% ($\mu1=90$, $\sigma1=10$; $\mu2=60$) for a sample size of 20. The minimum sample size per group to detect a difference between a clinical and a control group based on these scores is 4 per group. In other words, if children with VI reach similar scores compared to children with communication disorders, a sample size of 4 and above would be necessary to detect the difference compared to a typical group.

Next, reported results for children with visual impairment were used for power calculations. Tadić et al. reported a GCC of 61.8 ($\sigma1=18.8$) in the visually impaired group and of 86.8 ($\sigma2=14$) for the matched control group. Based on these scores, the minimum sample size required to detect a difference between a VI and sighted group is 6 children per group for a two-sided t-test.

In order to estimate the required sample size to detect correlations between neuroimaging and behavioural measures, power calculations were carried out based on a bivariate normal model. At a significance level of 0.05, a power of 0.8 and a correlation of 0.5, a total sample size of 23 participants would be required. The strength of the correlation could not be assessed from previous studies, therefore a moderate effect size of 0.5 was used for the calculation. Figure 17 shows the relationship between correlation strength and required sample size.

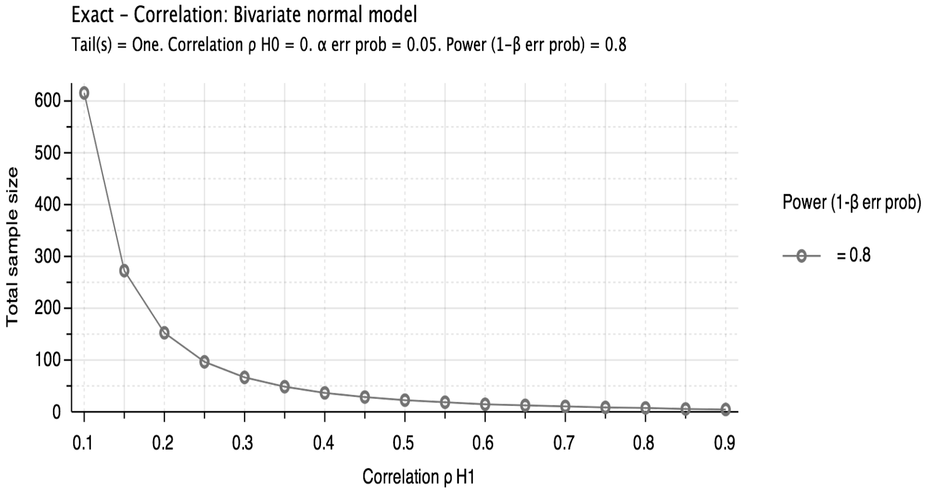


**Figure 17: Estimated total sample size as a function of correlation effect size.** The number of participants necessary to find a correlation declines with the strength of the underlying correlation between the measures (bivariate normal correlation, α = 0.05, β = 0.8). The strength of correlation between the measures is currently not known. The numbers of participants was sufficient to detect a correlation equal to and higher than 0.5.

## 2.10. Chapter Summary

The current chapter described the general methodological approach to the main research question regarding the influence of visual impairment on cognitive development. The chapter summarised the recruitment of children with congenital visual impairments that were restricted to the peripheral visual system according to the paediatric diagnosis with no indication of other brain involvement and no comorbid learning disabilities. Further, investigative tools and data reduction strategies were introduced that were used to characterise cognitive performance, brain structure, and brain function.

# Chapter 3: Background characteristics

## 3.1. Chapter Introduction

The current investigation aimed to assess cognitive differences in children with visual impairment that relate to possible reorganisation of dorsal stream connections. The present chapter aims to provide a background that characterises general differences in adaptive behaviour, strengths and difficulties, and parental factors based on widely used questionnaire measures. A further goal of this part of the investigation is to establish the impact of visual impairment on quality of life and everyday functioning, which warrants investigation. Questionnaire measures of adaptive behaviour, quality of life, and strengths and difficulties were expected to indicate a higher degree of difficulties across domains in the VI group based on previous investigations. More severe visual impairment was expected to be associated with more difficulties in these domains.

## 3.2. Adjustment & Wellbeing

### 3.2.1. Introduction

Adaptive behaviour describes everyday behaviours and skills that allow an individual to respond appropriately to the demands of different situations and environments (Ditterline, Banner, Oakland, & Becton, 2008; Harrison & Oakland, 2008), including communication, functional academics, self-direction, leisure, social function, community use, home living, health and safety, and self-care (Harrison & Oakland, 2008). Visual impairment may impact on different aspects of everyday life in school-age children, including academic adjustment, peer relationships, independence, mobility, and overall quality of life (Tadić et al., 2015).

A recent investigation by Papadopoulos and colleagues pronounced differences in adaptive behaviour between children and adolescents with VI compared to sighted peers, despite improvements in both groups with chronological age (Metsiou, Papadopoulos, & Agaliotis, 2011; Papadopoulos, Metsiou, & Agaliotis, 2011). Independent movement, i.e. mobility skills, were the most important predictor for daily living skills and socialisations (Douglas, Pavey, McLinden, & McCall, 2003; Haymes, Johnston, & Heyes, 2002; Papadopoulos et al., 2011). Further, a recent study by Pinquart and colleagues reported elevated levels of difficulties across all assessed domains of wellbeing and adjustment with around 40% of adolescents reaching highly elevated scores in at least one domain (Pinquart & Pfeiffer, 2014). Another study about wellbeing in adolescents with visual impairment reported higher incidence of difficulties in forming friendships and problems with feeling lonely. Further, girls with visual impairment were found to have lower self-esteem, lower academic achievement, and lower social-skills (Huurre & Aro, 1998).

## 3.2.2. Strengths & Difficulties

### 3.2.2.1. Materials & Methods

The Strengths and Difficulties Questionnaire (SDQ) was administered to assess the presence of behavioural and emotional problems. The SDQ is a single-sided questionnaire comprising 25 questions that are rated on a 3 point Likert scale to indicate to what degree a statement applies to the child (not true - somewhat true - certainly true). The UK version of the parent questionnaire was used for the current investigation, which is suitable for children between 4 and 17 years.

The ratings are used to derive scores for emotional symptoms, conduct problems, hyperactivity/inattention, peer problems and prosocial behaviour. All domain scores apart from the prosocial behaviour score are summarised in a total difficulties score (Goodman, 1997; 2001; Goodman, Ford, Simmons, Gatward, & Meltzer, 2000). The SDQ scoring website (http://www.sdqinfo.org/py/sdqinfo/c0.py last visited 25/7/14) was used to score the questionnaires and compare the results to the normative sample (Goodman, 2001). Scores above the 90%ile with references to the normative sample indicate borderline problems and scores on the 95%ile significant difficulties in a domain (Goodman, 2001).

### 3.2.2.2. Results

The Strengths and Difficulties Questionnaire (SDQ) was used to screen for the presence of problems in a variety of behavioural domains. Sixteen parents of children in the VI group (7 male, 8.27-13.32y, vIQ:75-148) and seventeen parents of children in the control group (8 male, 8.56-12.92y, vIQ: 83-144) completed the SDQ.

Three participants in the VI group reached total stress scores in the abnormal range with reference to the questionnaire norms. For single scales, two participants in the VI group and one participant in the control group scored above the cut-off for emotional symptoms. A further three participants in the VI group and one control participant fell in the borderline range. One participant in the VI group obtained scores above the cut-off for conduct problems and two participants had borderline scores. Two participants in the VI group had above-threshold ratings for hyperactivity/inattention and two scored in the borderline range. Three children with VI reached scores above the cut-off for problems in peer relationships and five scored in the borderline range. One participant in the VI group reached an unusually low rating for prosocial behaviour with a score in the abnormal range.

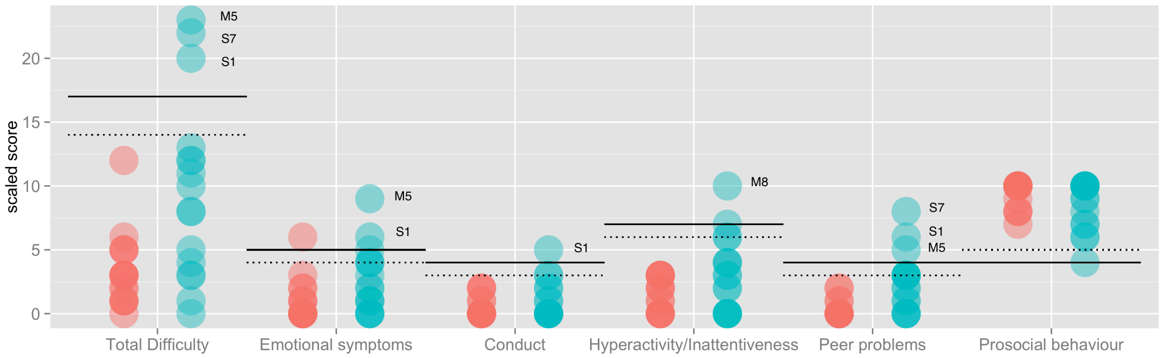


**Figure 18: Results of the Strengths and Difficulties Questionnaire.** Scores of children in the VI group are shown in blue and scores of children in the control group in red. Solid lines indicate the cut-off for the "abnormal" range and the dashed lines cut-offs for the "borderline" range according to the questionnaire manual. Please note that higher scores indicate a higher degree of difficulty for all scales except for Prosocial Behaviour. For Prosocial Behaviour, the scale is reversed, i.e. a higher scores indicates more prosocial behaviour. The colour intensity indicates the number of children that reached the same score. Labels for cases in the clinical range refer to the identifiers presented in Table 4.

## 3.2.3. Adaptive Behaviour

### 3.2.3.1. Materials & Methods

The Adaptive Behaviour Assessment Systems (ABAS) 2nd edition was administered to assess everyday adaptive skills and behaviour (Harrison & Oakland, 2008). The ABAS-II is a twelve-page questionnaire with questions about adaptive behaviour in 9 skill areas comprising communication, functional academics, self-direction, leisure, social, community use, home living, health and safety, and self-care. Please refer to Table 5 for a brief description of each scale taken from the questionnaire manual. The skill areas are summarised in a conceptual, social, and practical composite score as well as a general adaptive composite (GAC). The ABAS-II Parent Form was used, which is suitable between the ages of 5 to 21 years. The questionnaire was designed to assess adaptive skills in a range of childhood disabilities, including sensory disabilities (Harrison & Oakland, 2008).

The parents rated the frequency at which behaviours occur from 1 (Never when needed) to 3 (Always when needed). Parents could also indicate that the child is not able (0). Some items on the questionnaire refer to visual behaviours, e.g. Item 15 (Functional Academics): "Reads menus at restaurants". However, all items were included in order to maintain the psychometric integrity of the questionnaire. Further, the distinction between primary and secondary effects of visual impairment is often not clear-cut. For instance, low ratings on Item 3 (Community Use) "Finds the restrooms in public places" could indicate the greater difficulty associated with visual impairment or an associated deficit in spatial navigation and mobility. In addition, *a priori* exclusion of these items would hinder the full assessment of the impact of visual impairment on general adaptive behaviour.

Raw scores were transferred to scaled scores with references to the questionnaire norms. Skill area scores are normed to a mean of 10 and a standard deviation of 2. Domain composite scores are normed to a mean of 100 and a standard deviation of 10.

**Table 6 Description of skill areas of the Adaptive Behaviour Assessment System 2nd edition with sample items.** Adapted from the questionnaire manual (Harrison & Oakland, 2008).

| Skill Area | Description | Sample Items |
|---|---|---|
| Communication | Speech, language, and listening skills needed for communication with other people, including vocabulary, responding to questions, conversation skills etc. | Names 20 or more familiar objects, Ends conversation appropriately, Uses up-to-date information, to discuss current events |
| Community Use | Skills needed for functioning in the community, including community resources, shopping skills, getting around in the community etc. | Mails letters at the postalk box opt local post office, Finds and uses a pay phone, Orders his/her own meals when eating out |
| Functional Academics | Basic reading, writing, mathematics, abd other academic skills needed for daily, independent functioning, incl. telling time, measurement, writing notes and letters etc. | Reads his/her own written name, Finds somebody's telephone number in a phone book, Makes reminder notes or lists |
| Home Living | Skills needed for basic care of a home or living setting, including cleaning, straightening, property maintenance, and repairs, food preparation, performing chores etc. | Wipes up spills at home, Takes out trash when the trash can is full, keeps toys, games, or other belonging neat and clean |
| Health and Safety | Skills needed for protection of health and to respond to illness and injury, including following safety rules, using medicines, showing caution etc. | Carries scissors safely, Follows general safety regulations at school, Tests hot foods before eating them |
| Leisure | Skills needed for engaging in and planning leisure and recreational activities, including playing with others, engaging in recreation at home, following rules in games etc. | Plays along with toys, games, or other fun activities, Waits for his/her turn in games and other activities, Tries a new activity to learn about something new |
| Sef-Care | Skills needed for personal care, including eating, dressing, bathing, toileting, grooming, hygiene etc. | Buttons his/her own clothing, Uses public restrooms alone, Keeps hair neat during the day by brushing or combing |
| Self-Direction | Skills needed for independence, responsibility, and self-control, including starting and completing tasks, keeping a schedule, following time limits, following directions, making choices etc. | Stops a fun activity, without complaints, when told that time is up, Controls temper when disagreeing with friends, Completes large home or school projects on time |
| Social | Skills needed to interact socially and get along with other people, including having friends, showing and recognising emotions, assisting others, and using manners | Says "Thank you" when given a gift, Laughs in response to funny comments or jokes, Listens to friends or family members who need to talk about problems |

### 3.2.3.2. Results

Sixteen parents of children in the VI group and 17 parents of children in the control group completed the ABAS questionnaire (VI: 7 male, 8.27-13.32y, vIQ:75-148; control: 9 male, 8.56-12.92y, vIQ:83-144). Seven participants in the VI group reached a General Adaptive Behaviour Composite in the extremely low range with scores more than two standard deviations below the norm means (GAC: 54-67, <2.2%ile). One additional case in the VI group had a score in the borderline range (74, <6.7%ile). All other GAC scores were within the normal range.

In the conceptual domain, five children in the VI group reached scores in the extremely low range (19-69). Two additional children with VI reached scores in the borderline range (74-75). For the Social Composite score, four children in the VI group and one child in the control group reached scores in the extremely low range (17-60).

One child in the VI group scored in the borderline range (78). On the Practical Composite score, seven children in the VI group and one child in the control group obtained ratings in the extremely low range (11-65). Two children in the VI group and two children in the control group had scores in the borderline range (72-75) (see Figure 19).

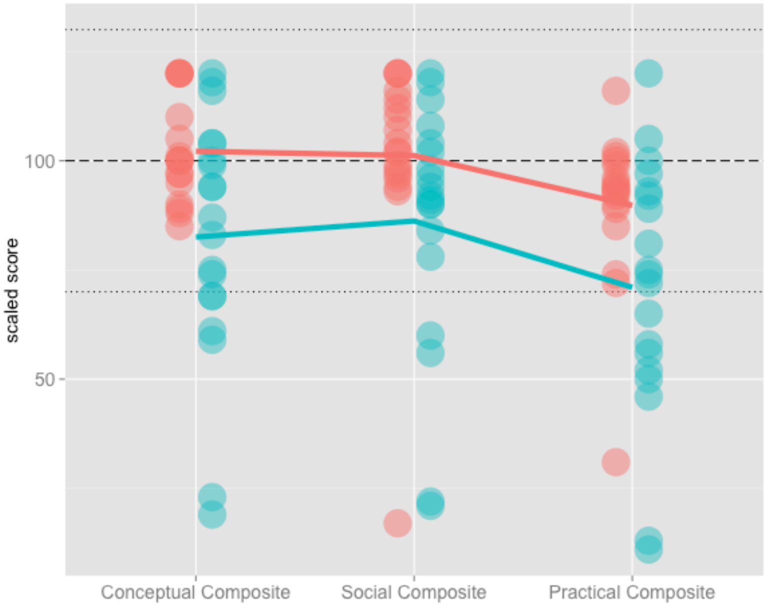


**Figure 19: Profile of composites scores for the conceptual, social and practical domains of the Adaptive Behaviour Assessment System 2$^{nd}$ edition.** Individual scores of children in the VI group are shown in blue and scores for children in the control group in red. The solid line indicates the profile of mean scores for each participant group.

**Figure 20: Scores on the single scales of the ABAS-II in the three adaptive behaviour domains (conceptual, social, practical).** Results of children in the VI group are shown in blue and results of children in the control group in red. The dotted line mark the cut-off for extremely low scores (left) and extremely high scores (right). The colour intensity indicates the number of children that reached the same score. Labels for scores more than one standard deviation above or below the mean of the normative sample refer to the identifiers presented in Table 4.

## 3.2.4. Quality of Life

### 3.2.4.1. Materials & Methods

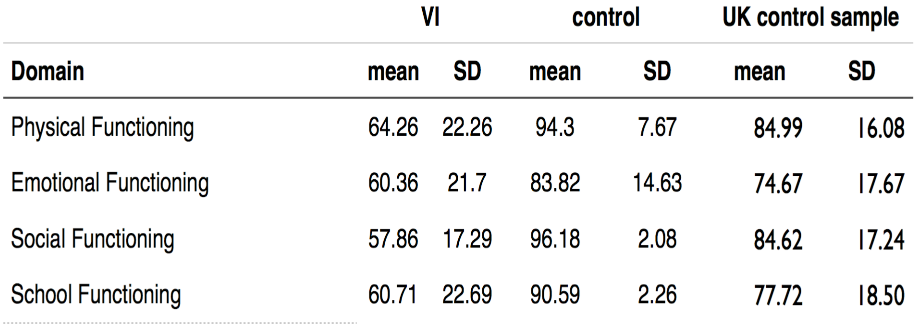
The Paediatric Quality of Life (PedsQL) questionnaire was administered to evaluate the impact of visual impairment on quality of life. The PedsQL is a one-sided questionnaire with 23 items relating to physical, emotional, social, and school functioning (Varni, Burwinkle, & Seid, 2005). The PedsQL is specially designed to assess quality of life in children in health care systems or children with disabilities. Parents rate the frequency at which problems occur on a scale from 0 (Never) to 4 (Almost always). The ratings are scored reversely to generate a measure of functioning ranging from 100% to 0%.

Results were compared between the VI and typically-sighted control group. Further, ratings were compared to reported results from the UK normative sample (Upton et al., 2005). Statistical comparison was based on a repeated-measures ANOVA model with participant group, questionnaire functional domain (physical, emotional, social, school) and their interaction as factors. Follow-up contrasts were based on Welch-correct t-tests.

### 3.2.4.2. Results

The Paediatric Quality of Life Questionnaire Parent Form was administered to assess the impact of visual impairment on general everyday function and wellbeing. Seventeen parents of children in the VI group and eighteen parents of children in the control group filled in the questionnaire. In comparison to the UK normative sample, children in the VI group reached low scores on all measures. Eight children in the VI group reached scores lower than two standard deviations below the mean of the normative sample on the Social and School Functioning scale. Five children reached low scores for all functional domains. None of the children in the control group reached scores below two standard deviations of the mean reported for the normative sample.[5]

**Table 7: Results of the PedsQL questionnaire.** The results of the UK normative sample were included for reference (Upton et al., 2005)



| | VI | | control | | UK control sample | |
|---|---|---|---|---|---|---|
| **Domain** | **mean** | **SD** | **mean** | **SD** | **mean** | **SD** |
| Physical Functioning | 64.26 | 22.26 | 94.3 | 7.67 | 84.99 | 16.08 |
| Emotional Functioning | 60.36 | 21.7 | 83.82 | 14.63 | 74.67 | 17.67 |
| Social Functioning | 57.86 | 17.29 | 96.18 | 2.08 | 84.62 | 17.24 |
| School Functioning | 60.71 | 22.69 | 90.59 | 2.26 | 77.72 | 18.50 |

Statistical comparison indicated a significant difference in PedsQL scores between the groups (rmANOVA: VI: mean=60.8, SE=2.76, Range=15-100; control: mean=91.22, SE=1.36, Range=60-100; F(1,29)=57.07, $p<0.001$). There was no statistically significant differences between functional domains (F(3,87)=1.768, p=0.159) or a significant interaction between functional domain and participant group (F(3,87)=1.583, p=0.199). Subsequent analysis focussed on the influence of vision level on PedsQL scores. Statistical comparison indicated a significant influence of vision group (rmANOVA: F(3,27)=21.77, $p<0.001$) and a trend-level interaction between vision group and functional domain (F(9,81)=1.851, p=0.072). Follow-up contrasts indicated different patterns for different vision groups: for physical function, children with severe and profound visual impairment had significantly worse ratings, whereas children with mild/moderate VI were statistically not distinguishable from the control group (see Table 8). A similar pattern was observed in the Emotional Function domain with similar scores in the mild/moderate and control group, and significantly lower scores in the severe/profound group. However, the difference between the mild/moderate and severe/profound was only on trend-level (p=0.065) and did not survive correction for multiple comparisons. For Social Function, all VI groups had lower ratings than children in the control group. In the School Function domain, children with SVI/PVI were rated significantly lower than children in the control and mild/moderate VI group. The mild/moderate group had ratings between the control and SVI/PVI group.

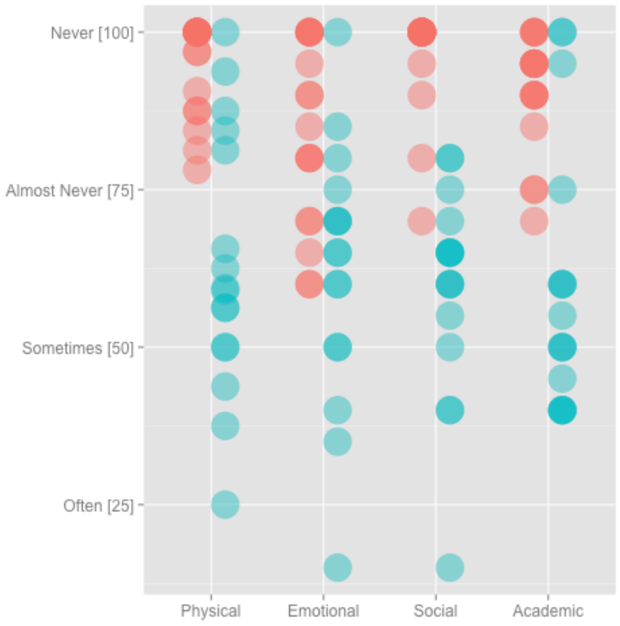


**Figure 21: Results of the Paediatric Quality of Life (PedsQL) questionnaire.** Results for children in the VI group are shown in blue and results for children in the control group in red. The colour intensity of the dots indicates the number of children that obtained the same score. Scales indicate the frequency at which difficulties in each domain occur, i.e. "Never" indicates that there is never a problem in this domain, while "Often" indicates that there are frequent problems.

**Table 8: Pairwise comparison of PedsQL results by vision group**

| | **Physical** | | | | **Emotional** | | | | **Social** | | | | **School** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mild/ moderate | | severe/ profound | | mild/ moderate | | severe/ profound | | mild/ moderate | | severe/ profound | | mild/ moderate | | severe/ profounf | |
| | t | **p** | t | **p** | t | **p** | t | **p** | t | **p** | t | **p** | t | **p** | t | **p** |
| control | 5.86 | **0.33** | 9.89 | **0.00** | 9.04 | **0.17** | 12.20 | **0.00** | 5.35 | **0.06** | 14.32 | **0.00** | 5.44 | **0.22** | 9.97 | **0.00** |
| mild/moderate | | | 11.17 | **0.00** | | | 12.98 | **0.07** | | | 5.90 | **0.39** | | | 8.58 | **0.20** |

**Table 9: Descriptives of the PedsQL questionnaire results broken down by vision group.** The severe and profound cases were combined to a severe/profound group for more meaningful statistical comparison.

| | control (n=18) | | mild/moderate (n=9) | | severe/profound (n=8) | |
|---|---|---|---|---|---|---|
| **Measure** | **mean** | **SE** | **mean** | **SE** | **mean** | **SE** |
| Physical | 93.95 | 1.94 | 86.46 | 6.73 | 53..67 | 2.99 |
| Emotional | 84.06 | 3.77 | 73.33 | 6.15 | 43.00 | 8.46 |
| Social | 95.94 | 2.20 | 67.50 | 11.81 | 56.00 | 4.85 |
| School | 90.00 | 2.33 | 74.17 | 11.14 | 59.00 | 11.00 |

### 3.2.5. Discussion

Different questionnaires were administered to assess everyday function, adaptive behaviour, and quality of life for children in the current sample. The measures consisted of standard questionnaires that are commonly used in research and clinical studies in order to facilitate comparison with reported findings in other participant populations.

The strengths and difficulties questionnaire was administered to evaluate difficulties in particular domains of everyday function. In line with previous reports, elevated scores were found for both the summary term of difficulties and across domains of psychological functioning (Pinquart & Pfeiffer, 2014). Difficulties were most pronounced in the social domain, which is consistent with previous studies that found particular problems in the social domain in adolescents with VI (Huurre & Aro, 1998; Kef, 2000). These difficulties may in part arise from deficits in social functioning (Brown et al., 1997; Hobson, Lee, & Brown, 1999; Tadić, Pring, & Dale, 2010), ostracism from typically-sighted peers (Horwood et al., 2005), or decreased opportunity for interaction due to decreased mobility and independence associated with severe or profound VI (Kef, 2000).

The Adaptive Behaviour Assessment Questionnaire was administered to assess skills that allow a child to meet demands of everyday living in the home and school environment. About half of the children in the VI group reached very low scores for general adaptive behaviour, whereas children in the control group obtained scores in the normal range. When analysed by functional domain, low scores were observed across domains (conceptual, social, practical) with the largest proportion of children with VI scoring low in the practical domain. However, the distribution of scores was also low in the control group compared to the normative data of the questionnaire. This could in part be driven by cross-cultural difference to the North American normative data in comparison to the current urban UK sample (Oakland, Iliescu, Chen, & Chen, 2013). Further, it is likely that some questions in the ABAS-II are no longer relevant due to societal changes, e.g. "Finds and uses a pay phone" (Community Use Item 15). Lower scores in the VI group may arise from a combination of inherent deficits, and disadvantage in an environment that is heavily reliant on visual information. For some behaviours, immediate detrimental effects of visual impairment are apparent, e.g. "Takes out trash when can is full" (Home Living Item 17). For other items, additional factors like mobility are likely to be important as suggested by previous research studies (Douglas et al., 2003; Haymes et al., 2002; Papadopoulos et al., 2011), e.g. for item "Attends fun activities at another's home" (Leisure Item 4).

The Paediatric Quality of Life questionnaire (PedsQL) was administered to assess the impact of visual impairment on quality of life. Both in comparison to the control group and the UK normative sample, children in the VI group reached low scores across all questionnaire domains (physical, emotional, social, and school functioning). Most low scores were found for school and social functioning. On the individual level, half of the sample scored within the same range as the UK normative sample. When analysed by vision level, the results suggested similar ratings for children with mild/moderate VI and children in the control on physical and emotional functioning, while children with severe to profound VI had lower ratings. For social and school functioning, the results suggest a stepwise distribution with the mild/moderate group being rated between the control and combined severe and profound group.

Together, the results indicate that visual impairment is associated with differences in everyday life skills and impacts on quality of life in children with VI. The effect of different degrees of visual impairment was dependent on the specific functional domain. Subsequent analyses in later chapters were carried out to link variation in adaptive skills, strengths and difficulties, and quality of life measures to possible underlying factors on the cognitive and neural level.

## 3.3. Parental factors

### 3.3.1. Introduction

The family environment plays a crucial role in the development of children (Belsky & de Haan, 2011). Childhood disability, such as visual impairment, may pose higher demands on parenting and increase parenting stress (Innocenti, Huh, & Boyce, 1992; Smith, Oliver, & Innocenti, 2001). Further, parents' mental health problems may impact on the social and cognitive development of children (Kurstjens & Wolke, 2001). In order to assess the potential differences in family environment factors between children with visual impairment and typically-sighted children in the current study, questionnaire measure of parent stress, anxiety, and depression were included.

Parent stress is generally described as being influenced by two main variables: family-related stress such as resources, life events, cohesion and support, and child-related stress, e.g. severity of disability, age of caregiver, presence of siblings among other factors (Boyce, Behl, Mortensen, & Akers, 1991; Innocenti et al., 1992). A study of 880 families with children with disability conducted by Smith et al. found that family function explained most of the variance in parent stress, while severity of childhood disability itself had little impact on parent stress(Smith et al., 2001).

Depression may impact on the cognitive and social development of children, particularly if depressive episodes are recurrent and severe (Grace, Evindar, & Stewart, 2003). Further, a recent statistical modelling study suggests that chronic physical disability, such as visual impairment, may be associated with maternal depression, which in turn increases the likelihood for anxiety and depression for the child (Ferro et al., 2015). In order to assess the prevalence of anxiety and depression symptomatology, a standard clinical questionnaire was filled in by the caregiver.

### 3.3.2. Materials & Methods

#### 3.3.2.1. Parenting Stress Index

The short form of the Parent Stress Index 4th edition (PSI) was administered to assess stress in the parent-child relationship. The PSI is a single-sided form with 36 items suitable for parents of children between 1 month and 12 years (Haskett, Ahern, Ward, & Allaire, 2006). The PSI ratings are used to generate composites in three domains comprising Difficult Child, Parent Distress, and Parent-Child Dysfunctional Interaction as well as a Total Stress Index (Abidin et al., 1990). The PSI also contains a Defensive Responding validity scale, which indicates if parents responded in a defensive way.

#### 3.3.2.2. Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) is a single-sided questionnaire with 14 items consisting of questions that relate to symptoms of either anxiety or depression (Zigmond & Snaith, 1983), e.g. "I feel tense or 'wound up' "(Anxiety) or "I can laugh and see the funny side of things" (Depression). Each item is rated in terms of frequency from "most of the time" to "not at all". A total score for anxiety and depression is derived, which can be compared to cut-off scores derived from normative samples. The most recent meta-analysis of HADS scores reported optimal sensitivity and specificity at a cut-off score of 8 for both anxiety and depression (Bjelland, Dahl, Haug, & Neckelmann, 2002) (sensitivity and specificity about 0.8 for both scales).

### 3.3.3. Results

#### 3.3.3.1. Parent Stress

Seventeen parents of children in the control group and fourteen parents of children in the VI group filled in the Parenting Stress Index. Eight parents in the control group and three parents in the VI group reached significant ratings on the Defensive Responding validity scale (score of 10 or less). However, the data is included because scores were close to the cut-off (9 or 10) and were found in more than half of the parents in the control group.

One parent in the VI group and one parent in the control group had a Total Stress score above the 85th percentile with reference to the norms of the test. Five scores in the control group and two scores in the VI group fell below the 5th percentile. Statistical comparison of Total Stress scores indicated no significant effect of participant group or age of the child (rmANOVA: VI: mean=63.43, SE=4.37, Range=34-97; control: mean=54.18, SE=3.54, Range=41-97, F(1,28)=2.720, p=0.11).

Two participants in the control group and three participants in the VI group scored above the 85th percentile in the Difficult Child subdomain. Five ratings in the control group and one ratings in the VI group fell below the 5th percentile compared to the norms of the test. There was no significant differences between the groups (rmANOVA: VI: mean=24.5, SE=2.32, Range=12-47; control: mean=20.35, SE=2.22, Range=13-47, F(1,28)=1.632, p=0.212).

In the Dysfunctional Parent-Child Interaction domain, one parent in the VI group and one parent in the control group reached scores above the 85th percentile. There was no significant difference between the groups (rmANOVA: VI: mean=18, SE=1.17, Range=12-29; control: mean=15.65, SE=1.06, Range=12-29, F(1,28)=2.16, p=0.153).

For Parent Distress, one participant in the VI group scored above the 85th percentile. Two ratings in the control group and one in the VI group were below the 5th percentile. Statistical comparison indicated a significant difference between the groups with higher scores in the VI group (rmANOVA: VI: mean=22.43, SE=1.6, Range=13-34; control: mean=17.65, SE=0.88, Range=13-25; F(1,28)=7.272, p=0.0117).

### 3.3.3.2. Parent Anxiety and Depression

Fifteen parents in the VI group and 16 parents in the control group completed the HADS. Two parents in the VI group reached scores above the cut-off for depression (9 and 15) and anxiety (10, 13). One additional parent in the VI group scored above the cut-off on anxiety alone (13). None of the parents in the control group reached scores above the cut-off for both depression or anxiety.

## 3.3.4. Discussion

The potential influence of family environment factors was evaluated for the current sample. The investigation focussed on parent stress, parent anxiety and depression that are suggested to impact on the social and cognitive development of the child (Kurstjens & Wolke, 2001)

Analysis of a parent stress questionnaire did not indicate a significant difference on total stress between the VI and typically-sighted control group. There was also no difference between the groups on child-related or parent-child interaction factors.

For parent anxiety and depression, a higher number of parents in the VI group reached scores above the clinical cut-off for anxiety/depression or anxiety alone. The Hospital Anxiety and Depression Scale is not validated for quantitative comparison between groups and the present study does not have sufficient statistical power to adequately establish the prevalence of anxiety/depression symptoms in parents of children with visual impairment, but this finding may indicate higher prevalence of anxiety/depression in this group. Further, difference in response biases between a clinically recruited group and group of volunteers cannot be excluded. Further investigations, ideally using data available from national databases, would be needed to investigate relationships between visual impairment in children and anxiety/depression in parents.

## 3.4. Chapter Discussion

The present chapter reported results of questionnaire measures of adaptive ability, strengths and difficulties, and parental factors. Lifestyle factors including adaptive behaviour, strengths and difficulties in everyday situations, and quality of life indicated significantly more difficulties in children with visual impairment in line with previous reports. Comparison by vision level indicated differences depending on the functional domain with similar ratings of children in the mild/moderate group and the control group for physical and emotional function, but worse ratings than controls for social and school function. Self-ratings of parent stress indicated no significant difference between parents of children with VI or control parents. However, there was some indication of higher prevalence of anxiety in parents of children with VI in the current sample.

# Chapter 4: Parieto-prefrontal pathway: executive function

## 4.1. Chapter Introduction

The parieto-prefrontal pathways contains connections that are implicated in the top-down control of eye movements (Kravitz et al., 2011) and spatial working memory (Georgieva, Peeters, Kolster, Todd, & Orban, 2009). Studies in typically-sighted infants implicated the control of eye movement as an early precursor of executive abilities (Johnson & de Haan, 2010). Executive functions (EF) are a set of cognitive processes responsible for coordinating different cognitive skills in order to make plans and solve problems (Lezak, 1982; Welsh & Pennington, 1988). These skills are considered more important for school readiness and academic achievement than a child's IQ, or level of reading and math ability (de Haan, 2014; McDermott, Westerlund, Zeanah, Nelson, & Fox, 2012; Stevens & Bavelier, 2012). Major subcomponents of executive functioning have been described as attention, inhibition, self-regulation, working memory, cognitive flexibility, planning, organisation, problem-solving, and performance-monitoring skills (Anderson, 2002).

Behavioural studies found  greater difficulties in executive domains, particularly attention, in children with visual impairment including a higher prevalence of ADHD symptomatology (Decarlo et al., 2014) and lower parent ratings on questionnaires probing executive skills (Tadić, Pring, & Dale, 2009). However, differences seem to be in part dependent on the specific executive domain and implementation of executive tasks. For instance, a classic study by Witkin and colleagues identified an overall advantage in auditory sustained attention tasks in children with VI (Witkin et al., 1968), but other studies found increased vulnerability of executive skills in children with VI based on the prevalence of ADHD diagnosis (Cavézian et al., 2013; Leat & Lovie-Kitchin, 2008).

Further, the influence of vision level is unclear. Some early functional vision, even if degraded, might have a protective effect (Tadić et al 2009). On the other hand, it is possible that degraded vision during early infancy is disruptive as children rely on a sense that provides inferior information and do therefore not develop compensatory ability in other modalities. Indeed, some studies found attention deficits in a group of children with mild to moderate VI (Cavézian et al., 2013; Leat & Lovie-Kitchin, 2008).

In summary, the extended dorsal stream model suggested an impairment of top-down control of eye movement and spatial working memory as a result of changes to parieto-prefrontal connections. Both functions could not be directly assessed in the current sample of children with visual impairment, because no suitable standard assessment tools for these functions are currently available for children with VI. However, developmental studies indicate that differences in these domains may lead to differences in executive function development as indicated by the high overlap of substrates and test score variation in executive function in the early years (Kane & Engle, 2002). A literature review of a small number of available behavioural studies investigating executive skills in children with visual impairments provided an inconsistent picture suggesting that certain aspects of executive function may be enhanced or adversely affected by congenital VI depending on the specific executive function and task design.

In order to clarify inconsistencies, the current study took a wide approach to the assessment of executive function probing multiple domains of EF including sustained and selective attention, and cognitive flexibility as well as a questionnaire measure that quantifies everyday executive skills. Further, executive function was assessed using a selective attention ERP paradigm in order to investigate neural correlates of the ability to selectively attend to auditory stimuli and suppress task-irrelevant information.

## 4.2. Neuropsychological assessment of executive functions

The current investigation aimed to investigate the cognitive profile of children with VI with a particular focus on executive skills. Further, the study aimed to identify potential protective cognitive factors and relate behavioural differences to neural markers. Children with VI were assessed with standard neuropsychological instruments, including auditory subtests of the Test of Everyday Attention for Children (TEA-Ch) (Manly et al., 2001) and verbal tests of the Delis-Kaplan Executive Function System (D-KEFS) (Baron, 2004). Further, questionnaire measures that are commonly used for clinical evaluations were filled in by the parents to assess executive function abilities in everyday life settings (Behavioural Rating Inventory of Executive Function (BRIEF) Parent Form (Gioia, Isquith, Guy, & Kenworthy, 2000b)). In addition to the behavioural measures, participants completed an ERP task of selective auditory attention.

Based on previous reports of questionnaire results and coded video observations of pre-schoolers with VI (Tadić, Pring, & Dale, 2009), lower scores on tests that require attention switching were expected in the VI group, while tests of sustained attention or verbal fluency were hypothesised to fall within the typical range for age and general cognitive ability.

## 4.2.1. Verbal working Memory

### 4.2.1.1. Introduction

Working memory (WM) is the ability to temporarily store and manipulate information (Baddeley, 1992). A widely supported model of working memory by Alan Baddeley suggests that working memory consists of three main components: a visuospatial sketch pad that is involved in the short-term storage and manipulation of spatial information, a phonetic loop for similar manipulation of verbal information, and a domain-general central executive system that is involved in the maintenance and updating of information (Baddeley, 1992; 2003). The predictions of the extended dorsal stream model suggested that spatial working memory is particularly affected when parieto-prefrontal connections are changed. However, due to the greater overlap between parts of the working memory system in children (Gathercole, Pickering, Ambridge, & Wearing, 2004), it is also conceivable to verbal aspects may be affected as a result of changes to spatial WM. Several studies reported higher performance for congenitally blind adults and children compared to typically-sighted controls on short-term memory tasks, but similar performance on verbal working memory tasks (Hull & Mason, 1995; Raz et al., 2007; Roder et al., 2001; Smits & Mommers, 1976; Swanson & Luxenberg, 2009; Tillman & Bashaw, 1968; Veispak et al., 2013).

### 4.2.1.2. Materials & Methods

Task comprising the Working Memory (WM) composite of the Wechsler Intelligence Scale for Children 4th edition (Wechsler, 2004) were administered to determine working memory performance. The WM composite consists of the Digit Span and Letter-Number Sequence task.

In the Digit Span task, children have to repeat a sequence of letters of increasing length that are read out to them. In the forward condition, the child had to repeat the number as presented. In the backwards conditions, the sequence of numbers had to be reversed. The sequences were read to the children at an approximate rate of one digit per second following the instructions in the test manual. The answer was scored as correct when the child repeated the sequence correctly and the next sequence was presented. A mistake in the response or omissions was rated as incorrect. Sequences were not repeated. Increasingly longer sequences were administered until the end of the test was reached or the child failed to respond correctly on two consecutive trials. The total raw score consisted of the number of correct responses in the forward and backward condition.

For the Letter-Number Sequence task, children were read a sequence of numbers and letters. The child had to repeat the numbers and letters with the numbers in numerical order and the letters in alphabetical orders starting with the lowest number, e.g. the correct answer for the sequence 1-A-2-B is 1-2-A-B. The answer was scored as correct when the child repeated the sequence correctly following these rules. Sequences were administered to the end of the test or until criteria of the break-off rule were reached (mistakes on three consecutive trials of the same length). The number of correct responses yielded the total raw score.

Raw scores for both tasks were transferred to scaled scores according to participant age with reference to test norms (Wechsler, 2004). The sum of scaled scores for both tests were summarised in the Working Memory Composite using the sum of scaled score equivalence table (Wechsler, 2004). WISC-IV subtest scores are normed to yield a mean score of 10 and a standard deviation of 3. Composite scores are normed to a mean of 100 and a standard deviation of 15.

### 4.2.1.3. Results

Working memory scores were obtained from all participants in the study. Statistical comparison did not indicate significant differences in the scaled Working Memory Composite score between the groups (Independent two-sided t-test: VI: mean=96.21, SE=4.29, Range=61-146; control: mean=100.5, SE=2.41, Range=88-123; t(28.171)=-0.871, p=0.39). Separate analysis of the subtests revealed a trend-level difference on Letter-Number Sequence with lower scores in the VI group (Independent two-sided t-test: VI: mean=9.26, SE=0.94, Range=1-17; control: mean=11.17, SE=0.32, Range=9-14, t(22.026)=-1.9268, p=0.067). There was no indication of a significant difference between groups on Digit Span scores (Independent two-sided t-test: VI: mean=9.32, SE=0.7, Range=5-19; control: mean=9.22, SE=0.66, Range=5-15, t(34.963)=0.0972, p=0.92).

Next, the influence of vision level on test scores was investigated. Statistical comparison did not indicate a significant effect of vision group on verbal WM composite scores (one-way ANOVA: MVI: mean=101.25, SE=4.08; P/VI: mean=99.1, SE=12.59; control: mean=99.18, SE=2.14; F(2,31)=0.079, p=0.971).

Post-hoc power calculations showed that at a significance of 0.05, a power of 0.80, a sample size of 18 participants in two groups, a Cohen's d effect size of 0.94 and above could be detected.

### 4.2.1.4. Discussion

The extended dorsal stream model suggested differences in spatial working memory and top-down control of eye movement. It was hypothesised that these differences in early development may have lead to a different trajectory of general executive function development so that different aspects of verbal executive function are also affected, such as verbal working memory. The results of the current investigation do not suggest that verbal working memory is affected in children with VI. Composite test scores and single scale scores were statistically indistinguishable between the groups. A trend-level effect with low performance in the VI group on Letter-Number Sequence scores was found, but comparison to the age-appropriate norms of the test suggests that this difference is likely driven by biases towards higher performance in the control sample rather than a genuine disadvantage in the VI group. However, the current sample differed from previously reported samples, because children with mild to moderate visual impairment were included, whereas previous studies focussed on legally classified 'blind' children, i.e. children with severe to profound visual impairment. However, statistical analysis indicated no significant effect of vision level on composite WM scores. In line with these results, the only child with profound VI in the current sample reached as score in the average range compared to typically-sighted children of the same age.

## 4.2.2. Verbal Fluency

### 4.2.2.1. Introduction

The previous experiment suggested that verbal working memory is not affected in children with VI. However, differences may arise from a more executive component rather than a storage component. In order to further investigate executive aspects of verbal ability in children with VI, a verbal fluency task was administered as an additional task probing executive function. Verbal fluency tasks assess the ability of a participant to generate words that belong to either a phonemic or semantic category within a pre-specified time (Baldo, Graves, Brugger, & Schwartz, 2003). The task is considered to rely on executive control as performance requires the use of a self-devised strategy to generate words, selection of appropriate items, suppression of irrelevant items, rule following, performance monitoring, and control of performance anxiety (Matute, Rosselli, Ardila, & Morales, 2004). Support for a contribution of executive skills to verbal fluency task performance comes from a latent variable analysis in older adults that identified a verbal (vocabulary size, lexical access speed) and executive factors (updating, inhibition) as significant contributing factors. In the current investigation, verbal fluency is employed as a measure of verbal executive abilities.

### 4.2.2.2. Materials & Methods

The Verbal Fluency task of the D-KEFS consists of three conditions. In the Letter Fluency (LF) condition, the participant has to name as many words as possible that starting with a given letter within 60s. The participant is further instructed that words cannot be repeated and cannot be names of people, places are numbers. In the Category Fluency (CF) task, the participant has to name words within 60s that belong to a semantic category, i.e. animals and boys'/girls' names. In the third condition, Category Switching (CS), participants have to switch between words that belong to different semantic categories, i.e. naming a fruit and a piece of furniture. All tasks are thought to engage several cognitive processes, including working memory, response monitoring, and cognitive flexibility {Schwartz:2003fv}. The LF condition requires are search through lexical or phonological memory, whereas the CF condition taps into semantic or conceptual memory (Baldo, Schwartz, Wilkins, & Dronkers, 2006). The CS conditions requires a similar semantic memory search, but makes additional demands on switching and cognitive flexibility skills (Baron, 2004). Neuropsychological investigations found a dissociation in deficits in LF and CF in patients with focal lesions: lesions to left frontal regions affected performance in the LF condition, whereas lesions to the left temporal cortex affected CF (Baldo et al., 2006; Henry & Crawford, 2004). This is in line with fMRI investigations in typical controls that found greater activation in frontal areas in the LF and greater activation in temporal areas during the CF condition (Birn et al., 2010).

Raw scores were transferred to scaled scores with reference to the test norms. The D-KEFS subtest scores are normed to a mean of 10 and a standard deviation of 3. Statistical comparison was based on a repeated-measures ANOVA model with subtest, participant group, and their interaction as factors, and WISC Verbal Comprehension as a co-variate (test score ~ subtest + participant group + vIQ + all interactions). Mauchly's test of sphericity was applied to test for homoscedasticy (Mauchly, 1940). Greehouse-Geisser correction was applied to correct for heteroscedasticy and corrected F-statistics are reported.

### 4.2.2.3. Results

Seventeen children in the VI (7 male, 8.27-13.32y, vIQ: 75-148) and 17 children in the control group (10 male, 8.56-12.92y, vIQ: 83-144) completed the Verbal Fluency task. An overall comparison of scores across subtests indicated a trend-level interaction between verbal fluency subtest and participant group (rmANOVA: F(3,93)=42.6,p=0.081). Differences between participant groups on each subtest were subsequently investigated in separate models.

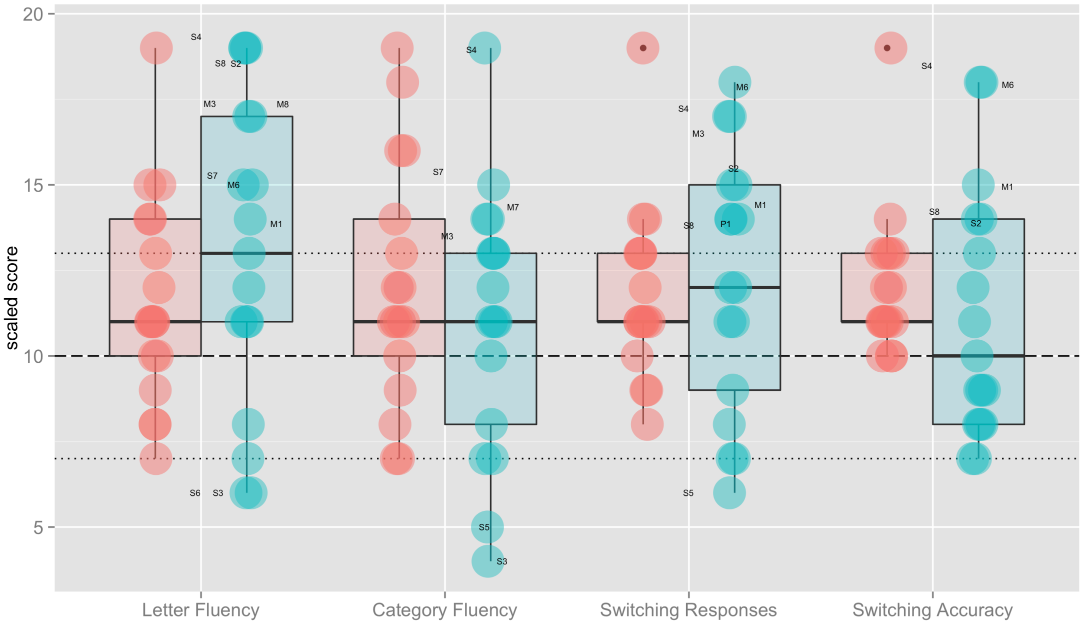


**Figure 22: Results of the Verbal Fluency assessment for the VI group (blue) and control group (red).** The dashed line indicates the mean score of the normative sample of the test and the dotted lines indicate one standard deviations difference from the mean (12.2-20 and 79.8-87.8%ile bands). Labels for scores more than one standard deviation above or below the mean of the normative sample refer to the identifiers presented in Table 4.

Letter Fluency condition

Nine children in the control group and 12 children in the VI group scored within 2 standard deviations of the norm mean. Two children with VI reached scores below one standard deviation. Eight children in the VI group and 5 children in the control group reached scaled scores more than one standard deviation above the norm mean. There was no significant effect of participant group on scores on the Letter Fluency subtest (Independent two-sided t-test: VI: mean=11.65, SE=0.75, Range=6-19; control: mean=12.63, SE=0.99, Range=7-19, t(24.11)=1.07,p=0.297). Separate analysis by vision group did not indicate a significant effect (one-way ANOVA: MVI: mean=13, SE=1.3, Range=6-17, S/PVI: mean=12.75, SE=1.95, Range=6-19, F(2,27)=0.529, p=0.595).

Category Fluency condition

Twelve children in the VI group and 11 children in the control group scored within 2 standard deviations of the norm mean. Four children with VI scored lower than one standard deviation from the norm mean. Five children in the control group and 4 children in the VI group reached scores more than one standard deviation above the norm mean. There was no significant effect of participant group on category fluency scores (Independent two-sided t-test: VI: mean=10.94, SE=0.96, Range:4-19; control: mean=12.06, SE=0.87, Range=7-19; t(28.61)=-10.93, p=0.283). Follow-up analysis did not indicate significant differences between vision groups (one-way ANOVA: MVI: mean=11.12, SE=0.93, Range=7-14; S/PVI: mean=9.25, SE=1.86, Range=4-19, F(2,27)=2.099, p=0.142).

Switching condition

A) Responses

Nine children in the VI group and 14 children in the control group scored within 2 standard deviations of the norm mean. Three children in the control group and 8 children in the VI group reached scores more than one standard deviation above the norm mean. There was no significant difference between participant groups (Independent two-sided t-test: VI: mean=12.29, SE=0.87, Range:7-19; control: mean=11.76, SE=0.62, Range=8-19; t(23.33)=0.253, p=0.802). Subsequent analysis by vision group also did not indicate significant differences (one-way ANOVA: MVI: mean=12.5, SE=1.32, Range=7-18; S/PVI: mean=11.12, SE=1.52, Range=6-17, F(2,27)=0.485, p=0.621).

B) Accuracy

Nine children in the VI group and fourteen children in the control group reached scores within 2 standard deviations of the norm mean. One child in the VI group fell one standard deviation below the norm mean. Eight children in the VI group and 3 children in the control group reached scores more than one standard deviation above the norm mean. No significant difference between participant groups was found (VI: mean=11.94, SE=0.89, Range=6-18; control: mean=11.76, SE=0.62, Range=8-19; t(21.94)=-0.482, p=0.635). Separate analysis showed no significant difference between vision groups (one-way ANOVA: MVI: mean=12, SE=1.16, Range=8-18; S/PVI: mean=10.5, SE=1.5, Range=7-18, F(2,27)=1.035, p=0.369).

### 4.2.2.4. Discussion

Verbal fluency tests were administered as a verbal measure of executive function. There was no indication of significant differences between the VI and typically-sighted group. The D-KEFS battery also contained a task in which children had two switch between semantic categories, which poses higher executive demands compared to the single category condition (Delis, Kramer, & Kaplan, 2001). There was also no indication of significant differences between the groups on either the total number of correct responses or the number of correct switches. These findings are in line with a previous study in adolescents with VI that reported typical to superior performance on verbal fluency tasks in this group (Wakefield, Homewood, & Taylor, 2006). In conclusion, the results of verbal fluency assessment did not indicate that verbal executive function abilities are affected in the current sample of school-age children with VI.

## 4.2.3. Sustained and Divided Auditory Attention

### 4.2.3.1. Introduction

The extended dorsal stream model suggested that connections between the parietal lobe and prefrontal cortex (particularly the ventrolateral PFC) are important for spatial aspects of executive function. Vision is thought to play an important role in the development of a spatial representations that is associated with supramodal effects in attention tasks (see Chapter 1 for a detailed discussion of unitary vs supramodal views of attention). Differences in the development of a representational space for attention may therefore impact on the performance on attention tasks in other modalities. For instance, additional visual cues may aid the auditory attention, e.g. when looking at a person who is talking. Visual impairment may therefore be associated with differences in higher-level attention that are apparent in other sensory modalities. A previous study based on coded video observations of infants with VI interacting with their primary caregiver suggested weaker performance in responses to attentional bids (requiring attention switching from one object to another), particularly in whose with the most profound VI (Tadić, Pring, & Dale, 2009). In addition, studies of inattention and hyperactivity symptoms found a higher prevalence in children with VI. In order to test the hypothesis that higher-level attention is affected in school-age children with VI, auditory tests of sustained and divided attention were administered to the current sample of children with VI.

### 4.2.3.2. Materials & Methods

Auditory tests from the Test of Everyday Attention for Children (TEA-Ch) suitable for children with visual impairment were selected. In the Score! subtest of the TEA-Ch, children have to count infrequently presented sounds in several trials over a 6 min period (Manly et al., 2001). The test is designed to assess sustained and focussed attention, i.e. the ability of the child to respond consistently and reliably to a specific stimulus during a continuous and repetitive activity. The load on other aspects of executive function is minimised: working memory load is low, because the rules of the test are simple with clear instructions and feedback practice before the scored trials. Further, the number of counts that have to be kept in mind is low with a short trial duration. In addition, the test is administered in a assessment setting with minimal distraction.

The Score Dual Task condition requires children to count the number of scoring sounds while listening out for an animal name in a simultaneously presented news broadcast. This test is designed to assess selective and divided attention. Selective attention needs to be employed to keep focus on the counting, while the news story that contains mostly irrelevant information acts as a distracting stimulus. Divided attention is required to fulfil both task demands. Other aspects of executive function like sustained attention and working memory are also likely to contribute to task performance (Manly et al., 2001).

Raw scores were transferred to scaled scores with reference to the test manual. Subtest scores of the TEA-Ch are normed to a mean value of 10 and a standard deviation of 3 (7: 12.2-20.2%ile; 10: 43.4-56.6%ile; 13: 79.8-87.8%ile).

### 4.2.3.3. Results

All children that participated in the study completed the TEACh Score and Score DualTask assessment. In the sustained attention condition (Score), fourteen children in the VI group and 12 children in the control group scored within one standard deviations of the norm mean. Two children in the VI group and two children in the control group reached scaled scores below one standard deviations of the mean of the normative sample of the test (VI: 3.3-12.2 %ile band; controls: 6.7-12.2 %ile band). Four children in the control group and one child in the VI group reached scaled scores above one standard deviations of the norm mean (87.8-98.5%ile band). There was no significant difference in standard scores between the VI and control group in the sustained auditory attention condition (Independent two-sided t-test: VI: mean=10.11, SE=0.66 Range=6-15

I control: mean=10.94, SE=0.7 Range=5-14, t(31.904)=-0.707, p=0.495). Subsequent analysis by vision group did not indicate a significant difference between the control group, children with mild/moderate VI and children with severe/profound VI (one-way ANOVA: MVI: mean=10.38, SE=0.84, Range=7-13; SVI/PVI: mean=10.11, SE=1.02, Range=5-14, F(2,31)=0.285, p=0.754)

In the divided attention condition, 10 children in the VI group and 10 children in the control group scored within two standard deviation of the norm mean. One participant in the VI group fell below two standard deviations from the mean of the norms (score: 2, 0.2-0.6 %ile). Five children in the VI group and 8 children in the control group reached standard scores more than one standard deviation above the norm mean (87.8-99.8%ile). A trend-level effect of participant group was found with lower scores in the VI group (Independent two-sided t-test: VI mean=10.88, SE=0.87, Range=2-16 I control mean=12.89, SE=0.64, Range=7-17, t(34)=-1.653, p=0.0759). The trend-level effects were driven by a participant with VI who achieved only a scaled score of 2 (0.2-0.6 percentile band). No significant effects of participant group were found when excluding this participant (VI: mean=11.35, SE=0.68 Range=7-17 I control: mean=11.35, SE=0.68, Range=7-16; t(32.737)=-1.643, p=0.12). Analysis by vision group did not indicate significant differences between vision groups (one-way ANOVA: MVI: mean=11, SE=1.1, Range=7-16; S/PVI: mean=10.78, SE=1.39, Range=2-16; F(2,31)=1.689, p=0.201, including all participants).

Three children in the VI group performed substantially better in the sustained compared to the divided attention condition (The manual does not provide a difference score for these tasks. Differences of more than 3 standard scores were classified as a substantial difference). Six children in the VI group and 5 children in the control group performed substantially better in the dual task condition compared to the sustained attention condition. Positive difference scores were statistically compared separately for the Score and Score DT conditions, but participant group did not emerge as a significant factor for either Score or ScoreDT.

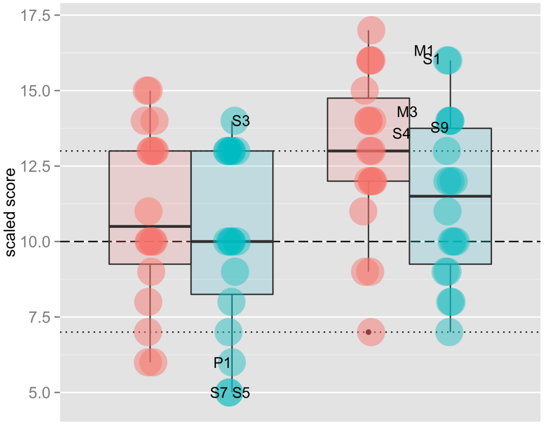


**Figure 23: Scale-score results of a sustained and divided auditory attention test for children with VI (blue) and typically-sighted controls (red).** The TEA-Ch Score and Score DualTask were administered. Results represent age-adjusted scaled scores based on the normative sample of the test. The dashed line indicates the mean of the normative sample and the dotted lines 2 standard deviations difference from the mean (12.2-20 and 79.8-87.8%ile bands). Labels for scores more than one standard deviation above or below the mean of the normative sample refer to the identifiers presented in Table 4.

Post-hoc power analysis indicated that moderate effect sizes of Cohen's f larger than 0.54 could be detected at a significance level 0.05, a power of 0.80, and a total sample size of 33 participants in 2 groups.

### 4.2.3.4. Discussion

The participants were assessed on two auditory tasks of the Test of Everyday Behaviour for Children (TEA-Ch). The Score! condition is described as a test of sustained auditory attention (Anderson, 2002; Manly et al., 2001). Because of long pauses between tones and simple task demands, children have to actively sustain their attention to perform the task (Anderson, 2002). There was no indication of significant differences in task performance between the VI and the control group. This suggests relatively intact sustained auditory attention under low load conditions.

In the Dual Task condition, the children had to count sounds while simultaneously listening for an animal name in a short news story. This task is described as a measure of divided auditory attention (Manly et al., 2001). There was no significant difference in task performance at the group level. A high proportion of participants in both groups reached scores in the superior to highly superior range compared to the normative sample of the test. However, there was also considerable variability in scores in the VI group including scores in the extremely low range. These results suggest sustained attention skills in the average to high average range for most children with VI in this group.

Three children in the VI group performed better in the sustained attention compared to the divided attention task. The scores in the sustained attention task fell in the above average range, whereas divided attention scores fell in the below average range. These participants were also lower functioning in other parts of the assessment (vIQ: 76-98; WM:71-97) so that the higher cognitive load of the dual task condition are likely to have contributed to the weaker performance in the divided attention condition. Unexpectedly, a large proportion of the current sample performed substantially better in the supposedly more demanding dual task condition. The test manual notes that a small proportion of children in the normative sample also performed better in the divided attention compared to the sustained attention condition. However, this pattern was observed in almost half of the children in the current sample. There was no indication that difference in vIQ or WM contributed to the positive difference scores so that it is difficult to explain the causative factors behind this effect. Behavioural observation during testing suggested that children were more easily distracted and were more likely to be off task in the sustained attention condition, e.g. day dreaming. In comparison, children appeared more engaged and on task during the divided attention condition that appeared more stimulating due to multiple task demands.

In summary, assessments on sustained and divided attention condition did not indicate a deficit in the VI group. It may therefore be concluded that vision is either not necessary for the development of auditory sustained and divided attention or that low-level vision, i.e. limited shape perception in severe VI, is sufficient for its development. Differences between the VI and the typically-sighted control group may exist that could not be detected in the current study, because differences are either only apparent in more demanding tasks or may be too subtle to be detected with the limited sample size in the present study.

## 4.2.4. Everyday executive skills

### 4.2.4.1. Introduction

The term "executive function" is used to describe an individuals ability to adapt flexibly and appropriately to demands in the environment. Executive functions are thought to comprise a range of distinct, yet related cognitive skills (Anderson, Anderson, Jacobs, & Spencer Smith, 2008). On these grounds, the validity of neuropsychological tests of executive function that attempt to assess the integrity of an isolated executive function has been criticised (Isquith, Roth, & Gioia, 2013). Function-specific tests mostly provide detailed instructions on how to perform the tasks and often also contain prompts for children that show initial difficulties with the task. Therefore, it is not clear that difficulties in planning and problem solving that are relevant to the child's everyday coping are measured in function-specific tests (Isquith et al., 2013). In order to capture everyday executive abilities in children with VI, a standard questionnaire was filled in by the parents.

Based on a high demand for psychological assessment of executive function in the context of educational concerns in the clinical setting, difficulties in everyday executive function were expected in children with VI. Further, previous preliminary studies had suggested a deficit in everyday executive abilities in children with VI (Tadić et al., 2010).

### 4.2.4.2. Materials & Methods

The BRIEF is a two-sided questionnaire with 86 items, which is suitable between 5 and 18 years of age (Gioia, Isquith, & Kenworthy, 2000a). The questionnaire rates executive skills in domains of Inhibition, Shifting, Emotional Control, Initiation, Working Memory, Planning/Organising, Organisation of Materials and Monitoring. Ratings are transferred to standard scores that are adjusted for the child's age with reference to the questionnaire's normative data.

The scores in these scales are summarised into composites, namely a Behavioural Regulation Index (BRI) (Inhibition, Shifting, Emotional Control), a Metacognitive Index (MI) (Initiation, Working Memory, Planning/Organising, Organisation of Materials, Monitoring) and a Global Executive Composite (all scales) (Gioia, Isquith, Retzlaff, & Espy, 2002b). The BRI summarises the ability of the child to modulate the emotional and behavioural response via inhibitory control. In contrast, the MI is a measure of higher-order executive skills.

BRIEF composite scores were transferred to scaled scores according to the questionnaire manual. The BRIEF cut-off composite score for further clinical investigation (t-score of 65 or above) was designed to be 1.5 standard deviations above the mean of the normative sample (Gioia et al., 2000a) (mean: 50, standard deviation: 10).

### 4.2.4.3. Results

Seventeen parents in the VI group and eighteen parents in the control group completed the BRIEF questionnaire. All Inconsistency scores were below the 98th percentile and were therefore in the acceptable range according to the questionnaire manual. There were two cases of highly elevated Negativity scores in the VI group (above the 98th %ile). High negativity scores may indicate an excessively negative attitude of the rater, but may also suggest extreme executive dysfunction (Gioia et al., 2000a). Therefore, the data was analysed both including and excluding these cases.

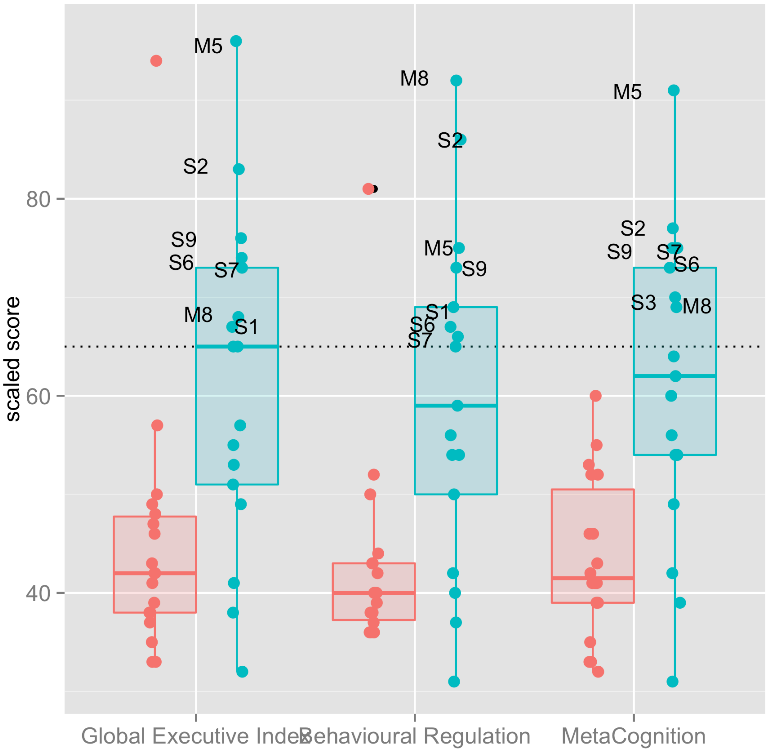


**Figure 24: BRIEF composite scores: Scaled scores are shown for the VI group in blue and for the control group in red.** Cases with high negativity scores were included in this graph. The dashed line indicates the cut-off for further clinical investigation of executive dysfunction (>2 standard deviations above the norm means). Labels above the clinical cut-off refer to indentifiers presented in Table 4.

Nine children in the VI group and 1 child in the control group reached Global Executive Index scores above the cut-off score of the questionnaire that warrants further clinical investigation for executive dysfunction. Statistical comparisons indicated a main effect of participant group with significantly higher scores in the VI group (Independent two-sided t-test: VI: mean=61.35, SE=4.06, Range=32-96; control: mean=45.11, SE=3.25, Range=33-94; t(28.66)=2.964,p=0.006). The effect were also observed when the cases with high negativity scores were excluded (Independent two-sided t-test: VI: mean=58.67, SE=3.87, Range=32-83, control: mean=45.11, SE=3.25, t(25.325)=2.494, p=0.019).

Eight children in the VI group and one child in the control group scored above the cut-off score on the Behavioural Regulation Index. There was a significant effect of participant group with higher scores in the VI group (Independent two-sided t-test: VI: mean=59.76, SE=2.49, Range=36-81; control: mean=42.83, SE=4.1, Range=31-92, t(24.171)=3.313, p=0.003). These effects were also detected when the high negativity cases were excluded (Independent two-sided t-test: VI: mean=58.13, SE=4.48, Range=31-92; control: mean=42.83, SE=2.49, Range=36-81, t(19.902)=2.747, p=0.013).

On the Metacognition Index, there were 7 children in the VI group above the cut-off. Scores in the VI group were significantly higher compared to the control group (VI: mean=61.24, SE=3.77, Range=31-91; control: mean=43.5, SE=1.93, Range=32-60, t(21.732)=3.951, p<0.001). The same effect was observed when the high negativity cases were excluded (VI: mean=59.2, SE=3.72, Range=31-77; control: mean=43.5, SE=1.93, Range=32-60, t(19.016)=3.471, p=0.003). On the individual participant level, two children in the VI group reached both BRI and MI scores above the cut-off. Five children reached MI scores above the cut-off, but had BRI scores in the normal range (Descriptors for single item scores are presented in Table 10)

**Table 10: Comparison of single item scores on the BRIEF.** In line with analyses of composite scores, single items scores show significant differences between the VI and control group in domains of behavioural regulation and metacognition. Scores are higher in the VI group across all measures.

| | | VI | | | control | | | Group effect | |
|---|---|---|---|---|---|---|---|---|---|
| | **Item** | **mean** | **SE** | **Range** | **mean** | **SE** | **Range** | **F(1,30)** | **p** |
| Behavioural Regulation | Inhibit | 56.94 | 3.85 | 37-86 | 44.61 | 2.66 | 37-86 | 7.864 | 0.0088** |
| | Shift | 59.35 | 3.80 | 39-88 | 44.39 | 2.05 | 36-71 | 16.316 | <0.001*** |
| | Emotional Control | 59.24 | 4.40 | 36-98 | 43.67 | 2.80 | 34-85 | 9.393 | 0.005** |
| Metacognition | Initiate | 58.88 | 3.36 | 36-79 | 46.83 | 2.94 | 35-89 | 7.990 | 0.008** |
| | Working Memory | 61.53 | 3.16 | 39-80 | 46.78 | 2.95 | 36-89 | 14.515 | <0.001*** |
| | Plan/Organize | 59.18 | 3.27 | 36-77 | 48.39 | 2.90 | 33-88 | 6.630 | 0.015* |
| | Organization of Materials | 55.06 | 2.29 | 33-70 | 50.89 | 2.57 | 34-70 | 1.511 | 0.229 |
| | Monitor | 58.12 | 2.93 | 33-78 | 44.28 | 2.83 | 34-86 | 12.000 | 0.002** |

*** sign. at p<0.001 **sign at p<0.01 *sign. at p<0.05

Subsequent analyses focussed on the influence of vision level on BRIEF scores. There was a significant effect of vision group on GEC (one-way ANOVA: MVI: mean=58.12, SE=7.33, Range=32-96; S/PVI: mean=62.86, SE=5.43, Range=41-83, F(2,27)=4.444, p=0.022). Follow-up contrasts indicated a significant difference between the control group and the severe/profound group and the control group (t(10.58)=2.806,p=0.018, Bonferroni-corrected p=0.054) that dropped to trend-level with correction for multiple comparison. Other contrasts did not reach significance level.

For BRI scores, there was also a significant effect of vision group (one-way ANOVA: MVI: mean=58.88, SE=6.96, Range=31-92, S/PVI: mean=59.14, SE=6.51, Range=40-86, F(2,27)=6.248, p=0.006). Post-hoc contrasts revealed a significant difference between the severe/profound and the control group (t(7.827)=2.339, p=0.048, Bonferroni-corrected p=0.144) and a trend-level difference between the mild/moderate and control group (t(8.851)=-2.171, p=0.058, Bonferroni-corrected p=0.173) that did not survive correction for conservative correction for multiple comparison. There was no significant difference between the two VI groups.

There was also a significant difference between vision groups on MI (one-way ANOVA: MVI: mean=57.75, SE=6.85, Range=31-91; S/PVI: mean=62.86, SE=4.68, Range=42-77, F(2,27)=8.020, p=0.001). Follow-up contrasts indicated a significant difference between the S/PVI and the control group (t(3.82)=8.127, p=0.005, Bonferroni-corrected p=0.015) as well as a trend-level difference between the MVI and control group (t(8.134)=-2.01, p=0.079, Bonferroni-corrected p=0.237) that did not survive conservative correction for multiple comparisons. The difference between the VI groups was not statistically significant.

### 4.2.4.4. Discussion

The Behavioural Rating Inventory of Executive Function (BRIEF) was filled in by the parents to evaluate difficulties in domains of executive function in everyday behaviour (Isquith et al., 2013). The inconsistency scale scores indicate acceptable rater consistent for all questionnaires that were obtained. High negativity scale scores were found in two cases in the VI group. Usually, high scores are interpreted as a negative bias of the rater, but may also indicate severe executive dysfunction particularly in disorders with prominent inflexibility like pervasive developmental disorder (PDD) according to the questionnaire manual (Gioia et al., 2000a). Because both cases reached extremely low scores on behavioural tests of executive function domains as well, the latter explanation seems likely. Separate analyses confirm that the group-level results are not driven by the high negativity cases.

Group comparison on the Behavioural Regulation Index (BRI) and the Metacognitive Index (MI) showed significantly higher scores of the VI group compared to the typically-sighted control group. Almost half of the children with VI reached BRI and MI scores above the questionnaire cut-off warranting further clinical investigation for executive dysfunction. BRI and MI were empirically derived according to factor loading in principle component analysis based on the normative sample of the questionnaire (Gioia et al., 2002b), but are interpreted to reflect different aspects of executive function: The BRI consists of items in the Inhibit, Shift and Emotional Control scale and is thought to reflect more basic inhibitory and regulatory abilities. The MI consists of scales that reflect higher order aspects of executive function, including planning, problem solving, organisation etc., that depend on the more basic aspects of EF (Diamond, 2013).

Individual item analysis shows that high scores on the BRI are due to higher ratings on all scales in the VI group. High scores on the BRI are therefore likely to reflect general problems in basic executive function in the VI group. Similarly, the scales that feed into the MI were higher in the VI group, apart from non-significant or marginal differences in the Plan/Organize and Organisation of Materials scales. Elevated MI scores indicate difficulties with higher level EF in the VI group. However, higher scores may also be explained by differences in demand on cognitive control and working memory associated with cognitive processing strategies due to visual impairment rather than executive function deficits per se. Even though no item on the questionnaire directly relates to visual dependent behaviour, executive demands may be higher in the absence of vision leading to greater difficulties when executive capacities are reached. For instance Item 67 "Cannot find things in room or on school desk" is more demanding for a child with VI, who might have to rely much more on working memory to find items in the immediate environment.

The profile of elevated scores across BRI and MI domains is similar to published results reported for other groups of children with executive function deficits, i.e. combined-type ADHD, severe traumatic brain injury, children with low birth weight and children with higher functioning autism (Gioia et al., 2000a; Gioia, Isquith, Kenworthy, & Barton, 2002a).

## 4.3. Neurophysiological investigation of auditory selective attention

### 4.3.1. Introduction

Neurophysiological methods, particularly the event-related potentials methods, are well suited for investigations of executive control, because they provide additional insight into underlying mechanisms that are not necessarily reflected in the behavioural performance. For instance, difference in selective attention between groups of participants may be due to differences in the ability to selectively attend to a target stimulus or may be due to differences in the ability to suppress interfering stimuli (Sanders et al., 2006). Impaired performance on an executive function task may arise from deficits in either one or both of these processes.

Neurophysiological methods have been used to investigate the contribution of additional neural substrates to enhanced task performance in auditory working memory tasks and speech discrimination tasks in adults with congenital PVI (Bedny, Pascual-Leone, Dodell-Feder, Fedorenko, & Saxe, 2011; Roder et al., 1996; 2001). These studies identified faster latencies in early ERP components that related to better task performance (Roder et al., 2000). Further, differences in response topography indicated the recruitment of additional substrates in congenitally blind adults compared to typically-sighted controls (Roder et al., 2001). These differences in processing of auditory information may provide advantages or compensatory mechanisms in auditory attention paradigms.

#### 4.3.1.1. ERP markers of auditory selective attention

British cognitive psychologist Colin Cherry first described the so-called cocktail party problem in a paper in 1953: "how do we recognise what one person is saying when others are speaking at the same time" (Cherry, 1953). This question is particularly important for individuals with visual impairment as the additional visual focus that may be used to separate different sound sources is degraded or absent.

In a classic study by Steven Hillyard in 1973, different sequences of pure tones were presented to the participant's left and right ear and participants were instructed to attend to changes in only channel and perform a counting task (dichotic listening paradigm). Event-related potentials in response to the pure tones over a vertex electrode displayed modulation of the auditory N1 component with attention. N1 amplitude was found to be significantly larger in response to tones in the attended compared to the unattended channel (Hillyard, Hink, Schwent, & Picton, 1973). The auditory N1 is a negative deflection with a maximum over fronto-central channels, which peaks between 80 and 120ms after the onset of an auditory stimulus (Naatanen & Picton, 1987). Source localisation studies suggested N1 sources in Heschl's gyrus, the planum temporale (Herdman, 2011), and the primary auditory cortex (Virtanen, Ahveninen, Ilmoniemi, Naatanen, & Pekkonen, 1998).

The paradigm also introduced an important principle for research design, which is now known as the Hillyard principle. It states that attention effects are best investigated in response to stimuli with identical physical characteristics so that any difference in the neurophysiological response is directly attributable to attentional modulation.

### 4.3.1.2. Development of auditory selective attention

A limited number of studies have investigated the developmental changes in ERP responses in dichotic listening paradigms with pure tones similar to the classic Hillyard paradigm. A study by Bartgis compared 5 year olds, 7 year olds and 9 year olds. The authors reported increasing amplitude of the difference between attended and unattended tones (early Negative deflection (Nd)) with age (Bartgis, Lilly, & Thomas, 2003; Maatta, Paakkonen, Saavalainen, & Partanen, 2005). Further, some studies investigated the functional significance of ERP differences in dichotic listening paradigms in relation to executive function in developmental samples. Lackner and colleagues investigated the relationship between BRIEF scores and ERP responses in a dichotic listening paradigm (Lackner et al., 2013). A correlation between N1 latency to unattended tones and the Behavioural Regulation Index (BRI) was found with shorter latencies being associated with better scores. Further, larger amplitudes of an early positive deflection with a maximum over frontal channels in response to unattended tones were associated with poorer Metacognitive Index scores. Further, a study by Gomes et al. compared the early Nd between adults, typically developing children and children with an ADHD diagnosis (Gomes et al., 2012). They found that early Nd could reliably be detected in TD children and adults, but not in children with ADHD. In summary, these studies illustrate that ERP components in dichotic listening paradigms are sensitive markers of executive function differences.

The number of studies that investigated the development of auditory selective attention is limited. A probable reason is that the standard paradigms, like the Hillyard paradigm, are difficult to administer to children as they require listening to long sequences of pure tones. However, more child-friendly paradigms have been developed and tested in recent years. Coch and colleagues describe a novel selective attention paradigm based on continuous presentation of narratives through speakers in different spatial locations. Linguistic and non-linguistic probes were inserted in the continuous audio-stream to derive ERPs to identical stimuli following the Hillyard principle (Coch et al., 2005; Sanders & Zobel, 2012). While adults displayed the typical N1-P2 complex, children displayed a longer-lasting broad negativity that was modulated by attention (see Figure 25). The group also applied this paradigm to investigate difference in auditory selective attention in samples of children at risk for low executive function skills, including reading disability, selective language impairment and low socio-economic status. Most strikingly, Stevens et al. 2013 found a reduced attention effect in the broad positivity in children with low literacy skills that was no longer detected after 8 weeks of reading intervention training (Stevens et al., 2013).

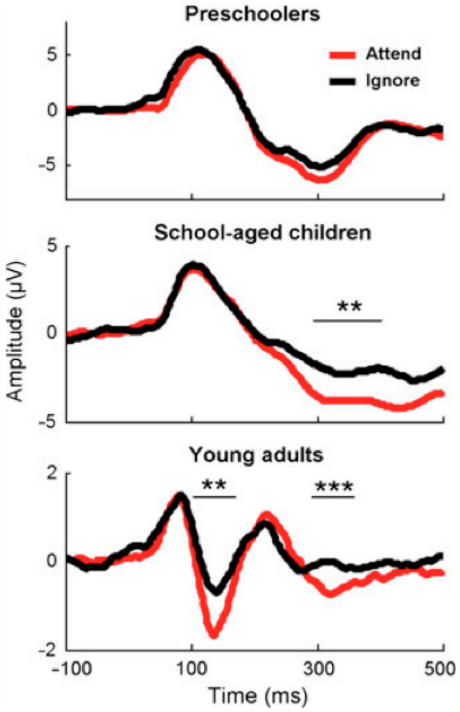


**Figure 25: Development of ERP response at Cz to probes presented to the attend or ignored speaker in 3-5 year olds, 7 to 13 year olds and adults (18-35 years) reported by Strait et al. 2014.** Adults display the typical P1-N1-P2 complex, whereas

children displayed broader deflections. The N1-P2 complex emerges during adolescence, school-age children show an early positivity followed by a prolonged negativity. Differences in ERPs to attended versus unattended responses are apparent at school-age. Response variability to the ignored condition decreases with age, but response variability in the attended condition remains the same. This suggests that the ability to suppress irrelevant information increases between mid-childhood and adult, but that the ability to selectively attend is established earlier (Strait et al., 2014).

#### 4.3.1.3. Hypotheses

The current investigation implemented a similar task to Coch et al. 2005 (Coch et al., 2005). Children were simultaneously presented with stories to their left and right ear and were instructed to pay attention to only one side. White noise bursts were inserted into the continuous audio streams to obtain ERPs to physically identical sounds that differed in attention. Following previous reports, we expected to find a broad positive deflection between 100 and 300ms with a maximum over frontal channels that is more positive for attended compared to unattended stimuli (Coch et al., 2005; Sanders & Zobel, 2012). Further, based on source-analysis of similar components in pure tone paradigms, we expected to find sources in left parietal and temporal sites (Herdman, 2011). Following behavioural reports about attention deficits in children with VI (Tadić, Pring, & Dale, 2009), we anticipated reduced differences in the frontal component between the attended and unattended condition in the VI group compared to the control group. The question of whether these differences are driven by differences in the ability to selectively attend or the ability to suppress irrelevant information is not distinguishable through the available behavioural evidence and was a central objective of this investigation.

### 4.3.2. Materials & Methods

#### 4.3.2.1. Participants

Thirty children participated in the EEG part of the study (VI: 16; control: 14). Twenty-five participants provided a sufficient number of useable trials in the selective attention task (VI:12, control: 13). The experiment was aborted in two cases, because the child felt uncomfortable or was too tired. Another dataset was lost due to technical problems. Two participants were excluded due to a high degree of movement artefact in the EEG.

### 4.3.2.2. Stimuli

The stimuli consisted of recordings of Aesop's fables from a free online resource (www.librivox.org). Stories were selected for length and child-friendly content. The stories were read by either a male or a female narrator. Each story was read by a unique narrator so that simultaneously presented stories could be distinguished by the timbre of the voice. The stories were adjusted for loudness level using a dynamic compressor (https://github.com/eddyp/chrisdynamiccompressor last visited 10/9/2014) under Audacity 2.0.2 (http://audacity.sourceforge.net). Long pauses in the narrative were manually removed. This resulted in 15 stories ranging from 32 s to 1 minute in duration.

The probes consisted of white noise bursts on the same loudness level as the recording that were inserted randomly in the audio stream of the attended and unattended story. The probes had a duration of 20ms with a random inter-trial interval between 1 and 2 s (minimum 1 s). Presentation to the attended or unattended ear was randomly assigned.

### 4.3.2.3. Testing Procedure

In addition to the general EEG procedures (see General Methods section), children received instructions on task completion before the recordings. The response pad consisted of two buttons that were assigned for a "Yes" or "No" response. Before the recordings, the experimenter asked the child which button corresponded to a "Yes" or "No" and corrected the child if necessary. Further, the experimenter asked the child to show their right hand. None of the children in the study failed this test.

In addition to the personal instructions, each participant listened to pre-recorded instructions that explained the experimental procedure at the beginning of the task.

At the beginning of each story, the child had to press the "Yes" button to start the trial in answer to the question "Are you ready?". This was followed by the instruction on which side to attend, i.e. "Listen left" or "Listen right". Subsequently, the attended and unattended stories were presented simultaneously with sound probes that were randomly presented in either channel. Due to the difference in length, the longer story continued after the shorter story finished, but sound probes were only presented while both stories were playing. After both stories finished, three Yes/No questions about the content of each story were presented. Children had to answer these questions by pressing the corresponding button on the response pad.

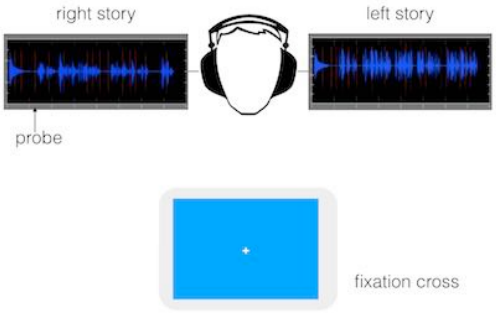


**Figure 26: Illustration of the selective attention ERP paradigm.** Two stories were simultaneously presented to the left and right ear. Probes were randomly inserted into the audio stream that served as onset markers for the event-related response. A fixation cross was presented to help sighted participants to minimise their eye movements.

### 4.3.2.4. EEG processing

Please refer to the General Methodology chapter and the methods paper (Bathelt, O'Reilly, de Haan 2014) for details about EEG processing. Briefly, the raw EEG was exported to Matlab format, high-passed at 0.1Hz and low-pass filtered at 30Hz. Subsequently, the data was segmented according to event-markers set during the recording encompassing a 100ms pre-stimulus baseline and 500ms post-stimulus activity. Epochs that contained activity with a peak-to-peak amplitude over 100$\mu$V in more than 20% of channels were rejected. Also, channels that had peak-to-peak amplitudes above this threshold in more than 30% of epochs were removed and interpolated from surrounding channels. Datasets with more than 15 rejected channels were excluded from the analysis (n=2). The average reference was calculated after threshold-based rejection and baseline correction was applied. Trials that contained movement and eye artefact were rejected through visual inspection.

There was no difference in the number of epochs between conditions (All following values in $\mu$V -Attended: mean= 41.68, SE=1.43; Unattended: mean=42.84, SE=1.26; t(1)=-0.6089, p=0.54). There was a difference in the number of epochs in the attended and in the unattended condition between the participant groups (Attended: VI: mean=32.75; SE=1.81; control: mean=49.92, SE=2.68; t(1)=-5.307,p<0.001; Unattended: VI: mean=38.25, SE=2.35; control: mean=47.08, SE=2.06, t(1)=-2.827, p=0.005). The number of epochs was therefore included as a nuisance regreesor for subsequent analyses and supplementary analyses were carried out in which the number of epochs was randomly down-sampled to match the mean number of epochs in the control group (see supplementary analysis section).

### 4.3.2.5. Analysis of event-related potentials

Following previous reports, channel time series within 4 regions were averaged to create a left frontal, right frontal, mid frontal and central virtual channel (see Figure 27). Time window and channels regions of interest were based on published reports using a similar paradigm (Coch et al., 2005; Sanders & Zobel, 2012; Strait et al., 2014). The mean amplitude between 100 and 300ms after stimulus onset was extracted for the attended and unattended condition for each region. The mean amplitude was compared in a repeated-measures ANOVA model containing participant group, condition, region and number of epochs and interactions between participant group, condition and region as covariates (Model: Participant Group + Region + Condition + Number of Epochs + Region x  Condition + Region x Condition x Participant Group).

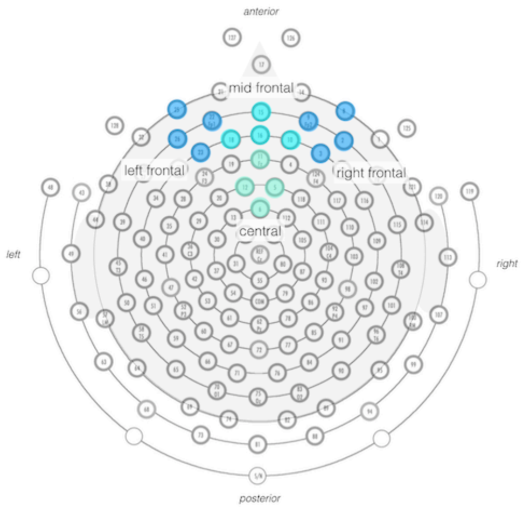


**Figure 27: Channel selection for calculation of virtual channels for left, right, mid frontal and central regions of interests.** The channel selection was based on a study that used a similar paradigm with the same EEG system as used in this study (Sanders & Zobel, 2012).

### 4.3.3. Results

Task performance was low, but above chance level (observed mean ratio of correct responses: 0.6049). There was a trend-level difference in the number of correct answers between the VI and control group (VI: mean=0.59, SE=0.02; control: mean=0.62, SE=0.01; t(1)=-1.834, p=0.07).

#### 4.3.3.1. Channel-level analysis

Grand-average ERPs showed a broad positive deflection between 100 and 300ms with a maximum over mid-frontal channels. Statistical comparison revealed a significant participant group by region by condition interaction (rmANOVA: F(1,126)=20.774, p<0.001). Post-hoc contrasts showed a significant difference in the right frontal channel region for the unattended condition between participant groups with higher mean amplitudes in the VI group (VI: mean=0.98, SE=0.27; control: mean=0.20, SE=0.13; t(1)=2.6, Bonferroni corrected-p=0.03). Simple contrast comparisons for the attended condition and for other channel regions did not reach significance level.

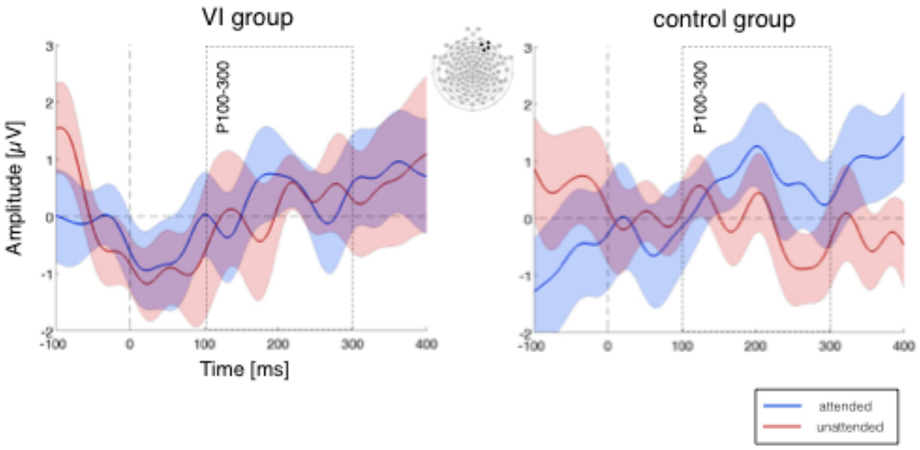


**Figure 28: Grand-average ERP in right frontal channels for the VI and control group for the attended (blue) and unattended (red) condition.** The solid line indicated the mean response. The shaded area shows the standard error of the mean. The dotted box indicated the time window of interest.

**Table 11: Mean amplitude between 100 and 300ms in left, right, mid-frontal and central channels in the attended and unattended condition for the VI and control**

**group.** All values are in *μ*V. Asterisks mark significant differences in post-hoc single contrast comparisons.

| | condition | left frontal | | mid frontal | | right frontal | | central | |
|---|---|---|---|---|---|---|---|---|---|
| | | mean | SE | mean | SE | mean | SE | mean | SE |
| VI | attended | -0.01 | 0.95 | 0.02 | 0.80 | -0.80 | 0.52 | -0.59 | 1.07 |
| | unattended | 1.59 | 0.66 | 0.93 | 0.54 | 0.81 | 0.62 | 0.58 | 0.34 |
| control | attended | 0.52 | 0.47 | 0.93 | 0.47 | 0.73 | 0.40 | 0.87 | 0.33 |
| | unattended | 0.06 | 0.27 | 0.36 | 0.29 | -0.05 | 0.23 | 0.42 | 0.21 |

#### 4.3.3.2. Relationship between cognitive measures and ERP

The relationship between cognitive measures of executive function skills and ERP amplitudes in the attended and unattended condition was explored separately for the VI and control group.

There was a significant negative linear correlation between ERP mean amplitude of the broad positive deflection over right frontal channels in the unattended condition and performance on the divided auditory attention task (TEA-Ch Dual Task) in the VI group (r(23)=-0.51, p=0.027 - excluding outlier with extremely low performance). The correlation did not reach significance level in the control group.

There were negative correlations between ERP mean amplitude over right frontal channels and the BRIEF Behavioural Regulation Index in the attended and unattended condition in the VI group (attended: r(23)=-0.22, p=0.014; unattended: r(23)=-0.24, p=0.005). Pearson correlations did not reach significance in the control group). No linear relationships between BRIEF Metacognitive Index (MI) and ERP amplitude over right frontal channels were found in either participant group.

#### 4.3.3.3. Source-level analysis

Source activation was compared between the attended and unattended condition collapsing across participant groups. A paired t-test comparison of cortical activations across all vertices corrected for multiple comparison using false-discovery rate showed significantly higher source current density in the left supramarginal gyrus. Source activity within the left and right supramarginal gyrus was extracted and averaged over all vertices within the ROI to obtain source-level activations. Due to the broad activity observed in the source level waveform, the time window of interest was extended (see Figure 29). Statistical analysis of mean current density within the ROIs between 100ms and 500ms after stimulus onset indicated higher activation in the VI group compared to the control group (rmANOVA: VI: mean=-2.08, SE=1.6, Range=-44.7 -19.7; control: mean=6.21, SE=3.24, Range=-46.2-93.5 - all values in pA, F(1,22)=5.617, p=0.027). There was also a significant effect of task performance (rmANOVA: F(1,22)=4.598, p=0.048) with higher activation being associated with lower task performance.

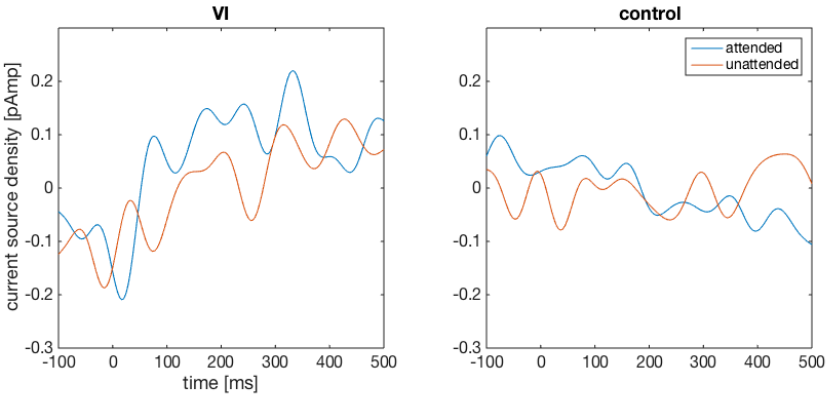


**Figure 29: Source time series of responses to attended and unattended stimuli in the right supramarginal gyrus in the VI (left) and control group (right).** Current source density values are in picoAmpere. Statistical analysis indicated higher activity in the right supra marginal gyrus in the VI group.

### 4.3.3.4. Supplementary Analyses

Supplementary analyses were carried out to investigate if the observed ERP differences between participant groups were driven by differences in task performance. In order to investigate the influence of task performance on ERP difference, the amplitude of the positive deflection in response to attended and unattended stimuli was separately compared between the four highest and the four lowest performing participants regardless of participant group (higher: 3 control, lowest: 2 control). The repeated-measures ANOVA model contained channel region, condition, participant group, and the interaction between the factors as covariates. In the high performance subsample, there was a trend-level effect of condition (Attended: mean=1.29, SE=0.38; Unattended: mean=0.73, SE=0.22, F(1,18)=1.925, p=0.068). There was no condition effect in the lowest performing subgroup (Attended: mean=0.44, SE=0.3; Unattended: mean=0.05, SE=0.29).

### 4.3.4. Discussion

The participants in the study completed a selective attention ERP task similar to the paradigm described by Coch et al. (Coch et al., 2005). Participants were simultaneously presented with recordings of stories in their left and right ear and were instructed to selectively attend to only one story. At the end of each trial, participants had to answer questions about the content of the stories. At the behavioural level, the response accuracy was low with many participants performing at chance level. Even the highest performing participant did not exceed 80% correct answers. The low performance is in line with the perceived difficulty of the task according to participants' reports. Previous studies with a similar paradigm maintained the same two audio streams for the entire recording and ask only a very limited number of comprehension questions at the end of the recording (Coch et al., 2005; Sanders et al., 2006; Sanders & Zobel, 2012; Stevens, Sanders, & Neville, 2006; Strait et al., 2014) so that it is not possible to compare task performance with these studies. The difficulty in the current paradigm is likely to be higher, because visual attention cues were removed in order to avoid biasing the setup towards more visually able participants. The original paradigm provided arrows on screen that indicated the location of the speaker that the participant had to attend to, which provides a continuous cue of the task instruction. However, the participant group in the current study was considerably older so that task performance was not predicted to reach floor levels. The low performance observed in this study highlights the importance of integrating a monitoring task as continuing attention and adherence to task instructions can otherwise not be assumed. These behavioural differences may bias results of ERP findings and lead to incorrect conclusions.

At the neurophysiological level, similar response topography to previous reports was observed. The morphology of the responses generally reflected the broad positive deflection over frontal channels between 100 and 300ms after stimulus onset that would be expected for this age group in this paradigm (Coch et al., 2005; Mueller, Brehmer, Oertzen, Li, & Lindenberger, 2008). However, the waveforms reported here deviated from published grand-average waveforms in their baseline activity and in variability. The baseline in the observed waveforms was more variable and further from 0 than typically observed in auditory ERPs. The fact that ERPs were calculated in response to probe stimuli that were inserted into an continuous audio stream rather than in response to a tone against a silent baseline is likely to contribute to the observed baseline variation. Further, fewer trials per participant were included in comparison to the only available high density, low-impedance EEG study that used the same paradigm (Sanders & Zobel, 2012).

At channel-level, there was a significant difference between the groups with higher response amplitude in the unattended condition over right frontal channels in the VI group. The suppression of broad positivity mean amplitude in the unattended compared to the attended condition observed in the control group is in line with previous reports in typically developing children. A lack of condition effects as observed in the VI group has been reported for groups with executive function deficits, e.g. executive deficits in specific language impairment (SLI) and low socio-economic status (SES) groups (Stevens, Fanning, Coch, Sanders, & Neville, 2008; Stevens, Lauinger, & Neville, 2009). Based on the observation that there was no effect of participant groups for mean amplitudes in the attended condition, selective attention appears to be similar in both groups. The finding that mean amplitudes are similar in the attended and unattended condition in the VI group suggests that suppression of task-irrelevant auditory information is less successful than in the control group.

However, several factors may be contributing to this effect. First, there were significant differences in the number of epochs per condition between the groups, because a larger number of epochs had to be rejected in the VI group due to non-EEG artefact contamination (head movement, eye movement, blinks). A lower number of epochs leads to a lower signal to noise ratio, which decreases the chance to detect small differences between the conditions. However, when the number of epochs was included as a nuisance regressor in the statistical analysis, the result remained significant.

Performance differences are another potential confounding factor. There was a trend-level difference in task performance between the control and VI group. Supplementary analysis that compared mean amplitudes between the condition in the highest and lowest performing participants suggested that condition effects are associated with task performance. Unfortunately, it is not possible to match VI and control participants one-to-one on performance due to limited variability in performance scores in the current sample. Therefore, the present analysis cannot disentangle if the observed mean amplitude differences between the VI and control group reflect difference due to VI per se or reflect associated differences in task performance.

On the source level, differences between conditions were observed within the supramarginal gyrus. Previous MEG and source localisation studies in Hillyard-type attention paradigms reported cortical sources in Heschl's gyrus, the planum temporale, primary auditory cortex (Herdman, 2011). The locus of statistical difference between the groups in the left supramarginal gyrus is in close spatial proximity to the reported areas and might reflect source mis-localisation. Alternatively, differences between attention conditions may be more apparent in language-related areas, because a language task was used in the current paradigm rather than pure tone stimuli. Statistical comparison of current source density between stimulus indicated significantly higher activation in the VI group. Further, supramarginal gyrus activity was negatively related to task performance. A possible interpretation is that the task was more taxing for lower performing individuals so that more cortical processing resources had to be recruited to perform the task.

#### 4.3.4.1. Relationship between behavioural and ERP measures

The relationship between the ERP measures and the cognitive assessments suggested that the ERP components were sensitive to differences in executive skills. A significant negative correlation between ERP mean amplitude in the unattended condition and TEA-Ch Dual Task condition was found in the VI group, but not in the control group. It is likely that the auditory selective attention ERP task and the TEA-Ch Dual Task share similar cognitive demands, i.e. the ability to sustain attention and simultaneously suppress irrelevant information. In addition, group-level comparison of the scores in the sustained and divided attention task suggested a dissociation with similar scores in both groups in the sustained condition, but a trend-level difference in the divided attention condition with lower scores in the VI group. Similarly, analysis of ERP amplitudes found significant difference in ERP amplitudes between the attended and unattended condition in the control group, but not in the VI group indicating possible deficits in the suppression of task-irrelevant information. Together, both measures provide evidence for greater difficulty with more demanding auditory attention tasks that require selective attention and suppression of interfering stimuli in the VI group.

Further, the relationship between the composite indices of the BRIEF (Metacognitive Index (MI), Behavioural Regulation Index (BRI)) and ERP mean amplitude in the attended and unattended condition were investigated. According to factor analysis of BRIEF items, BRI reflects more basic aspects of executive function that are related to behavioural inhibition, whereas MI reflects higher aspects of executive control (Gioia et al., 2002b). There were linear negative relationships between BRI and mean ERP amplitude in the VI group with smaller amplitudes in the attended and unattended condition being related to higher BRI scores. This suggests that smaller amplitudes are related to a higher degree of behavioural regulation difficulties.

Lackner and colleagues reported that smaller ERP amplitudes in the unattended condition of selective auditory attention task predicted worse MI scores in typically developing children (Lackner et al., 2013). No significant relationships between MI scores and ERP amplitude could be detected in the current sample.

## 4.4. Chapter Discussion

The parieto-prefrontal pathways contains connections that are implicated in the top-down control of eye movements (Kravitz et al., 2011) and spatial working memory (Georgieva et al., 2009). Studies in typically-sighted infants implicated the control of eye movement as an early precursor of executive abilities (Johnson & de Haan, 2010). Based on predictions of the extended dorsal stream model, non-visual executive skills were investigated in children with VI to establish if VI is associated with deficit in general executive function.

In line with verbal abilities in the typical range, tests of phonological and categorical verbal fluency as well as verbal mental flexibility did not indicate differences between children with VI and typically-sighted controls of the same age. Further, comparisons between children with SVI/PVI and typically-sighted children did also not show significant differences.

Assessments of sustained and divided auditory attention also did not indicate significant differences between the groups. Nonetheless, high variability in the divided attention condition suggested deficits in this function in at least some of the children with VI. However, variability in divided attention scores was not explained by vision level or verbal ability. Therefore, it is not clear from the current investigations what factors might lead to non-optimal performance on the divided attention task.

Parent ratings indicated significant difficulties in everyday executive skills in both behavioural regulation and metacognitive control domains with elevated scores across all scales in the VI group. Further, a large proportion of children with VI reached scores above the cut-off for executive dysfunction. These were also found to be significantly influenced by vision level with a higher degree of difficulty in children with lower visual function.

Further, the ability to selectively attend to auditory information in the presence of interfering stimuli was investigated in an event-related potentials paradigm. The results indicated less efficient suppression of responses to interfering stimuli in the VI group compared to the typically-sighted controls.

In conclusion, the current investigations suggested mostly intact executive functions in standardised neuropsychological assessments of isolated constructs (verbal working memory, auditory attention, verbal fluency), but significantly worse performance on parent ratings of everyday executive function behaviour and ERP measures of auditory selective attention. It has been argued that neuropsychological tests of executive function place little demand on executive skills by providing clear instructions, training items, and a problem solving scaffold. These aids are rarely available in everyday situations (Isquith et al., 2013). Discrepancies in scores might indicate that underlying executive skills per se are similar in both the VI and the control group, but that everyday behavioural demands on executive skills are higher for children with VI. This view is supported by finding that greater severity  of visual impairment is associated with higher ratings of executive function difficulties. Alternatively, discrepancies could also indicate a true dissociation of vulnerabilities with age-appropriate abilities in verbal fluency and sustained attention, but greater difficulty in everyday executive skills and more demanding selective attention. Furthermore, the current findings could be explained by a combination of both models, i.e. higher vulnerability in some executive functions in addition to higher demands. A possible way to differentiate these explanations would be to assess a larger number of children with VI with a more comprehensive battery of tasks that includes some more ecologically-valid tasks as well as traditional assessment of single executive function constructs.

# Chapter 5: Parieto-motor cortex pathway: social cognition & communication

## 5.1. Chapter Introduction

The parietal-premotor pathway of the extended dorsal stream is implicated in vision for the guidance of action in personal space and also for the observation of action (Rizzolatti, Fogassi, & Gallese, 2001). Target areas within the inferior parietal lobe contain so-called mirror neurons that respond to the observation and executive of a movement. This system is thought to play an important role in social cognition (Corradini & Antonietti, 2013; Engel, Maye, Kurthen, & Konig, 2013; Gallese, 2013). Social cognition refers to the ability of an individual to detect communicative signals from conspecifics, decode them and ultimately adjust behavioural responses or physiological state appropriately (Adolphs, 2001; Beauchamp & Anderson, 2010; Cacioppo, 2002). Likewise, social communication refers to the active exchange of information between conspecifics. In humans, different forms of communication including verbal communication, non-verbal auditory cues, facial expression, gesture, posture or touch may be used (Frith & Frith, 2010). Disruption in social function can lead to significant reduction in quality of life through social isolation and reduced self-esteem (Adolphs, 2001). For children in health care, the ability to regain social function and being able to interact with peers is the most valued treatment goal (Anderson, 2012).

Middle childhood is a particularly important period for social development as children are spending more time away from parents in formal educational settings or structured leisure groups (Thompson et al., 2013). Relationships with peers become more important and gain in complexity (Ladd, 1999). These relationships also pose higher demands on cognitive and social competence of children requiring the child to understand the needs of others and negotiate his or her own needs and goals with other children. Development in cognitive areas, including executive function, as well as internal and external factors are likely to contribute to the development of these social skills (Beauchamp & Anderson, 2010).

Previous studies demonstrated that social functioning is particularly challenging for children with VI. A classic observational study by Brown and colleagues found that the social interaction and play behaviour of school-age children with profound visual impairment deviated significantly from peers (Hobson & Bishop, 2003). Children with PVI spent less time in the vicinity of peers, showed less pleasure in peer interactions, displayed less varied play behaviour, and less equivocal or reciprocal play. These behaviours also extended to language with less language directed to peers, more non-reciprocal and less reciprocal speech (please see the General Introduction for a more detailed discussion of social development in VI). Previous studies highlighted areas of increased vulnerability in children with visual impairment including delays in the development of mentalizing abilities and differences in social communication.

Based on the prediction of the dorsal stream model that suggested difficulties in social cognition due to differences in parieto-motor cortex connections, the current study investigated socio-cognitive functions using neuropsychological tests in school-age children with VI.

## 5.2. Neuropsychological assessment of social cognition & social communication

### 5.2.1. Prevalence of ASD characteristics

#### 5.2.1.1. Introduction

Previous studies reported a high prevalence of behavioural characteristic associated with autism spectrum disorder (ASD) in children with VI (Absoud et al., 2011; Brown et al., 1997; Mukkades et al., 2007; Parr et al., 2010; Rogers & Newhart-larson, 1989; Williams et al., 2013). The current study aimed to assess the prevalence of ASD traits in the current sample in order to relate findings to previous reports. It was expected that more children in the VI group than children in the control group would reach scores in the ASD range on a standard clinical screening questionnaire.

### 5.2.1.2. Materials & Methods

The Social Communication Questionnaire (SCQ) is double-sided 40 item questionnaire filled in by a parent or other primary caregiver, which is suitable for the rating of children from 4 years of age. All items require yes/no responses. The questions focussed on behaviours that are rare in typically developing children without autistic features (Rutter & Bailey, 2007). There are two versions of the SCQ for either the 3 month period before the assessment (Current form) or a Lifetime form that assesses behaviour observed over the child's life. Half of the Lifetime version focusses on behaviours observed between 4 and 5 years. Therefore, the Current Form was used for this investigation in order to achieve greater age-specificity.

The total number of unusual behaviours is scored from the questionnaire and compared to a cut-off score based on validation studies. The cut-off indicates a high degree of behaviours that are more typically observed in individuals that received an ASD diagnosis. Possible scores for verbal children range from 0 to 39. In addition to the total score, abnormalities in reciprocal social interaction, communication, and restricted, repetitive or stereotyped behaviours were obtained by evaluating responses in these domains according to the questionnaire manual. However, it is important to note that sub-domain scores have not been extensively validated to date (Rutter & Bailey, 2007) and are therefore less reliable than the primary Total Score measure.

### 5.2.1.3. Results

17 parents in the control group and 13 parents in the VI group provided valid responses on the SCQ. The results of two questionnaires were excluded, because parents skipped several items. Two participants in the VI group reached scores above the questionnaire's cut-off (cut-off: 15, observed: 19). One participant reached scores above the cut-off for clinical risk warranting further investigation for autism disorder (cut-off: 22, observed: 23). In general, higher mean scores were observed in the VI group compared to the control group (VI: mean=9.15, Range:2-23; control: mean=1.28,

Range=0-5). All three participants that reached total scores above the cut-off had severe visual impairment.

Sub-scale scores for reciprocal social interaction, communication and, restricted, repetitive and stereotyped patterns were also derived from the ratings according to the questionnaire manual. VI children scored between the control and published results for children with ASD. See Table 12 for results.

**Table 12: The table presents descriptives statistics of the SCQ scores observed in the current sample.** As a reference, data from a study about children with ASD is included.

| | VI | | | control | | | ASD* | |
|---|---|---|---|---|---|---|---|---|
| **Domain** | **mean** | **SD** | **Range** | **mean** | **SD** | **Range** | **mean** | **SD** |
| Total | 9.15 | 7.3 | 2-23 | 1.28 | 1.41 | 0-5 | 22.32 | 6.47 |
| Reciprocal Social Interaction | 2 | 2.37 | 0-7 | 0.44 | 0.78 | 0-3 | 7.98 | 3.48 |
| Communication | 3.92 | 2.35 | 0-8 | 0.78 | 0.88 | 0-3 | 6.87 | 2.53 |
| Restricted, Repetitive, and Stereotyped Patterns of Behaviour | 3 | 3.02 | 0-8 | 0.33 | 1.41 | 0-6 | 5.88 | 1.86 |

data reproduced from Sasson et al. 2013 *J. o. Neurodevelopmental Disorders*

### 5.2.1.4. Discussion

The Social Communication Questionnaire was administered to assess the presence of traits associated with autism spectrum disorder in children with visual impairment. Previous reports in the literature using coded observations, autism assessment protocols or clinical assessments had indicated a high prevalence of autism-like traits in children with severe to profound VI in a similar age range to the present study (Brown et al., 1997; Mukkades et al., 2007; Rogers & Newhart-larson, 1989; Williams et al., 2013). In the current sample, 3 out of 17 participants scored above the suggested cut-off for autistic spectrum disorder of the questionnaire. At this cut-off, the sensitivity and specificity of distinguishing an ASD from other diagnoses are .96 and .80 respectively (Rutter, Bailey, & Lord, 2003). The mean scores reported for children with ASD in the normative sample of the questionnaire were above 20 points on the total score. A mean score of around ten points was observed in the current sample of children with VI, which is elevated but below the range for ASD. However, the mean score in the control group was lower at 5 points, which is in line with reports for typically developing children in this age range (Mulligan, Richardson, Anney, & Gill, 2009). Similarly elevated scores were found in investigations of autistic traits in neurodevelopmental disorders like ADHD (Cooper, Martin, Langley, Hamshere, & Thapar, 2014), preterm birth (Johnson et al., 2011), and children with pragmatic language impairment (Reisinger, Cornish, & Fombonne, 2011). The higher scores on the group level in comparison to control scores might therefore reflect behavioural atypicalities that are not specific to ASD.

Compared to other studies that investigated the prevalence of autistic traits in children with visual impairment, the observed proportion of children meeting criteria for ASD was lower, e.g. around one third in children with septo-optic dysplasia or optic nerve hypoplasia (Jutley-Neilson, Harris, & Kirk, 2013; Parr et al., 2010). Both referenced studies noted significantly higher likelihood of meeting ASD cut-off criteria in children with lower vision level and lower verbal ability. Further, Brown et al. suggested that children with visual impairment may be categorised into groups of children with lower verbal abilities that show many autistic traits and higher children with higher verbal abilities that do not typically display ASD-like behavioural traits (Brown et al., 1997). The current sample was selected for good verbal abilities to avoid confounding effects of additional learning disabilities. Further, half of the sample consists of children that have mild to moderate visual impairment at the time of assessment. Both these factors are likely to contribute to the lower incidence of autistic traits in the sample compared to other studies involving children with lower vision level and lower verbal IQ. The lower incidence may suggest that both factors play a protective role for children with VI. Nonetheless, 3 out of the 17 children assessed on the SCQ met criteria for ASD/AS. Further, these children were neither the children with the extremely low vision level nor the lowest verbal ability in the normal range suggesting that factors other than the current level of visual impairment may play a role in the development of autistic traits in children with VI.

## 5.2.2. Pragmatic Language

### 5.2.2.1. Introduction

Pragmatic language is the ability to use language appropriately in a social context (Bishop & Norbury, 2002). Children with deficits in pragmatic language display difficulties in understanding and producing conversation, giving responses that are socially appropriate, and have more problems with turn-taking in conversations, often talk excessively, and have less coherent and organised responses (Bishop & Norbury, 2002; Green, Johnson, & Bretherton, 2014). In children with selective language impairment, deficits in pragmatic aspects of language are associated with poor peer relationships and increased behavioural problems (Ketelaars, Cuperus, Jansonius, & Verhoeven, 2009; Mok, Pickles, Durkin, & Conti-Ramsden, 2014). Pragmatic language deficits have been described in a number of neurodevelopmental disorders including ADHD (Green et al., 2014), reactive attachment disorder (Sadiq et al., 2012), Williams syndrome (Laws & Bishop, 2004), conduct disorder (Oliver, Barker, Mandy, Skuse, & Maughan, 2011) and other disorders (Dennis, Guger, Roncadin, Barnes, & Schachar, 2001; Holck, Sandberg, & Nettelbladt, 2010). Further, impairments in pragmatic and social language have also been identified in parents of children with ASD that meet criteria for the broader autism phenotype (Bishop, Maybery, Wong, Maley, & Hallmayer, 2006; Taylor et al., 2013).

Social and pragmatic language is particularly salient for children with VI that have limited access to other channels of social communication like facial expression and gesture. Social and pragmatic language may provide an important non-visual gateway for social development (Tadić, 2012). Moreover, a previous investigation about structural and pragmatic language abilities in school-age children with severe to profound VI reported that more than two thirds of the children were rated in a similar range to typically-sighted children with either ASD or Asperger syndrome (Tadić et al., 2010). Therefore, the current study aimed to replicate these findings in a new sample of school-age children with VI and relate pragmatic and social communication abilities to measures of social ability. In addition, the current study intended to assess if deficits in social and pragmatic language are also present in children with mild to moderate VI.

### 5.2.2.2. Materials & Methods

The Children's Communication Checklist 2nd edition (CCC-2) was used to assess structural and pragmatic language abilities (Bishop, 1998). The CCC-2 is a three-sided questionnaire with 70 questions relating to language abilities in seven domains (speech, syntax, semantics, coherence, inappropriate imitation, stereotyped language, use of context, nonverbal communication, social relations, interests). The respondent is asked to rate the frequency at which behaviours occur on a scale from 0 ("less than once a week [never]") to 3 ("several times [more than twice] a day [or always]"). The CCC-2 is suitable for verbal children between 4 and 16 years. The item scales (except interests and social relations) are used to generate a General Communication Composite (GCC) to indicate potential global communication difficulties. In addition, the Social Interaction Deviance Composite (SIDC) is derived from the social interests and social relations scales that highlights discrepancies between structural and pragmatic abilities that are often observed in high-functioning ASD (Bishop & Norbury, 2002).

Correlations with outcome measures of social function were investigated using bivariate correlations. The PedsQL Social scale and the SDQ Peer Relations and Prosocial Behaviour scale were used as indicators of social function. The control group was not included in the correlation analyses with SDQ measures, because limited variation on SDQ scores suggested ceiling effects in the control group.

### 5.2.2.3. Results

Seventeen parents in the VI group and eighteen parents in the control group completed the CCC-2. Two questionnaires in the control group had to be excluded. In one case more than 3 responses were missing and in the other case, responses indicated that the parent had not filled in the questionnaire appropriately (Included sample: VI: 8 male, 8.49-13.32y, vIQ: 75-148; control: 10 male, 8.56-12.92y, vIQ: 83-144).

Six children in the VI group reached single scale scores below the 5%ile on more than two scales indicating clinically significant communication deficits according to the questionnaire manual (Bishop, 2003). Low scores were observed in speech (n=1), syntax (n=1), semantics (n=3), coherence (n=1), inappropriate imitation (n=6), stereotyped speech (n=3), use of context (n=6), non-verbal communication (n=4), social communication (n=5) and age-appropriate interests (n=4). Two additional cases in the VI group had three scale scores below the 10%th percentile warranting further clinical investigation for communication deficits.

At the composite level, 4 children in the VI group reached Global Communication Composites below the 5%ile compared to the questionnaire norms. Two children in the VI group fell between the 5th and 10th percentile. Four children in the VI group and one child in the control group reached Social Deviance Composite Scores (SIDC) in the clinically significant range (Range: -16 to -27). Five of the children in the VI group with low SIDC reached GCC scores below the 10th percentile (<55). Two additional cases had a GCC below the 10%ile with a SIDC near 0. One child in the control group reached a negative SIDC, but had a GCC above 55 (see Fig 30 for a graphical representation of the results).

Verbal comprehension was lower in the children that reached GCC scores below 45 (vIQ: 65-93). Therefore, the relationship between GCC scores and vIQ was further investigated. Separate fitting of linear regression lines indicated a different relationship between vIQ and GCC in the VI and control group: whereas the slope indicated no relationship in the control group, there was a positive association between vIQ and GCC in the vIQ group. The groups were subsequently analysed separately to meet the homogeneity of regression slopes assumption. However, an analysis of correlation between vIQ and GCC in the VI group did not indicate a significant association between the variables (Pearson correlation: r=0.39, n=18, p=0.11).

In comparison to the results of the SCQ analysis, two individuals reached cut-off scores for ASD (n=2, score=19) on the SCQ and also had data available on the CCC-2. Both participants fell in the ASD range on the CCC-2 with low GGC and negative SIDC scores (GCC= 46,46; SIDC=-16,-27).

Bivariate correlation analysis indicated strong agreement between SIDC and the PedsQL Social Scale in the VI (n=13, r(11)=0.58, p=0.0383) and control group (n=17, r(15)=0.57, p=0.017). There was also a trend-level positive association between GCC scores and PedsQL Social scores in the VI group (r(11)=0.54, p=0.0566). Further, a strong negative correlation between GCC and scores on the SDQ Peer Relationships scale was found in the VI group (r(11)=-0.75, p=0.003). There was also a strong negative correlation between SIDC and SDQ Peer Relationships in the VI group (r(11)=-0.69, p=0.0093). Correlations between SDQ Prosocial Behaviour and GCC or SIDC did not reach significance level (GCC: r(11)=0.5, p=0.0812, SIDC: r(11)=0.49, p=0.0859).

Subsequent analysis by vision groups indicated a significant difference between vision groups on GCC with lower scores in the S/PVI group (one-way ANOVA: MVI: mean=75.86, SE=8.62, Range=41-104; S/PVI: mean=55, SE=6.04, Range=32-74, F(2,28)=9.202, p<0.001). Follow-up contrasts indicated a significant difference between the S/PVI and the control group (t(9.982)=4.589, p=0.001, Bonferroni-corrected p=0.048) and a trend-level difference between the mild/moderate and S/PVI group (t(10.743)=1.982, p=0.074, Bonferroni-corrected p=0.296) that did not survive conservative correction for multiple comparisons. There was no significant difference between the mild/moderate group and the control group. For the SIDC scores, there was also a significant difference between vision groups (rmANOVA: MVI: mean=-3, SE=4.17, Range= -26-8; S/PVI: mean=-13, SE=3.99, Range=-27-5, F(2,28)=6.879, p=0.004). Post-hoc contrasts indicated a significant difference between the S/PVI and control group (t(8.548)=3.354, p=0.009, Bonferroni-corrected p=0.036). Other contrasts did not reach significance criteria.

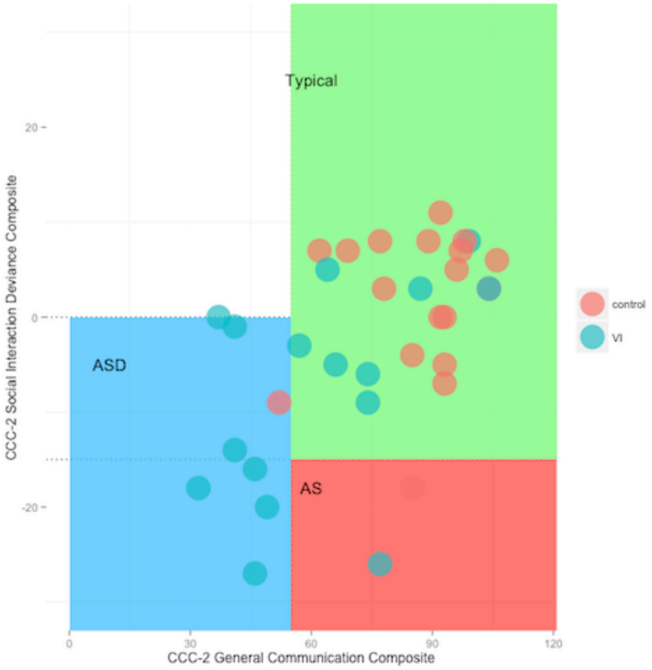


**Figure 30: Distribution of General Communication Composite (GCC) and the Social Interaction Deviance Composite (SIDC) of the Children's Communication Checklist 2 (CCC-2)** with reference to cut-off that warrant further clinical investigation of pragmatic language deficits frequently observed in children with either Asperger Syndrome (AS) or autism spectrum disorder (ASD). Cut-offs are defined as: ASD: GCC<55, SIDC<0; AS: GGC>55, SIDC<-15 (Bishop & Norbury, 2002).

**Figure 31: Single scale score results of the Children's Communication Checklist 2. VI group scores are shown in blue and control scores in red.** The colour intensity indicates the number of children that reached the same score. The lines indicate the approximate scaled score equivalent of the 15th, 50th, and 95th percentile according to the questionnaire manual.

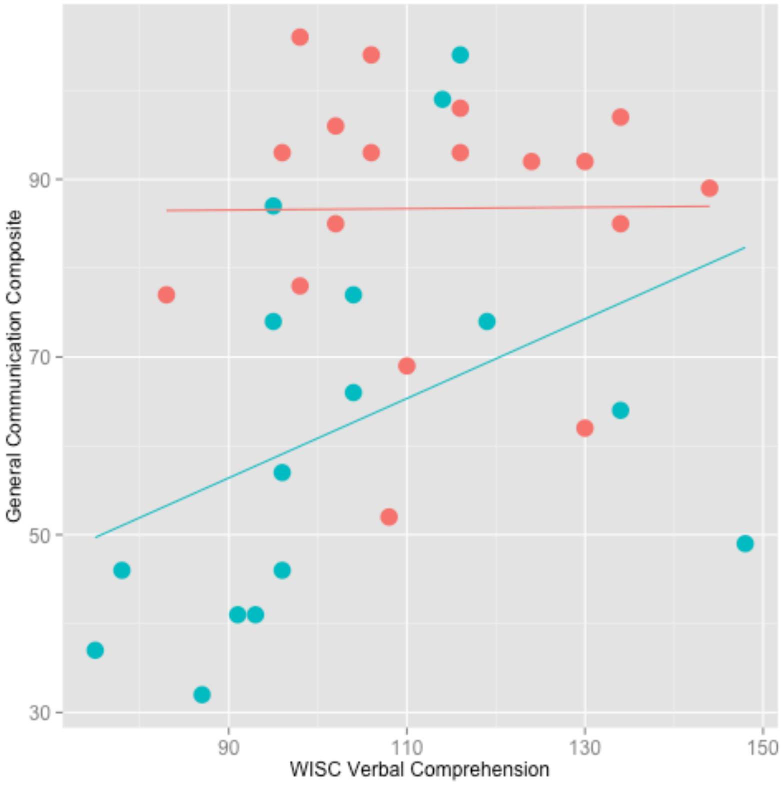


**Figure 32: Relationship between General Communication Composite (GCC) and WISC-IV Verbal Comprehension (vIQ) scores in the VI (blue) and control group (red).** The lines represent a linear model fit using the stat_smooth function in ggplot2 (Wickham, 2009).

### 5.2.2.4. Discussion

The Children's Communication Checklist 2nd edition (Bishop, 2003) was employed to investigate the structural and pragmatic language integrity. A previous investigation using the same instrument had identified pragmatic language deficits in large proportion of school-age children with severe and profound VI (Tadić et al., 2009). The present study aimed to replicate these findings in a new sample, assess the influence of vision level in a group with more varying degrees of visual impairment, and relate pragmatic language measures to performance on other measures of social understanding.

In line with the previous investigation, a large proportion of children in the VI group reached General Communication Scores in the very low range indicating communication deficits. Further, most children that reached low communication scores also reached low scores on the social interaction composite. The profile of a large proportion of the current sample with low general communication and low social interaction scores is similar to the profile described for children with ASD (Bishop, 2003; Bishop et al., 2006). Some authors had suggested that behavioural traits associated with ASD are more common in children with VI with low verbal ability (Brown et al., 1997). However, no strong indication of an association between ASD-like profiles on the CCC-2 and composite scores of verbal ability of the WISC-IV could be identified in the current sample. However, extremely low scores were associated with lower verbal IQ, but some participants with high verbal ability reached scores below the 10%ile on the GCC. Further, correlations between GCC and measures of social adjustment (SDQ Peer Relationships and PedsQL Social) indicated a strong association between general communication abilities and social behaviour. This suggests that communicative abilities might be a protective factor for better social abilities in children with VI.[6]

Another potential concern is the discrepancy between scores on the SCQ and scores on the CCC-2. Only three participants reached scores above the cut-off for ASD on the SCQ, but a large proportion showed communication profiles similar to typically-sighted children with ASD on the CCC-2. However, both questionnaires are aimed to measure different aspects of social communicative behaviour. While the SCQ assesses rare behaviours that are typically only observed in typically-sighted children with ASD, the CCC-2 assess a communication profile and is not designed as a specific diagnostic tool for ASD. Other studies reported similar ASD-like profiles in other neurodevelopmental disorders ( Oliver et al., 2011; Sadiq et al., 2012) suggesting that such profiles are more indicative of deficits in social and pragmatic language that are not specific to ASD (see Norbury 2014 for a review). Further, other findings suggest that ASD-like communicative profiles in individuals that do not meet criteria for ASD on diagnostic instruments represent a subliminal or milder ASD, or part of the broader autism phenotype (Reisinger et al., 2011; Taylor et al., 2013). In addition to general controversies about the specificity of pragmatic and social language assessment (Norbury, 2014), there are limitations to the interpretation of findings in the current study. In order to maintain the psychometric integrity of the CCC-2 questionnaire and not influence findings through *a priori* assumptions, the questionnaire was administered with all items and in the original wording. However, some items, particularly on the non-verbal communication scale, might introduce biases towards children with better visual ability, e.g. "smiles at people". Other investigations have shown that the sensitivity and specificity of standard assessment instruments designed for sighted children is compromised in groups of children with low vision (Jutley-Neilson et al., 2013). However, low scores were observed across different scales, including scales that do not make reference to visual behaviours. Therefore, the findings support that communication and pragmatic language deficits are present in the current sample of children with VI as previously proposed (Tadić et al., 2009).

In conclusion, the findings that social and communication difficulties are even present in children with good verbal ability and only mild to moderate visual impairment suggests the contribution of multiple underlying factors as well as visual impairment of any degree. Studies including participants with single VI disorders provide some evidence that ASD-like traits are more common in some VI disorders like septo-optic dysplasia (Jutley-Neilson et al., 2013; Parr et al., 2010) and Leber's amaurosis (Fazzi et al., 2007). Because of the rarity of these disorders and the limited sample included in the current investigation, questions about differences between VI disorders cannot be addressed with the available data. Further, the genetic background leading to the VI disorders may contribute to the development of ASD-like features in some children with VI. Unfortunately, the majority of diagnostic categories of CDPVS disorders are complex and the contribution of many genes is assumed, e.g. see Stone 2007. Therefore, future studies will need to address the contribution of genetic variations in samples that are carefully characterised through individual genetic testing.

## 5.2.3. Mentalizing and Theory of Mind

### 5.2.3.1. Introduction

Mentalizing refers to the ability to understand that there are individual intentional states underlying the actions of oneself and others (Happé & Frith, 2014). Commonly used tasks to measure mentalizing abilities include false belief tasks that create a mismatch between the mental representation of a character in a story and the mental representation of the observer, e.g. the Sally-Anne task (Baron-Cohen, Leslie, & Frith, 1985). Even though most typically developing children will pass simple false belief tasks in their preschool years, adult-like performance on more difficult tasks, e.g. requiring third degree inferences ("I know that you know that I know), is only reached in mid-childhood (O'Hare, Bremner, Nash, Happé, & Pettigrew, 2009).

Mentalizing abilities extend beyond comprehension of false belief to the attribution of mental states including emotion and intention in different social situations.

Happé argued that the ability to understand metaphor also requires mental state attribution, because the metaphor creates a conflict between the literal meaning of the sentences and the intention of the speaker (Happé, 1993). For instance, the sentence "It's raining cats and dogs" is not intended to be interpreted literally in most situations, but is used to indicate heavy rainfall.

Several studies found delays in passing basic false belief tasks in children with visual impairment (Brambring & Asbrock, 2010; Minter et al., 1998; Peterson et al., 2000). While older children (12 years) performed on ceiling level on basic mentalizing tasks, younger children (4-6y) performed significantly worse than typically-sighted children matched for age and verbal ability (Green, Pring, & Swettenham, 2004; Pijnacker, Vervloed, & Steenbergen, 2012). It is currently not clear which factors contribute to delayed development of mentalizing abilities in children with VI. There are conflicting accounts about influence of vision level and verbal ability in the available literature (Brambring & Asbrock, 2010; Minter et al., 1998; Peterson et al., 2000; Pijnacker et al., 2012). Differences in the inclusion of varying vision levels and verbal ability, and the differences in the tasks employed to assess mentalizing abilities are possible reasons for this discrepancy.

Brown and colleagues argued for a dichotomy of mentalizing ability between children with low versus good intellectual function (Brown et al., 1997). Children with low verbal ability displayed more features associated with autistic traits in typically-sighted children including compromised social understanding and communications. In contrast, children with VI and verbal abilities in the normal range resembled their typically-sighted and typically developing peers. However, there is some indication that subtle impairments in social understanding exists even in children with verbal abilities in the normal range (Tadić, 2012). In contrast to previous studies, the current investigation aimed to assess social understanding directly in a sample of children with VI using advanced theory of mind tests that provide higher sensitivity for school-age children with verbal abilities in the normal range. Further, in contrast to previous investigations, the sample included a high proportion of children with mild to moderate VI in order to assess the influence of varying degrees of VI on mentalizing ability. Based on previous studies, lower scores on tests of mentalizing abilities were expected in the VI group - at least on tests of advanced mentalizing. The influence of vision level could not be assessed from the literature and was a central focus of the current investigation.

### 5.2.3.2. Basic Social Understanding

#### 5.2.3.2.1. Materials & Methods

The NEPSY (Developmental Neuropsychological Assessment) is a comprehensive battery of tests for children between 3-16 years that assesses performance across six cognitive domains (Korkman, Kirk, & Kemp, 2007). The second edition includes assessment of social perception, which comprises two subtests: affect recognition in images of emotional facial expression and theory of mind (ToM). The ToM task in turn consists of a verbal subtest, in which children have to answer questions about mental states of agents in short stories, and a picture subtest that requires children to select an image that matches the context of a social story.

Because the use of pictorial materials would bias the investigation towards children with better vision, only items from the NEPSY-II Theory of Mind Verbal task were administered (Korkman et al., 2007). Items for children younger than 8 years were excluded. Further, items that require visual materials were excluded. For items that included visual materials for illustration, the visual material was not used. Sentences and questions with direct reference to visual experience were rephrased to address other sensory modalities. The remaining set of questions consisted of seven items including three questions relating to figurative language understanding and four questions relating to ToM.

If required, the stories were read several times, but no prompts were given. Children were encouraged to perform the task, but no direct feedback on performance was provided. The items were scored according to the instructions in the test manual. Because many items had to be excluded and other items had to be modified, the scores were not transformed to scaled scores. Instead, the raw scores were compared between the groups.

The relationship between social understanding and outcome variables was investigated using bivariate Pearson correlations. Scores on the PedsQL Social scale and the SDQ Prosocial Behaviour and Peer Relations scale were selected as outcome measures. The VI and control group were analysed separately, because of ceiling effects in SDQ scores in the control group.

Modified items of the NEPSY-II Theory of Mind Verbal Task as administered:

**Item 1: Theory of Mind**

Brandon has a hard time with spelling. He didn't do well on his spelling test in school. That afternoon, Mom said, "You'll feel better if you go play with Cameron." Brandon went to Cameron's house. Cameron wanted to play Word Spell. Brandon decided to go home. Why? (*no alterations to NEPSY-II*)

**Item 2: Theory of Mind**

Reggie and Patrick wanted to ride the Ferris wheel. Audrey and Hannah didn't want to ride it so they decided to go on the merry-go-round. When they boys got to the Ferris wheel, the line was too long, so they went to the fun house instead. When Audrey and Hannah were finished at the merry-go-round, where would they look for the boys, at the fun house or at the Ferris wheel? (*illustrative material excluded*)

**Item 3: Theory of Mind**

Listen carefully to this story: Laurie Lamb asked Mother Sheep if she could go play. Mother said, "Yes, dear, but don't go near the forest. Mr. Wolf is hiding there." Laurie skipped off with her friends to play hide and seek. Laurie ran into the woods to hide behind a tree. Just then she *felt* (saw) a big sheep with a (white) wooly coat that had *a deep, husky voice* (a long noise and big teeth, smiling as it came toward her). Mother Sheep was watching. Suddenly she grabbed Laurie and they ran from the woods!

**Item 4: Figurative Language**

Mrs. Russell's class was making presents for the people at the nursing home. It was almost time to recess. Mrs. Russell said, "Class, we'd better wrap it up now." What did she mean? *(illustrative material excluded)*

**Item 5: Figurative Language**

Denise and Emily are sisters. Mama says they are like two peas in a pod. What does that mean? *(illustrative material excluded)*

**Item 6: Theory of Mind**

This story is a lot like the story I read before, but listen for something different: Laurie Lamb asked Mother Sheep if she could go play. Mother said, "Yes, dear, but don't go near the forest. Mr. Wolf is hiding there." Laure skipped off to play hide and seek with her friends. Laurie ran into the woods to hide behind a tree. Just then she *felt* (saw) a big sheep with a (white) wholly coat and skinny grey legs that had *a deep, husky voice* (a long noise and big teeth, smiling as it came toward her). Suddenly, a funny-looking, *wooly* (brown) bear came roaring into the woods and chased off the big sheep. Laurie was so scared that she ran all the way home. Just then Mother Sheep came up the path out of breath. Her wool was all wet (and it was muddy brown in places.) Laurie ran to her and said, "Mama, I won't ever go into the woods again. There is a (funny-looking) roaring bear in there!" Mama hugged Laurie and laughed. Who was the (funny-looking) wooly bear?

**Item 7: Figurative Language**

Oscar said, "Mom, Uncle Carlos is going to take me for ice cream!" Mother smiled and said, "Oscar, you have Uncle Carlos wrapped around your finger." What does Oscar's mother mean? *(illustrative material excluded)*

### 5.2.3.2.2. Results

An adapted form of the NEPSY-II Theory of Mind Verbal Task was administered. Thirteen children in the VI group (7 male, 8.27-12.06y, vIQ:75-148) and 16 children in the control group (9 male, 8.73-12.72y, vIQ: 83-144) completed the NEPSY-II assessment. There was a significant effect of participant group on the total score with lower values in the VI group (Independent two-sided t-test: VI: mean=4.77, SE=0.5, Range=2-7; control: mean=6.69, SE=0.44, Range=1-8, t(26.658)=-2.804, p=0.009).

Separate analysis of the Figurative Language sub-scores indicated similar effects of participant group (VI: mean=0.92, SE=0.24, Range=0-2; control: mean=2.25, SE=0.23, Range=0-3; t(26.587)=-3.976, p<0.001). There was only a significant effect of participant group on the Theory of Mind subscore (VI: mean=3.85, SE=0.32, Range=2-5; control: mean=4.44, SE=0.27, Range=1-5, t(30.536)=-1.440, p=0.081).

The relationship between outcome variables relating to social adjustment and quality of life was investigated. Bivariate correlations indicated a strong relationship between total raw scores on the NEPSY-II Theory of Mind verbal task and the Social scale of the PedsQL in the VI group (n=11, r(9)=0.72, p=0.013), but not in the control group (n=15, r(13)=-0.07, p=0.804). There was also a trend-level negative correlation between NEPSY scores and ratings on the PedsQL Peer Relationships scale (n=11, r(9)=-0.55, p=0.082) indicating a greater amount of peer relationship difficulties in children with lower NEPSY scores. The correlation between NEPSY scores and Prosocial Behaviour did not reach significance (n=11, r(9)=0.45, p=0.1695).

Separate analysis by vision category indicated a significant difference on the total NEPSY-II score (one-way ANOVA: MVI: mean=5.5, SE=0.67, Range=3-7; S/PVI: mean=4.14, SE=0.67, Range=2-7; F(2,22)=11.905, p<0.001). Follow-up contrasts indicated a significant difference between the control and S/PVI group (t(11.55)=3.164, p=0.008, Bonferroni-corrected p=0.034). Other contrasts did not reach significance level.

#### 5.2.3.2.3. Discussion

Adapted items of the NEPSY-II Theory of Mind task were administered to assess basic mentalizing abilities in children with visual impairment. It was found that children with VI reached lower total scores compared to the control group. Separate analysis of items relating to ToM and items relating to figurative language understanding indicated similar scores in both groups on ToM items, but significantly worse performance in figurative language items in the VI group. Further, verbal comprehension scores emerged as significant factors for task performance in both groups with higher vIQ being associated with higher scores. Analysis by vision group indicated that children with severe to profound VI performed significantly worse than the control group. Difference between the mild/moderate group and severe/profound group or the control group did not reach significance indicating that overlapping distributions of scores in both groups.

Verbal abilities are generally associated with better performance on verbal social tasks both in sighted children (Fisher et al., 2005; Loukusa, Makinen, Kuusikko-Gauffin, Ebeling, & Moilanen, 2014) and children with VI (Peterson et al., 2000), but there was no indication that the VI group was influenced more strongly by this effect than the control group.

Correlations with outcome measures indicated that abilities that contributed to better performance on the social understanding items are also associated with less problems in social function and less problems in peer relationships according to parent report.

#### 5.2.3.3. Advanced Social Understanding

##### 5.2.3.3.1. Materials & Methods

The social understanding questions of the Strange Stories task were administered (Happé, 1994). The Strange Stories task consists of 24 stories that probe theory of mind, figurative language understanding, and comprehension of communication concepts like white lies, sarcasm, persuasion etc. Each story is followed by one or two comprehension question and a question involving mental state attribution. The questions were obtained from the author of the original publication, Prof. Francesca Happé, and were administered verbatim. All stories were read to the children and their answers were digitally recorded. Question were repeated, if necessary. If a child did not answer the question ("I don't know", "not sure"), the answer was probed and scored as incorrect, if no answer was provided. Children were encouraged to answer, but no direct feedback on task performance was given. No prompts were given.

The answers were transcribed by an assistant and independently scored by two raters that were masked to the vision level of the participants. The answers were scored for correctness and the use of mental state attribution. Binary rating scales were used for rating for comprehension questions (correct/incorrect) and mental attribution (present/not present). Some questions could be correctly answered with either a physical or mental attribution answer. For instance, in a story about a boy that calls a very big dog an elephant, the child could answer that the boy called the dog an elephant "because the dog is very big" (physical) or "because he was making a joke" (mental) (Happé, 1994; Kaland et al., 2005).

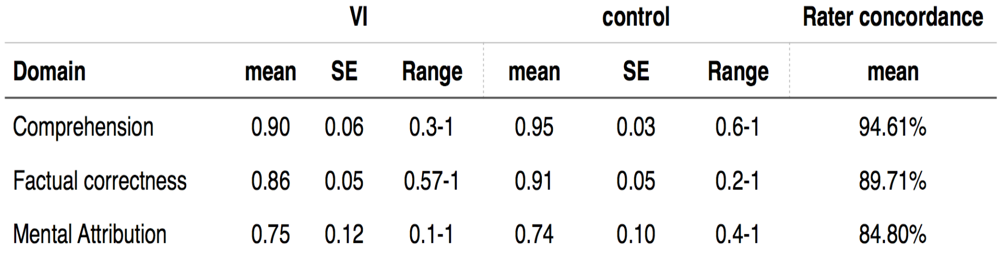
##### 5.2.3.3.2. Results

Nine children in the VI group (6 male, 9.19-13.32y, vIQ: 87-148) and nine children in the control group (4male, 8.73-11.78, vIQ: 83-144) completed the task. The agreement between the masked raters was high for all measures (85-95%). Rater concordance was lower for mental attribution, when raters had to indicate if the response of the child indicated mental or physical attribution.

There was no significant difference between participant groups on comprehension (see Table 13 for descriptives, F(1,14)=1.934, p=0.188). There was no significant effect of vIQ, participant age or their interaction. There was also no difference between the groups in the use of mental attribution to answer the 'social' question. Error analysis indicated that mental attribution was not used in any of the incorrectly answered questions in both groups (VI: n=26, control: n=17).

Table 14 shows the breakdown of incorrect responses per construct. The highest number of incorrect responses in the control group was given in response to the Forget question. Most incorrect responses for this question were omission ("I don't know", "not sure", etc.). There were more incorrect responses to the Figure of Speech, Double Bluff and Persuasion questions in the VI group compared to the control group. When Forget questions were excluded, a significant difference between the VI and control group in the ratio of correct answers emerged with lower scores in the VI group (VI: mean=0.81, SE=0.02, Range=0.75-0.92; control: mean=0.87, SE=0.03, Range=0.67-0.92, F(1,14)=5.103, p=0.0403). There was no difference in mental attribution between the groups, when Forget questions were excluded.

**Table 13 The table summarises the mean scores for comprehension, factual correctness and mental attribution across all Strange Stories items.** Comprehension refers to the factual questions that ascertain that the child understood the content of the story. Factual correctness refers to the correctness in the 'social' question. The ratio of correct responses is given for each group and measure.



| | VI | | | control | | | Rater concordance |
|---|---|---|---|---|---|---|---|
| **Domain** | **mean** | **SE** | **Range** | **mean** | **SE** | **Range** | **mean** |
| Comprehension | 0.90 | 0.06 | 0.3-1 | 0.95 | 0.03 | 0.6-1 | 94.61% |
| Factual correctness | 0.86 | 0.05 | 0.57-1 | 0.91 | 0.05 | 0.2-1 | 89.71% |
| Mental Attribution | 0.75 | 0.12 | 0.1-1 | 0.74 | 0.10 | 0.4-1 | 84.80% |

**Table 14 Number of factually incorrect responses and use of mental attribution per construct.** Each construct was probed by two questions. The number of incorrect responses per group is presented.

| | Incorrect responses | | | | Mental attribution | | | |
|---|---|---|---|---|---|---|---|---|
| | VI (n=9) | | control (n=9) | | VI (n=9) | | control (n=9) | |
| | n (n=18) | % | n (n=18) | % | n (n=18) | % | n (n=18) | % |
| Pretend | 0 | 0.00 | 0 | 0.00 | 15 | 88.24 | 15 | 83.33 |
| Joke | 3 | 16.67 | 2 | 11.11 | 5 | 27.78 | 4 | 22.22 |
| Lie | 0 | 0.00 | 1 | 5.56 | 17 | 100.00 | 17 | 94.44 |
| White Lie | 1 | 5.56 | 1 | 5.56 | 18 | 100.00 | 18 | 100.00 |
| Figure of speech | 5 | 27.78 | 2 | 11.11 | 2 | 11.11 | 1 | 5.56 |
| Misunderstanding | 2 | 11.11 | 1 | 5.56 | 18 | 100.00 | 14 | 77.78 |
| Double bluff | 5 | 27.78 | 2 | 11.11 | 14 | 77.78 | 15 | 83.33 |
| Sarcasm | 1 | 5.56 | 0 | 0.00 | 15 | 83.33 | 15 | 83.33 |
| Persuasion | 4 | 22.22 | 1 | 5.56 | 15 | 83.33 | 17 | 94.44 |
| Contrary emotion | 1 | 5.88 | 0 | 0.00 | 15 | 88.24 | 17 | 94.44 |
| Appearance/reality | 1 | 5.56 | 0 | 0.00 | 17 | 94.44 | 15 | 83.33 |
| Forget | 3 | 17.65 | 7 | 38.89 | 14 | 82.35 | 10 | 55.56 |
| Total \| Mean | 26 | 12.15 | 17 | 7.87 | 14 | 78.05 | 13 | 73.15 |

## 5.2.3.3.3. Discussion

The Strange Stories task was administered as an assessment of advanced social understanding consisting of naturalistic stories that require inferences about the mental state of others (Happé, 1994; O'Hare et al., 2009). There were no significant differences in the total score between the VI and control group indicating that both groups performed on a similar level on comprehension questions and also answered questions that require inferences about the state of mind of characters equally well. There was also no difference in the use of mentalizing to answer these questions. Notably, error analysis showed that mentalizing was not used when wrong answers were given indicating that the use of mental state attribution aided task performance.

The original 24 stories were grouped into 12 categories for different social contexts comprising Pretend, Joke, Lie, White, Figure of Speech, Misunderstanding, Double Bluff, Sarcasm, Persuasion, Contrary Emotion, Appearance/Reality and Forget. A breakdown of errors indicated differences in the distribution of errors by construct between the VI and control group: more than a third of all errors in the control group related to the Forget questions, whereas only around 10% in the VI group gave incorrect answers to Forget items. The questions in the Forget category are more open to different interpretations. For instance, question 22 about a girl that left out her doll in the garden could be interpreted as the girl forgetting that she left the doll or imply that the girl is lying, because she was not supposed to leave it out, or that she does not want to go out in the rain. This ambiguity is in contrast to the other stories that generally show obvious motivations or intentions. However, the high error rate for these questions in a typically developing control group deviates from previous reports (Happé, 1994; Kaland et al., 2005; O'Hare et al., 2009). This discrepancy could be due to the omission of the illustrations in the current investigations compared to the original reports. It is possible that the illustrations were especially helpful to resolve ambiguity for the Forget questions. In addition, children may have been less likely to guess answers after having completed a protocol of neuropsychological tests that mostly demanded unambiguous correct responses to structured questions.

When excluding the Forget questions, significant difference in performance between the groups emerged. In contrast to the control group, there were more errors in classic ToM questions (Double Bluff, Persuasion) as well as stories that require the understanding of metaphor or simile (Figure of Speech). Both Double Bluff and Persuasion questions require second order theory of mind understanding (Happé, 1994). However, answers in both groups still reflect a similar frequency of mental attribution usage suggesting that both groups applied similar strategies when solving the task. In summary, the findings implicate that children with visual impairment are less able to solve tasks that require advanced mentalizing, but employ similar strategies involving inferences about other's emotions or intentions. Therefore, the findings may suggest that children in the VI group perform more like younger typically-sighted children (O'Hare et al., 2009) rather than typically-sighted children with ASD (Happé, 1994). The limited number of participants in the current study and narrow age range do not allow for a meaningful assessment of the impact of participant age. Further studies with a larger sample and age range or ideally longitudinal studies would be needed to establish if the observed deficits represent a developmental delay or persistent subtle deficits in social understanding.

## 5.3. Neurophysiological investigation of social cognition

### 5.3.1. Introduction

Previous research studies found that social cognition is often challenging for children with visual impairment (see Chapter 1 for a review). These difficulties are particularly prominent in infancy (Dale et al., 2014), but evidence suggests that deficits are also present in childhood and adolescence (Greenaway et al. *submitted for publication*; Tadić et al., 2009). However, differences in tests of social understanding in older children are subtle and are only revealed through sensitive targeted tests (Hobson, Lee, & Lee, 2010). A possible explanation is that older children have learned strategies to solve social understanding tasks and cope with social situation in everyday life, but use strategies that are different from the strategies employed by unaffected peers and might be more effortful and less effective. These differences may be due to underlying differences in social cognition (Beauchamp & Anderson, 2010). Social cognition refers to the decoding, storage and retrieval of information about signals from conspecifics (Shettleworth, 2009). It is likely that the development of social cognition is altered in individuals with visual impairment due to the importance of visual signals particularly during the preverbal years, e.g. through communication through shared gaze, facial expression etc. (Dale & Sonksen, 2002) and later through visual materials and information from the social environment that may support the ongoing development of mentalizing and advanced social cognition.

The current study aimed to investigate the response to basic social signals using electrophysiological methods. These provide several advantages for this purpose: First, event-related potentials can track the processing of stimuli with high temporal resolution. Differences in ERP timing may indicate differences in the efficiency of processing or provide evidence that processing is qualitatively different (Kappenman & Luck, 2013). Further, topographic analysis, particularly in combination with biophysical modelling procedures (Michel & Murray, 2012), can be used to identify possible differences in the cortical substrates involved in processing these stimuli.

In the subject's-own-name (SON) paradigm, participants are presented with recordings of their own name or a control name (CN). At the behavioural level, own-name stimuli have been found to be processed preferentially, automatically, and uncontrollably (Alexopoulos, Muller, Ric, & Marendaz, 2012). This effect is thought to be mediated by preferential processing through bottom-up attentional capture of self-relevant information (Alexopoulos et al., 2012; Koole, Dijksterhuis, & van Knippenberg, 2001; Pfister, Pohl, & Kunde, 2012). Differences in preferential processing of self-relevant information have also been related to differences in mentalizing abilities in individuals with high-functioning autism. On the cognitive level, behavioural findings in individuals with Asperger syndrome (AS) suggested reduced performance for attention and memory for self-relevant information (Cygan, Tacikowski, Ostaszewski, Chojnicka, & Nowicka, 2014; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007). Similarly, delays in the development of mirror recognition and use of personal pronouns have been found in toddlers with ASD (Carmody & Lewis, 2012). In both studies, reduced performance on assessments of self-processing related to reduced scores on assessments of mentalizing ability (Frith & Happé, 1999). An invariant preference for an egocentric interpretation has also been suggested (naive egocentrism hypothesis) (Frith & de Vignemont, 2005; Gillberg & Gillberg, 1989), which is supported by neuroimaging results that show similar self and other processing in AS (Lombardo et al., 2010). Both accounts converge on the interpretation that an executive system that mediates bottom-up preference for self-relevant information is affected in AS. The difference in behavioural and neurophysiological findings may be driven by developmental differences (chronological age, mental age) and differences in tasks.

Electrophysiological methods are particularly useful for the investigation of fast automatic attentional processes that are implicated in the preferential processing of self-relevant information. Consistent findings include enhanced amplitudes; P300 amplitudes were reported for SON as the deviant stimulus compared to control stimuli in an oddball paradigm (Eichenlaub, Ruby, & Morlet, 2012; Tacikowski & Nowicka, 2010; Tateuchi, Itoh, & Nakada, 2012). These attention effects were also found to be persistent during sleep (Perrin et al., 1999) and in minimally-conscious patients (Fischer, Dailler, & Morlet, 2008). A simultaneous ERP and PET investigation localised the specific effects of SON to the right superior temporal sulcus (STS), left precuneus, right medial prefrontal cortex (PFC) and right inferior parietal sulcus (IPS) (Holeckova et al., 2008; Perrin et al., 2005) in line with a social brain response (Johnson & de Haan, 2011).

Specific effects of SON were also found to be present when SON is presented with the same probability as other stimuli. A study by Eichenlaub and colleagues investigated the effect of different deviant stimulus presentation frequencies on responses to SON and a control name. The authors found a negative deflection over central channels following the P3 response that was significantly enhanced in response to SON. Further, SON elicited a specific long lasting positive deflection over central and occipital channels between 450 and 800ms after stimulus onset (Eichenlaub et al., 2012; Muller & Kutas, 1996). Even earlier specific effects of SON were reported within the N1 window (80-120ms) in a study by Holler and colleagues that also used equiprobable stimulus presentation (Holler, Kronbichler, Bergmann, Crone, Ladurner, et al., 2011a). However, a second article by the same authors reports large inter-individual variability in the response (Holler, Kronbichler, Bergmann, Crone, Schmid, et al., 2011b).

Based on the existing literature about event-related potential responses to subject's own name stimuli and the behavioural investigations of social understanding in children with visual impairment, the following findings were predicted:

- Higher peak amplitudes for SON compared to the CN in the N1 time window as well as between 270 and 320ms (SON-related negativity) over central channels
- Higher mean amplitudes in late latencies in response to SON (450-800ms) over central channels
- Correlations between ERP amplitude in response to own name stimuli and behavioural measures of social function

## 5.3.2. Materials & Methods

### 5.3.2.1. Participants

Twenty-five children participated in this part of the EEG study (VI: 13; control: 12). One participant with VI was not included in the analysis because of excessive movement artefact due to a nervous tic. Two participants in the control group were rejected because of time-locked blinks that contaminated the ERP. One further participants in the control group was rejected because less than 10 trials were left after threshold artefact rejection (Final sample: VI=12, control=10).

#### 5.3.2.2. EEG recording & pre-processing

Please see the General Introduction for details about recording procedures and processing of EEG data for event-related potentials analysis details.

#### 5.3.2.3. Stimuli

The participants' first name and a control name were recorded from 2 female and 2 male speakers in a quiet environment using the in-built microphone on an Apple MacBook Pro (late-2010) under MacOS 10.8 using Audacity software V 2.0.5 (http://audacity.sourceforge.net). The control name was selected to have the same number of syllables as SON and start with a different phoneme. In order to signal communicate intent, the recordings included "Hey" followed by the name (Kampe et al., 2003). The sound amplitude was normalised for each stimulus using dynamic compression in Audacity.

#### 5.3.2.4. Testing procedure

Participants were instructed to passively listen to the sounds and minimise movements and blinks while the recordings are playing. The stimuli were presented in random order with an inter-stimulus interval with a random duration between 1000 and 2000ms.

#### 5.3.2.5. Channel-level analysis

Channel groups and time windows of interest were selected based on previous reports using a similar paradigm (Holler, Kronbichler, Bergmann, Crone, Ladurner, et al., 2011a). The channel areas of interest contained left, right, mid-frontal, central and left and right fronto-lateral channels. Three time windows were analysed: 50-150ms after stimulus onset (~N1 time window), 150-250ms (~P2 time window), and 270-320ms (~own name-related negativity). Due to the broader and more variable event-related response and the general concerns about peak measurements in ERP research (Luck, 2005), the mean amplitude was used for statistical comparison rather than the peak amplitude that was used in the published adult literature. Latencies were calculated at the point at which the cumulative sum of absolute values within a given time window had reached half of the total cumulative sum within that time window (fractional area latency) (Luck, 2005).

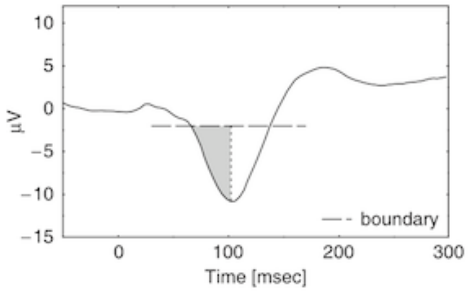


**Figure 33. Illustration of the 50% fractional area latency for measuring N1 latency taken from Kiesel et al. 2008.** Component latency is defined as the point at which 50% of the total area under the curve is reached, i.e. the point at which the cumulative sum of absolute values reaches half of the total cumulative sum.

## 5.3.3. Results

### 5.3.3.1. Channel-level analysis

There was no significant difference in the number of epochs between participant groups (Independent two-sided t-test: VI: mean=28.65, SE=0.47, Range=20-52; control: mean=28.06, SE=0.37, Range=22-36, t(21)=0.999, p=0.32). There was a trend-level difference in the number of epochs per conditions with fewer epochs for the control name (Independent two-sided t-test: Own name: mean=29, SE=0.57, Range=20-52; control name: mean=27.82, SE=0.28, Range=21-32; t(21)=1.8682, p=0.063). However, the difference in epochs was negligible with only 1 repetition on average.

The ERP waveforms displayed the expected morphology of components for this age group with a small early negative deflection followed by a large positive deflection. A negative going wave between 270 and 320ms after stimulus onset with larger amplitude in the own name condition over fronto-central channels was also observed (SON-related negativity) (Tateuchi et al., 2012). The N1 minimum over fronto-central channels appeared earlier in the VI group and fell outside the N1 range reported in the studies of typical adults that used a similar paradigm (Holler, Kronbichler, Bergmann, Crone, Ladurner, et al., 2011a; Holler, Kronbichler, Bergmann, Crone, Schmid, et al., 2011b). Therefore, the N1 window was extended to contain earlier latencies.

There was an effect of condition in the earliest time window (50-150ms) with more negative amplitudes in the own name condition (rmANOVA: Own name: mean=0.69, SE=0.16, Range=-6.21-4.26; Control name: mean=1.47, SE=0.21, Range=-4.88-8.06, F(1,209)=11.05, p=0.011). There was also a significant effect of channel region with more positive amplitudes in frontal channels (left fronto-lateral: mean=0.98, SE=0.25; right fronto-lateral: mean=1.53, SE=0.43; left frontal: mean=0.98, SE=0.25; right frontal: mean=1.53, SE=0.33; mid-frontal: mean=1.67, SE=0.34; central: mean=0.71, SE=0.26, F(5,209)=10.647, p=0.0013, Bonferroni-corrected p=0.0078). There were no significant effects on fractional area latency within the 50-150ms time window.

Significant effects of region were found in the second time window (150-250ms) with the highest amplitudes over central channels (left fronto-lateral: mean=0.2, SE= 0.42; right fronto-lateral: mean=1.88, SE=0.47; left frontal: mean=1.93, SE=0.37; right frontal: mean=2.79, SE=0.35; mid-frontal: mean=3.56, SE=0.45; central: mean=2.65, SE=0.35, F(5,209)=10.266,p<0.001, Bonferroni-corrected p=0.0054). A significant participant group by channel region interaction was observed for fractional area latency (VI: left fronto-lateral: mean=208.5, SE=2.1; right fronto-lateral: mean=204.17, SE=2.32; left frontal: mean=210.5, SE=2.08; right frontal: mean=203.67, SE=1.94; mid-frontal: mean=208.5, SE=2.1; central: mean=213, SE=1.96; control: left fronto-lateral: mean=202, SE=2.61; right fronto-lateral: mean=206.44, SE=2.68; left frontal: mean=197.33, SE=2.27; right frontal: mean=207.78, SE=2.99; mid-frontal: mean=203.33, SE=2.48; central: mean=206, SE=2.33). Follow-up simple contrasts indicated smaller FAL over left frontal channels in the control group (VI: mean=210.5, SE=2.08; control: mean=197.33, SE=2.27; t(37.79)=4.2812, p<0.001, Bonferroni-corrected p=0.004).

A significant participant group by region by condition interaction was observed in the 270-320ms time window (F(5,209)=4.064, p=0.002). Follow-up simple contrasts revealed significant differences between the group with more positive amplitudes in the VI group over right frontal channels in the own name condition (Right frontal: VI: mean=2.78, SE=0.73, Range= -7.87-8.25 ; control: mean=-0.77, SE=0.32, Range=-3.81 2.23; t(31.024)=4.4525, p<0.001; Central: VI: mean=2.78, SE=0.73; control: mean=-0.77, SE=0.32; t(31.02)=4.453, p<0.001,Bonferroni-corrected p=0.003). There were no significant effects on FAL in the N270-320 time window.

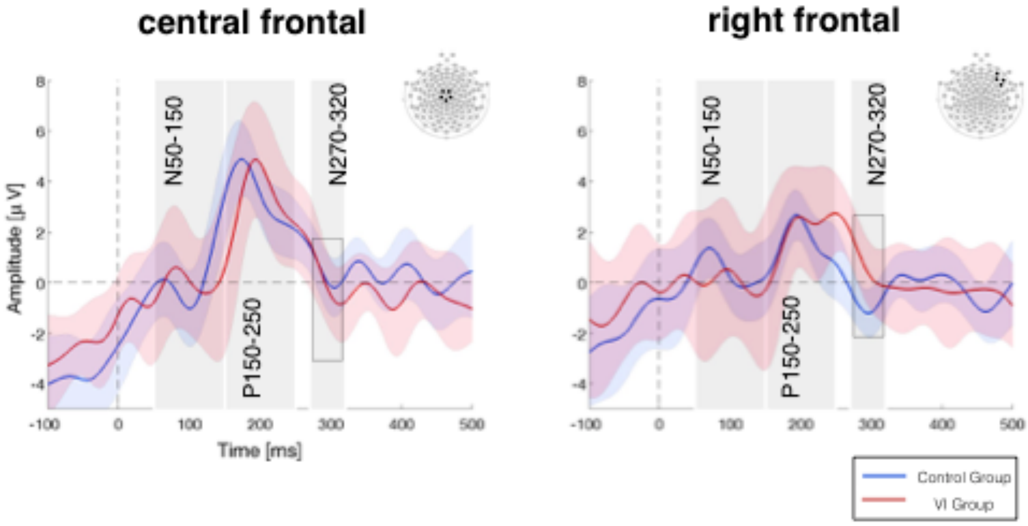


**Figure 34: Grand-average ERP waveforms in the VI and control group for the own name condition for mid-central and right frontal channels.** Solid line indicated the mean response, shaded areas indicate the standard error of the mean. Grey boxes mark the time windows of interest. Solid boxes indicated the time window of significant difference between the groups.

#### 5.3.3.2. Relationship to behavioural measures

A multiple regression analysis was conducted to evaluate the relationship between behavioural measures of social communication ability and mean amplitude of the event-related response. The analysis focussed on the 150-250 and 270-320ms time window, where the largest differences between conditions were observed. Further, the analysis focussed on central (P150-250) and frontal channels (N270-320) were effects were indicated in the channel-level analysis. The Social Interaction Deviance Composite (SIDC) and General Communication Composite (GCC) of the Children's Communication Checklist (CCC-2) (Bishop, 1998) and, the total score of the adapted version of the NEPSY-II Theory of Mind verbal task were used as predictors. The results of the Strange Stories task were not used, because only a small subgroup of participants had data available on both measures. The factors were selected to test the relationship between brain-level responses to an auditory social stimulus and behavioural indices of social understanding.

The linear combination of factors was not significantly related to the variance in mean ERP amplitude in response to own name stimuli over central channels in the 150 to 250ms time window (F(4,11)=1.448, p=0.283). In the 270-320 time window, there was a trend-level linear effect of the factors on mean amplitude in the frontal channel region (F(4,11)=3.318, p=0.051, multiple $R^2$=0.5468, adjusted $R^2$=0.382). There was a significant effect of participant group (b=2.253, t(11)=3.307, p=0.007). Post-hoc bivariate correlations revealed a trend-level positive correlation between GCC and mean amplitude in the 270-320 time window in the VI group (GCC (t(11)=2.016, p=0.069)).

There was no significant effect of the behavioural factors on fractional area latency in either time window (P50-150: F(4,11)=2.16, p=0.141; N270-320: F(4,11)=1.866, p=0.187).

**Table 15: Bivariate correlations between behavioural measures of social communication and ERP mean amplitude in the 150-250ms and 270-320ms time window.** Correlations were analysed in the central channels region for the early time window and frontal channels region. There was a significant negative correlation between SIDC and P150-250 amplitude and a positive correlation between GCC and N270-320 amplitude in the VI group. Test statistics were corrected for multiple comparison using Bonferroni correction for strong control of type-II errors.

| | | | VI | | Correlations | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Domain** | **n** | **mean** | **SE** | **1** | **2** | **3** | **4** | **5** |
| **1** | Mean amplitude (150-250ms) | 12 | 2.95 | 0.4 | 1.00 | | | | |
| **2** | Mean amplitude (270-320ms) | 12 | 1.03 | 0.59 | -0.21 | 1.00 | | | |
| **3** | NEPSY-II ToM total score | 9 | 5.22 | 0.39 | 0.23 | 0.18 | 1.00 | | |
| **4** | CCC-2 GCC | 11 | 64.64 | 5.91 | 0.02 | 0.61* | 0.47 | 1.00 | |
| **5** | CCC-2 SIDC | 11 | -8.45 | 2.45 | 0.23 | -0.28 | -0.22 | 0.41 | 1.00 |

* p<0.05, **p<0.01, ***p<0.001

| | | | control | | Correlations | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Domain** | **n** | **mean** | **SE** | **1** | **2** | **3** | **4** | **5** |
| **1** | Mean amplitude (150-250ms) | 9 | 2.75 | 0.62 | 1.00 | | | | |
| **2** | Mean amplitude (270-320ms) | 9 | -1.03 | 0.45 | 0.10 | 1.00 | | | |
| **3** | NEPSY-II ToM total score | 8 | 6.12 | 0.55 | -0.38 | -0.03 | 1.00 | | |
| **4** | CCC-2 GCC | 9 | 87.44 | 4.44 | 0.17 | -0.01 | 0.22 | 1.00 | |
| **5** | CCC-2 SIDC | 9 | 2.22 | 1.35 | -0.09 | -0.48 | -0.21 | -0.20 | 1.00 |

* p<0.05, **p<0.01, ***p<0.001

### 5.3.4. Discussion

Previous studies indicated deficits in social communication in children with visual impairment with a high proportion of children displaying behavioural traits associated with ASD in typically-sighted children (Brown et al., 1997; Hobson et al., 1999; Mukkades et al., 2007; Pring, 2008; Pring & Tadić, 2005; Tadić et al., 2010). Studies investigating responses to basic social stimuli in typically-sighted children with ASD (Senju, 2013) or relatives that match the broader autism phenotype (Sasson, Nowlin, & Pinkham, 2013) consistently reported differences in the neural response to social stimuli. These findings suggest a fundamental difference in the processing social information in individuals with autistic traits. It is not clear from the previous behavioural studies of social communication in children with visual impairment if a similar processing difference exists or if deficits are restricted to social behaviour. The current study aimed to investigate the response to a basic auditory social stimulus in high-functioning children with congenital visual impairment using the event-related potentials method. For this purpose, children were presented with recordings of strangers that either signalled communicative intent to them or a different person (Kampe et al., 2003). The ERP response was calculated in time windows and channel regions of interested based on the reports using similar paradigms (Holler, Kronbichler, Bergmann, Crone, Ladurner, et al., 2011a; Holler, Kronbichler, Bergmann, Crone, Schmid, et al., 2011b; Hu, Wu, & Fu, 2011).

A negative deflection was observed in the first time window (50-150ms) with a fronto-central topography consistent with reported features of the auditory N1 component. Similar to previous studies, there was a significant modulation of N50-150 mean ERP amplitude with more negative values in the own name condition with a maximum over central channels (Holler, Kronbichler, Bergmann, Crone, Ladurner, et al., 2011a; Muller & Kutas, 1996; Perrin et al., 1999; Proverbio, Lilli, Semenza, & Zani, 2001). The difference between self-relevant and other stimuli in this time window is generally interpreted as an automatic capture of auditory processing resources by self-relevant information based on the early latency and reports that this difference persists even during sleep (Perrin et al., 1999) and in patients in minimally conscious state (Perrin et al., 2006). No significant differences in mean amplitude or fractional area latency were found between the participant groups for the N50-150 suggesting that early preferential processing of self-relevant stimuli is similar in both groups.

The second time window between 150 and 250ms after stimulus onset displayed a strong positive deflection with a maximum over fronto-central channels. These characteristic are consistent with properties of the auditory P2 component (Crowley & Colrain, 2004). No significant differences in mean component amplitude were found between the conditions for P150-250. Modulation of P2 amplitude by own name stimuli is inconsistent in the literature with some studies indicating higher amplitudes in own name conditions (Muller & Kutas, 1996), while other studies report no differences (Holler, Kronbichler, Bergmann, Crone, Ladurner, et al., 2011a). A possible reason for the discrepancy in findings is the presentation frequency of the stimuli. While the Muller et al.

compared responses between self-relevant and control stimuli as deviants in an oddball design, Holler et al. as well as the present study compared response in a paradigm with equiprobable stimulus presentation. Modulation of P2 amplitudes by frequent and infrequency stimuli in oddball tasks was consistently reported in the literature and has been linked to auditory feature detection (Crowley & Colrain, 2004). Analysis of fractional area latency indicated a significant participant group by channel region interaction with shorter latencies over left frontal channels in the control group. This finding is likely to reflect an artefact of the fractional area latency measure: the response topography indicates a more right lateralised response in the control group compared to a more bilateral response in the VI group. Left frontal channel in the control group show little discernible event-related response with amplitudes around baseline variation. Because of the low area under the curve, the cumulative sum reaches 50% faster in channels with little activity. However, waveform morphology indicated that responses in the VI and control group over left frontal channels are not comparable. In summary, the findings suggest no difference between the self-relevant and control stimulus for the P150-250 component. However, the responses indicate a more bilateral distribution in the VI group compared to a more right lateralised response in the control group. A similar topography effect in this time window has been reported by Roder, Rosler and Neville for congenitally blind adults in a language processing paradigm (Roder et al., 2000). In general, differences in ERP topography indicate differences in the neural substrate or combination of neural substrates to contribute to the response (Murray, Brunet, & Michel, 2008). Therefore, the lateralisation differences may indicate differences in the neural substrates involved in processing the auditory stimuli between the VI and control group. These differences might reflect general differences in auditory processing between the VI and control group as suggested in previous studies (Roder et al., 2000).

The third time window between 270 and 320ms showed a more negative deflection in response to the own name compared to the control name condition with a maximum over right frontal channels in the control group. A similar response has been observed by Tateuchi and colleagues using a similar presentation paradigm with adults (Tateuchi et al., 2012). A similar effect is also apparent in other studies although not explicitly discussed (Berlad & Pratt, 1995; Holeckova et al., 2006; 2008). Because of the specificity of the deflection to own name stimuli, the Tateuchi et al. named this deflection the subject's own name negativity (SON negativity). The results indicated a more right lateralised response in the control group and a more central response in the VI group. The statistical comparison did not indicate a significant differences in the magnitude of the response between the participant groups. These findings indicate that both the VI and control group distinguished between the stimuli to a similar degree, but differ in the substrates involved in the processing based on the difference in response topography. The differences could indicate a difference in lateralisation by which similar regions are active in both groups, but are preferentially processed in one hemisphere in the control group, but not in the VI group. Alternatively, a different combination of substrates could be active in both groups. These questions could be investigated with EEG source reconstruction with a higher number of repetitions and/or individual recordings to obtain a higher signal to noise ratio. However, reports about high variability of subject-own name related responses (Holler, Kronbichler, Bergmann, Crone, Schmid, et al., 2011b) suggests that single trail analysis probably aided by machine learning classification of trials would be necessary (Michel & Murray, 2012). The most insight could be gained from using fMRI to discern the contribution of cortical activation with higher spatial resolution analogous to a study in adults by Kampe and colleagues in typically-sighted adults (Kampe et al., 2003).

In order to explore how processing of auditory social stimuli relates to the performance on behavioural tests of social understanding and questionnaire rating of social communication, a regression analysis was conducted. The results indicated a difference between the participant groups with a stronger relationship between the behavioural measures and mean amplitude over frontal channels in the own name condition in the VI group. Follow-up analyses identified a significant correlation between N270-320 mean amplitude on CCC-2 General Communication Composite score. This finding could indicate that the processing of own name stimuli in the 270-320ms time window may be subserved by substrates involved in language processing. Therefore, a possible explanation for the difference in topography between the groups is that more neural substrates related to language processing are active in the VI group than in the control group. However, no strong conclusions can be drawn from this finding due to the low statistical power and low variation in the behavioural measure in the control group. Further, the analysis was restricted to central channels to reduce the number of comparisons, which only partially captures the variance in the control group that displayed response maxima over right frontal channels.

In summary, the findings of the ERP investigation about processing of auditory social stimuli suggest similar early preferential processing of self-relevant information in the VI and typically-sighted control group and later differences in the neural substrates involved in processing own name stimuli with more right lateralised responses in the control group compared to bilateral or central responses in the VI group. Analyses of the relationship between variance in the ERP measures and behavioural measures of social understanding and communication may suggest that neural substrates related to language processing contribute to the subject's own name response in the VI group, but not in the control group. Further experiments, optimally incorporating other neuroimaging methods, would be needed to support this interpretation.

## 5.4. Chapter Discussion

Based predictions of the extended dorsal stream model and on previous reports about the high prevalence of behavioural traits associated with ASD (Brambring & Asbrock, 2010; Minter et al., 1998; Peterson et al., 2000) and delays in the development of mentalizing abilities in children with VI (Absoud et al., 2011; Brown et al., 1997; Mukkades et al., 2007; Parr et al., 2010; Rogers & Newhart-larson, 1989; Williams et al., 2013), the current investigation aimed to assess social abilities children with visual impairment of varying degrees. In with the predictions, the prevalence of behavioural characteristics associated ASD was higher in the current sample of children with VI than would be expected for a random population sample. In addition, half of the sample reached scores of communication profiles that were similar to children with either autism or Asperger syndrome on a questionnaire of pragmatic language use and communication. Further, behavioural assessments indicated deficits in advanced and basic mentalizing in children with VI, which were also significantly related to parent ratings of everyday social skills. In addition, analysis of event-related potential responses indicated differences in the processing of basic auditory social stimuli on the neural level in children with visual impairment.

In summary, the findings in the current investigation suggest that deficits in social understanding are present in children with visual impairment with good verbal ability. Regarding the influence of vision level, intermediate scores were observed for children with mild/moderate VI suggesting a dosage dependent effect of visual impairment. These findings are consistent with the predictions of the extended dorsal stream model that suggested deficits in social understanding as a consequence of altered integration of occipito-parietal areas with targets in the premotor cortex following visual impairment.

# Chapter 6: Parieto-medial temporal pathway: spatial memory function

This part of the current investigation aimed to assess functions relating to the indirect parieto-medial temporal connections of the extended dorsal stream model. These connections are thought to be involved in visuospatial memory and spatial representation (Kravitz et al., 2011; Margulies et al., 2009; Vincent et al., 2010).

## 6.1. Chapter Introduction

The extended dorsal stream model suggested an indirect parietal-mediotemporal pathway involved in visuospatial memory and spatial representation (Kravitz et al., 2011; Margulies et al., 2009; Vincent et al., 2010). The following chapter reports on investigations of spatial memory in the current sample of children with visual impairment. Based on the extended dorsal stream model, disrupted communication between visual areas and medial temporal areas was expected, which would lead to impaired performance on spatial memory tasks. In order to exclude the possibility that deficits on the spatial memory task arise from a general memory deficit, verbal short-term memory was also assessed.

### 6.2.1. Introduction

Spatial memory refers to the ability of an individual to hold spatial locations in mind and retrieve them. Several studies reported difference in spatial memory in congenitally blind adults and children including lower spatial memory capacity (Afonso et al., 2010; Cornoldi et al., 2009), and use of non-optimal spatial learning strategies (Schmidt et al., 2013; Ungar et al., 1995). Based on these reports and predictions of the extended dorsal stream model, lower performance on the spatial memory and cognition task was expected for the VI group.

### 6.2.2. Materials & Methods

The House Plan test of the Intelligence Test of Children with Visual Impairment (ITVIC) (Dekker, 1993) was administered. In this test, children are presented with a haptic map of a house with different rooms that contain landmarks, e.g. an arrangement of rectangles to represent a table with six chairs in the dining room. The child is introduced to the landmarks and is then given time to explore the map. Subsequently, the map is taken away and correct identification of the rooms is checked on a map that does not contain the landmarks. In the test phase, the child has to answer questions about the house plan without the aid of a map, e.g. "How many doors to I go through when I go from the bathroom to the dining room?" The number of correct responses is scored and is transformed to scaled scores with either correction for age or for both age and vision according to the normative sample of the test. The ITVIC scaled scores are normed to a mean score of 10 and a standard deviation of 2.

The HousePlan questions were administered according to the ITVIC manual (Dekker, 1993) with VI sample norms. Raw scores were corrected for age. Correction for vision level was applied for children with severe to profound VI using ITVIC Braille student norms. This correction was applied to account for the disadvantage of the lowest vision level and disentangle differences in vision from cognitive performance.

### 6.2.3. Results

Fourteen children in the VI group and 16 children in the control group completed the ITVIC HousePlan assessment (VI: 7 male, 8.27-12.26y, vIQ=75-148; control: 8 male, 8.56-12.77y, vIQ= 83-144). Statistical comparison indicated a significant effect of participant group with lower scores in the VI group (rmANOVA: VI: mean=8.79, SE=1.15, Range=2 -16; control: mean=13.56, SE=0.63, Range=7-17; F(1,26)=14.046, $p<0.001$). Subsequent analysis by vision group indicated a significant difference with lower scores in children with severe to profound VI (rmANOVA: MVI: mean=11.33, SE=1.63, Range=7-16; S/PVI: mean=6.88, SE=1.3, Range=2-11, F(2,25)=12.05, $p<0.001$). Follow-up contrasts also indicated a significant difference between the control and S/PVI group (t(10.422)=4.622, $p<0.001$, Bonferroni-corrected p=0.006) and a trend-level difference between the mild/moderate and the S/PVI group (t(10.408)=-2.140, p=0.057, Bonferroni-corrected p=0.171) that did not survive correction for multiple comparisons. There was no statistically significant difference between the mild/moderate group and the control group.

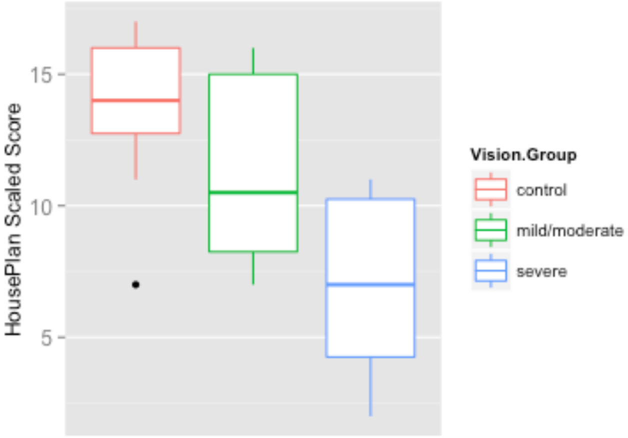


**Figure 35: Results of the ITVIC House Plan assessment of spatial representation and memory.** Summary statistics for the control (left), mild/moderate VI (middle), and severe/profound group (right) are presented. Statistical comparison indicated significant differences between the S/PVI and control group and a a trend-level difference between the mild/moderate and S/PVI group. There was no significant differences between the mild/moderate VI and control group.

## 6.2.4. Discussion

In line with previous investigations about spatial memory and spatial cognition in congenitally blind adults (Afonso et al., 2010; Cornoldi et al., 2009; Schmidt et al., 2013), significant differences were found between the VI and control group with lower performance in the VI group. This effect was driven by worse performance in children with severe to profound visual impairment, while the performance of children with mild to moderate VI were statistically not distinguishable from the typically-sighted control group. This finding is in line with a study by Vecchi and colleagues that also reported similar performance in participants with moderate binocular VI to typically-sighted control (Vecchi et al., 2006). This indicates that even degraded visual function is sufficient to sustain similar performance on a spatial memory and spatial cognition task. However, the demands of the tasks are substantially simplified compared to the demands placed by real world navigation and memory. Difference between typically-sighted individuals and children with mild to moderate VI may be more apparent in these real-world situations as indicated by lower independence and community use scores on questionnaires of adaptive behaviour (see Chapter 3 and Pinquart & Pfeiffer, 2014; Schmidt et al., 2013).

## 6.3. Short-term verbal memory

### 6.3.1. Introduction

In order to exclude the possibility that deficits in spatial memory are associated with a general memory deficit in children with VI, verbal short-term memory was assessed as another aspect of memory. In contrast to spatial memory, verbal memory is not likely to require visual input through the extended dorsal stream.

Several previous studies investigated verbal short-term memory performance in congenitally blind adults. Generally, higher performance is reported for congenitally blind groups compared to matched sighted controls (Roder & Rosler, 2003). Neurophysiological investigations using fMRI or ERP methods found that superior short-term memory performance in congenitally blind adults was associated with the recruitment of additional neural substrates, particularly typically visual areas of the occipital cortex (Roder & Rosler, 2003). Similar higher performance in short-term memory was also reported for school-age children with congenital blindness (Hull & Mason, 1995; Smits & Mommers, 1976; Swanson & Luxenberg, 2009; Withagen et al., 2013). A study by Hull and colleagues reported findings from a large sample of children with visual impairment including different vision levels. The authors reported that only children with light perception at best (profound VI) reached significantly higher scores compared to typically-sighted controls. Children with better functional vision performed on the same level as sighted controls (Hull & Mason, 1995).

Based on the literature on short-term memory performance in individuals with congenital VI and predictions of the extended dorsal stream model, similar performance to typically-sighted children of the same age was expected for children with visual impairment with potentially higher performance in children with the most severe degrees of VI.

### 6.3.2. Materials & Methods

The Word Pairs test of the Children's Memory Scale (CMS) was administered to assess short-term verbal memory (Cohen, 1997). In this test, children were presented with a list of arbitrary word pairs, e.g. nurse goes with fire, apple goes with cloud etc. After the list was read to the child, the first word of a pair was given as a prompt and the child has to respond with the second word in the pair. This process is repeated three times with a different order of word pairs in the sequence at each repetition. The number of correct responses is scored. After the three repetitions, the child is asked to name all the word pairs that he/she can remember without the aid of a prompt. The total number of correctly recalled word pairs is scored. The number of correct responses in the learning phase yields the Learning score, and the number of correct responses during the learning phase plus the number of correct word pairs in the recall phase leads to the Immediate Recall score. Both scores were transferred to scaled scores according to participant age using the norms of the test. The CMS scaled scores are normed to a mean score of 10 and a standard deviation of 2.

### 6.3.3. Results

The Word Pairs test of the Children's Memory Scale was administered to assess verbal short-term memory. Eighteen children in the VI group (9 male, 8.27-13.32y, vIQ: 75-148) and 18 children in the control group (10 male, 8.56-12.92y, vIQ: 83-144) completed the Word Pairs task.

On the Immediate Recall score, two participants in the control group and three participants in the VI group reached a scaled score more than two standard deviations below the mean of the norms (<16%ile). Two participants in the VI group and two participants in the control groups scored more than 2 standard deviations above the mean of the test norms (>91%ile). There was no significant difference between the groups (rmANOVA: VI: mean=10.11, SE=0.81, Range=3-15; control: mean=10.67, SE=0.66, Range=4-15, F(1,33)=0.282, p=0.599). Separate analysis by vision group did not indicate significant differences (rmANOVA: MVI: mean=10.56, SE=1.15, Range=3-19; S/PVI: mean=9.44, SE=0.84, Range=3-16; F(2,30)=0.328, p=0.723).

For the Learning score, two participants in the control group and 4 participants in the VI group reached scores lower than one standard deviation below the norm mean (<16%ile). One participant in the VI group and 4 participants in the control group scored more than one standard deviation above the mean norm (>91%ile). There was no significant difference in Learning scores between the groups (VI: mean=10.37, SE=1.02, Range=3-19; control: mean=10.39, SE=0.66, Range=5-15; F(1,33)=0.000, p=0.987). Subsequent analysis of the effect of vision level did not indicate significant differences between vision groups (rmANOVA: MVI: mean=11, SE=1.88, Range=4-19; P/SVI: mean=9.33, SE=1.33, Range=3-16, F(2,30)=0.419, p=0.662).

### 6.3.4. Discussion

Previous studies of short-term memory in congenitally blind children and adults reported higher performance compared to typically-sighted controls (Hull & Mason, 1995; Roder & Rosler, 2003; Smits & Mommers, 1976; Swanson & Luxenberg, 2009; Withagen et al., 2013). These findings have been interpreted to reflect an adaptive cognitive mechanism due to higher demands on short-term memory in the absence of visual cues. Further, higher performance has been linked to the recruitment of typically visual areas of the occipital cortex that are suggested to act as additional higher-order association areas in congenitally blind individuals (Amedi et al., 2003). However, a study involving children with visual impairment of varying degree reported that only children with profound VI show enhanced short-term memory performance, whereas children with better functional vision performed on a similar level as typically-sighted controls (Hull & Mason, 1995). The current investigation did also not find significant differences between children with visual impairment in the mild/moderate to severe range and typically-sighted controls on short-term memory scores. The performance of children with profound visual impairment, i.e. light perception at best, cannot be assessed as only one individual with PVI took part in the study.

## 6.4. Chapter Discussion

The present chapter investigated the integrity of spatial memory based on predictions about the importance of indirect projections of the dorsal stream to medial temporal areas for spatial memory. Visual deprivations was hypothesised to lead to changes in these connections that would impair performance on a spatial memory task. In line with these predictions and in accordance with previous investigations (Afonso et al., 2010; Cornoldi et al., 2009; Schmidt et al., 2013), lower performance was found on an assessment of spatial memory in children with visual impairment. This difference was driven by lower performance in children with severe to profound VI, whereas children with mild to moderate VI performed on a similar level to typically-sighted controls.

In order rule-out the possibility that differences in spatial memory are explained by a general memory deficit, verbal short-term memory was investigated as another aspect of memory that is not predicted to depend on parietal to medial temporal connections. In line with these predictions, the current study did not find significant differences between children with VI and typically-sighted controls, nor statistically significant differences between children with mild to moderate VI and children with severe to profound VI (also see Hull & Mason, 1995; Smits & Mommers, 1976; Swanson & Luxenberg, 2009; Withagen et al., 2013).

In summary, assessments of different aspects of memory in the current sample identified significantly lower performance in a spatial memory task in children with severe to profound VI, but age-appropriate performance on tests of verbal short-term memory across all VI groups. The dissociation between impaired performance in spatial memory and good performance in verbal memory is in agreement with the predictions of the extended neuroanatomical model, which would suggest that parieto-mid-temporal connections are more likely to be affected in visual impairment; these connections have been particularly implicated in spatial memory (Kravitz et al. 2011).

# Chapter 7: Structural Brain Organisation

## 7.1. Chapter Introduction

While previous chapters focussed on discussion of investigations of specific cognitive function related to connections of the extended dorsal stream, the following chapters will report results of analyses of brain structure and function that investigated the connections of typically visual areas of the occipital cortex in children with VI. The extended dorsal stream hypothesis suggested a difference in the integration of these areas with downstream targets that relate to specific cognitive differences. The aim of the following investigations was to test if differences in the integration of typically visual areas could be detected in children with VI using non-invasive neuroimaging methods. In addition, connections were related to the results of behavioural assessments following the predictions of the extended dorsal stream model.

Previous studies in early or congenitally blind adults suggested differences in brain structure related to the integrations of typical visual areas. Consistent findings included a increased thickness and decreased surface area of the pericalcarine cortex (Jiang et al., 2009; Leporé et al., 2010; Noppeney et al., 2005; Park et al., 2009) in blind participants compared to typically-sighted controls. Further, alterations were described in white matter tracts related to the transfer of visual information, including reductions in the optic radiations (Schoth & Krings, 2004; Shimony et al., 2006), the posterior corpus callosum (Ptito et al., 2008; Shimony et al., 2006), the inferior longitudinal fasciculus (Liu et al., 2007; Shu, Li, Li, Yu, & Jiang, 2009), and the fronto-occipital fasciculus (Shu, Li, Li, Yu, & Jiang, 2009). Based on the adult literature, differences in the integrity of brain structures involved in perceptual processing of vision were expected, i.e. increased thickness of the pericalcarine cortex, decreased diffusion within the optic radiations and posterior corpus callosum. Further, differences in white matter structures involved in the transfer of information between occipital areas and target areas in the temporal (inferior longitudinal fasciculus) and frontal cortex (inferior fronto-occipital fasciculus) were expected. Differences in these structure were hypothesised to relate to variation in scores of cognitive assessments, e.g. pragmatic communication, executive function, that have been reported to be affected in a large proportion of children with VI. Further, reorganisation of global white matter was expected with decreased integration of occipital areas.

## 7.2. General methods

### 7.2.1. Participant Sample

Magnetic resonance imaging data was acquired at the Radiology department of Great Ormond Street Hospital for Children NHS Trust. The duration of the scanning protocol was around 30 min. All scans were performed by a paediatric radiographer. Due to constraints of funding and scanning time only a subset of the children that participated in the study underwent MRI. Participation was mostly based on pragmatic reasons, like the ability to find an MRI appointment that was suitable for the family. Also, families were informed that children with claustrophobia or metal implants are not able to partake in the MRI assessment, but no family in the current sample declined for those reasons. Two families indicated that they did not want their child to participate in the MRI assessment, mostly because of concerns about the duration of the scanning and the restrictive environment. Characteristics of the sub-sample of participants that participated in the MRI assessment are presented in Table 16.

The control sample consisted of scans that were collected for a study about sickle cell anaemia that was conducted in parallel with the present study and used the same scanning protocol. Control participants for this study were selected to be right-handed, have normal or corrected to normal vision, and no neurological disorders. All participants scored within the normal range on procedural tests of the Wechsler Abbreviated Scale of Intelligence (WAIS). Due to limited funding resources, it was not possible to collect MRI data of typically developing control participants matched to the VI sample for the present investigation.

**Table 16: Demographic information about participants in the VI group that took part in the MRI assessment.** Two participants that had visual acuities that could only be assessed on the non-continuous Near Detection Scale (Sonksen et al., 1991) were analysed separately for correlations with vision level and are therefore marked as highly severe VI (hSVI) in the table. Abbreviations: MVI = mild to moderate visual impairment; SVI = severe visual impairment; hSVI = highly severe visual impairment; N/A: not available, i.e. not measurable.

| ID | Gender | Age [y] | WISC Verbal Comprehension | Sonksen LogMar | Near Detection | Vision Group | Visual Disorder |
|---|---|---|---|---|---|---|---|
| MV 1 | male | 12.34 | N/A | 0.54 | - | MVI | Rod-cone dystrophy |
| MV 2 | female | 8.27 | 104 | 0.6 | - | MVI | oculocutaneous albinisim |
| MV 3 | male | 12.06 | 104 | 0.6 | - | MVI | congenital nystagmus |
| MV 4 | male | 9.82 | 93 | 0.7 | - | MVI | ocular albinism, congenital nystagmus |
| MV 5 | female | 12.26 | 96 | left: 0.23, right: light perception | - | MVI/ PVI | unilateral optic nerve hypoplasia |
| SVI 1 | male | 11.69 | 148 | 0.9 | - | SVI | oculocutaneous albinisim |
| SVI 2 | male | 9.57 | 119 | 1.2 | - | SVI | Leber's congenital amaurosis |
| SVI 3 | male | 9.91 | 96 | 1.225 | - | SVI | Norrie's disease |
| hSVI 1 | female | 11.04 | 75 | N/A | yellow smartie | SVI | Leber's congenital amaurosis |
| hSVI 2 | female | 9.86 | 95 | N/A | wooly ball 50cm | SVI | bilateral micro-ophthalmia, retinal coloboma, right eye removed |

**Table 17: Demographic information about participants that served as a typically-sighted comparison group.** Participants were recruited for a different study with inclusion criteria of normal or corrected to normal vision and exclusion of neurological or psychiatric disorders. Detailed ophthalmological or neuropsychological information was not available for this group.

| ID | Gender | Age [y] |
|---|---|---|
| C1 | male | 9.86 |
| C2 | female | 10.07 |
| C3 | female | 10.48 |
| C4 | female | 10.96 |
| C5 | female | 11.48 |
| C6 | male | 11.81 |
| C7 | male | 12.07 |
| C8 | female | 12.13 |

### 7.2.2. Acquisition

All scans were performed on a Siemens Avanto 1.5 T clinical system (Siemens Healthcare, Erlangen, Germany), using a self-shielding gradient set with maximum gradient strength of 40 mT m–1 and a 32 channel quadrature head coil. The imaging protocol consists of three sequences: T1-weighted MRI, diffusion MRI and T2-weighted MRI.

T1-weighted volume scans for cortical parcellation were acquired using a whole brain coverage 3D Fast Low Angle Shot (FLASH) structural image acquired using a 1 × 1 × 1 mm image resolution. Echo time was 4.9 ms, and repetition time was 11 ms.

Diffusion MRI was acquired using echo-planar diffusion-weighted images with an isotropic set of 60 non-collinear directions, using a weighting factor of b = 1000 s mm–2, interleaved with 4 T2-weighted (b = 0) volumes. Whole brain coverage is obtained with 60 contiguous axial slices and image resolution of 2.5 x 2.5 x 2.5 mm. Echo time is 89 ms and repetition time is 7300 ms.

T1-weighted images were used for cortical thickness analysis and as high-resolution anatomical reference images for other analyses. Further, surface reconstructions based on the T1-weighted images were used to derive a structural connectome together with the diffusion-weighted images. Diffusion-weighted images were used for analyses of diffusion parameters across the whole brain volume and within key white matter structures.

### 7.2.3. Surface reconstruction

Cortical thickness analysis was based on T1-weighted MRI volumes (please see General Introduction for details about MR sequences). Reconstruction of cortical surfaces was performed using the FreeSurfer recon-all v. 1.379.2.73 (http://surfer.nmr.mgh.harvard.edu) running under Mac OS 10.9 on an Apple iMac (Core i7, built 2011) (Apple Computers, CA). Please refer to Dale & Fischl for a detailed description of the method (Fischl & Dale, 2000). In summary, after correction for magnetic field inhomogeneities, skull stripping and intensity normalisation, surface reconstruction is achieved through segmentation of the boundary between subcortical white matter and grey matter based on intensity differences. Next, a triangular mesh is generated to construct a three dimensional representations of the cortical sheath.

Surface-based registration was used for group level comparison (Fischl et al., 1999). Because of non-optimal co-registration between adult templates and paediatric data, the surfaces were co-registered to an average template based on all scans included in the analysis rather than co-registration to a standard adult template. After surface reconstruction, surfaces were co-registered to a spherical atlas, and subsequently parcellated for region-wise comparison. Labels of the Desikan-Killiany atlas were used for subsequent comparisons. Cortical thickness was measured in the surface space of each participants as the mean of the two shortest distances between the pial and the white matter mesh (Fischl & Dale, 2000). The spatial distribution of thickness measures was smoothed using a Gaussian kernel with 10mm radius. Accurate surface reconstruction in FreeSurfer depends on the contrast between grey and white matter. Because of changes in myelination, the contrasts changes over development, which can cause artefacts in surface reconstruction in developmental studies (Ghosh et al., 2010). In the age range included in the current study, the contrast between GM and WM is deemed sufficient for reconstruction (Ghosh et al. reported accurate results in children from 4 years of age).

Cortical thickness was analysed in regions of interest based on previous reports in the adults literature. ROI measures were statistically compared between the participant groups in an analysis of co-variance (ANCOVA) model using participant group and participant age as covariates.

## 7.2.4. Tractography

Diffusion-weighted imaging allows for the quantification of water diffusion in vivo. Based on the diffusion measurement a diffusion model can be fitted to estimate the orientation of maximum diffusion presumed to be co-aligned with the underlying tissue orientation within each voxel. Tractography is the method used to follow the dominant directions of diffusion within each voxel to reconstruct white matter pathways (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010; Le Bihan, 2003; Wedeen et al., 2005; Yamada, Sakai, Akazawa, Yuen, & Nishimura, 2009). Diffusion-based tractography is the only available method to assess white matter structure in humans in vivo and has provided many insights into the role of white matter structures in health and disease since it's inception in the early 1990s (Besseling et al., 2012; Dell'Acqua & Catani, 2012; Johansen-Berg & Behrens, 2006).

The general processing of diffusion-weighted images (DWI) followed the recommendations given for MRTrix software (Tournier et al., 2012): The fibre tracking algorithm was set to a minimum and maximum track length of 10mm and 200mm respectively. The minimum radius of curvature was set to 1 mm and the track size to 0.2mm. The track termination threshold was set to an FA value of 0.1. Due to better results with motion correction and skull-stripping, FSL routines were used for the pre-processing of DW images based on affine co-registration (Smith et al., 2004):

DW images were imported from dicom format to FSL Nifti-4D format using dcm2nii (version: 6 June 2013) (Rorden, Karnath, & Bonilha, 2007). The images were corrected for eddy currents in FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004). A brain mask was derived from the corrected b0 image using FSL BET (Smith, 2002). Motion-corrected and skull-stripped high-resolution T1-weighted images were co-registered to the b0 image using affine registration with 6 degrees of freedom with correlation ratio as a cost function using FSL FLIRT {Jenkinson:2002hn}.

Different measures are used in the literature to quantify diffusion within areas of interest. The most commonly used measure is fractional anisotropy (FA), which provides an index of the directionality of diffusion (see Equation 1 and 3 for the formula to calculate FA) (Alexander et al., 2011). FA is sensitive to changes in changes in microstructural integrity of white matter pathways, but does not provide specific indication of the nature of this change.

$$MD = (\lambda_1 + \lambda_2 + \lambda_3)/3 \qquad (1)$$

$$FA = \sqrt{\frac{2}{3}\frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \qquad (2)$$

λ: eigenvalue
MD: mean diffusivity
FA: fractional anisotropy

Axial diffusivity is the value of the primary eigenvector, i.e. the magnitude of diffusion along the principal direction.

$$AD = \lambda_1 \quad (3)$$

λ: eigenvalue
AD: axial diffusivity

Radial diffusivity (RD) is the mean of the values of the secondary and tertiary eigenvector and therefore indicates the degree of diffusion in directions other than the main direction (see Equation 3). RD is sensitive to changes in myelination, axonal diameter, and membrane density (Alexander et al., 2011).

$$RD = \frac{\lambda_2 + \lambda_3}{2} \qquad (4)$$

λ: eigenvalue
RD: radial diffusivity

Eigenvector and FA maps were calculated from the diffusion-weighted images in MRTrix (Tournier et al., 2012). A spherical constrained deconvolution (CSD) model was fitted to the 60 gradient direction images using a maximum harmonic order of 8. Correct anatomical orientation of CSD glyphs was visually inspected for white matter tracts of known orientation (corpus callosum, cortico-spinal tract).

Different procedures to model the direction of diffusion are currently used in the literature. The most prevalent model has been the diffusion tensor model, which describes the direction of diffusion as a combination of the three eigenvectors. The principle component, i.e. primary eigenvector, determines the direction of dominant diffusion in a given voxel (Alexander et al., 2011). However, the assumption of a single dominant diffusion direction in each voxel is deemed unrealistic in the brain due to the crossing fibre pathways in many brain regions (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Tournier et al., 2012). Therefore, newer diffusion models that are capable of modelling several diffusion directions in each voxel have gained in use over recent years (Dell'Acqua & Catani, 2012; Johansen-Berg & Behrens, 2006). Multi-parametric models assume a discrete number of diffusion directions(e.g. ball-and-stick model) (Behrens et al., 2003), while other models like the constrained spherical deconvolution (CSD) model aim to determine the number of fibre per voxel from the data. For this purpose, a model for single fibre orientations is determined in areas of higher FA to then determine likely deformations in the presence of multiple fibre orientations (Tournier, Calamante, Gadian, & Connelly, 2004). One of the advantages of this method is that it provides high angular resolution that is achievable with standard protocols (Dell'Acqua & Catani, 2012).

## 7.2.5. Graph Theory measures for connectomics

A variety of graph measures have been derived to characterise network organisation. The following section will summarise common measures that were used for graph analysis of structural and functional connectome data (Please see Rubinov et al. 2010 for a more detailed technical review of graph theory).

### 7.2.5.1. Node degree

The node degree is the number of edges connected to a node (Sporns, 2002). The distribution of node degree provides an indication of the network organisation: Hierarchical networks are skewed towards a small number of hub regions with a high node degree and a large number of nodes with a low node degree (Bullmore & Sporns, 2009; Van den Heuvel, Stam, Boersma, & Hulshoff, 2008).

$$k_i = \sum_{j \in N} w_{i,j}$$

N: all Nodes
i,j:Nodes
w: connection weight

### 7.2.5.2. Characteristic path length

The characteristic path length is the average shortest distance between any two nodes in the network (Sporns, 2002). The shortest path length is related to ease of information transfer. A network with a short characteristic path length will be able to transfer information more quickly. However, short path length is traded off with wiring cost in real-world networks (Bullmore & Sporns, 2012).

$$L^w = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^w}{n-1}$$ (1) Characteristic path length

$$E^w = \frac{1}{2}\sum_{i \in N} \frac{\sum_{j \in N, j \neq i} (d_{ij}^w)^{-1}}{n-1}$$ (2) Global efficiency

N: Nodes
i,j: Node
w: connection weight

#### 7.2.5.3. Clustering coefficient

The local clustering coefficient characterises the degree to which neighbouring nodes are connected within clusters (Bernhardt, Chen, He, Evans, & Bernasconi, 2011; Watts & Strogatz, 1998). Real-world networks show a high degree of local clustering (Watts & Strogatz, 1998), which is thought to be related to modularisation within networks. See (Onnela, Saramaki, Kertész, & Kaski, 2005) for details about the algorithm.

$$c = \frac{1}{n}\sum_{i \in N} \frac{2t_i^w}{k_i(k_i - 1)}$$

N: all Nodes
i: Node
k: Node degree
w: connection weight

#### 7.2.5.4. Density

The density of a graph the number of all connections divided by the number of all possible connections (Rubinov & Sporns, 2010). Density may be used as a proxy for network cost for energy or resources (Bullmore & Sporns, 2012).

#### 7.2.5.5. Betweenness Centrality

Betweenness centrality indicates the importance of a node for the information transfer across the whole network (Bullmore & Sporns, 2009). It is calculated as the number of shortest paths from all nodes to all other nodes that pass through a node. In the present study, the maximum betweenness centrality is used to compare the importance of the most important node between participants.

$$b_i = \frac{1}{(n-1)(n-2)} \sum_{h,j \in N, h \neq j, h \neq i, i \neq j} \frac{\rho_{hj}(i)}{\rho_{hj}}$$

h,j: Node

$\rho_{hj}$: number of shortest paths between h and j

$P_{hj}(i)$: number of shortest paths between h and j that pass through i

### 7.2.5.6. Rich club coefficient

The rich club coefficient has received increased attention in the analysis of brain networks in recent years. The measure is based on the observation that a small number of highly interconnected high-degree nodes play a crucial role in brain network organisation (van den Heuvel & Sporns, 2011). Modelling approaches found that disruptions within the rich club have a disproportionate impact on overall network organisation and efficiency (Crossley et al., 2014). Further, disruptions of rich club regions were consistently identified in meta-analysis of network studies of neurological and neurodevelopmental disorders (Tymofiyeva et al., 2014).

$$\phi(k) = \frac{2E_{>k}}{N_{>k}(N_{>k}-1)}$$

N: Node

E: Observed nodes

k: degree

## 7.3. Analysis of cortical thickness and surface area

### 7.3.1. Introduction

Cortical thickness indicates the length of grey matter between the cortex surface and the subcortical white matter (Fischl & Dale, 2000). Cortical thickness measures have been used extensively to characterise morphological changes in development and in various neurodevelopmental disorders (Sowell et al., 2004; Toga, Thompson, & Sowell, 2006). Further, it has been found that adults with congenital or early blindness show increased cortical thickness in primary and secondary visual cortex, but that adults with late onset blindness do not show the same effect (Jiang et al., 2009; Park et al., 2009). Different interpretations of this effect are present in the literature: some authors support the view that increased thickness of cortical areas represents a reduction in activity-dependent maturation, e.g. through synaptic pruning, dendritic reorganisation, neuronal apoptosis etc. (Jiang et al., 2009; Noppeney, 2007). An alternative account suggests that increased thickness is indicative of adaptive changes based on findings that activation of the occipital cortex has been linked to better performance in word generation (Burton et al., 2002), episodic memory retrieval (Raz et al., 2005), tactile discrimination (Sadato et al., 1996), and sound localisation (Gougoux et al., 2005; Voss & Zatorre, 2012; Weeks et al., 2000).

Currently no data is available on cortical thickness changes in congenitally blind children. Therefore, the present investigation aimed to replicate findings reported in adult samples. Based on the early maturation of primary visual areas (Sowell et al., 2004), we expected to find similar increases in pericalcarine thickness in school-age children. A further question concerned the influence of varying degrees of visual impairment. Due to the limited characterisation of visual function in the available adult literature, the influence of residual visual function is unclear. It is conceivable that a limited amount of vision, e.g. limited form vision, is sufficient to drive activity-dependent maturational mechanisms that lead to thickness reductions in the pericalcarine cortex as observed in typically-sighted individuals. Further, relationships between cortical thickness and working memory, short-term memory, and verbal fluency were investigated in the VI group based on published reports of percalcarineinvolvement in these functions in adults with congenitaly VI (see Chapter 1 for a detailed discussion).

### 7.3.2. Materials & Methods

Cortical thickness analysis was based on T1-weighted MRI volumes using Freesurfer software (please see General Introduction for details about MR sequences).

## 7.3.3. Results

Statistical comparison of overall thickness in the left and right hemisphere indicated significantly lower cortical thickness in the VI compared to the control group (rmANOVA: VI: mean=2.52, SE=0.03, Range=2.14- 2.76; control: mean=2.67, SE=0.02, Range=2.48-2.8; [all values in centimetres], F(1,16)=5.819, p=0.0282). Within participant groups, cortical thickness was higher in the right compared to the left hemisphere (Left: mean=2.57, SE=0.03, Range=2.14-2.75; Right: mean=2.61, SE=0.03, Range=2.19-2.8, F(1,19)=28.71, p<0.001), but did not interact with participant group.

Analysis of cortical thickness of the pericalcarine cortex in the left and right hemisphere indicated a significant participant age by participant group interaction. Follow-up correlation analysis identified a significant negative correlation between pericalcarine thickness and age in the left hemisphere in the VI group (r(11)=-0.65, p=0.032). Trend-level positive correlations were found in the control group in both hemispheres (Right: r(9)=0.64, p=0.0609; Left: r(9)=0.6, p=0.0886). In order to account for influences of overall changes in cortical thickness with age, mean cortical thickness across both hemisphere was included as a nuisance regressor in the ANCOVA model. Mean cortical thickness emerged as a significant factor for pericalcarine thickness (F(1,13)=9.828, p=0.0079). However, interactions with participant age or participant group did not reach significance.

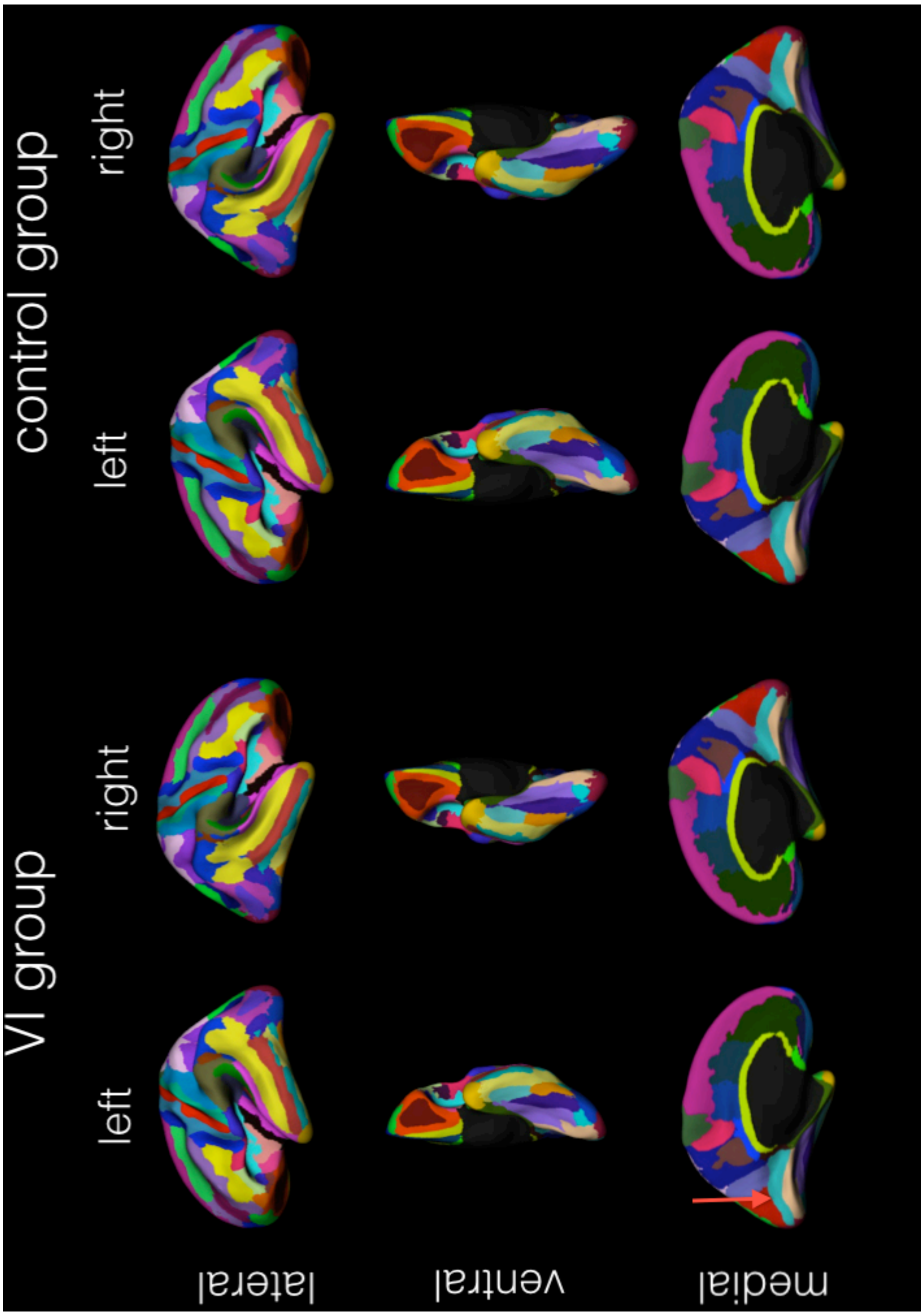


**Figure 36: Group average results of the surface reconstruction and cortical parcellation.** The pericalcarine cortex is shown in light blue in the medial view (indicated by the red arrow).

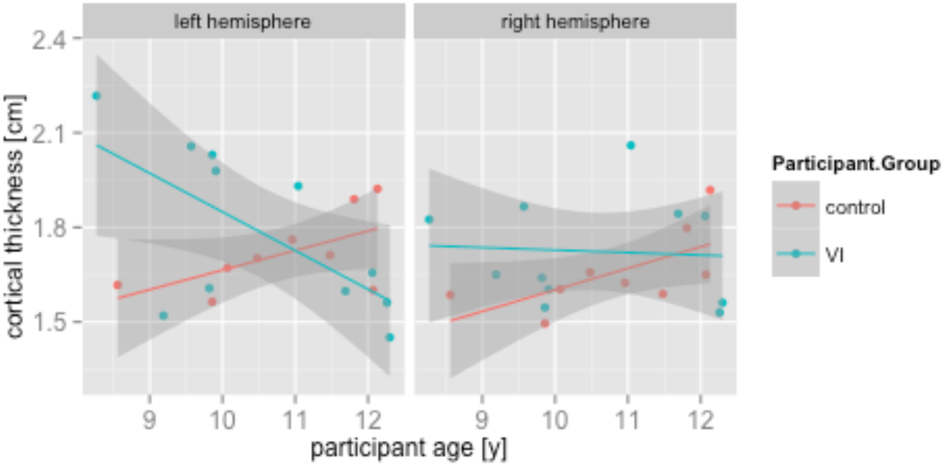


**Figure 37: Relationship between pericalcarine thickness in the left and right hemisphere and participant age in the VI (blue) and control group (red).** The thickness of the pericalcarine cortex negatively correlated with participant age in the left hemisphere in the VI group. There was a positive correlation between participant age and thickness in the control group for both hemispheres.

## 7.3.4. Discussion

Based on previous investigations that reported increased cortical thickness in primary and secondary visual cortex in congenitally blind adults (Jiang et al., 2009; Park et al., 2009), the present study aimed to investigate cortical thickness of the pericalcarine cortex in children with congenital visual impairment of varying degrees. The results show an unexpected decrease in mean cortical thickness across the whole brain surface. Cortical thickness follows different developmental patterns across the brain with general thinning of the cortex, but increases in left hemisphere language areas in mid-childhood (Sowell et al., 2004; 2007). The observed difference in mean cortical thickness may indicate differences in maturational patterns between the VI and typically-sighted control group due to different perceptual and cognitive demands. Further, difference in lateralisation for specific functions as observed in this and previous electrophysiological studies (Roder et al., 2000) may contribute to overall differences in cortical thickness. In order to investigate these possibilities in more detail, a comparison across the surface would be necessary. However, the current study does not have sufficient statistical power to detect difference with effect sizes as reported in previous developmental studies (Sowell et al., 2004). Studies comparing markers of cortical maturation between typical developing children and neurodevelopmental disorders, e.g. ADHD (Shaw et al., 2012) or autism (Zielinski et al., 2014), also report decreases in the 8 to 12 year age range. Consequently, decreased mean cortical thickness could also be interpreted as a non-specific marker of atypical brain development.

Based on reports in congenitally blind adults, an increase in thickness of the pericalcarine cortex was predicted (Jiang et al., 2009; Park et al., 2009). Indeed, a group effect with higher cortical thickness, particularly in the left hemisphere, was found in the VI group. However, this effect also interacted with participant age displaying a pattern of decreasing pericalcarine thickness with participant age. Given the small sample size and unequal sampling of different degree of visual impairment, no firm conclusions can be drawn from this finding. Further investigations with a larger sample of children with VI would be needed to investigate the relationship between visual acuity, participant age, and pericalcarine thickness.

## 7.4. Analysis of white matter

### 7.4.1. Comparison of key white matter tracts

#### 7.4.1.1. Introduction

Previous neuroimaging investigations of congenitally or early blind adults consistently reported differences in structural brain organisation in comparison to typically-sighted control groups (Breitenseher et al., 1998; Jiang et al., 2009; Leclerc, Saint-Amour, Lavoie, Lassonde, & Lepore, 2000; Liu et al., 2007; Noppeney et al., 2005; Pan et al., 2007; Ptito et al., 2008; Schoth & Krings, 2004; Shimony et al., 2006; Shu, Li, Li, Yu, & Jiang, 2009). Differences in white matter are of particular interest as these changes may indicate differences in the integration between different brain areas that may provide adaptive advantages (Fornito & Bullmore, 2014; Johansen-Berg & Behrens, 2006; Le Bihan, 2003). In order to investigate differences in white matter organisation in school-age children with VI, different methodological approaches were pursued:

First, key white matter tracts that are directly or indirectly involved in the transfer of visual information were assessed individually through diffusion tractography. These tracts included the optic radiations that transfer visual information from the thalamus to the primary visual cortex, the inferior longitudinal fasciculus that connects the visual areas of the occipital lobe with areas of the temporal lobe, the inferior fronto-occipital fasciculus that relays information between the frontal and occipital lobe, and the posterior part of the corpus callosum that is involved in the transfer of information between analogous areas of the visual cortex in the left and right hemisphere.

Second, a white matter connectome was constructed to compare white matter network organisation across the whole brain. Together with the application of graph theory, this approach allows a comparison of the efficiency of information transfer.

### 7.4.1.2. Optic radiations

#### 7.4.1.2.1. Introduction

The optic radiations, also called geniculo-calcarine tract, are a collections of fibres that project from the lateral geniculate nucleus (LGN) of the thalamus to the pericalcarine cortex. The optic radiations are relaying visual information that reached the LGN from the retina via the optic nerve to the primary visual cortex (pericalcarine cortex) (Prasad & Galetta, 2011). The optic radiations follow a characteristic trajectory with an anterior projection followed by a high angle posterior turn called Meyer's loop (Ebeling & Reulen, 1988). From there on, the OR extend along the lateral ventricle before terminating in the pericalcarine cortex.

The *in vivo* mapping of the OR with diffusion weighted imaging techniques have been of major interest to identify predictive factors of visual function and planning of surgical interventions (Benjamin et al., 2014). Changes in volume and diffusion parameters of the OR have been linked to visual function (Groppo et al., 2012; Kelly et al., 2014a; Thompson et al., 2014) and spatiotemporal VEP amplitude (Glass et al., 2010) in premature birth. Further, the percentage loss of OR fibres tracked before and after temporal lobe surgery was found to be predictive of vision loss (Borius et al., 2014). Similarly, anisotropy in the OR correlated with visual acuity in children with neurofibromatosis and was predictive of visual acuity one year later (de Blank, Berman, Liu, Roberts, & Fisher, 2013; Filippi et al., 2012).

The available literature about the integrity of the OR in individuals with congenital visual impairment is limited. A tractography study by Shimony in colleagues reported reduced anisotropy in the OR in early blind adults compared to typically-sighted control (Shimony et al., 2006). These findings are in line with whole-brain analyses that reported reduced FA in other early and late blind groups (Ptito et al., 2008; Schoth & Krings, 2004; Shu, Li, Li, Yu, & Jiang, 2009; Wang et al., 2013). Further, two cases of infants with septo-optic dysplasia presented by Salmela and colleagues also displayed reduced anisotropy in the OR suggesting that differences in diffusion parameters in the OR are detectable from early in life (Salmela, Cauley, Nickerson, Koski, & Filippi, 2010). Reductions in FA within the OR have also been reported for a sample of children with optic nerve hypoplasia and mild to moderate visual impairment using whole-brain white matter statistics (Webb et al., 2013)

The current study aimed to investigate the integrity of the optic radiation in children with congenital disorders of the peripheral visual system. It is thought that any changes in central parts of the visual system are secondary effects of 'simple' CDPVS. Further, a close association between diffusion parameters of the OR and measures of visual acuity were assumed based on findings in other patient groups (Glass et al., 2010; Groppo et al., 2012).

### 7.4.1.3.2. Materials & Methods

The optic radiations (OR) are known to pose significant challenges for diffusion tractography due to their curved progression (Benjamin et al., 2014). Previous studies in typically-sighted children had established that the optic radiations can be reconstructed with diffusion MRI methods (Dayan et al., 2013). Seed and inclusion regions were defined for fibre tracking to selectively reconstruct the OR. A spherical seed ROI with a 3 mm radius was defined in the white matter adjacent to the thalamus as described in Benjamin et al. 2014 (see Figure 38). A second ROI with a 6mm radius was placed in the white matter adjacent to the lateral ventricles a few slides dorsally from the seed ROI. Another inclusion ROI with 20mm radius was placed in the occipital lobe centred on the calcarine fissure. Exclusion ROIs were placed anteriorly on the level of the anterior tip of the brain stem in axial view, ventrally to exclude streamlines of the cortico-spinal tract, and along the midline to avoid fibres of the corpus callosum. In addition, a brain mask was used for exclusion.

Probabilistic tracking was performed based on a constrained spherical deconvolution (CSD) model in MRTrix (Tournier et al., 2012) with a target of 1000 streamlines. The step size for probabilistic tracking was set to 0.2mm, and the maximum curvature to 1mm. Minimum and maximum length were set to 10mm and 200mm respectively. Further, a termination FA value of 0.1 was used. Following probabilistic tracking, a visitation map of all voxels that contained at least 100 streamlines was calculated. The mean value of diffusion parameters was calculated from the FA, ADC, and RD images with the visitation map as an inclusion mask.

Statistical comparison was based on a repeated measures analysis of variance model. The relationship between diffusion parameters in the OR and visual acuity was assessed in a correlation model.

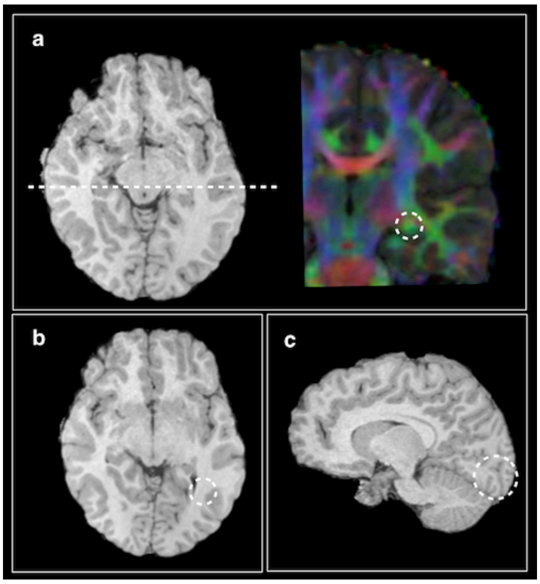


**Figure 38: Illustration of ROIs for probabilistic tracking of the optic radiations shown on a representative individual participant.** a) A spherical ROI was placed in the white matter proximal to the lateral thalamus (Benjamin et al., 2014) b) an additional ROI was placed in the white matter next to the lateral ventricles a few slides dorsal of the seed ROI c) a final inclusion ROI was placed in the occipital lobe including the calcarine fissure.

### 7.4.1.3.3. Results

Statistical comparison indicated a significant difference in fractional anisotropy (FA) between the VI and typically-sighted control group in the left and right optic radiations (OR) with smaller values in the VI group (VI: mean=0.44, SE=0.01, Range=0.37-0.5; control: mean=0.47, SE=0.01, Range=0.42-0.54; F(1,17)=5.049, p=0.037). There was also a significant difference for mean diffusivity (MD) with lower values in the VI group(VI: mean=0.63, SE=0.02; control: mean=0.56, SE=0.092 (all in [mm$^2$/ms]), F(1,18)=4.923,p=0.0404). Radial diffusivity (RD) was also significantly different with higher RD in the VI group (VI: mean=0.67, SE=0.02, Range=0.55-0.98;

control: mean=0.6, SE=0.02, Range=0.55-0.68 (all in [$mm^2/ms$]); F(1,17)=5.709, p=0.028).

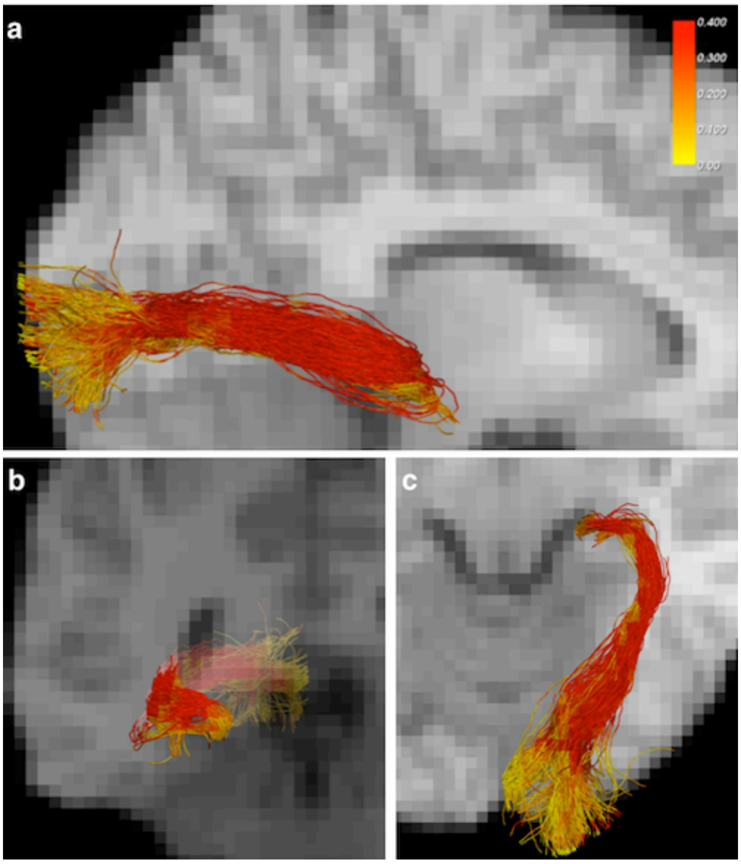


**Figure 39: Illustration of optic radiation tractography.** The streamline reconstruction is presented from different perspectives to illustrated the progression of the optic radiations as they ascend from the thalamus and curve around the lateral ventricles (a: sagittal view, b: coronal view on the level of the lateral ventricle c: axial view). The colour map shows the FA values in each voxel along the optic radiations.

Subsequently, the relationship between diffusion parameters in the optic radiations and visual acuity was investigated. Fractional anisotropy in the OR showed the expected pattern of decreasing FA with decreasing vision (see Figure 40). Comparison was based on grouping of participants according to vision level. Children that could not be assessed on the Sonksen LogMAR test of visual acuity, but had functional vision on the Near Detection Scale were classed as "highly severe VI" - two participants with unilateral involvement are discussed separately below. Statistical analysis indicated a trend-level difference in OR FA between vision groups (rmANOVA: control: mean=0.47, SE=0.01, Range=0.42-0.54; mild/moderate: mean=0.48, SE=0.01, Range=0.47-0.5; severe: mean=0.44, SE=0.01, Range=0.42-0.46; highly severe: mean=0.43, SE=0.01, Range=0.42-0.46, F(3,13)=2.58, p=0.098). Follow-up analysis indicated significant differences between the typically-sighted and highly severe group (all Welch-corrected independent sample two-sided t-tests: t(10.712)=0.0053) and the typically-sighted and severe group (t(16.337)=2.663, p=0.0168). There was no significant difference between the typically-sighted and the mild/moderate VI group ((t(0.8806)=18.726, p=0.3897)). There were significant differences between the mild/moderate group and the highly severe VI group (Welch-corrected t-test: t(6.778)=4.73, p=0.0023, Bonferroni-corrected p=0.092) and the mild/moderate and severe group (t(9.795)=3.83, p=0.0034, Bonferroni corrected p=0.014). There was no significant difference between the severe and highly severe group (t(7.435)=0.869, p=0.412, Bonferroni-corrected p=1).

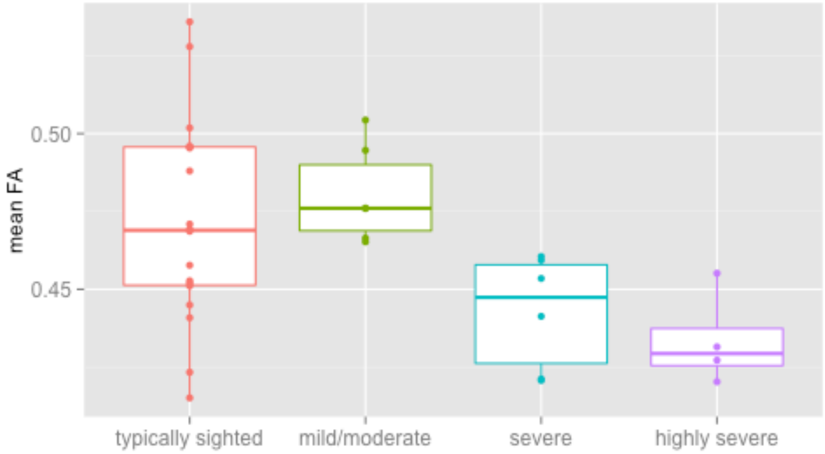


**Figure 40: Fractional anisotropy in the optic radiations in the mild/moderate, severe, and highly severe VI group.** Statistical analysis indicated significant differences between the typically-sighted control group and the severe and highly severe groups as well as significant differences between mild/moderate and the severe and highly severe groups. There was no significant difference between mild/moderate and the control group or the severe and highly severe group.

Next, the relationship between FA in the optic radiations and visual acuity were analysed in a correlation model. Only children that were assessed with the Sonksen logMAR scale (Salt et al., 2007) were included in this analysis, i.e. children in the mild/moderate to severe VI group (n=8). Correlation analysis indicated a negative correlation between FA in the left and right optic radiations and visual acuity that did not reach significance level (left: r=-0.36, p=0.38; right: r=-0.45, p=0.26) (see Figure 41)

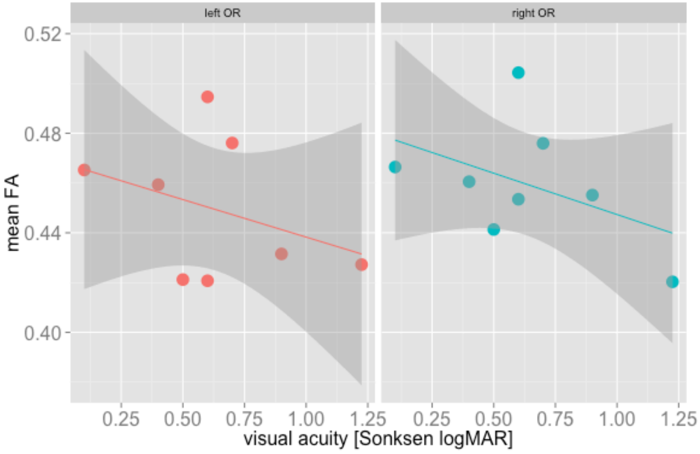


**Figure 41: Correlation between visual acuity and FA within the left and right optic radiation in children with mild/moderate to severe VI.** Correlation analysis indicated negative correlations between visual acuity and FA, i.e. lower FA with decreasing visual acuity, but did not reach significance level.

### 7.4.1.3.3.1. Cases with unilateral involvement

Two participants in the VI group had conditions with unilateral involvement. Participant 1 was a 9.86-year-old girl with micro-ophthalmia that most severely affected the left eye. The eye was surgically removed. The right eye had residual visual function that had degraded in the year previous to study participation. On the day of the assessment, the participant could reliably detect a non-light reflecting, spinning wooly ball at a distance of 50cm (Near Detection Scale). Fractional anisotropy of the optic radiations displayed a large discrepancy between the left and right hemisphere with lower values on the side contralateral to the removed eye (left FA: 0.445, right FA: 0.369).

Participant 2 was a 12.26-year-old girl with a diagnosis of unilateral optic nerve hypoplasia. The participant reached a Sonksen LogMar score of 0.23 with the left eye and had only light perception with the right eye. A discrepancy was also detected in the

FA of the optic radiations with a lower FA value in the optic radiations contralateral to the more severely affected eye (right: 0.367, left:0.436).

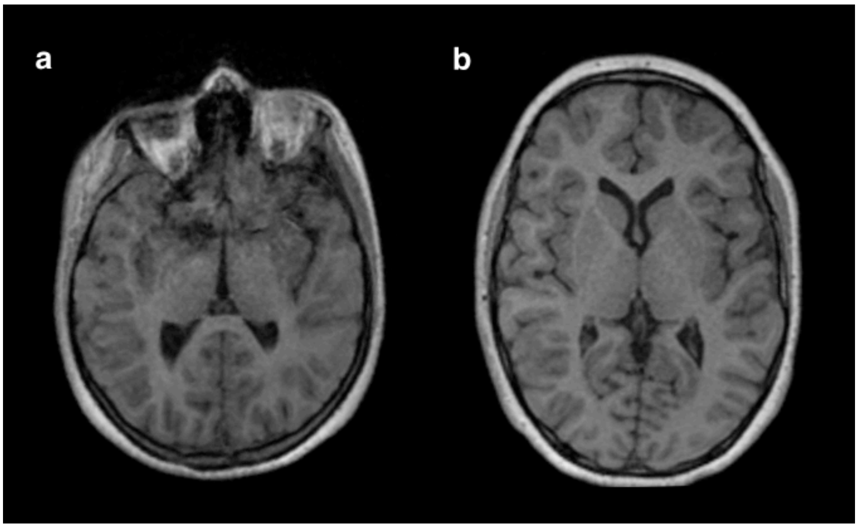


**Figure 42: T1-weighted scans of cases with unilateral involvement of the peripheral visual system.** a) 9 year-old girl with micro-ophthalmia, who had the left eye surgically removed b) 12 year -old girl with optic nerve hypoplasia on the right side. Axial images are shown on the level of the lateral ventricle to show the progression of the optic radiations along the ventricle.

A recent study by Neveu and colleagues reported comparisons of VEP amplitudes in typically-sighted children, children with Albinism, or unilateral anopthalmia (Neveu & Jeffery, 2007; Neveu et al., 2006). Typically-sighted children displayed equal VEP size and timing in both hemispheres for monocular presentation of stimuli to either eye, which reflects typical decussation of fibres in the optic chiasm. The Albinism group on the other hand, displayed much smaller amplitudes and latency differences between the left hemisphere with shorter latency and higher amplitude in the hemisphere contralateral to the stimulated eye. The authors interpreted this result to reflect atypical presentation that had been documented in individuals with Albinism before. Children with monocular micro-ophthalmia displayed the same symmetry response pattern as typically-sighted children indicating that visual input is not required for typical decussation of fibres. However, an MRI study of the effects of early enucleation (retinoblastoma that lead to surgical removal before the age of 5 years) reported a contralateral bias for optic tract volume (Kelly, McKetton, Schneider, Gallie, & Steeves, 2014b) similar to the effect observed in the two cases presented here. Consequently, monocular deprivation appears to be associated with changes in the anatomical lateralisation of the optic radiations that are not apparent from VEP measures.

### 7.4.1.4. Corpus callosum

### 7.4.1.4.1. Introduction

The corpus callosum (CC) is the largest white matter structure in the human brain connecting homologous areas in both hemispheres. For visual processing, the posterior part of the corpus callosum, the splenium, plays a critical role in combining the separate representations of the visual hemifields between the two hemispheres (Berlucchi, 2014; Pietrasanta, Restani, & Caleo, 2012). Psychophysics experiments with paradigms utilising separate presentation of stimuli to both eyes indicate that integration of visual information, most likely via the CC, not only plays a role in perceptual processing, but also in imagery processing (Savazzi, Mancini, & Marzi, 2008). Further, thickness of the splenium has been linked to procedural cognitive ability (Fine, Musielak, & Semrud-Clikeman, 2014; Navas-Sánchez et al., 2014).

Work in animal models suggest that the development of the posterior corpus callosum is strongly activity dependent (Innocenti, Clarke, & Kraftsik, 1986; Mizuno, Hirano, & Tagawa, 2007; Pietrasanta et al., 2012). Unsurprisingly, studies of congenitally blind or early blind groups also report a reduction in volume and anisotropy of the CC, particularly of the isthmus and splenium (Leporé et al., 2010; Ptito et al., 2008; Schoth et al., 2006; Shimony et al., 2006). Leporé and colleagues found reductions in anisotropy of the splenium of the cc only in an early blind but not in a late blind group suggesting that early visual experience is critical for the development of the posterior cc. However, a study by Bock et al. did not confirm this finding in a sample of participants with anophthalmia or early blindness (Bock et al., 2013). Currently, little is known about the influence of varying degrees of visual impairment on corpus callosum maturation. A study about the visual development of children born prematurely found a strong correlation between thickness of the splenium and visual acuity, but effects of CNS damage associated with premature birth cannot be distinguished from effects of low vision in this group (Lindqvist et al., 2011). The current study aimed to assess associations between visual function and diffusion parameters in segments of the corpus callosum in children with 'simple' CDPVS with varying degrees of visual impairment. Based on the existing literature, greater reduction in the anisotropy of the splenium of the cc was expected in children with higher degrees of visual impairment. Further, a correlation between visuospatial abilities and the splenium measures were hypothesised.

In addition, the role of corpus callosum integrity on functional coupling between the left and right hemisphere was investigated based on resting-state EEG measures. Given the central role of the cc in the communication between hemispheres, a reduction in the micro-structural integrity of the cc is likely to influence functional relationships between hemispheres. Indeed, a study by Pogarell and colleagues found a reduction in interhemispheric coherence in patients with Alzheimer's diseases that displayed degeneration of the cc (Pogarell et al., 2005). This effect was most pronounced in the posterior region of the cc (Pinkofsky, Struve, & Meyer, 1997; Pogarell et al., 2005). Based on these reports, an association between FA in the cc and interhemispheric, but not intrahemispheric source correlation was expected.

### 7.4.1.4.2. Materials & Methods

The corpus callosum (CC) was identified on mid-saggital sections and segmented according to the segmentation scheme suggested by Hofer and colleagues (Hofer & Frahm, 2006). The segmentation is based on the target regions of white matter projections from the CC. The anterior third contains projections to the prefrontal cortex, the anterior midbody contains projections to the premotor and supplementary motor regions, projections to motor regions are found in the posterior midbody, the isthmus contains projections to and from sensory areas, and the splenium contains projections between parietal, temporal and occipital areas (see Figure 43).

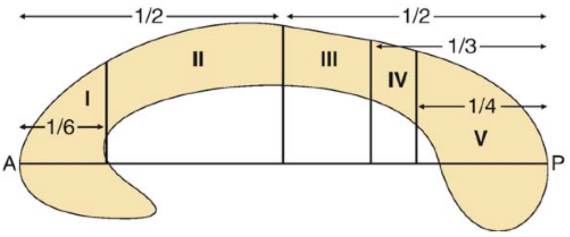


**Figure 43: Segmentation of the corpus callosum** reproduced from Hofer et al. 2006. I: Anterior Third, II: Anterior Midbody, III: Posterior Midbody, IV: Isthmus, V:Splenium

Statistical comparison was based on a repeated measures ANOVA model. The influence of vision level on anisotropy within the CC was investigated using an analysis of covariance model controlling for difference in mean FA. The impact of differences in diffusivity within the CC on functional brain organisation was assessed through analysis of correlations strength between EEG source time series. The relationship between FA in the CC and mean correlation was compared between intrahemispheric and interhemispheric cortical regions of interest. In addition, the relationship between CC anisotropy in the splenium and correlation between source time series in the left and right hemisphere was evaluated.

### 7.4.1.4.3. Results

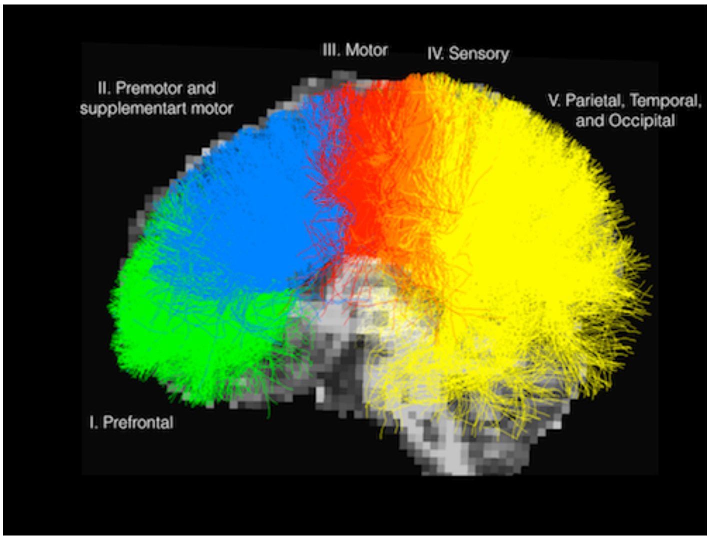


**Figure 44: Visualisation of representative tractography results of corpus callosum segments.** The Hofer et al. 2006 parcellation scheme was applied.

Statistical analysis indicated a significant effect of participant group and an interaction between participant group and CC region (Interaction: F(4,72)=3.998, p=0.006, see Table 18 for descriptives). Post-hoc analysis indicated significantly higher FA values in the anterior and posterior mid-body in the VI group (anterior mid body: t(11.993)=-4.3951, p=0.0009 posterior mid body: t(11.315)=-3.2034, p=0.0081, p=0.04). There were smaller FA values in the splenium in the VI group that did not reach significance criteria. There was no significant difference between the mild/moderate and the severe group.

**Table 18 Results of corpus callosum tractography**

| | VI | | | | control | | | | group comparison | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | **mean** | **SE** | **Range** | | **mean** | **SE** | **Range** | | **t** | **p** |
| Anterior Segment | 0.372 | 0.012 | 0.306 | 0.432 | 0.377 | 0.008 | 0.345 | 0.412 | -0.29 | 0.775 |
| Anterior Midbody | 0.373 | 0.012 | 0.358 | 0.431 | 0.364 | 0.005 | 0.341 | 0.388 | -4.40 | 0.001 |
| Posterior Midbody | 0.379 | 0.014 | 0.342 | 0.468 | 0.360 | 0.006 | 0.310 | 0.390 | -3.20 | 0.008 |
| Isthmus | 0.381 | 0.012 | 0.325 | 0.453 | 0.363 | 0.008 | 0.328 | 0.397 | 1.25 | 0.227 |
| Splenium | 0.412 | 0.010 | 0.374 | 0.460 | 0.430 | 0.011 | 0.413 | 0.443 | -1.41 | 0.182 |

Subsequently, the influence of anisotropy within the CC on functional brain organisation was investigated. The correlation between FA within the CC and mean linear coupling of EEG time series within and between hemispheres were analysed controlling for differences in mean FA. Both within and between hemisphere connection strength correlated significantly with anisotropy in the CC, but with a larger effect size for interhemispheric connections (Interhemispheric: r=0.47, p=0.0012; Hemispheric: r=0.44, p=0.0031). When controlling for mean connection strength (hemispheric & interhemispheric) as well as mean FA, the correlation between interhemispheric connection strength and FA in the CC increased (r=0.61, p<0.0001).

### 7.4.1.5. Inferior longitudinal fasciculus

### 7.4.1.5.1. Introduction

The inferior longitudinal fasciculus (ILF) connects the occipital and temporal lobe (Catani, Jones, Donato, & Ffytche, 2003). The ILF originates in visual association areas of the occipital cortex and projects from there to lateral and anterior regions of the temporal lobe (Ashtari, 2012). Parts of the ILF overlap with the optic radiations and the inferior fronto-occipital fasciculus in the occipital lobe (Catani et al., 2003). The ILF is thought to play a major role in the fast transfer of visual information from visual areas of the occipital cortex to structures related to stimulus evaluation in the limbic system (amygdala) and structures related to memory storage and retrieval (extended hippocampal system) (Ashtari, 2012; Catani et al., 2003). Consistent with this model, differences in ILF integrity have been linked to deficits in object and face processing, visual memory, and emotional responses to visual stimuli in patients (Girkin & Miller, 2001). Further, differences in diffusion parameters of the ILF have been found in a number of neurodevelopmental disorders, incl. dyslexia, schizophrenia, and autism

(Koldewyn et al., 2014; Vandermosten, Boets, Wouters, & Ghesquière, 2012). Developmental studies have linked increases in ILF volume and anisotropy to increased functional activation of the fusiform face area (Suzanne Scherf, Thomas, Doyle, & Behrmann, 2013) and better object recognition in children with visual perceptual impairment (Ortibus et al., 2012).

A study by Shu and colleagues also reports reduced anisotropy in the ILF in early blind adults (Shu, Li, Li, Yu, & Jiang, 2009). Similar reductions in FA were also found in a group of congenitally blind adults using voxel-based morphometry (Ptito et al., 2008). There is currently no literature on the influence of different degrees of visual impairment on the microstructural integrity of the ILF. Based on established reductions of visual cortex volume and optic radiations in visual impairment (see General Introduction for a review of findings), vision level dependent reductions in ILF anisotropy were expected. Further, reduced anisotropy in the right ILF has been consistently associated with ASD in sighted children (Koldewyn et al., 2014). Based on the high prevalence of communicative features akin to autistic traits in children with VI (Brown et al., 1997; Hobson et al., 1999; Hobson & Bishop, 2003; Parr et al., 2010; Tadić et al., 2010), the relationship between communication profiles and measures of right ILF integrity were also investigated.

### 7.4.1.5.2. Materials & Methods

The inferior longitudinal fasciculus was reconstructed from whole brain tractography using a two ROI approach (Catani & Thiebaut de Schotten, 2008). An occipital ROI was identified on a slice posterior to the occipito-parietal sulcus for the left and right hemisphere. Another ROI was identified on the temporal lobe on a slice on which the temporal was no longer directly attached to the frontal lobe (Catani et al., 2003) (see Figure 45). The structure of the ILF was checked against atlas reconstructions (Mori, Wakana, Van Zijl, & Nagae-Poetscher, 2005). Streamlines that were likely to belong to other white matter structure (posterior corpus callosum, inferior fronto-occipital fasciculus) were manually excluded.

Statistical analysis was based on an analysis of covariance (ANCOVA) model with participant group and mean FA in the white matter skeleton as covariates. Participants with highly severe VI and typically-sighted control participants were compared using a Welch t-test. Correlation between FA in the ILF and vision level was analysed for participants with Sonksen LogMAR scores in a partial Pearson correlation model with mean FA in the WM skeleton as a covariate.

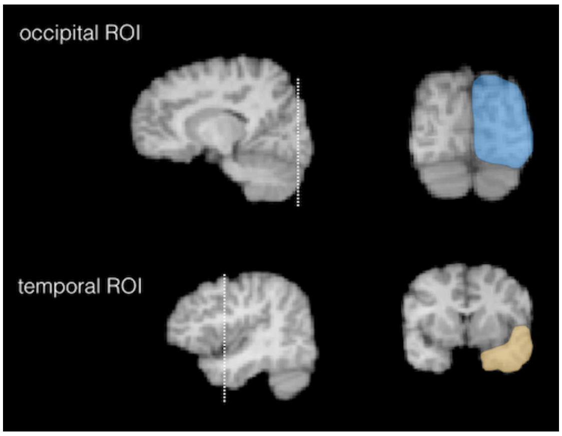


**Figure 45: ROIs used for tractography of the Inferior Longitudinal Fasciculus.** A two ROI approach was used with an occipital ROI on a slice posterior to the occipito-parietal sulcus and a temporal ROI (Catani & Thiebaut de Schotten, 2008).

### 7.4.1.5.3. Results

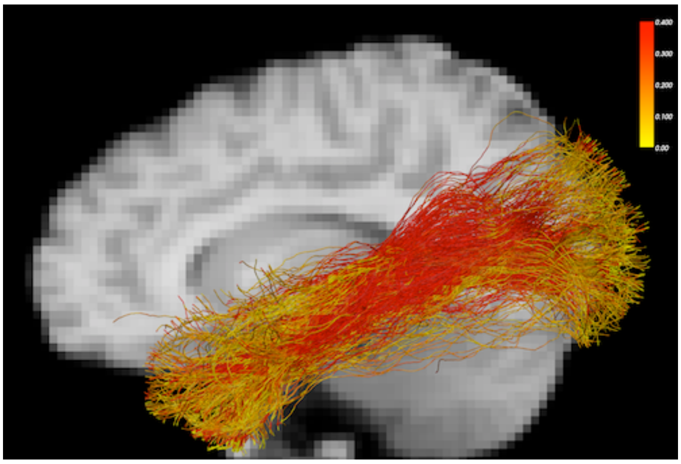


**Figure 46: Result of left inferior longitudinal fasciculus (ILF) tractography in a representative participant.** The colour bar indicates fractional anisotropy values of voxels within the tract.

The Inferior Longitudinal Fasciculus (ILF) reconstructions were consistent with previous reports using similar methods (Catani & Thiebaut de Schotten, 2008; Shu, Li, Li, Yu, & Jiang, 2009) and atlas descriptions (Mori et al., 2005) (see Figure 46 for a representative result). Statistical analysis indicated no significant difference between the groups for either left or right ILF (Left: VI: mean=0.33, SE=0.01, Range=0.3-0.37; control: mean=0.33, SE=0.01, Range=0.3-0.36; F(1,17)=0.002, p=0.97; Right: VI:

mean=0.34, SE=0.01, Range=0.29-0.38; control: mean=0.33, SE=0.01, Range=0.3-0.34; F(1,17)=2.084, p=0.17).

There was also no significant difference in FA in the left and right ILF between participants with highly severe VI (n=2) and the control group (highly severe: left: 0.3, 0.34; right: 0.29, 0.35; control: see previous descriptives; left: t(1.294)=-0.3123, p=0.79; right: t(1.287)=0.52, p=0.68). Bivariate correlations did not indicate a significant influence of vision level on FA in the ILF in children with mild/moderate to severe VI (n=8, left: r=0.24, p=0.57, right: r=0.43, p=0.29).

Based on previous reports about the role of the ILF in behavioural regulation and communication (Ashtari, 2012; Catani et al., 2003; Koldewyn et al., 2014), correlations between FA in the left and right ILF with the Global Communication Composite of the Children's Communication Checklist (CCC-2) (Bishop, 2003) and the Behavioural Regulation Index (BRI) of the Behavioural Rating Inventory of Executive Function (BRIEF) were investigated. Correlation analysis indicated no significant linear relationship between FA in the left or right ILF and BRI scores (n=10, left: r=-0.37, p=0.29; right: r=-0.39, p=0.27). There was a trend-level significant correlation between FA in the left ILF and GCC scores (n=9, r=0.56, p=0.091), but no significant effect for the right ILF (r=0.097, p=0.81).

### 7.4.1.6. Inferior fronto-occipital fasciculus

#### 7.4.1.6.1. Introduction

The inferior fronto-occipital fasciculus (iFOF) is a long association fibre tract that connects the ventro-medial occipital cortex with the orbito-polar frontal cortex (Caverzasi, Papinutto, Amirbekian, Berger, & Henry, 2014; Forkel et al., 2014). It originates from the occipital lobe and projects ventrally into the stem of the temporal lobe before curving dorsally to enter the frontal lobe terminating in the medial orbito-frontal cortex (Forkel et al., 2014). The function of the iFOF is not well understood, probably due to controversies about the anatomical structure of the iFOF (Forkel et al., 2014; Schmahmann & Pandya, 2007). However, alterations in iFOF diffusion parameters have been implicated in the transfer of information for stimulus evaluation in the OFC (Liao et al., 2013), semantic processing (Almairac, Herbet, Moritz-Gasser, de Champfleur, & Duffau, 2014) and visuospatial processing (McGrath et al., 2013).

Previous studies reported changes in the integration of typically visual areas of the occipital lobe in early blind adults (Klinge et al., 2010). Further, Shu and colleagues found a reduction in the iFOF that correlated with the connections strength between occipital and inferior frontal areas in early blind adults (Shu, Liu, Li, Li, Yu, & Jiang, 2009). Based on these findings, reductions in microstructural integrity of the iFOF were expected in the current investigation.

### 7.4.1.6.2. Materials & Methods

The inferior fronto-occipital fasciculus (iFOF) was delineated using a two ROI approach (Forkel et al., 2014). The occipital ROI was defined on a coronal slice posterior to the parieto-occipital sulcus. The frontal ROI was defined on a coronal slice at the anterior end of the lateral ventricles and included the ventral part of the slice (see Figure 47). Streamlines from other tracts, e.g. superior fronto-occipital fasciculus, were manually removed.

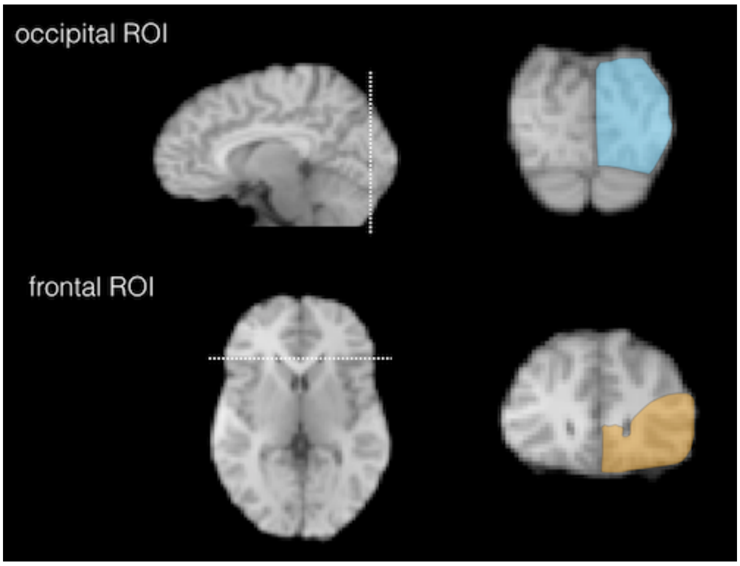


**Figure 47: Delineation of ROIs for tractography of the inferior longitudinal fasciculus.** Two ROIs were defined in the occipital and frontal lobe following Forkel et al. 2014.

### 7.4.1.6.3. Results

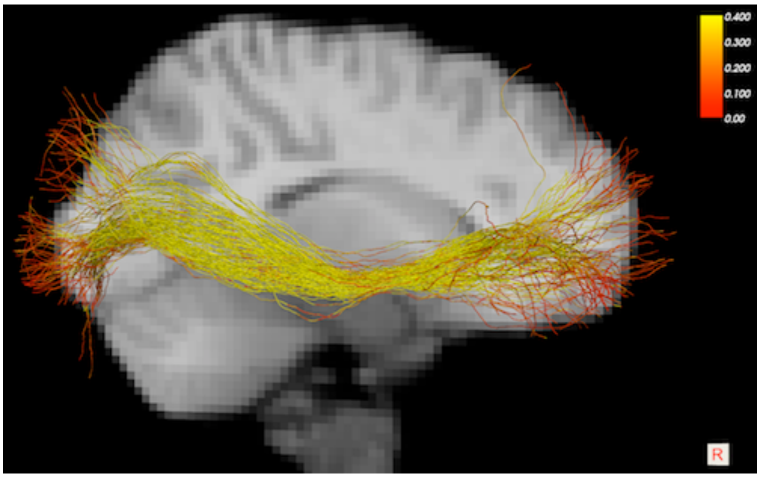


**Figure 48: Representative tractography result of the right inferior fronto-occipital fasciculus of a participant in the control group.** The iFOF reconstruction is in line with reports in the literature (Caverzasi et al., 2014; Forkel et al., 2014). The colour map indicates FA values along the tract.

The inferior fronto-occipital fasciculus (iFOF) could be reconstructed using methods described in the literature in all participants (see Figure 48 for a representative example). There was no difference in fractional anisotropy (FA) between the groups in either the left or the right iFOF (Left: VI: mean=0.36, SE=0.01, Range=0.32-0.39; control: mean=0.36, SE=0.01, Range=0.33-0.4; t(15.667)=-0.4598, p=0.652; Right: VI: mean=0.36, SE=0.01, Range=0.34-0.41; control: mean=0.37, SE=0.01, Range=0.3 0.4, t(15.324)=-0.763, p=0.457).

Secondary analysis focussed on the influence of vision level on diffusivity measures in the iFOF. There was no significant difference between the control group and participants with highly severe visual impairment (n=2) (Left: mean=0.34, SE=0.02, Range=0.32-0.38, t(3.044)=-1.021, p=0.426; Right: highly severe: mean=0.35, SE=0.03, Range=0.3-0.38; t(2.445)=-0.798, p=0.259). Correlation analysis of the relationship between vision level and FA in left and right iFOF in participants with mild/moderate to severe VI indicated strong, but non-significant positive correlations in the left and right iFOF (n=8, Left: r=0.55, p=0.2547; Right: r=0.8, p=0.056) (see Figure 49).

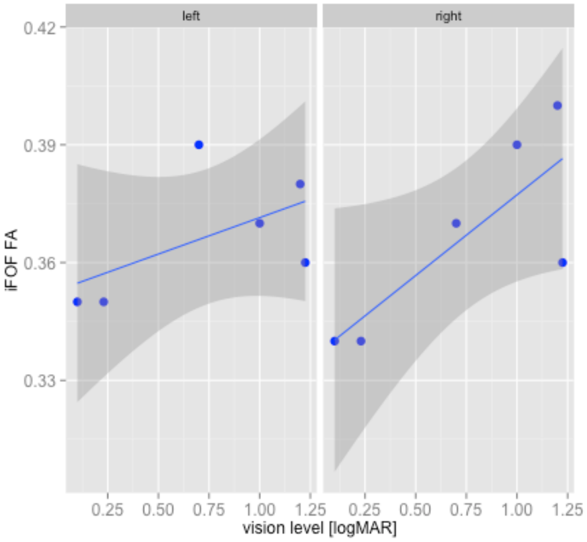


**Figure 49: Correlation between vision level measured in Sonksen LogMAR and fractional anisotropy (FA) in the left and right inferior fronto-occipital fasciculus (iFOF).** Strong, but non-significant correlations between the FA and vision level were found.

Based on previous reports about the role of the iFOF in visuospatial processing (McGrath et al., 2013), the influence of diffusion within the iFOF on scores on a spatial memory tests was investigated (Intelligence Scale for Visually Impaired Children House Plan - see General Ability chapter). Correlation analysis indicated no significant linear relationship between the factors (n=9, left: r=-0.18, p=0.65, right: r=0.36, p=0.34).

### 7.4.1.7. Discussion

Following reports about white matter reorganisation in early blind or congenitally blind adults, the current study aimed to assess white matter integrity in key white matter areas that are involved in the transfer of visual information in school-age children with congenital disorders of the peripheral visual system and varying degrees of visual impairment.

First, the integrity of the optic radiations that relay information from the thalamus to the primary visual cortex was investigated. Previous reports found reductions in diffusion parameters within the optic radiations (OR) in congenitally blind adults (Bauer et al., 2014; Shimony et al., 2006; Wang et al., 2013a) as well as associations between visual acuity and diffusion parameters in disorders with comorbid visual impairment

(Glass et al., 2010; Groppo et al., 2012; Kolbe et al., 2012) or specific VI disorders (Barcella et al., 2010; Milesi et al., 2012). The present study aimed to assess diffusion parameters in the OR in school-age children with congenital disorders of the peripheral visual system and varying degree of visual impairment with mixed aetiology. As expected, a reduction of fractional anisotropy and an increase in radial diffusivity was found in the VI group compared to typically-sighted controls. Further, a relationship between the degree of visual impairment and the reduction of fractional anisotropy (FA) was found. However, the present data was more consistent with a step function rather than a linear relationship: participants with mild to moderate visual impairment (visual acuity: 0.1-0.7 LogMAR) were statistically not distinguishable from the control group. Further, there was no indication of a difference in FA between participants with residual vision (severe VI) and those with only light perception (profound VI). Previous studies in children born preterm had indicated a linear relationship between diffusion parameters of the OR and visual acuity (Thompson et al., 2014) and VEP amplitude (Glass et al., 2010), although within a narrow range of visual acuity. Further, there are limitations in the current study. First, very low visual acuities had to be measured on a different scale (Near Detection Scale). Therefore, visual acuity and FA in the OR could not be assessed in a regression model as in previous studies of samples with higher visual acuities. Instead, the statistical model had to rely on a comparison between vision groups, even though the underlying variable of visual acuity is likely to be continuously distributed. Further, the present study has low statistical power, particularly to distinguish differences between children with very high degrees of visual impairment. This limitation is in part due to the rarity of cases with very high degree of visual impairment. In summary, the present study found reductions in FA in the OR in children with severe to profound visual impairment in line with previous studies of disorders that are associated with this degree of VI (Barcella et al., 2010; Milesi et al., 2012).

Next, difference in diffusion parameters of the corpus callosum were investigated given the role of the corpus callosum in transfer of information between visual areas between the two hemispheres. Previous studies found reductions in FA in the posterior corpus callosum in congenitally or early blind adults (Leporé et al., 2010; Ptito et al., 2008; Shimony et al., 2006), but not in late onset or acquired blindness (Leporé et al., 2010; Schoth et al., 2006) indicating experience dependent maturation during an early critical period. Contrary to expectations, there was no significant difference in fractional anisotropy of the posterior corpus callosum. However, lower FA values were found that did not reach reach statistical significance probably due to high inter-individual variability and limited statistical power in the current study.

However, a significant increase in FA in the anterior and posterior mid-segment of the CC was found in the VI group. In the Hofer et al. segmentation scheme, the anterior and posterior mid segment contain fibres connecting areas of the premotor and supplementary motor, and primary motor cortex respectively (Hofer & Frahm, 2006). It is possible that increased FA in these segments are linked to greater reliance on tactile exploration, e.g. for Braille reading, in the VI group (Sadato, 2005; Sadato et al., 1998; Shu, Li, Li, Yu, & Jiang, 2009). Future studies could investigate the link between diffusion parameters within segments of the corpus callosum and fine motor skills by incorporating assessments of motor skills, e.g. Movement Assessment Battery for Children (Movement ABC), and tests of Braille discrimination.

Further analysis focussed on fibre tracts that connect areas of the occipital lobe with target areas in the temporal lobe (inferior longitudinal fasciculus ILF) and frontal lobe (inferior fronto-occipital fasciculus iFOF). Some tractography studies with congenitally or early blind adults reported reductions in fractional anisotropy in these tracts (Ptito et al., 2008; Shu, Li, Li, Yu, & Jiang, 2009; Shu, Liu, Li, Li, Yu, & Jiang, 2009). No significant differences were found for either ILF nor iFOF between the VI and typically-sighted control group. A possible reason could be that the participants in the present study had varying degrees of visual function, whereas previous adult research focussed on legally blind participants, i.e SVI/PVI only. Further, there was no correlation between visual acuity and FA for the ILF, but a moderate yet non-significant correlation in the iFOF. If the observed Pearson correlation coefficient for the left iFOF was a true representation of the relationship, a sample size of at least 22 participants would be needed to detect a significant effect ($n=22$, $t(20)=1.726$, $p=0.049$). The current study was only sufficiently powered to detect a correlation with an effect size higher than 0.72 ($n=6$, $t(4)= 2.136$, $p=0.049$). Further, the interpretation is unclear as FA was positively correlated with logMAR scores, i.e. worse visual acuity, which contradicts previous reports of reduced FA in congenitally blind adults (Shu, Liu, Li, Li, Yu, & Jiang, 2009).

In summary, analysis of white matter integrity based on tractography of diffusion-weighted MRI indicated difference in the microstructural integrity of white matter structures. Comparison of diffusion parameters of the optic radiations indicated reductions in the optic radiations in children with severe to highly severe CDPVS.

Further, an increase in fractional anisotropy in the middle region of the corpus callosum was found in children with mild/moderate to highly severe VI. Based on the role of the mid-segment of the corpus callosum in the transfer of information between homologous regions of the premotor and motor cortex in the left and right hemisphere, this finding may reflect adaptive changes due to higher reliance on tactile exploration in children with visual impairment. However, further studies including assessments of fine motor skills would be needed to establish this link. Finally, the current study does not find evidence of changes in diffusion parameters of the ILF or iFOF in children with CDPVS. Differences in these tracts as indicated by previous adult studies may either only be present in highly severe to profound VI, may be too subtle to detect with the statistical power of the study, or become more pronounced with later development, e.g. through reorganisation of white matter during puberty.

## 7.4.2. White matter connectome analysis

### 7.4.2.1. Introduction

In recent years, approaches to describe the brain as an integrated network of modules that dynamically interact to subserve various functions has gained in popularity ( Bullmore & Sporns, 2009; Fornito & Bullmore, 2014; Hagmann et al., 2008; Tymofiyeva et al., 2014). The emphasis on this new approach is illustrated by the multi-million dollar Human Connectome Project funded by the National Institute of Health (www.humanconnectomeproject.org). Generally, brain networks can be derived from different modalities and different scales of resolution. Due to limitations of neuroimaging methods that can be used with human participants, the term connectome usually refers to the macroscopic connections between brain regions rather than synapses between individual neurons (Tymofiyeva et al., 2014). For the white matter connectome, local brain regions are used as nodes and inter-regional white matter pathways as the edges between the nodes. Typically, surface reconstructions based on high-resolution structural imaging are parcellated according to anatomical knowledge to derive the nodes. White matter pathways connecting these regions are then selected from tractography of diffusion-weighted images to construct the edges (Hagmann et al., 2008).

The connectome approach has been applied to study typical and atypical development between infancy and adulthood. Studies of typical development consistently identified increases in global network efficiency accompanied by decreases in local clustering with increasing age (Dennis et al., 2013; Hagmann et al., 2008; Huang et al., 2013), i.e. better integration between all nodes of the network while minimising wiring cost (Bullmore & Sporns, 2012). Biologically, these developmental tendencies are thought to mostly reflect changes in myelination as FA is most sensitive to myelin changes in the large fibre bundles that are already laid down in early development (Fornito & Bullmore, 2014). Studies of atypical development show alterations in the white matter networks in common neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and preterm birth. Generally, decreases in global and local network efficiency were found (Cao et al., 2013; Goch et al., 2014; Hong et al., 2014; Jakab et al., 2013; Pandit et al., 2014; Panigrahy et al., 2012). The pattern of changes differed between neurodevelopmental disorders. Changes in prefrontal connectivity were implicated in ADHD (Cao et al., 2013; Hong et al., 2014), whereas changes in the connectivity of the language network were associated with autistic traits (Goch et al., 2014; Jakab et al., 2013). Changes in network organisation with preterm birth were more diffuse (Ball et al., 2013; Pandit et al., 2014; Panigrahy et al., 2012).

Only one study investigated difference in the white matter connectome in visual impairment (Shu, Li, Li, Yu, & Jiang, 2009). Shu and colleagues compared graph metrics and node degrees between 17 early blind adults and 17 age- and gender-matched controls. The study revealed decreased global network efficiency in the early blind group. Further, reductions in the node degree of occipital and inferior frontal nodes as well as increases in the node degree of the precentral gyrus were identified. The reduction in node degree of inferior frontal and occipital regions was explained by reduced FA in the inferior longitudinal fasciculus in the early blind group. The authors interpret the increase in the node degree of the precentral gyrus as an adaptive change in the early blind group following more experience with tactile exploration, e.g. for Braille reading (Sadato, 2005; Sadato et al., 1998; Shu, Li, Li, Yu, & Jiang, 2009). Importantly, apart from difference in occipital regions, the same hub regions were identified in both groups indicating similar overall brain network organisation.

#### 7.4.2.2. Materials & Methods

The structural connectome was calculated using the Neuroimaging in Python Pipelines (NiPyPe) package (Gorgolewski et al., 2011). NiPyPe provides Python interfaces for commonly used neuroimaging analysis tollboxes, e.g. FSL, SPM, AFNI, etc., so that algorithms from each package can be easily combined into workflows.

Documentation and source code of the interfaces are available online under the open licence agreement. The following processing pipeline was based on a group connectivity mapping example script on the NiPyPe website (http://nipy.sourceforge.net/nipype /interfaces/generated/nipype.workflows.dmri.mrtrix.connectivity_mapping.html last visited September 2015).

The following section will describe the processing steps in more detail: T1-weighted structural scans were segmented and automatically labelled using FreeSurfer software as described in the "Analysis of cortical thickness and surface area" chapter. A network was obtained based on a parcellation with 128 ROIs.

Diffusion-weighted images were fitted with a constrained spherical deconvolution model (CSD) using MRTrix algorithms as described in the General Methods chapter. Probabilistic whole-brain fibre tracking was performed with a white-matter seed mask that was determined for each participant using iterative erosion of the FA image. The fibre tracking algorithm was set to a maximum total number of 150,000 tracks with a minimum and maximum track length of 10mm and 200mm respectively. The minimum radius of curvature was set to 1 mm and the track size to 0.2mm. The track termination threshold was set to an FA value of 0.1. Apart from the number of fibres, which was set to the maximum number within reasonable computation time, these values correspond to the default settings recommended by the authors of MRTrix (Tournier et al., 2012, https://github.com/jdtournier
/mrtrix3/wiki).

The tracks generated through probabilistic tracking were transformed to the participant's structural space using affine transformation using a DiPy (Diffusion in Python) algorithm (Garyfallidis et al., 2014). This step of transforming track information from dwi to structural space is recommended by the authors of the algorithm to avoid issues associated with downsampling ROIs from structural to dwi space (personal communication & see Methods section of Ziegler et al., 2013 for a discussion).

Network analysis was based on the number of fibres between ROIs. The network was binarised using 50% of the maximum edge weight as the threshold. Subsequently, the network was binarised. Network properties were characterised using graph theory measures. Group comparisons were based on network-based statistics (Zalesky et al., 2010) with 1000 permutations and cluster-wise correction for multiple comparison.

### 7.4.2.3. Results

#### 7.4.2.3.1. Network-based statistics analysis

Network properties of the white matter connectome were analysed to investigate differences in brain organisation in children with visual impairment. Statistical comparison based on permutation tests and cluster-wise correction for multiple comparison indicated significantly different connections between the groups. There was a total number of 5 significantly different edges that were grouped in the same cluster: right lateral orbitofrontal cortex to right insula (VI: mean=0.818, SE=0.122; control: mean=0.125,SE=0.125, p=0.004); right supramarginal gyrus to right middle temporal cortex (VI: mean=0, SE=0; control: mean=0.158, SE=0.086, p=0.004); brainstem to paracentral cortex (VI: mean=0, SE=0; control: mean=0.625, SE=0.183, p=0.004), left postcentral cortex to left superior parietal cortex (VI: mean=0.636, SE=0.151, control: mean=0, SE=0, p=); left inferior temporal to left superior temporal cortex (VI: mean=0.727, SE=0.141; control: mean=0.875, SE=0.125, p=0.004).

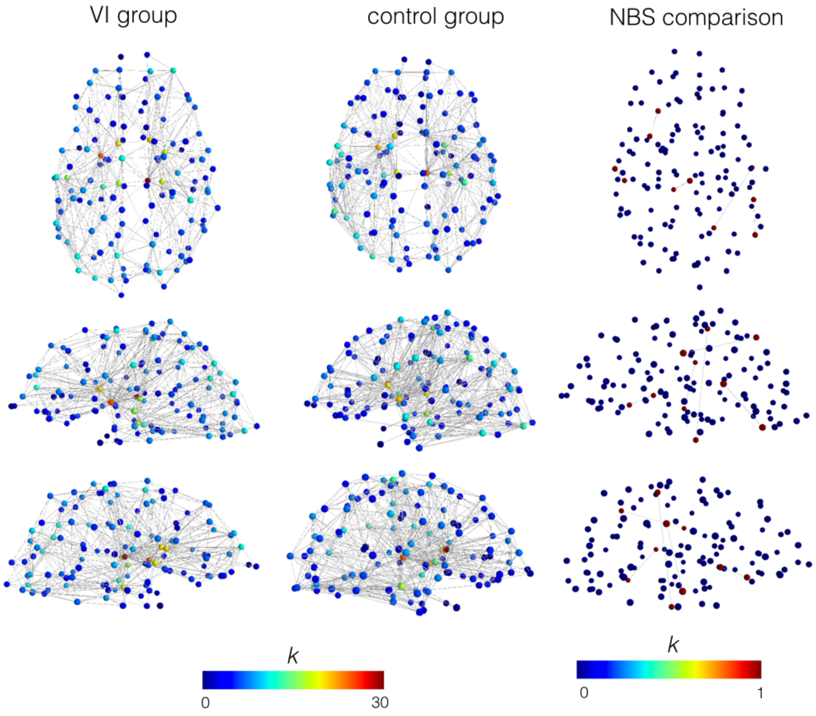


**Figure 50: Results of structural connectivity analysis with 128 ROIs based on FreeSurfer parcellation.** The left column shows the average network of the VI group, the middle column shows the average network of the control group, the last column shows the results of network-based statistics comparison between the groups. The top

row shows a top axial view, the second row shows a sagittal view on the left, and the bottom row shows a sagittal view from the right. The colour of nodes indicates the node degree (k). The colour map on the right refers to the average group networks and the right colour map to the statistical comparison network.

### 7.4.2.3.2. Graph theory analysis

Network properties of white matter connectomes were compared between the VI and the control group using graph theory measures to investigate differences in structural brain organisation between the groups as indicated by previous studies in congenitally or early blind adults (Liu et al., 2007; Shu, Liu, Li, Li, Yu, & Jiang, 2009). Statistical comparison indicated a significant difference between graph measures (F(6,108)=179.206, $p<0.001$) and a significant interaction between graph measure and participant group (F(6,108)=2.348, $p=0.036$). Follow-up contrasts using t-test comparisons did not indicate significant differences between the groups on any single graph measure. However, a trend-level difference between the groups was found for maximum betweenness-centrality (see Table 19).

Further, the relationship between graph theory measures and vision level was investigated in the subgroup of participants in the mild/moderate and severe VI group that were assessed on the Sonksen LogMAR test of visual acuity. No significant correlation between visual acuity and any graph measure were found. In addition, graph measures for two participants with highly severe VI that were assessed on the Near Detection Scale (Sonksen et al., 1991) were compared to the results of the control group. Differences on graph measures between these two cases and the control group did not reach significance level (F(6,54)=1.845, $p=0.108$).

**Table 19: Comparison of graph theory measure of white matter connectomes between the VI and control group.** The correlation with vision is based on participants with mild/moderate to severe VI that were assessed on the Sonksen LogMAR test of visual acuity (Sonksen et al., 2008).

| | VI | | | | control | | | | group comparison | | correlation with vision level (n=8) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | **mean** | **SE** | **Range** | | **mean** | **SE** | **Range** | | **t** | **p** | **r** | **p** |
| Mean node degree | 9.97 | 0.63 | 7.12 | 12.88 | 8.82 | 0.38 | 7.15 | 10.43 | 1.56 | 0.14 | -0.29 | 0.48 |
| Mean density | 1161 | 151 | 698 | 1956 | 1458 | 107 | 1131 | 1931 | -1.60 | 0.13 | 0.41 | 0.32 |
| Mean clustering coefficient | 0.08 | 0.00 | 0.06 | 0.10 | 0.07 | 0.00 | 0.06 | 0.08 | 1.56 | 0.14 | -0.29 | 0.48 |
| Maximum betweenness centrality | 0.337 | 0.008 | 0.293 | 0.373 | 0.316 | 0.007 | 0.291 | 0.342 | 1.99 | 0.06 | -0.32 | 0.45 |
| Mean rich club coefficient | 0.586 | 0.029 | 0.404 | 0.713 | 0.585 | 0.018 | 0.507 | 0.676 | 0.02 | 0.99 | -0.12 | 0.78 |
| Characteristic path length | 1.070 | 0.005 | 1.047 | 1.092 | 1.061 | 0.003 | 1.048 | 1.073 | 1.56 | 0.14 | -0.29 | 0.49 |
| Global efficiency | 0.961 | 0.002 | 0.950 | 0.972 | 0.966 | 0.001 | 0.959 | 0.972 | -1.56 | 0.14 | 0.29 | 0.48 |

### 7.4.2.4. Discussion

The current investigation was aimed to investigate difference in white matter organisation across the whole brain and link potential differences to metrics of network efficiency. Previous studies in early blind adults had identified decreases in the degree of occipital and inferior frontal nodes as well as increases in the node degree of parietal motor areas (Shu, Liu, Li, Li, Yu, & Jiang, 2009). Further, Shu et al. reported reduced global efficiency and increased characteristic path length in the early blind adult group. There was no indication of statistically significant differences in graph measures in the current investigation, apart from a trend-level decrease in maximum betweenness-centrality. However, there are important difference between the Shu et al. and the present study. First, Shu et al. reported results based on 17 early blind adults and 17 age- and gender-matched typically-sighted control participants. The present study had lower statistical power with 10 visually impaired and 8 control participants.

Second, the current study consisted of a heterogeneous group of varying degrees of visual impairment. Visual acuity is not stated in Shu et al., but judging by the reported recruitment method through a special education college, it is likely that participants included in the Shu et al. study had severe to profound VI. Given that the degree of visual impairment was associated with a higher effect size across a number of measures in the current investigation, graph measures of white matter networks are likely to show a similar pattern. Therefore, the current study would need a larger sample size, especially in the mild/moderate range, to detect these subtle differences. Third, Shu et al. did not report any cognitive assessments for their sample. Previous network investigations have consistently shown that global efficiency and characteristic path length are correlated with IQ (Li et al., 2009; Stam, 2014; van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). The present sample was recruited for intellectual function in the typical range. However, at least in paediatric samples, visual impairment has been associated with decreased cognitive ability compared to typically-sighted controls (Alimovic, 2013; Tillman, 1973). It is therefore not clear if the difference in graph theoretical measures reported by Shu et al. reflect primary effects of visual impairment or secondary effects associated with cognitive difference in visual impairment.

In addition to the graph theoretical analysis of white matter networks, a network-based statistics analysis was applied to identify connection differences between the groups. Similar to the tractography results of the corpus callosum, significantly different connection properties of the para- and postcentral cortex were implicated. Differences in the integration of these areas may be explained by higher demands for tactile exploration in the VI group. Further, connection differences between the regions within the left and right temporal cortex were found. These differences may indicate differences in the integration of ventral stream areas. Difference in the connection between insula and orbitofrontal cortex may be interpreted to reflect differences in behavioural regulation as suggested by the behavioural findings (see Chapter 3).

## 7.5. Chapter Discussion

The aim of the present chapter was to investigate structural brain organisation in children with congenital visual impairment of the peripheral visual system. The extended dorsal stream model suggested that differences in the integration of typically visual areas with other parts of the brain network may arise as a consequence of altered visual input. In line with a previous report in congenitally blind adults (Shimony et al., 2006), integrity of the optic radiations that transfer visual information between the lateral geniculate nucleus of the thalamus and the primary visual cortex was found to be decreased in children with VI. Further, diffusion parameters were found to be directly related to the degree of visual impairment. There were also indications of alterations at further processing stages within the visual brain with trend-level increases of cortical thickness in the pericalcarine cortex, and decreased diffusion in the posterior corpus callosum in the VI group. Further, differences in the white matter integrity of the mid-segment of the corpus callosum were found with higher FA values in the VI group. These differences might reflect adaptive changes due to higher demand for tactile discrimination in children with VI.

Analysis of white matter structures that are involved in the transfer of visual information between the occipital lobe and the temporal lobe (inferior longitudinal fasciculus), and the frontal lobe (inferior fronts-occipital fasciculus) that were found to be different in a study of congenitally blind adults (Shu, Li, Li, Yu, & Jiang, 2009) were not found to be significantly affected in the current study. In addition, no relationships between variation in the integrity of these pathways and variation in assessments of pragmatic language (ILF) or executive abilities (IFOF) were found. A graph theoretical analysis of the white matter connectome did also not indicate significant differences in network organisation between the VI and control group. However, differences in network edges in the parietal, temporal, and frontal lobe were found between the groups.

# Chapter 8: Functional Brain Organisation

## 8.1. Chapter Introduction

Together with the previous chapter, which reported analyses of structural brain differences in children with VI, the current chapter aimed to identify differences in functional brain organisation in children with visual impairment and relate these findings to variation in cognitive performance based on the predictions of the extended dorsal stream model. The following investigations focussed on differences in brain function that may indicate differences in the communication between brain areas. First, differences in the frequency content of resting-state EEG were assessed. These large scale rhythms are thought to be critical for effective communication between brain areas within dynamic networks (Buzsàki, 2006). Next, the network relationship between cortical areas was investigated on the source signal level. This type of analysis provides further detail through the application of graph analysis and network-based statistics, which provide a quantitative description of network efficiency and an indication of differences in connections strength between groups.

## 8.2. EEG power spectrum analysis

### 8.2.1. Introduction

The EEG power spectrum is a representation of the contribution of oscillators in specific frequency bins to the observed EEG signal. Historically, EEG has been described as a function of dominant frequencies that were named according to the sequence of their discovery. The current investigation focusses on commonly studied frequency bands including delta (1-4Hz), theta (4-8Hz), alpha(8-12Hz), beta (13-30Hz), and gamma (31-100Hz). Each frequency band has been associated with specific physiological and cognitive functions: Delta waves dominate during sleep and are thought to underlie basic homeostatic and motivational processes (Knyazev, 2012). Theta oscillations have been linked to memory encoding and emotional evaluation of stimuli (Klimesch, 1999; Uusberg, Thiruchselvam, & Gross, 2014). Alpha activity has been linked to shifts in the resting potential of large neural assemblies in the cortex (Palva & Palva, 2007) and is generally interpreted as an idling state of cortical assemblies (Başar & Guntekin, 2012; Klimesch, Sauseng, & Hanslmayr, 2007). Beta range activity has been associated with alertness and has also been studied in the context of motor behaviour (Neuper & Pfurtscheller, 2001). Activity in the gamma range has been shown to reflect hyperpolarisation of cortical neurons following action potentials in macaques (Başar, 2013; Whittingstall & Logothetis, 2009). Scalp EEG gamma has been linked to a variety of cognitive function in humans most prominently conscious perception and attention (Herrmann, Frund, & Lenz, 2010).

Resting-state EEG power spectra have been intensively studied in neuropsychiatric disorders (Fuggetta, Bennett, Duke, & Young, 2014; Strzelecka, 2014), children at risk for adverse outcomes (Marshall, Reeb, Fox, Nelson, & Zeanah, 2008; Tarullo, Garvin, & Gunnar, 2011), and to characterise brain maturation (Sankupellay et al., 2011; Segalowitz, Santesso, & Jetha, 2010; Somsen, Van't Klooster, Van Der Molen, Van Leeuwen, & Licht, 1997). Consistent findings in the developmental literature include a general decrease in absolute power across all frequency bands and regions with age (Boord, Rennie, & Williams, 2007; Dustman, Shearer, & Emmerson, 1999; Segalowitz et al., 2010; Whitford et al., 2007). The decrease in frequency power has been found to be most pronounced in the low frequency range (up to 8Hz) and in posterior regions. Maturational changes in EEG power are thought to reflect changes in cortical thickness, neural density, and neurotransmitter levels (Segalowitz et al., 2010; Whitford et al., 2007). Particularly, changes in dopaminergic and noradrenergic drive over development have been implicated (Segalowitz et al., 2010). For neurodevelopmental disorders, consistent alterations in EEG power spectra have been described in ASD and schizophrenia with increased low and high, and decreased middle frequency power (Kam, Bolbecker, O'Donnell, Hetrick, & Brenner, 2013). These findings have been interpreted to reflect changes in the excitatory-inhibitory balance probably caused by alterations in the function of GABAergic interneurons (Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012).

Studies of functional organisation indicate that cortical areas that are primarily involved in processing of visual information in sighted participants subserve multiple functions in congenitally blind adults including processing of sensory information from other modalities and higher-order processing (Gougoux et al., 2005; Klinge et al., 2010; Raz et al., 2007). Therefore, primary visual areas are thought to act like association areas in congenitally blind adults (Noppeney, 2007; Simon-Dack, Rodriguez, & Teder-Salejarvi, 2008), which is likely to be accompanied by physiological adaptation to aid this functional role. These changes are likely to be reflected in the spectral composition of the scalp EEG. Indeed, several studies report reductions in power spectral density over occipital electrode sites in blind adults (Bértolo et al., 2003; Kriegseis, Hennighausen, Rosler, & Roder, 2006). Further, slow potential differences have been reported in event-related potential studies (Roder, Rosler, & Hennighausen, 1997; Roder, Rosler, Heil, & Hennighausen, 1993) that are thought to related to difference in low frequency band power (Kriegseis et al., 2006). We expected to find similar reductions in low frequency band power in the current investigation. Later sections of the chapter will aim to relate differences in frequency band power to functional brain organisation.

## 8.2.2. Materials & Methods

### 8.2.2.1. Recording

Please refer to the General Methodology chapter for details about EEG recording procedures. For the resting-state, children were instructed to close their eyes and think of nothing in particular, let their mind wander and relax. A tone signalled the beginning and end of the resting-state. All children stayed awake during the 2.5 minutes resting-state period judged by video observation during the recording.

### 8.2.2.2. EEG processing

The resting-state EEG recording was segmented into 1s epochs. A Notch filter was applied to remove line noise contamination. The filter was set at 50Hz and at 100Hz for the first harmonic. A finite response filter (FIR) with 25% transition in a Hamming window and maximum filter order (length data -1) was used (Widmann & Schroger, 2012).

Epochs that contained absolute voltage above 200$\mu$V or peak-to-peak amplitudes above 150$\mu$V were rejected. Independent component analysis was applied and independent component were removed based on statistical thresholding using the

FASTER algorithm (Nolan et al., 2010). All recordings were visually inspected and segments that contained clearly identifiable movement or eye-related artefact were manually rejected (please see the General Methods section for further details about EEG processing).

One child with nystagmus had to be excluded, because persistent eye movements contaminated the resting-state EEG. One child in the control group was excluded, because EMG artefact from the neck contaminated more than 50% of the epochs. The final sample consisted of 26 children (16 VI, 10 control).

### 8.2.2.3. Power Spectrum Analysis

The EEG power spectrum was calculated for each epoch using Fast Fourier Transformation using code based on the MATLAB FFT function (The MathWorks, Natick, MA). Power spectra were averaged over all trials to derive individual subject averages. Mean power within frequency bins for delta (2-4Hz), theta (6-7Hz), alpha (8-12Hz), beta (15-29Hz), low gamma ( 30-60Hz), high gamma (61-99Hz) was extracted for each participants. The frequency band definitions were based on canonical ranges for healthy adults (Buzsàki, 2006).

The power spectra were averaged for left and right frontal, central, left and right lateral and left and right posterior channel regions (see Fig 52). Selection of channels for PSD analysis varies widely between studies using high-density EEG systems, e.g. Mathewson, Jetha, Drmic, Bryson, & Goldberg, 2012; and Tierney et al., 2012. In the absence of *a priori* guidelines, a compromise between head coverage and loss of statistical power had to be reached. Regions of interest were selected to provide broad coverage of the head with focus on approximate locations of 10-10 landmarks for frontal, central, temporal, and occipital channels (F7, F8, Cz, T3, T4, O1, O2) to facilitate comparison with studies using other channel placement systems (Jurcak, Tsuzuki, & Dan, 2007).

In addition to absolute power, relative power was derived to evaluate the specificity of observed effects. For relative power, power in each frequency bin was divided by the mean total power across the whole spectrum (1-100Hz).

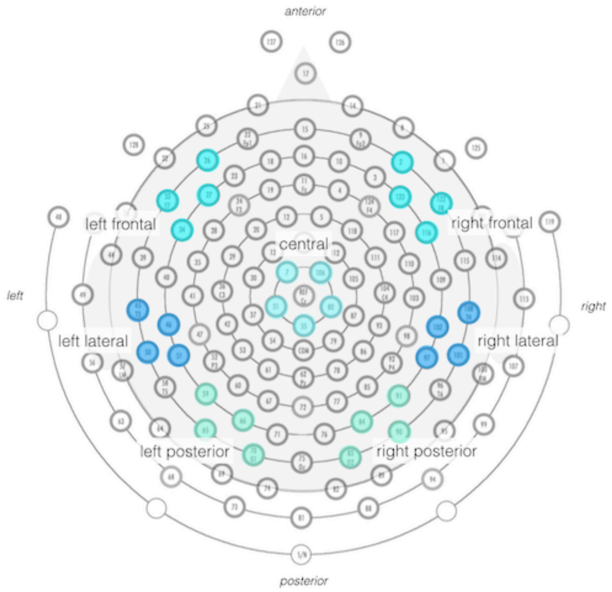


**Figure 51: Channel selection for power spectral analysis of resting-state EEG recordings.** The power spectrum was averaged over four channels to create left and right frontal, central, left and right lateral, and left and right posterior virtual channels.

### 8.2.2.4. Statistical Analysis

Absolute power spectral density (PSD) within delta, theta, alpha, beta, low and, high gamma bands was compared in a repeated-measures ANOVA model including channel region, participant group, participant age and the interaction between the factors as covariates. Significant effects were further investigated using post-hoc contrasts including t-tests and correlations. The effect of vision level was analysed as in a second model including region, frequency band and participant age,

## 8.2.3. Results

The power spectra displayed a log-dynamic power distribution of high power in low frequencies expected for EEG power spectra (Buzsàki, 2006). A distinct peak within the alpha range (8-12Hz) with a maximum over posterior channels was observed in all participants. Peaks within other low-frequencies ranges, namely theta and beta range, were also observed in some individuals, but were less consistently present in all participants and varied more in peak frequency. A sharp peak at 50Hz with high spectral power was observed in some individuals that is also prominent in the grand average response. The peak frequency, sharp onset and high power suggests that this peak represents residuals of line noise contamination that could not be completely attenuated through Notch filtering.

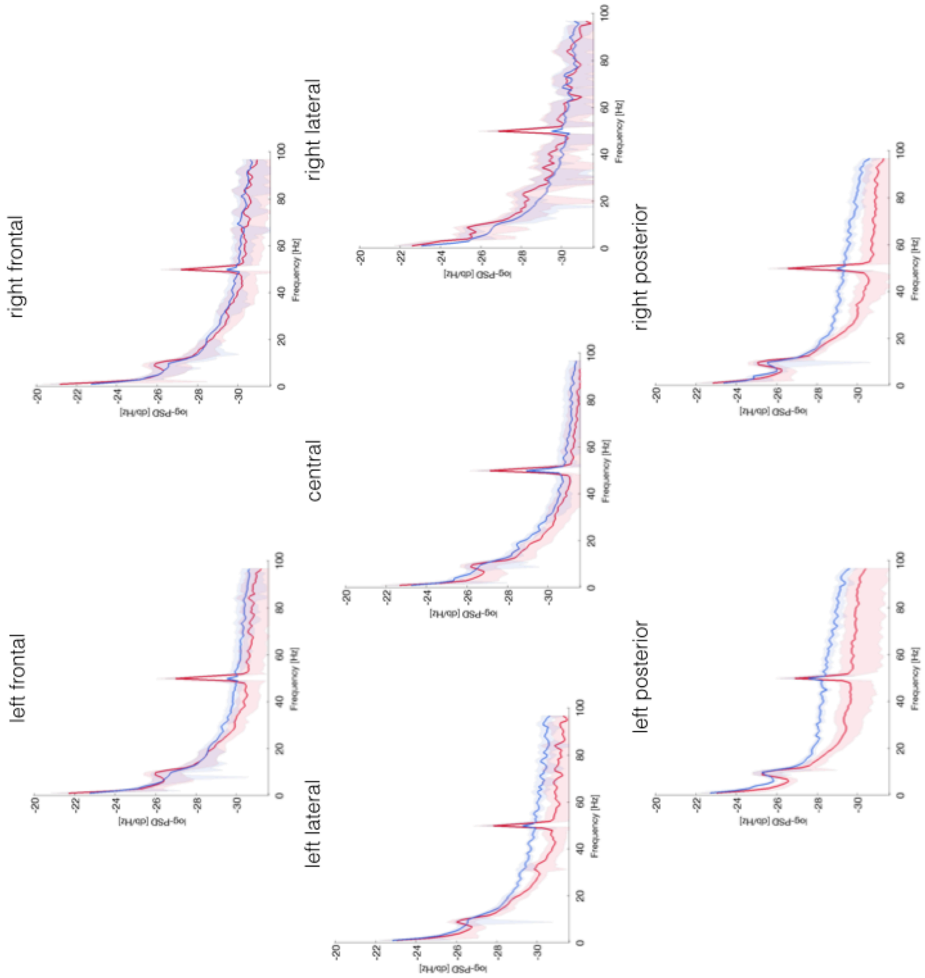


**Figure 52: Resting-state EEG power spectra.** The figure shows resting-state EEG power spectra between 1 and 99Hz in seven virtual channels distributed over the head. Power spectra results in the VI group are shown in red and control group results in blue. All values are presented in log transformed absolute PSD [log(dB/Hz)].

A significant three-way interactions between participant group, frequency band, and participant age was found (F(6,133)=7.714, p=0.0063). Follow-up correlation analysis identified a negative correlation between participant age and absolute PSD within the delta band in children with VI (r=-0.51, n=16, p<0.001,Bonferroni-corrected p=0.002). A similar negative correlation was found in the beta band (r=-0.54, n=16, p<0.001, Bonferroni-corrected p=0.004). No correlations between PSD and participant age were found in the control group (no uncorrected p-values <0.05). Analysis of relative spectral power identified additional negative correlations with age in the theta and high gamma band (n=16, delta: r=-0.57, p<0.001, Bonferroni-corrected p=0.004; theta: r=-0.35, p=0.001, Bonferroni-corrected p=0.005; beta: r=-0.62, p<0.001, Bonferroni-corrected p=0.002; high gamma: r=-0.23, p=0.038, Bonferroni-corrected p=0.19).

Subsequently, the influence of vision level on frequency band power was analysed excluding participants with highly severe VI or PVI. These participants had to be excluded from the statistical model, because vision level in children with very low vision had to be measured on a different, non-continuous scale (Near Detection Scale). Statistical analysis indicated a significant interaction between vision level and participant age (F(1,119)=10.093, p=0.0019). Follow-up correlation analysis indicated significant correlations between vision level and absolute spectral power density in the delta, theta and beta band (n=21, delta: r=0.2, p=0.0154, Bonferroni-corrected p=0.077; theta: r=0.29,, p<0.001, Bonferroni-corrected p=0.001, beta: r=0.24, p=0.0031, Bonferroni-corrected p=0.016) and a trend-level correlation in the alpha band that did not survive correction for multiple comparison (r=0.14, p=0.088, Bonferroni-corrected p=0.44).

Comparison of absolute PSD between children with mild/moderate or severe VI with children with highly severe to profound VI indicated smaller PSD in the delta, theta, alpha, and beta range as well as trend-level differences in the low and high gamma range that did not survive Bonferroni-correction for multiple comparison (see Table 20).

**Table 20 Statistical comparison of PSD between children with mild/moderate or severe VI (MVI/SVI) and children with highly severe to profound VI (hSVI/PVI).** The last column shows p values corrected for multiple comparison using Bonferroni correction.

| | MVI/SVI | | hSVI/PVI | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Frequency band** | **mean** | **SE** | **mean** | **SD** | **t** | **df** | **p** | **corrected p** |
| delta (2-4Hz) | 1.17E-11 | 2.04E-12 | 3.50E-12 | 2.09E-13 | 4.024 | 84.698 | 0.000 | 0.001 |
| theta (6-7Hz) | 3.97E-13 | 6.61E-14 | 1.91E-13 | 2.08E-14 | 2.973 | 94.312 | 0.004 | 0.022 |
| alpha (8-12Hz) | 4.03E-12 | 7.08E-13 | 9.88E-13 | 1.29E-13 | 4.234 | 87.959 | 0.000 | 0.000 |
| beta (15-29Hz) | 4.25E-12 | 5.67E-13 | 1.32E-12 | 1.64E-13 | 4.964 | 93.331 | 0.000 | 0.000 |
| low gamma (30-59Hz) | 1.75E-13 | 5.56E-14 | 6.91E-14 | 1.18E-14 | 1.871 | 89.494 | 0.065 | 0.388 |
| high gamma (60-99Hz) | 8.62E-14 | 2.47E-14 | 3.70E-14 | 6.38E-15 | 1.930 | 91.851 | 0.057 | 0.340 |

## 8.2.4. Discussion

The eyes-closed resting-state EEG power spectrum was compared between children with visual impairment and typically-sighted control children to investigate spectral signatures of functional brain organisation in congenital visual impairment. Based on previous reports, a decrease in alpha power over occipital electrode sites was expected (Bértolo et al., 2003; Kriegseis et al., 2006). The overall morphology of power spectra was similar in both the VI and control group and corresponded to the typical pink noise power distribution (Buzsàki, 2006). Differences between the groups were not restricted to the alpha frequency band as reported for adult samples using similar methods (Bértolo et al., 2003; Kriegseis et al., 2006). Instead differences in the interaction between frequency power and age were found. There was a significant negative correlation between spectral power and age in the VI group, particularly in the lower frequency bands. There was no significant negative correlation between PSD and age in the control group. Studies about the developmental changes in EEG power in typically developing children consistently reported a decrease of power in the lower frequency bands with age (Boord et al., 2007; Dustman et al., 1999; Whitford et al., 2007). Previous studies of developmental changes in EEG power employed large numbers of participants (Dustman et al: 222 participants (male only) between 4 and 90 years; Boord et al: 1831 participants between 6 and 86 years; Whitford et al. 2007: 138

participants between 10 and 30 years) and found changes with a small effect size, e.g. z-score of 1 at age 10 to 0.6 at age 15 years (Whitford et al., 2007). It is therefore likely that the current study was not sufficiently powered to detect decreases in spectral power in typically developing children[7] in this age range. However, a negative correlation between PSD and participant age was detected in children with VI.

The differences detected in the VI group are not consistent with changes observed in children with ASD or adolescents with schizophrenia where increased power in the low and high frequency with a concurrent decrease in the mid-frequency range is typically found (Kam et al., 2013). The pattern of decreases in the low frequency range with increasing participant age is more consistent with the developmental tendencies observed over typical development, but is more pronounced than in the control group of the same age. Power in the low frequency range with age decreases non-linearly in a function resembling exponential decay with larger changes in earlier development (Whitford et al., 2007). It seems therefore possible that the more pronounced decrease in low frequency power with age in the VI group reflects a delay in general brain maturation. This possibility is also in line with other findings in other markers of brain maturation, e.g. cortical thickness. However, a control group including younger children would be needed to investigate this hypothesis.

## 8.3. Cortical source functional connectivity

### 8.3.1. Introduction

Recent advances in brain imaging and analysis highlight the importance of interplay between brain regions[8]. Rather than investigating the role of individual brain regions for specific functions, brain connectivity analysis describes the dynamic engagement of multiple brain regions (brain 'networks'). The specific regions identified using various imaging methods differ, probably because the physiological processes underlying different imaging modalities are not the same (Darvas et al., 2004 and He et al., 2011). However, graph theory provides a common mathematical framework to compare the network architecture (Rubinov and Sporns, 2010), even when the anatomical regions are not identical. Constraints on efficient network organisation have been found to be remarkably similar across different scales, modalities, and even model systems (Van den Heuvel et al., 2008 and Watts and Strogatz, 1998).

The development of resting-state functional connectivity has been investigated with various techniques. Homae et al. report the development of functional networks in neonates and infants of up to 6 months of age using NIRS (Homae et al., 2010). They collected NIRS data while the children were asleep and calculated correlations between the time series of the channels. They reported an increase in correlation between channels in posterior regions and a decrease in frontal regions. Similarly, Thatcher and colleagues used EEG coherence to investigate the development of cortical functional connectivity in a large sample with age groups between 2 months and 16 years (Thatcher et al., 2008). They report stronger coherences with age, increased anterior–posterior connections and a decrease in overall coherence between electrodes with longer distances (Barry et al., 2004). This is in line with functional connectivity analysis of fMRI data reported by Fair and colleagues that compared the rs-fcMRI architecture of school-age children with adults. The authors found that 7-to-9-year-old children display little functional connectivity between the mPFC and posterior cingulate and parietal regions compared to adults. These areas appear highly integrated in adults. In contrast, there is a comparable degree of interhemispheric connections between homotopic regions in both children and adults, e.g. parahippocampal and superior frontal regions. A statistical comparison of connectivity between children and adults shows that the most pronounced differences are generally found in anterior-to-posterior connections. The decrease in correlation between regions is likely to reflect segregation of sub-networks that subserve different functions, and integration  of of sub-networks that mediate the same function (Thatcher et al., 2008). Increased connectivity between regions that are spatially segregated is likely to reflect functional integration (Uhlhaas et al., 2009 and Uhlhaas et al., 2010).

High-density recordings of EEG are inexpensive, easy to obtain even in young children and offer excellent temporal resolution. In spite of these advantages, one reason why researchers may not have embraced the use of EEG to study functional cortical networks is because of their limited spatial resolution. In order to overcome this barrier and obtain functional networks of cortical areas, we used EEG source reconstruction with age-matched average MRI templates (He et al., 1999). In contrast to previously reported channel-level analyses, this approach provides information about the cortical areas that are most likely to be involved as well as their functional relationship (Babiloni et al., 2005 and De Vico Fallani et al., 2007). Further, the independence of nodes in the network is less confounded than in channel-level analysis.

Network analysis results in a measure of association strength between areas of interest. The properties of the resulting networks can be characterised through the mathematical framework of graph theory (Bullmore and Sporns, 2009, De Vico Fallani et al., 2007 and Sporns, 2002). We applied commonly used graph measures such as node degree, average path length and clustering coefficient (Bullmore and Sporns, 2009 and Chu-Shore et al., 2011). These measures allowed qualitative comparison of the characteristics of functional networks derived from reconstructed EEG sources to the organisation of networks derived in other studies using other imaging modalities like fMRI, NIRS etc. Furthermore, graph theory has been used to quantify the efficiency of a variety of networks. Most networks display a characteristic network organisation that is optimised for a) maximal processing speed b) minimal wiring cost and c) resilience (Watts and Strogatz, 1998). These networks all display a high level of local connectivity with some long-range connections. This has been described as a small-world architecture. Network analysis of structural and functional MRI data reveals that the human brain shares this organisation with other biological and non-biological networks, like neurons in Caenorhabditis elegans and traffic on the world-wide web (Bullmore and Sporns, 2012, Watts and Strogatz, 1998 and Yu et al., 2008).

A study by Liu and colleagues investigated the functional connectivity of early blind adults with fMRI (Liu et al., 2007). Early blind adults showed reduced functional connectivity between ROIs within the occipital cortex and between the occipital cortex and ROIs in the parietal and frontal cortex. Increased functional connectivity between occipital ROIs and ROIs in the left frontal cortex correlated with experience in Braille reading.

Based on these reports, a reduction in edge weight of occipital connections was expected. Further, graph theory measures were hypothesised to indicate reduced global efficiency and increased characteristic path length. Differences were expected to be prevalent in the alpha band networks as differences in power spectral density had been identified within this frequency band in previous studies (Bértolo et al., 2003; Kriegseis et al., 2006).

## 8.3.2. Materials & Methods

### 8.3.2.1. EEG processing

Segmentation and preprocessing were identical to the procedures described for the power spectral analysis.

### 8.3.2.2. Source reconstruction

Source reconstruction was based on age-appropriate boundary element models (BEMs). An average template of the Neurodevelopmental MRI database (Sanchez et al., 2012) was selected that most closely matched the participant's age.

For the source connectivity analysis, current source density was averaged over all vertices within a cortical region of interested. Linear associations between cortical ROIs were obtained using pair-wise Pearson correlation. The correlation coefficients were averaged over all epochs for each recording to construct the cortical source connectome for each participant.

### 8.3.2.3. Graph theoretical analysis

Negative correlations were set to zero. Individual adjacency matrices were thresholded at their mean connectivity value to diminish the effect of spurious correlations and differences in signal-to-noise ratio between recordings (Bathelt et al., 2013). Graph measures were calculated using algorithms implemented in the Brain Connectivity Toolbox (Rubinov & Sporns, 2010). Graph measures were compared between participant groups in a repeated-measures ANOVA. Follow-up t-tests were used to investigate difference between the groups on individual graph measures. Because of the novelty of this method, the analysis is largely exploratory. There were no hypotheses to narrow the comparison space to specific frequency bands and graph metrics. Therefore, the number of comparisons is high. Strong control of Type I errors using Bonferroni correction would be excessively conservative in this exploratory analysis. Therefore, uncorrected pvalues are reported.

## 8.3.3. Results

### 8.3.3.1. Network structure

Analysis of connectivity strength by region indicated a significant difference between regions in the alpha band and beta band (Alpha: F(5,130)=6.634, p<0.001); Beta: F(5,130)=7.096, p<0.001, see Figure 53). There was no significant difference for the gamma band (F(5,130)=1.855, p=0.107). Effects of participant age or participant group did also not reach significance level. Differences between regions were driven by higher mean correlation in occipital and temporal regions (see Figure 53).

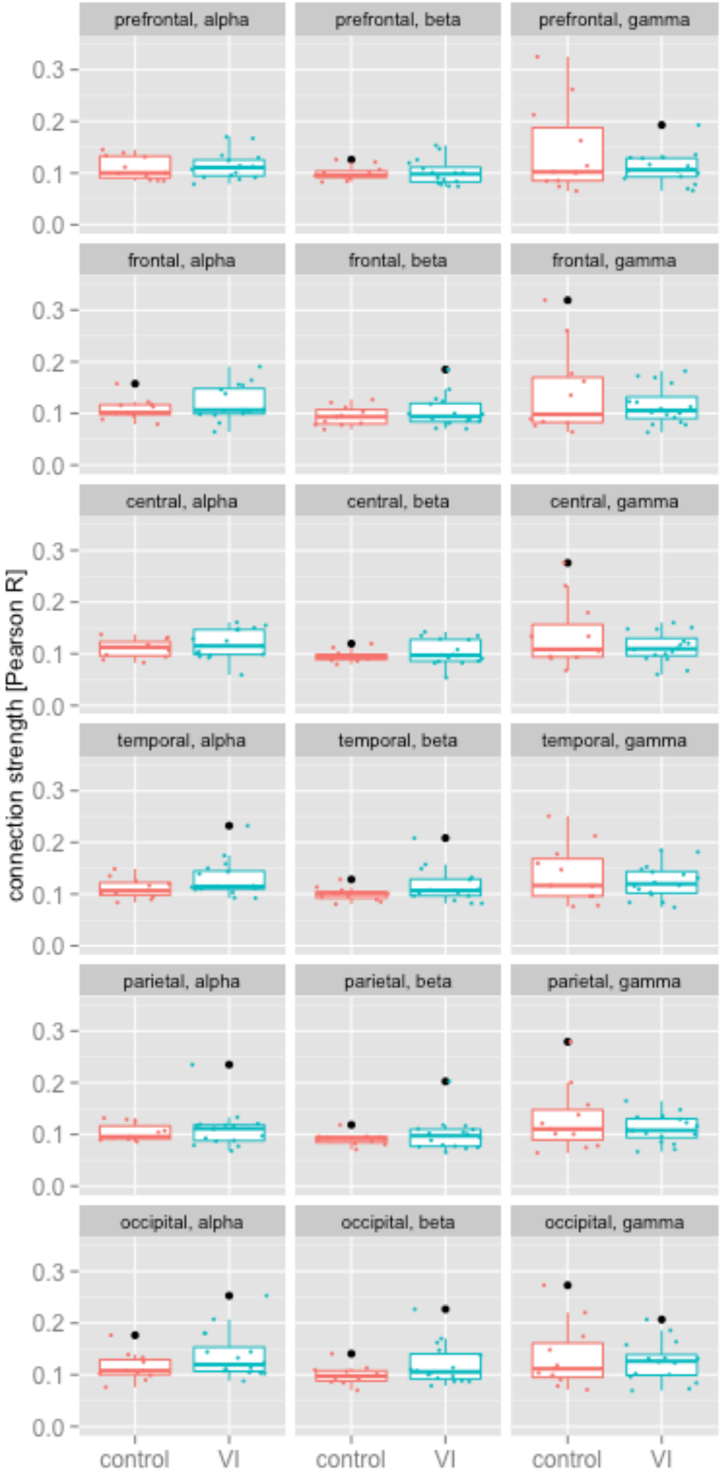


**Figure 53: Connection strength** within prefrontal, frontal, central, temporal, parietal, and occipital regions are shown for the alpha, beta, and gamma band for the VI and control group. The small coloured dots mark the original data point.

Subsequently, the influence of variation in vision level on individual connection strength was investigated using bivariate correlations with Bonferroni correction for strong control of multiple comparison problems. Only the connections between the lingual cortex in the left hemisphere and the orbital part (pars opercularis) of the inferior frontal gyrus (IFG) in the right hemisphere correlated significantly with the vision level after adjustment for multiple comparisons (n=25, r=-0.75, p=1.78e-05, p-corrected=0.041) (see Figure 54).

A previous study by Shu and colleagues reported a similar difference for white matter connectivity between early blind adult participants and matched controls (Shu, Liu, Li, Li, Yu, & Jiang, 2009). Shu et al. found a strong correlation between diffusion parameters of the inferior fronto-occipital fasciculus (iFOF) and the connection strength of the inferior frontal gyrus and occipital regions. Based on this report, the relationship between functional connection strength of the lingual-inferior frontal edge and fractional anisotropy in the left and right iFOF was investigated. Bivariate Pearson correlation indicated a strong, but non-significant correlation between FA in the left iFOF (n=5, r=0.67, 0.216). There was only a weak correlation between FA in the right iFOF and the IFG-lingual connection strength (r=0.23, p=0.713).

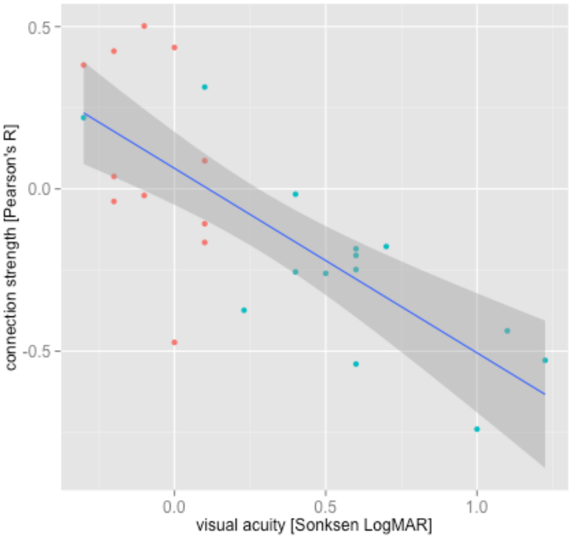


**Figure 54: Correlation between connections strength between the left lingual cortex and the right orbital part of the inferior frontal gyrus with vision level.** Data points of participants in the control group are shown in blue and participants in the VI group in red. The blue line shows the a linear model fit and the shaded area the confidence interval based on spline interpolation (Wickham, 2009).

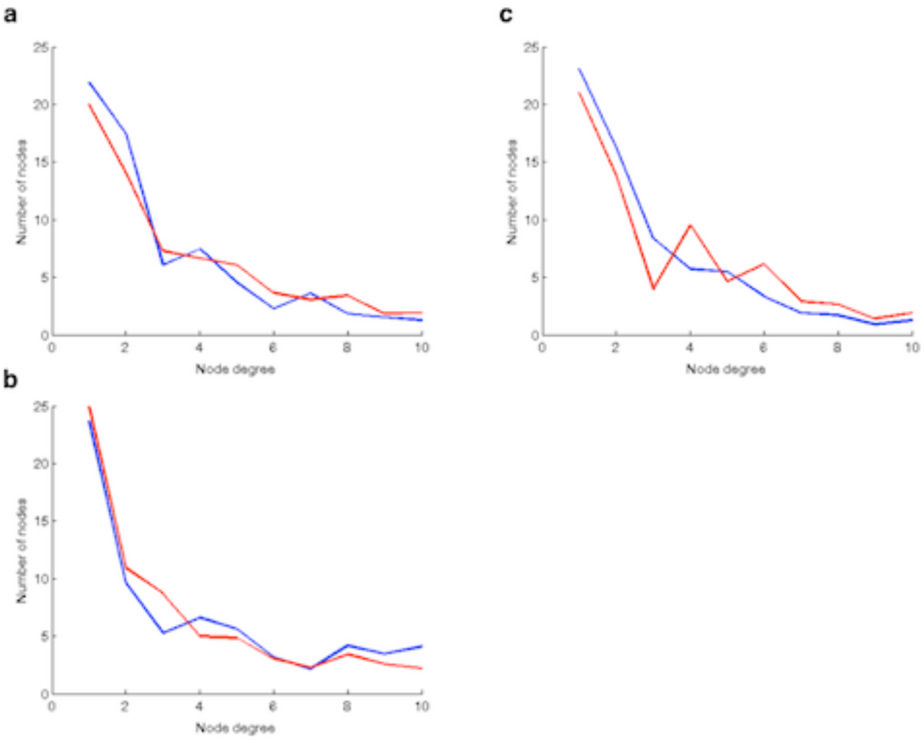


**Figure 55 Degree distribution in the alpha, beta, and gamma network in the VI (red) and control group (blue).** The figure shows the number of nodes in node degree bind

of 0 to 10. The distribution resembles a power law distribution as described for brain networks in other modalities (Bullmore & Sporns, 2009).

### 8.3.3.2. Graph theory analysis

An analysis of connections strength by cortical region indicated regional differences in connection strength with higher correlations between areas of the occipital and temporal lobe in the alpha and beta band. However, no differences were found between participant groups.

Graph theory analysis was used to compare network properties of the resting-state cortical source connectivity between participant groups and investigate the relationship of network properties and participant age within participant groups. Statistical comparison across graph measures in the alpha band indicated a significant difference between groups (VI: mean=88.66, SE=33; control: mean=25.87, SE=9.47; F(1,23)=4.487, p=0.0452) and a significant interaction between participant group and graph measure (F(6,138)=4.483, p<0.001). Follow-up simple contrasts indicated a significant difference between the groups on mean density and characteristic path length as well as a trend-level difference on global efficiency. Mean density, characteristic path length and global efficiency were higher in the VI compared to the control group (see Table 21a for descriptives). For the beta network, statistical comparison also indicated significant difference between the groups on graph measures (VI: mean=55.6, SE=21.25; control: mean=14.05; F(1,23)=4.623, p=0.0423) as well as a significant interaction between participant group and graph measure (F(6,138)=4.634, p<0.001). Post-hoc contrasts indicated significant differences on mean density, characteristic path length, and global efficiency similar to the findings described for the alpha network (see Table 21b). There were no significant effects of participant group or interactions between graph measure and participant group in the gamma band (VI: mean=41.02, SE=14.95; control: mean=33.32, SE=14.54; F(1,23)=0.21, p=0.651; participant group x graph measures: F(6,138)=0.233, p=0.965).

Subsequent analyses investigated the influence of vision level on characteristic path length in the alpha and beta band. A significant positive correlation between Sonksen LogMar scores and characteristic path length as well as mean density was found in the alpha band (n=23, r=0.43, p=0.038) indicating shorter characteristic path length and lower mean density with better LogMar scores. No significant correlation was found in the beta band (r=0.31, p=0.1482).

**Table 21 Graph theory measure comparison between the VI and control group for the a) alpha and b) beta.** Statical comparison did not indicate significant difference on graph measures between the groups for the gamma band network. Contrasts were based on Welch-corrected t-tests. The last two columns show the results of correlation analysis with visual acuity (Sonksen LogMAR score). All uncorrected p-values.

a)

| | VI (n=14) | | control (n=11) | | group | | age | | interaction | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Graph measure** | **mean** | **SD** | **mean** | **SD** | **F(1,23)** | **p** | **F(1,23)** | **p** | **F(1,23)** | **p** |
| mean node degree | 22.16 | 2.02 | 21.55 | 0.77 | 0.875 | 0.360 | 0.152 | 0.701 | 1.068 | 0.313 |
| mean clustering coefficient | 0.23 | 0.08 | 0.21 | 0.04 | 1.421 | 0.247 | 0.328 | 0.573 | 2.640 | 0.119 |
| characteristic path length | 1.09 | 0.02 | 1.05 | 0.1 | 1.279 | 0.271 | 0.521 | 0.478 | 0.903 | 0.353 |
| mean rich club coefficient | 0.81 | 0.06 | 0.79 | 0.06 | 1.006 | 0.327 | 2.791 | 0.110 | 6.448 | 0.019** |

b)

| | VI (n=16) | | control (n=11) | | group | | age | | interaction | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Graph measure** | **mean** | **SD** | **mean** | **SD** | **F(1,23)** | **p** | **F(1,23)** | **p** | **F(1,23)** | **p** |
| mean node degree | 21.13 | 1.81 | 20.08 | 0.61 | 0.373 | 0.548 | 0.605 | 0.445 | 2.081 | 0.164 |
| mean clustering coefficient | 0.18 | 0.03 | 0.2 | 0.07 | 1.228 | 0.280 | 0.726 | 0.404 | 2.798 | 0.109 |
| characteristic path length | 1.08 | 0.11 | 1.13 | 0.06 | 1.831 | 0.189 | 0.022 | 0.883 | 1.309 | 0.266 |
| mean rich club coefficient | 0.78 | 0.05 | 0.8 | 0.04 | 0.684 | 0.417 | 0.349 | 0.561 | 0.931 | 0.346 |

## 8.3.4. Discussion

Previous neuroimaging studies indicated reorganisation in congenitally or early blind adults, particularly involving integration of the occipital lobe (Burton, Snyder, & Raichle, 2004; Collignon et al., 2013; Klinge et al., 2010; Liu et al., 2007). The network structure of cortical source EEG was analysed to investigate differences in the integration of cortical areas in children with congenital VI and varying degrees of functional vision. Different temporal scales corresponding to the canonical definition of the alpha, beta, and gamma band were distinguished that displayed different trajectories in a previous investigation of typical development (Bathelt et al., 2013).

Analysis of the relationship between visual acuity and connections strength revealed a significant correlation with the connection between the left lingual cortex and the right inferior frontal gyrus. A study of white matter connectivity by Shu and colleagues reported a similar result for a comparison between congenitally blind adults and matched control participants involving a connection between occipital cortex and the inferior frontal gyrus (Shu, Liu, Li, Li, Yu, & Jiang, 2009). The negative correlation with vision level (positive for LogMAR scores) may indicate decreased importance of fronto-occipital connections with lower vision levels. Further, Shu and colleagues reported a strong correlation between diffusion parameters of the inferior fronto-occipital fasciculus and connection strength between occipital and inferior frontal ROIs in the white matter network. Therefore, the current investigation also assessed the relationship betwen iFOF diffusion parameters and functional connection strength of the occipital-IFG edge. A strong, but non-significant correlation between the IFG-lingual gyrus connection and FA in the right iFOF was found. However, the number of participants that had data available on both measures was limited (n=5). These findings indicate differences in the integration of the inferior frontal gyrus and occipital areas in children with visual impairment, particularly on the right side.

## 8.4. Chapter Discussion

The present chapter focussed on investigations of functional brain organisation using resting-state EEG. On the channel level, differences in low frequency bands were found indicating differences in large-scale synchronisation between cortical areas (Buzsàki, 2006). This is also supported by differences in graph theory measures of networks in the alpha band identified in the current investigation. Correlation analysis with vision level identified that connectivity between the medial temporal and right inferior frontal areas is most strongly influenced by visual impairment. This finding is in line with previous investigations of white matter structural connectome in congenitally blind adults (Shu, Liu, Li, Li, Yu, & Jiang, 2009). Further, this result matches the predictions of the extended dorsal stream model that suggested differences in the integration of occipital areas with prefrontal areas as a consequence of visual impairment.

# Chapter 9: Summary, Discussion & Conclusion

## 9.1. Aims of the study

Children with congenital visual impairment face a high risk of adverse developmental outcomes from early infancy (Dale & Sonksen, 2002; Sonksen & Dale, 2002), including social and cognitive deficits with potential consequences for academic success and quality of life. In cases of isolated visual impairment, cognitive differences are not likely to be directly tied to the aetiology of the visual disorder itself. The interactive specialisation framework suggests cascading consequences of early differences through changes to the interplay between the individual with their environment (Johnson, 2001; 2010; Johnson & de Haan, 2010; Karmiloff-Smith et al., 2002; Mareschal et al., 2007). Thus, cognitive differences probably arise from a different experience of the world for the child with visual impairment  and associated differences in experience-expectant brain development.

In particular, the extended dorsal stream model, which was based on studies of non-human primates and acquired brain disorders in adult humans, suggested an important role of connections between visual areas of the inferior parietal lobe with target areas in the frontal, parietal, and medial temporal lobe (Kravitz et al., 2011). These connections were reported to relate to attention and spatial working memory (Courtney et al., 1998; Curtis, 2006), integration between action and vision with implications for social understanding (Gamberini et al., 2009), and spatial representation (Kravitz et al., 2011; Margulies et al., 2009; Vincent et al., 2010). A review of the (limited) existing literature on cognitive differences in individuals with visual impairment  was consistent with the assumption that congenital VI is associated with alterations in functions related to the dorsal stream connections:

Executive function was found to be affected in a detailed analysis of the behaviour of infants with visual impairment (Tadić, Pring, & Dale, 2009a) as well as neuropsychological assessment of adolescents with VI (Greenaway et al., *in press*).

Social function was reported to be compromised in a large proportion of children with VI, even in children with verbal abilities in the typical range for their chronological age (Brambring & Asbrock, 2010; Minter et al., 1998; Peterson et al., 2000). A large proportion of children with visual impairment (VI) was reported to display characteristics similar to those associated with autism spectrum disorder (Absoud et al., 2011; Brown et al., 1997; Mukkades et al., 2007; Parr et al., 2010; Rogers & Newhart-larson, 1989; Williams et al., 2013).

Spatial memory and spatial navigation were found to be impaired in congenitally blind children and adults (Afonso et al., 2010; Cornoldi et al., 2009; Schmidt et al., 2013; Ungar et al., 1995).

However, it remained unclear if deficits in these cognitive domains co-occur in the same individuals as one would predict based on the extend dorsal stream model that suggested a shared input to all of these domains. The current investigation aimed to assess the neuropsychological profile of children with visual impairment at an age at which difficulties in domains of social and executive function were thought to be most apparent and have a large impact on wellbeing (Alimovic, 2013; Hobson et al., 2010). Mid-childhood is a particularly important period of development, during which children form closer friendships with their peers and are expected to function more independently in the school environment (Shaffer et al., 2013). Further, previous research found that deficits in the social domain in children with VI are particularly pronounced during this period, e.g. Hobson et al. 2003 (see Chapter 7: Social Cognition & Social Communication for a detailed discussion).

Further, previous studies largely focussed on children with the most severe degrees of visual impairment, but visual functions lies along a continuum in this group. Even low degrees of visual function may be sufficient to mediate the development of particular cognitive skills, but not others. Therefore, the current investigation set out to investigate the cognitive profile of children with congenital visual impairment during mid-childhood in an independent sample to previous study and establish whether deficits in cognitive scores in comparison to typically-sighted peers are influenced by vision level through the inclusion of a group of children with mild to moderate visual impairment.

## 9.2. Summary of main findings

A tabular overview of the main findings of the study is provided in Table 22. The following sections provide a summary of the main findings and brief recapitulations of the main discussion points from the domain-specific chapters.

**Table 22: Overview of findings in the current study.** Symbols indicate significantly better or worse performance between groups. For scales that associate higher scores with greater degree of difficulty, e.g. BRIEF, the sign was reversed to indicate lower function. Abbreviations: VI: visual impairment; MVI: mild to moderate visual impairment; S/PVI: severe to profound visual impairment; N/A: not available; Hz: Hertz [1/s]

| Chapter | Domain | Result | Effect of vision level |
|---|---|---|---|
| **Structural Brain Organisation** | Total cortical thickness | VI < control | N/A |
| | Pericalcarine cortex thickness | VI > control | N/A |
| | Optic radiations | VI < control | SVI < MVI < control |
| | Corpus callosum - Midbody | VI > control | ✖ |
| | Corpus callosum - Splenium | VI = control | ✖ |
| | Inferior Longitudinal Fasciculus | VI = control | ✖ |
| | Inferior Fronto-Occipital Fasciculus | VI = control | ✖ |
| **Functional Brain Organisation** | Power spectral density (2-29Hz) | VI < control | S/PVI < MVI < control |
| | Power spectral density (30-99Hz) | VI = control | ✖ |
| | mean density, characteristic path length, global efficiency (8-12Hz network) | VI > control | correlation between characteristic path length and mean density with visual acuity score |

| Chapter | Domain | Result | Effect of vision level |
|---|---|---|---|
| **General Characteristics** | Verbal Comprehension | VI = control | ✖ |
| | Strengths & Difficulties | VI < control | N/A |
| | Adaptive Behaviour | VI < control | N/A |
| | Quality of Life | VI < control | S/PVI < MVI ≤ control |
| | Parent Stress | VI = control | N/A |
| **Memory** | Verbal working memory | VI = control | ✖ |
| | Verbal short-term memory | VI = control | ✖ |
| | Spatial memory | VI < control | MVI = control<br>S/PVI < control |
| **Executive Function** | Sustained auditory attention | VI = control | ✖ |
| | Divided auditory attention | VI = control | ✖ |
| | Phonemic verbal fluency | VI = control | ✖ |
| | Semantic verbal fluency | VI = control | ✖ |
| | Everyday Executive Abilities | VI < control | MVI = control<br>S/PVI < control |
| **Social Communication** | Prevalence of ASD | VI > control | N/A |
| | Pragmatic Language | VI < control | S/PVI < MVI < control |
| | Mentalizing | VI < control | MVI = control<br>S/PVI < control |

## 9.2.1. Parieto-prefrontal pathway

The first pillar of the study investigated functions related to parieto-prefrontal connections of the extended dorsal stream model. These connections are thought to be involved in the transfer of information for spatial working memory and attention (Courtney et al., 1998; Curtis, 2006). In order to distinguish effects on these skills from more general deficits, executive functions were assessed broadly in the current sample. Executive functions (EF) are a set of cognitive processes responsible for coordinating different cognitive skills in order to make plans and solve problems (Lezak, 1982; Welsh & Pennington, 1988). Previous reports on the factor structure of behavioural assessments indicated that performance on executive functions can be explained by a single factor, but underlying factors with some independent variance can be distinguished (Gioia, Isquith, Retzlaff, & Pratt, 2001).

No differences were found between children with visual impairment on tests of verbal fluency (phonemic, semantic, switching) or auditory tests of sustained or divided auditory attention. However, parent ratings indicated significant difficulties in everyday executive skills in both behavioural regulation and metacognitive control domains in line with previous results (Tadić, Pring, & Dale, 2009a). These were found to be significantly influenced by vision level with a higher degree of difficulty in children with lower visual function. The discrepancy between the behavioural assessment and the parent questionnaire may be interpreted in different ways. For one, parents of children with visual impairment may be more biased to give lower ratings, especially when invited to participate in a research project about the development of children with visual impairment. However, similar biases would be expected for questionnaires across all the cognitive domains, i.e. general adaptive function, social behaviour, language, which was not the case.

Secondly, executive function may be modality-specifc and real life executive skills may require integration of visual, auditory and haptic or kinaesthetic problem-solving, memory and organisation. However, only auditory executive skills involving auditory fluency and verbal abilities could be assessed in this study. This limited repertoire of 'executive function' may not have provided an adequate assessment of executive abilities that are required in everyday life such as organisation in the spatial environment. Moreover as auditory and verbal abilities appear to be least affected in VI children, the auditory component of executive function may be the most protected dimension.

Thirdly, it has been argued that neuropsychological tests of executive function place little demand on executive skills by providing clear instructions, training items, and a problem solving scaffold. These aids are rarely available in everyday situations (Isquith et al., 2013). Questionnaire measures on the other hand, probe difficulties in domains of executive control as observed in everyday situations by the parents.

Alternatively, it is possible that executive skills per se are similar in both the VI and the control group, but that everyday demands on executive skills are higher for children with VI. This view is supported by finding that the most severe levels of VI are associated with higher ratings of executive function difficulties. Future research could investigate executive function further in children with VI by devising non-auditory measures of executive function (e.g. spatial, haptic problem solving and set shifting) and comparing auditory and non-auditory executive abilities. Moreover, it would be useful to investigate the ability to carry out less structured problem solving tasks, e.g. requiring taking initiative, set shifting, devising new solutions.

Further, differences in the behavioural performance between children with VI and typically-sighted controls may be too subtle to be detected with the assessments employed in this study. Even though no differences were found in behavioural measures of divided auditory attention, electrophysiological methods indicated differences in processing between children with VI and typically-sighted controls in a binaural listening paradigm. The results indicated less efficient suppression of responses to interfering stimuli in the VI group compared to the typically developing controls. Further, source level analysis indicated that channel-level differences were associated with higher activation in left supramarginal gyrus, which might indicate more effortful processing in the VI group. Higher ERP amplitudes to task-irrelevant stimuli indicating less suppression of the response showed significant negative correlations with performance on the divided attention behavioural task and with parent ratings of behavioural regulation in everyday life in the VI group. In summary, the ERP findings indicated greater difficult in suppressing responses to task-irrelevant stimuli, which was associated with difficulties in everyday executive skills similar to results reported for children with executive function deficits (Stevens et al., 2008; 2009).

### 9.2.2. Parieto-motor cortex pathway

The second pillar of the study investigated functions relating to parieto-motor cortex connections of the extended dorsal stream. These connections are thought to be important for mapping between vision and body representation (Gamberini et al., 2009). They are also implicated in social understanding via other-to-self mapping (Cook et al., 2012; C. Heyes, 2010).

A body of research had documented difficulties in social understanding in children with visual impairment  (Brambring & Asbrock, 2010; Minter et al., 1998; Peterson et al., 2000) and a high incidence of behavioural characteristics associated with autism spectrum disorder (ASD) in typically-sighted children (Absoud et al., 2011; Brown et al., 1997; Mukkades et al., 2007; Parr et al., 2010; Rogers & Newhart-larson, 1989; Williams et al., 2013). In agreement with these studies, the present investigation identified a high incidence of behavioural characteristics of ASD in the current sample. However, the number of children meeting cut-off criteria for core ASD characteristics on a standard clinical questionnaire was lower than previously reported for children with VI (Absoud et al., 2011; Brown et al., 1997; Mukkades et al., 2007; Rogers & Newhart-larson, 1989; Williams et al., 2013). All children that reached cut-off criteria had severe to profound visual impairment (S/PVI), which might indicate that children with more severe levels of visual impairment are more likely to display ASD-like behaviours.

The literature has shown some controversy regarding the development of theory of mind development in children with visual impairment with some studies suggesting persistent delays and other reporting no difference to typically-sighted peers (Brambring & Asbrock, 2010; Brown et al., 1997; Minter et al., 1998; Peterson et al., 2000). The current investigation found that performance on basic theory of mind tests was similarly high in both the VI and typically-sighted control group. However, performance on tests of advanced theory of mind (figurative language understanding, faux pas, joking, pretence, and higher order theory of mind) was significantly worse in the VI group.[9] This could either indicate a persistent deficit in social understanding or a delay that extends beyond the age range included in the current study.

These findings are in contrast to some previous studies that reported that deficits in social understanding are only present in low functioning children with VI (Hobson et al., 1999). Other studies however indicated that theory of mind development is delayed in all children with VI (Green et al., 2004). Few studies have investigated advanced theory of mind understanding in children with VI and this is the first report of using Happe's advanced theory of mind stories with this population. It is likely that the sensitivity of this measure to investigate advanced theory of mind plays a role in the findings reported here as the differences in children with VI were only found in this more sensitive test of social understanding.

Similarly, an ERP investigation of the processing of basic social stimuli indicated subtle differences between children with VI and typically-sighted peers. While electrophysiological measures of responses to basic social stimuli showed similar magnitudes of responses in both groups, but responses were found to be more bilateral in the VI group, whereas the control group showed a right-sided lateralisation. This finding indicates differences in the neural substrates involved in the processing of the stimuli between the groups (Michel & Murray, 2012). Analysis of relationships between ERP and questionnaire measures (Children's Communication Checklist-2) indicated a moderate correlation between communicative ability and mean amplitude in response to own name stimuli in children with VI in a late time window. This may indicate differences in the cognitive processing of own name stimuli in children with VI, potentially involving language processing substrates.

### 9.2.3. Parieto-medial temporal pathway

The third pillar of the current investigations aimed to assess functions relating to the indirect parieto-medial temporal pathway, which is thought to be involved in visuospatial working memory, spatial memory and spatial navigation (Kravitz et al., 2011; Margulies et al., 2009; Vincent et al., 2010).

Previous studies had indicated deficits in spatial memory and spatial navigation in adults and children with VI (Afonso et al., 2010; Cornoldi et al., 2009; Schmidt et al., 2013; Ungar et al., 1995). In line with the predictions of the extended dorsal stream model, children with VI displayed a significantly lower performance on a tactile spatial memory task compared to sighted peers, whereas verbal short-term memory was statistically indistinguishable from the sighted controls. Differences on spatial memory were driven by worse performance in the severe to profound group suggesting that the development of spatial memory is only affected if visual acuity is highly degraded or absent.

### 9.2.4. Structural & Functional Brain Organisation

In addition to investigations of particular functions related to the extended dorsal stream model, the current investigation aimed to assess differences in structural and functional brain organisation in children with visual impairment directly. Previous studies in early and congenitally blind adults have reported reorganisation of structural and functional brain networks compared to matched sighted controls (Noppeney, 2007; Sadato, 2005).

In line with previous investigations, reductions in optic radiations were found (Benjamin et al., 2014; Groppo et al., 2012; Kelly et al., 2014a; Thompson et al., 2014). Further, the findings indicated reduced diffusion within the optic radiation with more severe levels of visual impairment as suggested by previous research (Borius et al., 2014; de Blank et al., 2013; Filippi et al., 2012; Glass et al., 2010). This study provides further important evidence that in children with primary congenital disorders of the peripheral visual system show more central disturbance of the visual system in the optic radiations and pericalcarine cortex. Whether this is caused by early ontological factors affecting both the peripheral visual system and also the optic radiations or activity-dependent postnatal processes is currently unknown.

Tractography analysis of segments of the corpus callosum (CC) found increased fractional anisotropy (FA) in the mid-segment, which contains connections between premotor and motor cortical areas. These findings are in line with the increased node degree of motor areas reported by Shu and colleagues (Shu, Li, Li, Yu, & Jiang, 2009) and increased fractional anisotropy within motor tracts in highly practised Braille readers

(Yu et al., 2007). Based on these studies, the observed increased FA in the mid-segment of the corpus callosum might indicate an adaptation associated with the increased reliance on tactile exploration in individuals with VI.

A reduction of FA in the posterior part of the CC was expected, but did not reach significance level. The splenium of the CC contains fibres projecting to the temporal, parietal, and occipital lobe (Hofer & Frahm, 2006). Based on anatomical knowledge, one would predict posterior projections between early visual areas to be affected given the role of callosal fibres in the transfer of information between hemispheres representing visual hemi-fields (Hubel & Wiesel, 1967).

In contrast to previous studies in adults with congenital or early blind adults (Ptito et al., 2008; Shu, Li, Li, Yu, & Jiang, 2009; Shu, Liu, Li, Li, Yu, & Jiang, 2009), no significant differences in association tracts connecting the occipital lobe with the frontal lobe (inferior fronto-occipital fasciculus) or connecting the occipital lobe with the temporal lobe (inferior longitudinal fasciculus) were found. This might be due to power issues and inclusion of participants with mild to moderate VI as discussed in previous sections. Further, white matter difference as reported for adults in previous studies may emerge later in life with exposure to particular experience (Fields, 2008; Yu, Shu, Qin, & Jiang, 2007).

Investigations of functional connectivity based on resting-state EEG indicated differences in functional organisation in children with VI compared to typically-sighted controls. Specifically, differences in low frequencies were found. Low EEG frequencies are associated with synchronisation over large cortical areas, e.g. for the coordination of up and down states of network activities between distant areas (Buzsàki, 2006). Differences in this frequency range may therefore indicate alterations in the temporal coordination of cortical activity in children with VI. This is also supported by differences in graph theory measures of networks in the alpha band identified in the current investigation. Further, weight of a fronto-occipital connection in the alpha band was found to relate to both vision level and FA within the inferior fronts-occipital fasciculus indicating a correspondence between structural and functional network organisation.

## 9.3. Discussion

As the summary of the available literature and the main findings of the study have shown, congenital visual impairment influences the development of cognitive abilities and neural substrates. The degree of cognitive deficit was found to depend on the functional domain. For instance, performance on some cognitive tasks was only deficient in children with the most severe levels of visual impairment, but was on a similar level to typically-sighted controls in children with milder forms of VI, i.e. spatial memory. On the other hand, deficits were found across all levels of visual impairment, i.e. pragmatic language. Similarly, neurophysiological investigations highlighted differences in cortical morphology and white matter microstructure that related to ability in particular cognitive domains. The following section will discuss the interpretation of these findings and the implications of the results within a wider theoretical context. First, the findings will be discussed in a dynamical systems background. Interactive specialisation is specifically discussed here due to the direct predictions for brain development. However, relevant parallels in psychology applications of dynamic systems theory (Spencer, Thomas, & McClelland, 2009) and neuroconstructivism are noted (Farran & Karmiloff-Smith, 2011; Mareschal et al., 2007).

### 9.3.1. Interactive Specialisation

Interactive Specialisation and Neuroconstructivism are theoretical frameworks that explain how complex representations can be built on top of simpler ones over development. Further, both try to integrate models of cognitive development with knowledge about brain development (Farran & Karmiloff-Smith, 2011; Mareschal et al., 2007). This is in contrast to earlier theories that had assumed that the implementation of cognitive "software" is independent of the brain "hardware" (Marr, 1982).

Interactive specialisation further expanded on these ideas and proposed a more specific framework of interaction between cognitive and brain development (Johnson, 2001; 2010). Similar to non-linear dynamic systems theory, multi-directional interaction between different levels of observation are assumed to play a major role within a highly complex, self-organising system (Spencer et al., 2009). In the following paragraphs, the main assumptions of the interactive specialisation (IS) framework (based on Johnson 2000, 2001, 2009, and 2011) will be related to the findings of the current investigation.

#### 9.3.1.1. IS: Circular causality

IS assumes that different levels like genetic factors, brain organisation, and cognition interact. Observable behaviour is an emergent property of this dynamic interaction. The results of the current investigation are consistent with this notion. Even though not directly assessed in this study, genetic factors are known to cause congenital visual impairment in various diagnostic categories, e.g. Leber's congenital amaurosis (Hamel, 2007), optic nerve hypoplasia (Garcia-Filion & Borchert, 2013), and ocular Albinism (Lorenz and Brodsky, 2009). The current study found that differences in visual function are associated with structural brain changes including reductions in the white matter integrity of the optic radiations and increased cortical thickness of the pericalcarine cortex. This study provides further important evidence that in children with primary congenital disorders of the peripheral visual system, affecting the eye globe, retina and anterior optic nerve, more central disturbance of the visual system in the brain optic radiations is identified. Whether this is caused by genetic or early ontological factors affecting both the development of the peripheral visual system and also the optic radiations from the neural crest or the lack of incoming visual stimuli post-natally constrains the 'driving' of the further development of the central visual system is unknown. Further, the results of the current study show that visual impairment is associated with cognitive changes, e.g. deficits in spatial memory and social understanding. There is also evidence from other studies that suggests that interactions from higher levels to lower levels occur. For instance, primary visual areas were found to mediate Braille reading in adults, which was associated with changes in cortical organisation (Fujii, Tanabe et al. 2009, Burton et al. 2002, Burton, Snyder et al. 2004). This is generally interpreted to reflect reorganisation in response to increased demands of tactile discrimination in experienced Braille readers. Findings of deficits in processing social information in the current investigation can be interpreted along similar lines. Because visual information from salient visual signals like facial expression or body posture is largely inaccessible to individuals with visual impairment, neural substrates involved in the processing of social stimuli may develop differently. Differences in the response topography to basic auditory social stimuli between children with VI and typically-sighted peers in the own name ERP paradigm in the current investigation supports this view.

### 9.3.1.2. IS: Interactivity and brain networks

IS assumes that the specialisation of a cortical area depends on its context within a network of brain regions. Cortical thickness of the pericalcarine cortex was found to be increased, which is generally interpreted to reflect a less mature state of cortical development, i.e. reduced activity-dependent synaptic pruning. Therefore, morphological markers of structural maturation of the pericalcarine cortex in children with VI appear to be influenced by the microstructural integrity of the main afferent, the optic radiations. Further, reduced white matter integrity in the optic radiations was observed in the current investigation. Reduced FA may reflect reduced myelinations. Therefore, reduced FA in the optic radiations may represent a difference in experience-driven process brain maturation.

Alternatively arguing along the lines of the meta-modal organisation hypothesis (Pascual-Leone, Amedi, Fregni, & Merabet, 2005), findings about reorganisation in individuals with VI may also be interpreted to reflect un-masking of processing capacity within cortical areas that are usually pre-occupied with the processing of visual information (meta-modal organisation hypothesis) (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). This account assumes that cortical areas continuously compete for processing and do not become hardwired for a specific task in contrast to the suggestions of the IS framework. Experiments with typically-sighted individuals that were visually deprived for several days showed that processing of non-visual information in primary visual areas can occur after relatively short time (Pascual-Leone & Hamilton, 2001). Therefore, differences in cortical organisation could reflect a current equilibrium state within a meta-modal dynamic system that arises from ongoing processing demands (meta-modal account) rather than the more rigid stable state reached over developmental time (as proposed in the interactive specialisation account). This may be reflected in the differences of functional organisation observed in resting-state EEG analysis in the current investigation. Differences in the frequency composition may indicate an altered interaction between brain regions due to differences in visual experience over developmental time.

### 9.3.1.3. IS: Self-organizing and activity-dependent processes

IS assumes that self-organisation is an activity-dependent process. This assumption relates to the active pursuit of experiences that are important for the continuing adaptive development of the cognitive system. Visual impairment as a deprivation model of brain and cognitive development is a difficult case for this assumption, because visual information is not necessarily replaceable by seeking-out experiences in other modalities, such as auditory or haptic. The enhanced reliance on language (Edmonds & Pring, 2006) could be interpreted as an attempt to acquire "second-hand" information about the visual world. This sample of children with VI had all achieved verbal reasoning abilities (verbal IQ) comparable to their typically-sighted control peers and it could be speculated that they had actively pursued experiences through other modalities to learn about the world and experiences around them. The achievement of cognitive ability to such a level of learned information and reasoning ability suggests adaptive development of the cognitive system in the context of visual impairment. However, the current investigation was cross-sectional and could therefore not identify changes related to the active acquisition of information.

### 9.3.2. The extended dorsal stream hypothesis

A review of downstream targets of the dorsal visual stream indicated the integration of dorsal stream areas with target areas in the prefrontal, parietal, and medial temporal lobe (Hebart & Hesselmann, 2012; Kravitz et al., 2011) (extended dorsal stream model). Lesion studies in macacques and human neuroimaging of healthy participants and patients with focal brain damage suggested that these connections are associated with spatial aspects of attention and working memory (Courtney et al., 1998; Curtis, 2006; Watanabe, Igaki, & Funahashi, 2006), other-to-self mapping (Gamberini et al., 2009; Rizzolatti & Matelli, 2003; Rizzolatti et al., 1988), and spatial representation/spatial navigation (Bonino et al., 2008; Fiehler & Rosler, 2010; Vincent et al., 2010).

Due to differences in size and complexity of receptive fields, dorsal and ventral stream function may be differently affected by visual impairment. Indeed, previous investigations had suggested that the visual dorsal stream is particularly vulnerable to developmental insult (Atkinson & Braddick, 2011; Braddick, Atkinson, & Wattam-Bell, 2003). Deficits in dorsal stream function were reported in the literature across a range of neurodevelopmental disorders including ASD (Spencer et al., 2000), dyslexia (Cornelissen et al., 1995), fragile-X syndrome (Kogan, Bertone, et al., 2004a; Kogan, Boutet, et al., 2004b), hemiplegia (Gunn et al., 2002), premature birth (Atkinson et al., 2002), and William's syndrome (Atkinson et al., 1997).

Because visual functions related to the dorsal and ventral stream could not be accurately measured in the current investigation, cognitive function related to the extended dorsal stream connections were assessed. Based on the extended dorsal stream model, one would assume that all associated functions are impaired if the common input was changed. A review of the existing literature on cognitive function in congenital VI supported the assumption that there are differences in cognitive functions associated with the three streams.

#### 9.3.2.1. Parieto-prefrontal pathway

Downstream connections of the dorsal stream with target areas in the prefrontal cortex suggested a role of dorsal visual stream information in visuospatial working memory and aspects of attention with a spatial component (Courtney et al., 1998; Curtis, 2006; Marrett et al., 2011; Watanabe et al., 2006). There is evidence from adult studies that integration between dorsal stream areas with prefrontal targets for tactile spatial working memory is also present in congenitally blind individuals (Bonino et al., 2008; Fiehler & Rosler, 2010). However, differences in the development of this integration may explain deficits and individual differences in attention and spatial memory as reported for children with VI (Cornoldi et al., 1991; Halko, Connors, Sánchez, & Merabet, 2013; Liotti, Ryder, & Woldorff, 1998; Smits & Mommers, 1976; Tadić, Pring, & Dale, 2009a). However, the current investigation did not find evidence for a deficit in auditory attention in direct assessments. It is possible that adequate integration within the fronto-parietal attention network to support task performance is achieved earlier in development through other sensory input. Alternatively, domain-general cognitive control mechanisms within the prefrontal cortex may be more engaged, whereas activation in superior parietal areas is reduced. Along these lines, electrophysiological differences in the response to irrelevant stimuli in a divided attention task showed more frontal activation, which could be interpreted along these lines. However, task performance and ERP effects between the VI and typically-sighted control group were confounded, which limits the interpretation of these results.

#### 9.3.2.2. Parieto-motor cortex pathway

Motion sensitive areas (area MT) in the dorsal visual stream reach target areas in the motor and supplementary motor cortex (Gamberini et al., 2009; Rizzolatti et al., 1988; Rizzolatti & Matelli, 2003). Some neurons within the motor cortex are equally active when a motor action is observed in another agent as they are when the individual is carrying out the action himself (Keysers & Gazzola, 2010; Keysers, Kaas, & Gazzola, 2010; Rizzolatti et al., 2001). Based on these response properties, these neurons have been called mirror neurons. Mirror neurons are thought to play an important role in social interactions in humans by facilitating the decoding of other agent's intentions through self-other mapping (Blakemore & Frith, 2005; Iacoboni, 2005; Iacoboni et al., 2005; Kilner, Marchant, & Frith, 2009). Theoretical accounts suggest that mirror properties arise from learned associations between action execution and observation (Cook et al., 2012; Heyes, 2010; 2013). The mirror neuron system is thought to be supra-modal in typical individuals and activated both by vision and sound and has been shown to be active in adults with profound visual impairment (Ricciardi et al., 2009). However, learned associations between action and observation may develop differently in the case of visual impairment. Differences in the mirror neuron system function are likely to be most apparent in tasks that benefit from self-other mapping as a task strategy (Bonini, Ferrari, & Fogassi, 2013; Corradini & Antonietti, 2013). For instance, self-other mapping is one possible strategy to solve theory of mind tasks that require an understanding of intentions of agents.

Theory of mind and figurative language understanding were assessed in children with visual impairment in the current investigation. Deficits in social understanding were found in children with VI compared to typically-sighted peers. However, deficits were most pronounced for items of figurative language understanding. Further, verbal ability emerged as an important determinant of task performance. Therefore, the profile of difficulties on social understanding tasks might not suggest a deficit in theory of mind understanding that is mediated by connections between motion-sensitive areas of the dorsal visual stream and motor cortex targets. Instead differences in the resolution of figurative speech could be linked to language-specific differences in the processing of non-literal language. Correlations between general communication scores and altered response topography found in the ERP own name paradigm also suggested differences in the engagement of the language system (see chapter on social cognition and social communication for a detailed discussed on alternative interpretations). However, research in sighted children have found evidence of association between mirror neuron resolution and ASD characteristics, which include difficulties in pragmatic language and communication and social responses (Enticott et al., 2012). The findings of this project with VI children cannot rule out a deficiency in mirror neuron and perceptual-motor cortex responses which may underpin social development as these were not directly investigated. On the other hand, the current investigation neither found strong support for deficits in theory of mind understanding or structure and function of superior parietal areas associated with the human mirror neuron system (Kampe et al., 2003).

### 9.3.2.3. Parieto-medial temporal pathway

The extended dorsal stream model incorporated indirect connections between motion-sensitive areas of the dorsal stream with target areas in the medial temporal lobe (Kravitz et al., 2011). These connections are thought to provide visual information to areas involved in spatial navigation and spatial memory, i.e. hippocampus, parahippocampal cortex, entorhinal cortex (Gamberini et al., 2009; Margulies et al., 2009; Vincent et al., 2010). Differences in visual input are likely to result in deficit in these functions. The current investigation found deficits in spatial memory in children with congenital VI with the most severe level of vision reduction (P/SVI).

### 9.3.3. Conclusion

In summary, the extended dorsal stream model suggested common input to areas associated with spatial aspects of executive function, social understanding, and spatial memory via superior parietal areas of the dorsal stream (Kravitz et al., 2011). However, neuropsychological assessments of these functions did not indicate impairments in all of these domains in children with congenital VI. In the case of a deficit of dorsal stream function, downstream connections associated with attention, social understanding, and spatial memory would be expected to all show impaired function.

Analysis of white matter connections did also not suggest differences in long-range connections of the occipital. However, it is possible that differences in short-range cortico-cortical connections exist between dorsal stream areas of the parietal cortex and downstream target. Further, analysis of resting-state EEG data on the source level showed differences in long-range functional connectivity. Structural and functional connectome analysis further indicated differences in local edge weight, but not in global measures of network efficiency. Differences were not specific to posterior parietal areas as would be expected for an isolated deficit in integration along the extended dorsal stream.

Based on these findings and emerging attempts of characterising human in vivo imaging through the application of network science (Fox & Raichle, 2007; Hagmann et al., 2012; Sporns, 2002), an alternative view of visual area integration in visual impairment is suggested. Structural and functional connectomics in the human brain identified the presence of hub regions that show extensive connections to other brain areas (Ball et al., 2014; Sporns, 2013). Further, simulation studies and studies of neurodevelopmental disorders and acquired brain injury found that changes to connection properties of hub regions are associated with large effects on overall brain network architecture and lead to disproportionate decrements in functional measures (Crossley et al., 2014). Further, hub regions are found in areas that are highlighted within the dorsal stream model, including central hubs like the superior parietal lobe. Therefore, the extended dorsal stream model may be re-conceptualised to incorporate a whole-brain network perspective. Some dorsal stream connections are directly compatible with well characterised functional networks. For instance, posterior parietal connections with the prefrontal cortex are described as the fronto-parietal attention network in the connectomics literature (Ptak, 2012; Szczepanski, Pinsk, Douglas, Kastner, & Saalmann, 2013). However, the effect of primary sensory disorders on brain connectomics is currently understudied. Only a handful of studies applied a network perspective to the analysis of structural and functional neuroimaging data from congenitally blind adults (Jiajia Li et al., 2013; Sani et al., 2010; Shu, Liu, Li, Li, Yu, & Jiang, 2009). Further, accounts of interactions between sensory deprivation and network architecture over development are completely missing. Network analysis in the current investigation suggested similar network properties including similar global efficiency in children with congenital VI. On the other hand, structural differences in visual areas were observed, i.e. increased cortical thickness of the pericalcarine cortex. The mechanisms by which similar network efficiency can be achieved despite altered sensory experience should be addressed in future work.

### 9.3.3. Criticism of theoretical frameworks

The discussed theoretical framework is somewhat focussed on mechanisms within one individual and simplifies or ignores the influence of the social environment. The social environment consists of complex and adaptable systems, which is likely to fundamentally influence the development of the individual (Belsky & de Haan, 2011). For instance, parenting behaviour is thought to play a major role in the early development of infants. Previous studies found that parenting is less effective and more inconsistent for children with neurodevelopmental disorders (Modesto-Lowe, Danforth, & Brooks, 2008).

These differences in parental behaviour will introduce initial differences that may impact on the developmental trajectory. With reference to the current investigation, parents may differ in their ability to interact with children with visual impairment and may be more or less able to compensate for the challenges posed by sensory deprivation. Cognitive differences in children with visual impairment are likely to be in part influenced by this variation in parent behaviour. The current investigation found higher rates of anxiety in parents of children with visual impairment indicating that visual impairment of the child influences parent emotional state. However, the effect of parent behaviour on cognitive development in children with visual impairment is beyond the scope of the current investigation and will need to be addressed in future studies.

In addition to influences of the family environment, societal norms are also likely to influence development (Keller et al., 2009). It has been argued by advocates of integration and independence for visually impaired individuals that children with visual impairment are often prohibited from pursuing certain activities that would be appropriate for their age, because a predominantly sighted culture overestimates risk and underestimates the ability of these children (World Access for the Blind organisation, Santa Barbara US). Societal expectations influence the behaviour of people towards the developing child, which will influence the cognitive development by changing the opportunities and incentives (Lerner, 20120). However, there is currently no framework that integrates cognitive theory with social psychology/sociology to provide clear predictions that could be empirically tested.

## 9.4. Limitations

The current investigation was constraint in several ways, which limits some of the conclusions that can be drawn from the result. A general caveat is that the study was devised, carried out, analysed and interpreted by the same person (J.B.). Therefore, the main author was aware of the hypotheses and the vision level of each child, which might introduce examiner bias. Ideally, assessment and analysis would be assigned to different researchers, who are not aware of the purpose of the study. However, practical considerations prevented this approach. Further, it is highly impractical to avoid that a researcher is aware of the vision level of child with visual impairment in an assessment situation. Abnormalities of the anterior visual system are also apparent on MR images. Nevertheless, the investigator in this study used standardised assessment materials only requiring standard administration and where no subjective interpretation or judgement is required. The only assessment that required subjective judgment (Happé Theory of Mind stories) was independently assessed by raters, who were not aware of VI status.

In addition, testing material had to be selected that are suitable for children with visual impairment. Many standard assessments for social understanding and executive function are vision-based, e.g. reading the mind in the eyes test (Baron-Cohen, Riordan, Stone, Jones, & Plaisted, 1999), trial making (Anderson, 2002). Further, validity may be compromised because visual materials had to be excluded, i.e. NEPSY-II Theory of Mind task. Additionally, test scores were corrected for age effects based on norms derived from typically-sighted children. The Intelligence Test for Visually Impaired Children (Dekker, 1993) contained separate norms for children with visual impairment and sighted children.

In addition to methodological limitations, limitations are associated with the sample of the current study. For one, the sample size was very limited, which is mainly due to the inherent rarity of the congenital disorders of the peripheral visual system under investigation (Rahi et al., 2003) and geographical recruitment constraints in the time period of the study. Because of the small sample size, only large effects could be detected. Further, significant effects that were found are likely to overestimate the effect size (Button et al., 2013). An associated issue concerns the heterogeneity of the sample. In order to reach a sample size that allowed for a meaningful group comparison, a range of disorders were included that share common symptoms, i.e. visual impairment and CNS involvement restricted to the peripheral visual system. The individual disorders are extremely rare with often little understood and complex genetic causes so that heterogeneity is even found within diagnostic categories, such as Leber's amaurosis or other retinal dystrophies. Therefore, the possible argument that differences in a subgroup of cases that fall in one diagnostic category is skewing the group differences in the VI group cannot be excluded. This might especially be the case for disorders that are also associated with lower visual acuity. In fact, some researchers have argued that autistic features are particularly prevalent in Leber's congenital amaurosis (Fazzi et al., 2007; Rogers & Newhart-larson, 1989). However, newer investigations with larger clinical samples support the view that visual function is the most predictive factor of early developmental difficulties including 'developmental setback' and autistic features and that they occur across a wide range of congenital disorders of the peripheral visual system (Dale & Sonksen, 2002; Parr et al., 2010; Sonksen & Dale, 2002).

The representativeness of the current sample also demands cautious interpretation of findings. Children were recruited to have intellectual function within the typical range for their age, which is not the case for a large proportion of children with visual impairment who have additional intellectual disabilities (Alimovic, 2013; Rahi et al., 2003). Further, children were mostly recruited through specialised clinical services so that the sample is potentially clinically biased towards children with specific problems; nevertheless a proportion of the children were identified via the clinic database and had been referred to and attended the clinical service in their earlier years for routine specialised guidance and had been subsequently discharged once they entered mainstream school environment. In addition, some families with children with VI with severe autistic features initially agreed to participate, but were prevented from attending due to concerns about sensory overload associated with travelling to the appointment. For this reason, the sample is also likely to be biased towards higher functioning children with less severe autistic features or behaviour difficulties. In conclusion, it cannot be assumed that the current sample is representative of children with visual impairment. It is known that it is not representative of the total range of intellectual ability and cognition found in the population of children with visual impairment, but this was not sought from outset. However, insights gained from the present investigation are informative about the potential impact of visual impairment on a heterogeneous sample of higher functioning children with 'simple' congenital disorders of the peripheral visual system. The findings in turn highlight potential mechanisms that may translate across visual disorders and degrees of severity. The findings therefore signify a proof of principle, which indicates that even in the children with the "purest" visual impairment deficits in certain cognitive domains and associated neural differences are present.

## 9.5. Implications for Clinical and Educational Practice

The results of the current investigation have implications for the education and assessment of children with VI. First, the results of the executive function and social communication assessment show that large proportion of children with VI display some deficit in these domains. These results demonstrate that cognitive skills that do not seem directly linked to vision may be affected in children with VI. In addition, tasks may pose additional demands in children with VI that exceed the capacity of a particular cognitive skill even when the skill itself is on a similar level to sighted peers. For instance, in a classroom setting, an exercise may be more demanding for a child with VI, because the location of objects needs to be held in memory alongside the task instructions. It is therefore important to evaluate additional task demands for children with VI and adjust exercises to their needs, e.g. by providing additional aids or training children with VI in strategies that minimise cognitive demands.

In addition, the largest effects were observed in children with the most severe degree of VI, but a large proportion of children with milder forms of VI also showed deficits in some domains compared to typically-sighted children. Children with mild to moderate VI usually attend mainstream education and commonly do not receive additional support like children with more severe degrees of VI. The findings of the current investigation indicate that some support may be necessary to help these children. It also calls for additional research to establish the particular needs of children with mild to moderate VI as this group has been largely neglected in previous research.

Further, research in individuals with VI from infancy to adolescence suggests that the trajectory of cognitive development is altered. This is illustrated in a number of publications that report delayed development of Theory of Mind abilities in children with VI (Brambring & Asbrock, 2010; Minter et al., 1998; Peterson et al., 2000). In contrast to typically-sighted children, children with VI pass Theory of Mind tests later, but show rapid development that seems to depend on vocabulary size (Brambring & Asbrock, 2010). The results of the current investigation add that these skills may still be developing at school age. These findings illustrate two important points for education and clinical practice. First, the development of children with VI with reference to typically-sighted children may not be a fruitful approach. Children who appear to be impaired in comparison to typically-sighted peers, may display typical development for children with VI. Furthermore, any cognitive deficit that may be apparent at one stage is not necessarily present at a later stage (see Hobson et al. 2010). These findings call for the development of comparative norms of children with VI (also see Sonksen et al. 1983 and Dekker et al. 1993) for accurate clinical assessment of children with VI.

## 9.6. Future Directions

The current investigation assessed the impact of visual impairment of varying degrees on the development of cognitive abilities in children with congenital visual impairment. In order to further expand on this hypothesis additional groups could be studied. For instance, the current study focussed on children with disorders affecting the anterior peripheral system. Future studies could investigate the impact of damage to central parts of the brain that affect higher areas along the visual processing stream, e.g. focal damage to areas of the ventral vs. dorsal visual stream. This would provide insight into the importance of particular aspects of visual function for the development of particular cognitive skills. Alternatively or in addition, visual abilities could be investigated in children, who score on extreme ends of the distribution on standard assessments of cognitive function. For instance, it is possible that children who perform poorly on assessments of spatial representation show deficits in psychophysics assessments of dorsal stream function.

Further, future work should address the role that sensory experience play over time in the development of cognitive skills. Cognitive skills should be compared between groups of children with different sensory impairments at different time points (Farran & Karmiloff-Smith, 2011). This methodology would help to distinguish non-specific effects of a sensory impairment from modality-specific effects and thereby inform theories of cognitive development.

In addition, the current study and previous work established that children with visual impairment are at risk for adverse developmental outcome (Dale & Sonksen, 2002). However, there was also evidence for inter-individual variation with some individuals performing within the typical range, despite having the most severe degree of visual impairment. Future work should focus on investigating factors that contribute to worse or better outcome in individuals with VI, which would be best addressed through multivariate longitudinal research programmes. This research would help to better understand and address the debilitating effects that these life-long condition have on many individuals and help every child to reach their full potential.

## 9.7. Conclusion

The present study investigated cognitive profiles and neural correlates of congenital visual impairment during mid-childhood. The results of the study show that certain cognitive functions, particularly social understanding and spatial memory, are affected by visual experience. Further, investigations of neural correlates indicated structural alterations in the development of neural substrates related to visual processing with effects on structural and functional brain network architecture. In addition, results of the present study indicated dose-response relationships between visual acuity and differences on the cognitive and neural level. The current investigation thereby provides evidence that visual experience influences neural and socio-cognitive development. These findings lend support to cognitive theories that suggest a role of interaction between the cognitive system and the environment during cognitive development and to theories that assume a role of experience in brain development.

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1. In addition to the photoreceptors, there are also light-sensitive ganglion cells that mediate the entrainment of the circadian rhythm and melatonin synthesis {Freedman:1999ez}.
2. It is important to note that segregation between areas for vision for action and vision for object recognition already exists within V1/V2 in the form of parallel pathways {GrillSpector:2004kp}
3. Please note that the following section is an adapted version of previously published work by the author. The full article can be found in the appendix.

Reference to the original article:
Bathelt, J., O'Reilly, H., de Haan, M. Cortical Source Analysis of High-Density EEG Recordings in Children. J. Vis. Exp. (88), e51705, doi:10.3791/51705 (2014).

4. Please note that complete independence between the signals is not assumed. There is a clear statistical relationship between peripheral biological artefacts, e.g. EMG contamination through movement, or EOG activity through ocular artefact, and brain signals. However, previous studies found that the EEG signals measured on different locations on the scalp are more similar to each other on the relevant measures (peak

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amplitude, amplitude variance etc.) than to peripheral "artefact" signals, which is sufficient for ICA-based separation.

5. Higher performance cannot be adequately compared due to ceiling effects and large variation in both the current and normative sample.

6. Please note that similar associations were found for other developmental groups , e.g. Bishop et al. 2006. Therefore, the association between language ability and social skills is by no means assumed to be unique to children with visual impairment.

7. NB: Differences in age range, participant gender, and methods do not allow for a direct comparison of statistical power with the previous studies.

8. Please note that this introduction is an adapted version taken of previously published original work by the author:

Bathelt, J., O'Reilly, H., Clayden, J. D., Cross, J. H., & de Haan, M. (2013). Functional brain network organisation of children between 2 and 5 years derived from reconstructed activity of cortical sources of high-density EEG recordings. NeuroImage, 82, 595–604. doi:10.1016/j.neuroimage.2013.06.003

The entire manuscript can be found in the appendix

9. NB: there were no interactions between verbal IQ and group indicating that differences in task performance between groups were not driven by verbal IQ differences

## Appendix I:

Bathelt, J., O'Reilly, H., Clayden, J. D., Cross, J. H., & de Haan, M. (2013). Functional brain network organisation of children between 2 and 5 years derived from reconstructed activity of cortical sources of high-density EEG recordings. *NeuroImage*, *82*, 595–604. doi: 10.1016/j.neuroimage.2013.06.003

# Supplementary Material

In order to exclude the possibility that the use of a relative threshold in the main analysis influenced the conclusions of the study, we analysed the same data with an absolute threshold. A threshold of 0.3 was chosen.

Further, in order to exclude the possible that the reported associations between participant age and graph theory measures are due to the use of different head models in the source reconstructions, we scrambled the topography of the EEG. The original channel order was randomised for each participant and subsequently analysed as described in the main study. The results of the analysis are presented in the following section.

In addition differences in the fit between inverse model and original data could lead to spurious results. In order to exclude this possibility, we calculated the goodness of fit between the recorded data and data predicted based on the inverse model for each epoch and each participant. Recordings were simulated using built-in BrainStorm functions. The simulation was based on the inverse solution for each epoch. We used $R^2$ as a measure of model fit. $R^2$ was averaged over channels for each epoch. $R^2$ in each frequency band was entered as a covariate in an analysis of covariance model (ANCOVA) with frequency band as a fixed factor and participant age as the dependent variable.

## Results

After thresholding with an absolute cut-off, the same network measures were obtained as in the main analysis. The same ANOVA model with frequency band as a fixed factor and age as a covariate was applied to the graph theory measures. There was a significant effect of age on mean node degree and mean clustering coefficient (F(1,92)=5.71, p=0.02; F(1,92)=8.21, p =0.005). There was also a trend for an effect of age on maximum betweenness centrality (F(1,92)=2.84, p=0.096). There was no significant effect of age on characteristic path length in the measures obtained from networks thresholded to an absolute threshold of 0.3 (F(1,92)=0.16, p=0.69).

There was a significant differences between frequency bands for mean node degree, mean clustering coefficient and characteristic path length (F(2,92)=5.17, p=0.008; F(2,92)=12.671, p<0.001; F(2,92)=5.724, p=0.005). There was no difference between measures obtained from networks based on activity in the three frequency bands for maximum betweenness centrality (F(2,92)-2.31,p=0.11).

After scrambling the EEG topography, there were no significant correlations between mean node degree, mean clustering coefficient, characteristic path length or maximum betweenness-centrality and age in all frequency bands that survived Bonferroni correction (see Supplementary Figure 2 and Supplementary Table 1).

Further, there was no association between participant age and $R^2$ (Age: F(1,92)=0.161, p=.69; Frequency band: F(3,92)=0.151, p=.93)(see Supplementary Figure 3). Further, all values are above 0.9 indicating a good fit between the model and the data (see Supplementary Table 2).

## Discussion

The analysis shows that the main outcomes of the analysis are robust to the application of an absolute threshold. The increase of node degree and clustering coefficient is replicated with the absolute threshold. Maximum betweenness centrality and characteristic path length show less consistent results. However, it is apparent from the scatter diagram that the general trend of a decrease in characteristic path length with age is present even with an absolute threshold. The increase in node degree and clustering coefficient indicate a decrease in path length. Maximum betweenness-centrality is particularly influenced by the threshold. It is important to note that the maximum betweenness centrality differs between the frequency bands under investigation. A possible cause is noise in the EEG recordings. Different frequency bands contain different amounts of artefact. The most pronounced differences can be seen in the 12-25Hz band, which might contain residual contamination of eye blink and movement artefacts even after artefact correction. In contrast to the lower frequency band, the signal in the 12-25Hz band is not as strong, because it does not overlap with prominent activity like the alpha oscillations (5-12Hz depending on age) (Marshall et al., 2002). Consequently, this frequency band might especially be affected by noise.

In summary, the analysis shows that certain graph measures are more liable to the influence of thresholds. However, thresholds need to be applied to obtain networks that are sparse enough to make use of the graph measures. A threshold that is set relative to the mean connectivity of the network controls the influence of network-specific noise. The main findings of the study can be replicated with absolute thresholds, but the limitations of graph measures in densely connected networks and the influence of network-specific noise need to be considered.

Topographical scrambling of the EEG data maintains the all features of the data, but leads to scalp maps that are not meaningful. Minimum-norm estimation aims to match the distribution of voltage on the scalp to the predictions of the forward head model. The results based on the topographically scrambled data do not replicate the associations between participant age and graph theory measures found in the main study. We therefore conclude that these associations cannot be explained by the use of different templates for different age groups alone. It is instead more likely that they reflect dynamics that are present in the original EEG data.

Similarly, the finding that there is no significant association between participant of age and goodness of fit between data predicted by the model and original data indicates that differences in the quality of the inverse model for participants of different age do not explain the observed associations in graph measures derived from the inverse solution. Further, no significant differences was found between goodness of fit in the three frequency bands. Therefore, differences between frequency band in graph theory measures based on the inverse model cannot be ascribed to differences in the fit of the model in each frequency band. The high values of the goodness of fit measure, $R^2$, further increase the confidence in the accuracy of the inverse solution.

# Supplementary Figures

Captions:

**Supplementary Figure 1: Correlation between mean node degree, clustering coefficient, maximum betweenness-centrality, characteristic path length and age of the participant derived from networks thresholded to an absolute threshold of 0.3** There is a significant effect of age on mean node degree and clustering coefficient (Node degree: F(1,30)=6.542, Clustering coefficient: F(1,30) = 7.169, $p<0.05$). There is a significant effect of frequency band on all measures (Node degree: F(1,30)=6.69; clustering coefficient: F(1,30)=13.99; betweenness-centrality: F(1,30)=4.08; characteristic path length: F(1,30)=6.46, $p<0.05$). The lines show least-square fitted lines for each frequency band to make linear associations easier to visually assess.

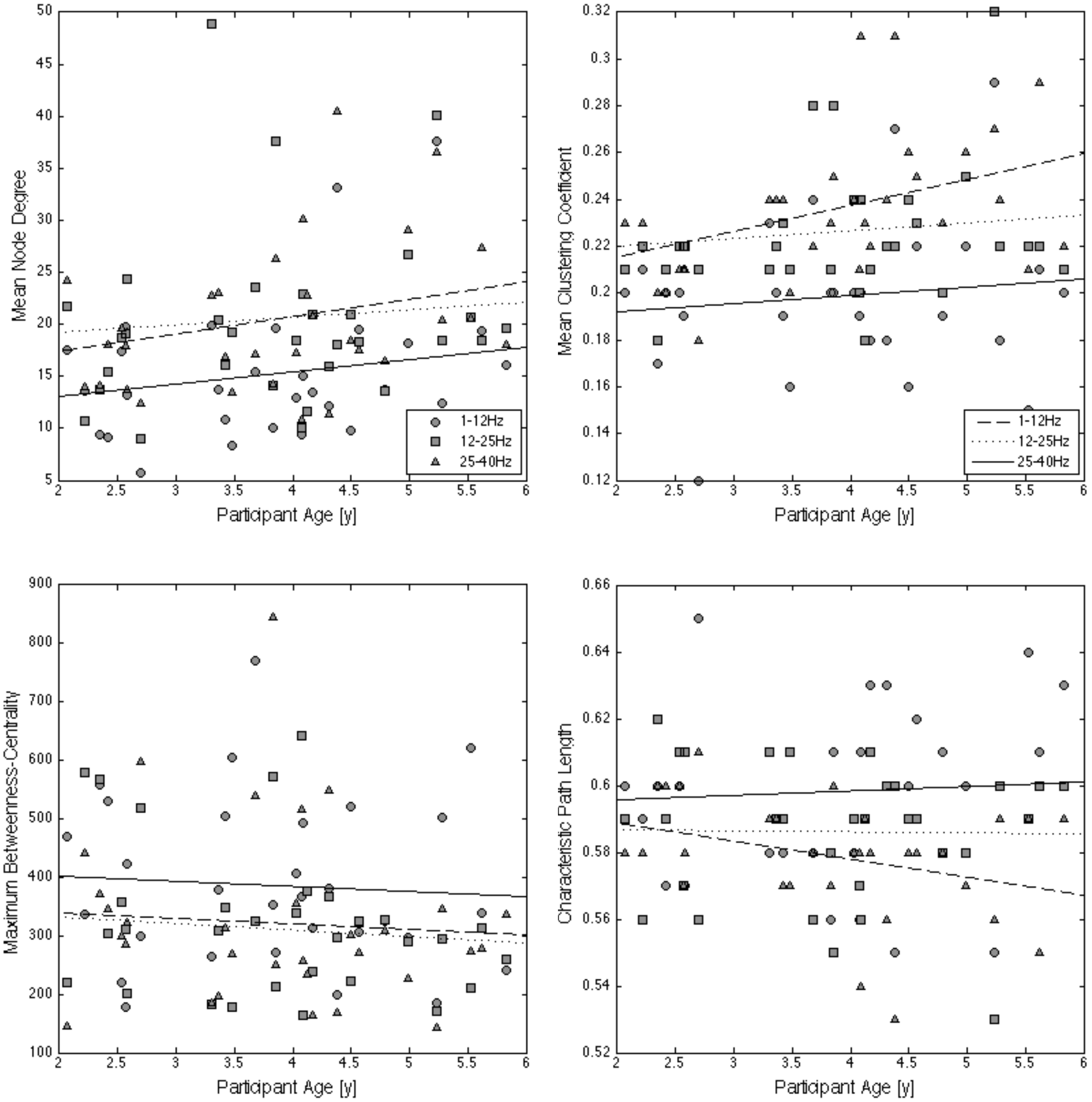
**Supplementary Figure 2: Correlation between mean node degree, clustering coefficient, maximum betweenness-centrality, characteristic path length and age of the participant derived from networks averaged channel locations were scrambled**

**Supplementary Figure 3: Fit between data predicted by the inverse model and the actual data in all frequency bands for each participant** The fit of the predictions of the inverse model and the actual data was measured as R2. R2 were calculated for each epoch and were averaged over EEG channels. The graph shows the average R2 value for each participant in each frequency band. The dotted lines show least squared fitted regression lines. There was no significant association between participant age and R2. There was also no significant difference in R2 between the frequency bands.

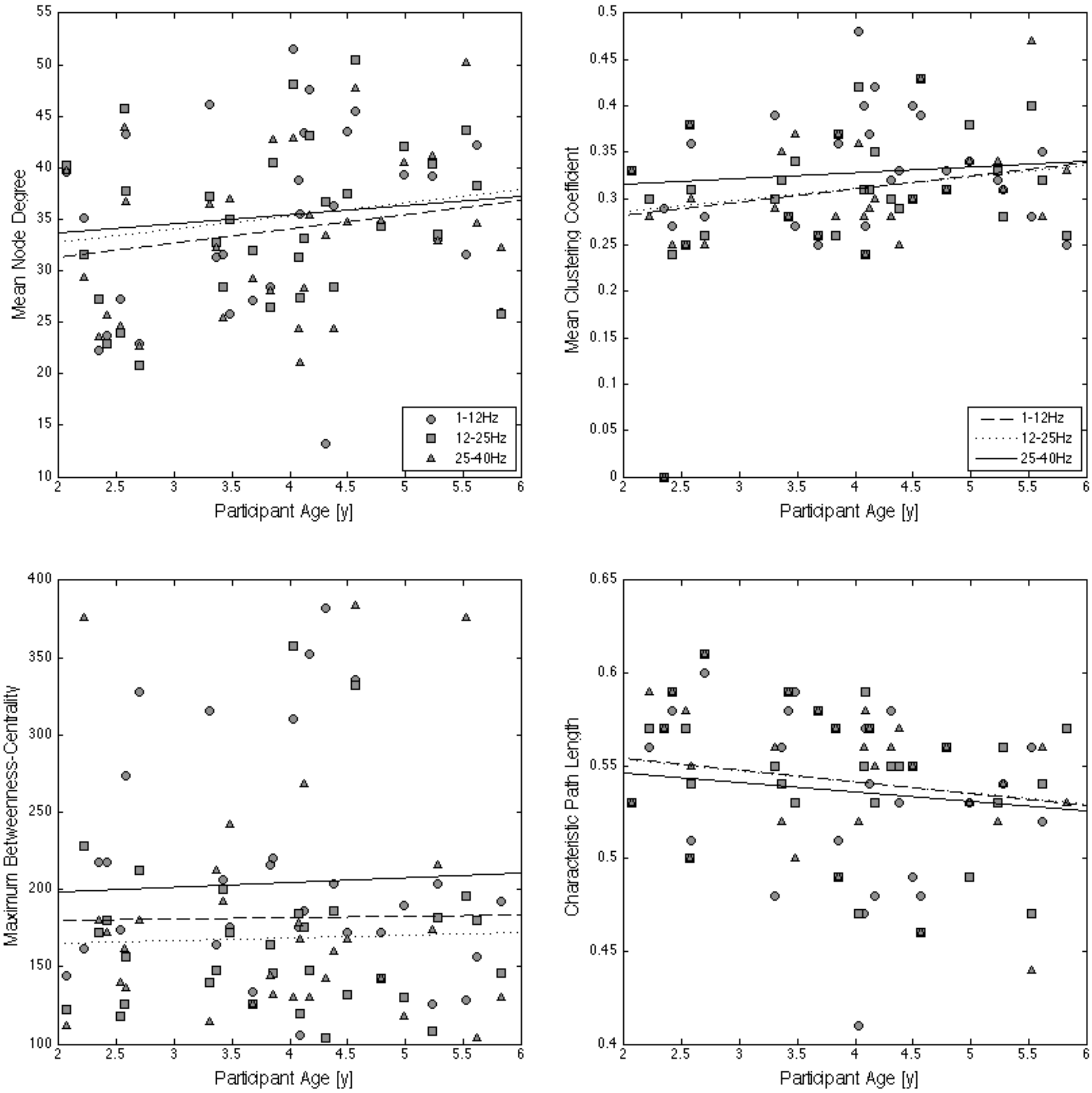
**Supplementary Table 1: Results of correlation analysis between graph measures and participant age for topographically scrambled EEG data in each frequency band** No significant correlations between graph measures and participant age were found in all frequency bands for graph measures based on topographically scrambled EEG data. Correlations are reported as Pearson correlation coefficients. Uncorrected and Bonferroni-corrected *p*-values for multiple comparison are presented.

**Supplementary Table 2: Goodness of fit and variation of goodness of fit in each frequency band.** Goodness of fit between model and recorded data is expressed as R2. The values represent the mean value, standard deviation and standard error of R2 for all participants in each frequency band.

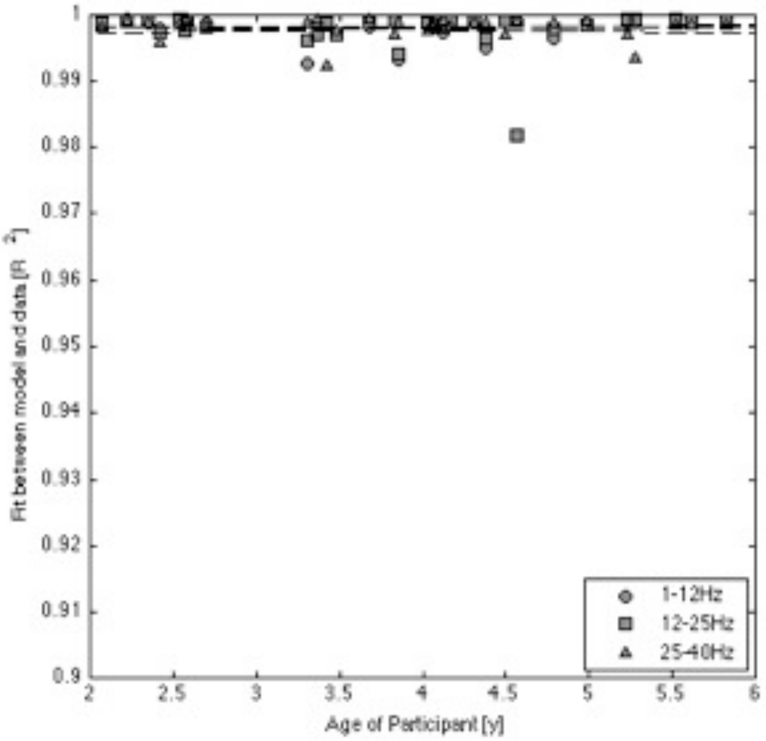
**Supplementary Figure 1:**



**Supplementary Figure 2:**



**Supplementary Figure 3:**



## Supplementary Table 1

1-12Hz:

| **Graph Measure** | **Pearson correlation coefficient (r)** | **Significance Value (p)** | **Bonferroni-corrected p** |
|---|---|---|---|
| Mean node degree | 0.133 | 0.237 | 0.948 |
| Mean clustering coefficient | 0.117 | 0.266 | 1 |
| Characteristic Path Length | -0.78 | 0.339 | 1 |
| Maximum Betweenness-Centrality | -0.168 | 0.183 | 0.732 |

12-25Hz:

| **Graph Measure** | **Pearson correlation coefficient (r)** | **Significance Value (p)** | **Bonferroni-corrected p** |
|---|---|---|---|
| Mean node degree | 0.282 | 0.62 | 1 |

| Graph Measure | Pearson correlation coefficient (r) | Significance Value (p) | Bonferroni-corrected p |
|---|---|---|---|
| Mean clustering coefficient | 0.337 | 0.032 | 0.128 |
| Characteristic Path Length | 0.028 | 0.441 | 1 |
| Maximum Betweenness-Centrality | -0.288 | 0.058 | 0.232 |

25-40Hz:

| Graph Measure | Pearson correlation coefficient (r) | Significance Value (p) | Bonferroni-corrected p |
|---|---|---|---|
| Mean node degree | 0.314 | 0.043 | 0.172 |
| Mean clustering coefficient | 0.386 | 0.016 | 0.064 |
| Characteristic Path Length | 0.033 | 0.431 | 1 |
| Maximum Betweenness-Centrality | -0.354 | 0.025 | 0.1 |

## Supplementary Table 2:

| Frequency Band | Mean Goodness of Fit | Standard Deviation | Standard Error |
|---|---|---|---|
| 1-12Hz | 0.9980 | 0.0016 | 0.0001 |
| 12-25Hz | 0.9978 | 0.0030 | 0.0001 |
| 25-40Hz | 0.9977 | 0.0021 | 0.0001 |