VISUAL AND NEUROPSYCHOLOGICAL OUTCOMES FOLLOWING PAEDIATRIC OPTIC PATHWAY GLIOMA

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Abstract

Survival rates for children with brain cancer have dramatically increased in the recent decades, but evidence demonstrates long-term physical impairments, academic difficulties and neuropsychological deficits even among children with non-aggressive tumours and treatments. Children with optic pathway glioma (OPG) are at risk of neuropsychological difficulties due to the resulting visual impairment, the neural damage of the tumour itself and its treatment, and the comorbid neurodevelopmental disorder called Neurofibromatosis Type 1 (NF1). Yet, the literature on the sequelae of OPG beyond vision is scarce. This thesis is a comprehensive evaluation of long-term visual and neuropsychological outcomes in a group of 12 children who were diagnosed with a glioma in optic pathway, who received either chemotherapy or no treatment for their tumour.

On the ophthalmic exam*, c*hildren demonstrated a significant structural and functional damage to the optic pathway in terms of reduced thickness of the retinal nerve fiber layer and as well as poor visual acuity. Visuo-perceptual and visual-motor abilities, which reflect the ability to process of physical and asemantic stimuli, were significantly hindered and half of the sample performed below the level expected for their age in this domain (Chapter 3).

On the cognitive assessment, children had preserved reasoning abilities (both verbal and visuospatial), but mild difficulties in working memory and processing speed, similarly to other brain tumour survivors. Core scholastic abilities of reading and maths comprehension were intact, but children had mild problems in writing and oral language. Only a minority of children (mostly with NF1) showed severe problems in these domains (Chapter 4).

Significant associations were found among measures of vision and visual perception; cognitive and scholastic abilities were associated with each other, but not with visual perception. Among the risk factors, younger age at diagnosis was associated with poor visual outcomes in the best eye and poor binocular vision had a negative impact on visuoperceptual, cognitive and scholastic abilities that heavily relied on

sight. In addition, children with NF1 tended to underperform, unlike children without NF1 (Chapter 5).

Finally, participants were examined on a series of abilities (i.e., fine motor control, attention, short-term and working memory, mathematics and English comprehension), using parallel tasks that rely on either visual or auditory input. In comparison to a large group of typically developing children (N = 96), OPG survivors performed overall in line with the level expected for their age in both visual and auditory domains, although some children with NF1 exhibited problems in maths and English comprehension. In addition, strong significant correlations between the two ophthalmic measures and neuropsychological skills indicated that more severe structural and functional damage in the best eye was associated with faster responses on the auditory attention task. This result, in combination with the mild working memory difficulties reported with the standardised assessment, suggests that a compensatory mechanism in the auditory modality might take place in children with OPG, but this does not enable them to develop superior auditory abilities (Chapter 6).

Overall, this study demonstrated that children with OPG experience significant visual and visuo-perceptual problems, as well as mild and specific cognitive and scholastic difficulties. About half of the children were at risk of great visuoperceptual problems, while only a minority was specifically at risk of severe underperformance in terms of intellectual and academic functioning. Children with OPG do not develop superior auditory skills to compensate for the loss of sight.

Presentations

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Chapter 1 General introduction

Tumours in the brain and the central nervous system represent the second largest group (20%) of neoplasms after leukaemia, and the most common type of solid cancers in children (National Research Council, Institute of Medicine, & National Cancer Policy Board, 2003). In the last decades, advances in early diagnosis (Wilne, Dineen, Dommett, Chu, & Walker, 2013), tumour characterisation and treatment (Saletta, Seng, & Lau, 2014) in paediatric oncology have significantly improved survival rates. However, the tumour itself and its treatment often leave children with neuropsychological (Raghubar et al., 2017; Robinson et al., 2010) and physical (Piscione, Bouffet, Mabbott, Shams, & Kulkarni, 2014) problems, including for example visual impairment (Jariyakosol & Peragallo, 2015), which can affect quality of life in childhood (Jariyakosol & Peragallo, 2015) and beyond (Brinkman et al., 2018; de Blank et al., 2016).

Low-grade gliomas are a group of tumours characterised by benign nature, slow growth rate and excellent survival rates (Forst, Nahed, Loeffler, & Batchelor, 2014; Ostrom et al., 2015). Whilst survivors of low-grade gliomas were traditionally considered at low risk of neurobehavioural morbidity compared to malign tumours (Ris & Beebe, 2008), accumulating evidence demonstrates cognitive sequalae also in this understudied group of patients (Aarsen et al., 2006; Armstrong et al., 2011; Merchant, Conklin, Wu, Lustig, & Xiong, 2009; Ris et al., 2008). Specifically, children with brain tumours in the chiasmatic regions were found in greater need of special education, possibly because of the high percentage of visual impairments (Aarsen et al., 2006). Therefore, more research is needed for patients with tumours in this brain area to elucidate their educational needs (Ris & Beebe, 2008).

This thesis will investigate the neurodevelopmental outcomes of the optic pathway gliomas (OPGs), a group of low-grade gliomas that arise along the visual pathway and result in some degree of visual impairment (Dodgshun, Elder, Hansford, & Sullivan, 2015) that impacts on adult life (de Blank et al., 2016). Children with OPG are at risk of

long-term neuropsychological sequelae resulting not only from the tumour itself and its treatment (Ris et al., 2008; Willard, Conklin, Wu, & Merchant, 2015), but also secondarily from the visual impairment (Aarsen et al., 2006). In addition, some of these children have a pre-existing genetic condition called Neurofibromatosis type 1 (NF1) that, whilst highly variable, might exacerbate cognitive difficulties during development (Ferner et al., 2007; Moore III, Ater, Needle, Slopis, & Copeland, 1994).

Despite this cumulative risk, there is paucity of research on neurobehavioural outcomes following OPG and this is arguably due to the limitations posed on neuropsychological testing by the visual impairment (Deramore Denver, 2019). Indeed, sensory impairment such as vision and/or hearing loss is often an exclusion criterion in neuropsychological research on childhood cancer (e.g., King, Ailion, Fox, & Hufstetler, 2019; King, Wang, & Mao, 2015) and NF1 (e.g., Hyman, Shores, & North, 2005; Payne, Hyman, Shores, & North, 2011; Pride, Payne, & North, 2012). As a result, children with OPG are overall neglected.

This thesis will address the gap in the literature by conducting a systematic and comprehensive evaluation of ophthalmic measures of vision as well as visual and auditory neurocognitive outcomes in a cohort of young patients with a diagnosis of an OPG. The concurrent examination of a range of visual and neuropsychological outcomes will provide a comprehensive profile of these children that could be used to elucidate the impact of critical risk factors such as vision loss and NF1. While there is a general need for new tools to evaluate the cognitive development of children with vision problems, this project will assess the utility of a multidisciplinary assessment that can better inform treatment strategy and rehabilitation following paediatric OPG (Aihara, Chiba, Eguchi, Amano, & Kawamata, 2018).

In this chapter, some key notions about the sense of vision, the visual system and the concept of visual impairment, as well as the NF1 disorder will be provided first. A description of paediatric OPG in terms of epidemiology, tumour location, clinical management and treatment options will follow. Then, a review of the literature about visual and neuropsychological outcomes will be presented and critically discussed.

Finally, the new framework used in this thesis to investigate multilevel outcomes following OPG will be presented.

1.1 Key notions

1.1.1 The sense of vision

It could be argued that vision is the most sophisticated and developed sensory function in humans and the one on which we rely the most. Approximately 27% of the human cortex is primarily involved in the processing of visual stimuli, as compared to about 7-8% responsible for either auditory, sensorimotor, or motor functioning (Van Essen, 2004).

The visual system is fully present at birth, but it has an extended developmental trajectory after birth involving structural (Graven & Browne, 2008b) and functional (Braddick & Atkinson, 2011) changes throughout childhood. For example, the eye grows dramatically in the first year of life and then its growth decelerates until the age of 13 (Fledelius, Christensen, & Fledelius, 2014), whereas visual acuity reaches adult-like levels between the age of 5 and 10 years (Leat, Yadav, & Irving, 2009). Visual experience in childhood is crucial for the development of the visual system itself (Farroni & Enrica, 2008), but also to allow optimal interactions with the environment (Thelen, 2005) that are foundational for cognitive development (Piaget, 1952). Further, it has been estimated that most of education is conveyed through vision (Chadha & Subramanian, 2011) and primary school children spend 30-60% of the school time engaging with visual tasks such as reading, writing and drawing (McHale & Cermak, 1992).

1.1.2 The visual system

The visual system is organised into three major components, namely the eye, the central visual pathway and the visual brain (Figure 1.1), which are responsible to the reception, transmission and elaboration of the visual information, respectively.

Figure 1.1. The visual system and the effects of lesions. Adapted from "Blindsight: a conscious route to unconscious vision" by J. Danckert and M. A. Goodale, 2000, *Current Biology, 10*, p. R65. Copyright 2000 by Elsevier Science Ltd.

In the eye, the light from the outside world undergoes several mechanical refractions to ensure it is focused on the point of maximal visual acuity in the retina at the back of eye (fovea), where it is translated into electrical signal. Axons of the retinal ganglion cells merge as they exit the retina and project towards the central visual pathway (Gregg, McCall, & Massey, 2013), where OPGs arise. Here, the visual information passes through a series of pre-cortical structures (in order: the optic nerve, optic chiasm, optic tract, lateral geniculate nucleus, and optic radiation) that finally project posteriorly in the occipital lobe (Crossman & Neary, 2015).

At the cortical level, signals from the two eyes are first integrated in the striate primary visual cortex (V1), which in turn activates the extra-striate visual association cortex in the temporal and parietal regions for specific and progressively more complex processing of the visual information (Purves et al., 2011). For example, V4 is specialised in colour recognition (Grill-Spector, Kourtzi, & Kanwisher, 2001) whereas V3 is sensitive to simple motion (Felleman & Van Essen, 1991). This primary pathway, connecting the retina to the primary visual cortex via the lateral

geniculate nucleus of the thalamus and the optic radiations (also called geniculo-striate pathway), is thought to underpin conscious vision. Damages at different levels of this pathway would lead to different vision defect or partial blindness (Figure 1.1). However, other secondary visual pathways have been described that bypass V1 and carry visual information from the retina to the extrastriate cortex, either directly (i.e., the geniculo-extrastriate pathway; Abed Rabbo, Koch, Lefèvre, & Seizeur, 2015) or indirectly through the superior colliculus and the pulvinar (i.e., the retino-tectal pathway; Berman & Wurtz, 2010). These pathways might explain the sub-conscious visual abilities documented in blindsight patients (Ajina, Pestilli, Rokem, Kennard, & Bridge, 2015) and be responsible for rapid responses to emotionally and socially relevant stimuli (Almeida, Soares, & Castelo-Branco, 2015).

Within the visual brain, two main streams of information are important in relation to visual cognition in children (Milner & Goodale, 2008). The "what" ventral stream runs in the inferior temporal lobe and elaborates the static landmark features of a visual percept, whereas the "where" dorsal stream ends in the posterior parietal lobe and analyses the spatial characteristics of location and motion and contributes to skilled motor control (Goodale, 2010). Whilst relatively independent (Braddick, O'Brien, Wattam-Bell, Atkinson, & Turner, 2000), these networks interact and play a role in visuospatial processing at a subconscious level (Dutton, 2003; Figure 1.2).

[Figure removed due to copyright]

Figure 1.2. Cortical processing of visual information through the ventral and dorsal visual streams. From "Visual dysfunction in Parkinson's disease" by R. S. Weil, A. E. Schrag, J. D. Warren, S. J. Crutch, A. J. Lees and H. R. Morris, *Brain*, *139*, 2016, p. 2828. CC BY 4.0.

Hierarchical models of visual processing consider visual perception as the intermediate process between low-level sensation (sensory functions; e.g., visual acuity) and high-level cognition (mental functions, such as reading; Figure 1.3; Schneck, 2010). Visual perception pertains to the analysis of physical pre-symbolic aspects of visual stimuli (Hammill, Pearson, & Voress, 1993; Warren, 1993b, 1993a). Some visuo-perceptual abilities involve the processing of static features such as size, location, shape and orientation of a visual percept; others involve additional real-time motor control of action (Goodale, 2010). These skills tap into the ventral and dorsal stream respectively (Goodale, 2010). In typical development, these perceptual domains may operate independently (Parush, Yochman, Cohen, & Gershon, 1998) but are interdependent systems (Brown, 2012) and may impact on scholastic abilities (Brown & Link, 2016; Carlson et al., 2013; Kulp, 1999).

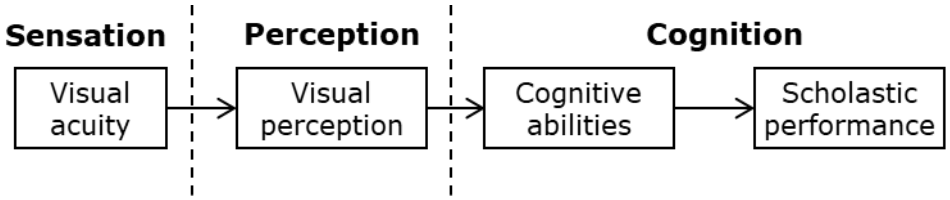


Figure 1.3. Hierarchical model of visual processing.

The above description gives an indication of why the visual system is conceptualised as a system with predominantly hierarchical structure across different pre-cortical and cortical levels (Felleman & Van Essen, 1991). Empirical evidence also supports this view. For example, the activation of the visual wordform area, an inferior temporal functional region specifically involved in the processing of letters (Vinckier et al., 2007), is substantially dependent from the activation of the occipital primary visual cortex (Cohen et al., 2000), which in turns requires the input from the structure of central visual pathway (Ajina & Bridge, 2017). This suggests that high-level visual cognition (e.g., reading a letter) relies on low-level visual cortical processes (e.g., recognition of the lines and curves of a grapheme) as well as on primary reception of the light in the eyes and transmission through the central visual pathway. A feedforward hierarchical model of the visual system will be taken in this thesis for the purpose of simplicity.

Nonetheless, it should be emphasised that more complex combinations of both hierarchical and parallel strategies (Zeki & Shipp, 1988), with feed-forward as well as feed-back connections among cortical (Kafaligonul, Breitmeyer, & Öğmen, 2015) and subcortical areas (Sillito, Cudeiro, & Jones, 2006), contribute to the processing of visual information and its integration with other sensory modalities (Stein, Stanford, & Rowland, 2014).

1.1.3 Visual impairment

Neuropsychological investigations on the consequences of injuries to the central nervous system have focused on the distinction between anterior and posterior damages to the visual system. Most experts agree that posterior damages involve retro-geniculate structures (from the optic radiations to the associative visual cortices), whereas there is more

debate as to whether anterior damages extend beyond the eyes and the optic nerves to encompass also the chiasm and the optic tracts (Baker-Nobles & Rutherford, 1995; Good, 2009; Martín et al., 2016). Nevertheless, it has been proposed that eye conditions or anterior lesions lead to "ocular visual impairment", which negatively affects visual acuity (see next section), whereas posterior lesions lead to "cortical visual impairment", which represents difficulty in processing and interpreting visual information, even in absence of visual acuity deficits.

Since OPGs can arise in either anterior or posterior regions or both simultaneously, the anatomical classification has limited utility in these patients. Interestingly, a systematic review demonstrated that, due to the poor correlation between aetiology, location and neuropsychological difficulties, emphasis should be placed on functional outcomes of the neurological damage rather than neuroanatomical landmarks (Boot, Pel, van der Steen, & Evenhuis, 2010). However, it may be difficult to fully disentangle ocular/anterior difficulties and more complex cortical/posterior problems because the latter may present also visual acuity deficits. Nevertheless, Baker-Nobles and Rutherford (1995) point out that ocular impairments can be addressed with additional magnification, whereas this adaptation is not effective with cortical impairment. This approach will be taken in this thesis, where forefront and posterior problems will refer to difficulties that can and cannot be addressed with test adaptations, respectively. Conversely, "visual impairment" will broadly refer to a generic condition of sight loss based on visual acuity, in line with the ICD-10 definition (World Health Organization, 2010).

1.1.4 Visual acuity assessment

Visual acuity is the most important ophthalmic measure that reflects the clarity and sharpness of vision. For children aged around 5 years or older, visual acuity assessment involves the presentation of letters or figures of progressively smaller sizes (optotypes) to the child, who stands at a fixed distance from the stimulus booklet or chart. Using one eye at the time, the child is asked to identify the stimuli presented by naming them or pointing at the matching stimuli on a key card. The

visual acuity recorded is the smallest size optotype that the child can identify (Avery et al., 2012). The type of tests, optotypes and responses used for visual acuity assessment varies depending on the age and literacy level of the child (Anstice & Thompson, 2014).

In clinical practice, visual acuity is usually recorded as a fraction: the numerator denotes the testing distance (e.g., 20 feet or 6 metres), whereas the denominator denotes the distance at which a normal eye can read the line. Normal vision corresponds to 20/20 or 6/6; poor vision, for example at 6/12, would indicate that the child is able to read at 6 metres what a child with normal vision would read at 12 metres. For research purpose, scientists are encouraged to convert fractions into scores of a standardised linear scale called logMAR (Fisher et al., 2013), where score 0 indicates intact vision and no sight loss, whereas high scores represent poor vision and severe sight loss. Figure 1.4 shows the relationships between different fraction and linear scales of visual acuity and the definitions of low vision and blindness according to different classification systems provided by the World Health Organisation (WHO) and the International Classification of Diseases (ICD; Colenbrander, 2003).

[Figure removed due to copyright]

Figure 1.4. Scales and classification system of visual acuity scores. ICD = International Classification of Diseases; ICO = International Commission for Optics; NPL = no perception of light; WHO = World Health Organisation. Adapted from "Aspects of vision loss – visual functions and functional vision" by A. Colenbrander, 2003, *Visual Impairment Research*, *5*, p. 127. Copyright 2003 by Taylor & Francis.

1.1.5 Neurofibromatosis type 1

Neurofibromatosis Type 1 is an autosomal dominant syndrome with a birth frequency of 1 in 2,500–3,000 and it is caused by a genetic mutation that is equally likely to be spontaneous or inherited (Evans et al., 2010). Such mutation affects the production of a tumour suppressor protein (*neurofibromin*) and predisposes patients to developing benign and malignant tumours (*neurofibromas;* Ferner, 2010). NF1 is a neurocutaneous disorder that affects multiple systems and is associated also with cardiovascular, respiratory and musculoskeletal problems (Ferner, 2010).

Being a tumour-prone syndrome, NF1 is a risk factor for paediatric brain cancer (Ullrich, 2008). About 15% of children with NF1 develop an OPG (Listernick, Charrow, Greenwald, & Esterly, 1989; Segal, Darvish-Zargar, Dilenge, Ortenberg, & Polomeno, 2010). The relationship between these two conditions is so well-establish that the diagnosis of OPGs is one of the diagnostic criteria for NF1 ("Neurofibromatosis," 1988).

NF1 is also characterised by neuropsychological difficulties. Key aspects can be identified from a consensus statement on current guidelines for the diagnosis and management of NF1 (Ferner et al., 2007; see also Lehtonen, Howie, Trump, & Huson, 2013, for a systematic review and critical considerations). IQ is typically at the lower end of the normal range (IQ ≈ 90, compared to the normative mean of 100; Champion et al., 2014; Hyman et al., 2005, 2006; Lehtonen et al., 2015); intellectual disability (IQ < 70) is rare (Lehtonen et al., 2015). About half of children with NF1 present either general or specific learning disability, especially in reading and writing (Coudé, Mignot, Lyonnet, & Munnich, 2006; Hyman et al., 2006), and require additional support at school (Krab et al., 2008). Visuospatial difficulties emerge as the hallmark of this condition, with highly consistent findings for motor-free tasks, such as the Judgment of Line Orientation Test (Clements-Stephens, Rimrodt, Gaur, & Cutting, 2008; Hyman et al., 2005; Krab et al., 2008; Schrimsher, Billingsley, Slopis, & Moore III, 2003); poor visuomotor functioning and motor control are also reported (Champion et al., 2014; Johnson et al., 2010). Deficits in executive functions such as

working memory, inhibitory control and attention are also common (Huijbregts, Swaab, & de Sonneville, 2010; Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009) and about 40% of children meet diagnostic criteria for attention-deficit-hyperactivity disorder (Schrimsher et al., 2003).

Despite these general characteristics, the astonishing variability found within the NF1 population has led researchers to hypothesise that there is no one universal profile of NF1, but rather multiple subgroups with distinctive characteristics (Lehtonen et al., 2013). For example, children with comorbid ADHD diagnosis are more likely to have learning difficulties (Hyman et al., 2006), and visuo-spatial difficulties are more marked in children with reading disability (Cutting & Levine, 2010). Compared to other neurological abnormalities that characterise the NF1 population (e.g., T2 MRI hyperintensities), the role of OPG is less studied and still unclear (Pride & North, 2012).

1.2 Paediatric optic pathway glioma (OPG)

1.2.1 Epidemiology

OPGs account for about 5% of all intracranial neoplasms in childhood (Jahraus & Tarbell, 2006) and can arise at any point along the visual pathway. OPGs are typically regarded as childhood tumours with early onset (Sellmer et al., 2018). The mean and median age at diagnosis is around 4-5 years, and most OPGs are diagnosed before the age of 6 (Czyzyk, Jóźwiak, Roszkowski, & Schwartz, 2003; Nicolin et al., 2009; Singhal, Birch, Kerr, Lashford, & Evans, 2002). Late-onset can also occur in the second decade of life (Listernick et al., 2004), but this is rare. Overall, girls and boys appear to be equally affected (Nicolin et al., 2009). About half of OPGs are associated with NF1 and these are called syndromic; the remainder, not related to NF1, are called sporadic (Czyzyk et al., 2003; Nicolin et al., 2009). Histologically, almost all OPGs are low-grade pilocytic astrocytomas (Freeman, Farmer, & Montes, 1998), and therefore are benign tumours characterised by non-cancerous and slow-growing cells that do not spread to remote parts of the body producing secondary tumours (metastases). The prognosis of OPG is

quite favourable, with excellent overall survival rates exceeding 94% after 5 and 10 years (Gnekow et al., 2012; Mishra et al., 2012; Nicolin et al., 2009).

Although mortality rates are low, OPGs pose a risk to children's development as these tumours arise in the brain during a sensitive period of anatomical and physiological changes to the central nervous system (Brown & Jernigan, 2012). Indeed, preschool years are a developmental period of "blossoming", growth and neural proliferation in preparation for later selective reduction with maturation and experience (Brown & Jernigan, 2012). Because OPGs affect very young children, investigating the severity and the impact of these tumours is important to establish to what extent OPGs make them either vulnerable to long-lasting detrimental effects or instead prone to advantageous early plastic processes (Anderson, Spencer-Smith, & Wood, 2011).

1.2.2 Tumour location

OPGs can affect any point of the central visual pathway, with unilateral or bilateral involvement, and with invasion of the adjacent structures, such as the hypothalamus (Dodgshun et al., 2015; Nicolin et al., 2009). Overall, about 25% of OPGs arise in the anterior (pre-chiasmatic) portion of the optic pathway, whereas 40 to 75% affect the optic chiasm, with potential involvement of other posterior regions (Binning, Liu, Kestle, Brockmeyer, & Walker, 2007). Children with NF1 are more likely to exhibit optic nerve involvement, while chiasmal/hypothalamic and posterior lesions are more common among sporadic OPGs (Chateil et al., 2001; Czyzyk et al., 2003; Listernick et al., 1995; Taylor et al., 2008). In addition, sporadic tumours have larger volume at presentation (Astrup, 2003).

Given the developments in magnetic resonance imaging (MRI) techniques and the greater understanding of precise structural correlates of vision (see also Figure 1.1), precise description of tumour location is paramount for the management of OPGs. In the past, the Dodge classification system was required for optimal surgical planning (Dodge et al., 1958). Nowadays, more precise anatomical definitions, such as the modified Dodge (otherwise called PLAN) classification (Taylor et al., 2008), have shown utility for outcome prediction in clinical practice

(Walker et al., 2013), and research trials through repeated evaluations before, during and after modern non-surgical treatments (Dalla Via et al., 2007; Falzon, Drimtzias, Picton, & Simmons, 2018; Segal et al., 2010). In comparison, the relationship between this classification system and neuropsychological outcomes of OPG has been investigated only in one study (Lacaze et al., 2003) and it will be examined again in this thesis in the attempt to identify structural biomarkers of neurocognitive outcomes following OPG.

1.2.3 Clinical management

The management of OPGs is a highly controversial topic because of the erratic and highly variable natural history of these tumours (Fried, Tabori, Tihan, Reginald, & Bouffet, 2013; Thomas, Gibbs, Xu, & Recht, 2015).

On one hand, some OPGs do not present with visual symptoms. The majority of asymptomatic OPGs are syndromic as they are discovered during MRI screening and ophthalmologic assessment conducted within the NF1 clinics (King et al., 2003). Incidental findings or tumours presenting with hypothalamic dysfunction also occur for sporadic cases (Nicolin et al., 2009). On the other hand, symptomatic OPGs are likely to progress and require treatment at some point (King et al., 2003; Nicolin et al., 2009; Thiagalingam et al., 2004). Visual symptoms are the most common signs at diagnosis (Singhal et al., 2002; Tow, Chandela, Miller, & Avellino, 2003); endocrine dysfunction and diencephalic syndrome might also be found for tumours with hypothalamic invasion (El Beltagy et al., 2016).

The management of OPGs is centred around the evaluation of vision in order to diagnose the tumour, monitor its progression if indolent, decide treatment start in case of vision decline, and evaluate outcomes at follow-up (Campagna et al., 2010; Falzon et al., 2018; Fisher et al., 2012; Friedrich & Nuding, 2016; Thiagalingam et al., 2004). Radiological progression with MRI is also monitored, but it poorly correlates with visual acuity, which is the key functional measure (Campagna et al., 2010; Fisher et al., 2012). Preservation of sight is the

priority with a treatment philosophy that has "the longest survival at the lowest possible cost" as its ultimate goal (Perilongo, 2005, p. 305).

1.2.4 Treatment

The main management options include observation, chemotherapy and radiotherapy.

Observation is the preferred strategy for non-progressive tumours and consists of a period of about 12-18 months with regular visits that include in-depth ophthalmology examinations and MRI scanning (Fisher et al., 2012; Shamji & Benoit, 2007). As mentioned above, observation is more frequent for NF1-related tumours, although it can also be used with sporadic OPGs associated with mild clinical signs (Nicolin et al., 2009).

Nowadays, chemotherapy represents the front-line treatment for symptomatic OPGs (Jahraus & Tarbell, 2006). It enables achievement of stable vision in about half of the patients (47%) after treatment, although another 39% experience deterioration of sight at follow-up (Moreno, Bautista, Ashley, Duncan, & Zacharoulis, 2010). Vision deterioration might be the indirect result of multiple cycles of treatment, each started at visual symptoms onset, resulting in a cumulative visual morbidity in the long term (Moreno et al., 2010). Whilst not fully satisfactory for visual outcome, chemotherapy is overall preferred because it reduces tumour growth and postpones or avoids the implementation of more aggressive and detrimental treatments like radiotherapy (Perilongo, 2005) that would have costly neuropsychological morbidity (Merchant et al., 2009), especially for the vulnerable brains of these young patients (Silva et al., 2000).

The protective effect of chemotherapy in comparison to radiotherapy (Aarsen et al., 2009) does not mean that this treatment is free from side effects for children with OPG. Several studies found that chemotherapy is a risk factor for worse neurocognitive sequelae in survivors of childhood tumours not affecting the central nervous system (Sleurs, Deprez, Emsell, Lemiere, & Uyttebroeck, 2016), leukaemia (Buizer, De Sonneville, van den Heuvel-Eibrink, Njiokiktjien, & Veerman, 2005; Genschaft et al., 2013), brain tumours (de Ruiter, Van Mourik, Schouten-Van Meeteren, Grootenhuis, & Oosterlaan, 2013) and even low-grade gliomas like OPGs (Armstrong et al., 2011). Direct attentional

problems (Pierson, Waite, & Pyykkonen, 2016) or indirect effects of hearing loss attributed to the ototoxic effects of specific chemotherapy agents (Nathan et al., 2007) could have potential downstream effects on children's development and learning (Stavinoha, Askins, Powell, Pillay Smiley, & Robert, 2018).

Cranial radiation is a secondary option for managing OPG, mainly reserved for older children (Merchant et al., 2009) and in those without NF1 (Listernick, Ferner, Liu, & Gutmann, 2007). The harmful effects of radiotherapy versus chemotherapy on cognitive functioning are well established (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004) and the shift to the chemotherapy regimen in the management of OPG as well as other low-grade gliomas established a new treatment era (Armstrong et al., 2011; Lacaze et al., 2003; Tsang, Murphy, & Merchant, 2017). Unlike other low-grade gliomas (Freeman et al., 1998), surgical resection is too invasive for OPGs due to their deep location and surgical procedures are restricted to biopsy only if necessary (Avery, Fisher, & Liu, 2011).

Overall, the possibility of avoiding treatment, using neuroprotective regimens of chemotherapy and avoiding or postponing neurotoxic radiological protocols make the prognosis of OPGs highly favourable in terms of survival and cognitive morbidity, unlike other malign and aggressively treated brain tumours (e.g., medulloblastoma; Chevignard, Câmara-Costa, Doz, & Dellatolas, 2017; Palmer et al., 2013). However, understanding the impact of vision loss on children's development is critical for OPGs especially in the "chemotherapy era", with drug therapy being the front-line and almost sole modality of treatment (Duffner, 2010). Indeed, avoiding or postponing radiotherapy allows the preservation of neural development, but often comes at the cost of limited ultimate control over tumour progression, resulting in progressive vision loss (Moreno et al., 2010) and poorer visual outcomes (Awdeh et al., 2012).

1.2.5 Visual outcomes

Visual impairment is by far the most investigated functional outcome in children with OPG. However, it is extremely difficult to quantify the extent of impairment from the large available literature due

to a multitude of interrelated factors pertinent to samples (small cohorts, heterogeneity of age range and NF1 status), tumour variables (tumour locations or treatments), visual acuity assessments (variety of tests, units of measurements, classification systems) and general methodologies (retrospective or prospective designs, purely descriptive statistics or limited statistical analyses, per-eye versus per-child analyses, definitions of threshold to define progression, decline or improvements).

A recent follow-up study with both sporadic and syndromic OPGs estimated that, based on the WHO criteria, about 70% of children have no or mild visual impairment, 17% have low vision and 10% are blind or near blind. Outcomes based on individual eyes are less favourable, with normal visual acuity for only 42% of study eyes (Dodgshun et al., 2015). Overall, visual impairment is highly variable: it can range from mild to profound deterioration up to legal blindness and can affect either or both eyes. Visual outcomes are still considered unsatisfactory: although sight loss is not irreversible, only a minority of children with OPG enjoy improvement of vision after treatment whereas many others experience deterioration (Campagna et al., 2010; Dalla Via et al., 2007; Dodgshun et al., 2015; Fisher et al., 2012; Wan et al., 2016). Nonetheless, defining vision changes and outcomes is complicated by intrinsic measurement problems (see below).

Visual acuity is the most important visual function in the management of OPGs (Avery, Fisher, et al., 2011; Fisher et al., 2013; Robert Listernick et al., 2007; Moreno et al., 2010). There is growing interest towards the relationship between visual and psychological outcomes of OPG, with initial evidence demonstrating an association for visual acuity in the best eye with visual perception (Lacaze et al., 2003) and broader vision-related quality of life (Avery & Hardy, 2014). However, visual acuity is also limited by its psychophysical assessment, as it inherently relies on children's willing and abilities to cooperate. In addition, inherent variability may arise from the assortment of tests available to accommodate attentional and literacy skills of young patients (Avery et al., 2012); for example, picture-based vision tests, that are used with pre-literate children, overestimate visual acuity in comparison

to letter-based tests, that are the first option for literate children (Anstice et al., 2017). Therefore, research on OPG is currently investigating the clinical utility of unbiased structural biomarkers of vision, such as the thickness of the retinal nerve fiber layer (RNFL) as measured by optical coherence tomography (OCT; Avery et al., 2014; Avery, Liu, et al., 2011; Topcu-Yilmaz et al., 2014). To date, no studies have concurrently investigated RNFL thickness, visual acuity and neuropsychological outcomes in children with OPG and this will be done for the first time in this thesis. Detecting potential associations of structural and/or functional markers of vision with neurobehavioural abilities would enable the identification of children with OPG who are at risk of developmental difficulties in certain psychological domains.

1.2.6 Neuropsychological outcomes

While a plethora of publications have described visual outcomes in children with OPG, few studies examined the impact of OPG and its treatment on neurodevelopmental outcomes. Five studies were identified that conducted retrospective analyses of hospital records about OPG cases treated between the 1970s and 1980s, all before 1991, and therefore in the radiotherapy era (Cappelli et al., 1998; Janss et al., 1995; Pierce, Barnes, Loeffler, McGinn, & Tarbell, 1990; Sutton et al., 1995; Tao et al., 1997). These studies did not report exact measures of cognitive and scholastic abilities in this group of survivors, but generally described decline of intellectual functioning and memory after treatment, as well as high rates of learning disability and special educational needs in about half of the children. These studies will not be discussed here because they have limited utility to make predictions about more recent cohorts of OPG. Only four studies were found that examined the neurodevelopmental outcomes of OPG survivors in the chemotherapy era; the key aspects are summarised in Table 1.1. Details about the search strategy are reported in 240Appendix A.

Table 1.1

Key aspects of the publications investigating neurocognitive outcomes of OPG in the chemotherapy era.

Reference	Design	Measures	Sample	Analyses	Key findings	Treatment	NF1	Vision	Other factors
Fouladi et al. (2003)	Retrospective longitudinal	IQ	*n* = 31 (16 with NF1), representing 43% of the whole OPG cohort studied (*N* = 73)	- Longitudinal analysis (up to 7 years after diagnosis) - Between-group comparisons (R vs. non-R; NF1 vs. non-NF1)	IQ at diagnosis = 86, no deterioration over time	O, C and/or R Similar time trajectory between children treated with and without R	NF1 and non-NF1 children had similar IQ at diagnosis and time trajectory	Not assessed	- Age at diagnosis: pre-schoolers significantly poorer IQ at diagnosis (IQ = 79) compared to school-aged children (IQ = 96), but similar time trajectory - Tumour location: only hypothalamic/chiasmatic tumours examined
Nicolin et al. (2009)	Retrospective cross-sectional	VIQ, PIQ, FSIQ	*n* = 35 (11 with NF1), representing 26% of the whole OPG cohort studied (*N* = 133)	Only descriptive score, no statistical comparison to norms	- FSIQ and VIQ < 1 *SD* (81 and 77) - PIQ within norm (95)	O, C and/or R	FSIQ borderline (85), VIQ below (83), PIQ above (87)	No analyses in relation to IQ	Not examined

Note. O = observation, C = chemotherapy, R = radiotherapy, NF1 = neurofibromatosis type 1, FSIQ = full-scale IQ, VIQ = verbal IQ, PIQ = performance IQ, SES = socio-economic status, VA = visual acuity.

Table 1.1 (continued)

Key aspects of the publications investigating neurocognitive outcomes of OPG in the chemotherapy era.

Reference	Design	Measures	Sample	Analyses	Key findings	Treatment	NF1	Vision	Other factors
Lacaze et al. (2003)	Prospective cross-sectional	VIQ, PIQ, FSIQ + perception (3 tasks from different batteries)	*n* = 21 (5 with NF1); 6 pre-schoolers were also tested for psychosocial and motor development	Between-group comparisons (5 NF1+C, 8 non-NF1+C, 8 non-NF1+C+R)	- Group FSIQ, VIQ and PIQ within norm (92, 97, 88), only descriptive - Group VIQ > PIQ within-group comparison - Individual FSIQ < 1 SD for more than 50% of sample - Deficit in perception (visual agnosia task, but not other tasks)	C and/or R	NF1+C worse than non-NF1+C on VIQ and PIQ	Correlation between VA and perception (visual agnosia task)	Age at diagnosis, SES and radiological Dodge classification: not correlated with IQ, not examined for other measures
Riva et al. (2009)	Prospective case series	General intelligence and attention at both T1 and T2, other scattered tests at each time point	8 (3, but only 2 confirmed)	Longitudinal analyses (before vs. after C)	- All scores within the norm at follow-up (many scattered missing data points) - No changes over time except for VIQ	C only	3 NF1 patients (2 NF1 with poor vision at diagnosis) with deterioration	Vision status in case series, no analyses	Age at diagnosis and time post treatment: correlated with attention and motor speed (rho = ± 1) Tumour location: only hypothalamic/chiasmatic tumours examined

Note. O = observation, C = chemotherapy, R = radiotherapy, NF1 = neurofibromatosis type 1, FSIQ = full-scale IQ, VIQ = verbal IQ, PIQ = performance IQ, SES = socio-economic status, VA = visual acuity.

1.2.6.1 Scholastic outcomes

Although Ris and Beebe (2008) highlight the need to understand neurocognitive sequelae of low-grade glioma (including OPGs) in relation to their educational needs, no studies so far have investigated scholastic abilities in children with OPG. Children with OPG were found to require special education or remedial teaching (Aarsen et al., 2006), with learning disability equally reported in NF1 and non-NF1 cases (Avery & Hardy, 2014). However, without a detailed investigation of different aspects of academic functioning it is not possible to ascertain which scholastic domains are more affected (Holland, Hughes, & Stavinoha, 2015) and how cognitive and physical deficits impact on them (Aarsen et al., 2006). This shows a clear gap in the literature that needs to be addressed.

1.2.6.2 Cognitive outcomes: group performance and variability

General intelligence is the domain most consistently and reliably assessed, particularly full-scale IQ, but the results are conflicting. While IQ was below the test norm in studies that retrospectively looked at early data from the 80s, 90s and the beginning of 2000s (Fouladi et al., 2003; Nicolin et al., 2009), the mean score was adequate for the age in investigations that prospectively collected more recent data in the chemotherapy era (Lacaze et al., 2003; Riva et al., 2009). This might be due to the progressively reduced use of radiotherapy in the management of these tumours (Lacaze et al., 2003; Riva et al., 2009), as contended by the authors. However, results vary within or below the test norms when considering specific aspects of IQ (verbal versus performance) or subgroups (NF1 versus non-NF1 children).

At group level, none of the studies compared the IQ results with a control group or with the normative data of the standardised tests. Total group means were only interpreted as above, within or below the normal range expected based on test norms (M = 100, SD = 15), but it remains difficult to establish if children with OPG have adequate or impaired development without comparative norms. Since the protective effect of chemotherapy is established in comparison to radiotherapy (Merchant et al., 2009), potential long-term effects induced by other factors are expected to be less evident and statistical analyses need to be sensitive

to this issue. To ascertain if children with OPGs treated in the most recent chemotherapy develop in line with the age-expected standards, the compounding effect of radiotherapy should be fully removed and sensitive comparison with control groups or normative data should be conducted. This is particularly critical for OPGs because of its association with NF1, which is characterised by mild (only rarely severe) cognitive difficulties (see section 1.1.5).

The results by Lacaze et al. (2003) clearly demonstrate another common problem with these clinical populations which is the variability among patients. Despite a group mean IQ within the normal range, individual scores were found below the test norms for 52% of the sample, suggesting that some children are specifically at risk of deficits. While group analyses enable the definition of accurate prognoses for patients as a whole, it is vital to consider the variability pattern for a critical evaluation of findings with small case series (Davis, Pitchford, Jaspan, McArthur, & Walker, 2010; Levisohn, Cronin-Golomb, & Schmahmann, 2000).

1.2.6.3 Vision, vision loss and visual perception

Although visual perception is conceptualised as the intermediate neuropsychological domain between low-level sensation and high-level cognitive functioning and it is critically affected in children with NF1 (see section 1.1), only Lacaze et al. (2003) examined this domain. The authors demonstrated a significant deficit in one perceptual test of object picture naming (visual agnosia) but not in the others (shape recognition and judgement of line orientation). The task of visual agnosia required the child to name real objects shown through pictures, therefore it can be argued that it assessed semantic knowledge through the visual modality (e.g., Ptak, Lazeyras, Di Pietro, Schnider, & Simon, 2014) rather than the ability to interpret physical aspects of an object picture. Therefore, it is unclear whether children with OPG have problems on low-level perception or high-level semantic processing requiring vision; this demonstrates a problem of task impurity and poor construct definition, also reflected by the collection of perceptual subtests taken from different batteries. Clear definition of neuropsychological constructs is particularly necessary in studies involving NF1 children (Lehtonen et al., 2013), for whom the

distinction of overlapping visuo-perceptual, visual motor and fine motor difficulties might enable identification of subgroups of NF1 children at specific risk in other neuropsychological domains (Pride & North, 2012).

In addition, only Lacaze et al. (2003) examined the impact of vision loss on neuropsychological outcomes and found a significant correlation between visual acuity in the best eye and the visual agnosia perceptual task, but not with performance IQ. This suggests that visual acuity as measured in the ophthalmology clinics is related to the evaluation of physical aspects, but not to the semantic aspects, of visual stimuli. Investigating these associations after addressing the task impurity problems previously described could be valuable to understand which neuropsychological domains are related to the measurements taken in ophthalmology clinics. In addition, because children's performance during testing relies on binocular vision, both per-eye and per-child analyses should be conducted for additionally informative results (Fisher et al., 2013). Finally, a detailed analysis of the characteristics of the individual tasks (e.g., vision involvement, motor response and timed performance) would facilitate the interpretation of any significant results involving the visual tests (Roizen et al., 2006).

1.2.6.4 NF1 status

Some degree of consensus emerges from the studies reported in Table 1.1 regarding the negative effect of NF1 co-diagnosis. The most compelling evidence comes from those not restricted on specific tumour locations, which reported borderline intellectual functioning in NF1 participants (Nicolin et al., 2009), in line with the general NF1 cognitive profile (see section 1.1.5), as well as diminished performance on several verbal and nonverbal intellectual abilities in comparison to the non-NF1 counterparts (Lacaze et al., 2003). In addition, Riva et al. (2009) found that the three children with NF1, who also had poor vision at diagnosis, showed significant cognitive deterioration after treatment, whereas non-NF1 patients reported stable intellectual functioning over time. This suggests that there is a cumulative risk for children with NF1, although the protective effect of intact vision has yet to be established. Of note, conflicting findings of similar IQ at diagnosis in the two OPG subgroups

was reported by Fouladi et al. (2003), but these might have been influenced by the higher rates of radiotherapy used with sporadic cases.

As discussed in section 1.1.5, the cognitive phenotype of NF1 is highly variable and possibly clustered in subgroups of disability. Based on the three studies which investigated the impact of OPG on the NF1 profile, it remains unclear whether a brain tumour/OPG per se (Moore III et al., 1994) or its treatment (De Winter, Moore III, Slopis, Ater, & Copeland, 1999) exacerbate the cognitive difficulties of children with NF1, or if the presence of an OPG determines only brain volume abnormalities without implications on neuropsychological functioning (Moore III, Slopis, Jackson, De Winter, & Leeds, 2000). Whilst children with OPG and NF1 are typically excluded from neuropsychological research because of the brain abnormalities and/or visual impairment (e.g., Billingsley et al., 2003; Champion et al., 2014; Clements-Stephens et al., 2008; Descheemaeker, Ghesquière, Symons, Fryns, & Legius, 2005; Gilboa, Josman, Fattal-Valevski, Toledano-Alhadef, & Rosenblum, 2010; Hyman et al., 2005, 2006; Pride, Payne, & North, 2012; Schrimsher et al., 2003), this thesis will combine group-level and case-level analyses to elucidate the cognitive progression of these children.

1.2.6.5 Asymptomatic tumours

Interestingly, Fouladi et al. (2003) dispute that the OPG itself (at least in case of chiasmatic/hypothalamic involvement) was responsible for lowered intellectual functioning in their sample because no effect of radiation therapy was found. This consideration leaves open the possibility that untreated patients too may suffer from tumour-related problems, for example because of structural neuronal loss (Seano et al., 2019) and functional disruption of brain networks (Heimans & Reijneveld, 2012) induced by the solid stress of the tumour itself. The studies in Table 1.1 examined treated OPG patients, because they explicitly investigated the impact of chemotherapy (Fouladi et al., 2003; Nicolin et al., 2009) or retrospectively examined clinical records, which tend to be biased towards referred subgroups of children with more severe problems, for example due to radiotherapy (Armstrong et al., 2011). Similar bias also affects the research on visual outcomes of this tumour (Friedrich & Nuding, 2016; Shamji & Benoit, 2007). A systematic

investigation across domains would help to delineate a clearer picture of the physical and psychological difficulties of all children diagnosed with an OPG.

1.2.6.6 Other prognostic factors

From the studies in Table 1.1, the impact of other prognostic factors is unclear and disentangling individual contribution is difficult. For example, in line with the oncology literature (e.g., Aarsen et al., 2009), a negative effect for young age at diagnosis was found in relation to general measures of IQ (Fouladi et al., 2003) or specific measures of attention and motor speed (Riva et al., 2009). However, the most comprehensive study by Lacaze et al. (2003) found no correlations between age at diagnosis and IQ, but did not test the impact of this clinical factor on other specific cognitive or perceptual measures.

The role of tumour location is also unclear. Studies selecting at-risk patients with hypothalamic/chiasmatic involvement found conflicting results of adequate (Riva et al., 2009) and impaired (Fouladi et al., 2003) cognitive performance, whereas no effect of tumour location was found in a group with a-specific tumour localisation along the visual pathway (Lacaze et al., 2003). A systematic investigation of the impact of clinical factors is therefore necessary.

1.2.6.7 Visual and auditory processing

Another limitation that arises from the studies on OPG is the lack of clarity about the extent to which the sensory modality of the tasks impacts on the abilities examined. This can be explained in relation to the distinction between verbal and performance IQ used by most of the studies in Table 1.1, but in particular to the results by Lacaze et al. (2003). The authors described an advantage of the intact verbal IQ over the hampered performance IQ, both at group and individual levels, in their sample. Within the context of the IQ test, this result reflects a discrepancy between cognitive abilities; however, it may also indicate an incongruency between auditory versus visual processing, as well as between linguistic versus nonlinguistic skills. Indeed, verbal IQ relies on verbal and auditory stimuli, whereas performance IQ relies on visual and pictorial stimuli.

To reduce the interference of visual input on standardised testing, one solution could be to systematically allow children with poor vision to use low vision aids or adapt the test setting. It is possible that this accommodation was already used in the research on OPG because of the clinical nature of the studies in Table 1.1. Research shows that psychologists prefer to use and adapt standardised tests with which they are familiar when examining visually impaired individuals, even if the tools are not fully suitable (Miller & Skillman, 2003). In addition, many researchers call attention to the need to adapt the test setting to children's need (Limond et al., 2015; Nathan et al., 2007). However, this is difficult to ascertain from the works published on OPG.

Nonetheless, this approach would not fully address the compounding effect of the sensory modality on the neuropsychological assessment. To achieve this, it would be necessary to concurrently use analogous tasks that examine the same (not different) ability and that are carefully matched on all task characteristics except for the input sensory modality. This would enable the evaluation of whether the ability itself is developing at, above or below the age-appropriate level (congruent results of average, above-average or below-average performance in different sensory domains) or if the superior/inferior performance is driven by the sensory modality (incongruent performance across sensory domains). Evaluating these relationships across different sensory modalities would also help to determine whether children with OPG can develop compensatory strategies. Extensive research on retinoblastoma, another early developing cancer affecting the retina with either unilateral or bilateral involvement, showed that young and adult long-term survivors treated for this tumour develop superior cognitive abilities, memory and attention in the auditory domain (Ek et al., 2002; Levitt, Rosenbaum, Willerman, & Levitt, 1972; Thurrell & Josephson, 1966; Tobin, Hill, & Hill, 2010; Williams, 1968), especially if they experienced great vision loss and were diagnosed within the first year of life (Brinkman et al., 2015). Exploring potential mechanisms of auditory compensation is valuable to provide guidelines for supportive strategies in the school setting for children with OPG.

1.2.7 Summary

Overall, the prognosis of OPG is favourable and the vast majority of children survive after the treatment. However, in the chemotherapy era, many are left with some degree of visual impairment in order to preserve the developing brain from highly toxic treatment. Most research on OPG investigates visual outcomes because they are still considered poor and hence unsatisfactory by clinicians. In addition, the subjectivity involved in visual acuity testing and the poor correlations between this measure and objective description of the tumour (e.g., anatomical extension) make difficult to predict both tumour and vision progression.

Beyond vision, little is known about neuropsychological outcomes of these children, with a paucity of studies that are affected by several limitations including small samples, disused treatments, limited domains examined, inadequate neuropsychological tests or adaptations for the visually impaired, lack of or inappropriate statistical analyses, no control over critical confounding variables (e.g., radiotherapy, NF1 comorbidity) and poor reporting. Therefore, a systematic examination that encompasses the domains of visual perception, general intelligence and scholastic progression is necessary to define if children with OPG treated in the modern chemotherapy era experience neuropsychological difficulties and explore the impact of vision loss and NF1, as well as other prognostic factors on these outcomes. In addition, it is vital to examine the relationship between visual and auditory processing using a new assessment method that would enable the investigation of potential compensatory mechanisms in response to the loss of sight following childhood OPG.

1.3 Current study: aims and hypotheses

This thesis has two main aims. First, to systematically investigate visual and neuropsychological outcomes in a cohort of children who had a diagnosis of OPG and were observed or treated with chemotherapy, and thus reflect the modern approach to the management of this tumour. Second, to examine the relationship between visual and auditory

processing in children with OPG and to investigate whether they make up for the loss of sight.

1.3.1 Part I: A hierarchical model for assessing visual and neuropsychological outcomes following OPG

Since vision is to some extent a hierarchical system (see section 1.1.1), assessment of vision-related skills should distinguish and simultaneously involve low-level and high-level visual skills (Hammill, 1978; Warren, 1993a) because "without knowledge of where the deficit is located in the visual hierarchy, it is difficult to design appropriate evaluation or treatment strategies" (Warren, 1993a, p. 42).

Colenbrander (2001, 2003, 2010) proposes a bio-psycho-social model that encompasses different levels of functioning/disability to investigate the outcomes of conditions affecting the visual system and causing vision loss. Colenbrander's (2003) model provides a useful framework to systematically organise multi-level outcomes following OPG and it will be used in the current thesis to examine extent of impairment, associations and impact of clinical factors across different visual and neuropsychological domains (Figure 1.5).

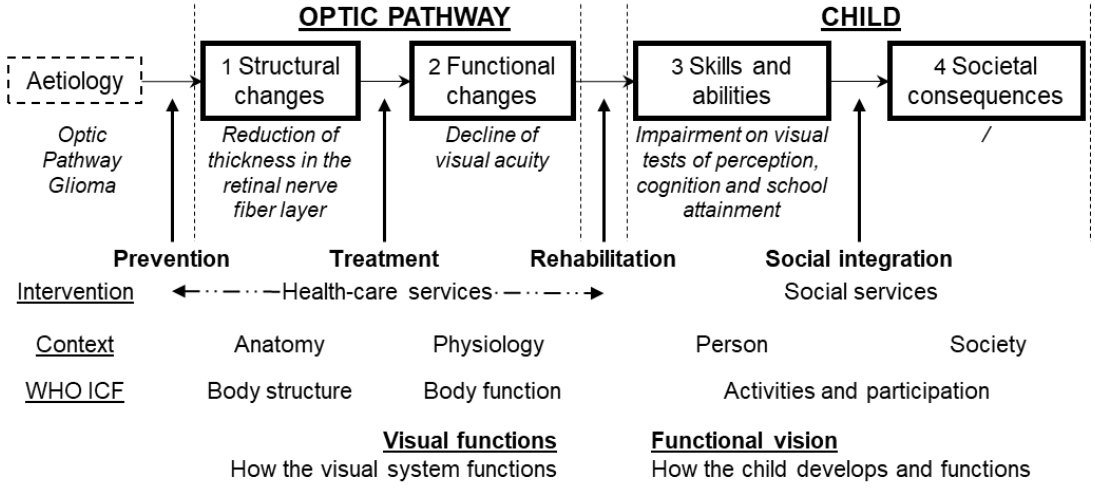


Figure 1.5. Aspects of vision and vision loss following paediatric OPG. Adapted from "Aspects of vision loss – visual functions and functional vision" by A. Colenbrander, 2003, *Visual Impairment Research*, *5*, p. 116. Copyright 2003 by Taylor & Francis.

On the one hand, the *organ-related* aspects of vision refer to the structural and functional aspects of the organs, either the eyes, the central pathway or the brain (see section 1.1.2). The structural level (1) refers to the anatomy of the organ and indicates how intact the visual system is. This will be examined in terms of changes to the thickness of the retinal nerve fiber layer (RNFL; Fisher et al., 2013), the bundle of axons of the retinal ganglion cells that merge to form the pre-geniculate portion of the central visual pathway. Thickness of the RNFL can be measured using optical coherence tomography (OCT; Avery, Rajjoub, Trimboli-Heidler, & Waldman, 2015), a non-invasive interferometry-based ocular imaging technique that measures the intensity of the backscatter of infrared light (Banc, Stan, & Florian, 2018).

The functional level (2) refers to the physiology and so-called visual functions and describes how well the visual system works. This will be described in terms of visual acuity (VA; see section 1.1.4; Avery et al., 2012). During assessment of VA, children are presented with progressively smaller figures or letters (optotype) at a fixed distance and are asked to identify each stimulus by naming it or pointing to the correct matching stimulus on a key card. The smallest size optotype that the child can identify corresponds to the measure of VA.

On the other hand, the *child-related* aspects of vision refer to performance on vision-related activities and societal participation of the child in general. The individual level (3) refers to the *functional vision*, which indicates how the child performs in vision-related tasks. Measurements at this level involve complex tasks similar to real-life situations but in a standardised setting, in which the performance reflects not only the visual functions, but also non-visual factors (e.g., cognitive skills or psychological variables). Cognitive and visuo-perceptual abilities and executive functions requiring vision, such as performance IQ and visual attention, would tap into level 3 of this model (Lacaze et al., 2003; Nicolin et al., 2009; Riva et al., 2009). This thesis will include also auditory/verbal measures related to this level of the model. However, unlike previous research on OPG, a systematic evaluation of the level of vision, motor and speed demand of each task will be conducted in order

to better evaluate the effect of vision loss on children's performance on different tasks (Roizen et al., 2006).

This thesis will not consider the societal level (4), which refers to the broader impact of vision loss on school participation and progression and quality of life, with implications for health and educational services and national policies (Colenbrander, 2003). This level of analyses falls beyond the scope of the current project.

Whilst level 1 and 2 related to the optic pathway are the area of competence of medical specialties (e.g., paediatric oncology, neuro-ophthalmology and neuro-radiological) that deal with the diagnosis and treatment of these tumours, cognitive and scholastic outcomes are the competence area of neuropsychology, which aims to support the rehabilitation of young OPG survivors (Figure 1.5). This framework might facilitate the communication among health-care providers and enhance synergy across these disciplines to provide better assistance to children with OPG.

1.3.1.1 Hypotheses for visual and neuropsychological outcomes of OPG

Chapter 3 and Chapter 4 of this thesis will establish the extent of impairment on visual and neuropsychological outcomes on the whole sample of young OPG survivors. Because of the paucity of research on OPG, some general hypotheses will be drawn from the literature of paediatric brain cancer and based on the hierarchical models of visual perception.

a. Visual outcomes following OPG are a major concern and still unsatisfactory in the management of this type of tumour (Fisher et al., 2012). Therefore, it is predicted that neuro-ophthalmology measures related to the optic pathway (RNFL thickness and visual acuity) and visual perception will demonstrate a significant impairment and a systematic negative effect (i.e., less degree of variability) across participants (Chapter 3).
b. Studies on OPG suggest that general intelligence of these children is intact thanks to the use of neuroprotective strategies of tumour management (Lacaze et al., 2003; Riva et al., 2009). This is in line

with evidence from malign and aggressively treated tumours, which show significant decrease in IQ after the treatment (Chevignard et al., 2017). However, increasing evidence from paediatric cerebral and cerebellar tumours suggest that specific problems in attention, working memory and processing speed represent the core deficit of brain tumour survivors, which might explain the cognitive decline over time (Stavinoha et al., 2018). It is possible that different mechanisms take place among OPG survivors due to the pre-cortical location of the tumour. However, deficits in these domains were found also among children treated for other subcortical midline tumours (e.g., germ cell tumors; Mabbott et al., 2011). Alternatively, such difficulties could be attributed to the chemotherapy, as shown in children with leukaemia (Buizer et al., 2005; Pierson et al., 2016). Therefore, it can be hypothesised that, if any, deficits in children with OPG would affect the domains of attention, working memory and processing speed (Chapter 4).

c. Studies on OPG have not investigated scholastic outcomes. However, different neuropsychological cascade models have been put forward in the paediatric oncology literature suggesting that cognitive deficits in working memory and processing speed, in interaction with individual (e.g., sex) and tumour (e.g., type of treatment) variables, would lead to scholastic difficulties (King et al., 2019; Palmer, 2008; Wolfe, Madan-Swain, & Kana, 2012). Evidence partially support these models as children with brain tumour demonstrate poor academic fluency on tasks that require timed performance, but intact scholastic abilities when there is no emphasis on speed (Holland et al., 2015). Because the most recent research on OPG suggests that general intelligence is overall preserved (Lacaze et al., 2003; Riva et al., 2009), it can be predicted that, if these children exhibit working memory and processing speed problems (see point *b* above), they will display a cascade effect from the cognitive to the scholastic domain. However, these deficits would be evident only if academic tests rely on timed performance; otherwise, OPG children would demonstrate intact basic scholastic abilities (Chapter 4).

d. In the chemotherapy era, by averting harmful treatments (i.e., surgery and radiotherapy), NF1 and vision loss are the most critical risk factors for neuropsychological difficulties in children with OPG. Overall, it can be predicted that vision loss (e.g., neuro-ophthalmology measures of visual acuity and RNFL thickness and degree of deficit on binocular vision) will have an impact on tasks that require vision (Lacaze et al., 2003), especially on those with high motor and timed demand. In addition, it can be predicted that NF1 co-diagnosis will act on all developmental domains as a reflection of specific deficits (e.g., visual perception problems and learning difficulties) or as a consequence of deficits in transversal skills (e.g., attention) (Chapter 5).
e. Complex interactions may exist between the co-diagnosis of NF1 and visual outcomes. While children without NF1 may exhibit an "ocular" visual impairment and therefore a major forefront problem due to the tumour but relatively intact downstream visual processing abilities, children with NF1 might exhibit a "cerebral visual impairment" and therefore visuo-spatial difficulties (a hallmark of this condition) in spite of intact visual acuity. While Chapter 5 will examine these interactions at group level, some considerations about individual patterns will be conducted in Chapter 7 when the results will be collectively discussed in relation to Colenbrander's (2003) model.

In Chapter 7, the results obtained from the analyses of Colenbrander's (2003) model will be collectively summarised and examined in relation to individual patterns of performance. Colenbrander (2003) argues that in his model the chain of cause and effect runs from left to right, as in Figure 1.5. While it is reasonable to agree with this to some extent, research on OPG suggests that such a deterministic approach should not be taken when investigating this condition. Indeed, some OPGs do not present visual symptoms and are not treated (King et al., 2015), the radiological progression of the tumour and visual acuity are poorly correlated (e.g., Fisher et al., 2012) and neuropsychological difficulties might be driven by the cognitive phenotype of the NF1 (Lacaze et al., 2003) regardless of the integrity of sight. A global

evaluation of Colenbrander's (2003) model across the study levels will be conducted in Chapter 7.

1.3.2 Part II: Visual and auditory processing

In the second part of this thesis, the impact of visual and auditory processing on the assessment of children with OPG will be investigated.

First, in order to define visual and auditory processing, it is useful to refer to the cognitive theory of multimedia learning by Mayer (2001). This theory aims to understand how to use words and pictures as well as different multimedia devices to facilitate human learning. One assumption underpinning this theory is that the human mental processing system relies on an auditory/verbal channel and a visual/pictorial channel (*Figure 1.1*Figure 1.6). Specifically, these channels can be conceptualised in two ways based either on the presentation mode or the sensory modality. According to the presentation-mode approach, one channel processes verbal materials (such as spoken or written words) and the other channel processes pictorial materials and nonverbal sounds (such as pictures, videos and background sounds). According the sensory-modality approach, one channel processes aurally presented material and the other channel processes visually presented material. In other words, the former approach focuses on the format of the stimuli themselves at presentation, whereas the latter approach focuses on the sensory modality used to convey them.

[Figure removed due to copyright]

Figure 1.6. Cognitive theory of multimedia learning. Adapted from "*Multimedia learning*" (p. 44), by R. E. Mayer, 2001, Cambridge, UK: Cambridge University Press. Copyright 2001 by Cambridge University Press.

While the cognitive theory of multimedia learning proposes a compromise of mixed verbal-auditory and visual-pictorial channels (Mayer, 2001), this thesis will focus on the sensory-modality features of neuropsychological tests (i.e., auditory versus visual) because OPGs directly affect the visual system and therefore one of the senses that the patients use to perceive the incoming material. In addition, the sensory-modality approach offers advantages to the current neuropsychological research for task manipulation in comparison to the presentation-mode approach, as it will be delineated in Chapter 2.

Because children with OPG would benefit from a comprehensive assessment of visuo-perceptual, cognitive and scholastic development as previously discussed, the second part of this thesis will focus on specific skills within these domains, namely fine motor skills, attention, short-term and working memory, mathematics and English comprehension. Parallel tasks that rely on either visual or auditory input will be developed for each skill whilst controlling for the other task features as much as possible. This battery will be presented in detail in Chapter 2 and its results will be analysed in Chapter 6.

1.3.2.1 Sight loss compensation in OPG survivors

In the literature, there are two definitions of "compensation" that are relevant for this thesis.

In sensory research, compensation refers to the "improvement in the remaining senses after the loss of one sensory system in order to counteract the lost capabilities" (Röder & Rösler, 2004, p. 719). In neuropsychological rehabilitation, compensation refers to "use of alternative behavioural strategies such as devising alternative methods for completing a task or solving a problem" (Robinson & Weeks, 2008, p. 209). This thesis will focus primarily on the first meaning of compensation to align with the sensory-modality approach discussed in the previous section. However, the second broader meaning of compensation will also be considered because some abilities are intrinsically embedded in a certain sensory system and changing the sensory modality would alter the skills themselves (for example, writing

is inherently linked to the visual system and relatively independent from the hearing system).

Based on the research on blindness and visual impairment, different possible outcomes pertaining to the visual deprivation model can be predicted:

1) *Inferior performance*: visually deprived individuals perform worse than sighted counterparts. The ability assessed either relies on sight or needs the interaction between sight and the other senses/skills to develop. This outcome would suggest that no compensation occurs.

2) *Equal performance*: visually deprived individuals perform at the same level as sighted counterparts. If the ability assessed does not rely necessarily on sight, this outcome reflects a lack of impairment. Alternatively, if the ability examined involves vision, the other sensory channels or skills can lead to normal acquisition and equal performance can be taken as a compensation given the sight loss experienced.

3) *Superior performance*: visually deprived individuals perform better than sighted counterparts. The ability assessed overdevelops in non-visual modalities to compensate for the loss of sight. This outcome would suggest that hyper-compensation occurs.

As previously discussed, children with OPG are expected to underperform on visual tasks because of the degree of vision loss and because of the visuo-spatial difficulties related to the NF1 mutation.

On nonvisual tasks, the literature available on OPG (Table 1.1) suggests that children with these tumours do not develop superior auditory skills. Verbal IQ, which measures verbal working memory and comprehension, was found below the test mean (Nicolin et al., 2009), close to norms but deteriorated (Riva et al., 2009), or at the best within the normal range (Lacaze et al., 2003) after treatment, but never superior, in children with OPG. Further, Lacaze et al. (2003) described the significant discrepancy between the IQ indices in terms of impaired

performance IQ and preserved (not superior) verbal IQ. While in studies before the chemotherapy era lowered verbal IQ might be attributed to the radiation effects (Nicolin et al., 2009), it seems more likely that children with OPG treated more recently do not hyper-compensate with superior auditory skills but they may perform like their sighted peers on which the test norms are based.

Interestingly, considerable evidence of marked auditory hyper-compensation and/or compensation in cancer survivors comes from studies on paediatric retinoblastoma, an eye tumour with either unilateral or bilateral involvement. Starting from observations in the 1960s (Thurrell & Josephson, 1966), superior verbal but also haptic intelligence, attention and memory in children and adult survivors have consistently been reported (Brinkman et al., 2015; Levitt et al., 1972; Thurrell & Josephson, 1966; Tobin et al., 2010; Williams, 1968). Some studies suggest that retinoblastoma survivors develop a general cognitive superiority. For example, two studies found verbal IQ of these children to be one (Williams, 1968) or more (Tobin et al., 2010) standard deviation above the norms. In contrast, Witkin and colleagues (1971) found a cognitive-specific superiority on the working memory tests, but normal performance on the verbal comprehension tasks (as cited in Levitt et al., 1972). Whether it is a general or specific cognitive superiority, retinoblastoma patients hyper-compensate.

The oncology literature of retinoblastoma offers an interesting model to make better predictions about outcomes in OPG patients. These studies will be reviewed here below in relation to other important features such as the severity of the visual impairment and time related variables, including the age at which the vision deterioration occurred and how long the person has lived with such impairment (Miller, 1992).

1.3.2.2 Sequelae of retinoblastoma: a model of auditory compensation

It is possible that the hyper-compensation demonstrated by retinoblastoma survivors depends on the severity of visual impairment experienced by these patients. Studies involving only bilaterally blind patients (Williams, 1968; Witkin, Birnbaum, Lomonaco, Lehr, & Herman,

1968) or conducting separate analyses based on lateral involvement (Brinkman et al., 2015; Ek et al., 2002; Levitt et al., 1972) showed that the hyper-compensation occurs for bilaterally blind patients. Within the OPG population, bilaterally blind adult survivors were found impaired on the task efficiency subscale of a cognitive battery, and overall less adjusted (e.g., less college attendance) in comparison to the sighted counterparts (de Blank et al., 2016), suggesting that a severe visual impairment is not advantageous for OPG patients. Information about lateral involvement and degree of visual impairment was not given in the studies reported in Table 1.1 to make further predictions (Fouladi et al., 2003; Lacaze et al., 2003; Nicolin et al., 2009; Riva et al., 2009). However, a small proportion of OPG survivors is expected to be bilaterally blind a year or more after treatment (Dodgshun et al., 2015) therefore their performance would have little impact at group level. Most OPG survivors are expected to have some degree of residual sight, therefore the impact of unilateral blindness in the studies with retinoblastoma patients should be assessed.

Adequate performance was found among retinoblastoma survivors when mixed groups of blind and partially sighted individuals were involved. For example, Levitt et al. (1972) found that, whilst bilaterally blind children had a significant superiority on verbal IQ in comparison to sighted siblings, the whole mixed group of unilaterally and bilaterally blind children had a non-significant advantage on the same outcome measure. Similarly, Ek et al. (2002) found that mean full-scale IQ was slightly above the norms for children with unilateral blindness, but 2 standard deviations above the norms for children with bilateral blindness. This suggests that residual sight is likely to result in adequate (not superior) performance. Because children with OPG are likely to have some residual sight, adequate performance can be expected for these patients. The sparse literature on OPG (Lacaze et al., 2003; Riva et al., 2009) reporting verbal IQ closed to the test mean also supports this.

More compelling evidence in support of the hypothesis that adequate (but not superior) performance may occur in OPG patients, as compared to the superior ability exhibited by retinoblastoma patients,

comes from one study by Tobin et al. (2010). The authors demonstrated that retinoblastoma patients (mostly with bilateral blindness) have not only a superiority of over 30 points in verbal IQ in comparison to the test normative mean (based on sighted individuals), but also a significant advantage in comparison to visually impaired individuals without retinoblastoma, who instead performed within the normal range of the test norms. This further suggests that OPG survivors, like other visually impaired groups, can be expected to perform at the same level as their sighted peers in the auditory/verbal domain, but not above the normal range as retinoblastoma survivors.

However, it is also possible that residual sight leads to specific difficulties in verbal/auditory skills. For example, among adult survivors of retinoblastoma, Brinkman et al. (2015) found that individuals with unilateral blindness were more likely to have impairment on short-term verbal memory and attention compared to those with bilateral blindness. This aligns with some evidence from OPG patients showing lowered verbal IQ after the treatment (Nicolin et al., 2009), although this might have been due to the radiotherapy effects. Nonetheless, deficits in specific verbal/auditory tasks of memory and attention can be expected based on the literature of childhood brain tumour previously discussed.

To better elucidate the relationship between absolute performance in the auditory domain and compensatory mechanisms, it would be useful to consider the impact of time-related variables in studies about retinoblastoma survivors, such as age at diagnosis. Brinkman et al. (2015) found that younger age at diagnosis was associated with better short-term and long-term memory, learning and intelligence in the verbal domain, and most correlations remained significant after adjusting for laterality involvement. This suggests that survivors with residual sight like OPG patients can develop compensatory mechanisms in the verbal/auditory domain. However, as previously reported, Brinkman et al. (2015) also showed that partially sighted retinoblastoma survivors were more likely to have difficulties on short-term verbal memory and attention compared to those with bilateral blindness. This indicates that evaluating the absolute performance on the auditory domain as well as

the relationship with time-related variables would help to better elucidate the effect of potential compensatory mechanisms that may occur among visually impaired survivors. The importance of time-related factors is well-established in the research of blindness/visual impairment (Miller, 1992) as well as brain injury (Anderson et al., 2011; Taylor & Alden, 1997) to evaluate the recovery and plasticity continuum in both conditions.

1.3.2.3 Hypotheses for visual-auditory processing in children with OPG

The literature on retinoblastoma demonstrates that it is important to have normative data to understand the extent of compensation implemented by visually impaired individuals, and to better evaluate the effect of clinical factors. Overall, it can be predicted that OPG survivors do not hyper-compensate but perform like their sighted peers, even if time-related compensatory processes may occur. Nonetheless, while research on retinoblastoma is based on a sharp dichotomy (unilateral versus bilateral blindness), studies on OPG should explore potential linear relationships between the degree of visual impairment and the performance on auditory tasks.

1.3.3 Thesis aims

To summarise, in the first part of this thesis, Colenbrander's (2003) model will be used to examine the extent of impairment, associations and impact of clinical factors across different visual and neuropsychological domains.

The aim of Chapter 3 is to establish the extent of impairment on neuro-ophthalmic measures of vision (visual acuity and RNFL thickness) and visual perception. This study will extend the ophthalmology research on OPG, which examines functional aspects of sensory reception or their structural surrogates, by assessing visual-spatial abilities that do not involve semantic processing and therefore do not tap into high-level cognition.

The aim of Chapter 4 is to investigate the degree of deficit on cognitive and scholastic abilities exhibited by children with OPG. This

study will overcome many of the limitations emerged from the scarce available literature about cognitive sequelae of paediatric OPG and will examine if children with OPG display difficulties in specific cognitive or scholastic areas.

The aim of Chapter 5 is to study relevant prognostic factors which may impact upon visual and neuropsychological outcomes in this patient group, including NF1 co-diagnosis, vision loss, posterior extension of the tumour, age at diagnosis, time after treatment, and socio-demographic factors.

The aim of Chapter 6 is to study the performance of the young OPG survivors on the assessment of fine motor control, attention, short-term and working memory, mathematics and English comprehension using a series of analogous tests administered in either the visual or auditory modalities. A large normative sample of typically developing children was also examined on the same tests to provide normative models of development in these domains. By evaluating the performance of children with OPG in comparison to a normative dataset and the effect of clinical factors on patients' skills, this chapter will assess if children with OPG can compensate with superior auditory skills.

Chapter 7 will summarise and critically reflect on the findings from the current research, discuss the limitations and make recommendations for future research and clinical practice.

Chapter 2 General methods

This thesis reports on a proof-of-concept study that investigated the utility and validity of a new methodology to assess neural, visual and neuropsychological outcomes in children with history of optic pathway glioma (OPG). Whilst the use of well-known vision tests and standardised neuropsychological tools allowed for comparison to normative data and test norms, the employment of some experimental measures to concurrently investigate auditory and visual processing made it necessary to recruit and test a control group of typically developing children.

2.1 OPTIC-MRI study

The OPTIC-MRI study is a research project based at the Department of Radiological Sciences (School of Medicine) of the University of Nottingham that aims to identify neuropsychological and neuroimaging predictors of scholastic performance in patients treated for brain tumour in either the optic pathway or the cerebellum. Ethical approval was granted from the NHS London Camberwell St Giles Research Ethics Committee (16/LO/2149). The study was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed parental consent and child assent were obtained for each participant prior to participation in the study.

This thesis focuses on only the optic pathway patient group. The research protocol included three parts: ophthalmologic examination, magnetic resonance imaging scan, and neuropsychological assessment. The neuroimaging scanning is not part of this thesis.

The author of this thesis designed the neuropsychological assessment of the study with the supervisor NJP and actively collaborated with the supervisor RAD to obtain the sponsorship of the University of Nottingham and the approval of the Health and Research Authority (Appendix B), including the Research Ethics Committee and the local Research and Development department. The author of the thesis was fully responsible for the neuropsychological evaluation and collaborated with other members of the OPTIC-MRI team (BEH and CB) to collate

medical records, recruit the patients and coordinate the ophthalmology examination with the hospital ophthalmology department.

2.1.1 Participants

NHS records of children treated for OPG at the Queen's Medical Centre (Nottingham UK) between 2006 and 2017 were consulted to identify young patients suitable for participation in the study. Besides the diagnosis of optic pathway glioma, additional inclusion criteria were: i) age between 6 and 16 years, ii) off-treatment for at least 6 months. English as a first language was not considered an exclusion criterion in order to maximise participants' enrolment, at least into the MRI and visual components of the study. However, language proficiency of each child was assessed to decide whether it could affect the neuropsychological testing. Details of most patients were extracted from clinical records by two medical students as part of their BMedSci dissertation projects. Collected information included age at diagnosis, comorbidity of NF1, treatment undertaken and progression of visual outcome. A radiological classification of the tumour based on the PLAN classification system (Taylor et al., 2008) was provided by a professional radiologist, who was also principal investigator of the study and co-supervisor of this project (RAD). Socio-economic status (SES) was estimated for each child using the 2015 Income Deprivation Affecting Children Index (IDACI; Department for Communities and Local Government, 2015). The IDACI rank is a postcode-based index that measures the proportion of children under 16 years of age who live in low-income families within a small geographical area. In England, IDACI scores range between 1 and 32,844, with lower scores indicating most deprived areas.

Of a group of 27 patients who were eligible for the study, 12 agreed to take part. Participating and non-participating children did not differ in age at diagnosis ($t(21) = 1.08$, $p = .292$), sex ($\chi^2(1) = 1.50$, Fisher's exact $p = .398$) or NF1 co-diagnosis ($\chi^2(1) = 0.49$, Fisher's exact $p = .683$). The OPG patient sample included 7 boys and 5 girls; 7 children (4 boys) had co-diagnosis of NF1. SES ranged from 8,498 to 32,309 (*Mdn* = 25,242.5). Age at assessment ranged between 6.2 and

13.7 years (*M* = 10.1, *SD* = 2.2 years); all children were diagnosed with OPG before 6 years of age (*M* = 2.5, *SD* = 1.6 years; range: 0.7 – 5.6 years). One child had English as additional language; all children were fluent in English and were deemed able to complete the neuropsychological evaluation. Three children did not receive treatment for OPG; the others received chemotherapy. Tumour histology of pilocytic astrocytoma was confirmed in two children who underwent biopsy and was suspected in all other cases. Six children, most with sporadic OPG, had visual symptoms at presentation. Based on the Modified Dodge (or PLAN) classification (Taylor et al., 2008) applied by the radiologist on the MRI scan after management, all children had tumour in the anterior optic pathway (sites 1 and/or 2), 6/12 also had posterior involvement to the optic radiations (site 4), and 8/12 had hypothalamic invasion (H+). There were no significant differences between sporadic and NF1-associated OPGs in terms of sex ($\chi^2(1) = 0.01$, Fisher's exact $p = 1.00$) and treatment ($\chi^2(1) = 0.11$, Fisher's exact $p = 1.00$). Case details of the patients are provided in Table 2.1.

Table 2.1
Case details of the 12 participants with OPG studied.

Case	Sex	NF1	Age at diagnosis (years)	Age at assessment (years)	Symptoms at presentation		Biopsy, histology[a]	PLAN classification			Management strategy	Time post management (years)
					visual	other		Before	After	Posterior		
P1	M	Yes			None	None	Yes, PA	1cB 2a 3L 4L H+	1cB 2a 3bL 4L H+	Yes	OBS	
P2	M	Yes			None	None	No, -	1bL 1cbL 2a 3B 4R H+	1aL 1cbL 2a 3B 4R H+	Yes	CT	
P3	F	Yes			None	None	No, -	1bR 2a 4R H+	1bR 2a 4R H+	Yes	OBS	
P4	F	Yes			VD	None	n/a	n/a	1cB 2a 3B 4B H+	Yes	CT	
P5	M	Yes			None	None	No, -	1aR 1cR H+	1cR H+	No	OBS, then CT	
P6	M	Yes			None	Behavioural change	No, -	1aR 1cB 2a	1cB 2a 3bR H+	No	CT	
P7	F	Yes	[Data removed for anonymity]	[Data removed for anonymity]	N	Diencephalic syndrome	No, -	1cbR 2bR 3bR 4bR H+	1cB 2bR 3R 4R	Yes	CT	[Data removed for anonymity]
P8	M	No			VD	None	No, -	1aR 2a 3B H+	1aR 2a H+	No	CT	
P9	F	No			VD	None	No, -	1cB 2bR 3R 4R	1cB 2bR 3R 4R	Yes	OBS	
P10	M	No			N	None	No, -	1cbL 2a 3B H+	1cL 2bL 3B	No	CT	
P11	M	No			N, P, VD	None	Yes, PA	1aL 1cL 2bL 3bL H+	1aL 1cL 2bL 3bL	No	CT	
P12	F	No			Abnormal eye movement	Head bobbing doll syndrome	No, -	2a 3B H+	2a 3B H+	No	CT	

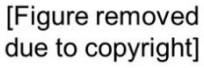
Note. F = female; M = male; NF1 = Neurofibromatosis Type 1; N = Nystagmus, P = proptosis, VD = vision decline; PA = pilocytic astrocytoma; CT = chemotherapy; OBS = observation.
[a] Histology was suspected PA when biopsy was not conducted.

2.1.2 Ophthalmologic examination

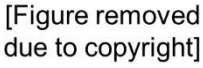
The ophthalmologic examination included assessment of visual acuity (VA) and measurement of the thickness of the Retinal Nerve Fiber Layer (RNFL) through Optical Coherence Tomography (OCT). Results and VA scores were collected retrospectively from the hospital databases.

VA scores were retrieved from the hospital databases NotIS and Unity. Depending on the child's age and literacy level, three different tests were used: Bailey-Lovie test (Bailey & Lovie, 1976) for older literate children, and the Keeler LogMAR crowded test (McGraw & Winn, 1993) or Kay Picture crowded test (Kay, 1983) for younger and/or illiterate children (Figure 2.1). Scores were provided in logMAR scale and visual function of each pair of eyes was classified using the 2014 SIOP-e NF1 OPG Nottingham Workshop criteria (Walker et al., 2016).

A)



B)



C)

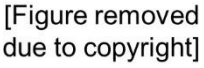


Figure 2.1. Example of visual acuity test materials. A) Bailey-Lovie chart. Reprinted from "Visual acuity testing. From the laboratory to the clinic", by I.L. Bailey and J. E. Lovie-Kitchin, 2013, *Vision Research*, *90*, p. 4. Copyright 2013 by Elsevier Ltd. B) Keeler LogMAR Crowded test material. Reprinted from "The effect of adherence to spectacle wear on early developing literacy: a longitudinal study based in a large multiethnic city, Bradford, UK" by A. Bruce, B. Kelly, B. Chambers, B. T. Barrett, M. Bloj, J. Bradbury and T. A. Sheldon, 2018, *BMJ Open*, *8*, p. S1. CC BY 4.0. C) Crowded Kay Picture test material. Reprinted from "Kay Picture Brochure 2019" by Kay Pictures, 2019, p. 3 (https://kaypictures.co.uk/Kay_Pictures_Brochure_2019.pdf). In the public domain.

OCT results were accessed via the Heidelberg Eye Explorer system. OCT data were collected using either Spectralis OCT or Spectralis OCT+HRA (Heidelberg Engineering Ltd, Heidelberg, Germany). For each eye, the software generated a map reporting RNFL thickness by quadrants (inferior, superior, temporal and nasal) and the global RNFL thickness (average of the four sectors), expressed in μm. These maps were coded with colours in green, yellow and red to indicate values within normal limits, borderline or outside normal limits respectively, in comparison to a normative dataset included in the software. Figure 2.2 shows an example of the OCT output. The value of global RNFL thickness from each eye was used for statistical analyses.

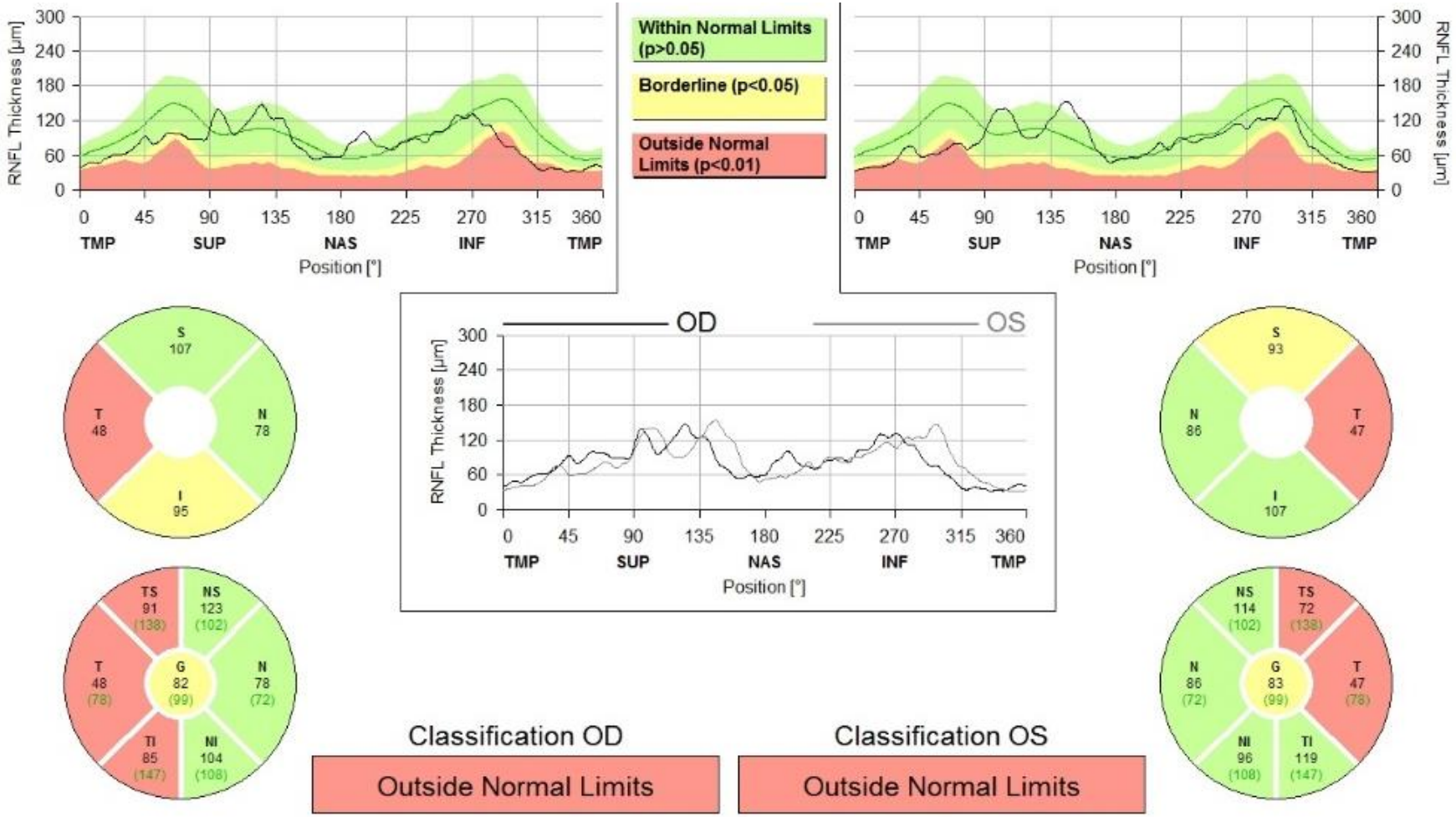


Figure 2.2. Example of Spectralis OCT results displaying the thickness of the retinal nerve fiber layer. INF/I = inferior; G = global; N/NAS = nasal; NI = nasal inferior; NS = nasal superior; OD = oculus dextrus (right eye); OS oculus sinister (left eye); S/SUP = superior; T/TMP = temporal; TI = temporal inferior; TS = temporal superior.

2.1.3 Neuropsychological assessment

For the first part of the thesis, where Colenbrander's (2003) model will be used for a comprehensive evaluation of visual and neuropsychological outcomes in children with OPG, three standardised tests were employed to evaluate the hierarchical domains of visual perception, general intelligence and scholastic attainment. For the second part of the thesis, the auditory and visual processing in children with OPG was examined in relation to specific perceptual, cognitive and scholastic abilities using a novel battery of analogous auditory and visual tests with a mix of experimental and standardised subtests.

2.1.3.1 Hierarchical domains

2.1.3.1.1 *Visual perception*

The Developmental Test of Visual Perception – Second Edition (DTVP-2; Hammill, Pearson, & Voress, 1993) and the Developmental Test of Visual Perception – Adolescent and Adult (DTVP-A; Reynolds, Pearson, & Voress, 2002) were used to assess perceptual processes. These tests rely on a definition of perception as the set of "those brain operations that involve interpreting and organizing the physical elements of a stimulus rather than the sensory or symbolic aspects of a stimulus" (Hammill et al., 1993, p. 2; Reynolds et al., 2002, p. 3). The two versions of the DTVP are based on the three-level model by Hammill et al. (1993), which postulates three levels of information processing involved in receptive processes: 1) sensation, 2) perception, and 3) cognition. Within the visual modality, low-level sensation can be measured through ophthalmological indices such as visual acuity, while high-level cognition can be measured through more complex tasks such as reading. The DTVP tests aim to assess intermediate perceptual processes.

Both the DTVP-2 and DTVP-A have been normed for the US population. The DTPV-2 is suitable for children aged 4 to 10 years, whereas the DTVP-A is designed for adolescents and adults aged 11 to 74 years.

The DTPV-2 is organised in eight subtests that provide a composite measure in two domains: Visual Perception and Visual-Motor Integration.

Examples of test items from each subtest of DTVP-2 are shown in Figure 2.3.

1) Visual Perception is a motor-reduced scale, in which the motor component is minimal. It includes four subtests: i) Position in Space involves identifying a target stimulus within a row of similar but different figures; ii) Figure-Ground requires recognising different shapes that are hidden in a complex background; iii) Visual Closure involves identifying a figure which represents the incomplete version with a dotted contour of a target stimulus; iv) Form Constancy requires recognising a target shape within a series of stimuli that contain the same shape but with different size, position and/or border thickness.

2) Visual-Motor Integration is a motor-enhanced scale, in which the integration between visual information and motor control is essential. It includes four subtests: i) Eye-Hand Coordination, in which the child has to draw a line within a straight, crooked, or circular path of decreasing width; ii) Copying, in which the child is asked to copy different shapes of increasing difficulty below the target stimulus; iii) Spatial Relations, in which the child is shown two grids of equally distributed dots and is required to reproduce on the bottom grid the pattern of lines represented in the top grid; iv) Visual-Motor Speed, in which the child is presented four shapes, big and small squares and circles, with different or no internal marks, and is required to complete a page filled with the target shapes by reproducing the marks as appropriate within a certain time.

Figure 2.3. Example items of each DTVP-2 subtest. Reprinted from "Visual-perceptual impairment in children with periventricular leukomalacia" by E. Fazzi, S. M. Bova, C. Uggetti, S. G. Signorini, P. E. Bianchi, I. Marauccia, M. Zoppello, G. Lanzi, 2004, *Brain and Development*, *26*, p. 508. Copyright 2004 by Elsevier Inc.

The DTVP-A is organised into six subtests. Similar to the DTVP-2, this battery provides a composite measure in two domains: Visual Perception and Visual-Motor Integration. The Visual Perception scale includes equivalent subtests of Figure-Ground, Visual Closure, and Form Constancy. The Visual-Motor Integration scale includes analogous subtests of Copying and Visual-Motor Speed; it also includes the additional subtest Visual-Motor Search, in which the examinee is presented a page of randomly displaced circles and is asked to connect with a line the circles with numbers in numerical order while ignoring the empty circles, as quickly as possible.

In both the DTVP-2 and DTVP-A, the composite measures of Visual Perception and Visual-Motor Integration contribute to a third composite score of General Visual Perception. Using the test norms, raw scores of

each subtest can be transformed into scaled scores (μ = 10 and σ = 3), which can then be used to generate standard scores for the composite indices (μ = 100 and σ = 15).

2.1.3.1.2 *General intelligence*

The Wechsler Intelligence Scale for Children - Fourth UK Edition (WISC-IV^{UK}; Wechsler, 2004) was used to evaluate general intelligence. This standardised test has been normed for the UK population and designed for children aged 6 to 16 years. It was chosen as it is the most commonly used test of IQ in clinical practice. It consists of 10 core subtests that combine to provide a composite measure of full-scale IQ and index scores in four major intellectual domains, namely Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed.

1) Verbal Comprehension (VC) assesses verbal reasoning, word knowledge, concept formation and expression. It consists of three core subtests: i) Similarities requires the child to describe how two stimuli are alike by abstracting a common concept or category; ii) Vocabulary involves the child giving a name or a definition of objects represented in pictures or words read aloud by the examiner; iii) Comprehension requires the child to explain the function of common objects, the expected behaviour in familiar situations, some societal practices, and their underlying motivation. This index relies on aurally presented verbal stimuli.

2) Perceptual Reasoning (PR) assesses non-verbal reasoning, problem solving, and visuo-perceptual organisation. It consists of three core subtests: i) Block design, in which the child is given 9 red-and-white cubes to arrange on a table to reproduce a model constructed by the examiner or represented in a picture; ii) Picture Concepts, in which the child is shown a series of pictures organised in two or three rows and is asked to indicate one picture from each row that shares a common characteristic with the others; iii) Matrix Reasoning, in which the child is required to complete a matrix by identifying the missing element from a range of options. This index employs visually presented nonverbal (pictorial) stimuli.

3) Working Memory (WM) measures attention and the ability to retain and manipulate verbal information for a short period of time. It includes two core subtests: i) Digit Span, in which the child recalls, in the same or reverse order, sequences of digits of increasing length read aloud by the examiner (see also section 2.1.3.1); ii) Letter-Number Sequencing, in which the child listens to a list of letters and numbers read aloud by the examiner and then repeats the numbers and the letters respectively in ascending numerical and alphabetical order. This index uses aurally presented verbal stimuli.

4) Processing Speed (PS) assesses speed of thinking, graphomotor writing, visual search, and discrimination. It includes two core subtests, all of which are timed: i) Coding involves completing a grid by copying for each number listed the corresponding symbol based on a paired-association reported in the key; ii) Symbol Search involves scanning a string of symbols to decide if the target symbol is present or not. This index relies on visually presented nonverbal (pictorial) stimuli.

Using the test norms, raw scores were transformed into scaled scores for the subtests ($\mu = 10$ and $\sigma = 3$), which were then used to generate standard scores for the composite indices ($\mu = 100$ and $\sigma = 15$). The total composite index full-scale IQ was also generated from the total sum of the 10 core subtests.

2.1.3.1.3 *Scholastic attainment*

The Wechsler Individual Achievement Test – Second UK Edition (WIAT-II^{UK}; Wechsler, 2005) was used to assess scholastic attainment. This standardised test has been normed for the UK population and designed for children aged 4 to 16 years. It was chosen for this study because it is co-normed with the WISC-IV^{UK}. Of note, this test does not emphasise speed and timed performance. It consists of 9 subtests that combine to provide composite measures in four major academic domains: Reading, Mathematics, Written Language, and Oral Language.

1) Reading (R) assesses low- and high-level skills of reading and comprehension at different levels of language (word segment, word, and text). It includes three subtests: i) Word Reading, in which the child names single letters or objects, recognises sounds or rhymes, and reads

aloud whole words; ii) Pseudoword Decoding, in which the child reads a series of non-words on the basis of grapheme-phoneme associations; and iii) Reading Comprehension, in which the child matches a written word with the corresponding picture, or reads a sentence or a paragraph and answers a question on its content (see also section 2.1.3.2.5).

2) Mathematics (M) measures the acquisition of pure mathematical procedures and the ability to apply them in real-word situations. It includes two subtests: i) Numerical Operations, that involves identifying or writing a number, counting real objects, and solving arithmetic calculations and equations (see also section 2.1.3.2.4); and ii) Mathematical Reasoning, that involves counting items, identifying geometric shapes, and solving real-world mathematical problems with numbers, fractions, graphs and statistics.

3) Written Language (WL) assesses the maturity and automaticity of writing mechanism in terms of visuo-motor organisation and content. It includes two subtests: i) Spelling, where the child writes a letter embedded within a word, and a word embedded within a sentence; and ii) Written Expression, in which the child writes letters of the alphabet, words, sentences, a paragraph, and an essay.

4) Oral Language (OL) measures a combination of listening and speaking skills, expressive and receptive vocabulary, and oral comprehension. It includes two subtests: i) Listening Comprehension, where the child indicates the picture that matches a word or sentence, or generates the word corresponding to an oral description; and ii) Oral expression, in which the child repeats some sentences, generates words based on a semantic category, creates a story based on a comic strip, and describes the actions required to perform an action.

Using the test norms, raw scores for each subtest were transformed into standard scores ($\mu = 100$ and $\sigma = 15$), which were then summed up and converted into standard scores for the composite indices ($\mu = 100$ and $\sigma = 15$). Composite scores in these four domains were also combined to obtain a Total Composite (TC) score.

Similar to Roizen et al. (2006), each subtest was reviewed before study commencement to determine if it required vision (i.e., it cannot be

completed with eyes closed), fine motor response (i.e., it requires the child to draw or write) and timed performance (i.e., the child is asked to perform as quickly as possible). The results of this evaluation are reported in Table 2.2.

Table 2.2
Analysis of the characteristics of each neuropsychological subtest.

Domain (Test)	Scale	Subtest	Vision	Fine motor	Timed
Visual perception (DTVP-2/DTVP-A)	MRP	Position in space[a]	1	0	0
		Figure-ground	1	0	0
		Visual closure	1	0	0
		Form constancy	1	0	0
	VMI	Eye-hand coordination[a]	1	1	0
		Copying	1	1	0
		Spatial relations[a]	1	1	0
		Visual-motor speed	1	1	1
		Visual-motor search[b]	1	1	1
Cognitive function (WISC-IV^{UK})	VC	Similarities	0	0	0
		Vocabulary	0	0	0
		Comprehension	0	0	0
	PR	Block design	1	0	0/1
		Picture concepts	1	0	0
		Matrix reasoning	1	0	0
	WM	Digit span	0	0	0
		Letter-number sequencing	0	0	0
	PS	Coding	1	1	1
		Symbol search	1	1	1
Scholastic attainment (WIAT-II^{UK})	R	Word reading	1	0	0
		Reading comprehension	1	0	0
		Pseudoword decoding	1	0	0
	M	Numerical operations	1	1	0
		Mathematical reasoning	1	0	0
	WL	Spelling	1	1	0
		Written expression	1	1	0
	OR	Listening comprehension	1	0	0
		Oral expression	1	0	1

Note. MRP = motor-reduced perception; VMI = visual-motor integration; VC = verbal comprehension; PR = perceptual reasoning; WM = working memory; PS = processing speed; R = reading; M = mathematics; WL = written language; OL = oral language.
[a] Subtest included only in the DTVP-2.
[b] Subtest included only in the DTVP-A.

2.1.3.2 Auditory and visual processing

In the second part of this thesis, the relationship between auditory and visual processing will be examined in relation to specific abilities encompassing the three domains of perception, cognition and scholastic attainment. Namely, these abilities will be fine motor control, attention, short-term and working memory, mathematics and English comprehension.

Fine motor skills refer to the set of abilities that can be assessed through tracing and non-tracing tasks like those included in the motor-enhanced DTVP subscale (e.g., Spatial Relationships and Copying respectively; Carlson et al., 2013; Pitchford et al., 2016). Difficulties at tasks such as finger tapping, small object manipulation and drawing are known among children with NF1 (Casnar, Janke, van der Fluit, Brei, & Klein-Tasman, 2014) and visual impairment (Bouchard & Tétreault, 2000; Brambring, 2007; Houwen, Visscher, Lemmink, & Hartman, 2008) and therefore warrant more investigation for children with OPG. While tracing tasks are inherently related to vision, non-tracing fine motor abilities can be investigated in the auditory modality as they are thought to sustain the interaction between language and motor systems in typical (Bishop, 2002; Brookman, McDonald, McDonald, & Bishop, 2013; Obeid & Brooks, 2018) and atypical development (DiDonato Brumbach & Goffman, 2014; Ho & Wilmut, 2010)

Attention is not a unitary construct but rather a multifaced mechanism of selection, modulation, and focus maintenance on information that are relevant for behaviour (Chun, Golomb, & Turk-Browne, 2011). Three attentional components have been recognised in both children (Rueda et al., 2004) and adults (Petersen & Posner, 2012): *alerting*, which refers to the ability to change and sustain the internal state of readiness to an impending stimulus; *orienting*, which is the capability to prioritise and select the most important sensory input; and *executive attention*, which encompasses a set of skills including task initiation and switching, continuous adjustment, conflict monitoring and set maintenance. This thesis will focus on executive attention due to its pivotal role during school age as it allows children to develop flexible self-

regulation of behaviour, which in turn is vital for emotional regulation and academic achievements (Rueda, Checa, & Rothbart, 2010). More specifically, the inhibitory mechanism of attentional control will be investigated because its experimental paradigm (as reviewed by Rueda, Posner and Rothbart, 2005) is the most suitable for designing analogous version in the visual and auditory modality. Increased auditory attention have been proposed to indicate a strategic compensation in blind children (Zia et al., 2015), making it worth further investigation in children with OPG.

Similar compensatory mechanisms have been found to involve also auditory short-term/working memory in visually impaired children (Swanson & Luxenberg, 2009; Withagen, Kappers, Vervloed, Knoors, & Verhoeven, 2013). While short-term memory refers to the passive temporary maintenance of the information in mind, working memory refers to the active process of information storage and manipulation (Alloway, Gathercole, & Pickering, 2006; Baddeley, 2012). Evidence demonstrates that these two memory components in the visual and auditory modalities rely on relatively separate cognitive processes in childhood (Alloway et al., 2006) and distinctively impact on school acquisitions (Gathercole & Pickering, 2000).

Attention and memory are considered intimately related because both contribute to the selection of the information from the environment and its control in mind (Cowan, 2014; Oberauer, 2019). Indeed, the forward digit span of the WISC-IV^{UK} Working Memory index is sometimes used as a measure of attention (e.g., Longo, Kerr, & Smith, 2013) and auditory attentional processes are also measured through the tasks of this index according to the manual (Wechsler, 2004). However, attention is not involved in the process of maintaining the information in mind and therefore is also dissociable from short-term/working memory (Fougnie, 2008) A systematic evaluation of attention, short-term memory and working memory across modalities would be beneficial for children with OPG.

Finally, within the scholastic domain, skills of literacy (English comprehension, through reading and listening) and mathematics

(numeracy and mathematical reasoning) were chosen as the focus for a detailed investigation as they are core aspects of the U.K. national curriculum for primary school children (Department for Education, 2013).

An overview and summary of the tests administered is presented in Table 2.3. Standardised subtests were preferred, either in original version or adapted, for the purpose of this thesis, to accommodate the wide age range of the patient group. For the tests of scholastic outcomes, tasks were chosen that resembled the learning activities that children do at school for ecological validity.

Each of these abilities was assessed with a separate task in which the input content material relied on either the auditory or visual sensory modality, referring to the sensory-modality approach proposed in the context of the cognitive theory of multimedia learning (Mayer, 2001; see section 1.3.2). Indeed, it is possible to design analogous tests with either visual or auditory stimuli; for example, two English comprehension tasks of similar difficulties administered through either written text (reading) or spoken words (listening). On the contrary, it would be difficult to design analogous tasks with verbal or pictorial stimuli, according to the presentation-mode approach; for example, an English comprehension task with visual stories that has the same complexity as a story presented through spoken words.

All the computer-based experimental tasks were implemented in PsychoPy 2 v1.84.2 (Peirce, 2007) and presented on a Lenovo laptop running 64-bit Windows 10. Visual stimuli were presented on the built-in screen with size 19 x 35 cm and resolution 1366 x 768 pixel and an approximate viewing distance of 50 cm. Auditory stimuli were played through a set of Beats EP on-ear headphones.

Table 2.3
Overview of the abilities assessed and the corresponding analogous tasks in the visual and auditory battery.

	Auditory domain		Visual domain	
Ability	test	variable	test	variable
Fine motor control	Oromotor Sequences (NEPSY-II)[a]	Time of completion (s)	Finger Tapping (NEPSY-II)	Time of completion (s)
Attention	Go/No-Go sounds	*d'* and hits RT (s)	Go/No-Go shapes	*d'* and hits RT (s)
Short-term memory	Digit span forward (WISC-IV^{UK})	N correct sequences recalled	Block span forward	N correct sequences recalled
Working memory	Digit span backward (WISC-IV^{UK})	N correct sequences recalled	Block span backward	N correct sequences recalled
Mathematics	Arithmetic (WISC-IV^{UK})	Scaled score	Numerical Operations (WIAT-II^{UK})	Standard score
English comprehension	Understanding Spoken Paragraph (CELF-5)	Scaled score	Reading Comprehension (WIAT-II^{UK})	Standard score

Note. Scaled scores: μ = 10, σ = 3. Standard scores: μ = 100, σ = 15.
[a] Adapted version of the original task.

2.1.3.2.1 *Fine motor control*

Broadly, fine motor control is the ability to perform fine actions arising from coordination of small groups of muscles, such as fingers-wrists-hands, toes-feet, and lips-tongue-diaphragm (Cameron et al., 2012). Within this broad definition, fine manual movement and oromotor speech production can be considered analogous fine motor skills in the auditory and visual modalities. Both speech production and manual dexterity require fine motor control: the former involves the small musculature of lips, tongue, and jaw, in synchronisation with respiratory and laryngeal activity, to produce an acoustically accessible utterance (Gracco, 1990); the latter involves the musculature of fingers, hands, in dynamic relationship with upper limb position and body posture, to produce a visually accessible action (Adolph & Franchak, 2017). Broadly, the common feature of motor output shared by manual and speech control is the precise and timely coordination of a sequence of task-

dependent goal-directed movements that correspond to the execution of a motor plan (Grimme, Fuchs, Perrier, & Schöner, 2011).

Further, both finger movement and speech production rely on the cerebellum as common neural substrate that might be involved in both motoric and sensorial processes. According to the most recent evidence on cerebellar functioning (see Manto et al., 2012, for a comprehensive overview) the cerebellum is involved in the control of various motor systems including upper limbs and oromotor structures, either directly (e.g., Holmes, 1917), or through the motor regulation of temporal (Breska & Ivry, 2016) and sequential (Khilkevich, Zambrano, Richards, & Mauk, 2018; Tedesco et al., 2011) patterns that are common to speech (Ackermann, Mathiak, & Riecker, 2007) and limb movements (Jueptner & Weiller, 1998). Furthermore, the cerebellum is responsible for continuous anticipation and detection of errors based on external feedback (Ogawa, Inui, & Sugio, 2006), therefore it is possible that it relies on visual and auditory information to control fine motor adjustments and to support, for example, the imitation of finger movements (Jack, Englander, & Morris, 2011) and speech (Carey, Miquel, Evans, Adank, & McGettigan, 2017).

In the nonverbal/visual domain, fine motor control was assessed with the subtest Finger Tapping from the NEPSY-II (Korkman, Kirk, & Kemp, 2007), a task designed for children aged 5 to 16 years. It consists of two items: 1) the repetition item, in which the child repeatedly opens and closes a circle made with the tips of the thumb and the index finger, and 2) the sequence item, in which the child makes a circle by tapping the tip of the thumb to the other fingers in sequence from the index to the little finger. Following standardised instructions, each item was administered for the dominant hand first and then repeated for the non-dominant hand. The examiner demonstrated each item first and allowed the child some practice before performing the task. The task required the child to make the finger movements as quickly as possible and any mistake (e.g., tap with straight fingers, skipping a finger in the sequence, etc.) was corrected by the examiner without stopping the stopwatch. For each hand, the child was required to complete 20 repetitions within a

maximum of 60 seconds and 5 sequences within a maximum of 90 seconds. Administration of each item was stopped if the child exceeded the maximum limit of time allowed. The amount of time taken to complete the required number of correct repetitions/sequences with each hand was recorded by the examiner using a hand-held stopwatch.

In the verbal/auditory domain, fine motor control was assessed with a modified version of the subtest Oromotor Sequence from the NEPSY-II (Korkman et al., 2007), a task suitable for children aged 5 to 12 years. The task requires the child to repeat a series of articulatory sequences (e.g., "mish mash") or tongue twisters (e.g., "Sue said she should sell shoes") that are verbally presented by the examiner. From the original subtest, 4 articulatory sequences and 4 tongue twisters were selected, and all 8 items were administered to the participants. The examiner presented each item first and allowed the child to practice before attempting the task. The task required the child to repeat the item as quickly as possible and any mistakes were corrected by the examiner without stopping the stopwatch. The child was required to repeat each articulatory sequence 8 times within a maximum of 30 seconds and each tongue twister 5 times within a maximum of 60 seconds. Administration of each item was stopped if the child exceeded the maximum limit of time allowed. The amount of time taken to complete the required number of correct repetitions for each item was recorded by the examiner using a hand-held stopwatch. More details about the experimental fine motor control tasks are provided in Appendix C.

2.1.3.2.2 *Attention*

Attention was assessed with two experimental Go/No-Go tasks that had the same structure across the two sensory modalities, whilst differed only in terms of stimuli deployed. The Go/No-Go paradigm is one of the experimental paradigms suggested by Rueda, Posner and Rothbart (2005) to assess executive attention in children and mainly taps into inhibitory mechanisms of control. The frequency of go trials was a key feature to ensure the task measured response inhibition (high frequency, > 80%) instead of sustained attention (low frequency, <20%; Jones et al., 2016).

In the visual task, stimuli were two solid shapes, a circle and a square (both 7x7 cm), presented in white against a black background for maximum contrast. In the auditory task, the stimuli were two pure tones, one low-pitch (300 Hz) and one high-pitch (700 Hz) sound presented against a noise-free background for maximum contrast. The circle and low-pitch tone were the target stimuli and the square and high-pitch tone were the non-target stimuli.

Each task consisted of 108 trials. In each trial, one stimulus was presented either in the middle of the screen (visual task) or binaurally through the headphones (auditory task) for 0.5 s, followed by a variable inter-stimulus interval (ISI) of 0.75 s, 1.5 s or 3 s. Participants were instructed to press the spacebar as quickly and as accurately as possible in response to the target stimulus (the circle or the low-pitch sound) – go trials, and to not respond when presented with the non-target stimulus (the triangle or the high-pitch sound) – no-go trials. Trials were organised into 18 consecutive blocks of 6 trials each. Each block consisted of a separate ISI and presented the target and non-target stimuli at the ratio of 5:1. The ISIs were block-randomized so that all three ISI conditions occurred every three blocks but in a different order. The overall task took about 6 minutes to complete without interruptions.

The two attention tasks were designed to be shorter versions of the Conners' Continuous Performance Task (CCPT-II Conners, 2008), a computerised test based on a Go/No-Go paradigm. The original task is widely used in clinical practice and recommended to test children with brain tumour (Limond et al., 2015), but unsuitable for the current study for its long duration (~ 14 minutes). To reduce the time of administration, the duration of the ISIs (1 s, 2 s, 4 s) was reduced whilst maintaining the same ratio (0.75 s, 1.5 s, 3 s). To ensure OPG patients could process the visual stimuli despite visual impairment, stimuli were presented for a longer time than in the CCPT-II. Also, different stimuli were used in the experimental tasks to those used in the CCPT-II to produce analogous tasks in the visual and auditory domains. Following the recommendation by Wessel (2017), the proportion of no-go trials was less than 20% of the overall trial number, to ensure the elicitation of pre-

potent motor responses. Both visual and auditory tests were piloted with three primary school children to ensure they were suitable for the study. More details about the experimental attention tasks are provided in Appendix D.

For statistical analyses, the Excel output files produced by PsychoPy at the end of the tasks were used to extract individual measures of performance. The trials with reaction times < 200 ms were considered anticipatory, hence discarded (Roebuck, Freigang, & Barry, 2016). For each participant, the information extracted included the number of hits (correct responses to target stimuli), omission errors (non-responses to target stimuli) and commission errors (responses to non-target stimuli) as well as mean reaction times (RT) of hits. Based on the signal detection theory (Green & Swets, 1966), d' and mean RT were taken as outcome measures linked to perceptual detectability (Conners et al., 2003). The sensitivity index *d'* was calculated as the standardised (z-score based) difference between hit rates and false alarm rates through the *psycho* R package (Makowski, 2018).

2.1.3.2.3 *Short-term and working memory*

Short-term and working memory were assessed with forward and backwards tasks involving either pictures of blocks or verbally presented digits in the two sensory modalities. These tasks are used also in clinical practice to assess children with brain tumour (e.g., Steinlin et al., 2003)

In the visual domain, an experimental computer-based 2D version of the original Corsi block-tapping task (Corsi, 1972) was created. A set of nine white squares (each square 4x4 cm in size) was used, with each square presented against a black background for maximal contrast at the distance of 1 cm from each other, was presented on a regular 3x3 grid. A regular grid was preferred over the irregular grid of the original Corsi tasks to limit the impact of possible oculomotor problems in OPG patients (Lacaze et al., 2003). Sequences of squares to be recalled were identified by each square turning red, one after the other. Each square remained coloured for 0.75 s and a pause of 1 s occurred between two consecutive coloured squares. At the end of the sequence, the child was required to

touch the squares on the screen in the same sequence that the red squares were presented (forwards) or in the reverse order (backwards).

In the auditory domain, memory capacity was assessed with the subtest Digit Span forwards and backwards from the WISC-IV^{UK} (Wechsler, 2004), which is suitable for children aged 6-16 years. Following the task instructions, the examiner read aloud a series of digits at the pace of about 1 digit per second and at the end of the presentation, the child was required to verbally repeat the digits in the same (forwards) or reverse (backwards) order as given by the examiner.

For consistency across the visual and auditory versions of each memory task, the test structure and standard administration procedure of WISC-IV^{UK} subtest was adopted in the experimental block-tapping task. The length of sequences increased progressively from 2 to 8 (backwards) or 9 (forwards) digits/blocks. Two trials were presented for each length, except for the 2-digit sequences in the backwards version that had four trials. The sequences in the block span task were created so as to avoid clearly meaningful or easy-to-remember patterns (e.g., L-shape sequences; Smirni, Villardita, & Zappalá, 1983). Two practice trials were given in both forwards and backwards span tasks. For both subtests, the administration started at the first trial for each child and it was stopped by the examiner if the child failed to report accurately both sequences of the same length. The outcome measure was the trial score, which was the number of trials correctly recalled. The span, which was the length of the longest sequence correctly recalled, was also recorded separately for the forwards and backwards task and the total score was calculated for each task as the product of trial scores and span. Studies with adults suggest that this measure is more informative and reliable than either of the two component measures (Kessels, van den Berg, Ruis, & Brands, 2008). More details about the experimental short-term memory and working memory tasks are provided in Appendix E and Appendix F, respectively.

2.1.3.2.4 *Mathematics*

In the visual domain, mathematics skills were assessed with the subtest Numerical Operations from the WIAT-II^{UK} (Wechsler, 2005),

which is suitable for children aged 4-16 years. The child was asked to identify or write a number, count real objects, and solve arithmetic calculations and equations, presented in written form on a booklet. In total, there were 54 problems of increasing difficulty to solve.

In the auditory domain, mathematics skills were assessed with the supplementary subtest Arithmetic from the WISC-IV^{UK} (Wechsler, 2004), which is suitable for children aged 4-16. The first 5 items were not administered as these are visually presented. Hence, the examiner started at item 6 and read out a series of arithmetical problems applied to everyday situations, one at a time, and the child had to mentally solve each problem within a limited time of 30 seconds. In total, there were 34 verbally presented questions of increasing difficulty to solve.

For each child, administration started with the first item and the discontinuity rule and scoring system of each test was used as specified in the test manual. The item scores were summed up to obtain a total raw score. Standardised scores generated from raw scores of each subtest were expressed in scaled scores for Arithmetic ($\mu = 10$, $\sigma = 3$) and standard scores for Numerical Operation ($\mu = 100$, $\sigma = 15$).

2.1.3.2.5 *English comprehension*

According to the U.K. national curriculum for primary school children (Department for Education, 2013), reading and listening are two complementary aspects of English comprehension.

In the visual domain, English comprehension through reading was assessed with the subtest Reading Comprehension in the WIAT-II^{UK} (Wechsler, 2005) which is suitable for children aged 6-16 years. The child was required to read a sentence or a short paragraph and to answer to some questions on its content presented by the examiner.

In the auditory domain, English comprehension through listening was assessed with the subtest Understanding Spoken Paragraphs in the CELF-5 (Wiig, Semel, & Secord, 2013) which is suitable for children aged 5 to 21 years. The child was given a series of short stories verbally, one at a time, followed by a corresponding set of verbal questions about general ideas, specific details, sequential and inferential information

related to the passages. The child was required to answer the questions verbally. The stories and the questions were read and recorded by a native English speaker and the audio files were organised and presented in Microsoft Power Point®.

For both tests, only the age-appropriate stories were presented to children. The scoring of each task followed the test manual guidelines. Standardised scores generated from raw scores of each test were expressed in scaled scores for Understanding Spoken Paragraph ($\mu = 10$, $\sigma = 3$) and standard scores for Reading Comprehension ($\mu = 100$, $\sigma = 15$).

2.1.3.2.6 *Sequential versus simultaneous processing and other confounding factors*

It is worth noting that the differentiation between auditory and visual modality considerably overlaps with the distinction between sequential and simultaneous processing. It can be argued that vision is a more "simultaneous" sense and hearing is a more "sequential" sense (Kemény & Lukács, 2013); further, it has been noted that there is a predominant use of simultaneous paradigm in vision research and sequential paradigm in audition research (Dyson, 2010). To some extent, these considerations apply to the battery presented above. For example, the maths and English comprehension tasks in the auditory domain are heavily dependent on working memory because children have to retain and manipulate maths problems and stories in their mind. On the contrary, the analogous tests in the visual domain rely on stimuli in written form and the test materials remain available while completing the task, with reduced working memory load. Therefore, it can be expected that, within each modality-specific battery, the tests are not fully independent.

However, many other confounding aspects could also be considered, such as the differentiation between verbal and pictorial stimuli within and across the sensory-specific batteries. This highlight a critical problem of task impurity and the difficulty to systematically control for multiple aspects, including verbal versus nonverbal contents, visual versus auditory channel as well as sequential versus simultaneous

processing. Therefore, more complex relationships might overall exist among the tasks of the present battery. Despite these limitations, the present visual-auditory battery focuses on the input modality while attempting to control as much as possible the other task features.

2.1.4 Procedure

Each child was invited for two assessment days, with no more than 4 weeks between them. When possible, research and clinical appointments were synchronised to reduce inconvenience for the participants.

The first visit was held at the Queen's Medical Centre (Nottingham) and included the visual examination, conducted by their clinical ophthalmologist as part of their routine check-up, and the MRI scan. Participants underwent a detailed ophthalmologic examination in a children's hospital ophthalmology department as part of the routine clinical assessment. The ophthalmological examination was conducted by the consultant ophthalmologist who was co-investigator in the project and his team. Participants also underwent an MRI scan, which is not considered in this thesis.

The second visit was arranged at the child's home and comprised the neuropsychological assessment. Before the visits, the neuropsychologists were contacted and confirmed that none of the standardised tests had been administered to children as part of the clinical care in the previous 6 months. The tests administration was always conducted in a quiet area, without distractions, by the author of this thesis. The tests were always administered in the following order: 1) auditory-visual processing – sensory battery 1, 2) auditory-visual functioning assessment – sensory battery 2, 3) visual perception, 4) general intelligence, 5) scholastic attainment. The administration order of the two sensory-specific batteries was counterbalanced across participants. The order of the first battery was: 1) fine motor control, 2) attention, 3) short-term and working memory, 4) mathematics, 5) English comprehension. The order of the second battery was: 1) English

comprehension, 2) mathematics, 3) short-term and working memory, 4) attention, 5) fine motor control.

All children wore their glasses, if prescribed. For subtests that required vision, children with moderate or severe visual impairment were allowed to hold print material close for tasks that required a fine motor response (regardless of the timing) and to use their own magnifier device for motor-free subtests. No adaptation was used with children with monocular/binocular normal vision or mild visual impairment (best corrected VA ≥ 0.50 logMAR score) to minimise disruption of standardised procedures.

During child testing, parents were asked to complete the Five-To-Fifteen (FTF; Kadesjö et al., 2004; Korkman, Jaakkola, Ahlroth, Pesonen, & Turunen, 2004) to gather information from the parents about the functioning of their children. This parent-rating scale, suitable for children between 5 and 15 years of age, consists of 181 statements concerning children's abilities and behaviour in 22 subdomains, further grouped into 8 developmental areas: motor skills, executive functions, perception, memory, language, memory and learning, social skills, emotional behavioural problems. Parents rated the extent to which each statement applied to their child using a 3-point scale and the degree of interference on daily life for each subdomain on a 4-point scale. This questionnaire was chosen for the whole OPTIC-MRI project as it is appreciated by parents for its brevity and for the opportunity to depict a fine-grained description of their child, well-balanced between positive and negative features (Kadesjö et al., 2004). However, these results were not analysed in this thesis because the FTF tool was not designed to address specific vision-related questions that are relevant for children with OPG.

2.2 Normative sample

Because the battery assessing auditory and visual processing included some experimental measures, a group of typically developing children was also recruited to allow for comparison on the measures of auditory-visual processing.

2.2.1 Participants

Ethical approval was obtained from the School of Psychology Ethics Committee at the University of Nottingham, which adheres to the ethical guidelines of the British Psychological Society. First, head teachers of participating schools gave permission to invite the pupils at their schools. Then, all children in a year group were invited to participate and those children for whom written parental consent was given were enrolled in the study.

Ninety-nine children in year 1 to 6 took part in the study. Information about statement of special education needs, English-as-Additional-Language status, and residential postcode for each child was released by their school at the end of the study. Socio-economic status (SES) was estimated for each child using the 2015 Income Deprivation Affecting Children Index (Department for Communities and Local Government, 2015).

Children were recruited from two primary schools in the local area, one from high SES (school IDACI rank = 23,095) and one from low SES area (school IDACI rank = 3,717). IDACI rank of individual children ranged between 56 and 31,769. The total sample included 49 girls and 50 boys, aged between 6y 0m and 11y 7m (M = 8.80, SD = 1.52 years). The frequency of boys and girls by schools and chronological year is display in Table 2.4. The distribution of children in each year group was not consistent across the two schools ($\chi^2(5) = 40.70$, $p < .001$); gender was equally distributed across schools, although there was a trend for girls to come from the high SES school ($\chi^2(5) = 3.02$, $p = .082$). Nine children (6 boys) had special educational needs and disabilities (SEND) referral. Three children (2 girls) had English as an additional language. Most (87%) of the sample was right-handed.

Table 2.4
Sample distribution (female/male) based on age group and school/SES.

Age group	High SES school (*n* = 56)	Low SES school (*n* = 43)	Total sample (*N* = 99)
6 years	0/0	8/8	16
7 years	1/3	3/5	12
8 years	10/8	0/3	21
9 years	9/3	2/7	21
10 years	11/9	1/2	23
11 years	1/1	3/1	6
Total	*32/24*	*17/26*	*99*

2.2.2 Assessment

Children were administered the auditory-visual battery described in section 1.2.6.7).

2.2.3 Procedure

Children were tested individually in a quiet area of their school over six separate sessions of about 20 minutes each. Similar to the OPTIC-MRI study (see section 2.1.4), the administration order of the two sensory-specific batteries was counterbalanced across male and females in each age group. The order of the first battery was: 1) fine motor skills, 2) attention, 3) short-term and working memory, 4) mathematics, 5) English comprehension. The order of the second battery was: 1) English comprehension, 2) mathematics, 3) short-term and working memory, 4) attention, 5) fine motor skills.

2.3 Statistical considerations

Data were analysed in SPSS v.24 (IBM Corporation, 2016) and in R v.3.5.0 (R Core Team, 2018) through R Studio v.1.1.456 (RStudio Team, 2016). Normality assumption was tested through Shapiro-Wilk tests and visual inspection. Significance level was set at $\alpha = 0.05$, which is the standard alpha value used in psychology and behavioural science (Lavrakas, 2013).

Considering the standardised neuropsychological scores as the primary outcomes, a power calculation was undertaken using G*Power

3.9.1.2 software (Faul, Erdfelder, Lang, & Buchner, 2007). With the total obtained sample of 12, the study had 35% power to detect a moderate size effect of 0.5 and, and 71% power to detect a large effect of 0.8, assuming a two-tailed hypothesis and critical significance level of .05. Since the accepted minimum level of power is 80% (McCrum-Gardner, 2010), the present study was underpowered because of the small sample. Only effect sizes in the large range should be considered reliable.

For the analyses of the standardised neuropsychological tests, the threshold of -1 *SD* (≤ 85) was considered the clinical cut-off for a mild difficulty that is worth noting in children with OPG. This was preferred over the -2 *SD* (≤ 70) threshold for clinical impairment because, based on the literature reviewed in Chapter 1 (Table 1.1), children with OPG were expected to display borderline performance or mild problems, but not severe impairments. Of note, the classification system proposed by the four standardised tests used in this study was not employed because the use of multiple categories was not suitable with the small sample of patients recruited, therefore the simpler system based on one single threshold of -1 *SD* was preferred. Although this cut-off does not match with the -2 *SD* used in clinical evaluation to qualify children for educational provision, the results with a lenient threshold may have relevance for special education of children at risk or with mild learning difficulties (O'Brien, 2001).

Two-tailed tests were computed throughout the thesis because it cannot be excluded that children with OPG, who are expected to have overall intact cognitive abilities (Lacaze et al., 2003; Riva et al., 2009), could obtain scores above the average in comparison to the test norms in some specific domains, especially in the auditory-verbal modality.

Finally, given the statistical criticisms due to the small sample, Bonferroni correction was apply only to calculate the associations *across* all the domains (Chapter 5) in order to adjust for multiple bivariate correlations. Instead, no correction was adopted for analyses *within* each domain independently; therefore, either for comparisons of each test/domain with the tests norms (Chapter 3 and Chapter 4) or for within-domain examinations of visual-auditory relationships (Chapter 6).

Specific analyses conducted in each study are explained in each chapter. Table 2.5 provides an overview of the participants and assessment included in each study of this thesis.

Table 2.5
Overview of the methods of the thesis chapters.

	Chapter 3	Chapter 4	Chapter 5	Chapter 6
Participants	OPG	OPG	OPG	OPG+TD
Ophthalmology examination				
RNFL thickness	✓		✓	✓
Visual acuity	✓		✓	✓
Neuropsychological assessment				
Visual perception	✓		✓	
General intelligence		✓	✓	
Scholastic attainment		✓	✓	
Auditory-visual processing				✓

Note. OPG = optic pathway glioma patients, from the OPTIC-MRI study; TD = typically developing children.

Chapter 3 Visual impairment and visual perception

3.1 Introduction

As outlined in Chapter 1, visual impairment based on visual acuity (VA) is certainly the most investigated functional outcome in children with OPG. However, there is concern about the reliability of this measure in children with OPG (Avery et al., 2012). Because VA assessment intrinsically relies on a child's cooperation as well as literacy (i.e., letter recognition) and cognitive (i.e., attention) abilities (see section 1.1.4), it is difficult to assess with young NF1 patients (Avery, Bouffet, Packer, & Reginald, 2013) who might suffer from ADHD (Pride et al., 2012) and learning disability (Hyman et al., 2006). In addition, it is problematic to compare VA measurements both across and within patients because different testing paradigms are used depending on children's age and literacy skills (Avery et al., 2012). Research has shown that these testing methods are not equivalent, although in good agreement; for example, preferential-looking tests overestimate VA in comparison to recognition tests (Kushner, Lucchese, & Morton, 1995), and picture-based recognition tests overestimate VA in comparison to letter-based tests (Anstice et al., 2017). Such variability inherent to the assessment tools in turn makes even more challenging to predict the natural history of OPG, which is known to be erratic and puzzling (Kelly & Weiss, 2013). Therefore, there is increasing interest towards more objective proxies of vision that reflect the structural integrity of the visual pathway. Research on OPG is currently investigating clinical utility and limitations of VA assessment, and two lines of research can be delineated.

On one hand, research is focusing on the utility of the retinal nerve fiber layer (RNFL) and particularly on its thickness (RNFL-t) as measured by optical coherence tomography (OCT) to be used as unbiased structural biomarkers of vision and valid surrogates of VA (Avery et al., 2014; Avery, Liu, et al., 2011; Topcu-Yilmaz et al., 2014). The retinal nerve fiber layer (RNFL; Fisher et al., 2013) is the bundle of axons of the retinal ganglion cells that merge to form the pre-geniculate portion of the central visual pathway. This can be measured using optical coherence

tomography (OCT), a non-invasive interferometry-based ocular imaging technique that measures the intensity of the backscatter of infrared light (Banc et al., 2018). Several studies with OPG patients have shown that this measure correlates with VA (Avery et al., 2014; Avery, Liu, et al., 2011; Kelly, Leary, Khanna, & Weiss, 2012). Case series about visual outcomes of OPGs have started to include a measure of RNFL thickness, showing reduced RNFL thickness in comparison to healthy controls (Chang et al., 2010) and correlations with VA (Zahavi et al., 2018). Banc et al. (2018) suggest that RNFL thickness, which does not appear to vary with age in OPG patients, is a promising measure for follow-up assessment and several normative datasets are available for comparisons and interpretation. A new method to contemporarily examine VA and RNFL thickness in comparison to normative references will be tested in this chapter. Whether RNFL thickness can be a useful indicator of high-level functioning for this tumour has not been investigated yet and will be tested in Chapter 5.

On the other hand, there is also growing interest towards the relationship between VA and psychological outcomes of OPG, including neuropsychological abilities (Lacaze et al., 2003; Riva et al., 2009) and broader vision-related quality of life (Avery & Hardy, 2014). Hierarchical models for the evaluation and treatment of visual dysfunction following acquired brain injury consider visuo-perceptual abilities as potential targets of intervention because these intermediate skills rely on visual functions and sustain high-level visual cognition (e.g., Warren, 1993b, 1993a).

In this chapter, multilevel vision-related outcomes will be concurrently evaluated in a sample of children with history of OPG (Figure 3.1). In relation to Colenbrander's (2003) model, structural and functional changes to the optic pathway will be measured in terms of RNFL thinning and VA reduction whereas skills and abilities of the child will be assessed through performance on a standardised test of visual perception.

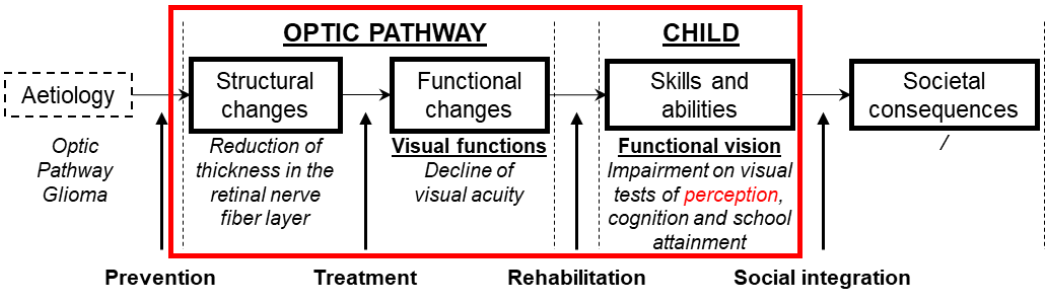


Figure 3.1. Study levels considered in Chapter 3 in red. Adapted from "Aspects of vision loss – visual functions and functional vision" by A. Colenbrander, 2003, *Visual Impairment Research*, *5*, p. 116. Copyright 2003 by Taylor & Francis.

Visual perception is the intermediate process between low-level visual sensation (e.g., visual acuity) and high-level visual cognition (e.g., visual memory) and concerns nonsymbolic features of visual information (Hammill, 1978). Different aspects of visual perception can be assessed through tasks that rely on eye-hand coordination as well as tasks that do not require motor responses (Hammill et al., 1993).

While Chapter 5 will focus on the associations across study levels and developmental domains, the aim of this chapter is to establish the concurrent damage to RNFL and impairment on VA and visual perception in a sample of children with OPG.

3.2 Methods

3.2.1 Participants and materials

All the 12 children with OPG partaking in the study underwent the ophthalmologic examination and completed the age-appropriate test of visual perception. Details about the participants and the measures are given in Chapter 2. RNFL thickness and VA were taken as measures related to the optic pathway. The individual and composite scores of visual perception were taken as measures related to the child. A summary of the outcome measures and tools used in this chapter in relation to Colenbrander's (2003) model is reported in Table 3.1.

Table 3.1
Summary of instruments and measures used at each study level.

Level	Optic pathway		Child
	1. Structural changes	2. Functional changes	3. Skills and abilities
Instrument	Spectralis Optical Coherence Tomography	Visual acuity test	Developmental Test of Visual Perception, 2nd edition or Adolescent/Adult version
Outcomes			
	Thickness of the Retinal Nerve Fiber Layer	Visual acuity logMAR score	Motor-Reduced Perception Visual-Motor Integration General Visual Perception

3.2.2 Statistical analyses

3.2.2.1 Preliminary analyses: establishing clinical cut-off

In the absence of a control group, it is important to establish some reference norms to interpret the study outcome. Neuropsychological scores were assessed in relation to test norms (M = 100, SD = 15); because mild neuropsychological morbidity was expected in this sample compared to other brain tumour groups (e.g., Davis, Pitchford, Jaspan, McArthur, & Walker, 2011), a standard score ≤ 85 (-1 SD) was taken as the threshold indicating a clinically relevant lowered score (see section 2.3).

However, no straightforward norms are available for VA and RNFL thickness. Indeed, there is a variety of classification criteria for VA, in accordance with WHO (Campagna et al., 2010; Dalla Via et al., 2007) or other standards (Avery & Hardy, 2014; Balcer et al., 2001; Dodgshun et al., 2015; Thiagalingam et al., 2004; Wan et al., 2016), which further confound the results reported in the literature. Instead, no norms are available for RNFL thickness: OCT devices provide colour-coded classification maps of RNFL thickness based on internal normative datasets, but these do not include subjects under the age of 18 (Banc et

al., 2018) and should not be used with children (Yanni et al., 2013). Therefore, measures of vision related to the optic pathway were examined in relation to normative data available from published studies that matched the age range and assessment tools used in this study.

A review of the literature was conducted, starting from key publications about VA (Anstice & Thompson, 2014; Dobson, Clifford-Donaldson, Green, Miller, & Harvey, 2009) and OCT (Al-Haddad et al., 2014) assessment that summarised normative data with a variety of VA tests and OCT devices. A summary of the relevant studies is provided in Table 3.2. Mean, standard deviation and number of eyes/children were extracted in order to estimate 95% prediction limits, when possible. The 95% prediction interval (95% PI) represent the normal limits within which the individual score of a newly tested child is expected to fall with 95% probability (Whitmore, 1986). As in other studies (Dobson et al., 2009; Leone, Mitchell, Kifley, Rose, & Sydney Childhood Eye Studies, 2014), the lower bound of the 95% prediction interval (95% PI_{low}) was taken as the threshold of a clinically relevant impairment expected at 95% probability for a newly tested child. The formula used to estimate the 95% prediction interval was: $M \pm t_{\alpha/2} (\sqrt{1+1/n} \times SD)$, with $t_{\alpha/2}$ = 2-tailed value from the Student *t* distribution for alpha at 0.05, and the other variables (*M* = mean, *n* = number of subjects, and *SD* = standard deviation) taken from each normative study (Whitmore, 1986). Of note, the threshold used for the VA and RNFL-t scores was more stringent than the cut-off used for the visuoperceptual scores and this was necessary to "bridge the gap" between the ophthalmology and neuropsychological research and their intrinsically different measurements.

Normative data for global RNFL thickness taken from Turk et al. (2012) were *M* (*SD*) = 106.45 (9.41) µm, and estimated 95% PI_{low} was 87.71 µm. Normative data for VA scores taken from Harvey et al. (2007) was *M* (*SD*) = 0.04 (0.15) logMAR, and estimated 95% PI_{low} was 0.34 logMAR, resembling the one found in another normative study (Dobson et al., 2009). This reference for VA was also chosen for analyses at group level because it employed the Early Treatment Diabetic Retinopathy Study chart, which follows the same principle as the Bailey-Lovie chart used to assess most children in the current study. The classification of

study eyes tested with Crowded Kay Picture test or Keeler LogMAR Crowded acuity test did not change when using test-specific prediction limits (Norgett & Siderov, 2011).

To validate the utility of 95% PI_{low} to classify RNFL thickness and VA, preliminary analyses were conducted on all study eyes (N = 24) to maximise the available data (Bunce et al., 2014). The agreement between the categorised normal or abnormal scores was estimated using a χ^2 test of independence and the relationship between continuous scores was computed using Spearman's ρ correlation to account for a possible non-linear relationship between VA and RNFL thickness, as suggested by the graphs in Avery, Liu, et al. (2011). Spearman's ρ correlation was estimated also for the best eyes based on VA, that was then taken as a proxy of residual sight (Lacaze et al., 2003). Scores of global RNFL thickness and VA on all study eyes are displayed in Figure 3.2 and descriptive statistics are reported in Table 3.3. With all study eyes, there was a significant association between scores of RNFL thickness and VA (ρ = -0.89, p < .001) and classification of normal and abnormal scores on the two measures ($\chi^2(1)$ = 7.46, p = .011; Figure 3.2). There was also a strong association between RNFL thickness and VA in the best eye (ρ = -0.93, p < .001). These results demonstrated that prediction limits of VA and RNFL thickness can also be useful clinically, when combined, given the good correspondence found between the two analogous classification criteria.

Table 3.2
RNFL thickness and VA norms for paediatric populations based on assessment tools similar to those used in the current study.

Reference	Tools	Age range (years)	Normative data	95% Prediction Interval (PI_{low} - PI_{up})[a]
RNFL thickness (µm)				
Turk et al. (2012)	Spectralis SD OCT (Heidelberg Engineering)	6 – 16	*M* = 106.45 *SD* = 9.41 *n* = 107	**87.71** – 125.19
Yanni et al. (2013)	Spectralis SD OCT (Heidelberg Engineering)	5 – 15	*M* = 107.6 *SEM* = 1.2 *SD*[b] = 10.93 *n* = 83	85.72 – 129.48
Visual acuity (logMAR)				
Harvey et al. (2007)	Early Treatment Diabetic Retinopathy Study (ETDRS) chart	4 – 13	*M* = 0.04 *SD* = 0.15 *n* = 446	**0.34** – -0.26
Dobson, Clifford-Donaldson, Green, Miller, & Harvey (2009)	Early Treatment Diabetic Retinopathy Study (ETDRS) chart	5 – 12	*M*, *SD* and *n* specific for each year group provided in reference	PI_{low} = 0.30 for 6- to 12-year-olds
Chen, Chandna, Norcia, Pettet, & Stone (2006)	Early Treatment Diabetic Retinopathy Study (ETDRS) chart	3 – 11	*M* = 0.10 *SD* = 0.09 *n* = 11	0.31 – -0.11
Stewart et al. (1989)	Early Treatment Diabetic Retinopathy Study (ETDRS) chart	6.05 ± 0.63[c]	*M* = 0.02 *SD* = 0.05 *n* = 27	0.12 – -0.08
Myers, Gidlewski, Quinn, Miller, & Dobson (1999)	Early Treatment Diabetic Retinopathy Study (ETDRS) chart	9 – 10	*M* = -0.01 *SD* = 0.08 *n* = 106	0.15 – -0.17
Birch, Strauber, Beck, & Holmes (2009)	Electronic - Early Treatment Diabetic Retinopathy Study (E-ETDRS) chart	5 – 11	Range -0.10 to 0.40 *n* = 142	Estimate not possible

Table 3.2 (continued)

RNFL thickness and VA norms for paediatric populations based on assessment tools similar to those used in the current study.

Norgett & Siderov (2011)	Crowded Keeler logMAR	4 – 6	*M* = 0.00 *SD* = 0.08 *n* = 39	**0.16** – -0.16
		7 – 9	*M* = -0.04 *SD* = 0.11 *n* = 64	0.18 – -0.26
Jones, Westall, Averbeck, & Abdolell (2003)	Crowded Keeler logMAR	2.5 – 16	*M* = 0.04 Range 0.3 to -0.125 *n* = 83	Estimate not possible
Simmers, Gray, & Spowart (1997)	Crowded Keeler logMAR	5 – 6	*M* = 0.1 *SD* = 0.08 *n* = 633	0.26 – -0.06
Norgett & Siderov (2011)	Crowded Kay logMAR	4 – 6	*M* = -0.10 *SD* = 0.09 *n* = 39	**0.08** – -0.28
		7 – 9	*M* = -0.17 *SD* = 0.11 *n* = 64	0.05 – -0.39
Jones et al. (2003)	Crowded Kay logMAR	2.5 – 16	*M* = -0.04 Range 0.225 to -0.10 *n* = 89	Estimate not possible

Notes. Bold indicates lower 95% prediction limits used in this study.

[a] For VA, lower logMAR score indicate better VA

[b] Formula to calculate: $SD = SEM \times \sqrt{n}$.

[c] Age range not provided; mean age reported as in the original reference.

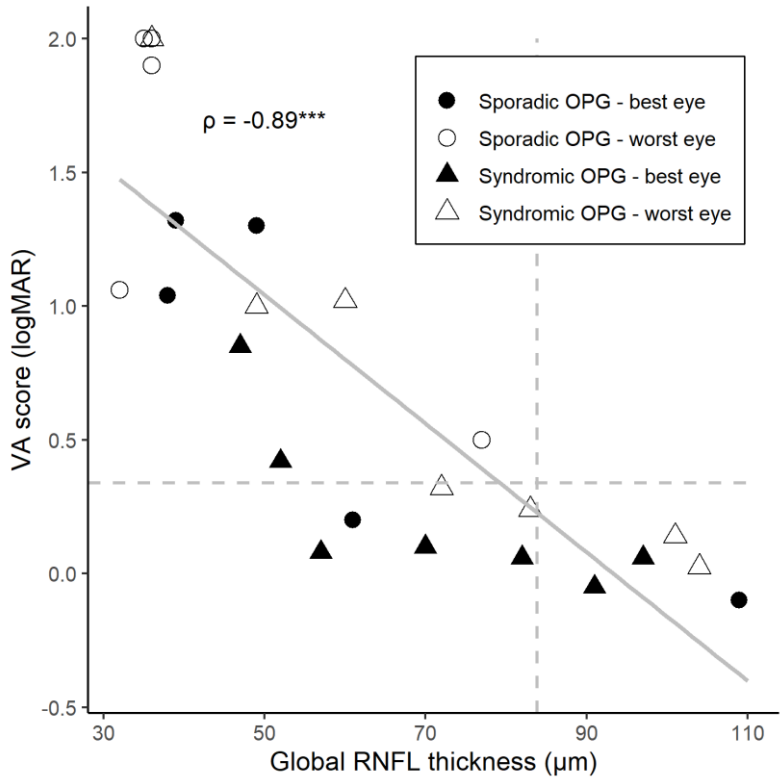


Figure 3.2. Association between global RNFL thickness and VA scores for all study eyes. Dashed lines represent the threshold for clinical impairment (95% PI_{low}). Solid line indicates the regression line. *** $p < .001$.

Table 3.3
Descriptive statistics of global RNFL thickness and VA scores across all study eyes (N = 24).

	% abnormal	Mean (*SD*)	Median (*IQR*)	Min - max
Global RNFL thickness (µm)	79	63.04 (24.86)	58.50 (43.50)	32 – 109
VA scores (logMAR)	54	0.73 (0.72)	0.46 (1.03)	-0.10 – 2.00

3.2.2.2 Main analyses

First, the extent of deviation across the level of the optic pathway and the child was examined by comparing group means of RNFL thickness and VA in the best eye to normative means (Harvey et al., 2007; Turk et al., 2012), and group means on visual perception scores to the test mean (M = 100) using a series of one-sample t-tests or one-sample Wilcoxon signed rank tests. A paired-sample t-test was also conducted to assess the discrepancy between the two individual indices of visual perception.

Then, the variability within the group was examined using the frequency of normal or lowered individual scores. A series of χ^2 goodness-of-fit tests assessed the frequency of RNFL thickness values and VA scores below the 95% PI_{low} out of all study eyes, and the frequency of neuropsychological scores below ≤ -1 *SD*.

Shapiro-Wilk tests were used to check for normality, and two-tailed parametric or non-parametric tests were conducted accordingly. For comparison across different outcomes, effect sizes (r) were calculated using the formula $r = \sqrt{t^2/(t^2+df)}$ for parametric tests (Field, 2009) and $r = z/\sqrt{N}$ for nonparametric test, with z being the critical value of the normal distribution associated with the test's p value (Field, Miles, & Fields, 2012). Effect sizes were interpreted as small or weak (0.1), medium or moderate (0.3) and large or strong (0.5) in accordance with conventional standards (Cohen, 1988).

3.3 Results

Five children showed moderate (1/12) or severe (4/12) visual impairment and used low vision aid (e.g., magnifier) in addition to prescribed glasses, if any, during neuropsychological testing. The remaining 7 children had either normal binocular (4/12) or monocular (2/12) vision or mild visual impairment (1/12) and did not use low vision aids (Figure 3.3). There were no differences in visual aid use between sporadic and NF1 cases ($\chi^2(1) = 1.19$, Fisher's corrected $p = .558$).

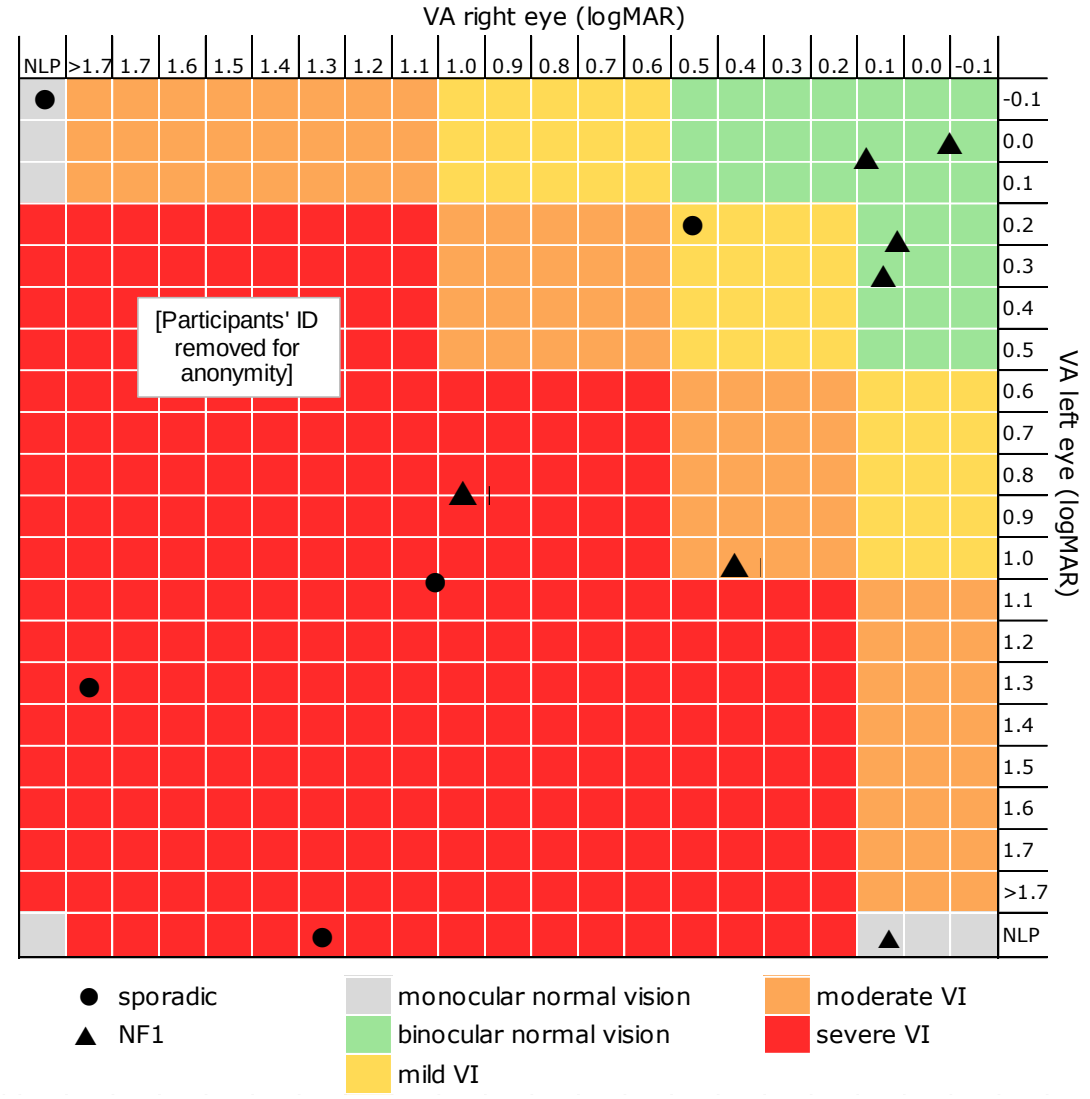


Figure 3.3. Classification of the visual acuity scores of the right and left eyes combined for each study participant. VA = visual acuity; VI = visual impairment; NLP = no light perception.

Descriptive statistics and results of the parametric and nonparametric one-sample tests for RNFL thickness and VA in the best eye and the indices of visual perception are reported in Table 3.4. The whole sample demonstrated mean scores below the norms on all study outcomes based on the statistical tests. Effect sizes were all large. There was no discrepancy between the motor-reduced perception and visual-motor integration ($t(11) = 1.10$, $p = .296$). Categorised individual scores as above or below the 95% PI_{low} on the visual perception test are reported in Table 3.5.

Table 3.4
Group statistics and comparison to the normative mean for the outcome measures.

	Optic pathway (best eye)		Child (visual perception)		
	RNFL-t[a]	VA[b]	MRP[c]	VMI[c]	GVP[c]
M (*SD*)	66.00 (23.69)	0.15 (0.84)	87.42 (14.00)	83.50 (17.81)	84.50 (15.80)
Min - Max	38 – 109	1.32 – -0.10	66 – 108	59 – 108	65 – 108
t	**-5.92**	**67**	**-3.11**	**-3.21**	**-3.41**
p	**< .001**	**.028**	**.010**	**.008**	**.006**
r	**0.87**	**0.63**	**0.68**	**0.70**	**0.72**

Note. Significant results highlighted in bold. RNFL-t = retinal nerve fibre layer thickness; VA = visual acuity; MRP = motor-reduced perception; VMI = visual-motor integration; GVP = general visual perception.
[a] RNFL-t normative data: *M* = 106.45, *SD* = 9.41 µm.
[b] VA normative data: *M* = 0.04, *SD* = 0.15 logMAR. Median (interquartile range) and *V* statistic are reported, instead of *M* (*SD*) and *t*, because VA scores were not normally distributed.
[c] Neuropsychological tests norms: *M* = 100, *SD* = 15.

Table 3.5
Classified scores on the individual and composite indices of visual perception.

		Posterior		Low vision	Visual perception		
Case	NF1	involvement	Vision	aid	MRP	VMI	GVP
P1	Yes	Yes	Normal	No	>	>	>
P2	Yes	Yes	M – Normal	No	≤	≤	≤
P3	Yes	Yes	Normal	No	>	>	>
P4	Yes	Yes	Severe VI	Yes	≤	≤	≤
P5	Yes	No	Normal	No	≤	≤	≤
P6	Yes	No	Normal	No	>	>	>
P7	Yes	Yes	Moderate VI	Yes	≤	≤	≤
P8	No	No	M – Normal	No	>	>	>
P9	No	Yes	Mild VI	No	>	>	>
P10	No	No	Severe VI	Yes	≤	≤	≤
P11	No	No	Severe VI	Yes	≤	≤	≤
P12	No	No	Severe VI	Yes	>	>	>

Note. NF1 = neurofibromatosis type 1; MRP = motor-reduced perception; VMI = visual-motor integration; GVP = general visual perception; VI = visual impairment; M = monocular vision.
Score categories: ≤ = equal or below -1 *SD* (≤ 85); > = above -1 *SD* (> 85).

The variability analysis showed that there was a significantly higher proportion of clinically damaged eyes based on global RNFL thickness ($\chi^2(1) = 8.17$, $p = .004$), but similar proportions of normal and abnormal VA scores across all study eyes ($\chi^2(1) = 0.17$, $p = .683$). The visual perception indices were equally likely to fall above or below the threshold of -1 *SD* (all $\chi^2(1) = 0.00$, $p = 1.00$). In addition, the categorisation of scores above and below the cut-off was consistent within participants for all the perceptual indices; that is, each participant had all the three scores either below or above the threshold.

3.4 Discussion

The aim of this chapter was to concurrently investigate the degree of clinical impairment due to OPG in terms of structural and functional integrity of the optic pathway and in terms of visuo-perceptual abilities of the child. The results demonstrate that at group level children with OPG concurrently exhibit a clinical damage on RNFL and a VA deficit at the level of the optic pathway, as well as neuropsychological difficulties on visual perception. However, some degree of within-group variability emerges on these study outcomes, especially on VA and visual perception.

At the level of the optic pathway, residual sight based on the best eye was significantly affected in children with OPG. Effect sizes were large for both RNFL thickness and VA, but the former exhibited the most relevant damage. Indeed, the group mean of RNFL thickness was more than four standard deviations below the normative mean, whereas the median VA was above the cut-off for a clinical deficit. This partial discrepancy between RNFL thickness and VA at group level was also confirmed by the variability analysis. Indeed, across all study eyes, OCT assessment was significantly likely to indicate a damage to the RNFL, whereas VA testing reported similar proportion of normal and abnormal VA scores. This partial incongruity could have important implications when assessing the relationship of RNFL thickness and VA with neuropsychological outcomes because structural and functional proxies of visual pathway integrity could be distinctively associated with high-level neuropsychological outcomes.

At the level of the child, mean scores of all measures of visual perception were around 1 standard deviation below the test norm and the minimum values of each scale were more than 2 standard deviation below the norm. The difference from the test mean produced large effect sizes for all the indices. This indicates that the domain of visual perception is significantly hindered in children with OPG and, although the sample was small, these difficulties detected at group level were all clinically relevant. Moreover, different aspects of visual perception were found similarly affected since there was no discrepancy between visual-perceptual abilities with and without motor demand. However, further analyses on categorised scores indicated wide variability on visual perceptual abilities in this small sample, as only 50% scored below -1 *SD* on these abilities. This represents a proportion higher than the 16% that would be expected in the general population of healthy children. Overall, the domain of visual perception is significantly at risk in children with OPG.

Upon inspection of individual scores, the current results can be better discussed by highlighting two distinct patterns concerning intra-individual and inter-individual variation. In terms of intra-individual variation, there is a clear consistency of scores above or below the -1 *SD* threshold across perceptual indices; that is, all scores of visual perception were either within the normal range or at least 1 standard deviation below the norm. This further confirmed the lack of discrepancy between visuo-perceptual abilities that did and did not require motor skills, despite the different level of vision adjustment achievable on different tasks.

The second pattern concerns the inter-individual variation, with half of the sample performing at least within the normal range and the other half scoring at least 1 *SD* below the average performance for the age. At this stage of the analyses, performance of the whole group is compared only to the test norms to fully exploit this small sample. Assuming low vision aids fully addressed the vision input problems (when necessary), it can only be argued for now that these visuoperceptual difficulties do not depend on the impact of low vision on the assessment. However, it cannot yet be distinguished if these differences are driven by a specific subgroup; for example, by children with NF1 (Lacaze et al.,

2003), who present marked visuospatial deficits (Dilts et al., 1996; Hyman et al., 2005; Schrimsher et al., 2003), or by children with posterior invasion, who are likely to exhibit more complex visual dysfunctions than children with anterior-only involvement (Dutton, 1994). Analyses on clinical and prognostic factors in Chapter 5 will investigate whether the impact of these factors is sufficiently strong to be detected even in such a small sample like this one (Davis et al., 2011).

Overall, the results of this study extend findings from previous research on paediatric OPG (Lacaze et al., 2003; Riva et al., 2009) by assessing the domain of visual perception with a reliable standardised test that has a clearly defined underpinning construct and that comprises motor-free and motor-enhanced visuo-perceptual abilities (Hammill et al., 1993). Difficulties with processing visual-perceptual stimuli, even without motoric response and after low vision adjustment, raise questions about the reliability of visual acuity tests in OPG patients (Avery et al., 2012), when children are required to analyse the physical properties of a stimulus to recognise and name a shape or letter without meaningful context. Because visual perceptual abilities are significantly hampered in children with OPG, ophthalmologic examination with this population might benefit from incorporating the visual perception assessment for a more comprehensive and hierarchical evaluation of the visual system (Warren, 1993a, 1993b).

To conclude, in relation to Colenbrander's (2003) model, the results of this chapter demonstrate long-term consequences of paediatric OPG at a structural and functional level related to the optic pathway and in the domain of visual perception related to the child. Thinning of the RNFL was more consistently reported, whereas wider variability in VA and visual perception warrants further investigation in relation to critical clinical factors. This will be undertaken in Chapter 5.

Chapter 4 Intellectual function and scholastic abilities

4.1 Introduction

As discussed in Chapter 1, ophthalmologic morbidity following OPG has received greater attention than neuropsychological sequelae. In a systematic review, Moreno et al. (2010) found over 80 papers published between 1990 and 2008 reporting visual outcomes in children with OPG. On the contrary, only four studies were found in the literature that investigated neuropsychological outcomes in this population (Fouladi et al., 2003; Lacaze et al., 2003; Nicolin et al., 2009; Riva et al., 2009). These studies were discussed in detail in Chapter 1 and several limitations in study design emerged, including the lack of visual adaptation for children with poorer vision (Hill-Briggs, Dial, Morere, & Joyce, 2007), task impurity and construct validity problems resulting from using collections of several individual subtests from different batteries (Lacaze et al., 2003; Riva et al., 2009), and the inclusion of children treated with cranial radiotherapy (Fouladi et al., 2003; Lacaze et al., 2003; Nicolin et al., 2009), the most critical risk factor for neurocognitive decline (Danoff, Cowchock, Marquette, Mulgrew, & Kramer, 1982; Mulhern et al., 2004) that is seldom employed to treat OPGs (Perilongo, 2005). In addition, no studies collected direct measures of academic attainment in children with OPG, although understanding scholastic acquisition and supporting learning is vital for children presenting with these tumours. Indeed, these children have a highly favourable survival prognosis, but remain at risk of reduced quality of life and neuropsychological outcomes (see Chapter 1).

Several limitations were also found with the analyses conducted in the previous reports. Retrospective studies with relatively large samples reported only broad IQ indices (Fouladi et al., 2003), in a descriptive manner (Nicolin et al., 2009). In contrast, prospective studies with smaller samples (Lacaze et al., 2003; Riva et al., 2009) conducted multiple between- or within-group comparisons involving two or more conditions or timepoints. Moreover, the latter studies compared children's

performance at the level of single tasks, whose examination is typically recommended only for within-subject analyses and individual profile description (Kotz, Watkins, & McDermott, 2008). Pinpointing to such specific impairments to characterise a clinical population is problematic with small samples.

This chapter addresses the above limitations of previous research by reporting a more comprehensive examination of long-term cognitive and scholastic outcomes following OPG using co-normed standardised batteries and visual adjustment in a relatively homogenous group of young OPG survivors (with and without NF1) managed only with chemotherapy or observation. First, this sample is more representative of modern cohorts of OPG patients whose management is based almost exclusively on observation and/or chemotherapy (Perilongo, 2005). Second, the employment of personal low vision aids represents the first attempt to control for problems of visual input and accessibility to visual test materials (Lee & Cho, 2007). From the available literature, three studies did not report whether such tools or similar adaptations were employed in either retrospective data from clinical records (Fouladi et al., 2003; Nicolin et al., 2009) or prospective assessments (Riva et al., 2009), whereas one study did not used low vision aids but excluded patients with poor vision (Lacaze et al., 2003). As in the previous chapter, under the assumption that this ecological approach to low vision aids fully addressed the input problems experienced by children with poorer vision, any normal or abnormal performance on cognitive or scholastic indices can be more reliably attributed to the processing of the visual information and therefore interpreted as a long-term deficit/capability associated with paediatric OPG rather than a testing problem. Third, statistical analyses will be conducted using individual and composite standardised indices, and group means will be compared to the test normative mean so as to maximise the resources of standardised tools in the absence of a control group.

In relation to Colenbrander's (2003) model, this chapter will provide a deeper examination of the skills and abilities related to the child by focusing on the domains of cognitive functioning and scholastic attainment (Figure 4.1). Specifically, intellectual and scholastic abilities

requiring vision will be considered as high-level visual processes that involve the elaboration of symbolic and semantic aspects of visual stimuli, unlike visuoperceptual abilities that concern only the physical aspects (Hammill, 1978).

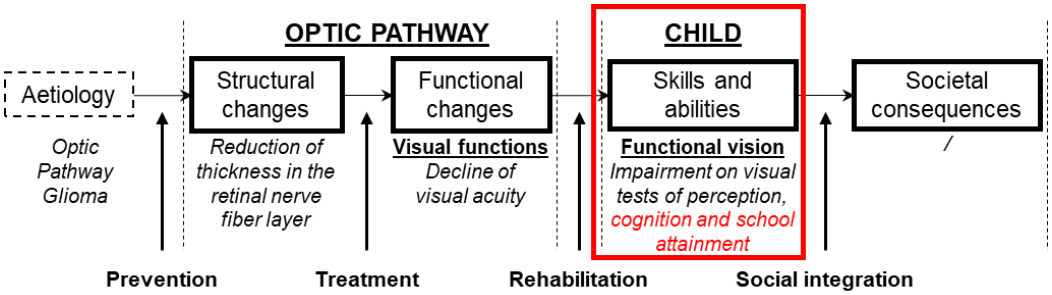


Figure 4.1. Study levels considered in Chapter 4 in red. Adapted from "Aspects of vision loss – visual functions and functional vision" by A. Colenbrander, 2003, *Visual Impairment Research*, *5*, p. 116. Copyright 2003 by Taylor & Francis.

However, this chapter will further extend Colenbrander's (2003) model by studying the impact of OPG not only on visual test performance, but also on auditory measures of cognition. Although vision and hearing are often described as two separate and relatively independent sensory systems with distinctive developmental trajectories and specialised in different sensorial stimuli (Graven & Browne, 2008a, 2008b), research indicates that these two sensory modalities interact to regulate children's development. For example, blind children with no residual vision were found to develop superior abilities for sequential and verbal information compared to their sighted peers (Withagen et al., 2013). Similar compensatory mechanisms have also been proposed to explain the cognitive profile of cancer survivors who developed a retinal malignancy (Brinkman et al., 2015; Ek et al., 2002). The relationship of cognition with visual and auditory sensory modalities is highly relevant to understand the outcomes following OPG. Lacaze and colleagues (2003) found a significant discrepancy between intact verbal IQ and hampered performance IQ, but the difference between these cognitive scores is intrinsically confounded by the sensory modality on which they were measured. Indeed, verbal IQ includes auditory/verbal subtests, whereas performance IQ involves visuospatial/nonverbal subtests, which were not adjusted for visual input in Lacaze's study (2003). Therefore, the

incongruency between visual and auditory measures of intellectual functioning will be examined again in this study, where the use of low vision aids ensures that the performance measured reflects the processing of visual information. These analyses would yield preliminary information about potential compensatory mechanisms in children with OPG, although it should be remembered that auditory/verbal and visuospatial/nonverbal measures of standardised tests not only rely on different sensory modalities but also tap into inherently different skills.

To summarise, the aim of this chapter is to systematically investigate the extent of impairment on developmental areas of cognitive functioning and scholastic attainment in children with OPG, and also to examine the relationship between auditory and visual measures of cognition. Like in the previous chapter, this study will investigate the extent of impairment in specific domains in comparison to data from the normal population provided by the standardised tests.

4.2 Method

4.2.1 Participants, materials and procedure

Of the 12 children with OPG partaking in the study, 10 completed the test of intellectual functioning (WISC-IV^{UK}) and scholastic attainment (WIAT-II^{UK}). Two children (P5 and P6) did not complete the cognitive and scholastic tests because they found the tests of the first session very difficult and exhausting, and consequently refused to take part in the following sessions. One child (P4) could not complete the Pseudoword Decoding subtest of the WIAT-II^{UK} because of its difficulty, therefore it was not possible to calculate the individual index of Reading (R) and the Total Composite (TC) index of the scholastic battery. Details about the participants (section 2.1.1), materials (section 2.1.3.1) and procedure (section 2.1.4) are given in Chapter 2. The analysis of specific indices and subtests of cognition and academic achievement that did and did not require vision is reported in Table 2.2. A summary of the outcome measures and tools used in this chapter in relation to Colenbrander's (2003) model is provided in Table 4.1.

Table 4.1

Summary of instruments and measures used at each study level of Chapter 4.

	Optic pathway		Child		
	1. Structural changes	2. Functional changes	3. Skills and abilities		
Level			Visual perception	Cognitive functioning	Scholastic abilities
Instrument	/	/	/	Wechsler Intelligence Scale for Children (WISC-IV^{UK})	Wechsler Individual Achievement Test (WIAT-II^{UK})
Outcomes	/	/	/	Full-scale IQ (FSIQ)[a] General Ability (GA)[a] Verbal Comprehension (VC)[b] Perceptual Reasoning (PR) Working Memory (WM)[b] Processing Speed (PS)	Total Composite (TC)[a] Reading (R) Mathematics (M) Written language (WL) Oral Language (OL)

[a] Composite indices.

[b] Verbal/auditory measures, not requiring vision.

4.2.2 Statistical analyses

Consistent with the previous chapter, two types of analyses were conducted using exact scores as interval variables and grouped scores as categorical variables.

First, the extent of impairment in each domain was examined by comparing group means on individual and composite indices of intellectual functioning and scholastic attainment to the test mean (M = 100) using a series of one-sample t-tests. At a cognitive level, additional paired-sample t-tests were conducted between verbal/auditory and nonverbal/visuospatial measures of IQ to examine discrepancies between these indices in comparison with previous research (Lacaze et al., 2003). Lacaze et al. (2003) compared the composite indices verbal IQ and performance IQ using the WISC-III. However, this comparison cannot be done with the WISC-IV because the computation of these indices is no longer allowed in this version of the Wechsler's scale. Indeed, the traditional verbal-performance dichotomy, a foundational aspect of Wechsler's (1939) theory of intelligence, was replaced with four separate intellectual components in the WISC-IV (and later versions) so as to recognise the greater contribution of working memory and processing speed to the general cognitive functioning, in line with contemporary research (Williams, Lawrence, & Rolfhus, 2003). Figure 4.2 summarises similarities and differences between the structures of WISC-III and WISC-IV; for a more detailed discussion, see Williams, Lawrence and Rolfhus (2003). Based on the sensory modality of the underlying tasks, the correspondence between indices based on either visual or auditory tasks across the two batteries was sought (Figure 4.2). Verbal comprehension and perceptual reasoning can be considered auditory and visuospatial components respectively of the general ability index, a measure of fluid and crystallised intelligence (Harrison, DeLisle, & Parker, 2008). Working memory and processing speed can be considered auditory and visuospatial components of the cognitive proficiency index respectively, a measure that reflects the neurological efficiency of the brain system (Bremner, McTaggart, Saklofske, & Janzen, 2011). Of note, additional country-specific normative tables in UK edition of WISC-IV are provided to estimate general ability (Raiford, Weiss, Rolfhus, & Coalson,

2008), but not cognitive proficiency. Based on the new structure of the WISC-IV, two separate paired-sample t-tests were conducted between verbal comprehension and perceptual reasoning and between working memory and processing speed.

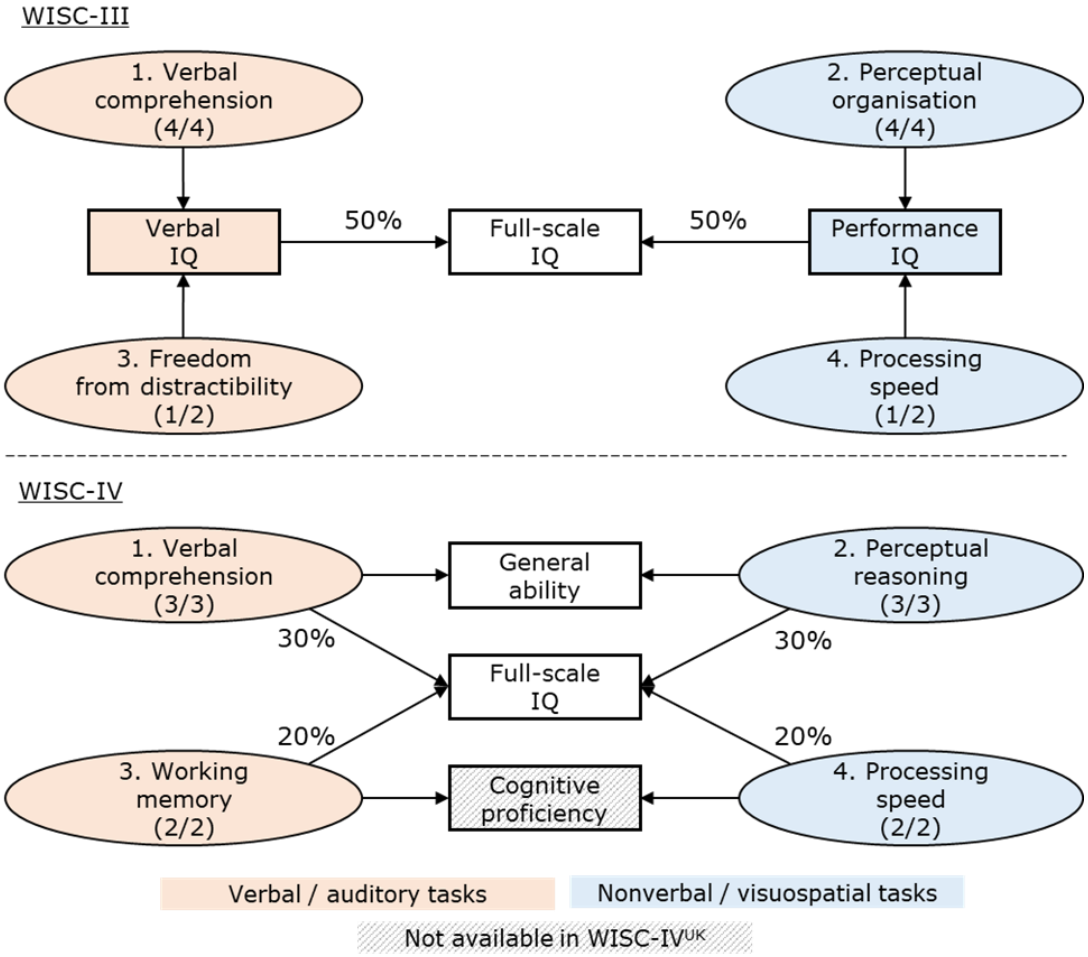


Figure 4.2. Verbal/auditory and nonverbal/visuospatial individual indices (circles) and their relationship with composite (rectangles) indices in WISC-III and WISC-IV. In brackets, proportion of subtests contributing to composite indices.

All indices met the assumption of normality based on Shapiro-Wilk tests, therefore two-tailed parametric tests were conducted accordingly. For comparison across different outcomes, effect sizes (r) were calculated using the formula $r = \sqrt{t^2/(t^2 + df)}$ (Field, 2009). Effect sizes were interpreted as small/weak (0.1), medium/moderate (0.3) and large/strong (0.5) in accordance with conventional standards (Cohen, 1988).

Finally, the variability of impairment within group was examined using a series of χ^2 goodness-of-fit tests to assess whether the frequency of normal (> -1 *SD*) or lowered (≤ -1 *SD*) neuropsychological scores was different to the frequency due to chance. Fisher's exact correction was used since the available data was further reduced on these two batteries.

4.3 Results

Descriptive statistics and results of the one-sample *t*-tests for the indices of intellectual functioning and scholastic abilities are reported in Table 4.2.

For intellectual functioning, there was a significant difference for the OPG group from test norms for full-scale IQ, but not general ability. The inconsistency between these two composite indices was further investigated using a paired-sample *t*-test and the difference between these scores was found to be statistically significantly ($t(9) = -3.52$, $p = .007$, $r = 0.76$). Scores for verbal comprehension and perceptual reasoning were close to the test norm, whereas scores for working memory and processing speed, which contribute towards full-scale IQ but not general ability, were significantly depressed. Assessment of the discrepancy between verbal/auditory and nonverbal/visuospatial cognitive abilities demonstrated that there was no significant difference between verbal comprehension and perceptual reasoning ($t(9) = 0.58$, $p = .577$), nor between working memory and processing speed ($t(9) = 0.45$, $p = .633$).

For scholastic achievement, a deviation from test norms was found for two abilities, written language and oral language, but not the total composite index.

Categorised individual scores and the results of the variability analysis are reported in Table 4.3. On all indices except Reading, 20 to 40% of the individual scores were below the normal range; scores were equally likely to fall above or below the -1 *SD* threshold. On Reading, scores were significantly more likely to indicate normal performance, although this result should be considered with caution because it was based on only 9 individual scores.

Table 4.2

Group statistics and comparison to the test norm for each individual and composite index.

	Cognitive functioning						Scholastic attainment				
	VC	PR	WM	PS	FSIQ	GA	R	M	WL	OL	TC
n	10	10	10	10	10	10	9	10	10	10	9
M (*SD*)	91.50	95.50	85.40	87.50	88.20	93.00	96.11	98.80	89.00	88.50	93.89
	(13.75)	(16.88)	(8.86)	(14.98)	(11.27)	(11.76)	(11.66)	(18.62)	(13.53)	(14.25)	(12.33)
Min - Max	66–108	59–108	65–108	63–116	61–121	74–99	56–109	70–102	71–110	74–114	69–135
t	-1.96	-0.84	**-5.21**	**-2.64**	**-3.31**	-1.88	-1.00	-0.20	**-2.57**	**-2.55**	-1.49
p	.082	.421	**.001**	**.027**	**.009**	.092	.346	.843	**.030**	**.031**	.175
r	0.55	0.27	**0.87**	**0.66**	**0.74**	0.53	0.33	0.07	**0.65**	**0.65**	0.47

Note. Significant results are highlighted in bold. VC = verbal comprehension; PR = perceptual reasoning; WM = working memory; PS = processing speed; FSIQ = full-scale IQ; GA = general ability; R = reading; M = mathematics; WL = written language; OL = oral language; TC = total composite.

Table 4.3
Classified scores on the individual and composite indices of cognitive functioning and scholastic attainment.

					Cognitive function						Scholastic attainment				
Case	NF1	Posterior involvement	Vision	Low vision aid	VC	PR	WM	PS	FSIQ	GA	R	M	WL	OL	TC
P1	Yes	Yes	Normal	No	>	>	≤	>	>	>	>	>	≤	>	≤
P2	Yes	Yes	M – Normal	No	>	>	≤	>	>	>	>	>	>	>	>
P3	Yes	Yes	Normal	No	>	>	>	>	>	>	>	>	>	>	>
P4	Yes	Yes	Severe VI	Yes	>	≤	≤	≤	≤	≤	n. a.	≤	≤	≤	n. a.
P5	Yes	No	Normal	No	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.
P6	Yes	No	Normal	No	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.
P7	Yes	Yes	Moderate VI	Yes	≤	A	≤	≤	≤	≤	≤	≤	≤	≤	≤
P8	No	No	M – Normal	No	≤	>	>	>	>	>	>	>	>	≤	>
P9	No	Yes	Mild VI	No	>	>	>	>	>	>	>	>	>	>	>
P10	No	No	Severe VI	Yes	>	>	>	>	>	>	>	>	>	>	>
P11	No	No	Severe VI	Yes	>	>	>	≤	>	>	>	>	≤	>	>
P12	No	No	Severe VI	Yes	>	≤	>	>	≤	≤	>	>	>	≤	>
% abnormal					20%	20%	40%	30%	30%	30%	11%	20%	40%	40%	22%
X^2					3.60	3.60	0.40	1.60	1.60	1.60	5.44	3.60	0.40	0.40	2.78
p					.109	.109	.754	.344	.344	.344	.039	.109	.754	.754	.180

Note. VC = verbal comprehension; PR = perceptual reasoning; WM = working memory; PS = processing speed; FSIQ = full-scale IQ; GA = general ability; R = reading; M = mathematics; WL = written language; OL = oral language; TC = total composite; VI = visual impairment; M = monocular vision.
Score categories: "≤" = equal or below -1 *SD* (≤ 85); ">" = above -1 *SD* (> 85); "n. t." = not tested; "n. a." = not available.

4.4 Discussion

This chapter reports a comprehensive standardised assessment of cognitive abilities and scholastic skills in a group of children with OPG with the aim to determine the extent of deviation on different developmental domains and examine the relationship between verbal/auditory and nonverbal/visuospatial cognitive abilities in these children.

Amongst composite indices of intellectual function, the mean score of general ability did not differ from test norm. General ability comprises only of verbal comprehension and perceptual reasoning, both of which were preserved. Verbal comprehension and perceptual reasoning of the WISC-IV are associated with crystallized and fluid intelligence more than the measures of working memory and processing speed (Harrison et al., 2008; Raiford et al., 2008). Therefore, these are promising results for non-irradiated OPG patients as they demonstrate that core reasoning abilities remain intact in these children despite the tumour and associated treatment.

In contrast, the mean score of full-scale IQ was significantly below the test mean. The full-scale IQ score reflects reasoning skills, but it also receives a substantial contribution from working memory and processing speed abilities, which showed significant weaknesses in this sample. Therefore, the discrepancy between average general ability and impaired full-scale IQ should be attributed to difficulties in working memory and processing speed, which reflects the proficiency and efficiency of cognitive processing (Bremner et al., 2011). The deficit shown on working memory and processing speed and their impact on general intelligence indicates that these two cognitive domains require clinical attention as they are critical for intellectual development (Coyle, Pillow, Snyder, & Kochunov, 2011; Fry & Hale, 1996, 2000) and scholastic progression (Blankenship, O'Neill, Ross, & Bell, 2015; Swanson, 1994). A persuasive explanation of the difficulties in both developmental domains is that deficits in working memory and processing speed reflect a global brain dysfunction due to the acquired brain injury caused by the tumour growth itself, as proposed by Aarsen et al. (2009). Indeed, using a large sample of children with low-grade pilocytic astrocytoma (like most OPGs)

in different parts of the brain, the authors demonstrated that problems in sustained attention and speed are associated with these non-aggressive tumours regardless of their specific location in the brain. Problems in attention, working memory and processing speed have widely been reported in young cerebellar tumour patients and deemed to result from the direct cerebellar lesion in combination with the indirect white matter damage induced by the radiotherapy (Law et al., 2011, 2017; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008). However, such explanations are not applicable to OPGs since they do not affect the cerebellum and do not require cranial radiation. Further, other clinical factors such NF1 co-diagnosis, posterior involvement and chemotherapy could also be implicated in these deficits. Depressed performance in processing speed and working memory has been reported in children with NF1 (Bulgheroni et al., 2019; Hernández Del Castillo et al., 2017; Lehtonen et al., 2013) and damage to the optic radiation was found implicated in lower processing speed in young brain tumour survivors (Scantlebury et al., 2016). The role of NF1 co-diagnosis and posterior involvement on cognitive and scholastic outcomes associated with OPG will be explored in the next chapter, along with other prognostic factors. In addition, research from childhood leukaemia shows that working memory abilities are particularly vulnerable to the harmful effects of chemotherapy, which in turn may results in a global intelligence dysfunction (Ashford et al., 2010).

Interestingly, the dissociation between full-scale IQ and general ability demonstrates the potential utility of evaluating both these composite indices when assessing children with OPG. Such value was previously demonstrated in another heterogeneous group of young brain tumour survivors, where all children received radiation therapy and all cognitive measures were below the test mean (Kahalley, Winter-Greenberg, Stancel, Ris, & Gragert, 2016). While full-scale IQ remains a valuable and more comprehensive measure of intelligence, considering the incongruity with general ability yields important information about how much a child (or a group of children) would benefit from task adaptations that do not burden working memory load, motor and speed demands (Lanfranchi, 2013). For example, children with OPG would

benefit from longer time limits on the WISC-IV cancellation task to fully express their cognitive potential, since they demonstrated adequate visuoperceptual reasoning skills to visually and semantically distinguish animals from objects and adequately. Similarly, Kahalley et al. (2013) argued that young brain tumour and leukaemia survivors, who showed slower processing speed but intact general reasoning ability, "may be better able to master new material and demonstrate the full extent of their understanding… with adequate adaptations (e.g., slower paced instruction with more repetition and extended time on tests)" (p. 1984). Conversely, a partial gain can be expected in more severely affected brain tumour survivors (e.g., irradiated children with a tumour in cortical areas; Kahalley et al., 2016): their performance might still be below the age-appropriate level because the visuospatial abilities of the child are hindered also during motor-free and untimed tests.

This type of information has direct implications for conducting neuropsychological assessment (Kahalley et al., 2013, 2016) and planning scholastic rehabilitation (Edwards, Marshall, & Haeems, 2019) in children with brain tumour as it would inform about the most appropriate adaptation and intervention for this group of survivors. At school, children with OPG might benefit from receiving new information or task instructions in smaller chunks, to accommodate for a weakness in working memory. Likewise, OPG children might also benefit from longer time to complete tasks to accommodate for slower processing speed than is typically given. Further, given the vision-specific problems experienced by children with OPG, alternative visual tasks with simplified stimuli (e.g., outline black-and-white, high-contrast pictures, as included in the DTVP batteries) would also be adequate for the neuropsychological evaluation of these patients, although the lack of well-established standardised tools designed for visually impaired children (Miller & Skillman, 2003) makes this solution not feasible.

In addition, the lack of discrepancy between the two pairs of verbal/auditory and nonverbal/visuospatial cognitive indices (verbal comprehension versus perceptual reasoning; working memory versus processing speed) disputes the argument by Lacaze et al. (2003) according to which the discrepancy between preserved verbal and

hampered performance IQ should be attributed at least to some extent to visual problems associated with the nature of this tumour. Indeed, in this study where low vision aids were permitted to children with poor vision, verbal and visuospatial abilities related to the same construct were found to develop similarly: both verbal and visuospatial reasoning skills were intact, whereas both verbal and visuospatial cognitive proficiency skills were impaired. This suggests that the distinction between different types of cognitive abilities examined is more relevant than the sensory modality tapped by the tests. This result is an advancement in the clinical literature that was possible thanks to the more sophisticated structure of the WISC-IV. Nonetheless, further investigation into the role of the sensory modality of the tests remains necessary to distinguish and this is possible only if tasks are matched to measure the exact same ability. This will be done in Chapter 6.

The results of this chapter also add to the literature on the long-term neuropsychological effects following paediatric OPG by reporting measures of academic achievement for the first time. Specifically, children with OPG had age-appropriate scholastic attainment based on the total composite index and this was also confirmed on the individual indices of reading and mathematics. Mild impairment was found only in written language and oral language. One possible explanation for the impairment in these areas is again a problem with speed and motor demands similar to the deficit underpinning processing speed at the cognitive level. Indeed, inspection of Table 2.2 shows that the tasks used to assess written and oral language in the WIAT-II^{UK} require more fine motor skills and speeded performance compared to the tasks of reading and maths. In addition, since a spelling subtest is included in the written language index, it is possible the overall deficit in this domain arises from spelling difficulties in writing, which in turn can be attributed to either low vision (Arter & Mason, 1994; Arter, McCall, & Bowyer, 1996) or NF1 syndrome (Barton & North, 2004; Gilboa et al., 2010; Hyman et al., 2005, 2006). The impairment in oral language might reflect difficulties at processing fine details of visual stimuli necessary for many of these tasks. In addition, working memory, which is below the age-appropriate level in this sample, could be implicated in both written and oral language

difficulties. Indeed, once alphabet transcription becomes automatic, verbal working memory is vital for writing skills by supporting the acquisition of more complex linguistic expressions and more coherent text structure (Adams, Simmons, & Willis, 2015; McCutchen, Covill, Hoyne, & Mildes, 1994). Moreover, working memory is essential in listening comprehension tasks, where the listener has to retain and manipulate the information to perform the task given the lack of possibility to listen again to the stimuli or control the pace of the delivery (Language and Reading Research Consortium, Jiang, & Farquharson, 2018; Montgomery, Polunenko, & Marinellie, 2009).

Finally, the variability analyses demonstrate that individual scores are not likely to indicate relevant difficulties in this population; on the contrary, individual scores tend to exhibit the opposite trend and be more likely to remain intact, as suggested by the result of reading. Inspection of individual scores to assess within-patient and between-patient variability showed no evident pattern of consistent normal or abnormal scores, unlike the visual perception domain reported in the previous chapter.

Of note, the interpretation of the current results should take into account that two children with OPG and comorbid NF1 did not complete these tests after they found mentally demanding and difficult to complete the first part of the assessment (visual-auditory battery and visual perception). For this reason, it is reasonable to expect that these two participants would have encountered difficulties with the cognitive and scholastic evaluation too and possibly performed poorly on these tests. Therefore, the current results could be somehow biased towards a positive picture of OPG survivors' functioning, and this adds to the criticism of small sample tested in this project.

In relation to Colenbrander's (2003) model, these results demonstrate that child-related cognitive and scholastic abilities that rely on vision are not systematically affected in children with OPG. Core visuospatial reasoning skills and the scholastic domains of reading and maths are preserved; instead, processing speed, written language and oral language are significantly lowered compared to the normal population. In addition, extending the assessment of child-related

abilities to non-visual abilities, this study demonstrates that core verbal reasoning abilities are not reduced following paediatric OPG, whereas auditory-verbal working memory skills are hindered. A possible common mechanism for the deficits found across the level of intellectual functioning and scholastic abilities pinpoint to a general brain dysfunction induced by the tumour itself or the chemotherapy that affect speed, attention and working memory.

To conclude, while the previous chapter showed a more systematic impairment on vision-related measures related to the optic pathway and intermediate measures of visual perception, more variable patterns of intact and hampered abilities in the visuospatial and verbal modality emerge at a higher level of cognition. The next chapter will further examine the relationships among measures related to the optic pathway and to the child, and will investigate the impact of clinical factors at different level of Colenbrander's (2003) model.

Chapter 5 Impact of clinical factors

5.1 Introduction

In oncology research, it is vital to identify prognostic factors and elucidate their impact on functional outcomes for several reasons. By knowing which socio-demographic and clinical variables influence the tumour outcomes, it is possible to gain greater understanding of the natural history of the tumour, select the most appropriate treatment option for specific groups of patients, and inform patients and families about risks associated with the tumour and the treatment (Halabi & Owzar, 2011).

The identification of prognostic factors is particularly relevant for OPGs given the erratic natural history of these lesions and the poor reliability of the measures available to monitor tumour progression, such as visual acuity and radiological description (Fisher et al., 2012; Kelly & Weiss, 2013). Research on OPGs has focused again on the role of these factors (such as age at diagnosis, NF1 co-morbidity and tumour location) in relation to survival rates, visual and radiological outcomes (for an extensive review, see Opocher et al., 2006). Little to nothing is known about the impact of these variables on neuropsychological morbidity, because studies investigating these outcomes in OPG survivors are rare. However, as shown in the previous chapters, paediatric OPGs are associated with some visuoperceptual and cognitive problems and identifying factors that make these children prone to exhibit such difficulties would inform rehabilitation programs targeted for young survivors in greater need.

Within the framework adopted in this thesis, it is important to recognise the complexity of the relationships between prognostic factors and functional outcomes due to the multiplicity of levels on which they can act (Figure 5.1). In other words, the same factor could have a congruent (either protective or detrimental) effect on the optic pathway integrity and on children's abilities, but it could also have an incongruent effect and therefore act as a risk and protective factor at the same time. For example, as it will be discussed later, children with NF1 are at lower

risk of vision problems due to OPG possibly because of genetic features of their tumours, but at higher risk of neuropsychological deficits because of the cognitive phenotype associated with their genetic mutation. Further, given the location of OPGs, some extent of psychological morbidity can be expected to derive directly from the damage to the visual system (Avery & Hardy, 2014; de Blank et al., 2016), but this effect has not been investigated systematically from a neuropsychological perspective.

This chapter will investigate the impact of clinical and socio-demographic factors that are relevant for visual and neuropsychological outcomes in children with OPG. For the first time, the role of these prognostic factors will be concurrently investigated on measures of vision integrity and child development using a comprehensive multilevel assessment. In addition, the impact of long-term visual deprivation on cognitive development will be examined.

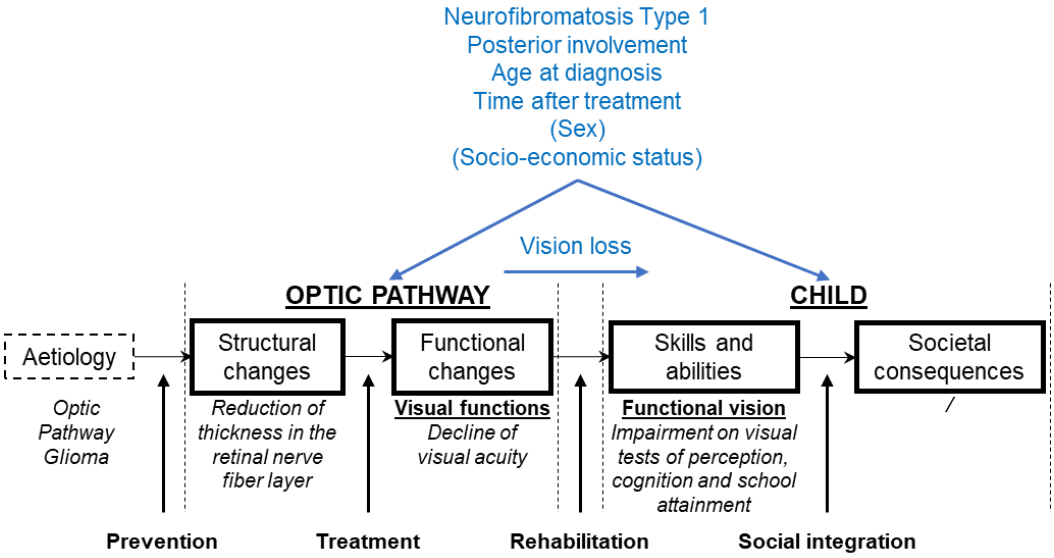


Figure 5.1. Impact of clinical and socio-demographic factors (in blue) on functional outcomes in OPG. Adapted from "Aspects of vision loss – visual functions and functional vision" by A. Colenbrander, 2003, *Visual Impairment Research*, *5*, p. 116. Copyright 2003 by Taylor & Francis.

5.1.1 NF1 co-diagnosis

Convergent evidence shows that NF1 co-diagnosis among children with OPG is associated with better visual morbidity. Children with syndromic OPG are less likely to report reduced visual acuity and other visual symptoms at presentation (Czyzyk et al., 2003; Singhal et al., 2002; Tow et al., 2003). In addition, most syndromic OPGs have stable

vision and indolent lesion that do not require treatment, resulting in good visual acuity and less morbidity at follow-up; instead, sporadic OPGs are more likely to exhibit vision problems, to be treated and develop visual morbidity after the treatment (Tow et al., 2003).

However, NF1 co-diagnosis is associated with higher risk of neuropsychological sequelae in children with OPG. Lacaze et al. (2003) found that, among children with OPG treated with the same chemotherapy protocol, those with NF1 obtained lower IQ scores than non-NF1 counterparts and underperformed on several auditory/verbal and nonverbal/visuospatial subtests. In general, NF1 is associated with neuropsychological difficulties in several developmental domains and these could be exacerbated by the co-diagnosis of brain tumour *per se* (Bartlett D Moore III et al., 1994) and its treatment (De Winter et al., 1999).

5.1.2 Vision loss

Blindness and visual impairment resulting from OPG are also risk factors for children's neuropsychological development and scholastic achievement. High rates of visual impairment among children with supratentorial low-grade glioma (including midline tumours such as OPGs) have been related to greater need of special education and remedial teaching in this group of patients (Aarsen et al., 2009). However, De Blank et al. (2016) reported lower educational and work success in adult OPG survivors who were blind compared to those who had some residual sight, suggesting that greater vision loss impacts more on psychological functioning and school progression but, impaired vision other than bilateral blindness was not associated with psychological outcomes. This indicates that complex relationships exist between vision loss and psychological functioning depending on the number of eyes affected and the degree of impairment. Using a neuropsychological approach, Lacaze et al. (2003) reported a significant association between visual acuity in the best eye and performance on a picture recognition task among OPG patients, suggesting a direct impact of vision loss on visuoperceptual skills. However, they point out a general entanglement of low visual acuity, poor object recognition and impaired high-level intellectual abilities that cannot be resolved (Lacaze et al., 2003).

Therefore, a more fine-grained approach to establish if and how prolonged visual deprivation affects high-level abilities is necessary.

5.1.3 Posterior involvement

Posterior involvement is a risk factor for more severe visual impairment at the level of the optic pathway in paediatric OPG. Wan et al. (2016) found that post-chiasmatic extension was associated with worse visual outcomes in the best eye for children with sporadic OPG. With the NF1 population, children with post-chiasmal involvement at diagnosis or start of treatment were more likely to experience vision loss after chemotherapy and throughout management (Balcer et al., 2001; Fisher et al., 2012). In addition, research on cerebral or neurological visual impairment (Good, 2007) indicates that damage to retro-geniculate portions of the optic pathway, including the optic radiations and the visual cortex, is associated with high-level visual dysfunction of greater complexity than those resulting from anterior lesions only (Dutton, 2003; Hoyt, 2003). For example, a strong coupling between ophthalmological problems and neurological abnormalities was found in children with cerebral visual impairment from different aetiologies, including brain tumours (Huo, Burden, Hoyt, & Good, 1999). Although OPGs usually extend across anterior and posterior portions of the optic pathway, it is possible that OPGs with posterior involvement lead to greater neuropsychological morbidity compared to those without posterior invasion.

5.1.4 Age at diagnosis

A great deal of studies indicate that younger age at diagnosis is a significant risk factor for more severe visual outcomes; this was consistently shown in separate cohorts of syndromic (Fisher et al., 2012; Thiagalingam et al., 2004) or sporadic (Campagna et al., 2010; Wan et al., 2016) OPGs as well as in mixed cohorts (Dodgshun et al., 2015). Younger age at diagnosis was also predictive of worse neurocognitive outcomes in studies that focused on low-grade brain tumours with the same histology as OPGs but different locations in the brain (Aarsen et al., 2009; Armstrong et al., 2011). However, Lacaze et al. (2003) found no correlations between age at diagnosis and their main neuropsychological scores in 21 school-aged OPG survivors, suggesting that there is no

temporal window of vulnerability for this group of patients. Likewise, de Blank et al. (2016) found no association between age at visual impairment onset and long-term psychosocial outcomes in adulthood. Conversely, Riva et al. (2009) found an association between younger age at diagnosis and worse performance on tasks of attention and motor speed ($\rho = \pm 1$): however, the interpretation of these perfect correlations is critical because of the methodological flaws in the study, such as the small sample of 8 patients, the inconsistent assessment across patients and the considerable amount of missing data.

5.1.5 Time post treatment

No effect of time post treatment is expected due to the pre-cortical location of the optic pathway. Vision problems are the most frequent reason to start treatment (Grill et al., 2000) and stability of vision is the most frequent outcome of chemotherapy for symptomatic cases (Dodgshun et al., 2015; Fisher et al., 2012); vision loss and improvement at treatment completion might also occur, but these effects are overall maintained over time. Provided that children remain under continuous regular surveillance, it is reasonable to assume that a new treatment would be started if children experience further vision loss (Dodgshun et al., 2015).

Conversely, it has been proposed that children who survived low-grade brain glioma continue to "grow into deficits" after the treatment and will display a cumulative effect of acquired brain damage on development (Aarsen et al., 2009, 2006): deficits become more marked over time because progressively more complex functions should develop and they cannot be subsumed by the damaged brain (Anderson et al., 2011). This time effect was also confirmed in a large meta-analysis with mixed tumour types, locations and treatments (de Ruiter et al., 2013). However, another meta-analysis on long-term effects of chemotherapy showed greater attentional problems in children tested within 5 years after treatment than in those assessed more than 5 years after treatment (Pierson et al., 2016), suggesting that some neuropsychological recovery can occur over time with this type of treatment.

5.1.6 Other factors and interactions

Although it is convenient to consider prognostic factors in isolation, it must be recognised that they are highly intertwined with each other and with other socio-demographic factors, such as sex. For example, girls with NF1 are more likely to exhibit visual problems and to require treatment for an OPG, whereas boys with NF1 are more likely to develop learning disabilities (Diggs-Andrews et al., 2014). Instead, boys and girls without NF1 seems to be equally affected by OPG (Helfferich et al., 2016). In addition, a protective effect of high parental SES on cognitive development and educational attainment was previously reported with brain tumour patients (e.g., Carlson-Green, Morris, & Krawiecki, 1995). However, Lacaze et al. (2003) found no associations between IQ scores and SES in children with OPG.

In this chapter, the same cohort of 12 children with OPG who received comprehensive ophthalmological and neuropsychological assessment will be examined to explore the concurrent effects of critical prognostic factors (namely NF1 co-diagnosis, posterior involvement, age at diagnosis, time post treatment, sex and SES) on outcome measures reflecting the integrity of the optic pathway and neuropsychological abilities of the children. In addition, the direct effect of vision loss measured on the optic pathway will be explored to see how it impacts on visuo-perceptual, cognitive and scholastic skills.

5.2 Methods

5.2.1 Participants and materials

All the available data from the 12 children with OPG partaking in the study were used. To summarise, at the level of the optic pathway, data about RNFL thickness and visual acuity were available for all participants (12 children, 24 eyes). At the level of child's neuropsychological abilities, all 12 children completed the age-appropriate test of visual perception, whereas only 10 children completed the tests of intellectual functioning and scholastic attainment. Details about the participants (section 2.1.1), the measures (section 2.1.2 and

section 2.1.3.1) and the procedure (section 2.1.4) were given in Chapter 2.

RNFL thickness and visual acuity in the best eye were the outcome measures at the level of the optic pathway. Composite and individual indices of visual perception, intellectual functioning and scholastic attainment were the outcome measures at the level of the child. A summary of outcomes and tools used in this chapter in relation to Colenbrander's (2003) model is reported in Table 5.1.

Table 5.1
Summary of instruments and measures used at each study level.

	Optic pathway		Child		
	1. Structural changes	2. Functional changes	3. Skills and abilities		
Level			Visual perception	Cognitive functioning	Scholastic abilities
Instrument	Spectralis Optical Coherence Tomography	Visual acuity test	Developmental Test of Visual Perception, 2nd edition or Adolescent/Adult version (DTVP-2/A)	Wechsler Intelligence Scale for Children (WISC-IV^{UK})	Wechsler Individual Achievement Test (WIAT-II^{UK})
Outcomes	Thickness of the Retinal Nerve Fiber Layer (RNFL-t)	Visual Acuity (VA) logMAR score	General Visual Perception (GVP)[a] Motor-Reduced Perception (MRP) Visual-Motor Integration (VMI)	Full-scale IQ (FSIQ)[a] General Ability (GA)[a] Verbal Comprehension (VC)[b] Perceptual Reasoning (PR) Working Memory (WM)[b] Processing Speed (PS)	Total Composite (TC)[a] Reading (R) Mathematics (M) Written language (WL) Oral Language (OL)

[a] Composite index.
[b] Verbal/auditory measures, not requiring vision.

5.2.2 Statistical analyses

First, a series of bivariate correlations were conducted among the OPG outcome measures in order to elucidate the relationships between the five study levels examined collectively in this chapter. Pearson's correlations were used throughout except for correlations involving visual acuity that required Spearman's *ρ* coefficients because it was not normally distributed. Correlation analyses were initially conducted on composite indices of neuropsychological performance and Bonferroni correction was applied to account for the five domains examined (α = .05/5 = .01). Further correlations using individual indices were explored with the same alpha level of .01. Effect sizes (*r*) were interpreted as small/weak (0.1), medium/moderate (0.3) and large/strong (0.5) in accordance with conventional standards (Cohen, 1988).

Thus, the influence of clinical prognostic factors and socio-demographic variables was consistently examined at each study level. Associations with tumour type (1: sporadic, 2: syndromic) and vision loss (1: poor vision, requiring visual aids, 2: good vision, not requiring visual aids), posterior involvement (1: no, 2: yes), and sex (1: female, 2: male) were examined using point-biserial correlations. Spearman's *ρ* correlations were used to examine the relationships with age at diagnosis, that was not normally distributed, and SES, that was an ordinal variable. The impact of time post treatment was examined with Pearson's *r* correlations. Point-biserial correlations, which provide the same *p* values as independent-sample t-tests, were used with categorical variables as an alternative to between-group comparisons (Chao, 2018) for a consistent correlational analysis and for easier comparison of effect sizes across different measures. The same approach as above was used to examine composite and individual indices and correct for multiple comparisons.

5.3 Results

5.3.1 Associations among outcome measures

Table 5.2 shows the relationships between all study outcomes related to the optic pathway and to the child.

RNFL thickness and visual acuity were strongly related with each other, but neither was associated significantly with the composite indices of neuropsychological performance. General visual perception was not associated with any of the composite cognitive and scholastic indices, suggesting a dissociation between neuropsychological skills that do and do not involve semantic processing. There were strong correlations among full-scale IQ, general ability, and total composite score of scholastic attainment.

When considering individual indices, visual acuity showed a strong correlation with processing speed, but it did not survive Bonferroni correction. Trends towards significant correlations were also found for RNFL thickness with motor-reduced perception and perceptual reasoning. Interestingly, although below the level of significance, moderate-to-strong correlations were found similarly for RNFL thickness and visual acuity with neuropsychological measures that heavily rely on vision and motor skills. Indeed, the correlations with motor-reduced perception, visual-motor integration, perceptual reasoning, processing speed and written language were all $|r| \geq 0.41$ and in the expected direction (i.e., positive for RNFL thickness and negative for visual acuity due to the logMAR scale, where higher scores indicate poorer vision). Conversely, mixed directions and lower magnitude was found throughout on the other measures.

Among measures of visual perception, visual-motor integration was associated with processing speed, but it did not survive Bonferroni correction, and no correlations were found with the scores of scholastic skills. Between the measures of intellectual functioning and scholastic attainment, strong correlations that survived Bonferroni corrections were found among language tasks (verbal comprehension, reading and oral language) and visual-motor tasks (written language and processing speed). Overall, a certain degree of dissociation between low-level visual perception and high-level cognitive functioning and scholastic attainment emerge.

Table 5.2

Associations (Pearson's r, unless otherwise stated) between all study outcomes related to the optic pathway and the child.

	Optic pathway (best eye)		Child													
			Visual perception			Intellectual functioning						Scholastic achievement				
Measure	RNFL-t	VA[a]	GVP	MRP	VMI	FSIQ	GA	VC	PR	WM	PS	TC	R	M	WL	OL
RNFL-t	—															
VA§	**-.93*** **	—														
GVP	.52^	-.48	—													
MRP	.56^	-.47	**.91*** **	—												
VMI	.41	-.47	**.95*** **	.72**	—											
FSIQ	.34	-.40	.48	.65*	.30	—										
GAI	.26	-.23	.26	.53	.02	**.93*** **	—									
VC	-.27	.17	-.16	.14	-.38	.53	.68*	—								
PR	.60^	-.46	.50	.58	.38	**.76***	.72*	-.01	—							
WM	.15	.15	.52	.62^	.38	.57^	.39	.39	.15	—						
PS	.44	-.63*	.65*	.53	.68*	.73*	.50	-.08	.74*	.32	—					
TC	-.05	-.18	.06	.31	-.13	**.88** **	**.82** **	**.88** **	.26	.55	.44	—				
R	.09	-.06	.27	.54	.02	**.91*** **	**.80** **	**.80** **	.34	.73*	.42	**.94*** **	—			
M	-.25	.15	-.18	-.05	-.22	.71*	.68*	.54	.41	.29	.51	**.84** **	.66^	—		
WL	.43	-.61^	.59	.54	.58^	**.81** **	.58^	.18	.61^	.55^	**.92*** **	.71*	.69*	.61^	—	
OL	.04	-.27	.03	.27	-.14	**.79** **	**.89*** **	**.84** **	.42	.35	.34	**.87** **	.74*	.73*	.54	—

Note. RNFL-t = Retinal Nerve Fiber Layer thickness; VA = visual acuity; GVP = general visual perception; MRP = motor-reduced perception; VMI = visual-motor integration; FSIQ = full-scale IQ; GA = general ability; VC = verbal comprehension; PR = perceptual reasoning; WM = working memory; PS = processing speed; TC = total composite; R = reading; M = mathematics; WM = written language; OL = oral language.

^ $p \leq .10$, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$. Bold indicates correlations that survived Bonferroni correction ($\alpha = 0.05/5 = 0.01$).

[a] Spearman' s ρ used because VA was not normally distributed.

5.3.2 Impact of prognostic factors on OPG outcomes

Table 5.3 shows all the correlations between the outcome variables and prognostic factors.

There were significant correlations of the classification of vision as good (not requiring low vision aids) or poor (requiring low vision aids) with RNFL thickness and visual acuity in the best eye. These correlations were reported for consistency, but they were not informative since the classification of vision was based on the combination of visual acuity scores in both eyes. Indeed, referring to Figure 5.1, the effect of vision loss corresponded to the horizonal arrow describing the effect of measures related to the optic pathway to those related to the child. In addition, some strong significant correlations were found for the classification of vision with perceptual reasoning, processing speed and written language. Interestingly, the classification of vision also showed trends towards significant correlations of strong magnitude with the three indices of visual perception. Further, strong significant correlations were found for the classification of vision with perceptual reasoning, processing speed and written language.

Age at diagnosis was also significantly correlated with RNFL thickness and visual acuity in the best eye. Both correlations were in the expected directions, with more damaged RNFL and worse visual acuity in children who were younger at diagnosis. No other associations were found between any prognostic factor and composite indices of neuropsychological tests.

Table 5.3

Correlations (point-biserial coefficient r_{pb}, Pearson's r and Spearman's ρ) of study outcomes related to the optic pathway and the child with clinical and socio-demographic factors.

Domain	Index	Tumour type (r_{pb})	Vision loss (r_{pb})	Posterior involvement (r_{pb})	Age at diagnosis (ρ)	Time after treatment (r)	Sex (r_{pb})	Socio-economic status (ρ)
Optic pathway								
Structural level	RNFL-t	.25, .427	**.78, .003**	-.13, .682	**.59, .044**	-.21, .591	.30, .347	-.21, .519
Functional level	VA	-.51, .088	**-.90, < .001**	-.34, .283	**-.68, .016**	.41, .270	-.18, .581	.14, .676
Child								
Visual perception	GVP	-.21, .518	.54, .068	.08, .811	.24, .450	-.34, .368	-.27, .388	-.23, .482
	MRP	-.37, .244	.52, .085	-.13, .686	.34, .280	-.05, .896	-.06, .848	-.18, .573
	VMI	-.07, .818	.50, .097	.23, .482	.28, .373	-.49, .183	-.40, .196	-.07, .828
Cognitive function	FSIQ	-.52, .120	.52, .120	-.27, .449	.32, .361	.56, .196	.36, .314	.36, .307
	GA	-.47, .174	.45, .194	-.31, .382	.36, .312	.60, .152	.59, .072	.22, .544
	VC	-.22, .537	-.02, .950	-.17, .634	.04, .913	.58, .176	.25, .481	.45, .197
	PR	-.41, .244	**.64, .045**	-.23, .524	.44, .199	.25, .586	.57, .087	.18, .625
	WM	-.55, .102	.07, .845	-.35, .322	-.21, .563	.55, .203	-.33, .347	.12, .736
	PS	-.29, .419	**.67, .035**	.01, .969	.43, .213	.04, .928	.08, .832	.23, .519
Scholastic attainment	TC	-.40, .292	.18, .636	-.24, .535	.19, .620	.49, .326	.20, .600	.30, .433
	R	-.58, .103	.13, .737	-.42, .263	.07, .864	.47, .350	.11, .777	<.01, 1.00
	M	-.44, .201	.07, .852	-.34, .330	-.11, .763	.71, .073	.43, .215	.54, .108
	WL	-.27, .460	**.64, .047**	-.03, .931	.37, .290	.18, .698	.03, .932	.29, .413
	OL	-.23, .524	.39, .262	-.17, .646	.42, .228	.63, .133	.53, .525	.61, .060

Note. Significant results highlighted in bold. RNFL-t = retinal nerve fiber layer thickness; VA = visual acuity; GVP = general visual perception; MRP = motor-reduced perception; VMI = visual-motor integration; FSIQ = full-scale IQ; GA = general ability; VC = verbal comprehension; PR = perceptual reasoning; WM = working memory; PS = processing speed; TC = total composite; R = reading; M = mathematics; WL = written language; OL = oral language.

5.4 Discussion

This chapter investigated the impact of prognostic factors on multilevel outcomes of OPG related to the optic pathway integrity and to the child's abilities. Overall, the prognostic factors considered in this study were found to have little impact on OPG outcomes. Therefore, the interpretation of the results will focus not only on significant and non-significant results, but also on emerging trends that could be further investigated in a larger sample.

No significant associations were found between OPG outcomes and NF1 comorbidity. At the level of the optic pathway, the direction of the correlations suggested greater structural and functional damage for children with OPG, which is consistent with the ophthalmology research on this tumour (Czyzyk et al., 2003; Singhal et al., 2002; Tow et al., 2003). At the level of the child, all the associations between tumour type and neuropsychological performance were in the negative direction and suggested a disadvantage for children with syndromic OPG, as expected. The neuropsychological phenotype of NF1 has consistently been linked to developmental difficulties in visuoperceptual and visuospatial functions (Bulgheroni et al., 2019; Clements-Stephens et al., 2008; Schrimsher et al., 2003), memory (Payne, Arnold, Pride, & North, 2012), attention (Isenberg, Templer, Gao, Titus, & Gutmann, 2013), general intelligence (Lehtonen et al., 2015) and learning (Orraca-Castillo, Estévez-Pérez, & Reigosa-Crespo, 2014). When comparing OPG patients who were treated with chemotherapy only (as in the current sample), Lacaze et al. (2003) found significantly lower neuropsychological scores in syndromic compared to sporadic OPGs. Therefore, although the associations in this study did not reach the level of significance, the consistency of these patterns and the agreement with previous literature suggest that the current analyses had insufficient power to clearly detect the NF1 effect due to the small sample, but the pattern of results do not challenge previous findings.

The impact of vision loss was examined based on the distinction between good or poor vision that was also used to decide whether children were entitled to use low vision aids. Significant correlations or trends were found with several neuropsychological measures that heavily

relied on vision and motor output and their direction consistently indicated that children with poor vision performed worse than those with good vision. Under the assumption taken in this thesis that low vision aids fully addressed visual input problems, these results indicate a long-term detrimental effect of vision loss on the ability to elaborate visually transmitted information. De Blank et al. (2016) proposed that early visual loss in glioma survivors may either lead to long-term neurocognitive, psychological and socioeconomic difficulties "because of a greater number of "blind years"" (p. 170), or facilitate timely neural re-organisation and behavioural adaptation resulting in adequate development. The current results support the first proposition as children with poor visual function obtained lower scores on neuropsychological tests despite the use of low visual aids. In addition, the lack of negative associations between vision loss and verbal/auditory tasks, such as verbal comprehension and working memory, suggests that children with OPG with poorer vision do not develop better auditory/verbal compensatory abilities to counter the sensory loss in the visual channel. This will be explored further in Chapter 6.

No significant correlations were found between posterior involvement and any OPG outcomes. The direction of the correlations suggested mixed effects at the level of the optic pathway, whereas a negative impact of damage to the optic radiation was associated with poor performance on most neuropsychological scores. However, these effects were small. The most plausible explanation for these null results is the fact that involvement of the optic radiation was not defined in isolation, but within a group of OPG patients with mixed anterior and posterior damage to the optic pathway. As for ophthalmology research (e.g., Tow et al., 2003), future studies should select OPGs limited to either the anterior or posterior portion of the optic pathway to clarify if these lesions distinctively affect vision and neuropsychological skills.

The correlations of age at diagnosis with RNFL thickness and visual acuity align with previous research that demonstrated worse visual morbidity in children who were diagnosed with OPG early in life (Campagna et al., 2010; Dodgshun et al., 2015; Fisher et al., 2012; Liu et al., 2016; Thiagalingam et al., 2004). Dodgshun et al. (2015) propose

two possible mechanisms for this: either biological features of these tumours make them inherently more aggressive, or delayed diagnosis in preverbal children due to assessment difficulties results in more severe and long-lasting visual impairment at diagnosis that is not expected to be ameliorated with chemotherapy. However, age at diagnosis did not correlate with children's neuropsychological abilities. This contrasts with previous research that found younger age at diagnosis to be a risk factor for more severe cognitive impairment and academic under-achievement in children with non-NF1 low-grade gliomas located in the brain (Aarsen et al., 2009) and in survivors of other childhood cancers (Mitby et al., 2003). Taken together, these results suggest that there may be a "temporal window of vulnerability" for the visual system, but this may not be the case for cognitive development.

No significant associations and mixed directions were found between time after treatment and any OPG outcome, suggesting a general stability of abilities after the chemotherapy. This was expected at the level of the optic pathway because chemotherapy has been shown effective at inducing stability of vision after treatment (Dodgshun et al., 2015; Fisher et al., 2012). Conversely, the lack of associations with child-related neuropsychological measures suggests neither a cumulative effect of tumour-related impairment over development (Aarsen et al., 2009, 2006) nor a "catch-up" effect of recovery after chemotherapy (Pierson et al., 2016) occur in children with OPG. However, these correlations should be interpreted cautiously because they were based on the only 9 children out of 12 who received chemotherapy.

Socio-demographic factors such as sex and SES did not show associations with either structural and functional measures of vision or neuropsychological outcomes. These factors possibly have too specific (e.g., sex and NF1) or too generic effects (SES and cognitive acquisition) that could have not been detected in such a small sample.

To summarise, a comprehensive approach was taken in this chapter to concurrently assess the impact of clinical and socio-demographic factors on OPG outcomes related to the optic pathway and to children's abilities. Prognostic factors did not correlate well with multilevel outcomes in the current sample, probably due to the small

sample. Visual outcomes are more severe in children with early diagnosis, whereas neuropsychological outcomes are not susceptible to time-related effects as shown by the null associations with age at diagnosis and time after treatment. Only poor vision based on both eyes was shown to be related to lowered performance on tasks involving vision and motor responses, indicating that visual morbidity has an impact on neuropsychological development and children with more severe impairment have long-term difficulties at processing visual information beyond the visual input.

The current results leave open an important question about the role of NF1 on OPG outcomes. The correlation analyses demonstrated consistent trends in line with the literature indicating that children with NF1 have better visual morbidity, but worse neuropsychological outcomes, although this did not emerge clearly from this study because of the small sample. When comparing two or more groups of subjects on certain characteristics, the smaller the expected effect size, the larger the sample needs to be in order to distinguish a real effect from a random variation (Hackshaw, 2008). Children with NF1 display high variability in the neurocognitive phenotype (Lehtonen et al., 2013) and mild degree of neurocognitive impairment, characterised by a left shift of IQ score within one standard deviation of the general population (IQ ≈ 85; Eliason, 1986; Ferner, Hughes, & Weinman, 1996; North et al., 1997; Ozonoff, 1999) and low prevalence of severe mental retardation (4-8% of the NF1 population; Ferner, Hughes, & Weinman, 1996; North et al., 1997). Therefore, it is likely that between-group analyses, as performed with point-biserial correlations, did not afford the possibility to detect this small effect size. In addition, although in this thesis it was necessary to study together NF1 and non-NF1 children because of the small sample, the developmental trajectories of NF1 children are so distinctive that ophthalmology research tends to study syndromic OPGs separately from sporadic tumours (e.g., Avery et al., 2011; Fisher et al., 2012), whereas neuropsychological investigations of childhood brain tumour exclude NF1 patients (Aarsen et al., 2009, 2006). To address this problem, a further follow-up analysis on all study outcomes can be conducted by splitting the sample into sporadic and syndromic OPGs, treating these groups as if

they were drawn from different populations. Similar to previous chapters, group means can then be compared to normative means. This approach would reveal whether the deficits detected on the whole group in comparison to the test norms (see Chapter 6; summary in Figure 5.2) could be ascribed to the NF1 patients.

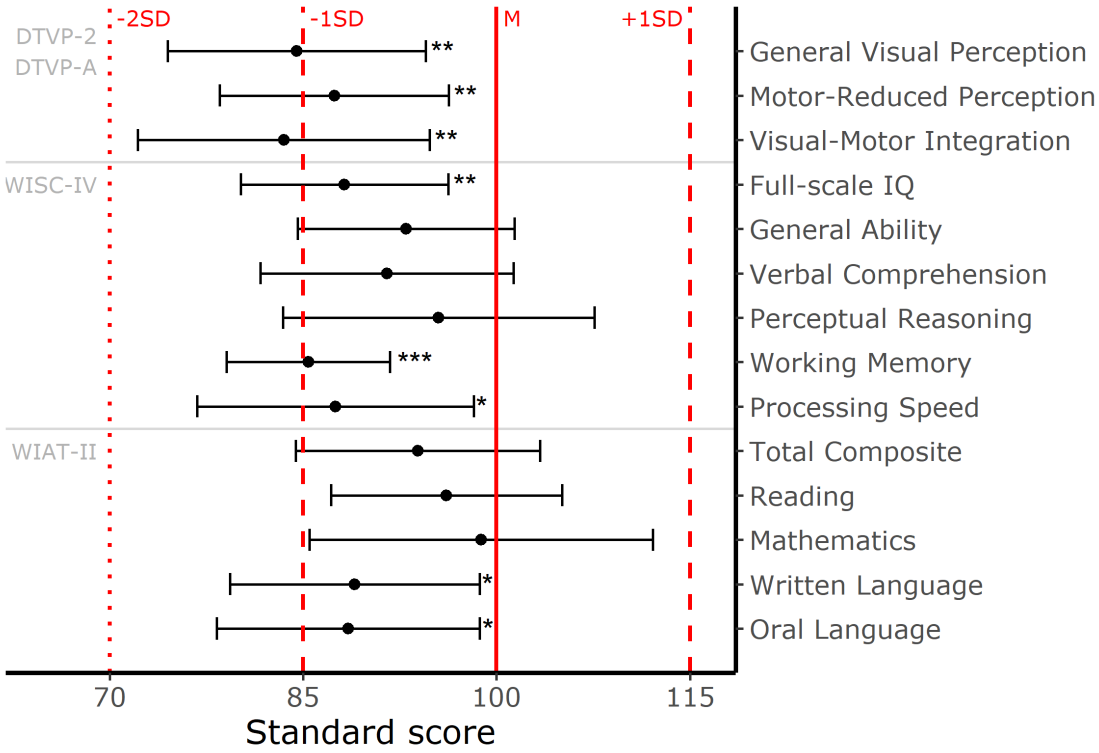


Figure 5.2. Group means and 95% CI of all neuropsychological indices in comparison to test norms (M = 100, SD = 15). Significance level: * p < .05, ** p < .01, *** p < .001.

5.4.1 Exploratory follow-up examination on NF1

5.4.1.1 Methods, materials and statistical analyses

The same outcome measures as in the first part of this chapter were considered. In addition, to maximise the available dataset, all study eyes (N = 24) were used. As described in Chapter 3, RNFL thickness and visual acuity measures of each eye were classified as normal or lowered based on whether they were above or below the 95% PI_{low}.

First, using all study eyes, the association between tumour type (sporadic or syndromic) and the frequency of normal or abnormal scores was assessed with a χ^2 test-of-independence with Fisher's correction, as necessary. Then, separate one-sample t-tests or equivalent non-

parametric Wilcoxon signed rank tests were conducted for each group. No Bonferroni correction (see section 2.3). Results should be treated with caution, providing potential additional insights for further investigation with a larger sample size.

5.4.1.2 Results and discussion

On all study eyes, there was no relationship between tumour type (sporadic or syndromic) and RNFL thickness ($\chi^2(1) = 1.22$, Fisher's exact $p = .358$), but there was an association between tumour type and visual acuity, with sporadic OPGs more likely to exhibit abnormal visual acuity scores ($\chi^2(1) = 4.61$, Fisher's exact $p = .047$).

Table 5.4 reports descriptive statistics and comparison to the normative means for all study outcomes in sporadic and syndromic OPGs. Again, a consistent deficit was found on RNFL thickness for both groups, whereas visual acuity tended to be more impaired in sporadic OPGs. On neuropsychological indices, non-NF1 children reported a statistically significant decrease only on working memory, whereas NF1 children showed impairment on all indices of visual perception and intellectual functioning that were impaired at a group level. Instead, neither of the subgroups demonstrated specific difficulties in oral or written language.

Table 5.4
Descriptive statistics (M and SD) and comparison to normative means (t and p, unless otherwise stated) for sporadic and syndromic OPGs.

		Sporadic OPGs			Syndromic OPGs		
Domain	Index	*n*	Mean (*SD*)	Statistics (*t*, *p*)	*n*	Mean (*SD*)	Statistics (*t*, *p*)
Optic pathway							
Structural level	RNFL-t	5	59.20 (29.35)	**-3.60, .022**	7	7.86 (19.71)	**-4.78, .003**
Functional level	VA	5	0.75 (0.66)	2.42, .073	7	0.08 (0.20)	23, .128[a]
Child							
Visual perception	GVP	5	88.20 (18.63)	-1.42, .230	7	81.86 (14.31)	**-3.35, .015**
	MRP	5	93.20 (13.23)	-1.15, .315	7	83.29 (13.96)	**-3.17, .019**
	VMI	5	85.00 (23.18)	-1.45, .222	7	82.43 (14.83)	**-3.13, .020**
Intellectual functioning	FSIQ	5	93.80 (8.64)	-1.60, .184	5	82.60 (11.52)	**-3.38, .028**
	GA	5	98.20 (9.83)	-0.41, .703	5	87.80 (12.11)	-2.25, .087
	VC	5	94.40 (13.78)	-0.91, .415	5	88.60 (14.64)	**0, .042[a]**
	PR	5	102.00 (15.51)	0.29, .787	5	89.00 (17.18)	-1.43, .225
	WM	5	90.00 (3.74)	**-5.98, .004**	5	80.80 (10.47)	**0, .042[a]**
	PS	5	91.60 (14.60)	-1.29, .268	5	83.40 (15.81)	**0, .042[a]**
Scholastic abilities	TC	5	98.00 (10.79)	-0.41, .700	4	88.75 (13.67)	-1.65, .198
	R	5	101.80 (7.98)	0.50, .641	4	89.00 (12.49)	-1.76, .176
	M	5	106.60 (17.01)	0.87, .435	5	91.00 (18.40)	-1.09, .335
	WL	5	92.40 (11.28)	-1.51, .206	5	85.60 (15.99)	-2.01, .114
	OL	5	91.60 (10.69)	-1.76, .154	5	85.40 (17.84)	-1.83, .141

Note. Bold highlights significant results. RNFL-t = Retinal Nerve Fiber Layer thickness; VA = visual acuity; GVP = general visual perception; MRP = motor-reduced perception; VMI = visual-motor integration; FSIQ = full-scale IQ; GA = general ability; VC = verbal comprehension; PR = perceptual reasoning; WM = working memory; PS = processing speed; TC = total composite; R = reading; M = mathematics; WL = written language; OL = oral language.

[a] Non-parametric Wilcoxon signed rank test used; V-statistics and p-values reported.

These results suggest that group effects on visual and visual-motor abilities of perception and cognition were overall driven by the NF1 children, who notably had better visual outcomes at least in terms of visual acuity. Instead, the impairment of working memory should be attributed to the tumour history itself (Brookshire, Copeland, Moore, & Ater, 1990; Margelisch et al., 2015) or to the chemotherapy (Pierson et al., 2016; Verstappen, Heimans, Hoekman, & Postma, 2003) because it was consistently found in both sporadic and syndromic OPGs, although inspection of descriptive statistics suggest that a different mechanism could underpin this deficit in the two subgroups. In fact, children with sporadic OPG had a mean score within the normal range, but very narrow variation around it, whereas children with syndromic OPG exhibited a mean score below -1 standard deviation, but wider variability. This deficit might be attributed to the chemotherapy in general, which has been shown to negatively affect the domain of attention in young brain tumour and leukaemia patients (Pierson et al., 2016), or to specific drugs, which cause memory and concentration problems among adult cancer survivors (Verstappen et al., 2003). In this domain could also be the result of the tumour itself as shown in studies with pre-treatment evaluations; specifically, the working memory deficit aligns with the verbal sequelae (working memory, verbal memory, and attention deficit) described by Margelisch et al. (2015) rather than visual-motor, fine motor and executive control profile reported by Brookshire et al. (1990). Indeed, one of the non-NF1 patients in the sample of this study (P9) was observed and never treated. This in particular warrants further investigation in future with larger number of both syndromic and sporadic cases to shed light on potential mechanisms of auditory compensation, as suggested in other clinical oncology literature (Brinkman et al., 2015; Ek et al., 2002). Finally, the decrease on oral and written language should be ascribed to a mild effect in both subgroups, since their mean scores were above (non-NF1 patients) or just above (NF1 patients) the threshold of -1 *SD* and therefore in the average range. Taken together with the main analysis, these results suggest that NF1 co-diagnosis had great impact on most difficulties found at group level, but also that some

aspects of such morbidity following OPG are not related to either NF1 or vision loss.

Chapter 6 Visual and auditory processing in children with OPG

6.1 Introduction

As outlined in Chapter 1, obtaining reliable measures when assessing children with visual impairment is extremely difficult because most measurement tools require or assume some ability to use vision (Deramore Denver, 2019). The most common approach to address this problem is to use only verbal and auditory tasks that rely on the intact hearing sense without requiring vision. For example, Bathelt and coworkers (2018) assessed a group of school-aged children with congenital visual impairment on a range of executive functions using tasks such as verbal working memory, auditory sustained attention and verbal fluency. Similarly, Greenaway and colleagues (2017) examined memory, attention and executive functions in visually impaired adolescents using an assessment that focused only on "auditory cognition" (p. 147). This approach is certainly valid to be used with children with severe visual impairment or blindness, who have no functional vision left and therefore cannot be examined with visual tasks (e.g., Setti, Cuturi, Cocchi, & Gori, 2018; Withagen, Kappers, Vervloed, Knoors, & Verhoeven, 2013; Zia et al., 2015), but it neglects the impact of residual sight in children with low vision. Since children with OPG exhibit a highly variable degree of visual impairment, it is valuable to consider multiple sensory modalities, therefore both vision and hearing, when conducting neuropsychological testing with this specific group of brain tumour survivors to obtain a complete picture of their strengths and weaknesses.

In Chapter 4, the modality effect on cognitive testing was examined by comparing WISC-IV indices that tap into the same construct but rely on different sensory modalities. Since no discrepancy was found between such indices, those results were taken as evidence of a limited effect of sensory modality of cognitive testing. Although those comparisons were appropriate for the internal structure of the WISC-IV and to address limitations of previous research (Lacaze et al., 2003), it is

important to recognise that the compared indices differed not only in their sensory modality, but also in the underpinning abilities themselves. For example, the Similarity subtest of Verbal Comprehension requires participants to explain in what way two things are alike, whereas the Matrix Reasoning subtest of Perceptual Reasoning requires children to identify the missing element within an array of pictures. Because the WISC-IV indices aggregate different abilities and encompass tasks with different designs (modality of administration, test materials, etc.), it remains difficult to evaluate the modality effect on neuropsychological abilities using this standardised tool. Instead, new measurement tools that, as far as possible, are matched on all task features except for the sensory input would be more adequate to concurrently examine the same skill in different modalities.

The auditory-visual processing battery presented in Chapter 2 responds to this need. Tests were carefully matched to ensure they had equivalent structure and therefore would tap into the same ability, whilst controlling for the *input* modality of the test materials, either auditory or visual. The tests of the auditory-visual processing battery aimed to evaluate a series of motor, cognitive and scholastic abilities that are known to be associated in typical development and that are also worth evaluating in children with OPG, with or without NF1 (see section 2.1.3.2).

As recently highlighted by Deramore Denver (2019), planning and delivering adequate interventions for visually impaired children require the evaluation of vision (unless a child is completely blind) as well as compensatory skills in other sensory modalities, and should encompass a broad range of developmental domains including fine and gross motor, socio-emotional, cognitive and linguistic skills. The aim of this chapter is to conduct such a comprehensive assessment across multiple developmental domains and sensory modalities in children with OPG. This could better inform interventions for children with OPG by elucidating strengths and weaknesses in different areas of development in relation to the sensory modality to which they are intrinsically linked.

Because the battery included some experimental measures, a control group of typically developing children was also examined on the same assessment tools to provide normative references against which the performance of children with OPG can be interpreted. Specifically, instead of recruiting healthy children that matched patients on socio-demographic characteristics, a large group of healthy children was recruited for two reasons. First, increasing the patient-control ratio is advised to increase the power of clinical studies that deal with rare conditions and therefore with small patient numbers (Grimes & Schulz, 2005; Riniolo, 1999). Second, in psychological research, assessing a large normative group make possible to capture the variability that is inherent to development (Molenaar, 2004) and provide a better framework to examine the heterogeneity associated with childhood brain tumours and their late effects (Stavinoha et al., 2018). The method of comparing a small sample of brain tumour patients against a large control group has already been successfully used in previous research. For example, Davis and colleagues (2010) compared 15 children with posterior fossa tumour with over 240 typically developing children on a group of motor and cognitive standardised tests. This approach is further valuable in this project where a variety of measures from different domains and without a common underlying construct are assessed with non-standardised tools.

This chapter will be divided into two parts. The first part will use a group of typically developing children aged 6 to 11 years to validate the novel battery of auditory-visual processing tests. Specifically, it will examine the appropriateness of the tasks for a wide age range and will examine whether the paired tasks can be considered analogous measures that tap into the same ability. Then, in second part, this normative dataset will be used to create a model of normal development against which the performance of children with OPG will be examined.

6.2 Part I: models of typical development

6.2.1 Participants, materials and procedure

The normative models of typical development were based on the group of 99 typically developing children recruited in local schools. All children were administered the novel battery of parallel tasks that examined fine motor control, attention, short-term and working memory, mathematics ability and English comprehension using either the visual or auditory input modality. Details about the study participants (section 2.2.1), visual and auditory battery (section 2.1.3.2) and administration procedure (section 2.2.3) were given in Chapter 2. A summary of outcome measures was provided in Table 2.3.

Three children were excluded from the analyses because of significant difficulties in the visual domain: two children (one with SEND) were not able to complete the visual task of English comprehension because of severe reading problems and one child (with SEND) had a visual impairment. With the remaining children, assessment of the boxplots for individual tasks did not reveal any extreme outliers, therefore all the remaining 96 controls, including those with SEND, were included in the analyses. Individual IDACI scores were clustered around the school IDACI scores rather than uniformly distributed across the range, therefore SES was accounted for as a dichotomous categorical variable based on high or low SES school (Figure 6.1). Age, SES and sex were added as covariate in the analyses as appropriate. Adding SEND status as further covariate did not alter the significance of the results, therefore the results without this covariate are reported.

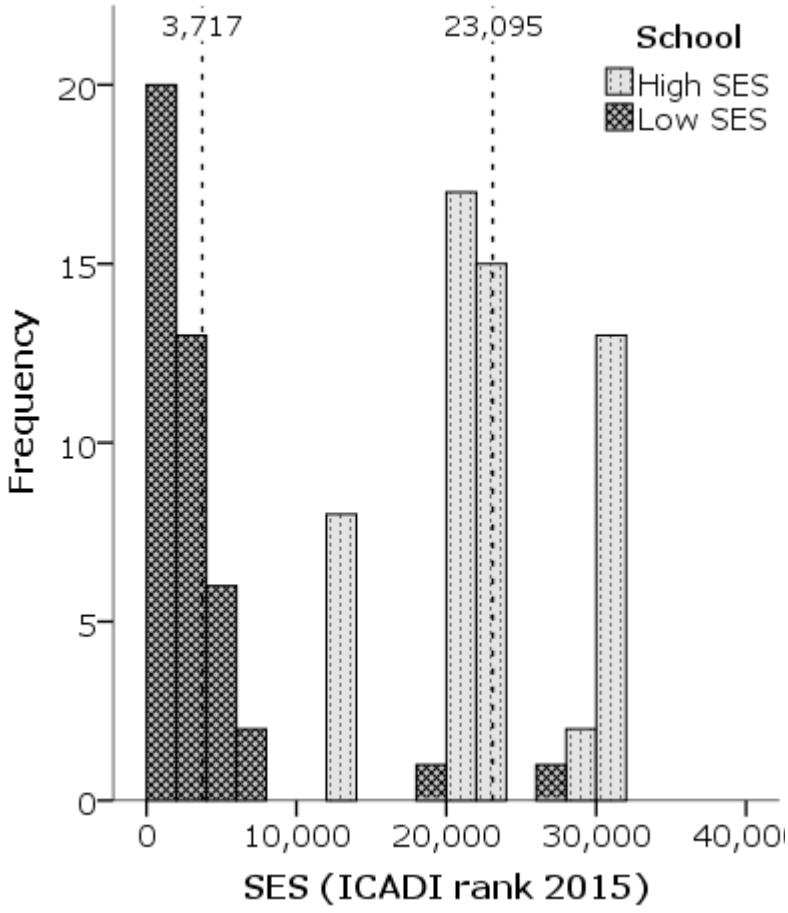


Figure 6.1. Distribution of individual SES ranks among control participants. Dotted lines indicate school IDACI ranks.

6.2.2 Statistical analyses

6.2.2.1 Preliminary assessment

Preliminary assessment was conducted on the two measures of oromotor speech production (articulatory sequences: *M* [*SD*] = 45.04 [12.93] s; tongue twisters: 82.35 [22.63] s) and the two measures of finger tapping (repetition: *M* [*SD*] = 29.70 [11.28] s; sequences *M* [*SD*] = 32.99 [13.22] s). This was necessary because it was a novelty to pair these tasks as analogous auditory and visual measures of motor control, and because their intrinsic differences made it not possible to fully match the task features (e.g., maximum time allowed). All four measures were significantly associated with each other ($\rho \geq 0.27$, $p \leq .008$) and with age ($\rho \geq 0.48$, $p < .001$). Two Wilcoxon signed-rank paired-sample tests indicated that there was a significant difference between the tasks of each pair (auditory modality: articulatory sequences and tongue twister,

z = -8.51, p < .001, r = 0.87; visual modality: repetition and sequence finger tapping, z = -2.58, p = .010. r = 0.37). The strong effect size for the auditory pair indicated a remarkable discrepancy between articulatory sequences and tongue twisters. Therefore, although all the measures were designed to reflect fine motor control skills (see section 2.1.3.2.1), it was preferred to use one measure for each modality, instead of averaging or summing the two. Finger tapping sequences and articulatory sequences were chosen for two reasons. First, NEPSY finger tapping sequences, but not NEPSY finger tapping repetition, was found to be associated with the NEPSY omotor task in a twin study (Brookman et al., 2013). Second, articulatory sequences were deemed to tap into sequential motoric aspects with no semantic component (e.g., "mish mash"), whereas tongue-twister repetitions as a sentence repetition task may rely also on language (Klem et al., 2015) and verbal memory (Poll et al., 2013). No child required all the time allowed to complete these tasks.

For short-term and working memory, preliminary analyses were also conducted on total scores as the product between trial score and span, as suggested in the literature with adults (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000). However, this procedure positively skewed the data distribution, which did not improve with either the logarithmic or the square root transformation; therefore, the trial score was used.

For the attention tasks, there was a ceiling effect on the hit rate, a common problem in CPTs (Berlin, Bohlin, Nyberg, & Janols, 2004; Lasee & Choi, 2014). However, such an effect was not found on false alarm rates, indicating that the time manipulation made the task cognitively demanding for children when they had to withhold their motor response. Consistently, *d'* did not show a ceiling effect.

6.2.2.2 Main analyses

First, a series of Spearman's r_s correlation were conducted between each task and age with SES and sex added as covariates, to ensure the tasks were sensitive to development within the age range of this sample. Then, for each ability, the association between auditory and visual measures was assessed using a series of zero-order (without

covariates) nonparametric correlations, to examine if the paired measures tap into the same underpinning skills. These associations were repeated as partial nonparametric correlations, with age, SES and sex as covariates. Spearman's coefficients r_s were computed throughout except for short-term and working memory, where the discrete scores generated a large number of ties and Kendall's τ was deemed more appropriate. Finally, for each pair of measures, linear regressions were conducted to assess whether performance on the auditory task could predict performance on the visual task, beyond the contribution of age, SES and sex. The attribution of sensory task to be the dependent and independent variables was based on the assumption that the sense of hearing is the reliable one for later analyses with OPG children (Bathelt et al., 2018; Greenaway et al., 2017). Regression diagnostics were examined to assess the presence of outliers and their influence on the models (Field, 2009).

Throughout the analyses, effect sizes (r_s/R^2) were reported to facilitate comparisons among tasks. These were interpreted as small or weak (0.1/0.01), medium or moderate (0.3/0.09) and large or strong (0.5/0.25) in accordance with conventional standards (Cohen, 1988); cut-offs of 0.2/0.04 were considered the minimum effect sizes representing a clinically (or "practically") relevant effect (Ferguson, 2009). Kendall's τ were also transformed to Spearman's r_s using the formulas provided by Walker (2003).

6.2.3 Results

Table 6.1 reports the descriptive statistics of the visual and auditory tasks of each skill for the control group. Mean, standard deviation and range are reported for the whole sample and for three age groups binned by the 33th and 67th percentiles of the age distribution in months, which leads to unequal numbers of children in the three groups. On all experimental measures of scholastic predictors, general improvements of performance were observed across the three age bands. On scholastic outcomes, mean standardised scores were all within the normal range except for the visual task of mathematics that fell just above 1 standard deviation from the test mean.

Table 6.1
Descriptive statistics [M(SD), min-max] of scores at auditory and visual tasks of each skill.

Skill	Modality	Total sample (*N* = 96)	Younger group (*n* = 33)	Middle group (*n* = 36)	Older group (*n* = 27)
Fine motor control (s)	A	45.04 (12.93) 25–80	53.60 (14.60) 26.50–80.00	42.16 (7.97) 29.25–67.75	38.42 (10.65) 25.00–76.00
	V	32.99 (13.22) 12.25–83.50	41.28 (14.43) 23.75–83.50	32.03 (11.63) 15.50–66.50	24.12 (5.49) 12.25–33.50
Attention sensitivity (d')	A	2.50 (0.87) 0.20–4.24	2.26 (0.97) 0.20–4.23	2.54 (0.79) 0.74–4.24	2.72 (0.77) 0.80–4.24
	V	2.25 (0.70) 0.69–4.24	2.11 (0.58) 0.79–3.15	2.24 (0.73) 0.69–4.24	2.43 (0.76) 0.95–4.24
Attention RT (s)	A	0.75 (0.14) 0.50–1.09	0.81 (0.12) 0.63–1.08	0.72 (0.11) 0.57–1.02	0.71 (0.15) 0.50–1.09
	V	0.50 (0.08) 0.36–0.80	0.55 (0.06) 0.46–0.75	0.48 (0.06) 0.37–0.69	0.47 (0.08) 0.36–0.80
Short–term memory (trial score)	A	7.18 (1.94) 3–12	5.94 (1.54) 3–9	7.56 (1.98) 4–12	8.19 (1.52) 5–12
	V	6.90 (2.24) 2–12	5.55 (1.82) 2–9	7.42 (2.06) 3–11	7.85 (2.20) 3–12
Working memory (trial score)	A	6.35 (1.56) 2–10	5.36 (1.17) 2–7	6.56 (1.04) 4–10	7.30 (1.51) 5–10
	V	7.34 (2.19) 1–14	5.73 (1.80) 1–9	7.94 (1.94) 4–13	8.52 (1.81) 6–14
Mathematics (standardised scores)	A	9.55 (2.79) 4–16	8.67 (2.18) 4–13	10.11 (2.95) 5–16	9.89 (3.07) 4–16
	V	110.50 (16.79) 69–144	104.24 (16.90) 73–135	110.78 (16.00) 69–137	117.78 (15.14) 70–144
English comprehension (standardised scores)	A	8.92 (2.13) 3–13	8.82 (2.42) 4–13	9.42 (1.63) 5–12	8.37 (2.27) 3–12
	V	103.52 (9.01) 77–121	101.06 (10.33) 77–117	105.83 (7.49) 91–121	103.44 (8.65) 91–118

Note. A = auditory task; V = visual task.

Table 6.2 reports the Spearman's r_s correlations between each task and age, with SES and sex as covariates. Correlations between experimental measures and age were all in the expected direction, including negative correlations with speed measures (motor control and attention RT) and positive correlations with the other score measures. All correlations were significant except for attention sensitivity in the visual modality, suggesting that the tasks were adequate for the sample age-range. A significant correlation was also found between age and the visual tasks of mathematics, despite using age-adjusted standard scores. This might have occurred because children in year 1, aged 6 years, who were from the low SES school, were tested during their first school term, at the start of the academic year (September-December). Conversely, the older children, many of whom were from the high SES school, were tested during their last term of the academic year (April-July).

Table 6.2
Spearman's correlations (r_s and p) between age and tasks, with SES and sex as covariates (N = 96, df = 92).

	Task modality (r_s and p)	
Ability	auditory	visual
Fine motor control	-0.44, <.001	-0.44, <.001
Attention sensitivity	0.27, .008	0.09, .390
Attention RT	-0.25, .017	-0.56, <.001
Short-term memory	0.36, .001	0.40, <.001
Working memory	0.47, <.001	0.56, <.001
Mathematics	0.10, .320	0.22, .033
English comprehension	-0.07, .485	0.05, .631

Scatterplots displaying visual and auditory scores for the same ability are represented in Figure 6.2. All zero-order and partial correlations are reported in Table 6.3. On zero-order correlations, the auditory and visual measures of each ability were significantly associated. After covarying for socio-demographic variables, all correlations between auditory and visual measures remained significant except for short-term memory, which was just above the significance threshold. The correlations between auditory and visual measures of fine motor control and working memory dropped from moderate-to-strong to weak-to-moderate when covarying for age, SES and sex, but they remained

statistically significant. Finally, stable correlations that did not drop after accounting for socio-demographic variables were found for the measures of attention and scholastic skills, with strong associations for mathematics, English comprehension and attention *d'* and a weak association for attention sensitivity.

Table 6.3
Zero-order and partial correlations (Spearman's r_s and p, unless otherwise stated), between auditory and visual measures of each ability (N = 96).

	Auditory-visual correlations	
Ability	zero-order (*df* = 95)	partial[a] (*df* = 90)
Fine motor control	0.46, <.001	0.26, .012
Attention sensitivity	0.28, .006	0.27, .009
Attention RT	0.60, <.001	0.54, <.001
Short-term memory[b]	0.24 (0.35), .016	0.13 (0.19), .058
Working memory[b]	0.36 (0.52), <.001	0.22 (0.33), .002
Mathematics	0.59, <.001	0.57, <.001
English comprehension	0.57, <.001	0.56, <.001

[a] Covariates: age, SES and sex.
[b] Kendall's τ; in brackets, conversion to Spearman's r_s for comparison with the other correlations (Walker, 2003).

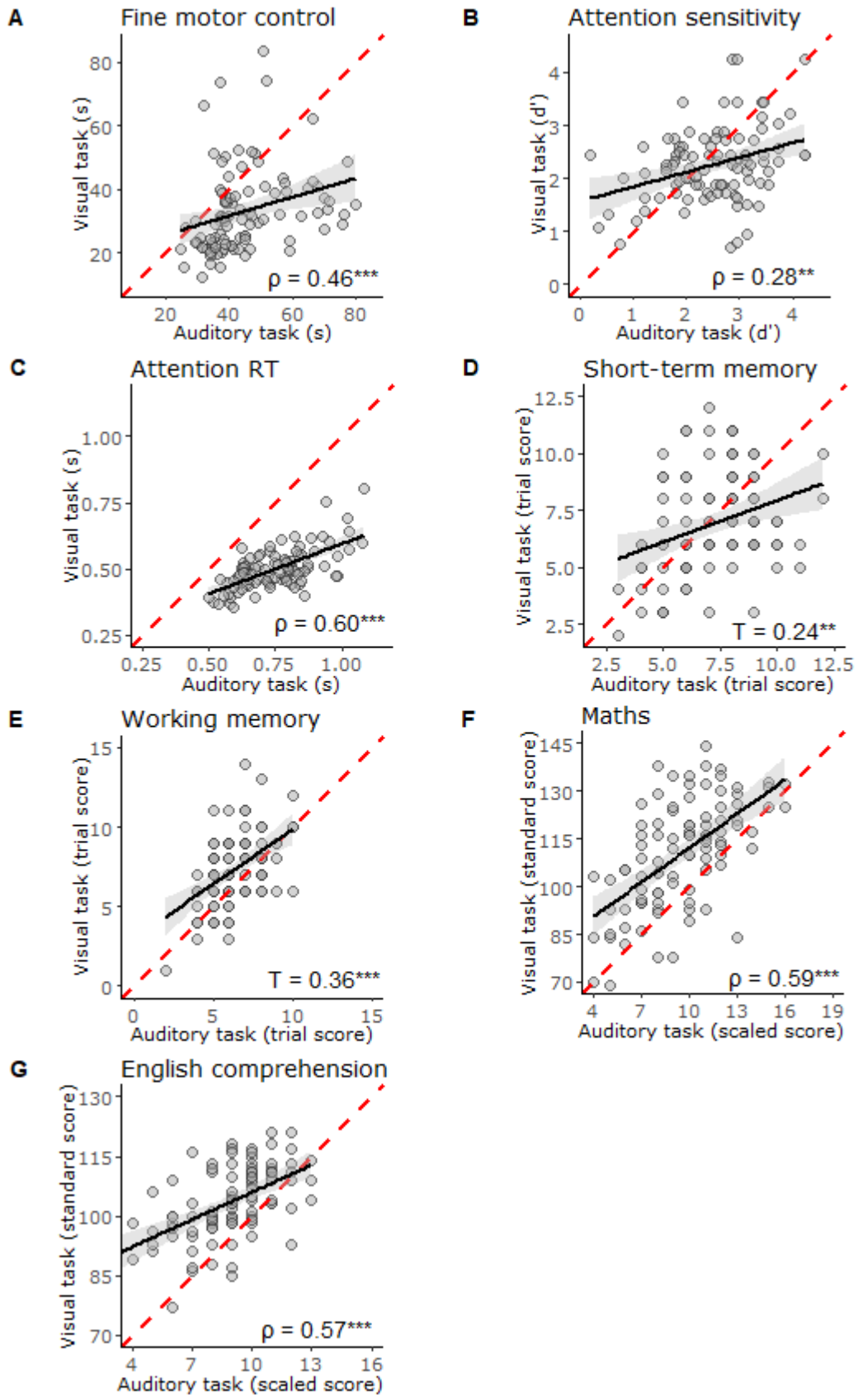


Figure 6.2. Zero-order correlations between auditory (x-axis) and visual (y-axis) task performance for each ability. The red dashed line is the line of equality, indicating perfect agreement between the two measures. The black solid line represents the regression line. ** $p < .01$, *** $p < .001$.

For each pair of auditory and visual measures, a series of linear regressions were conducted to assess whether visual scores could be predicted from the auditory scores, after controlling for sociodemographic variables. Results are reported in Table 6.4. All models were statistically significant and explained 14% to 56% of the variance in the visual task. However, the auditory scores were significant predictors of their visual counterpart for attention RT and sensitivity, working memory, maths ability and English comprehension, but not for short-term memory and fine motor control. Of note, for working memory, the auditory measure was a significant predictor, but inspection of standardised coefficients indicated that age was more important within this model. Age and SES, either alone or in combination, were significant predictors in all models except for attention sensitivity and English comprehension. Sex was not significant in any regression models. One to two outliers (standardised residuals > 3) were identified in the models of fine motor control, attention RT and short-term memory, but examination of Cook's (< 1) and Mahalanobis (< 15) distances ensured their influence on the models was not a reason of concern (Field, 2009).

Table 6.4
Linear regressions of the visual performance on the auditory performance for each ability, whilst controlling for age, SES and sex.

Variables	Model		Coefficients	
	R, R^2, adjusted R^2	*F(df)*	*B (SE B)*	β
Fine motor control	0.52, 0.27, 0.24	8.30 (4, 91)***		
Auditory task			0.07 (0.10)	0.06
Age			-3.12 (0.95)	-0.36**
SES			4.93 (2.75)	0.19^
Sex			1.41 (2.41)	0.05
Attention sensitivity	0.38, 0.14, 0.10	3.74 (4, 91)**		
Auditory task			0.25 (0.08)	0.31**
Age			0.06 (0.05)	0.12
SES			-0.05 (0.16)	-0.04
Sex			0.11 (0.14)	0.08
Attention RT	0.75, 0.56, 0.54	28.45 (4, 91)***		
Auditory task			0.35 (0.05)	0.61***
Age			-0.02 (<0.01)	-0.40***
SES			-0.03 (0.01)	-0.22*
Sex			0.01 (0.01)	0.06
Short-term memory	0.48, 0.23, 0.20	6.83 (4, 91)***		
Auditory task			0.15 (0.12)	0.13
Age			0.59 (0.16)	0.40***
SES			-0.02 (0.48)	< -0.01
Sex			0.30 (0.42)	0.07
Working memory	0.62, 0.39, 0.36	14.29 (4, 91)***		
Auditory task			0.34 (0.14)	0.24*
Age			0.66 (0.16)	0.46***
SES			-0.01 (0.42)	<-0.01
Sex			0.01 (0.37)	< 0.01
Mathematics	0.67, 0.45, 0.42	18.39 (4, 91)***		
Auditory task			3.22 (0.48)	0.54***
Age			2.04 (0.98)	0.18*
SES			-6.15 (3.03)	-0.18*
Sex			1.52 (2.67)	0.05

Note. SES = Socio-economic status; RT = reaction times.
^ not significant $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 6.4 (continued)
Linear regressions of the visual performance on the auditory performance for each ability, whilst controlling for age, SES and sex.

English comprehension	0.58, 0.34, 0.32	11.73 (4, 91)***		
Auditory task			0.44 (0.07)	0.52***
Age			0.05 (0.04)	0.13
SES			-0.15 (0.12)	-0.13
Sex			< -0.01 (0.10)	< -0.01

Note. SES = Socio-economic status; RT = reaction times.
^ not significant $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

6.2.4 Discussion

The purpose of the first part of this chapter was to evaluate the appropriateness of the novel battery of auditory-visual processing tasks developed in this project using a large sample of typically developing children. In particular, the analyses aimed to assess whether the tasks were appropriate for the wide age range of the sample and if each pair of tasks was significantly associated and therefore presumably tapped into the same ability.

Overall, the battery seemed adequate to the wide age range of the sample and sensitive to developmental improvement on task performance. The only measure that showed little age improvement just below the level of significance was the visual go/no-go attention task. This might be due to the ease of this type of task when visual stimuli are employed, which is a known problem in developmental research (Berlin et al., 2004; Mahone, Pillion, & Hiemenz, 2001). Qualitative inspection of descriptive statistics of *d'* and RT measures across modalities suggests that the ease of the visual task in this study led children to give faster responses at the cost of being less accurate, whereas better performance on the auditory task was achieved at the expense of longer reaction times.

This study provides initial proof-of-concept evidence that the visual and auditory tasks developed for this project could be used as equivalent tools in different sensory modalities because significant associations were found for each pair of measures. Even when age and socio-demographic factors were taken into account, the paired auditory and visual measures

remained significantly related for all abilities except for short-term memory. This supports the conceptualisation of children's memory system as structured into two separable short-term memory components, for separately storing verbal and visuospatial materials, and one single working memory component for storing and processing both types of materials (Alloway et al., 2006). For the present model, this implies that strong correlations between visual and auditory measures would also be expected for skills that rely on working memory, such as mathematics and English comprehension, which were indeed found. However, the evaluation of the significant associations for each skill requires the consideration of important differences between various characteristics of the task pairs, especially in relation to the wide age range of the sample used in this project.

On one hand, strong associations were expected for maths and English comprehension, at least in part due to the control of socio-demographic and task characteristics resulting from the standardisation and validation procedures. These correlations remained stable when accounting for socio-demographic variables because age-corrected scores were used. Strong associations were also expected for the attention measures, where mean RT and *d'* provided an average and normalised index of performance, respectively. Arguably, these coefficients did not vary when age, SES and sex were controlled for because the variation due to these factors still referred to the whole attention tasks completed by the children. Instead, the weaker associations found for motor control and the memory tasks might arise from the inherent sensitivity of these tasks to development. Indeed, the fine motor control tasks stopped at the best (fastest) performance of the child, whereas the memory tasks were interrupted when the child was considered no longer able to perform the tasks based on the discontinuity rule. These different discontinuity rules might explain the drop in the correlation magnitude when socio-demographic variables were controlled for, which even led the correlations between auditory and visual short-term memory below the significance level. While it remains difficult to ascertain whether this lack of association was a true dissociation between auditory and visual measures or the effect of the task characteristic aforementioned, it

should be recognised that other developmental studies demonstrated that serial recall of blocks and digits rely on different mental mechanisms (Mammarella & Cornoldi, 2005; Pickering, Gathercole, & Peaker, 1998), and therefore should not be considered analogous tasks of short-term memory.

The results of the regression analyses across sensory modality demonstrated that, for each ability, it was possible to create a model of typical development to predict the visual task scores based on the analogous auditory score as well as sociodemographic predictors in different combinations. Specifically, the auditory scores were the most significant predictors of their visual analogous scores for all abilities except for fine motor control, short-term memory and working memory. This is consistent with the drop of correlation magnitude found after controlling for sociodemographic factors and can be explained by the different developmental trajectories for these skills as discussed above. Notably, most models showed that age and SES were significant predictors, highlighting the importance of considering both sociodemographic factors in this sample. Overall, all models were significant and can be considered clinically relevant, therefore they provide a useful framework to interpret the performance of children with OPG on similar visual and auditory tasks.

In the next part of this chapter, these normative data from typically developing children will be used to evaluate the performance of children with a history of OPG. First, separate models will be created to predict the performance on the experimental tasks based on age. Conversely, standardised scores of scholastic attainments will be examined against the test mean and standard deviation. Then, for the abilities in which the auditory score was the most important predictor of the visual score, additional models were constructed to assess the relationship between visual and auditory scores.

6.3 Part II: visual and auditory processing in children with OPG

6.3.1 Methods

The control group of 96 children used in the first part was used in combination with the patient group of 12 children with a history of OPG who took part in this project. All children completed the auditory-visual processing battery. Of note, the age range of the control group did not fully cover the age range of the patient group and three children were older than the oldest control child (> 11.6 years).

Visual analyses were conducted throughout using *ggplot2* package (Wickham, 2016) in R. A series of graphs plotting age against task performance were constructed for each individual measure, but relevant statistics to interpret the performance of OPG children were different for experimental and standardised measures.

For each experimental task, the normative data obtained from the large control group were used to construct a normative model. Three key elements were displayed: regression line, confidence interval and prediction interval. The regression line represents the line of best fit, which is the linear function that predicts, as accurately as possible, the dependent variable (i.e., task performance) values as a function of the independent variable (i.e., age). The confidence interval is the range that likely contains the mean prediction of the dependent variable at certain values of the independent variable; the prediction interval is the range that likely contains the value of the dependent variable for a single new observation at certain values of the independent variable (Meeker, Hahn, & Escobar, 2017). In other words, the regression line indicates that a child of age *x* would obtain *on average* a score *y*. The 95% confidence interval around the regression line indicates that a child of age *x* would obtain *on average* a score *y* ranging between CI_{low} and CI_{up}. The 95% prediction interval for an individual score would indicate that there is 95% probability that a newly tested child with age *x* would obtain a score *y* between PI_{low} and PI_{up}. A prediction interval is always wider than a confidence interval because it accounts for both the uncertainty in knowing the value of the population mean, plus data scatter (Meeker et

al., 2017). Confidence and prediction limits can be easily displayed on scatterplots using *ggplot2*. Finally, the patient data from sporadic and syndromic OPGs were displayed on the individual scatterplots. If scores of children with OPG fall within the prediction interval, this means that they perform within the normal limits expected for a newly tested control child. Conversely, if scores of children with OPG fall outside the prediction interval, this means that they fall below or above the normal limits expected for a newly tested control child.

For the standardised measures, a series of graphs plotting age against task performance were also displayed. However, because scores were already corrected for age, the mean and standard deviation of the test norms were displayed instead.

Then, for the measures of attention RT and *d'* and for the two scholastic abilities, additional scatterplots were constructed that plotted auditory and visual scores. In this case, the prediction intervals indicated whether the performance on the visual task was within the normal range predicted from the auditory task.

Finally, to assess again the impact of residual sight and time variables, a series of Spearman's r_s correlations were computed between each auditory and visual task with the measures of RNFL thickness and visual acuity in the best eye as well as with age at diagnosis and time after treatment.

6.3.2 Results

Table 6.5 reports the descriptive statistics of visual and auditory tasks of each skill for the patient group.

Table 6.5
Descriptive statistics [M(SD) and min-max] for the patient group.

	Task modality	
Skill	Auditory	Visual
Fine motor control	40.73 (9.49)	33.58 (12.19)
	29.50–65.75	17.25–59.00
Attention RT	0.68 (0.11)	0.46 (0.07)
	0.50–0.90	0.40–0.61
Attention sensitivity	2.73 (0.74)	2.45 (0.44)
	1.56– 3.79	1.93–3.43
Short–term memory	5.92 (1.68)	6.75 (2.18)
	3–9	2–10
Working memory	5.75 (0.87)	7.42 (2.71)
	4–7	3–12
Mathematics	8.50 (2.28)	100.58 (21.72)
	4–12	63–137
English comprehension	8.08 (1.98)	92.58 (13.58)
	5–12	71–110

Figure 6.3 displays the age-by-task scatterplots for outcome measures of each ability. Computation of regression line and prediction limits based on the control group was extended beyond the range of control data so as to include also the older OPG children. The vertical alignment of the plots, with auditory tasks at the top and visual tasks at the bottom, makes possible to easily capture whether the same child performs within or outside the prediction limits on the two tasks. Table 6.6 also provides a summary of children falling outside the prediction interval in each task.

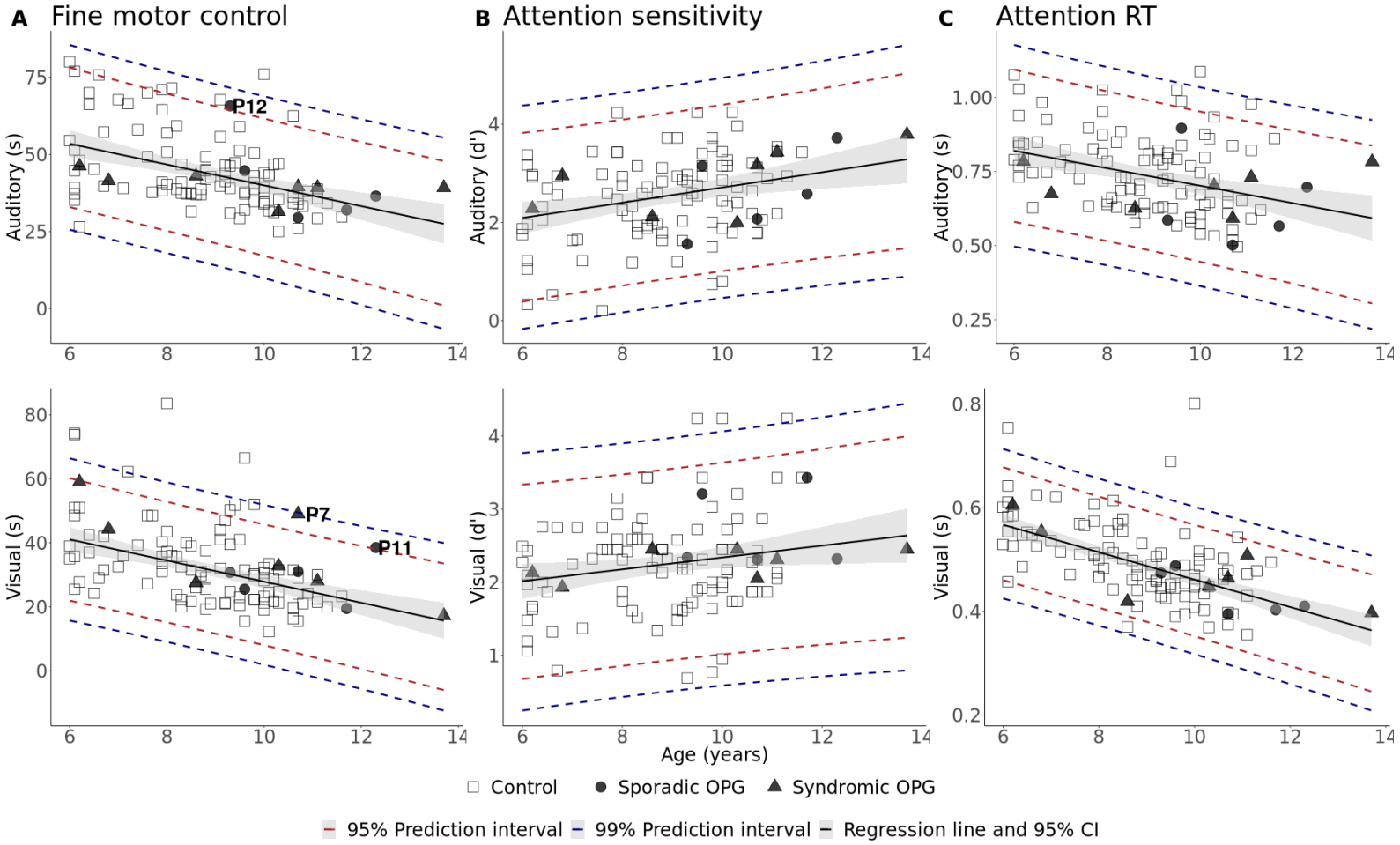


Figure 6.3. Scatterplot of age by task for each ability. Regression and prediction limits are based on controls. Labels indicate patients falling beyond the 95% prediction limits (for experimental tasks) or the normal range (for standardised tests).

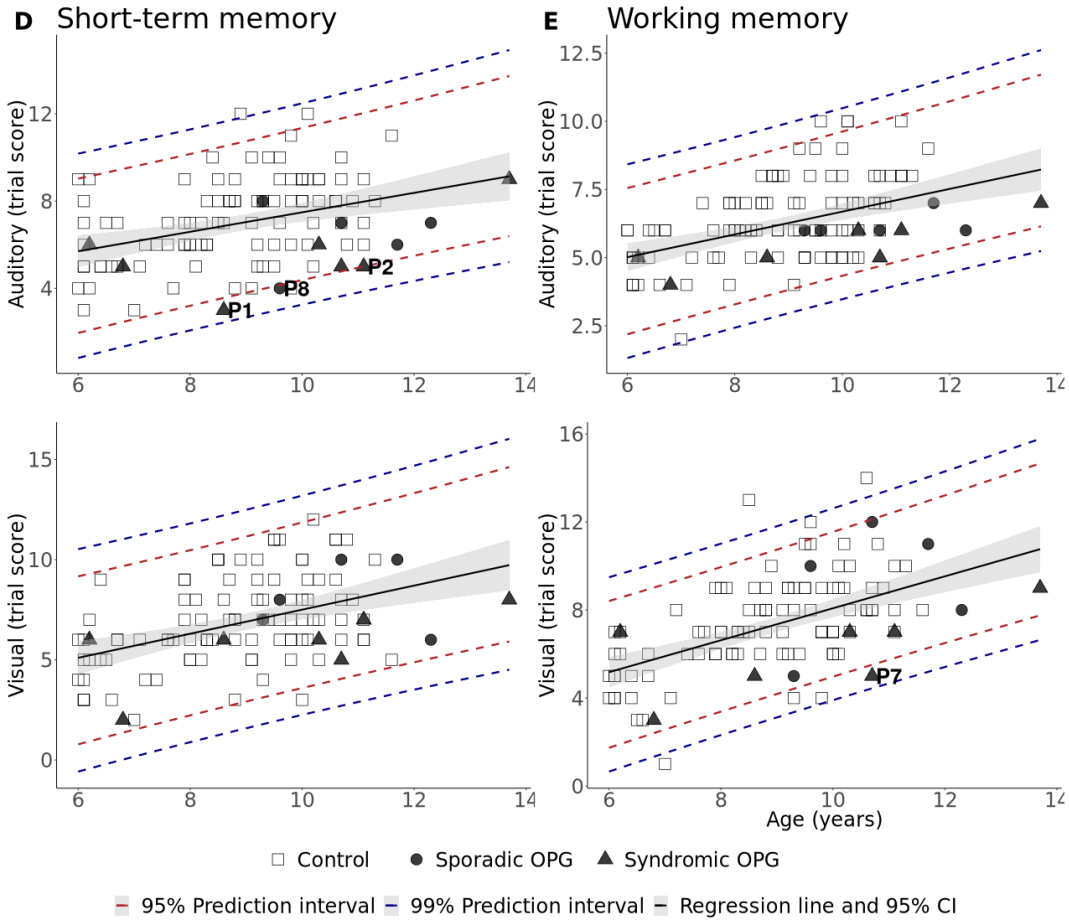


Figure 6.3 (continued). Scatterplots of age-by-task for each ability. Regression and prediction limits are based on controls. Labels indicate patients falling beyond the 95% prediction limits (for experimental tasks) or the normal range (for standardised tests).

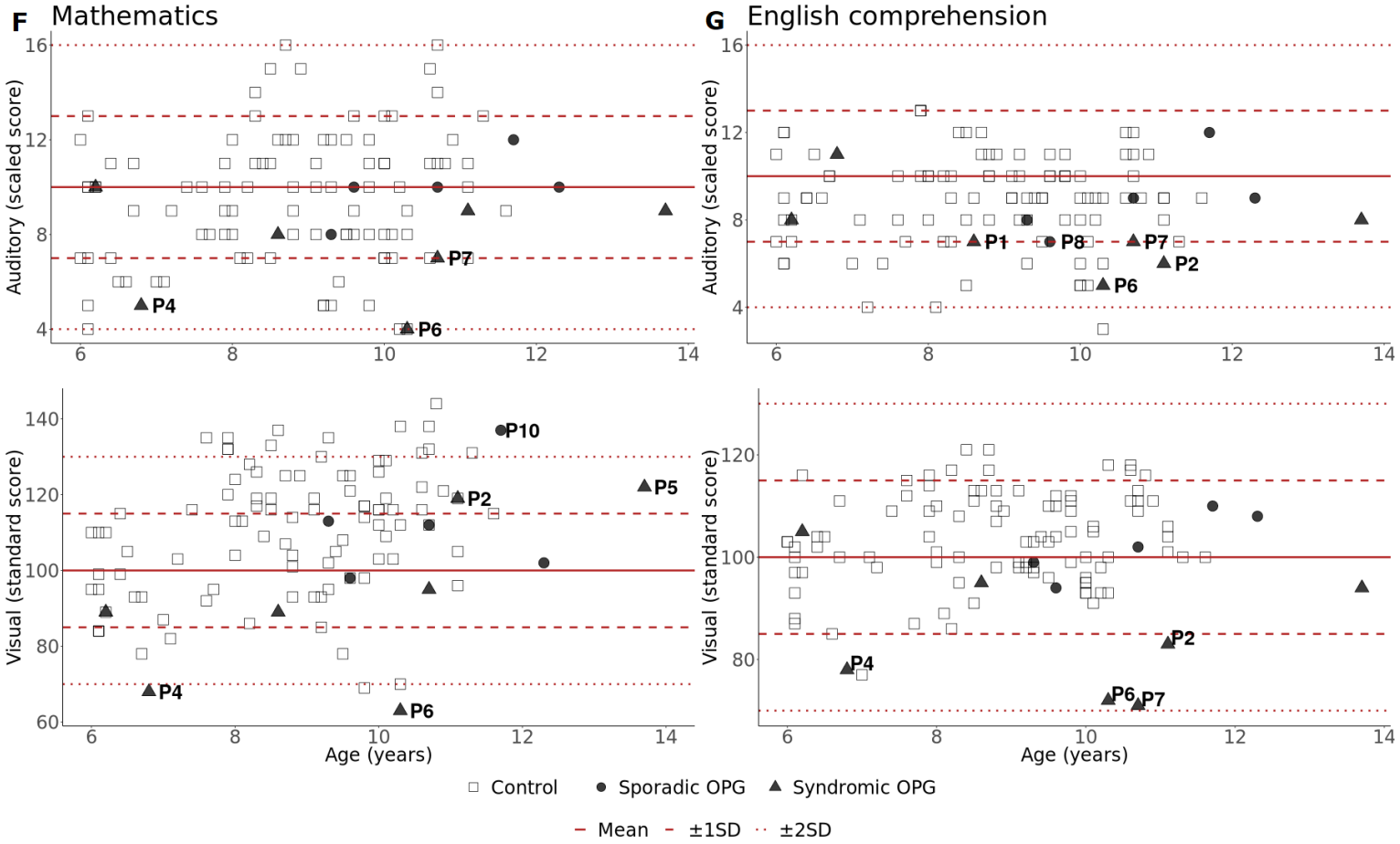


Figure 6.3 (continued). Scatterplots of age-by-task for each ability. Regression and prediction limits are based on controls. Labels indicate patients falling beyond the 95% prediction limits (for experimental tasks) or the normal range (for standardised tests).

Table 6.6
IDs of sporadic and syndromic cases falling outside the 95% prediction interval.

	Auditory task		Visual task	
Skill	sporadic	syndromic	sporadic	syndromic
Fine motor control	P12	/	P11	P7
Attention RT	/	/	/	/
Attention sensitivity	/	/	/	/
Short–term memory	P8	P1, P2	/	/
Working memory	/	/	/	P7
Mathematics	/	P4, P6, P7	P10*	P2*, P5*
English comprehension	P8	P1, P2, P6, P7	/	P2, P4, P6, P7

Note. Asterisk indicates children falling above the 95% prediction interval, therefore performing above the level expected for age.

For fine motor control (Figure 6.3A), one child (sporadic P12) fell above the 95% PI_{up} on the auditory task, but was within the PI on the visual task; conversely, two children who had normal performance on the auditory task fell above (syndromic P7 and sporadic P11) or around (syndromic P3) the 95% PI_{up} on the visual task. These children took longer or tended to take longer than expected to complete the speeded tasks of fine motor control. On both attention sensitivity (Figure 6.3B) and reaction times (Figure 6.3C), all OPG children were within the 95% PI and scores were roughly equally distributed above and below the mean prediction. On memory measures (Figure 6.3D and Figure 6.3E), scores of both auditory tasks tended to fall below the mean prediction. Specifically, three children (sporadic P8 and syndromic P1 and P2) fell below the 95% PI_{low} on auditory short-term memory (syndromic P7 was just around), but they were within the normal range on the visual task. On working memory, no OPG children fell below the 95% PI_{low} on the auditory task, although all scores were below the regression line; on the visual task, one syndromic case P7 fell below the 95% PI_{low} and sporadic case P9 tended to fall above the 95% PI_{up}.

On scholastic abilities (Figure 6.3F and Figure 6.3G), only children with NF1 fell more than 1 standard deviation below the test mean in either task modality. On mathematics, P4 and P6 fell at least 1 standard

deviation below the test norm on both tasks, whereas syndromic P7 underperformed only on the auditory task. Of note, two children with syndromic OPG (P2 and P5) scored 1 standard deviation above the mean and one child with sporadic OPG (P10) scored even 2 standard deviations above the mean. On English comprehension, NF1 children P2, P6 and P7 fell 1 standard deviation below the test mean on both auditory and visual tasks. Syndromic P4 also fell below 1 standard deviation on the visual task but had normal performance on the auditory task; non-NF1 child P5 and NF1 child P1 performed one standard deviation below the test mean.

Figure 6.4 displays the scatterplot of visual and auditory scores for the measures of attention and scholastic abilities. On both attention measures (RT and sensitivity) and maths, all scores of OPG children fell within the prediction limits based on the control group. On English comprehension, three children with NF1 (P4, P6 and P7) fell outside the prediction interval, indicating that their score on the visual task of English comprehension was below the score predicted on the basis of the auditory task.

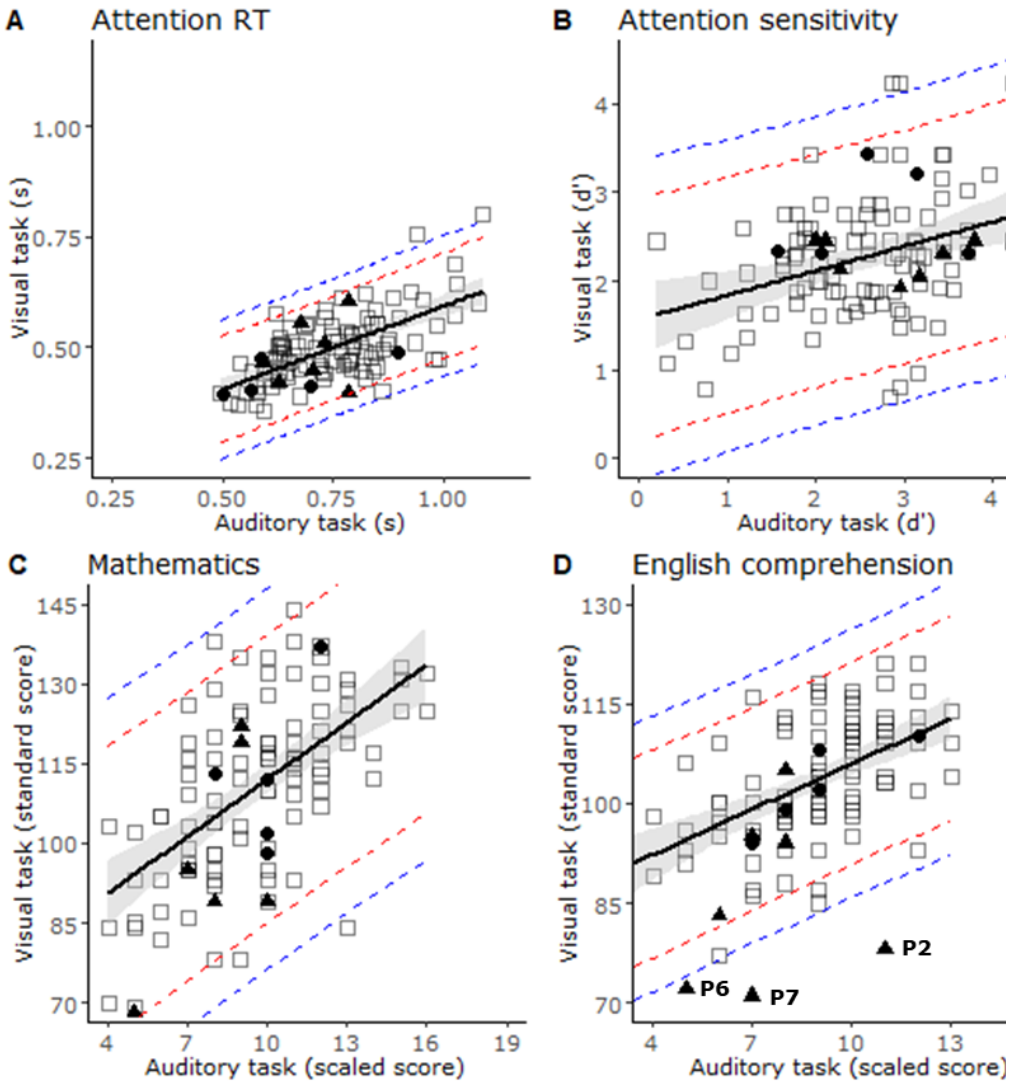


Figure 6.4. Scatterplot of auditory and visual scores for the measures of attention (sensitivity and reaction times) scholastic abilities (mathematics and English comprehension). Red and blue lines indicate 95% and 99% prediction limits, respectively.

The associations between each task and the measures of RNFL thickness and visual acuity in the best eye are reported in Table 6.7. There were significant strong correlations between the two measures taken from the best eye and reaction times on the auditory task of attention, with a positive correlation for RNFL thickness and negative correlation for visual acuity. These associations indicated that more severe damage to the RNFL and poorer visual acuity in the best eye were associated with faster responses on the attention task with auditory stimuli.

Table 6.7
Correlations (Spearman's r_s and p values) of each task with RNFL thickness and visual acuity in the best eye.

	RNFL thickness		Visual acuity	
Skill	Auditory	Visual	Auditory	Visual
Fine motor control	0.11, .737	-0.15, .633	-0.10, .757	0.13, .688
Attention RT	**0.73, .007**	0.05, .880	**-0.76, .004**	-0.24, .456
Attention sensitivity	0.14, .665	0.20, .531	-0.12, .712	-.17, .598
Short–term memory	-0.15, .651	0.12, .723	0.30, .339	-0.11, .739
Working memory	0.02, .944	0.26, .410	0.01, .972	-0.24, .456
Mathematics	0.03, .930	-0.26, .416	-0.04, .899	0.27, .402
English comprehension	-0.54, .072	-0.24, .463	0.56, .057	0.29, .355

Note. Significant results highlighted in bold.

The associations between each task and the time variables of age at diagnosis and time post treatment are reported in Table 6.8. Longer time after treatment was strongly correlated with higher scores on auditory working memory. There were also trends towards significant positive associations for auditory short-term memory with both age at diagnosis and time post-treatment as well as between visual maths and time after treatment.

Table 6.8
Correlations (Spearman's r_s and p values) of each task with time variables (age at diagnosis and time post treatment).

	Age at diagnosis		Time post treatment	
Skill	Auditory	Visual	Auditory	Visual
Fine motor control	0.30, .340	-0.30, .352	-0.28, .372	-0.27, .391
Attention RT	-0.48, .119	0.14, .662	0.31, .324	0.30, .345
Attention sensitivity	0.03, .992	0.15, .633	0.37, .236	0.36, .246
Short–term memory	-0.57, .053	0.05, .868	0.55, .061	0.21, .517
Working memory	-0.22, .493	-0.02, .956	**0.69, .014**	0.24, .450
Mathematics	0.05, .873	-0.23, .482	0.17, .602	0.53, .075
English comprehension	-0.31, .321	-0.09, .778	0.19, .565	0.20, .534

Note. Significant results highlighted in bold.

6.3.3 Discussion

The purpose of the second part of this chapter was to evaluate the performance of children with OPG on the novel battery of auditory-visual processing tasks developed in this project in comparison to normative models based on the large sample of typically developing children.

Overall, children with OPG do not display any obvious pattern of underperformance either in the visual domain or in the auditory domain on the tasks of fine motor control, attention and memory. This demonstrates that children with OPG do not compensate or hyper-compensate with auditory abilities like children with retinoblastoma (Brinkman et al., 2015; Levitt et al., 1972) but develop overall in line with the other children.

On the domain of fine motor control, it was not surprising that the three children (2 sporadic and 1 syndromic OPGs) with performance below the expected level had severe visual impairment. The slower performance of these children is in line with previous evidence of slower finger tapping speed in children with NF1 (Billingsley, Slopis, Swank, Jackson, & Moore III, 2003) and poor fine motor skills problems with visually impaired children (Bouchard & Tétreault, 2000), but it suggests that poor vision might impact on developmental areas not closely related to vision such as speech articulation. Lowered individual scores on short-term memory suggest that this domain is particularly at risk for these children, as already shown using the broader standardised index in Chapter 4 and Chapter 5. This further demonstrates that auditory memory is not a strength in children with OPG as it was found for retinoblastoma survivors (Brinkman et al., 2015; Levitt et al., 1972).

On scholastic abilities, however, there is an evident pattern of underperformance for children with syndromic OPG, and most scored below the norm on either listening or reading comprehension as well as auditory maths. Instead, written mathematics was found to be a strength in 3 children, 2 of which had NF1. Overall, these results are in line with the NF1 literature, which highlights the high frequency of reading and learning disability in this population (Cutting & Levine, 2010; Hyman et al., 2006). While most research focused on reading disability and some studies reported problems in expressive but not receptive language

(Lehtonen et al., 2013), the current data suggest that language comprehension is an area of difficulty for these children, with three children (P2, P6 and P7) consistently below the expected level of performance on both auditory and visual tasks.

The associations of RNFL-t and VA with reaction times of attention suggested that there might be some compensatory mechanisms involving attention in children with OPG, as already suggested in similar groups of patients with a tumour in the retina (Brinkman et al., 2015; Ek et al., 2002). This is a promising result for children with OPG, especially in light of the impairment in auditory memory found in this and the previous chapters. This suggests that auditory compensation occurs in children with poor vision due to an OPG. Compensatory techniques involving auditory attention, memory and concentration were hypothesised to explain the superior performance of blind and visually impaired patients treated for retinoblastoma (Brinkman et al., 2015; Ek et al., 2002; Levitt et al., 1972). However, while retinoblastoma patients exhibited superior auditory cognitive skills, children with OPG in this study showed lowered scores on working memory. This suggests that the compensatory auditory mechanism does not enable them to achieve adequate performance. Therefore, caution should be used at considering the hearing system as an alternative sensory system to convey information for children with OPG, for example in the school setting.

The associations between the time variables further suggest that the auditory memory is sensitive to the tumour history. The positive association (or trend) suggests that children who were diagnosed early in life develop greater auditory short-term memory capacity and that longer time of recovery results in better auditory working memory performance. While most studies on childhood brain tumours demonstrate that younger age at diagnosis is associated with worse neurocognitive outcomes (Aarsen et al., 2009; Armstrong et al., 2011), this study aligns with the results of retinoblastoma patients (Brinkman et al., 2015) and non-oncology research (Merabet & Pascual-Leone, 2010) which demonstrates that early sensory deprivation offers greater opportunity to change and adapt to sight loss. The effect of time post treatment might instead be attributed to the recovery from the hearing loss effect possibly resulting

from the chemotherapy (Aydogdu et al., 2000; Sleurs et al., 2016). Unfortunately, information about hearing conditions were not available for the study participants to verify any history of hearing problems from clinical records. Finally, potential recovery after treatment tended also to impact on vision tasks and in particular on maths ability, which is related to visuospatial abilities in typical development (Allen, Higgins, & Adams, 2019). This is also promising as it indicates that recovery after the tumour can lead to adequate or even superior performance, since some of the children (both with and without NF1) scored above the level expected for their age on this task. Overall, these results suggest that potential vision loss due to OPG does not result in downstream effects on visual abilities and compensatory auditory strategies, but more complex relationships exist.

Overall, this study demonstrated the potential utility of this novel auditory-visual processing battery to assess the same abilities using analogous tasks that rely on different sensory modalities. In addition, it shows the variability exhibited by children with OPG who do not necessarily underperform in a certain domain or in visual tasks. Overall, NF1 patients tended to exhibit more difficulties than cases of sporadic OPG.

Chapter 7 General discussion

This thesis investigated the developmental outcomes of a group of 12 patients with optic pathway glioma, a type of low-grade tumour that has high survival rates but also poses high risk of visual problems. While a great deal of neuro-ophthalmology research focuses on tumour management and the preservation of vision loss, little is known about neuropsychological development beyond sight in the chemotherapy era. To address the limited knowledge in the area, this thesis reports an in-depth examination of visual perception, cognitive and scholastic abilities, as well as ophthalmic measures of vision, in a small sample of children with OPG.

7.1 Summary and critical evaluation of the results

To summarise and critically evaluate the results reported in this thesis, the following section will be organised into two parts. First, the results of Chapters 3, 4 and 5 will be discussed in relation to Colenbrander's (2003) model and the hierarchical approach adopted in this thesis. Then, the results of Chapter 6 about the relationship between visual and auditory processing will be discussed.

7.1.1 Part I: A hierarchical model to assess visual and neuropsychological outcomes following OPG

7.1.1.1 Vision and visual perception

The aim of Chapter 3 was to concurrently examine the extent of impairment following OPG based on ophthalmology measures, namely retinal nerve fiber layer (RNFL) thickness and visual acuity (VA), and neuropsychological measures of visual perception. A new method to concurrently analyse the level of deficit on these outcomes was tested that involved the analyses of group means and individual scores in relation to normative data. Results showed a consistent impairment at group level on all the outcomes, suggesting that vision problems following OPG extend beyond the sequelae assessed with traditional ophthalmic examination and also affect the ability to process asemantic

visual stimuli in real life. The structural damage to the visual pathway was consistent, whereas variability was found on visual acuity in the best eye. Motor and non-motor abilities of visual perception were similarly affected and depressed after a diagnosis of OPG, but some children were specifically at risk of underperformance. The increase of variability of normal and abnormal individual scores from the structural level (RNFL thickness) to the functional levels (visual acuity and visual perception) of analysis indicates the need for identifying objective measures of vision in these patients.

7.1.1.2 Cognitive and scholastic outcomes

The aim of Chapter 4 was to investigate the degree of deficit on cognitive and scholastic abilities exhibited by children with OPG. The statistical results based on group average data demonstrated that core reasoning skills developed in line with age expected levels, whereas cognitive proficiency measures of working memory and motor speed were lower than expected for age. On the scholastic domains, maths and reading abilities were adequate for the age, but oral and written language were mildly affected. This suggests that, although OPG is a relatively favourable tumour in terms of survival, these patients can experience long-term adverse cognitive outcomes, even in developmental areas that are not directly related to vision. Problems of attention, working memory and processing speed are consistently found to be impaired among survivors of childhood brain cancer (Kahalley et al., 2013; Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013) and are possibly responsible for the slow rate of cognitive and scholastic development in these survivors (Roddy & Mueller, 2016). These results in children with OPG further suggest that the cognitive skills of motor speed and verbal working memory are the most at risk in childhood cancer survivors and might be responsible for the mild impairment in written and oral language seen in this sample, as suggested by the association between cognitive and scholastic outcomes (Chapter 5). Overall, these results suggest that mild cascade effects at the neuropsychological level might occur in children who have OPG, but these would be limited to domains of cognitive proficiency and scholastic domains of oral and written language.

While group average results suggest general guidelines by indicating areas at risk for children with OPG, it is worth noting that analyses of individual cases are quite encouraging since more than half of the patients scored at least within the normal range in cognitive and scholastic tasks. Therefore, although mild difficulties across patients lead to statistically significant group effects, only a minority of children are at risk of below-average performance.

7.1.1.3 Impact of clinical predictors

The aim of Chapter 5 was to study relevant prognostic factors which may impact upon visual and neuropsychological outcomes in this patient group, including NF1 co-diagnosis, vision loss, posterior extension of the tumour, age at diagnosis, time after treatment, and socio-demographic factors. The results showed that children who had OPG early in life had poor sight in the best eye, and that poor vision across the two eyes was associated with low scores on cognitive and scholastic measures that relied on sight. This suggests that vision loss acts on some cognitive and scholastic skills, such as conceptual reasoning, motor speed and writing, which are inherently associated with vision. Because young children rarely complain about vision problems (Dodgshun et al., 2015; King et al., 2003) and are difficult to test with visual acuity examination (Avery et al., 2013), the current results further indicate that early detection of vision problems is needed with these patients to avoid irreparable damage to the visual system and its development as well as cascade effects on other vision-related neuropsychological domains.

In addition, although it was not possible to establish the negative effect of the NF1 co-diagnosis possibly because of the small sample, consistent patterns of lowered performance compared to the test norms were found for this subgroup on all domains. While such perceptual and cognitive difficulties fit with the neuropsychological profile associated with NF1, the data from this cohort indicate the complex relationship between NF1 status and vision. The follow-up analyses suggested that group effects in the visual perception domain were specifically driven by the NF1 subgroup, as expected (Bulgheroni et al., 2019; Van Eylen et al., 2017). Although participants with NF1 had more favourable visual acuity than those without NF1 at group and individual level, performance of

these children was significantly below the norms on the visual perception indices. Difficulties in visual perception are well established among NF1 and particularly marked in those with learning disability (Cutting & Levine, 2010), but these neuropsychological studies on NF1 exclude children with OPG due to visual impairment and/or neurological abnormalities as potential confounders, leaving this group of patients understudied.

7.1.1.4 Case-by-case considerations

Further considerations about the relationship between vision and NF1 co-diagnosis, as well as between low-level vision, mid-level visual perception, and high-level cognitive and scholastic functioning can now be better discussed with case-by-base considerations. For this purpose, Table 7.1 summarises key socio-demographic and medical variables as well as categorised individual scores of the sample.

Table 7.1

Individual profiles of neuropsychological performance of the study participants on individual and composite indices; group statistics (M and SD) compared to test norms given below.

						Visual perception			Cognitive function						Scholastic attainment				
Case	NF1	Sex	Age at diagnosis	Vision	Aid	MRP	VMI	GVP	VC	PR	WM	PS	FSIQ	GA	R	M	WL	OL	TC
P1	Yes	M		Normal	No	A	A	A	A	A	–	A	A	A	A	A	–	A	–
P2	Yes	M		M – Normal	No	– –	– –	– –	A	A	–	A	A	A	A	+	A	A	A
P3	Yes	F		Normal	No	A	A	A	A	A	A	A	A	A	A	A	A	A	A
P4	Yes	F		Severe VI	Yes	–	– –	– –	A	– –	–	– –	– –	–	n. a.	– –	– –	–	n. a.
P5	Yes	M		Normal	No	–	– –	–	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.
P6	Yes	M	[Data removed for anonymity]	Normal	No	A	A	A	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.
P7	Yes	F		Moderate VI	Yes	– –	–	–	– –	A	–	–	–	–	–	–	–	– –	–
P8	No	M		M – Normal	No	A	A	A	–	+	A	A	A	A	A	A	A	–	A
P9	No	F		Mild VI	No	A	A	A	A	A	A	A	A	A	A	A	A	A	A
P10	No	M		Severe VI	Yes	–	– –	– –	+	A	A	A	A	A	A	+ +	A	A	+
P11	No	M		Severe VI	Yes	–	– –	– –	A	A	A	– –	A	A	A	A	–	A	A
P12	No	F		Severe VI	Yes	A	A	A	A	–	A	A	–	–	A	A	A	–	A
M						87.4*	83.5*	84.5*	91.5	95.5	85.4*	87.5*	88.2*	93.0	96.1	98.8	89.0*	88.5*	93.9
SD						14.0	17.8	15.8	13.7	16.9	8.9	15.0	11.3	11.8	11.7	18.6	13.5	14.2	12.3

Note. MRP = Motor-reduced perception; VMI = visual-motor integration; GVP = general visual perception; VC = verbal comprehension; PR = perceptual reasoning; WM = working memory; PS = processing speed; FSIQ = full-scale IQ; GA = general ability; R = reading; M = mathematics; WL = written language; OL = oral language; TC = total composite; VI = visual impairment; M = monocular vision.
Scores: "A" = between +1 and -1 *SD*; "–" = between -1 and -2 *SD*.; "– –" = below -2 *SD*.; "+" = between +1 and +2 *SD*; "+ +" = above +2 *SD*; "n. t." = not tested; "n. a." = not available.

First, in relation to the cumulative effect of NF1 and vision loss, it can be seen that the NF1 participant P7, with the youngest age at diagnosis (0.7 years) of the total cohort, demonstrated not only moderate visual impairment, but also consistent deficits across all but one of the developmental domains examined. Likewise, NF1 participant P4 who was diagnosed at the age of 2.8 years shows severe impairment across almost all areas of perception, cognition and scholastic attainment. Instead, P1 and P2 who were older at diagnosis performed overall well, at least in terms of intellectual functioning and scholastic progression.

A gender trend also emerges from these data, as P4 and P7 were girls, whereas P1 and P2 were boys. Unfortunately, data from P5 and P6 were limited to the domain of visual perception due to study drop out, so their pattern cannot be discussed. However, the individual patterns align with the evidence suggesting the occurrence of more symptomatic and progressive OPG for girls with NF1 which would require treatment (Diggs-Andrews et al., 2014) and may in turn lead to poor long-term visual outcomes (Tow et al., 2003). This suggests that a cumulative effect may occur in some children with NF1 and OPG, especially girls. Cognitive deterioration after chemotherapy was also described in NF1 patients with poor vision in a previous case series, although the gender of the patient was not reported (Riva et al., 2009).

Table 7.1 also demonstrates that visuo-perceptual problems may be specific for NF1 children and independent from low vision. For example, P5 and P6 were both male, with normal vision, NF1 and similar age at diagnosis, but only P6 had visuo-perceptual difficulties. Moreover, both P2 (syndromic) and P8 (sporadic) had monocular vision, but only P2 underperformed on the developmental test of perception whereas scores of P8 were within the test norms. In addition, P2 (with NF1) as well as P10 and P11 (without NF1) showed also that visuo-perceptual difficulties can be relatively independent from the other neuropsychological domains, since these patients performed overall within the average or above on cognitive and scholastic tests. Overall, these discrepancies at the individual level do not provide support to Colenbrander's (2003)

model (*Figure 1.5.* Aspects of vision and vision loss following paediatric OPG. Adapted from "Aspects of vision loss – visual functions and functional vision" by A. Colenbrander, 2003, *Visual Impairment Research*, *5,* p. 116. Copyright 2003 by Taylor & Francis.Figure 1.5) as difficulties on low-level domains (on the left) do not always lead to difficulties to high-level domains (on the right). This will be further discussed in the next section.

Finally, some considerations should be made in relation to the use of low vision aids for children with the most severe visual impairment and for the different adaptation for motor and non-motor tasks. Whilst it was not possible to control for the level of adaptation with personal devices for low vision, inspection of Table 7.1 shows that the three children without NF1 who used low vision aids managed to obtain several scores on scholastic and academic abilities within the norms, although some difficulties continue to emerge on visual perception. Instead, the two children with NF1 who used low vision aids underperformed throughout the assessment. This is to some extent in line with the idea that traditional low vision aids can successfully address the forefront input problems of ocular visual impairments (Baker-Nobles & Rutherford, 1995) as it was hypothesised for the children without NF1, but not the complex visuospatial processing problems like cerebral visual impairment exhibited by children with NF1 (Baker-Nobles & Rutherford, 1995). In addition, when focusing only on the visuoperceptual domain, the 4 participants with greater difficulties (< -2 *SD*) were half with and half without NF1, suggesting that these two subgroups are equally at risk of such impairments. However, the only child (P2) who showed such hampered performance in spite of an adequate vision (not requiring low vision aids) had the NF1 co-diagnosis. While the potentially beneficial effect of low vision aids remains a speculation that cannot be verified and this limitation will be later discussed (see section 7.2.2 below), this study attempted to systematically adjust and control the available tools in order to assess a group of patients typically neglected. While neuropsychological research on brain tumour survivors excludes children with NF1 (e.g., Aarsen et al., 2009, 2006) and neuropsychological research on NF1 excludes children with OPG (Hyman et al., 2005; Van

Eylen et al., 2017), greater attention is necessary for these understudied patients that are at high risk of severe developmental problems. Given the possibility to control and monitor NF1-related OPGs and potentially use visual and neuropsychological measures before and after the tumour onset (e.g., Diggs-Andrews et al., 2014), research on OPG progression should adopt a more comprehensive approach to identify young children at risk of such a snowball effect.

7.1.1.5 A critique to Colenbrander's model

Collectively, in relation to Colenbrander's (2003) model, the results of Chapters 3, 4 and 5 suggest that at the group level there is not an overall negative cascade effect from the structural damage to the optic pathway to the high-level neuropsychological functioning of the child. Therefore, the current results do not support Colenbrander's (2003) model (*Figure 1.5.* Aspects of vision and vision loss following paediatric OPG. Adapted from "Aspects of vision loss – visual functions and functional vision" by A. Colenbrander, 2003, *Visual Impairment Research*, *5,* p. 116. Copyright 2003 by Taylor & Francis.Figure 1.5) of individual consequence of structural and functional vision deficits. While children with OPG might exhibit a clinically relevant damage in the optic pathway, this results in highly variable VA scores, hampered development of visual perception (with consistent scores within or below the average range across specific skills), and overall adequate level of cognitive and academic performance (with only specific areas of weakness, not strictly related to vision). Therefore, the detrimental sequelae are more prominent in the domain of vision and then visual perception, which relates to a-symbolic aspects of visual processing (Hammill, 1978), than on high-level functions. Indeed, when semantic aspects are added to visual stimuli and high-level nonvisual abilities are also assessed, the overall performance becomes adequate at group level and less variable (e.g., overall adequate perceptual reasoning). The age-appropriate core reasoning skills might sustain the overall adequate school achievement. Nonetheless, specific areas at risk persist in both cognitive and educational domains, with severe deficits (< -2 *SD*) reported only in a minority of the children. In addition, the lack of association for the visuo-

perceptual domain with cognitive and scholastic development further supports the dissociations between low-level visual perception and high-level cognition, with no evident cascade effects at least on the core cognitive skills and the domain of reading and maths.

Taken together, these results indicate the modern chemotherapy approach to treatment of OPG overall protects the high-level neural development of children with OPG (Silva et al., 2000) but potentially at the expense of visual and visuo-perceptual difficulties (Awdeh et al., 2012). Further investigation is needed in future to disentangle the unique role of structural damage to the optic pathway, functional deficits of VA and visual perception, especially in NF1 children, in order to identify children at risk of progressive visual and cognitive deterioration. Overall, Colenbrander's (2003) model is useful to systematically differentiate vision-related outcomes in a multilevel system, but a strict downstream cause-effect relationship across domains was not found for children with OPG. Group results across multiple levels demonstrated, to a certain extent, some of these relationships for specific skills (for example, among visual acuity, processing speed and written language), but they also showed a dissociation between the broad domains of low-level visual perception and high-level cognitive functioning and academic attainment. In addition, a case-by-case examination demonstrated inconsistent patterns of functioning in the current sample: some children with vision loss achieved neuropsychological scores in line with the level expected for their age, whereas others with intact sight showed difficulties on visuo-perceptual but not on cognitive and academic skills. . Therefore, the current findings generally do not support the model proposed by Colenbrander (2003).

Nonetheless, the concurrent examination of these multiple outcome measures enabled a broader understanding of the neuropsychological sequelae of OPG, which can be summarised into three key points. First, OPG is overall not associated with cognitive and academic sequelae, with only few specific domains at risk; second, visual-perceptual abilities are not associated with cognitive and scholastic outcomes; third, both NF1 and non-NF1 survivors are potentially at risk of cerebral visual impairment, that is a set of complex visuo-perceptual

difficulties. These findings did not emerge from the previous limited studies in the literature (Lacaze et al., 2003; Riva et al., 2009) so this thesis adds to the current knowledge of the neuropsychological consequences of OPG in childhood.

7.1.2 Part II: Visual and auditory processing

The aim of Chapter 6 was to study the performance of the same group of young OPG survivors on the assessment of fine motor skills, attention, short-term and working memory, maths and English comprehension using a series of analogous tests in the visual and auditory modalities. A normative sample of typically developing children was also examined on the same tests to provide normative models of development in these domains.

The results demonstrated that children with OPG performed overall within the level expected for their age on both visual and auditory domains on the measures of scholastic predictors, although some difficulties in fine motor skills and auditory short-term and working memory were found, in line with the results of the standardised assessments reported in Chapter 3 and Chapter 4. Three patients with NF1 out of 7 showed scholastic problems on specific tests of both maths and English comprehension, in line with the prevalence of learning disabilities reported in the NF1 population (Hyman et al., 2006; Orraca-Castillo et al., 2014). Instead, only one non-NF1 patient performed just below the level expected for the age. Of note, two of these three NF1 patients (P4 and P7) were also found to have cerebral visual impairment through the standardised assessment.

No superior performance in the auditory modality was found overall, although poor vision in the best eye was associated with fast reaction times in the auditory attention tasks. This suggests that compensatory mechanisms may occur in children with OPG and these result in adequate but not superior auditory performance. However, because specific difficulties in verbal working memory and oral expressive language were identified in the previous chapters, the auditory domain should not be considered a compensatory sensory channel to be used to support children with OPG.

7.2 Limitations

Concerns about the participant samples and measures used may limit the findings of this thesis and these are discussed below.

7.2.1 Sample size

The main limitation is the small patient sample recruited in this project, a common problem in single-centre studies in oncology research (e.g., Davis, Pitchford, Jaspan, McArthur, & Walker, 2011). This problem first reflects the rarity of OPG in childhood. Although astrocytoma glioma is the most common (~ 40%) of all childhood solid tumours (National Cancer Registration and Analysis Service, 2018), incidence is low. UK statistics (2001-2010) for astrocytoma in the optic nerve estimate 3.2 cases a year per million children aged 0-14 years (Stiller, Bayne, Chakrabarty, Kenny, & Chumas, 2019). After the shift to the neuropsychological assessment of cognitive sequelae, research on childhood brain tumour has progressively become more focused on region-specific effects (Tonning Olsson, 2015). In line with this trend, the current thesis represents a preliminary investigation to document the vision-specific sequelae of OPGs, due to their anatomical locations in the optic pathway. Statistical analyses sometimes failed to reach significance arguably because of the small sample, but the direction of the effects was found in line with previous results, supporting the conclusions from this study. To replicate the study with the experimental tasks, on which healthy children obtained an average visual-auditory correlation of about .40, a power analysis in G*Power 3.1.9.2 (Faul et al., 2007) estimated that a total sample of 44 would be necessary to detect similar correlations in children with OPG, assuming a two-tailed hypothesis, P = .05 and power 80%. Along with larger samples, future study should involve a detailed ophthalmology and visuo-perceptual examinations, given the complex associations and dissociations found among visual domains in the current study. Finally, separate investigations for NF1 and non-NF1 patients should be conducted in future in order to understand the impact of poor vision in these two subgroups.

7.2.2 Assessment for visually impaired children

Another limitation of this thesis is related to the use of low vision aids and adaptations to address the vision problem of the most visually impaired children. To some extent, this "broke" the standardised setting of the neuropsychological assessment. The possibility of conducting a standardised assessment designed for visually impaired children was considered, but a literature review of non-visual standardised tools available for the visually impaired demonstrated critical problems with this, such as the lack of modern tools (especially for children), poor statistical properties for a psychometric test and lack of normative data for blindness, poor vision and intact sight (Mazella, Albaret, & Picard, 2014). The scientific community working with children with cerebral visual impairment (e.g., cerebral palsy) desperately needs reliable measures to assess children with complex conditions in addition to poor vision (Deramore Denver, 2019; Greenaway et al., 2017). Since a small portion of OPG survivors is blind after the tumour and the visual impairment is variable (de Blank et al., 2016), in this project it was preferred to use the traditional standardised tools. This approach also made it easier to replicate and compare the results with previous findings (verbal-performance IQ; Lacaze et al., 2003), with rather straightforward interpretation. The current results may also have a greater impact on clinical audience which is expected to be familiar with the batteries (or similar) used in this project (Greenaway et al., 2017). The use of low vision aids inevitably affects the solidity and interpretation of these findings, but this approach was deemed appropriate and practically feasible for a first comprehensive description of both visual and neuropsychological outcomes in children with OPG.

Nonetheless, aware of this limitation, an effort was also made to assess the reliability of other auditory measures that can be used for future assessment with visually impaired children. The results of Chapter 6 in this thesis provide promising results as they demonstrate that analogous visual and auditory measures developed for this thesis are correlated in typical development. New tools for clinical use could be developed and standardised to assess the same skills in multiple sensory modalities; information about absolute performance in each domain and

their association could provide a more reliable evaluation for children with either visual or auditory sensory impairment.

7.3 Further considerations

Further considerations from the overall experience of this project are discussed below.

7.3.1 Towards a more integrative approach

Childhood brain cancer is not a monolithic condition, but it is a spectrum of disorders. Tumour location is only one variable that contributes to make a type of tumour specific, whilst similar to other tumours affecting different brain areas (for example for histology and treatment). This project tried to integrate the unique needs concerning vision to the traditional neuropsychological assessment conducted in this field. The systematic inclusion of visual outcomes as tumour-specific variables in the neuropsychological assessment of this patient group represents a strength and a methodological advancement on previous research and this could be useful to extend to other tumours and/or functional outcomes. For example, studies on long-term outcomes of neuroendocrine tumours (e.g., pituitary adenomas; Keil & Stratakis, 2008) could include additional measurements of hormonal levels (Tooze, 2009) to examine if this highly-specific tumour variable predicts and explains the neurocognitive sequelae (Mabbott et al., 2011) and socioemotional outcomes (Liang et al., 2013) documented in these survivors and how they relate to changes in personality and behaviour typically associated with lesions in this area (Pereira, Tiemensma, Romijn, & Biermasz, 2012).

Another methodological strength is the use of mixed standardised and experimental measures to first address the limitation of previous research and second advance the field regarding potential compensatory mechanisms. Specifically, standardised tools used to examine different levels of Colenbrander's (2003) model in the first part of the thesis provided a standardised administration procedure with objective scoring, clear construct definitions and theoretical premises. Whilst the complete

disentanglement of forefront input and downstream visual processing may not be completely possible with a complex condition like NF1, the concurrent utilisation of these tools enabled the examination of different aspects of visual processing (perceptual versus cognitive) in a clearly defined manner. Conversely, experimental measures in the second part of the thesis overcame the constraints posed by standardised tools to address specific questions in relation to the role of sensory processing in the neuropsychological assessment of these children. Therefore, while standardised tests could be useful to identify skills at risk of impairment and thus should not be overloaded (Gathercole & Alloway, 2007; see section 7.4.2), the new experimental tasks could represent an innovative tool to examine also the relationships across different skills and modalities and could be used to design future intervention studies with these and other visually impaired patients. Nonetheless, this thesis represent an advancement to the research on OPG that goes beyond the mere description of the sequelae associated with this tumour, as reported in previous studies (Fouladi et al., 2003; Lacaze et al., 2003; Nicolin et al., 2009; Riva et al., 2009).

7.3.2 The importance of collaboration

After decades of significant improvements to save the lives of children with brain cancer (Saletta et al., 2014), the quality of survivorship of these young survivors has received global attention. The heterogeneity of tumour type, localisation, treatments and premorbid conditions, the influence of genetic factors and the variety of long-term health, cognitive and psychosocial problems, in face of the rarity of this condition, has led the clinical and research communities to jointly tackle this problem by establishing several survivorship cohorts world-wide (Bhatia et al., 2015).

Aware of the limits of a single-institution study, an effort was also made by the author of this thesis and the supervisory team to develop new collaborations in Europe and the United States within the context of this project. While administrative difficulties prevented the establishment of a partnership with Padua (Italy), potential barriers and limitations were noted during the preparation of this potential collaborative project due to the different languages and different assessment tools available in these

two countries, which render cross-cultural and cross-linguistic comparisons difficult.

More successful was the attempt to create a new partnership in North America, specifically with the Children's National Medical Centre in Washington (DC). This centre was specifically chosen by the author because of the presence of the Gilbert Family Neurofibromatosis Institute based in this hospital, a highly specialised research centre for children with NF1. Dr Karin Walsh, a clinical neuropsychologist at the Children's National, with specific clinical and research expertise in paediatric brain cancer and NF1, agreed with enthusiasm to extend part of the assessment reported in this thesis (visual and auditory processing) with her patients. Thanks to the support of the European Association of Cancer Research, the author of this thesis had the possibility to spend 3 months in Washington DC. Despite the effort to secure ethical approval and set the study before arriving in America, it was possible for the host team to recruit only one patient (with NF1 and OPG) during this time. This child was not included in the present thesis because she had not taken her usual medication for attention-deficit/hyperactivity disorder and therefore she struggled to complete the assessment (this patient was tested at the hospital the same day as another medical examination). Whilst invaluable and broader benefits are recognised from this international and collaborative experience, this further highlighted the difficulties of conducting research with this rare condition even for established and highly specialised centres.

7.4 Implications

The results of this project have three important implications for the management of children with OPG.

7.4.1 Clinical and ophthalmology management

The management of children with OPG should move towards an integrative approach that does not focus only on the integrity of the optic pathway but also on functional aspects of vision and perception. The variability on measures of visual acuity and visual perception confirms

the need for an objective evaluation of visual acuity in children with OPG (Avery, Cnaan, et al., 2015). However, while alternative methods like OCT (Avery et al., 2014; Gu, Glaug, Cnaan, Packer, & Avery, 2014), DTI (Hales et al., 2018) and visual evoked potentials (Kelly et al., 2012; Van Mierlo, Spileers, Legius, Casteels, & Cassiman, 2013) continue to be explored, the inclusion of simple visuo-perceptual tasks like those used in this thesis should be considered for a more complete ophthalmologic evaluation of children's visual functions. For example, the visual closer subtest used in this thesis is typically found to be particularly difficult for children with learning disabilities, both with (Cutting & Levine, 2010) and without NF1 (Moryosef-Ittah & Hinojosa, 1996). Administration of this task might help clinicians to identify abnormal visuo-perceptual difficulties beyond the visual impairment in children with OPG.

7.4.2 Scholastic support

The educational support of children with OPG should focus on school-based accommodations that reduce visual distractions, provide additional visual stimuli to direct attention and guide responses, and limit handwriting (Schneck, 2010). Environmental adaptations should also limit the short-term/working memory and speeded load of school tasks; for example, reduce amount of information to store and process, provide short and simple instructions, allow extra time for completing the tasks, repeat information, and encourage the use of memory aids (Alloway, 2006;Gathercole & Alloway, 2007). However, given the variability reported in the present study and since only few children exhibited significant deficits in these domains, it would also be important to provide individualised educational plans for those in most need.

Because it has been proposed that, in typical development, improvement in processing speed accounts for age-related development of working memory, which in turn corresponds to improvements in intelligence quotient (Fry & Hale, 2000), cognitive and scholastic progression in children with OPG should also be monitored over time to ensure that the deficits found in this study do not result in long-term developmental delay. Lack of association between neuropsychological outcomes and time post treatment suggest that this would not be the case for this patient group, but the small sample of this study and the

limited amount of research with this specific tumour could not exclude this possibility.

Although young OPG survivors with poor vision appeared to have fast attentional resources in the auditory domain, the difficulties in auditory short-term and working memory suggest that the hearing system should not be overloaded and thus not be considered a compensatory sensory channel. Unlike retinoblastoma survivors (Brinkman et al., 2015; Ek et al., 2002; Tobin et al., 2010), children with OPG cannot rely on superior verbal/auditory cognitive resources in comparison to what is expected in typical development. Overload of the hearing channel might alter the mechanism of auditory compensation that already seems to occur in these patients. Instead, environmental accommodations such as those mentioned above would ensure that the extra attentional resources deployed by patients with poor vision are maximised.

7.5 Future research

Future research should investigate the outcomes of OPG at the societal level, looking therefore at the implications in real school settings (Colenbrander, 2003). Aarsen et al. (2006) found that young survivors are more likely to need special education or remedial teaching because of the visual impairment resulting from the tumour. Lacaze et al. (2003) reported that about half of the school-age group received normal education, whereas the other half was attending specialised schools for the blind and visually impaired. The results of this study suggest that children with OPG perform well overall in visually based tasks, but those with NF1 have an overall different trajectory from those without NF1. Whilst the dramatic effect of sight loss and blindness on children's lives and their families must not be minimised (Chadha & Subramanian, 2011), the results of this study suggest that more research is needed to understand the impact of vision on the educational needs of OPG patients.

In the UK, over 65% of children with visual impairment are educated in mainstream schools alongside typically-sighted peers

(Chadha & Subramanian, 2011). The Royal National Institute of Blind People used the 2010 government statistics to examine educational progress in blind and partially sighted children. The results showed that primary school children with visual impairment did not progress as well as their sighted peers, but also that students with visual impairment only progress significantly better than those with visual impairment plus special educational needs (RNIB, 2011). About 50% of the children with NF1 have a learning disability and/or display ADHD symptomatology (Hyman et al., 2006; Schrimsher et al., 2003). An adequate diagnosis of the level and type of visual impairment is crucial to adequately support children with forefront visual problems and those with additional special educational needs (Das, Spowart, Crossley, & Dutton, 2010).

In a different vein, answers to the parental questionnaires were also inspected to identify areas of concerns for the parents that should be further investigated in future. When parents were asked to describe problems that are reasons of concern about their child, their answers were related to themes of social adjustment and behaviour; for example, difficulty with maintaining stable friendships, being victims of bullying, isolation from peers due to poor motor abilities, emotional control and limited accessibility to social occasions. Only one parent reported fear of accessing the national curriculum and progressive sight loss. Research shows that children who had brain tumours are rated by their peers as isolated, victimised at school and not very popular, and have poor effortful control according to their parents (Salley et al., 2015). Social maladjustment is also a recurrent problem among visually impaired and blind youth (Lang, Hintermair, & Sarimski, 2017; Pring, 2008). Ophthalmic and visuoperceptual abilities are important for the development of social cognition (Arioli, Crespi, & Canessa, 2018) and difficulties in these visual domains have been linked to socio-emotional problems in several neurodevelopmental conditions, such as cerebral visual impairment (Philip & Dutton, 2014), autism (Hellendoorn et al., 2014), preterm birth (Williamson & Jakobson, 2014) and genetic syndromes (Allen, Willard, Anderson, Hardy, & Bonner, 2016; McCabe et al., 2016). A deeper investigation of social adjustment in children with OPG, and into the potentially mediating role of sight loss and

visuoperceptual difficulties, could be explored in the future to meet parents' concerns that emerged in this study. Since research questions that are personally relevant to the cancer survivors would also lead to higher participation rates (Wakefield et al., 2017), psychosocial trajectories following OPG should also be considered for future investigation, and might possibly result in a higher recruitment rate than in this project.

Future research should specifically focus on the NF1 condition because of the possibility to prevent vision loss in these children, or at least to identify those at risk of generalised poor development. In a longitudinal study over 18 years, Payne et al. (2014) found that neurological abnormalities in the NF1 brain are associated with general cognitive improvement possibly thanks to the increased efficiency of white matter connections. As discussed in Chapter 1, the role of OPG in NF1 is less investigated than other brain abnormalities, and these children are excluded from studies that would be relevant for their neuropsychological profile. While a detailed examination of the NF1 condition was beyond the scope of this thesis, more investigation is necessary on the role of OPG within the NF1 population, combining ophthalmologic, neuropsychological and MRI investigations in order to predict visual and cognitive outcomes in these patients.

7.6 Conclusions

In conclusion, this thesis has demonstrated that, in the chemotherapy era, children who have or have been treated for an optic pathway glioma demonstrate visual and visuo-perceptual problems due to the tumour, but overall preserved core cognitive and scholastic skills. However, like other brain tumour survivors, children with OPG are at risk of experiencing difficulties on auditory short-term and working memory and motor speed, which may impact on specific scholastic abilities such as writing and oral language. However, only a minority of young OPG survivors would exhibit severe deficits in these domains. Further, children with an OPG do not develop superior auditory skills, but those with poorer vision might implement compensatory strategies of auditory

attention that enable them to achieve adequate performance. Whilst more research is necessary to unravel visual and visuo-perceptual difficulties in patients with and without NF1, the current findings should inform more accurate scholastic intervention for all children who have suffered an optic pathway glioma than has previously been possible.

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Appendix A. Literature review – search strategy

A systematic literature search was performed in March 2017. An automated alert was maintained until March 2019, with no new relevant publications added to the initial results. The OVID databases Medline, PsychInfo and Embase were searched for eligible studies using the following strategy.

First, the databases were searched for the term "brain tumo?r" using the Medical Terms Subject Heading (MeSH) option and relevant sub-headings. Next, the databases were searched for the following keywords: ("chiasmatic" OR "hypothalamic" OR "optic pathway") AND ("cog*" OR "neurocog*" OR "psych*" OR "neuropsych*"). Then, the combined search was limited to peer-reviewed publications written in English and involving humans. In addition, the reference lists of the retrieved articles were checked for other relevant studies.

Out of 133 publications, only 4 relevant studies were found that reported neuropsychological outcomes in children with optic pathway glioma. Given the paucity of research, no additional criteria were adopted based on study features such as research design, sample size, control group, etc. Information about sample size, proportion of NF1 patients, study design, outcome measures, type of analyses, main findings and impact of critical factors were extracted and reported in Table 1.1.
The grey literature was also explored using the same keywords as above. The examined sources included Google, Google scholar, PsyArXiv and BioRxiv preprint repositories, websites of well-known charities and research organisations (Children's Cancer and Leukaemia Group, Brain Tumour Charity, Brain Tumour Research, Brain Tumour Foundation of Canada, Astro Brain Tumour fund, etc.) and databases of large research institutions (Hospital for Sick Kids, St. Jude Children's Research Hospital, MD Anderson Centre) in the attempt to identify relevant doctoral theses, information leaflets, reports, etc. No additional material was found that reported and analysed data on neuropsychological outcomes in children with OPG.

Appendix B. Ethics review – letter of approval (without appendices)

NHS
Health Research Authority

Dr Robert Dineen
Room B1435 Radiological Sciences
Queen's Medical Centre
Nottingham
NG7 2UH

Email: hra.approval@nhs.net

09 February 2017

Dear Dr Dineen,

Letter of HRA Approval

Study title:	**TIP-TOP: Tensor Imaging in Paediatric Tumours for functional Outcome Prediction**
IRAS project ID:	**211855**
Protocol number:	**16089**
REC reference:	**16/LO/2149**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **211855**. Please quote this on all correspondence.

Yours sincerely

Rekha Keshvara
Assessor

Email: hra.approval@nhs.net

Copy to: *Mr Ryan Keyworth*
Dr Maria Koufali, Nottingham University Hospitals NHS Trust

Appendix C. Fine motor control tasks

Auditory task

Instructions

In this task you are going to pretend to be a broken machine that makes some weird noises. The first noise is "Clonk Clonk – Clonk Clonk". Now you repeat "Clonk Clonk – Clonk Clonk" until I tell you to stop.

Allow some practice without timing until the child understands the task.

Correct the child if he/she makes a mistake during the sound repetition.

Okay, now you do the real task and you repeat the noises as quickly as you can. The first noise is "Split Splat – Split Splat".

Start timing when the child starts the task.

Stop the child after 8 correct repetitions.

Correct the child if he/she makes a mistake during the sound repetition, but do not stop the timer.

Record the completion time in seconds.

Administer the next items.

Interrupt the item if the child takes more than 30 seconds to complete the item.

In this task you are going to repeat some weird sentences (or tongue twisters). The first sentence is "Red leather, yellow leather". Try to say it fast, but it is also important that you say the sentence without mistakes. Let's try.

Allow some practice without timing until the child remember the sentence.

Correct the child if he/she makes a mistake during the sentence repetition.

Okay, now keep saying it until I tell you stop.

Allow some practice without timing until the child remember the sentence (for each item).

Start timing when the child starts the task.

Stop the child after 5 correct repetitions.

Correct the child if he/she makes a mistake during the sentence repetition, but do not stop the timer.

Record the completion time in seconds.

Interrupt the item if the child takes more than 60 seconds to complete the item.

Record form

Discontinue: items 1-4, after 8 correct repetitions or > 30 seconds
items 5-8, after 5 correct repetitions or > 60 seconds

Item		Score	
T.	Clonk clonk		
1.	Split splat	Number repetitions 8	Completion time (Max 30'')
2.	Grinchy grouchy	Number repetitions 8	Completion time (Max 30'')
3.	Squish squash	Number repetitions 8	Completion time (Max 30'')
4.	Clinkety clankety	Number repetitions 8	Completion time (Max 30'')

Item		Score	
5.	Red leather, yellow leather	Number repetitions 5	Completion time (Max 60'')
6.	Sue said she should sell shoes	Number repetitions 5	Completion time (Max 60'')
7.	So much to do at a minute or two to two	Number repetitions 5	Completion time (Max 60'')
8.	The frothy fluid flows freely	Number repetitions 5	Completion time (Max 60'')

Visual task

Instructions

Identify dominant and non-dominant hand. *Which hand do you use to write?*

This is a game with your hands. Look what I do. I make a big circle with the tips of my fingers [demonstrate: touch the tips of the index and the thumb] *and I open and close the fingers to make a wide circle like this* [demonstrate: open and close the wide circle]. *Now you try to do it. Let's start with your* [dominant] *hand.*

Allow some practice until the child understands the task.

Correct the child if he/she keeps the fingers flat and straight, does not touch the fingertips or makes a small circle. Show the child how to do it.

Repeat with the non-dominant hand.

Well done. Now you repeat these circles as quickly as you can and keep going until I tell you to stop. Let's start with your [dominant] *hand. Remember to touch the tips of your fingers and make a big circle with your fingers.*

Start timing when the child starts the task.

Stop the child after 20 correct repetitions.

Allow some practice until the child understands the task.

Correct the child if he/she keeps the fingers flat and straight, does not touch the fingertips or makes a small circle. Show the child how to do it.

Record the completion time in seconds.

Interrupt the item if the child takes more than 60 seconds to complete the item.

Repeat with the non-dominant hand.

Now there is something different. Look what I do. Again, I make a big circle with the tips of my fingers [demonstrate: touch the tips of the index and the thumb]*, but then I go from the index finger to the other fingers* [demonstrate: touch the tips of the middle finger and the thumb, then the ring finger and the thumb, then the little finger and the thumb]*. Now you try to do it. Let's start with your* [dominant] *hand.*

Allow some practice until the child understands the task.

Correct the child if he/she keeps the fingers flat and straight, does not touch the fingertips, makes a small circle, or skips a finger. Show the child how to do it.

Repeat with the non-dominant hand.

Well done. Now you repeat this sequence as quickly as you can and keep going until I tell you to stop. Let's start with your [dominant] *hand. Remember to touch the tips of your fingers, make a big circle with your fingers and do not skip any finger.*

Start timing when the child starts the task.

Stop the child after 5 correct sequences.

Correct the child if he/she keeps the fingers flat and straight, does not touch the fingertips, makes a small circle or skips a finger. Show the child how to do it.

Record the completion time in seconds.

Interrupt the item if the child takes more than 90 seconds to complete the item.

Repeat with the non-dominant hand.

Record form

Discontinue: items 1-2, after 20 correct repetitions or > 60 seconds
items 3-4, after 5 correct sequences or > 90 seconds

Item		Score	
T1.	Repetitions		
1.	Repetitions Dominant Hand	Number repetitions 20	Completion time (Max 60'')
2.	Repetitions Non-Dominant Hand	Number repetitions 20	Completion time (Max 60'')

Item		Score	
T2.	Sequences		
3.	Sequences Dominant Hand	Number repetitions 5	Completion time (Max 90'')
4.	Sequences Non-Dominant Hand	Number repetitions 5	Completion time (Max 90'')

Appendix D. Attention tasks

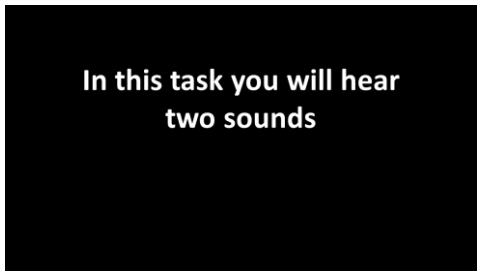
Auditory task

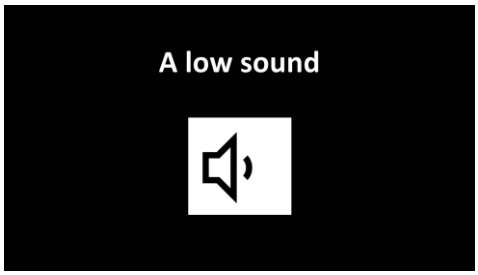
PsychoPy documents

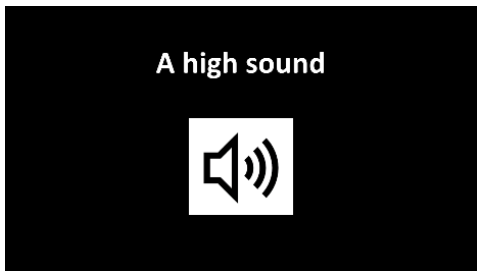
The PsychoPy experiment is available at
https://osf.io/q82xp/?view_only=7486742acd7248bfa35f4f7ee57d3eab

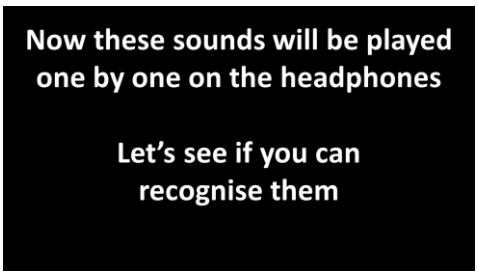
Instructions screens (created in Microsoft Power Point®)

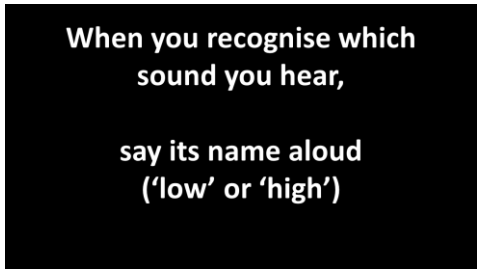
Read the instructions aloud to the child.

1) 

2) 

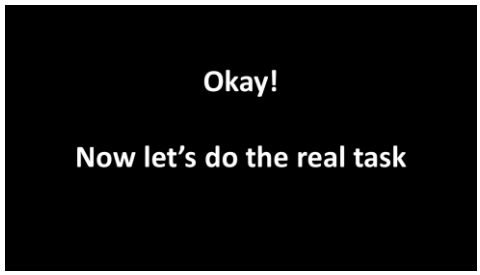
3) 

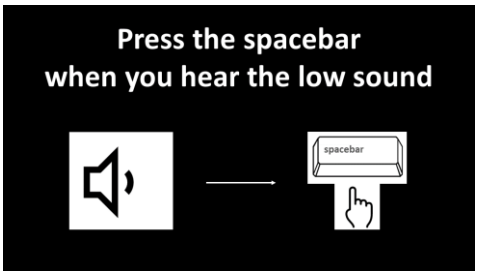
4) 

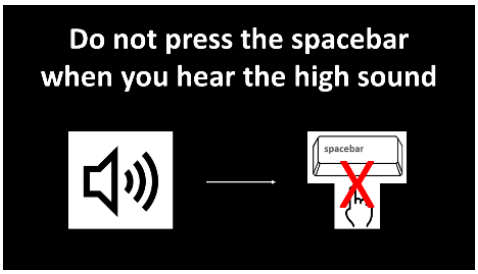
5) 

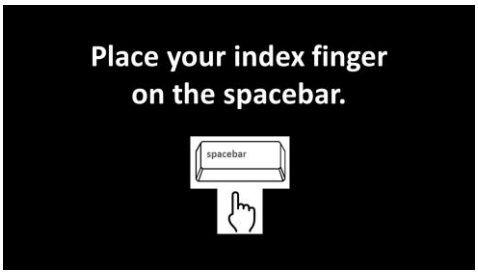
6) 

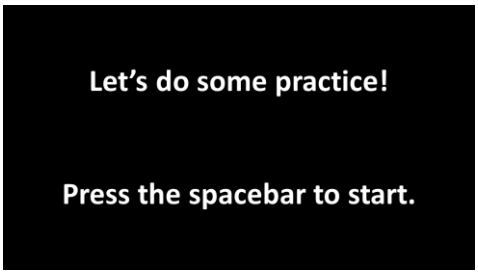
[The two sounds played in random sequence, 5 times each.]

7) 

8) 

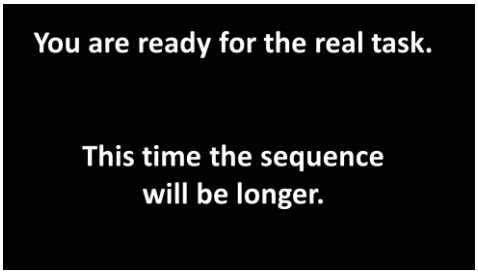
9) 

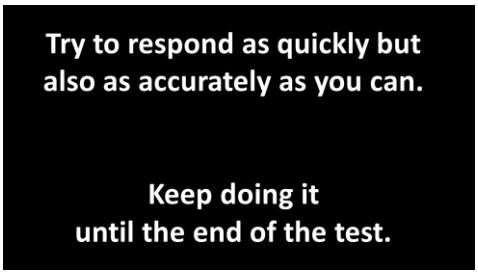
10) 

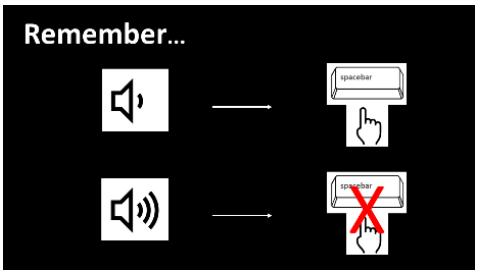
11) 

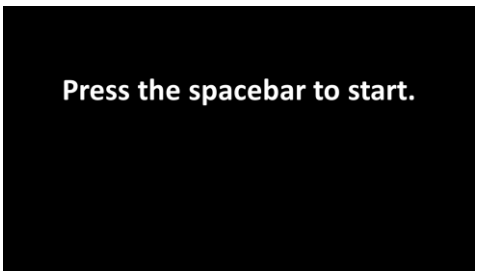
[Three practice blocks of 6 trials each presented.]

12) 

13) 

14) 

15) 

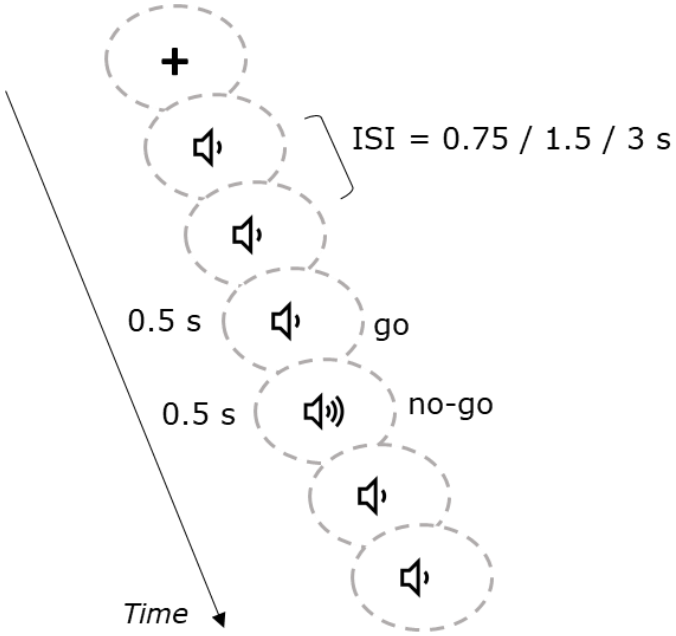
16) 

[At the end of the experiment.]

17) 

Schematic representation of one block of trials.

The auditory stimuli were aurally presented through headphones.



Visual task

PsychoPy documents

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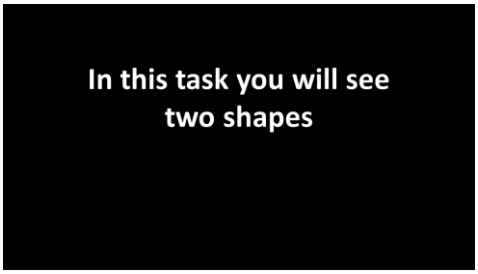
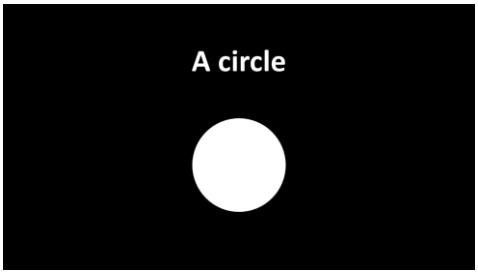
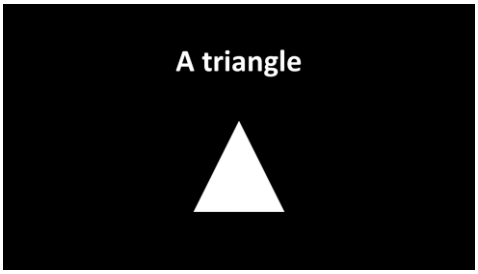
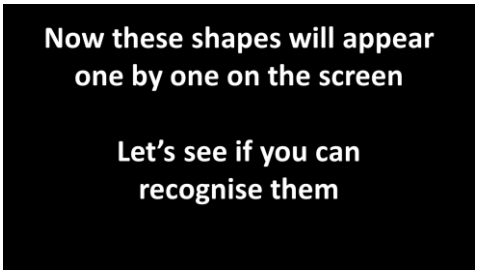
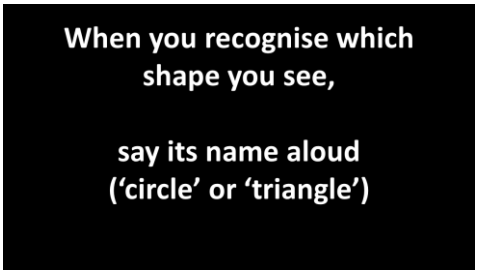
1) 

2) 

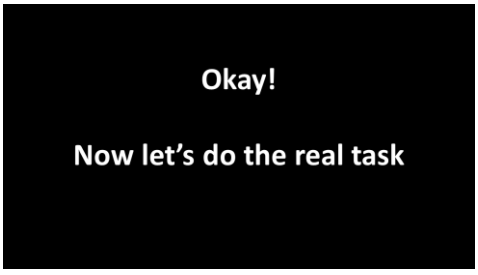
3) 

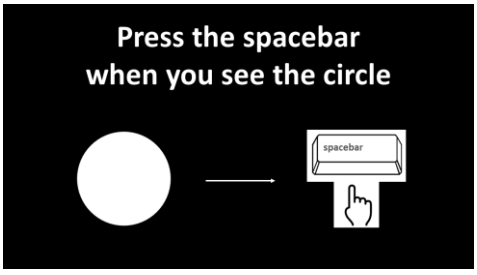
4) 

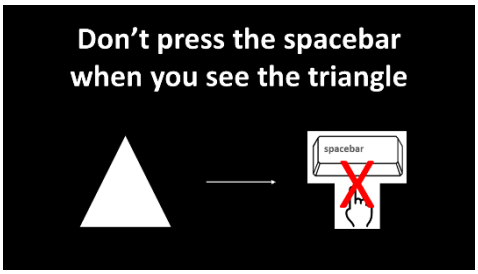
5) 

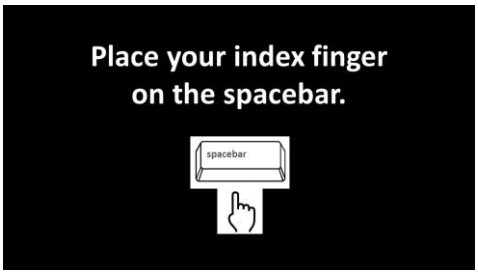
6) 

[The two shapes shown in random sequence, 5 times each.]

7) 

8) 

9) 

10) 

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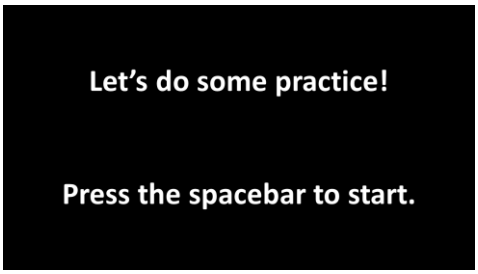
11) 

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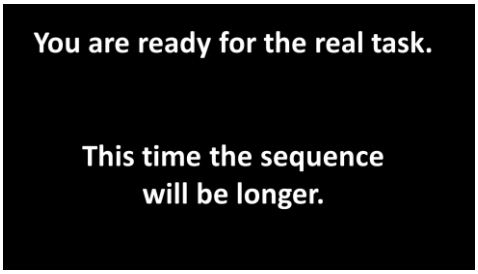
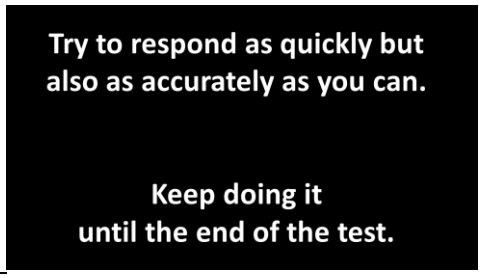
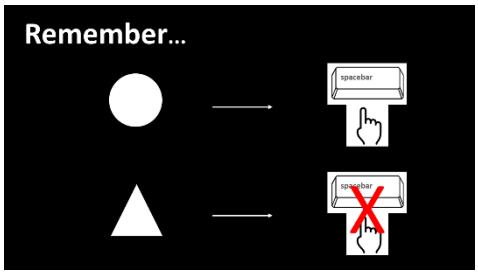
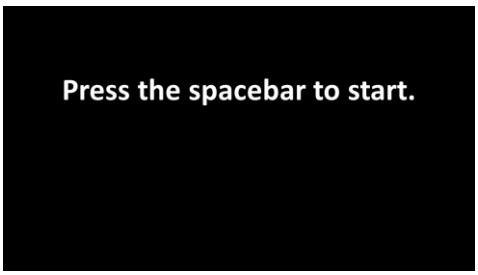
12) 

13) 

14) 

15) 

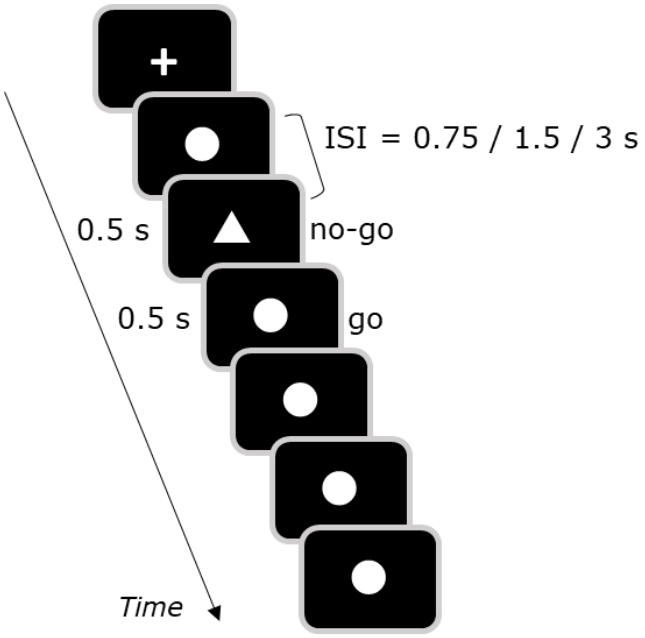
16) 

[At the end of the experiment.]

17) 

Schematic representation of one block of trials.

The visual stimuli were visually presented on the screen.



Appendix E. Short-term memory tasks

Auditory task

Instructions

Same standardised instructions and administration procedure as in the Digit Span task of the WISC-IV^{UK}.

Record form

Discontinue: after score 0 in both trials of an item

Trial		Response	Span	Trial score	Item score
S.	2 – 3				
1.	2 – 9		2	0 1	0 1 2
	4 – 6			0 1	
2.	3 – 8 – 6		3	0 1	0 1 2
	6 – 1 – 2			0 1	
3.	3 – 4 – 1 – 7		4	0 1	0 1 2
	6 – 1 – 5 – 8			0 1	
4.	8 – 4 – 2 – 3 – 9		5	0 1	0 1 2
	5 – 2 – 1 – 8 – 6			0 1	
5.	3 – 8 – 9 – 1 – 7 – 4		6	0 1	0 1 2
	7 – 9 – 6 – 4 – 8 – 3			0 1	
6.	5 – 1 – 7 – 4 – 2 – 3 – 8		7	0 1	0 1 2
	9 – 8 – 5 – 2 – 1 – 6 – 3			0 1	
7.	1 – 8 – 4 – 5 – 9 – 7 – 6 – 3		8	0 1	0 1 2
	2 – 9 – 7 – 6 – 3 – 1 – 5 – 4			0 1	
8.	5 – 3 – 8 – 7 – 1 – 2 – 4 – 6 – 9		9	0 1	0 1 2
	4 – 2 – 6 – 9 – 1 – 7 – 8 – 3 – 5			0 1	

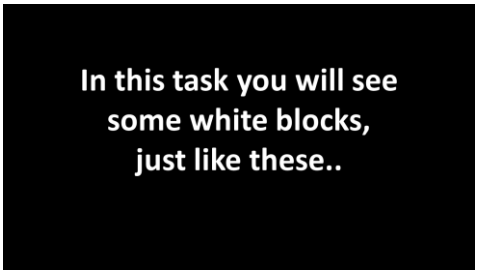
Visual task

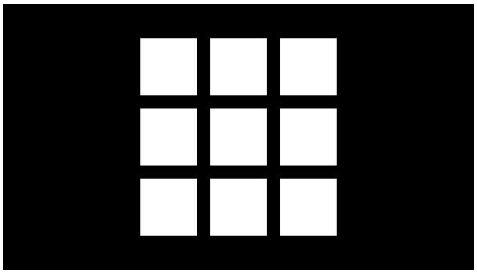
PsychoPy documents

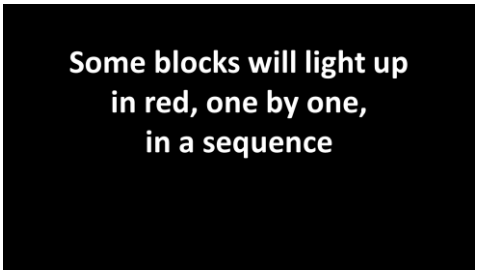
The PsychoPy experiment is available at
https://osf.io/q82xp/?view_only=7486742acd7248bfa35f4f7ee57d3eab

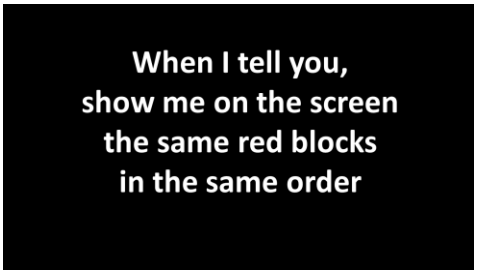
Instructions screens (created in Microsoft Power Point®).

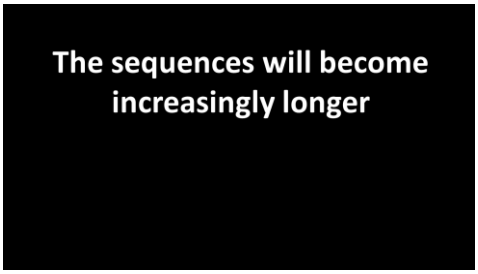
Read the instructions aloud to the child.

1) 

2) 

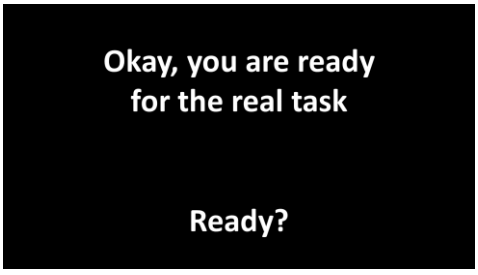
3) 

4) 

5) 

6) 

[Practice trial.]

7) 

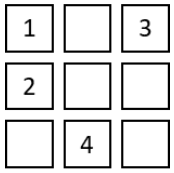
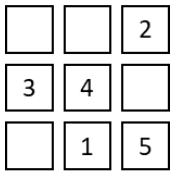
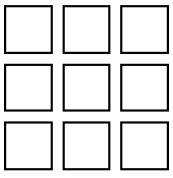
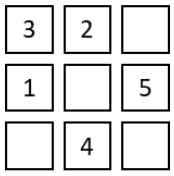
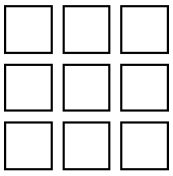
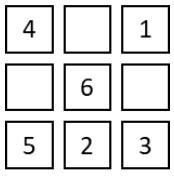
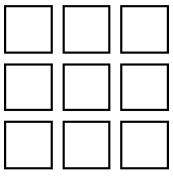
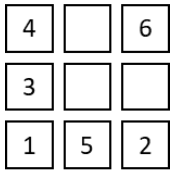
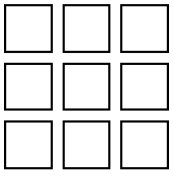
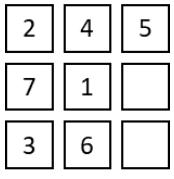
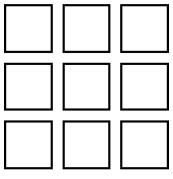
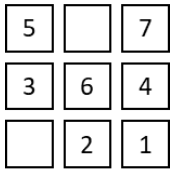
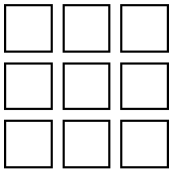
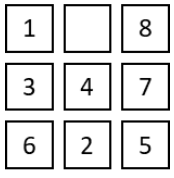
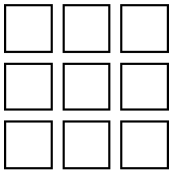
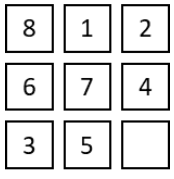
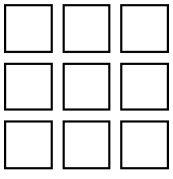
[At the end of the experiment.]

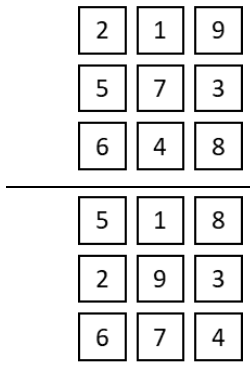
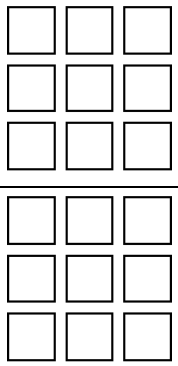
8) 

Record form

Discontinue: after score 0 in both trials of an item

	Trial	Response	Span	Trial score	Item score
S.	1 2				
1.	1 / 2		2	0 1	0 1 2
	2 1			0 1	
2.	1 / 3 / 2		3	0 1	0 1 2
	2 3 / 1			0 1	
3.	3 1 / 2 / 4		4	0 1	0 1 2

		0 1		
4. 		5	0 1	0 1 2
			0 1	
5. 		6	0 1	0 1 2
			0 1	
6. 		7	0 1	0 1 2
			0 1	
7. 		8	0 1	0 1 2
			0 1	

8. 		9	0 1 0 1	0 1 2

Appendix F. Working memory tasks

Auditory task

Instructions

Same standardised instructions and administration procedure as in the Digit Span task of the WISC-IV^{UK}.

Record form

Discontinue: after score 0 in both trials of an item

Trial		Response	Span	Trial score	Item score
S.	8 – 2				
	5 – 6				
1.	2 – 1		2	0 1	0 1 2
	1 – 3			0 1	
2.	3 – 5		2	0 1	0 1 2
	6 – 4			0 1	
3.	5 – 7 – 4		3	0 1	0 1 2
	2 – 5 – 9			0 1	
4.	7 – 2 – 9 – 6		4	0 1	0 1 2
	8 – 4 – 9 – 3			0 1	
5.	4 – 1 – 3 – 5 – 7		5	0 1	0 1 2
	9 – 7 – 8 – 5 – 2			0 1	
6.	1 – 6 – 5 – 2 – 9 – 8		6	0 1	0 1 2
	3 – 6 – 7 – 1 – 9 – 4			0 1	
7.	8 – 5 – 9 – 2 – 3 – 4 – 6		7	0 1	0 1 2
	4 – 5 – 7 – 9 – 2 – 8 – 1			0 1	
8.	6 – 9 – 1 – 7 – 3 – 2 – 5 – 8		8	0 1	0 1 2
	3 – 1 – 7 – 9 – 5 – 4 – 8 – 2			0 1	

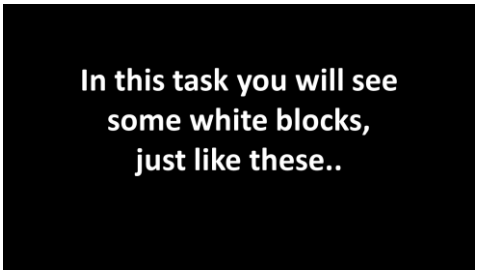
Visual task

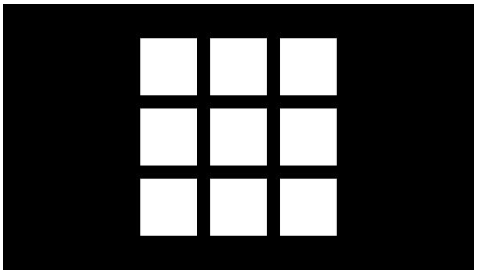
PsychoPy documents

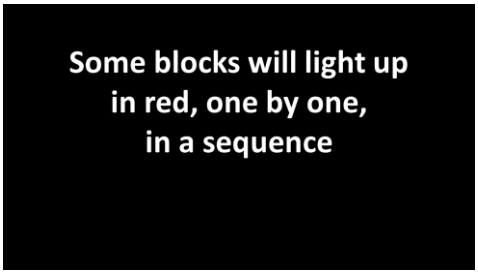
The PsychoPy experiment is available at
https://osf.io/q82xp/?view_only=7486742acd7248bfa35f4f7ee57d3eab

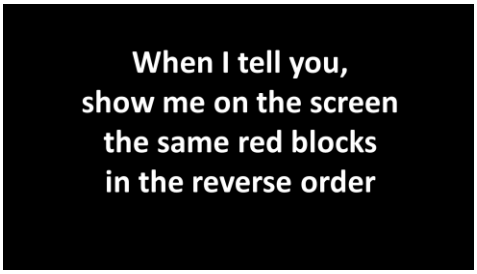
Instructions screens (created in Microsoft Power Point®)

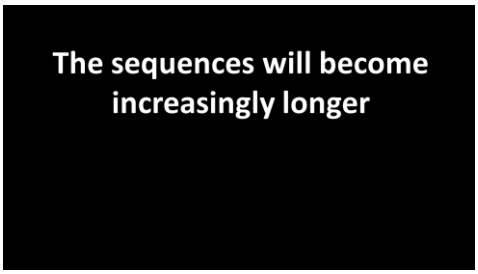
Read the instructions aloud to the child.

1) 

2) 

3) 

4) 

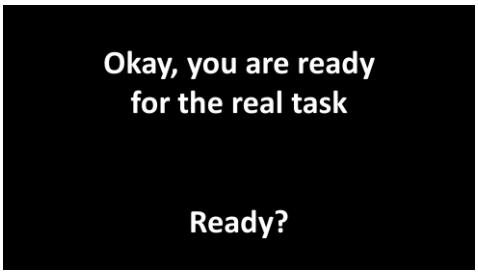
5) 

6) 

[Practice trials 1]

7) 

[Practice trial 2.]

8) 

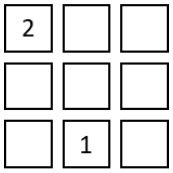
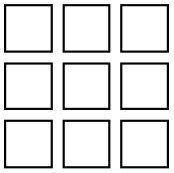
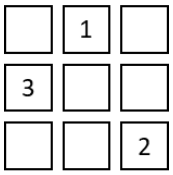
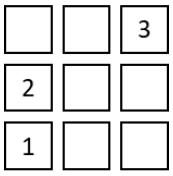
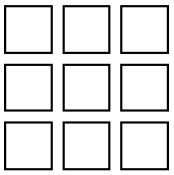
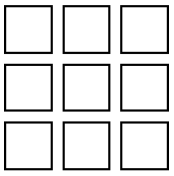
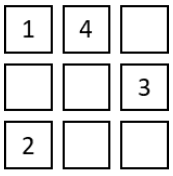
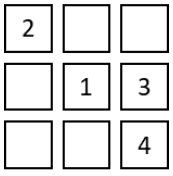
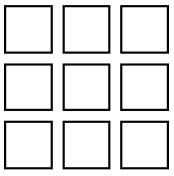
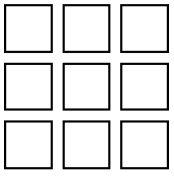
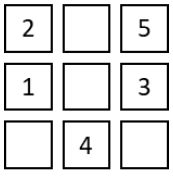
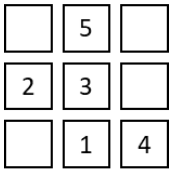
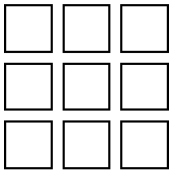
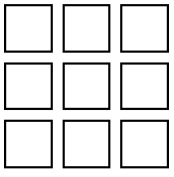
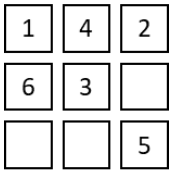
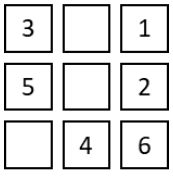
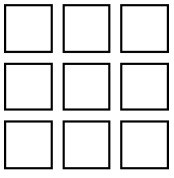
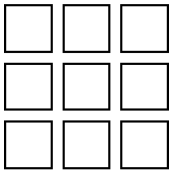
[Main experiment.]

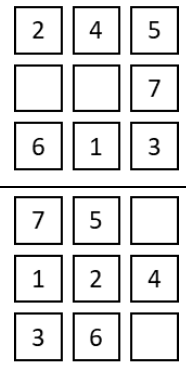
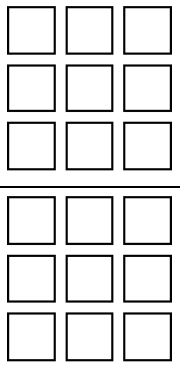
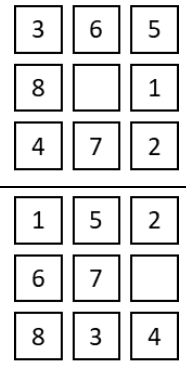
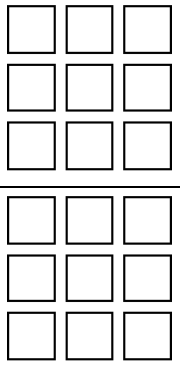
9) 

Record form

Discontinue: after score 0 in both trials of an item

	Trial	Response	Span	Trial score	Item score
S.	1 2 / 2 / 1				
1.	2 1 / 1 2		2	0 1 / 0 1	0 1 2
2.	1 / 2		2	0 1	0 1 2

			0 1	
3.  	 	3	0 1 0 1	0 1 2
4.  	 	4	0 1 0 1	0 1 2
5.  	 	5	0 1 0 1	0 1 2
6.  	 	6	0 1 0 1	0 1 2

7. 		7	0 1 0 1	0 1 2
8. 		8	0 1 0 1	0 1 2