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CENTRAL AND PERIPHERAL STEADY-STATE VISUAL EVOKED POTENTIALS IN CHILDREN WITH OPTIC PATHWAY GLIOMAS

DOCTORAL ESSAY

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ÉVALUATION DE L'INTÉGRITÉ DU CHAMP VISUEL D'ENFANTS ATTEINTS DE GLIOMES OPTIQUES À L'AIDE DES POTENTIELS ÉVOQUÉS VISUELS STATIONNAIRES

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I grew up in a family that places so much importance on contributing to society in a way that brings positive changes to other peoples lives. My family thought me that the greatest sence of inner gratification and happiness comes from giving. This notion became much more accessible to me when I began to work at the Sainte-Justine Hospital. This thesis is without a doubt my greatest achievement, and this sence of accomplishment stems from the numerous enjoyable and rich encounters that I had with the funny and curious children and their resilient families. This project has furthered my professional and personal development to an extent that I did not believe would be possible. This 4-year-long project would not be possible without the constant support of my family, my friends, as well as my research supervisors.

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LIST OF ABBREVIATIONS AND ACRONYM

ADHD: attention deficit hyperactivity disorder

CNS: central nervous system

DD: developmental delay

EEG: electroencephalography

LD: learning disability

LogMAR: logarithm corresponding to the minimum angle of resolution

LP: light perception

MRI: magnetic resonance imaging

NF1: neurofribromatosis type I

NLP: no light perception

OPG: optic pathway glioma

ssVEP: steady-state VEP

tVEP: transient VEP

VA: visual acuity

VEP: visual evoked potential

VF: visual field

WHO: World Health Organisation

LIST OF SYMBOLS AND UNITS

Hz: hertz

RPS: reversals per second

SNR: signal to noise ratio

RÉSUMÉ

Le gliome optique représente 4 à 6% des tumeurs cérébrales chez l'enfant. L'imagerie par résonance magnétique (IRM) est la méthode habituelle pour confirmer le diagnostic et mesurer l'évolution de la tumeur pendant le traitement par radiothérapie ou chimiothérapie. La croissance tumorale est généralement associée à une perte de vision progressive. Malgré le traitement, environ 40% auront néanmoins une détérioration visuelle. L'objectif du traitement repose en grande partie sur la préservation de la vision. Cependant, l'évaluation actuelle des fonctions visuelles n'est souvent pas fiable chez les enfants atteints d'un gliome optique, surtout lorque la collaboration de l'enfant est limitée. Ainsi, de nouveaux outils cliniques sont nécessaires pour évaluer les fonctions visuelles chez ces enfants. Le but de l'étude est d'évaluer l'utilité des potentiels évoqués visuels stationnaires comme un outil d'évaluation de l'intégrité du champ visuel central et périphérique d'enfants atteints d'un gliome optique.

Dix patients atteints d'un gliome optique et 33 témoins en bonne santé (âgés de 3 à 18 ans) ont été testés à l'aide des potentiels évoqués visuels stationnaires. Le stimulus circulaire consistait en un cercle central alternant à 16 inversions par seconde et un anneau périphérique alternant à 14,4 inversions par seconde, séparés par un anneau d'espaces gris. Le stimulus a été présenté monoculairement à deux contrastes différents, soit 30% et 96% de contraste. Les résultats ont indiqué que les réponses centrales (ratio signal sur bruit) étaient significativement plus faibles chez les enfants atteints d'un gliome optique par rapport aux groupe contrôle. Cependant, aucune différence significative n'a été détectée dans le champ visuel périphérique.

En conclusion, notre étude montre que les potentiels évoqués visuels stationnaires peuvent être utiles afin d'évaluer l'intégrité du champ visuel central chez les enfants non-coopératifs ou non-verbaux. Cependant, la méthode semble avoir une utilité limitée pour l'évaluation des déficits du champ visuel périphérique. Des études supplémentaires sont nécessaires afin d'identifier les paramètres optimaux pour l'évaluation du champ visuel complet.

Mots clés : electroencéphalographie; gliome optique, potentiels évoqués visuels stationnaires; champ visuel, nerf optique.

ABSTRACT

Optic Pathway Gliomas (OPG) represent 4-6% of brain tumors in children. Treatment of optic pathway gliomas is prompted by neuroradiological evidence of tumor growth, usually associated with progressive visual loss. Despite therapy, approximately 40% will show visual deterioration. Treatment outcome is largely based on the preservation of vision. However, current visual function assessment is often unreliable in children with optic pathway gliomas who have limited collaboration. Thus, there is a need for new clinical tools to evaluate visual functions in these children. The aim of the study was to assess the usefulness of steady-state visual evoked potentials as a tool to assess the integrity of the central and peripheral visual fields of children with optic pathway gliomas.

Ten patients with optic pathway gliomas and 33 healthy controls (ages 3 to 18 years) were tested using steady-state visual evoked potentials. The circular dart-board stimulus consisted of one central circle alternating at 16 reversals/second and one peripheral hoop alternating at 14.4 reversals/second, separated by a hoop of gray space. It was presented monocularly at 30% and 96% contrasts.

Results indicated that central signal-to-noise ratios were significantly lower in children with optic pathway gliomas compared to controls. However, no significant group difference was detected in the peripheral visual field.

In conclusion, our study shows that steady-state visual evoked potentials could be useful in the clinical assessment and follow up of central visual field deficits in uncooperative or non-verbal children but seems to have limited usefulness for the evaluation of peripheral visual field deficits. Additional studies are needed to identify testing parameters for full visual-field assessment.

Keywords : electroencephalography; steady state visual-evoked potential; optic pathway glioma; visual field assessment; optic nerve.

INTRODUCTION

According to the World Health Organization (2017), cancer is the leading cause of death in the world and it does not spare children. Although childhood cancer is not common in Canada and only accounts for less than 1% of cancer cases, it still places an important burden on the affected children and their families. Leukemia is the most common childhood cancer, followed by tumors of the central nervous system (CNS), the latter representing the leading cause of cancer related deaths in children (Canadian cancer society, 2017).

There are several types of CNS tumors, as well as diverse growth patterns and tumor sites. The most common brain tumors in the pediatric population are low grade gliomas, which are slow growing tumors (Avery, Fisher, & Liu, 2011). Optic pathway gliomas (OPG) are tumors of the optic nerve and represent four to six percent of pediatric CNS tumors (Kelly & Weiss, 2013; Fried et al., 2013; Jahraus & Tarbell, 2006). OPGs obstruct the visual pathway (Avery et al., 2011). Thus, the first sign often involves decreased visual functions, including visual acuity and visual field integrity. OPGs are more common in children than in teenagers and adults, and they are often diagnosed before the age of eight years (Avery et al., 2011). Currently, treatment options for OPGs include chemotherapy, which is the gold standard, as well as radiotherapy and/or surgery (Jahraus & Tarbell, 2006). Magnetic resonance imaging (MRI) and visual acuity measures are the tools used to evaluate tumor progression, as well as treatment response (Fisher et al., 2013; Kalin-Hadju et al., 2014). Since one of the main goals of treatment is to preserve vision, it is important to accurately measure

all the visual functions, including visual acuity and visual field integrity in an objective and reliable manner.

Current clinical evaluations of visual field integrity are subjective, as they require active cooperation, making it difficult and sometimes unreliable for young children. The need for a new objective method measuring visual field integrity is essential as it would aid in the diagnosis and monitoring of OPGs during treatment. Thus, the main goal of the current study is to assess the usefulness of electroencepahgraphy (EEG) to measure the extent of visual field deficits in children with OPGs using steady state visual evoked potentials (ssVEPs).

The following sections will further explain the symptoms, and possible treatments of childhood OPGs, as well as describe current diagnostic and follow up tools. Subsequently, the ssVEP method will be explained, along with a description of its current clinical usefulness. Finally, studies that have used similar methods to measure visual impairments in children will be described to support the potential clinical value of ssVEPs to measure visual field integrity in children with OPGs.

CHAPTER I

THEORETICAL BACKGROUND

1.1 Optic Pathway Gliomas

Gliomas, or glial tumors, consist of benign or malignant brain tumors, originating from glial cells. Neuroglia is essential for cortical functioning and is present throughout the brain. Among other functions, these cells are mainly responsible for supporting neurons, or keeping them in place, as well as supplying oxygen and nutrients to neurons (Jessen & Mirsky, 1980). There are many sites in which gliomas can form, one of which is the optic pathway glioma. Gliomas affecting the optic nerve are usually benign with a variable growth pattern ranging from slow to rapidly progressive, but most tumors progress slowly. Additionally, OPGs are classified as pilocytic astrocytoma (Grade I) when classified according to the World Health Organisation (WHO; Listernick, Charrow, & Gutmann, 1999). OPG's are indolent in 40% of cases, usually appearing in young children and frequently stop growing spontaneously in adolescence. Clinically, children with OPGs usually present with decreased visual acuity and visual field integrity, but can also have impaired color vision, limited eye movements, bulging of the eye (proptosis), and involuntary eye movements, i.e., nystagmus (Fisher et al., 2013). The prognosis of children with OPGs is variable, mainly related to the localization, size, degree of extension of the tumor, and age at diagnosis (Van Mierlo et al., 2013). Regardless of tumor size and localization, visual acuity and/or visual field

integrity is compromised. Additionally, many children with OPGs have comorbid neurofibromatosis type 1 (NF1).

1.1.1 Neurofribromatosis Type I

NF1 is an autosomal dominant disorder caused by a mutation of the *NF1* gene of the 17th chromosome. The distinctive feature of NF1 is the appearance of neurofibromas, a nerve sheet tumor that forms and grows on spinal, peripheral and/or cranial nerves (Gutmann et al., 2017). The condition is gradually progressive and lifelong, and there are no existing treatments. Thus, management typically involves a case by case symptom treatment with continuous surveillance of symptom evolution that aim to improve quality of life. Nonetheless, life expectancy in individuals with NF1 is reduced by 8 to 21 years compared to the general population and they have a higher rate of death prior to the age of 40 years due to the greater risk of developing malignant tumors. The worldwide prevalence of NF1 is 1 in 3000 individuals and 50% of affected children have inherited the gene, whereas the remainder of affected individuals results from a genetic NF1 mutation (Gutmann et al., 2017). Of these affected individuals, approximately 20% of children with NF1 are diagnosed with an OPG (Listernick, Ferner, Liu, & Gutmann, 2007). However, many researchers suggest that patients with comorbid NF1 and OPGs have a better prognosis than patients with sporadic OPGs alone, as the progression of the tumor is often slower and less expansive in individuals with the NF1 genetic mutation (Astrup, 2003; Listernick, Charrow, & Gutmann, 1999). In contrast, sporadic OPGs (non-comorbid) can grow considerably faster and be fatal without close monitoring and treatment (Wan et al., 2016; Kalin-Hajdu et al., 2014, Dotto et al., 2018). The clinical manifestation of NF1 is diverse, but typically involves pigmentation abnormalities (i.e. cafe au lait skin patches), skeletal dysplasia, and multiple low-grade gliomas of the central nervous system (CNS), as well as involvement of other organs (Gutmann et al., 2017). Cognitive symptoms vary based on tumor locations, but it is often associated with learning disabilities, attention deficit

hyperactivity disorder (ADHD), autism spectrum disorder traits, as well as other cognitive disabilities and visual impairment (Fisher et al., 2013; Kalin-Hajdu et al., 2014; Gutmann et al., 2017).

1.2 Tumor Localization

OPG lesions can be distinguished based on their anatomical position along the optic pathway. The affected field of view will vary from one patient to another and be determined by the anatomical position and infiltration of the tumor into the optic nerve. For circumscribed uncomplicated OPGs, visual field anomalies could point to the tumor location (Figure 1.1). There are three potential lesion sites: 1) the *optic nerve* glioma, 2) the *optic chiasmal* glioma and 3) the *retrochiasmal* glioma (Van Mierlo et al., 2013).

The *optic nerve glioma* is between the eye and the optic chiasm. In cases of involvement confined to the optic nerve, a proptosis is generally observed (Shapey et al., 2011). This localization is typically associated with unilateral blindness or a visual deficit in the ipsilateral eye.

The *optic chiasmal glioma* (figure 1.2) infiltrates the chiasm and is the most frequent type of OPG, consisting of approximately 80% of childhood OPGs (Kelly & Weiss, 2013). In cases of optic chiasm involvement, some rather characteristic losses of the visual field can occur such as a contralateral homonymous hemianopia or bi-temporal hemianopia.

The *retrochiasmal glioma* is posterior to the chiasm. The latter type is often accompanied by third ventricle or hypothalamic infiltration (Avery et al., 2011; Binning, Liu, Kestle, Brockmeyer, & Walker, 2007). In cases of hypothalamic-pituitary invasion, hormonal deficits may manifest, and in cases of invasion of the third

ventricle, a hydrocephalus may occur with signs and symptoms of increase intracranial pressure (Avery et al., 2011). Infiltration into these regions often results in heterogeneous clinical presentations as they are mainly involved in growth, sexual development, regulating sleep patterns, and appetite (Van Mierlo et al., 2013). Lesions beyond the optic chiasm typically result in contralateral homonymous hemianopia visual field defects.

Although there are general neuroanatomical guidelines facilitating tumor localization, anomalies of the visual field are non-systematic. In other words, even if two children have a tumor in the same region of the visual pathway, their functional impairment may differ. Additionally, tumors are not always well defined and circumscribed to one specific area of the optic nerve, such that a tumor may be categorized as retrochiasmal or pre chiasmal, but also expand to infiltrate the chiasm. Thus, regular assessment of the visual field during follow-up is essential and helpful in detecting tumor progression (Fisher et al., 2013; Kelly & Weiss, 2013). Contingent on tumor localization, size, and speed of progression, various treatments exist (Jahraus & Tarbell, 2006).

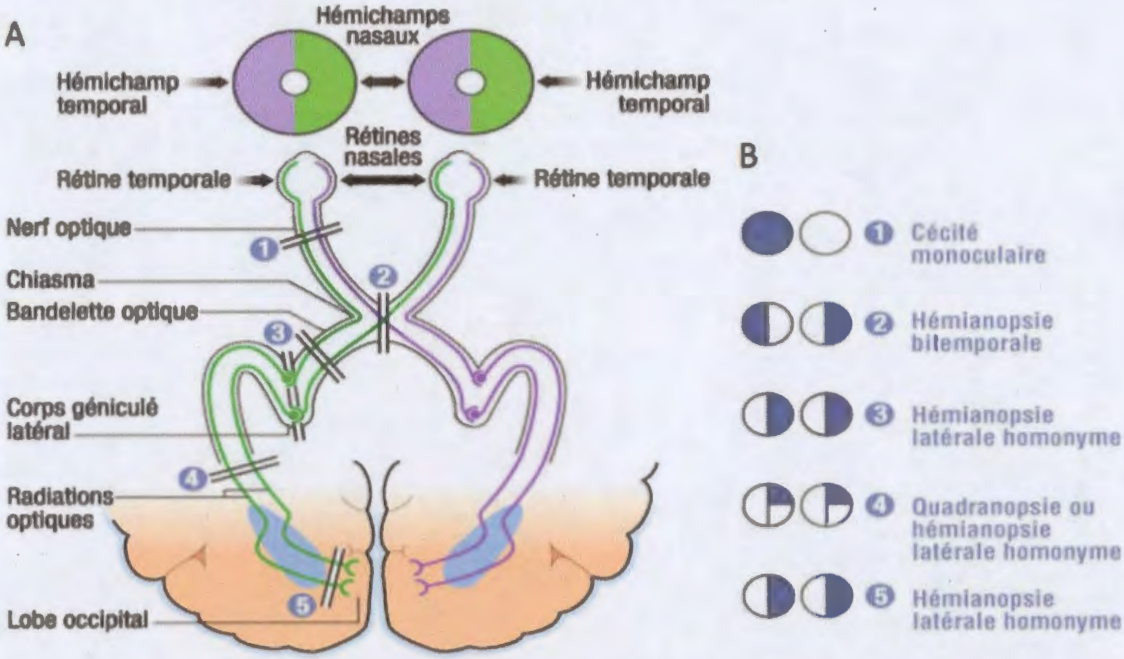

Figure 1.1 Optic pathway and associated visual deficit. A) illustration of the optic pathway from the retina to the occipital cortex; B) damage associated to the resulting visual field.

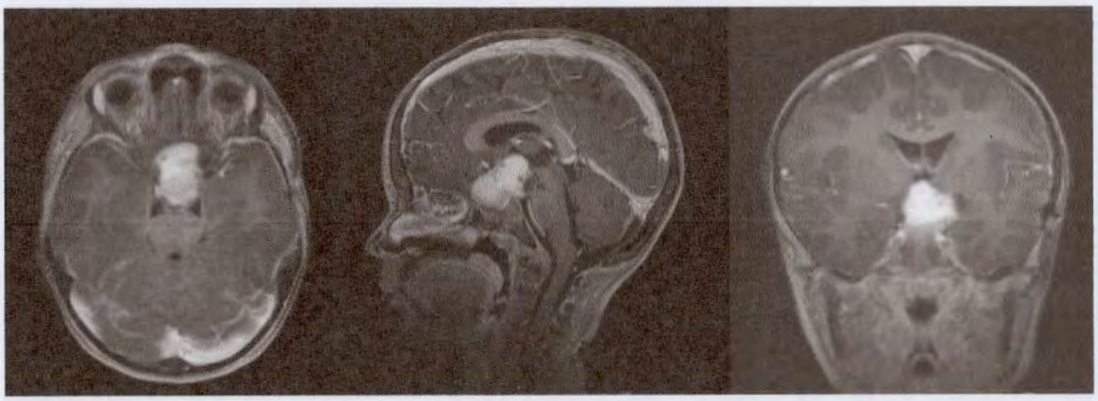

Figure 1.2 T1-weighted MRI with contrast. Axial, sagittal and coronal view of a 4-year-old boy with a sporadic OPG infiltrating the chiasm.

1.3 Treatment

The treatments of OPGs generally aim to stabilize tumor growth, maintain or improve visual function, as well as avoid mass effects and infiltration into other brain structures (Avery et al., 2011; Kelly & Weiss, 2013). Tumor progression is different from one patient to another and largely depends on the nature of the tumor, as well as its position. Some tumors are stable, non-evolving, and regularly monitored by visual acuity and visual field measurements, as well as MRI. Patients with this kind of small stable tumor can live normally without treatment but still require regular follow-ups. In contrast, some children suffer from a rapid tumor expansion, with a potential for a mass effect. These types of fast-growing tumors can substantially affect vision by infiltrating the optic nerve, which is responsible for decreased visual acuity and visual field integrity. In these severe cases, therapeutic management is crucial (Avery et al., 2011).

Treatment is only considered when necessary. Some circumstances requiring management include large tumors (with risk of mass effect), growing tumors, symptom aggravation, new symptom appearance and/ or functional impairment (Fisher et al., 2012). A review of the best treatment courses for OPGs was conducted by Jahraus and Tarbell (2006) as well as by Shapey et al., (2011). The following section will briefly describe treatment options.

1.3.1 Surgery

Surgery is rarely considered as a primary treatment option, as the risks of surgery often outweighs the benefits. The optic nerve and its surroundings are not easily accessible to neurosurgeons, making it a last resort treatment. Surgery of the optic nerve can lead to non-reversible vision loss in one or both eyes. Although there is no consensus on optimal timing for surgical intervention, it is generally considered when the tumor is causing disfiguring proptosis, blindness, a mass effect, hydrocephalus, or if the tumor

is growing and can potentially cause serious damage or be fatal (Medlock, & Scott, 1997; Binning et al., 2007; Shapey et al., 2011). However, diffuse invasion of the chiasm and/or large infiltrations are typically contraindications (Avery et al., 2011). If surgery is feasible, it has the advantage of reducing toxicity related to radio- and chemo- therapies.

1.3.2 Chemotherapy

Chemotherapy is the current gold standard for children with OPGs (Kalin-Hajdu, Décarie, Marzouki, Carret, & Ospina, 2014). It reduces the size of the tumor or steadies its growth. A study carried out on thirty young children compared chemotherapy and radiotherapy. The mean IQ after chemotherapy was 107 versus 88 in patients who had undergone radiotherapy (Lacaze et al., 2003). However, it is important to note that the results may be biased due to the fact that that radiotherapy is reserved for severe cases. Other recently published studies have examined the role of chemotherapy in low-grade gliomas, one of which included both newly and long-term diagnosed patients with OPGs. The results of this study indicated that molecules Carboplatin and Vincristine administered during a 10-week induction phase with a maintenance phase of 48 weeks led to a favorable outcome (Packer et al., 1993). Although chemotherapy can stabilize or reduce the tumor, 28-40% of children will show visual deterioration despite treatment (Kalin-Hajdu et al., 2014; Fisher et al., 2013).

1.3.3 Radiation Therapy

Radiation therapy is a regional treatment for cancers causing double-strand DNA damage to tumor cells, leading to cellular death. It is used to reduce tumor size or slow its growth (McGinn & Tarbell, 1990). The improvement of technology, in particular with 3D imaging devices, allows physicians to monitor the intensity and the target of the x-rays, avoiding excessive healthy tissue exposure. It can nevertheless be quite harmful for developing brains.

A study carried out on fifty patients indicated that only 65% of children treated with radiotherapy had a normal academic level (Cappelli et al., 1998). Children younger than seven years are at particular risk for long term neurocognitive sequelae (Jahraus & Tarbell, 2006). In the past, Horwich and Bloom (1985) reported that children under the age of seven should receive chemotherapy as a first-line of treatment, whereas those over the age of ten should receive radiotherapy. Present-day recommendations suggest that radiotherapy be used as a last resort for children with OPGs (Avery et al., 2011).

1.4 Magnetic Resonance Imaging

Treatment of OPGs is mainly prompted by functional changes in vision or by neuroradiological evidence of tumor growth. Magnetic resonance imaging (MRI) is the currently used method to monitor tumor progression, typically done every three months (Avery et al., 2011; Van Mierlo et al., 2013). However, progressive visual loss, or neurological signs can be indicative of tumor progression and result in further assessment, including additional MRIs (Van Mierlo et al., 2013). The disadvantage of conducting frequent MRIs is that it can be quite invasive for young children, since many must be anaesthetized to prevent movements during imaging (Chang et al., 2007; Van Mierlo et al., 2013). Nevertheless, it is an essential component in the management of OPGs. Another drawback is that there is often a poor correlation between tumor changes depicted by the MRI and residual visual functions measured by ophthalmologists (Fisher et al., 2012; Kalin-Hajdu et al., 2014; Kelly & Weiss, 2013; Van Mierlo et al., 2013). Since one of the main goals of treatment is to preserve visual functions, therapeutic success should consider functional visual assessments and imaging outcomes concurrently (Van Mierlo et al., 2013).

1.5 Functional Measures

Functional measures of vision are crucial for optimal diagnosis and follow up of children with OPGs. However, currently used functional visual assessments often require active cooperation and instruction understanding, which can be challenging in the young population, especially if there are comorbid cognitive deficits (Van Mierlo et al., 2013). Thus, it is crucial to find methods to evaluate children with limited attention and other learning disabilities.

1.5.1 Visual Acuity

Visual acuity (VA) assessments using consistent quantitative testing methods are recommended as the main measure of visual function (Fisher et al., 2013; Avery et al., 2011; Wan et al., 2016). VA refers to the sharpness or the clarity of vision, which varies based on the eyes ability to focus light onto the retina. There are various measures of visual acuity, usually assessed by optometrists or ophthalmologists. The Snellen Chart is the most commonly used measure, requiring that individuals read 11 lines of letters in descending order, from the largest letters to the smallest. The test is typically done monocularly from a distance of 20 feet. The smallest line of letters that can reliably be read by individuals corresponds to a number on 20, which indicates the visual acuity of the individual for that particular eye. According to the visual standard manual prepared for the International Council of Ophthalmology (2002), visual acuity of 20/12 to 20/25 is considered to be in the normal vision range (20/20 being the most common), whereas 20/80 or below is considered as low vision, with 20/200 being the threshold of legal blindness. This same measure can also be taken or transformed into a logarithm of the minimum angle of resolution (logMAR), which is increasingly used and recommended by Fisher and colleagues (2013) because it allows scores to be compared from one test to another. Other acuity tests exist for diverse populations, including young children that cannot read letters (i.e. Teller Acuity cards, Landolt C test). In fact,

many efforts have been made to measure VA as reliably as possible in the pediatric population.

Ophthalmic examinations, currently used to assess visual functions, are non-invasive and affordable. Their main limitation is the difficulty in making a precise evaluation in non-cooperating subjects, especially in children that cannot understand instructions. For instance, assessment may be a particular challenge with pre-verbal children and subjects with cognitive impairment (i.e. those associated with NF-1; Avery et al., 2011; Van Mierlo et al., 2013). In addition, VA scores are difficult to interpret due to the lack of consensus regarding the cutoffs that comprise a significant visual decline (Avery et al., 2011).

The method chosen to measure VA depends on several criteria, including age, level of cognitive development, ability to cooperate, etc. In our study, we chose to use the Functional Acuity Contrast Test (FrACT), which uses the 'Landolt C' stimuli to measure VA (Bach, 1996) . To complete this test, the child is positioned at a distance of 1.5 meters from a computer screen. The stimuli presented on the screen consists of the letter "C" presented in different orientations (Figure 1.3). The child must then indicate the position of the opening of the "C" (i.e. top, bottom, right or left), by choosing an option on the keypad containing four directional arrows. If the child is unable to distinguish the stimulus orientation, he or she is asked to respond randomly by selecting any of the four arrows. The size of the "C" is automatically adjusted at every trial based on the child's performance (i.e. if the answer is correct, the stimulus size is reduced on the next trial). This method allows us to determine the smallest font that is reliably perceived by each eye of participants. The FrACT is a monocular test, such that one eye is occluded with an eye patch during the stimulus presentation. Test results are automatically generated by the operating system, providing the logarithm corresponding to the minimum angle of resolution 'logMAR' for each eye, which was considered as the value of visual acuity at testing time.

For the purpose of this research project, we chose this test as it is suitable for young and older children alike. It does not require any alphabetical knowledge and does not require verbal cooperation. It has good sensitivity and test retest reliability, and is also considered to be a valid measure of VA (Visual Standards, 2002; Bach, 1996). Another advantage of the Landolt C test is that all targets have an equal level of difficulty, unlike other tests that use many letters of the alphabet, some being easier to distinguish than others. One disadvantage of this test is that there is a 25% chance of guessing the right orientation, even when the stimulus orientation is not detected.

Figure 1.3 FrACT - Landolt C stimuli with corresponding keypad answer.

1.5.2 Visual Field

Visual field (VF) is another visual function affected by OPGs. In fact, 89-100% of VF deficits are concurrent with VA deficits (Fisher et al., 2013). VF refers to the total area in space that can be perceived by the eye, including central and peripheral vision. The VF integrity is typically measured clinically by simple confrontation (verifying the ability to see fingers in all 4 quadrants using an arbitrary central fixation point) and computerized perimetry techniques (i.e. Humphrey and Goldmann), logically named

as they are meant to measure the perimeters of vision (Kelly & Weiss, 2006; Fisher et al., 2013; Van Mierlo et al., 2013).

Perimetry. In Goldman perimetry, currently used in clinical follow-ups for children with OPGs (Kelly & Weiss, 2006), the child is required to verbally specify whether or not they detect the presence of targets in various locations of their visual field while staring at a fixation point. Similarly, automated Humphrey perimetry requires that the child press the corresponding button when they detect targets in their VF (Kelly & Weiss, 2006). Perimetry tests are conducted monocularly and require approximately five to seven minutes per eye. Thus, although perimetry is useful in detecting blind spots or visual field deficits in cooperative patients, it is unreliable for children with poor cooperation, attention deficits and verbal comprehension difficulties (Fisher et al., 2013). Thus, perimetry remains a subjective method, as it relies on the responses of individuals to determine the perimeters of the visual field and could therefore yield invalid results for the population of interest (Kelly & Weiss, 2006). In fact, an audit was conducted on children with NF1 up to 7 years of age and none of the children were mature enough to reliably complete VF testing (Pilling, Lloyd, & Huson, 2010). In conclusion, it is important to adequately measure visual field integrity in children with OPGs, but it can be particularly difficult in this population as they are often diagnosed prior to the age of 8 years. Thus, there are concerns about the reliability of VF assessment and studies show that there are high false-positive and false-negative rates in children that are younger than 10 years of age (Fisher et al., 2013).

Since visual field integrity is often compromised in children with OPGs, and current methods (Goldman and automated perimetry) are unreliable in many cases, it is important to assess new ways of measuring visual field integrity in this population (Kelly & Weiss, 2006). It is also imperative that the method be rapid and require as little cooperation as possible since the population of interest is mostly young children, with or without verbal abilities and/or limited attention spans. Given the limitations of

perimetry, studies have been examining the potential role of electroencephalography (EEG) in measuring visual field integrity (Kelly & Weiss, 2006). Specific EEG procedures can be used as a direct measure of cortical activity in response to visual stimuli and require minimal cooperation. Thus, EEG may be a suitable tool to measure visual field integrity in the population of interest.

1.6 Electroencephalography (EEG)

Electroencephalography is the recording of electrical activity in the brain using electrodes. It is a method that has great temporal resolution, meaning that it measures cortical activity precisely within milliseconds. It is also painless, affordable, non-invasive, and easily conducted. EEG works by transcribing time plots of electrical potential variations, collected by electrodes placed on different areas of the scalp. One standard method of EEG is evoked potential (EP) analysis. Any event, whether it be perceptual, motor or cognitive, triggers a change in cortical activity in different populations of neurons. The EP is a neural signal reflecting the coordinated electrical activity of a set of neurons recorded on the surface of the scalp following stimulus presentation. Thus, EPs reflect the dynamics of cortical activity during various cognitive processes (Kiloh & Osselton, 1966).

This transient change in electrical activity in response to an external stimulus occurs almost immediately following stimulation. The extraction method developed to highlight the activity related to the stimulus was developed by P. Davis in 1939 and involves a synchronized averaging of neural firing (Chiappa, 1997). For example, EEG segments of each stimulation are averaged. This averaging method minimizes spontaneous cortical activity, allowing the specific activity of interest to emerge and appear more distinctly on recordings.

Visual evoked potentials (VEP) correspond to the cortical activity measured using EEG during presentation of a visual stimulus. There are two different types of VEPs that differ based on the rate of stimulus presentation and can be used to measure visual functions; transient VEPs (tVEPs) and steady state VEPs (ssVEPs). Typically, stimuli used to conduct VEPs are pattern reversal stimuli such as black and white flickering gratings (alternating black and white lines), or checkerboards (alternating black and white squares). The stimulus must alternate at a specific frequency in order to measure the cortical amplitude of response at that same frequency (Van Mierlo et al., 2013).

1.6.1 Transient Visual Evoked Potentials (tVEP)

VEPs are considered transient when the frequency of stimulus presentation is relatively slow (i.e. when checkers oscillate around 1 to 2 reversals per second). With this rate of stimulation, the visual system returns to its baseline state between two stimulations (Van Mierlo et al., 2013). The response obtained corresponds to a three-phase wave (negative-positive-negative; Tomoda, Tobimatsu, & Mitsudome, 1999), where each component represents the integrity of a different structure of the visual pathway from the ganglion cells of the retina to the visual cortex. In order to obtain a reliable assessment, several repetitive stimulations must be summed. The responses can then be analyzed in terms of latencies (to determine the time for the stimulus to propagate from the eye to the occipital cortex) and magnitude (Van Mierlo et al., 2013). This method typically requires good subject cooperation and a longer testing time than steady state VEPs.

1.6.2 Steady State Visual Evoked Potentials

In contrast to tVEPs, steady state VEPs are constant and repetitive, usually at a frequency of four reversals per second or more (Van Mierlo et al., 2013). This type of repetitive and rapid visual stimulation does not allow occipital neurons to return to their baseline firing rate. The main advantage of using this method is that it results in a

cortical response at the same frequency that is visually presented (Van Mierlo et al., 2013). Thus, if a pattern checkboard reverses at a frequency of 8 reversals per second (rps), there should be a high magnitude of cortical response at 8 rps in subjects with normal vision (Fig. 1.4). Another advantage of ssVEPs is that the EEG recording can be conducted in a very short period of time, and is minimally affected by movements and eye deviations, making it interesting for the pediatric population.

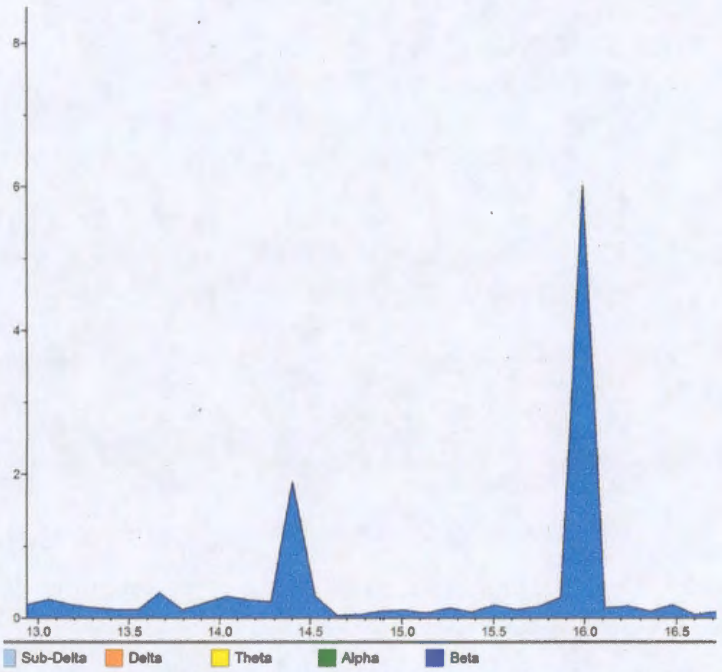

Figure 1.4 Steady-state VEP response of a participant with normal vision to a central flickering stimulus at 16 rps and a peripheral flickering stimulus at 14.4 rps.

1.6.3 Electrode placement

Electrodes do not only capture the signal, but also capture cortical noise. To reduce the influence of background cortical noise on the recorded signal, EEG amplifiers measure the signal with two electrodes: one being "active", placed over the cortical region of interest, and one being the "reference", placed far from the region of interest. Both electrodes capture approximately the same level of noise, but the active electrode also

captures the cortical activity corresponding to the specific stimulation. The amplifier then subtracts the two signals, reducing noise substantially.

The "International 10/20 System" is a standardized electrode placement recommendation system that is typically used as a guide for electrode placement in research (Jasper, 1958). Each electrode is identified by a letter and number, coding its position on various parts of the hemispheres. The letters F, T, C, P and O respectively indicate the frontal, temporal, central, parietal and occipital regions of the brain. Even numbers (2, 4, 6, 8) correspond to the right hemisphere and odd numbers (1, 3, 5, 7) correspond to the left hemisphere. The letter 'z' denotes electrodes on the central line of the brain (Figure 1.6).

To record visual processing, the active electrodes must be positioned over the occipital cortex. Some authors suggest placing 3 electrodes, one at Oz, O1 and O2 (Odom et al., 2010), but a recent study indicated that there was no significant difference in information harvested from one to three electrodes. The electrode placed at 'Oz' gathered significantly higher signals in response to central visual stimulations, and recorded a similar signal in all three electrodes for the peripheral visual stimulation (Hébert-Lalonde et al., 2014). Furthermore, using only one active electrode reduces electrode placement time, making it convenient for the population of interest.

Since the signal of interest collected by the active electrode is calculated with respect to the reference electrode, the position of the latter is critical in the recording of VEPs. Ideally, the reference electrode should be neutral, meaning that it should not be subject to the potential variations created by environmental stimuli. However, such an electrode does not exist. It is therefore a matter of choosing the best possible position. Some authors place the reference electrode on and ear lobe or at the level of the mastoid, but these two sites are lateralized. Since our active electrode is on the central line of the scalp, we opted to place the reference electrode centrally at the top of the skull at

location Fz, which is also the recommendation provided in the updated ISCEV standard for clinical VEPs (Odom et al., 2010).

Finally, a ground electrode (Jasper, 1958) is an indispensable passive electrode acting as the ground potential of the amplifier. This electrode can be placed at any location on the skull, as long as it remains constant from one participant to another. In our study, we placed the ground electrode at position C3, based on the 10/20 manual.

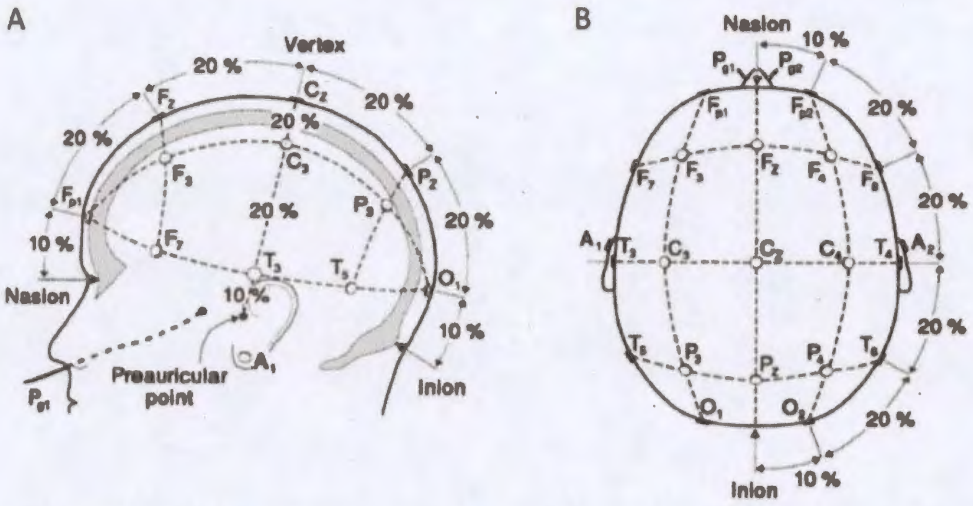

Figure 1.5 EEG electrode placement map by the international 10/20 system. A) sagittal view; B) transverse view.

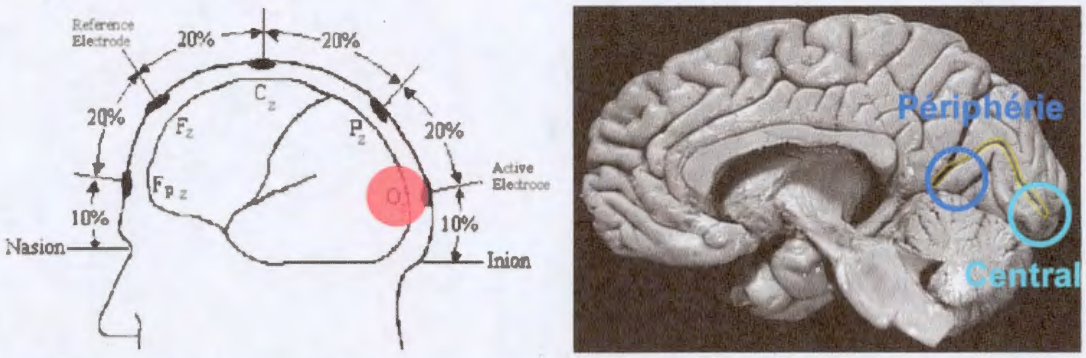

Figure 1.6 A) Illustration of active electrode at Oz. B) Calcarine fissure with underlying anatomical representation of central and peripheral visual field regions.

1.7 Using VEPs to assess visual functions

Many studies have examined the potential role of VEPs for measuring the integrity of the visual pathway (Dotto et al., 2018; Kelly & Weiss, 2006; Van Mierlo et al., 2013; Trisciuzzi et al., 2004; Falsini et al., 2008). The following section will review relevant studies that led to the premise that pattern reversal ssVEPs could be useful to assess visual functions in children with OPGs.

A recent study conducted by Dotto and colleagues (2018) used full-field transient pattern-reversal VEPs to assess visual functions in children with OPGs, with and without associated NF1. Results indicated that patients had a reduction of the P100 amplitude and a peak latency delay of the same component. The method was useful in detecting visual dysfunction in two-thirds of patients with OPGs by uncovering subclinical visual loss. Additionally, the study showed that the VEP method provides additional and complimentary information, which is not always provided by measures of VA and MRI. This research study also corroborated previous findings, indicating that visual abnormalities were more frequent and severe in patients with sporadic, non-NF1 related OPGs. This study concluded that VEPs are useful in detecting visual deterioration in children with OPGs and can help in adjusting the treatment before optic atrophy is detected.

Van Mierlo and his colleagues (2013) conducted a review of the literature that aimed to assess the role of transient pattern reversal visual evoked potentials in the screening and monitoring of OPGs in children with and without NF1. They included articles from years 1980 to 2012. Based on this literature review, they concluded that there was no unanimity regarding the added value of transient VEPs for children with OPGs. Many studies use different testing parameters and protocols, which makes it difficult to compare data. Many of these studies also have limitations that cannot be overlooked. For instance, some studies did not include a control group and most had small sample

sizes. This review therefore concludes that there is no consensus regarding the specificity and the sensitivity of this method for the diagnosis and follow up of OPGs. The authors recommend a prospective multicentric study, which would give a better indication of the usefulness of this method. However, this review mostly included studies that used transient VEPs, as very few studied have used a steady state stimulation protocol. The authors nonetheless allude to two research studies that have been conducted using ssVEPs. They conclude that this type of protocol seems to be a rapid alternative to transient VEPs but specify that further research is needed to determine the added value of this protocol relative to VA and MRI.

In both studies that were conducted using steady state VEPs (Trisciuzzi et al., 2004; Falsini et al., 2008), the visual stimulation was conducted using a uniform field flicker by means of a mini-ganzfeld (i.e. a type of light emitting goggle). This kind of stimulation is advantageous for young children with very limited cooperation and poor fixation abilities, but it comes at the cost of practical applicability, as it does not provide information about the affected areas of the visual field and the ability to perceive and focus on environmental stimuli. Nonetheless, the study by Trisciuzzi and colleagues yield a detection sensitivity of 83.3%, which supports the usefulness of adding ssVEPs as an additional tool to assess visual functions in uncooperative children with OPGs. A follow up longitudinal study conducted by Falsini and colleagues (2008) aimed to assess children with OPGs over time and verify the association between MRI tumor evolution and the ssVEP responses. Results indicated a 78.9% association between both methods and the authors conclude that VEPs can predict changes in MRI and should therefore be used as a complimentary tool to MRI for the follow up of OPG.

There is still controversy in the literature concerning the usefulness of VEPs for screening and monitoring of OPGs. Studies that claim that VEPs could be useful argue that it is cost effective and sensitive in detecting OPGs, as well as a good complimentary tool to perimetry in uncooperative children (Kelly & Weiss, 2006;

Wolsey, Larson, Creel, & Hoffman, 2006). Some studies also add that VEP testing is a better indicator of central visual field deficits than visual acuity testing in uncooperative children (Kelly & Weiss, 2006; Kelly & Weiss, 2013).

In contrast, other authors disagree that VEPs could replace any of the currently used methods. For instance, Siatkowski (2006) is against the cost-effective argument, as VEPs will never replace MRIs. The cost of VEPs should instead be compared to the cost of an ophthalmic examination, making it an equally affordable method. He also states that the specificity and sensitivity of the method is affected by the cooperation of the child, which is limited in perimetry, as well as in VEP testing. Siatkowski (2006) concludes that the VEP method cannot replace the classic ophthalmologic examination for now and emphasizes the need for the development of increasingly accurate VEP protocols. However, it is important to emphasize that most studies examining the potential usefulness of VEP testing in the diagnosis and monitoring of OPGs do not state that it can replace any of the current methods, but can add value to them (Ammendola, Ciccone, & Ammendola, 2006; Kelly & Weiss, 2006; Wolsey, Larson, Creel, & Hoffman, 2006; Dotto et al., 2018).

Another ambiguous part of the literature regarding the use of VEPs to assess vision in children with OPGs involves the uncertainty in the testing parameters. For instance, some studies use flash VEPs (Trisciuzzi et al., 2004; Groswasser, Kriss, Halliday, & Mcdonald, 1985), others use sweep VEPs (Chang et al., 2007), multifocal VEPs (Hood et al., 2006), and full field stimulation (Ammendola et al., 2006; Falsini et al., 2008; Dotto et al., 2018). Groswasser and his colleagues (1985) tested 25 children with pattern and flash/flicker evoked potentials and concluded that flash potentials were less sensitive and reliable in monitoring tumor progression in children with OPGs. Generally, there is no consensus regarding ideal stimulation conditions to measure the integrity of the visual field using VEPs (Van Mierlo et al., 2013).

The rate of stimulus presentation is another debated part of the literature as some use transient stimulation (Kelly & Weiss, 2006; Falsini et al., 2008), and others opt for steady state stimulation (Trisciuzzi et al., 2004; Falsini et al., 2008). Also, there seems to be diverse electrode placements throughout studies measuring visual field integrity. For instance, Kelly and Weiss (2006) used three electrodes at locations O3, Oz and O4, whereas Falsini and colleagues (2008) used one electrode placed three centimeters above the inion.

Taken together, these studies reveal that there is no agreement on testing conditions and no consensus regarding the clinical usefulness of VEP testing in children with OPGs. Many authors emphasize the need for additional studies, allowing us to determine whether VEPs could potentially improve diagnosis and management of childhood OPGs (Van Mierlo et al., 2013).

1.8 Problematic

Visual acuity and visual field integrity are both compromised in children with OPGs. Current clinical methods to assess visual functions in children include visual acuity testing and perimetry; two methods that require understanding of instructions and active verbal cooperation. Therefore, these methods are often unreliable for the pediatric population, especially for pre-verbal children or those with added cognitive disabilities. Since the average age at diagnosis is 4 years old and most children are diagnosed prior to the age of eight years, it is important to find appropriate methods to measure visual functions in that population.

One method that has been explored and shows promise in its ability to detect visual field deficits is VEPs. Field-specific VEPs have been used to measure visual responses to central and peripheral visual stimuli (Harding, Robertson, & Holliday, 2000; Hébert-Lalonde et al., 2014; Dotto et al., 2018). Although this approach is useful for some

populations, its current clinical application for children with OPGs is not optimal since field-specific VEPs are usually tested from transient VEPs (i.e., from low-rate abrupt stimulus presentations). This type of presentation requires a relatively high number of trials and patient collaboration to ensure reliable responses, making it difficult to measure visual functions in children with limited attention.

A field-specific method using steady-state VEPs to assess visual functions has recently been examined in adolescents (Hébert-Lalonde et al., 2014). By contrast to transient VEPs, ssVEPs are obtained following fast-rate stimulus presentation (4 rps or more) so that the brain generates electrical activity at the same frequency as the displayed visual stimulus. This technique can be conducted in a very short period of time (on the second scale rather than the minute scale), which makes ssVEPs a potentially valuable tool for examining visual functions in children with a limited attention span in a clinical setting. Since future OPG clinical trials must include reliable visual function assessments, ssVEPs could be a potentially useful tool to reliably and rapidly assess the visual field, as well as to evaluate treatment response.

1.8.1 Objective and hypotheses

The goal of this thesis was to validate a non-invasive, well-tolerated, fast and reliable electrophysiological tool to measure visual field integrity that requires minimal participant comprehension and cooperation. Accordingly, the aim was to assess whether ssVEPs can become a valuable tool to measure central and peripheral visual processing in children with OPGs. We hypothesize that children with OPGs will have a lower magnitude of response to flickering visual stimuli in the central and peripheral visual fields compared to an age matched control group with normal vision.

1.9 Ethics

This project was approved by the Sainte-Justine ethics committee (#2016-1038). The consent form is attached in annex. Parents of children were permitted to be present during testing and were provided with all the information pertaining to the research project verbally, as well as on paper. Children were also provided with all information in concise and simplified language. All participants and guardians were told that they were free to discontinue at any time without judgment nor consequences (compensation will still be given if study is discontinued). Given that the study used electroencephalography as an objective measure of visual functioning, participants were given all the relevant and genuine information about the goals of the study. All information is kept in a locked cabinet with restricted access and participants were given a number ID to ensure confidentiality and anonymity. Young children were made comfortable prior to the study using toys and they were reassured that the procedure is completely safe and painless. Finally, participants and their parents were informed that they would not directly benefit from the study, but that they will be contributing to the advancement of knowledge and science in the field of vision.

CHAPTER II

RESEARCH ARTICLE

CENTRAL AND PERIPHERAL STEADY-STATE VISUAL EVOKED POTENTIALS IN CHILDREN WITH OPTIC PATHWAY GLIOMAS

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Central and Peripheral Steady-State Visual Evoked Potentials in Children with Optic Pathway Gliomas

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2.1 Abstract

Purpose: Treatment of optic pathway gliomas is prompted by neuroradiological evidence of tumor growth, usually associated with progressive visual loss. Despite therapy, approximately 40% will show visual deterioration. Treatment outcome is largely based on the preservation of vision. However, current visual function assessment is often unreliable in children with optic pathway gliomas who have limited collaboration. Thus, there is a need for new clinical tools to evaluate visual functions in these children. The aim of the study was to assess the value of steady-state visual evoked potentials as a tool to assess function in the central and peripheral visual fields of children with optic pathway gliomas.

Method: Ten patients with optic pathway gliomas and 33 healthy controls (ages 3 to 18 years) were tested using steady-state visual evoked potentials. The circular dart-board stimulus consisted of one central circle alternating at 16 reversals/second and one peripheral hoop alternating at 14.4 reversals/second, separated by a hoop of gray space. It was presented monocularly at 30% and 96% contrasts.

Results: Results indicated that central signal-to-noise ratios were significantly lower in children with optic pathway gliomas compared to controls. However, no significant group difference was detected in the peripheral visual field.

Conclusion: Steady-state visual evoked potentials could eventually be implemented in the clinical assessment and follow up of central visual field deficits in uncooperative or non-verbal children but seem to have limited usefulness for evaluation of peripheral visual field deficits. Additional studies are needed to identify testing parameters for full visual-field assessment.

Keywords: steady state visual-evoked potential; optic pathway glioma; visual field assessment, optic nerve

2.2 Introduction

Optic pathway gliomas (OPG) represent 4 to 6% of pediatric central nervous system (CNS) tumors and are usually diagnosed prior to the age of 8 years [1-3]. They are classified as pilocytic astrocytoma's (Grade I) by the World Health Organisation [4]. Children with OPGs typically develop visual impairments, including decreased visual acuity (VA), and abnormal visual fields (VF). Patients can also present limited eye movements, proptosis, and nystagmus [5-8]. OPGs develop in 15%–20% of children with the common autosomal dominant cancer-predisposition syndrome called neurofibromatosis type 1 (NF1)[9]. The prognosis of children with OPGs is variable, mainly related to the localization, size, degree of extension of the tumor, as well as the age at diagnosis [10].

There are three potential lesion sites. The optic nerve glioma is typically associated with a unilateral visual deficit and may cause proptosis [6, 11]. The optic chiasmal glioma infiltrates the chiasm and is the most frequent type consisting approximately 80% of child OPGs [1]. In cases of chiasm involvement, some rather characteristic losses of the VF can occur such as a contralateral homonymous hemianopia or bi-temporal hemianopia [12]. The retrochiasmal glioma is often accompanied by third ventricle or hypothalamic infiltration. In cases of hypothalamic-pituitary invasion, hormonal deficits may manifest, and in cases of invasion of the third ventricle, a hydrocephalus may occur [6, 10, 13]. Infiltration into these regions results in heterogeneous clinical presentations and can affect growth, sexual development, sleep patterns and appetite [10].

Magnetic resonance imaging (MRI) is typically the modality of choice to evaluate tumor progression, location, as well as treatment response [6, 11, 14]. Additionally, assessment of visual function is essential and the '*Response Evaluation in Neurofibromatosis and Schwannomatosis Visual Outcomes Committee'* suggested that

VA measurement be the main functional outcome measure for NF1-OPG clinical trials [5]. Evaluation of optic nerve pallor is also useful [5] and more recently, optical coherence tomography (OCT) has enabled identification of decline in the circumpapillary retinal nerve fiber layer thickness of children with progressive OPGs [15]. Although OCT is effective, it sometimes requires sedation in young and/or uncooperative children. Despite the use of various assessment tools in children with OPGs, the objective and reliable evaluation of the VF remains problematic.

VFs are typically measured clinically using perimetry, but this modality requires active cooperation of subjects, making it unreliable for pre-verbal and uncooperative children, as well as for children with attention deficits and cognitive disabilities, which are common in NF1 [5, 8, 16]. Since VF integrity is often compromised in young or uncooperative children with OPGs, the need for new clinical tools that allow rapid and reliable measurement of the VF is imperative [9]. Given the drawbacks of perimetry, studies have explored the potential of visual evoked potentials (VEPs) as a tool for evaluating VF integrity [17-19]. One study by Fortune and colleagues compared multifocal VEPs and standard automated perimetry in patients with high-risk ocular hypertension or early glaucoma. Results indicated similar levels of specificity in detecting visual deficits and the two methods agreed on 80% of cases, suggesting that they measure slightly different functional deficits. Nevertheless, there was an 80% agreement between methods, indicating that VEPs could be a valuable tool to measure VF deficits.

Interestingly, VEPs allow for direct measurement of occipital activity, can be obtained without verbal statement, and necessitate minimal cooperation. VEPs can be obtained using various presentation methods, yielding transient VEPs or steady state VEPs (ssVEP) depending on the rate of stimulation. Many studies have used transient VEPs, which require multiple trials, a relatively long testing time (approximately 30 minutes)

and are greatly affected by gaze deviations. On the other hand, ssVEPs can be obtained faster (second time scale) and are less affected by gaze deviations, making it interesting for the paediatric population. Steady state stimulation requires a higher reversal rate which does not allow the visual system to return to baseline, resulting in a cortical response at the same frequency as the visual stimulation. Thus, if a pattern reverses 10 times per second, there should be a cortical response at 10 Hz (in subjects with normal vision). Moreover, ssVEPs do not involve any physical discomfort which offers the possibility to repeat the assessment as many times as it is deemed relevant by the clinician, allowing for regular follow up of tumor progression.

Given the advantages of ssVEPs for the paediatric population, the current study aimed to establish the feasibility of recording field specific ssVEPs in children with OPGs, whose comprehension and cooperation capacity can be limited. We hypothesized that children with OPGs will have a lower amplitude of response to visual stimulation in the central and peripheral VFs compared to an age matched control group with normal VA.

2.3 Method

2.3.1 Participants

Ten patients with a diagnosed OPG between the ages of 3 and 18 years were recruited (M = 8.10, SD = 4.18). Patients were either in therapy or followed conservatively at the *Centre Hospitalier Universitaire Sainte-Justine* in Montreal. MRI and neuro-ophthalmogic evaluations were required one month prior to enrollment. Patients with photosensitive epilepsy and moderate to severe cognitive delay were excluded from the study (see Table 2.1 for description of patients). Additionally, 33 healthy control participants ages 4 to 18 years ($M = 9.67, SD = 4.05$) were recruited through snowball sampling. Controls had normal acuity (with or without spectacle correction ranging

from -0.22 to 0.28, $M = 0.12$, $SD = 0.12$) and were excluded if they had any known neurological disease or visual dysfunction. One control participant had a VA measure slightly over the normal cut-off in one eye (LogMAR = 0.28), but the data was maintained for analyses as all SNRs were similar to other controls and the other eye had normal vision. VA was measured using the Landolt C procedure described below and normal visual acuity was defined as an acuity score below the cut-off of 0.2 LogMAR based on the visual standards described by the International Council of Ophthalmology [20]. Informed consent was obtained from all individual participants for whom identifying information is included in this study. The protocol was approved by the CHU Sainte-Justine Ethics Committee (reference number 2017-1445).

2.3.2 Stimuli

The stimulus was a circular dart-board consisting of one central circle and one peripheral hoop separated by a hoop of gray space measuring 9.9 centimeters (Fig. 2.1). The area of each check element of the pattern stimulus was increased with eccentricity to account for cortical magnification [21]. To make a dissociation between central and peripheral vision, the pattern-reversal rates were different in the central and peripheral areas of the VF and separated by a hoop of gray space. The central circle was 3.75 centimeters in diameter, stimulating 10° of the VF (5° in each hemifield). The central dart-board alternated at a rate of 16 reversals/second (8 Hz). The peripheral hoop, 33.75 centimeters in diameter, stimulated 20 to 60° of VF and alternated at a rate of 14.4 reversals/second (7.2 Hz). The temporal frequencies were selected based on previous studies using pattern-reversal ssVEPs [22], and were selected to include an integer number of screen refresh cycles. The stimulation consisted of field specific pattern reversal checkers alternating between maximal and minimal luminance levels. The mean luminance of the stimuli was 49 cd/m^2. Stimuli were presented at two contrast levels: 96% and 30%. The low contrast condition was used to prevent potential ceiling

effects in the high contrast condition and to avoid transient luminance changes associated with LCD screen at high contrast levels [23].

The center of the dart-board had a chromatic central fixation dot to draw visual attention of children to the center of the target. The fixation dot was 1 degree of visual angle in diameter and alternated slowly from yellow to green at a random rate (between 0.3 to 1 Hz) to prevent any interference on the steady state responses. The stimulus was designed using Matlab® and presented on LED backlight technology LCD monitor (model BenQ XL2730Z) with a resolution of 1920 x 1080 pixels and a refresh rate of 144 Hz.

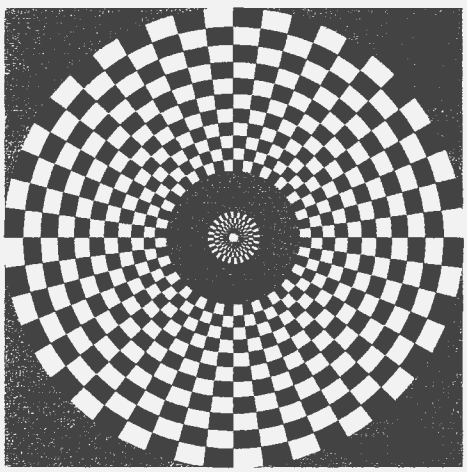

Figure 2.1 The illustrated stimulus was presented at two different contrast levels, at 96% (maximal contrast as seen in the figure) and at 30% contrast. Central circle alternated at a reversal rate of 16 reversals/s and peripheral hoop at 14.4 reversals/s.

2.3.3 Steady State VEP Recordings

Visual acuity was assessed at a distance of 150 cm from the screen for each eye using the 'Landolt C' test, implemented by the Freiburg Vision Test program (FrACT; Version 3.9.8c) [24]. Test results were reported using the logarithm corresponding to the minimum angle of resolution 'logMAR'. Near acuity was not assessed. Following the acuity test, three electrodes were placed on the participant's scalp based on the International 10/20 System [25]. The active and the reference electrodes were located

at Oz and Fz, respectively, and the ground electrode at C3.

A chin rest was placed 20 cm away from the screen to standardize viewing distance and minimize head movements. Participants were instructed to fixate the central dot on the screen, as well as avoid moving and blinking during presentation. Breaks were permitted after each 10-second stimulation period to rest the eyes and move. An eye patch was placed on one eye, while the other eye was being stimulated. The stimulus was presented at 96% contrast for 10 s, followed by the same stimulus at 30% contrast for 10 s. The eye patch was then switched, and the same stimulation followed for the other eye. This formula was repeated four times per eye, totaling 80 seconds of ssVEP recordings per eye. This procedure was implemented for all participants, including three patients without light perception in one eye.

2.3.4 Signal Analysis

EEG data was recorded with the V-Amp system (Brain Products, Inc., Munich, Germany), using passive Ag/AgCl electrodes at a sampling rate of 1000 Hz. A Butterworth Zero Phase filter was applied with cutoffs from 1 to 30 Hz and a time constant of 0.159. Data was extracted for the 16 segments of 10 seconds per participant (2 contrast levels repeated 4 times per eye). The magnitude of response for each identical condition was averaged, yielding four separate ssVEP magnitudes per participant (left and right eyes at 30% and 96% contrasts). EEG data was extracted using a Discrete Fourier Transform (DFT) with a spectral resolution of 0.06 Hz conducted with Brain Vision Analyzer version 2.1. To avoid spectral leakage, segments were re-sampled and truncated to a whole number of cycles of the frequencies of interest. The central frequency time window was 8125 milliseconds resulting in 65 full cycles and the peripheral frequency window was 8195 milliseconds, yielding 59 full cycles. Signal analysis was conducted according to the recommendations of Bach & Meigen [26].

Magnitudes at the two frequencies of interest were extracted, as well as the background noise levels at two neighboring frequencies, that is 15 and 17 Hz for the central stimulation frequency and at 13.4 and 15.4 Hz for the peripheral frequency. Noise bins were then averaged and used to calculate a signal-to-noise ratio (SNR) for each participant and then log10-transformed for statistical analyses, using SPSS Statistic® software (version 18.0). The signal at the 14.4 and 16 Hz had to exceed the average noise calculated at two neighboring frequencies by a factor of 2.8 to reach a 5% significance level [27].

Table 2.1 Patient characteristics.

Patient	Sex	Age	NF1	Chemo	Surgery	Radio-therapy	VA RE	VA LE	Localization	NDD
1	M	4	N	Y	STR	N	.81	NLP	Hypothalamic Chiasmatic	None
2	M	16	Y	Y	N	Y	1.11	NLP	Prechiasmatic (bilateral) Chiasmatic	ADHD LD
3	F	8	N	Y	STR	N	0.12	LP	Hypothalamic Chiasmatic	None
4	F	5	Y	Y	N	N	.58	.28	Prechiasmatic (right) Chiasmatic	ADHD SD
5	F	9	Y	Y	N	N	-.01	LP	Prechiasmatic (bilateral)	ADHD LD
6	F	9	Y	N	N	N	.05	.28	Prechiasmatic (bilateral)	None
7	M	11	N	N	STR	N	NLP	-.13	Hypothalamic Chiasmatic	None
8	F	3	Y	Y	N	N	.27	.16	Prechiasmatic (right) Chiasmatic	None
9	M	12	Y	N	N	N	.05	.23	Prechiasmatic (right)	ADHD LD
10	F	5	Y	Y	N	N	.67	LP	Prechiasmatic (left)	ADHD DD

Y = yes; N = no; NF1 = neurofibromatosis type 1; VA= Visual Acuity (in LogMAR), RE = Right Eye, LE = Left Eye, LP = light perception, NLP = No Light Perception; STR = SubTotal Resection (all in the right eye); NDD = neurodevelopmental disorder; ADHD = Attention Deficit Hyperactivity Disorder; LD= Learning Disabilities; SD = Speech Delay; DD = Developmental Delay.

2.4 Results

Total testing time was approximately 15 minutes, including explanation, electrode placement and stimulation time (160 seconds). The method successfully measured ssVEPs in all participants, except for one control that was excluded due to technical issues during stimulus presentation. All ssVEPs were transformed to SNRs prior to statistical analyses (see method section). Additionally, cortical noise levels were compared across all conditions between the patient group ($M = 0.09$, $SD = 0.05$) and the control group ($M = 0.11$, $SD = 0.12$) and results indicated no significant group differences [$F(1,300) = 0.48$, $p = .494$, $f^2 = .009$]. The datasets analysed during the current study are available from the corresponding author on reasonable request.

First, analyses were conducted to assess general features of the method in the control group. There were no significant SNR differences between the left ($M = 16.37$, $SD = 26.44$) and right ($M = 12.64$, $SD = 16.34$) eyes of controls [$F(1,230) = 0.55$, $p = .461$, $f^2 = .002$]. Specifically, there was no interaction between eyes and contrast level [$F(1,228) = 0.06$, $p = .812$, $f^2 = .004$], nor between eyes and visual field [$F(1,228) = 0.63$, $p = .429$, $f^2 = .002$]. Additional analyses were conducted to determine if there was a correlation between the age of participants and the SNRs. An average of the left and right eyes of control participants was calculated for each condition and results revealed no correlation between age and SNRs at 96% contrast for both the central [$r(31) = 0.28$, $p = .116$] and the peripheral [$r(31) = -0.01$, $p = .950$] SNRs, nor at 30% contrast, for central [$r(31) = 0.24$, $p = .184$] and peripheral [$r(31) = -0.14$, $p = .432$] stimulations (Fig. 2.2).

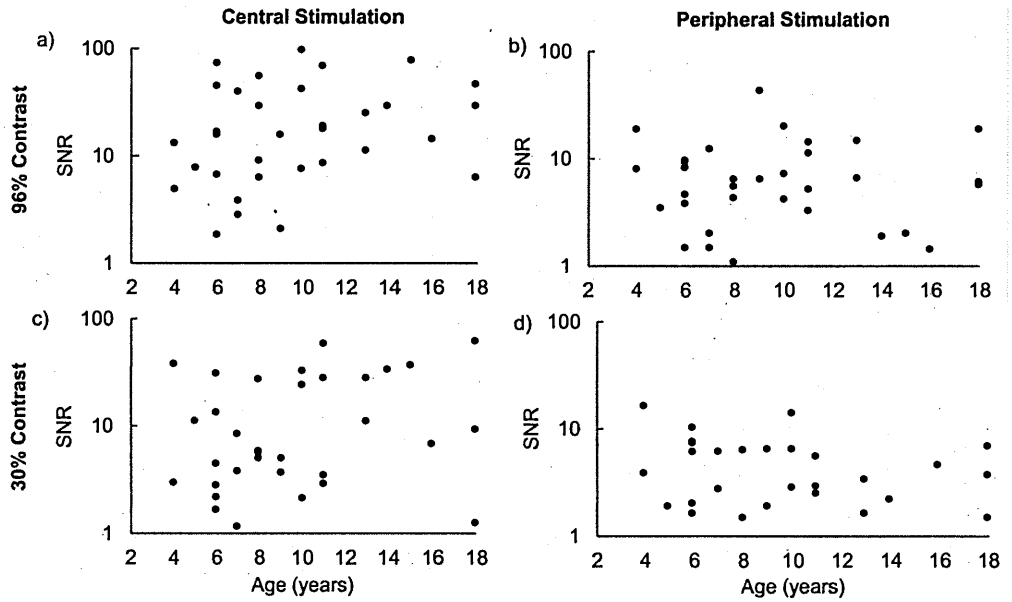

Figure 2.2 Scatterplots showing the lack of association between the age of control participants and their averaged signal to noise ratios (left and right eyes) to central stimulation at 96% contrast level (a) and 30% contrast (b) and to peripheral stimulation at 96% contrast level (c) and 30% contrast (d).

To assess test re-test reliability, ten control participants were tested twice with an average interval of 82 days ($SD = 58$). The agreement and systematic error between the two measures is qualitatively illustrated in Figure 2.3 using a Bland-Altman plot. Data points close to the zero line indicates that the SNR of the participant in question remained similar from the first testing session to the second. Almost all data points lie within the upper and lower 95% CI for both eyes at both contrast levels, indicating similar test-retest magnitudes at the central VF stimulation for all participants tested twice.

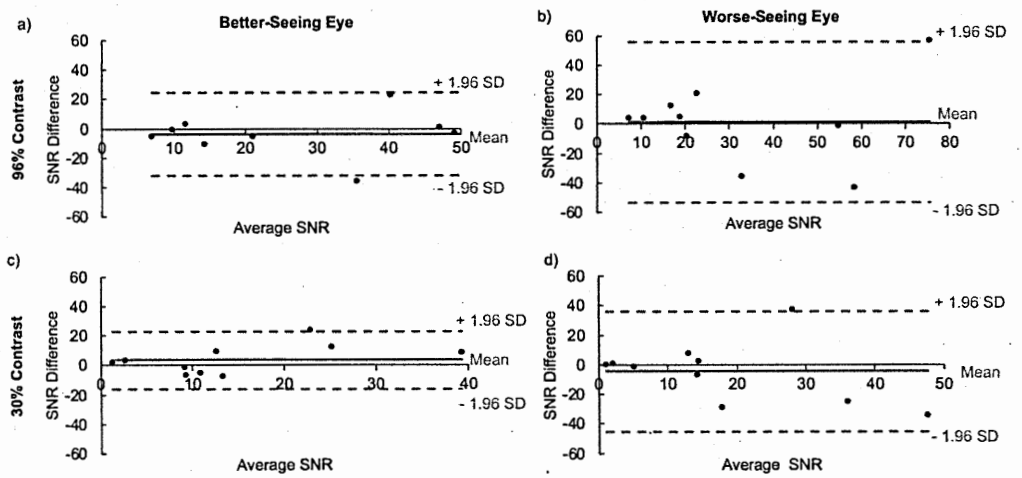

Figure 2.3 Bland-Altman plots illustrating the SNR difference for the central stimulation between the first and second assessment time of 10 control participants (SNR time 1 – SNR time 2). The solid black lines at the 0 value indicates perfect agreement between the first and second testing session. The gray lines represent the mean difference between both testing sessions for all participants. The dotted lines represent the 95% confidence intervals. a) Better-seeing eye, 96% contrast; b) Better-seeing eye, 30% contrast; c) Worse-seeing eye, 96% contrast; d) Worse-seeing eye, 30% contrast.

For the following analyses, a better-seeing eye was determined based on the VA score of each participant (logMAR) and the other eye was assigned as the worse-seeing eye. For control participants that had no inter-ocular differences in VA, either eye was randomly selected as worse-seeing eye. Patients with light perception or worse were given a logMAR of 3 for analyses, which is the highest logMAR value [28]. Pearson correlations were carried out to determine whether there was an association between the SNRs of the central VF and VA for all participants grouped together (Fig. 2.4). As expected, there was a significant correlation between the VA in the better-seeing eye and central SNRs at 96% contrast [r (41) = -.50, p = .001], as well as at 30% contrast [r (41) = -.40, p = .008]. This correlation was also significant between the VA in the worse-seeing eye and the central SNRs at 96% contrast [r (41) = -.68, p < .001] and at 30% contrast [r (41) = -.65, p < .001]. Correlation coefficients are negative because a

lower VA score in logMAR indicates better VA, whereas a higher SNR indicates a greater signal magnitude. The correlations were also carried out within the control and patient groups separately and results indicated no statistically significant correlation (p values > 0.2) when conducted within the control group alone, yet the coefficients were all negative (r *values* ranging from - .1 to - .21). Similarly, correlations conducted in the patient group were all negative (r values ranging from - .21 to - .67) and there was a statistically significant relationship for the worse-seeing eye at 96% contrast ($p = .04$). However, correlations in the patient group may be artificially inflated because patients with a VA of light perception or worse were assigned a logMAR of 3 for analyses.

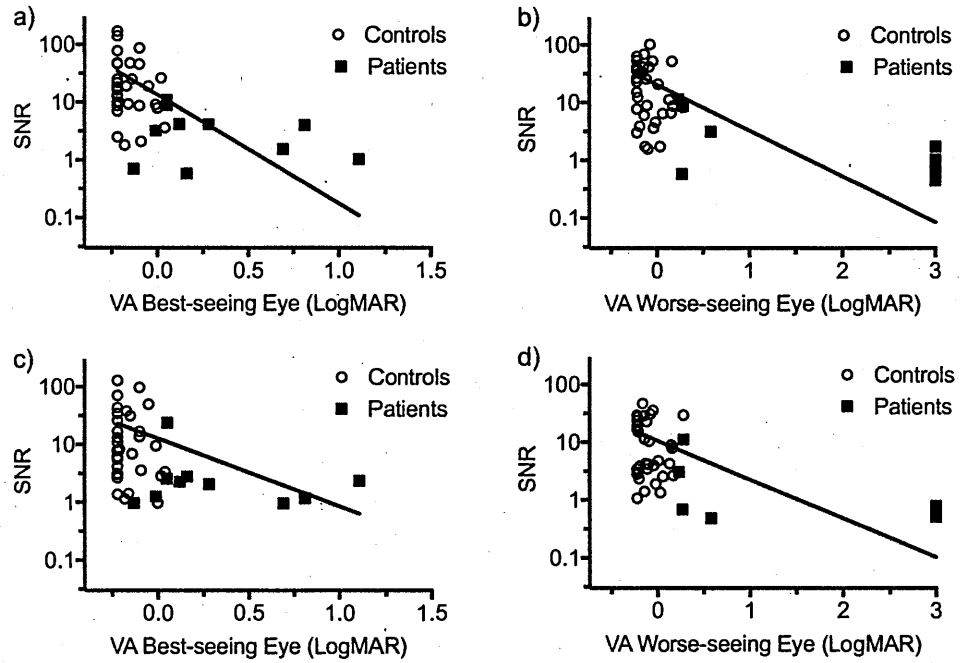

Figure 2.4 Scatterplots showing the correlation between the visual acuity and central stimulation SNRs of the patients and control participants. Control participants are represented by black circles and patients are represented by the white squares. a) Better-seeing eye, 96% contrast; b) Worse-seeing eye, 96% contrast; c) Better-seeing eye, 30% contrast; d) Worse eye, 30% contrast. Lower LogMAR values represent better visual acuity and higher SNRs indicated a higher ssVEP magnitude of the stimulation frequency. Straight lines (linear regressions) illustrate the statistically significant relationships between SNR and logMAR visual acuity (see result section for details).

For the main analysis of this study, a factorial mixed ANOVA was conducted to assess group differences in all conditions (Fig. 2.5 for central VF stimulation; Fig. 2.6 for peripheral VF stimulation). Overall, the patient group had a significantly lower SNR ($M = 4.88, SD = 7.39$) compared to the control group ($M = 14.50, SD = 22.01$), yielding a significant main effect [$F(1,43) = 22.21, p < .001, f^2 = .516$]. There was a significant

group by eye interaction [F (1,301) = 8.85, p = .003, f^2 = .030]. The patient group had a significantly lower SNR compared to the control group for both the better-seeing (patients: M = 7.08, SD = 9.55; controls: M = 16.37, SD = 26.44) and the worse-seeing eye (patients: M = 2.69, SD = 3.07; controls: M = 12.64, SD = 16.34), where the difference between groups was significantly greater in the worse-seeing eye. There was also a group by visual field interaction [F (1,301) = 51.08, p < .001, f^2 = .170]. The patient group had a significantly lower SNR compared to the control group in the central visual field (patients: M = 3.20, SD = 5.58; controls: M = 22.21, SD = 28.14), but this difference was not present in the peripheral visual field (patients: M = 6.56, SD = 9.15; controls: M = 6.80, SD = 7.84). Lastly, there was no group by contrast interaction [F (1, 301) = 1.48, p = .225, f^2 = .005], such that the effect was present in both contrasts. A second analysis was conducted using the identical model described above while controlling for VA to ensure that the group differences in SNRs are not solely explained by the differences in VA. Thus, the factorial mixed ANCOVA was conducted with visual acuity as the control variable. This analysis yielded very similar findings to the original model, indicating that the observed group differences were not exclusively a result of the lower VA in the patient group.

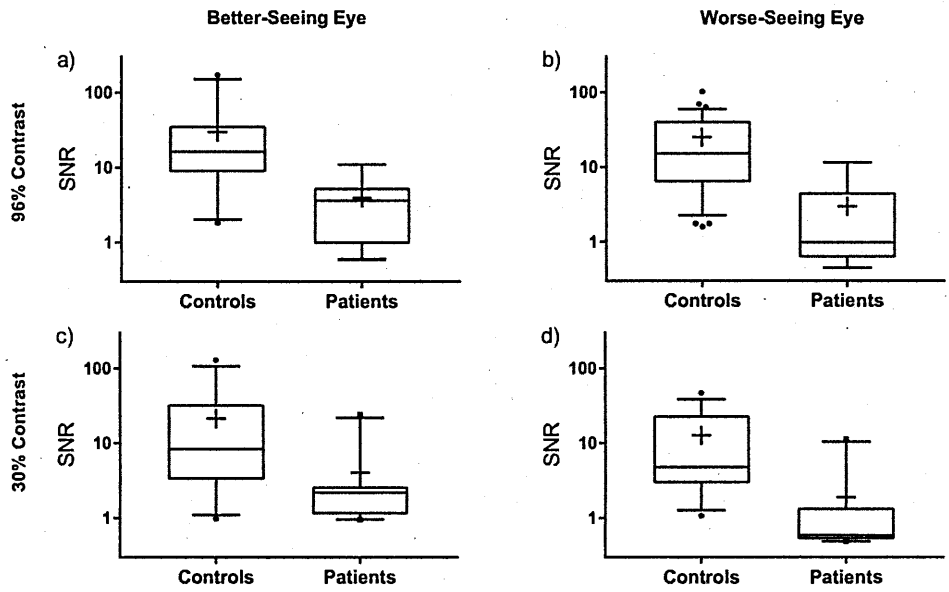

Figure 2.5 Boxplots depicting the SNRs of patients and controls for the central VF stimulation. a) Better-seeing eye, 96% contrast; b) Worse-seeing eye, 96% contrast; c) Better-seeing eye, 30% contrast; d) Worse-seeing eye, 30% contrast. Error bars depict the 5% and 95% percentiles, the length of the box represents the upper and lower quartiles (i.e., the 75th and 25th percentiles, respectively), the median is identified by the line inside the box and the mean is identified by the plus sign.

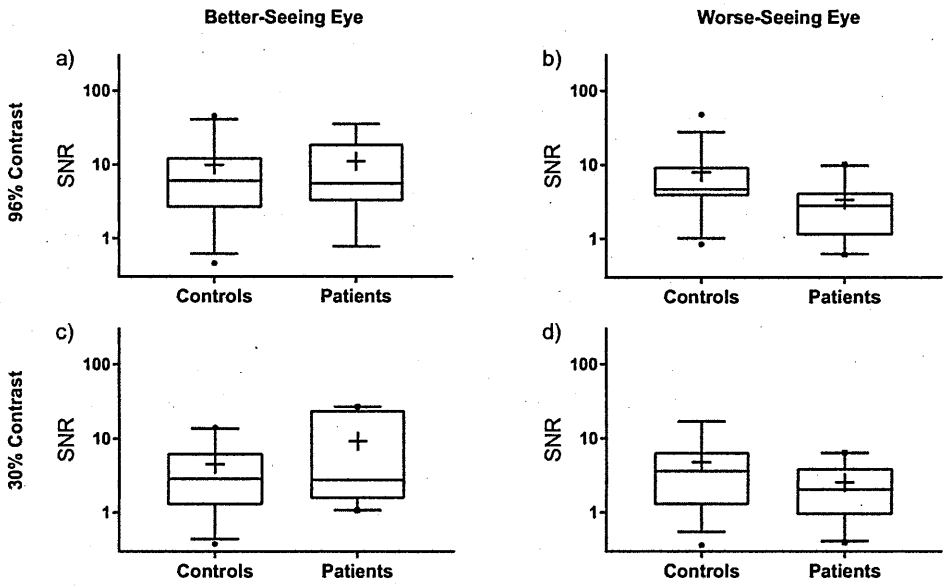

Figure 2.6 Boxplots depicting the SNRs of patients and controls for the peripheral VF stimulation. a) Better-seeing eye, 96% contrast; b) Worse-seeing eye, 96% contrast; c) Better-seeing eye, 30% contrast; d) Worse-seeing eye, 30% contrast. Error bars depict the 5% and 95% percentiles, the length of the box represents the upper and lower quartiles (i.e., the 75 and 25th percentiles, respectively), the median is identified by the line inside the box and the mean is identified by the plus sign.

Further analyses were conducted on the three patients with unilateral prechiasmatic tumors (see Table 2.1) to compare the visual functions between both of their eyes, and to compare their unaffected eye to the average SNR of the control group using z-scores. Visual acuity in patients 4 and 10 was inferior in the affected eye compared to the unaffected eye. Unexpectedly, patient 9 exhibited the opposite pattern where the VA of the unaffected eye was lower than the affected one; the latter being in the normal VA range (0.05 logMAR units). Interestingly, a more coherent pattern of results was observed with ssVEPs, where the mean SNRs of the central VF stimulation (i.e., mean of both contrast conditions) was always higher in the unaffected eye compared to the affected one, i.e., 3.12 versus 1.50 in patient 4, 17.39 versus 7.25 in patient 9, and 1.24 versus 0.59 in patient 10. Additionally, ssVEPs of the unaffected eyes of these three

patients were not statistically different ($p > 0.05$) from the mean ssVEPs of the control group (z-scores ranged from 0.16 to -1.94), suggesting that processing by the unaffected visual pathway was within normal limits. Additionally, all patients that had completely impaired vision in one eye (light perception (LP) or no light perception (NLP)) had undetectable signals (SNR ≤ 2.8) with the exception of two patients. One patient with NLP had a SNR of 3.38 in the low contrast peripheral field condition and another patient with LP had a detectable SNR of 10.15 in the peripheral field at the high contrast condition.

A Chi-Squared test was conducted to compare the proportion of participants with undetectable signals in each condition. Results indicated that the control group had a significantly higher proportion of detectable signals in the central VF condition at both contrast levels for both the better and worse-seeing eyes compared to the patient group. However, no significant group differences were detected in the peripheral VF. A contingency table was used to illustrate the proportion of detectable SNRs in each group (Table 2.2).

Given that there is no set cut-off determining that a SNR is indicative of an OPG, two ROC curve analyses were conducted, one for the better-seeing eye and one for the worse-seeing eye. For both analyses, the Youden index was used to determine the most suitable cut-off for sensitivity and specificity. For the better-seeing eye at 96% contrast, the sensitivity, or the true positive rate, was 82% and the specificity, or the true negative rate, was 80% (cut-off = 0.92). The sensitivity and specificity were increased to 85% and 90%, respectively, when conducting the same analysis at 30% contrast (cut-off = 0.45). For the worse-seeing eye at 96% contrast, the sensitivity was 82% and the specificity was 80% (cut-off = 0.62). Identical sensitivity (82%) and specificity (80%) were obtained at 30% contrast (cut-off = 0.42). Similar scores were obtained when calculating sensitivity and specificity with the VA of the better-seeing eye, such that

the sensitivity in detecting OPGs was 90% and the specificity was 88% (cut-off = 0.03).The best sensitivity was obtained when using the VA of the worse seeing eye, with a sensitivity of 100%, with a slight tradeoff of specificity at 70% (cut-off = 0.04).

Table 2.2 Contingency table of meaningful SNRs.

	Controls ($N = 33$)	Patients ($N = 10$)	Significance
Central VF	*n (%)*	*n (%)*	*P*
Better-seeing eye			
96% contrast	30 (91%)	6 (60%)	.040 *
30% contrast	29 (88%)	3 (30%)	.001**
Worse-seeing eye			
96% contrast	30 (91%)	3 (30%)	<.001**
30% contrast	28 (85%)	2 (20%)	<.001**
Peripheral VF			
Better-seeing eye			
96% contrast	26 (79%)	8 (80%)	1.00
30% contrast	21 (64%)	5 (50%)	.481
Worse-seeing eye			
96% contrast	29 (88%)	6 (60%)	.070
30% contrast	19 (58%)	4 (40%)	.473

Contingency table illustrating the proportion of participants in each group with a meaningful SNR. A signal is considered meaningful when the recorded ssVEP signal magnitude is significantly greater than the recorded cortical noise level (SNR > 2.8). VF = visual field.

2.5 Discussion

The goal of this study was to establish the feasibility of recording field specific pattern ssVEPs, an objective and fast test, to measure visual functions in children with OPGs. Accordingly, ssVEPs were gathered during presentation of an alternating circular dart-board, stimulating central and peripheral VFs of children with an OPG, as well as controls with normal vision.

To begin, analyses were conducted to assess the feasibility of the ssVEP method in the control group. These analyses indicated that there were no differences between both eyes of controls and no correlation between SNRs and the age of participants, suggesting that the method can be used to assess the visual system of young children and older ones alike. Furthermore, ten control participants were tested at two different time points to assess the replicability of the method. Given that control participants have stable vision across time, no differences in SNRs were detected between both testing sessions. We also verified if there was a correlation between VA and the SNRs of all participants. Significant correlations were identified between VA and the central SNRs, which was consistent with previous findings [1, 5]. However, these results were no longer significant when conducting analyses within the control group and patient group separately. Although we cannot exclude the possibility that the relationship observed in all-participant analyses were artificially created by group differences, the within-group data suggests a lack of variability in VA within groups, which may explain the failed attempt in detecting significant correlations between VA and SNRs. It is important to note that there were also large individual differences in the SNRs within the control group with normal VA, which is in agreement with the literature [29].

Results in patients with OPGs revealed significantly lower SNRs compared to the control group for the central VF stimulation in both eyes, regardless of the stimulus

contrast level. This group difference in the central condition remained significant, even when controlling for the visual acuity. This finding indicates that ssVEPs are assessing visual function beyond that of simple visual acuity, which gives further support for the potential usefulness of this tool in the follow up of children with OPGs. However, this group difference was not detected in the peripheral VF stimulation. In fact, many of the control participants showed similar peripheral SNRs to that of the patient group and their signals barely exceeded noise levels. Overall, the lack of difference in peripheral responses between groups is likely due to the lack of sensitivity of the test protocol or to the chosen parameters. A different reversal rate may have been more adequate and perhaps transient VEPs may be the necessary alternative, as a recent study has successfully measured the full visual field of patients using transient level frequencies [13]. Nonetheless, additional research is needed to confirm this result and assess various testing parameters that could effectively identify both central and peripheral VF integrity simultaneously while using steady-state stimulation.

Another potential explanation to this lack of difference in the peripheral field may be that some patients with low vision had difficulty keeping their eyes focused onto the central fixation point of the stimulus. This effect may have resulted in eye deviations toward the peripheral stimulus, artificially amplifying their peripheral response, making it similar to that of the control group. Although an experimenter was always present with participants during the data acquisition to interrupt the recording when the eye deviated from the central fixation dot, a better control to ensure central fixation would be through an eye tracker system.

In all conditions, the central SNR is greater than that of the corresponding peripheral SNR. The explanation for this difference is mainly due to the anatomy and organization of the calcarine fissure. Specifically, cortical processing of low-level visual functions, such as VA and contrast sensitivity mainly rely on the primary visual areas. The

macular retinal area (central vision) is mainly treated at the occipital pole, while the peripheral retinal areas are treated deeper into the calcarine fissure. Consequently, the active electrode located at Oz naturally receives a weaker signal from the deep part of the calcarine fissure, as it is anatomically farther from scalp [30]. Thus, visual stimulation of the central/macular VF results in a greater amplitude of response than stimulation of the peripheral VF. Individual differences in skull thickness and cortical architecture can also affect the VEP signals [29]. These anatomical explanations may have led to floor effects in the detection of peripheral signals, which could be yet another contributing factor that prevented the detection of differences in the peripheral VF between groups.

One major limitation pertaining to the peripheral VF analyses in this study is the comparison of SNRs between groups with a substantial proportion of non-significant VEPs (SNR < 2.8). Thus, the ratio is effectively noise/noise and close to random, limiting the interpretation of results. Another limitation of this study is the recruitment method, which may have resulted in greater sociodemographic advantages in the control group.

There is controversy in the literature concerning the usefulness of VEPs for screening and monitoring OPGs [10, 31-33]. For instance, Kelly and Weiss [31] suggested that pattern VEPs can become a reliable replacement of perimetry to measure VF integrity in uncooperative children. On the other hand, Siatkowski [33] argues that VEPs cannot replace any of the currently used methods but can add value to them. Limitations of VEPs include the inability to differentiate symptomatic from asymptomatic patients [34], and the lack of standard testing parameters. Indeed, some studies use a uniform flickering field presented in a mini-ganzfeld VEPs [35, 36], others use field-specific VEPs [19, 37], multifocal VEPs [38], and full-field pattern-reversal VEPs [2, 13]. Despite limitations and challenges of this method, standard checkerboard VEPs have

been found useful in studies investigating patients with NF1 with or without OPGs. For instance, abnormal VEPs in NF1 children were detected prior to visible tumor changes using MRI and before clinical symptoms arose, suggesting that the inclusion of VEPs in the diagnostic protocol together with MRI was relevant [2]. More recently, Dotto and colleagues [13] showed a reduction of the P100 amplitude and a peak time delay of the same component using full-field transient pattern-reversal VEPs in patients with optic pathway low-grade gliomas. In these studies, the visual stimulation involved central, paracentral and near-peripheral VF (17 x 17 degrees in [13] and 38 x 38 degrees in [2]). Our results support the notion that the central/paracentral region is likely the most efficient VF stimulation to detect visual alterations in OPG patients.

Visual acuity (VA) is commonly used as the main functional outcome to assess the visual pathway and disease progression in patients with OPGs. However, it has been shown that VA scores do not always change as a function of ongoing tumor growth [39], suggesting that it would be useful to have additional tools to monitor functional alterations in vision. This notion is supported by our data in patients with unilateral prechiasmatic tumors. Moreover, VA can be difficult to measure in young children due to its subjective nature and it does not give any information pertaining to VF integrity. Given that VEPs provide useful and complementary information that go beyond VA and considering that sensitivity and specificity of ssVEPs were similar to that of VA, the present study supports the relevance of using ssVEPs as an additional tool for the evaluation of patients with OPGs.

In conclusion, our findings indicate that field-specific pattern ssVEPs are quite promising in assessing central visual deficits in children with OPGs. Our protocol allowed us to obtain a functional and objective measure of vision within 3 minutes of testing. Given that similar results were found at both low and high contrasts, testing time can be even shorter by using only the maximum contrast level (e.g., > 80%). Our

study suggests that ssVEPs can be a complementary and objective tool to quickly evaluate visual functions in preverbal and uncooperative children with OPGs. The proposed ssVEP approach might also be successfully applied to other pathologies affecting the central VF (i.e. macular degeneration, acute glaucoma, etc.). Additional studies are needed to identify optimal testing parameters for ssVEP visual-field assessment, in particular for the peripheral VF. The potential usefulness of ssVEPs to detect abnormalities in the visual pathway in OPGs should be considered in the diagnostic protocol together with MRI and as a tool to prompt therapeutic intervention.

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Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

2.6 References

1. Kelly, J.P. and A.H. Weiss, *Detection of tumor progression in optic pathway glioma with and without neurofibromatosis type 1*. Neuro-oncology, 2013. **15**(11): p. 1560-1567.
2. Ammendola, A., G. Ciccone, and E. Ammendola, *Utility of multimodal evoked potentials study in neurofibromatosis type 1 of childhood*. Pediatric neurology, 2006. **34**(4): p. 276-280.
3. Jahraus, C.D. and N.J. Tarbell, *Optic pathway gliomas*. Pediatric blood & cancer, 2006. **46**(5): p. 586-596.
4. World Health Organisation, *Cancer Fact sheet*. 2017.
5. Fisher, M.J., et al., *Functional outcome measures for NF1-associated optic pathway glioma clinical trials*. Neurology, 2013. **81**(21 supplement 1): p. S15-S24.
6. Avery, R.A., M.J. Fisher, and G.T. Liu, *Optic pathway gliomas*. Journal of Neuro-Ophthalmology, 2011. **31**(3): p. 269-278.
7. Robert-Boire, V., et al., *Clinical Presentation and Outcome of Patients With Optic Pathway Glioma*. Pediatric Neurology, 2017. **75**: p. 55-60.
8. Aquilina, K., et al., *Optic pathway glioma in children: does visual deficit correlate with radiology in focal exophytic lesions?* Child's Nervous System, 2015. **31**(11): p. 2041-2049.
9. Listernick, R., et al., *Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations*. Annals of neurology, 2007. **61**(3): p. 189-198.
10. Van Mierlo, C., et al., *Role of visual evoked potentials in the assessment and management of optic pathway gliomas in children*. Documenta Ophthalmologica, 2013. **127**(3): p. 177-190.
11. Binning, M.J., et al., *Optic pathway gliomas: a review*. 2007.
12. Balcer, L.J., et al., *Visual loss in children with neurofibromatosis type 1 and optic pathway gliomas: relation to tumor location by magnetic resonance imaging*. American journal of ophthalmology, 2001. **131**(4): p. 442-445.
13. Dotto, P., et al., *Visual function assessed by visually evoked potentials in optic pathway low-grade gliomas with and without neurofibromatosis type 1*. Documenta Ophthalmologica, 2018: p. 1-13.
14. Dhermain, F.G., et al., *Advanced MRI and PET imaging for assessment of treatment response in patients with gliomas*. Lancet Neurol, 2010. **9**(9): p. 906-20.
15. Avery, R.A., et al., *Longitudinal change of circumpapillary retinal nerve fiber layer thickness in children with optic pathway gliomas*. American journal of ophthalmology, 2015. **160**(5): p. 944-952. e1.

16. Kalin-Hajdu, E., et al., *Visual acuity of children treated with chemotherapy for optic pathway gliomas*. Pediatric blood & cancer, 2014. **61**(2): p. 223-227.
17. Hood, D.C., et al., *Detecting early to mild glaucomatous damage: a comparison of the multifocal VEP and automated perimetry*. Investigative ophthalmology & visual science, 2004. **45**(2): p. 492-498.
18. Fortune, B., et al., *Comparing multifocal VEP and standard automated perimetry in high-risk ocular hypertension and early glaucoma*. Investigative ophthalmology & visual science, 2007. **48**(3): p. 1173-1180.
19. Harding, G., et al., *Field-specific visual-evoked potentials identifying field defects in vigabatrin-treated children*. Neurology, 2002. **58**(8): p. 1261-1265.
20. Colenbrander, A., *Visual standards aspects and ranges of vision loss with emphasis on Population Surveys*, in *Report prepared for the International Council of Ophthalmology at the 29th International Congress of Ophthalmology*. 2002: Sydney Australia.
21. Horton, J.C. and W.F. Hoyt, *The representation of the visual field in human striate cortex. A revision of the classic Holmes map*. Arch Ophthalmol, 1991. **109**(6): p. 816-24.
22. Norcia, A.M., et al., *The steady-state visual evoked potential in vision research: A review*. J Vis, 2015. **15**(6): p. 4.
23. Matsumoto, C.S., et al., *Liquid crystal display screens as stimulators for visually evoked potentials: flash effect due to delay in luminance changes*. Documenta Ophthalmologica, 2013. **127**(2): p. 103-112.
24. Bach, M., *The Freiburg Visual Acuity Test-automatic measurement of visual acuity*. Optometry & Vision Science, 1996. **73**(1): p. 49-53.
25. Jasper, H.H., *The ten twenty electrode system of the international federation*. Electroencephalography and Clinical Neuroph siology, 1958. **10**: p. 371-375.
26. Bach, M. and T. Meigen, *Do's and don'ts in Fourier analysis of steady-state potentials*. Documenta Ophthalmologica, 1999. **99**(1): p. 69-82.
27. Meigen, T. and M. Bach, *On the statistical significance of electrophysiological steady-state responses*. Documenta Ophthalmologica, 1999. **98**(3): p. 207-232.
28. Holladay, J.T., *Visual acuity measurements*. Journal of Cataract & Refractive Surgery, 2004. **30**(2): p. 287-290.
29. Abdullah, S., M. Boon, and T. Maddess, *Contrast-response functions of the multifocal steady-state VEP (MSV)*. Clinical Neurophysiology, 2012. **123**(9): p. 1865-1871.
30. Wu, J., et al., *Retinotopic mapping of the peripheral visual field to human visual cortex by functional magnetic resonance imaging*. Human brain mapping, 2012. **33**(7): p. 1727-1740.
31. Kelly, J.P. and A.H. Weiss, *Comparison of pattern visual-evoked potentials to perimetry in the detection of visual loss in children with optic pathway*

gliomas. Journal of American Association for Pediatric Ophthalmology and Strabismus, 2006. **10**(4): p. 298-306.

32. Wolsey, D.H., et al., *Can screening for optic nerve gliomas in patients with neurofibromatosis type I be performed with visual-evoked potential testing?* Journal of American Association for Pediatric Ophthalmology and Strabismus, 2006. **10**(4): p. 307-311.
33. Siatkowski, R.M., *VEP testing and visual pathway gliomas: not quite ready for prime time*. Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, 2006. **10**(4): p. 293-295.
34. de Blank, P.M., et al., *Optic Pathway Gliomas in Neurofibromatosis Type 1: An Update: Surveillance, Treatment Indications, and Biomarkers of Vision*. Journal of Neuro-ophthalmology, 2017. **37**: p. S23-S32.
35. Falsini, B., et al., *Longitudinal assessment of childhood optic gliomas: relationship between flicker visual evoked potentials and magnetic resonance imaging findings*. Journal of neuro-oncology, 2008. **88**(1): p. 87-96.
36. Trisciuzzi, M.T.S., et al., *A fast visual evoked potential method for functional assessment and follow-up of childhood optic gliomas*. Clinical neurophysiology, 2004. **115**(1): p. 217-226.
37. Hébert-Lalonde, N., et al., *A frequency-tagging electrophysiological method to identify central and peripheral visual field deficits*. Documenta Ophthalmologica, 2014. **129**(1): p. 17-26.
38. Hood, D.C., et al., *The role of the multifocal visual evoked potential (mfVEP) latency in understanding optic nerve and retinal diseases*. Transactions of the American Ophthalmological Society, 2006. **104**: p. 71.
39. Kuenzle, C., et al., *Follow-up of optic pathway gliomas in children with neurofibromatosis type 1*. Neuropediatrics, 1994. **25**(6): p. 295-300.

CHAPTER III

DISCUSSION AND CONCLUSION

To our knowledge, this is the first study to assess the value of field specific pattern ssVEPs to measure the integrity of the central and peripheral visual pathway of children with OPGs. Many studies have evaluated the usefulness of transient VEPs to assess visual functions and the results are mixed regarding its usefulness for the pediatric population. Two studies have evaluated the usefulness of steady state stimulation, but these studies were both conducted within a uniform flickering field paradigm by means of a mini-ganzfeld (Trisciuzzi et al., 2004; Falsini et al., 2008). This type of visual stimulation protocol shows less clinical value in monitoring tumor progression in children with OPGs compared to the pattern reversal paradigms (Groswasser et al., 1985). Thus, the main goal of this thesis aimed to establish the feasibility and assess the value of using field specific pattern ssVEPs to measure the integrity of the visual field in children with OPGs. Accordingly, ssVEPs were gathered during the presentation of an alternating circular dart-board, stimulating both the central and peripheral VFs of children with an OPG, as well as controls with normal vision.

3.1 Summary of main findings

The main results of this thesis showed that the method was useful in detecting central visual field deficits, as the patients with OPGs had significantly lower SNRs in response to the central stimulation compared to the age-matched control group.

Interestingly, this group difference remained significant, even when controlling for visual acuity, suggesting that VEPs provide additional information, which goes beyond the measure of simple VA. This finding is in line with previous research findings that also illustrated that VEPs are associated with VA but provide additional information about the integrity of the visual pathway (Kuenzie et al., 1994; Kelly & Weiss, 2006; Dotto et al., 2018; Trick, 2003; Kelly et al., 2012; Van Mierlo et al., 2013). Consistent with these research findings, our study showed that one patient with a unilateral prechiasmatic right tumor had normal VA scores in the affected right-eye, but a low magnitude VEP in the right eye, which provides additional support that VEPs may identify visual deficits that are not detected by VA measurements.

On the other hand, the pattern specific ssVEP method was unable to detect group differences for the peripheral visual field stimulation, as many of the peripheral responses were similar between groups. In fact, the magnitude of the peripheral stimulation responses were so low that they barely exceeded cortical noise levels for many participants in both the patient and the control group. There are many potential explanations for this lack of difference. In fact, it may simply be due to the chosen parameters of the protocol, such as the selected alternating frequencies, the size of the checkers, the distance between the central and peripheral stimuli or the fact that both frequencies alternated simultaneously. The parameters of this study were selected based on a recent experimental study that showed that the pattern ssVEP method was useful in detecting central VF deficits in children with central abnormalities, as well as in one adolescent with a peripheral VF deficit (Hebert-Lalonde et al., 2014). However, these parameters were never validated in young children, nor in children with OPGs. Thus, there is a need for further research in order to find the appropriate testing parameters using ssVEPs to detect VF deficits in both central and peripheral VFs simultaneously in children, including those with OPGs.

It is possible that transient VEPs may be the necessary alternative to measure the full VF of these children, as a recent study has successfully measured it in children using transient level frequencies (Dotto et al., 2018). However, this type of stimulation has its limitations, as it takes a greater length of time, requires further child cooperation and is more affected by gaze deviations. These are all important considerations when working with the pediatric population, especially when assessing children with learning disabilities and/or attention deficits. Thus, there are many advantages to pursuing research with steady state frequencies and attempting to find the appropriate testing parameters. This type of protocol can be implemented easily and quickly as a complimentary tool to assess visual functions during in the clinical follow ups of patients with OPGs.

Another potential explanation for the lack of detected differences in the peripheral VF may be due to the difficulty of patients with poor vision to keep their eye focused onto the central fixation point of the stimulus. This effect may have resulted in eye deviations toward the peripheral stimulus, artificially amplifying their peripheral response, making it similar to that of the control group. However, this second postulation is unlikely as it does not provide an explanation for the undetectable peripheral VF responses in the control group with normal vision.

An interesting pattern of results that consistently emerged throughout the result analysis in both groups is the lower peripheral signal magnitude compared to the corresponding central magnitude. The explanation for this difference is mainly due to the anatomy and organization of the calcarine fissure. Central VF processing is mainly treated at the occipital pole of the calcarine fissure, while the peripheral retinal areas are treated deeper into the calcarine fissure. Thus, the active electrode located on the scalp over the occipital cortex naturally records a weaker signal from the deep part of the calcarine fissure, as it is anatomically farther from scalp (Wu et al., 2012). Thus,

visual stimulation of the central/macular VF results in a greater magnitude of response compared to the peripheral VF stimulation. There are also individual differences in skull thickness and cortical architecture, which can also affect the magnitude of the recorded signals and explain the large inter-subject variability in SNRs (Hood & Greestein, 2003; Abdullah et al., 2012). There is a possibility that these anatomical configurations may have led to floor effects in the detection of peripheral signals for many individuals, which could be yet another contributing factor that prevented the detection of differences in the peripheral VF between groups.

Other interesting findings emerging from this thesis is the lack of correlation between ssVEPs and age, indicating that this method could be used for young and older children alike. Testing time was slightly longer with the youngest children as they needed longer breaks between the stimulation periods. Nonetheless, they were generally able to remain seated while staring at the fixation point during the 10 second stimulation blocks, which allowed us to reliably record their ssVEPs. Additionally, the specificity and sensitivity of the method in detecting eyes affected by an OPG using the central VF data illustrated similar values to that of VA measures. One study conducted by Kelly & Weiss (2013) demonstrated that sensitivity and specificity in detecting tumor evolution over time was superior with VEPs compared to VA. Thus, our results provide additional support for the added value of the method in detecting visual deficits.

3.2 Clinical value of the method

Currently, the clinical monitoring of vision in patients with OPGs generally includes regular MRIs and VA assessments with occasional perimetry or confrontation VF assessments. The following sections will provide information about the added value of using VEPs in combination with each of the currently used methods.

3.2.1 VEPs and MRI

Magnetic resonance imaging is typically conducted every three months in patients being monitored for OPG evolution (Avery et al., 2011). MRIs could be quite invasive for young patients, especially for children with cognitive deficits or children aged six years or younger, as they require sedation or anesthesia to reduce movements during neuroimaging (Van Mierlo et al., 2013). Additionally, it has been shown repeatedly that there is a poor correlation between tumor changes detected by MRI and the evolution of visual functions (Van Mierlo et al., 2013; Kuenzie et al., 1994; Ammendola, Ciccone & Ammendola, 2006), which speaks to the importance of extensively and frequently assessing visual functions. In fact, a longitudinal study conducted by Ammendola, Ciccone and Ammendola (2006) found that some children with OPGs had abnormal VEPs in the absence of detectable MRI changes and prior to functional visual changes. Thus, the authors highlight the importance of including VEPs as part of the diagnostic and follow-up protocol of encephalic lesions. Although MRIs provide extremely valuable information about tumor progression over time and cannot be replaced by any other method, the frequency of the imaging may be adjusted or optimized with the addition of other functional visual measures. Specifically, MRIs could be prompted sooner if functional changes are uncovered, which could aid in the early detection of dysfunction and corresponding treatment adjustments (Ammendola, Ciccone and Ammendola, 2006).

3.2.2 VEPs and VA

Visual acuity is recommended as the main functional measure of vision for the diagnosis and monitoring of tumor progression (Fisher et al., 2013; Avery et al., 2011; Wan et al., 2016; Van Mierlo et al., 2013). However, VA only offers a measure of the spatial resolution of vision and there are many other visual functions that can be affected by lesions along the optic nerve, including contrast sensitivity, color vision, and the visual field (Van Mierlo et al., 2013). For instance, a child may have normal

visual acuity, but still have a peripheral visual field deficit or slower visual processing due to an obstruction along the visual pathway. Thus, solely using VA measures provides an incomplete assessment of visual function and could results in overlooking very important functional visual changes, which could indicate the need for prompt therapeutic intervention. It is therefore important to assess other dimensions of functional vision, including the visual field and the integrity of the visual pathway, which is feasible with VEPs.

3.2.3 VEPs and the VF

There is disagreement in the literature concerning the potential clinical usefulness of VEPs for screening and monitoring the VF in patients with OPGs (Van Mierlo et al., 2013; Kelly & Weiss, 2006; Siatkowski, 2006). Some authors suggest that pattern VEPs could replace perimetry to reliably assess VF integrity in uncooperative children (Kelly & Weiss, 2006) but others argue that VEPs cannot replace any of the currently used methods to assess visual functions is children with OPGs (Siatkowski, 2006). On the other hand, all authors tend to agree that further research is needed to identify the ideal testing parameters to assess the integrity of the visual pathway and the VF in children with OPGs using VEPs (Van Mierlo et al., 2013).

The testing parameters used for the current thesis allowed the detection of visual deficits in the central visual field, but it did not provide any information about the precise affected VF region. Although perimetry is not always reliable in uncooperative children, it is still the best tool we currently have to aid clinicians in determining the affected VF. Thus, the results suggest that pattern reversal ssVEPs cannot replace perimetry. As mentioned in the introduction of this thesis, OPGs can result in particular visual field abnormalities depending on the location of the tumor, including hemifield losses. Thus, it is crucial to pursue research in order to find new objective and reliable ways of assessing the entire VF of uncooperative and/or non-verbal children.

A multifocal full field tVEP paradigm may be the useful alternative, as it was demonstrated in a study by Abdullah and colleagues (2012). However, the authors specify that the testing method would require 8-10 repeats of the stimulus presentation in each VF quadrant to reliably detect VF deficits, which substantially limits its clinical applicability for the pediatric population. This result shows that there is a need to validate a new method that is similar in nature, such that is assesses all areas of the VF, but with the added value of fast rate presentations, which may be feasible with ssVEPs.

3.3 Practical implications

Although the VEP protocol used for this study failed to detect peripheral VF deficits in children with OPGs, it still allowed us to successfully measure central VF integrity in children of all ages in less than three minutes. In fact, the results using the high contrast and low contrast conditions were essentially identical, which suggests that the testing time could be diminished to 1.5 minutes by presenting only one contrast level. The ssVEP method also provided additional information about the visual pathway, which goes above and beyond visual acuity.

EEG is a cortical recording method that is extensively used since the works of the German scientist Hans Berger in the 1920's. It has been used for a multitude of pathologies and has consistently proven to be a completely safe and harmless method for all age groups (Odom et al., 2010). It can be conducted quickly and does not inflict any pain or discomfort. Therefore, it is clear that there is no harm in adding this tool in the clinical diagnosis protocol and follow up of patients with OPGs. It could denote important changes in central visual functions that may not be detected by the currently used methods. It is also an affordable method of brain recording that can be portable, facilitating worldwide access. In fact, all that is needed to record VEPs is a computer screen, electrodes and a small recording transmitter (Odom et al., 2010). Thus, it may

be a useful tool to assess visual functions in underdeveloped regions of the world with limited resources or reduced access to medical equipment, such as MRI and perimetry systems.

This study focused on the feasibility of the method for detecting visual deficits. However, one important follow up study will be to monitor tumor changes over time and verify the association between tumor changes and functional visual changes using ssVEPs. As a side analysis, this thesis examined the test-retest reliability of the method in the control group with stable vision and found stability in responses over time. The results stemming from this analysis are quite valuable as they illustrate the importance of assessing patients at baseline since there are very large inter-individual differences in response magnitudes, but the responses remained relatively stable over time. Thus, the implications of this finding allude to the necessity of comparing ssVEP magnitudes to the patient's own baseline or to their own previous visual assessment, rather than determining a "visual deficit" cutoff.

Other important implications of this thesis include the rapid convenience, reliability and objectivity of the ssVEP method to assess central visual deficits. Therefore, this method could potentially be useful for several populations with central VF deficits. For instance, it may be a valuable tool to assess vision in patients with macular degeneration or other visual deficits in the senior population, who may also have difficulties to cooperate during ophthalmic examinations due to possible cognitive decline. In fact, the population of the world is aging, with the Canadian population above the age of 65 expected to double between the years 2014 and 2031 (Statistics Canada, 2017). Along with an aging population comes many normal age-related consequences, such as cognitive impairments and normal sensory declines (Naveh-Benjamin & Kilb, 2014). Statistics Canada predicts that by 2031, one person in four will be above the age of 65 years (Statistics Canada, 2017), and of those seniors, 19%

will have a visual disability (Brennan & Sleightholm, 2006). These statistics indicate the need to develop reliable tools to assess vision in a large range of age groups with varying levels of cognitive and verbal abilities.

Some studies have examined the usefulness of VEPs in assessing vision in the senior population with visual deterioration. For instance, it has been shown useful to assess visual progression in seniors with age-related macular degeneration (Vottonenet al., 2013) and in assessing central visual input in patients with retinitis pigmentosa (Parisi et al., 2010). It has also been validated as a useful complimentary tool to assess vision in patients with Glaucoma (Hood & Greestein, 2003). Thus, it is clear that there are many other pathologies for which VEPs could be used as a valid measure of visual functions. In fact, authors often specify the need for less time consuming VEP protocols, which would facilitate the clinical applicability of the method (Hood & Greestein, 2003). This is where the steady state stimulation parameters could be useful and should be validated with other pathologies.

As mentioned previously, current VF assessments are subjective as they require child cooperation and rely on verbal or motor responses to determine the affected visual field. Thus, validating an objective method of assessing VF integrity could reduce the anxiety associated with child cooperation during ophthalmological visits. It can be challenging and stressful to verbalize internal sensory experiences, even for adults with adequate cooperation and verbal skills. This objective method could therefore provide a more reassuring way of assessing vision for the children and their families who are aware of the child's cognitive limitations. Thus, ssVEPs could reduce the pressure and anxiety that comes with the verbalization of sensory experiences for the children themselves, as well as for their caretakers.

3.4 Limitations

Although this study was a noteworthy first attempt at measuring VF deficits using a fast pattern specific ssVEP protocol in children with OPGs, there are important clinical implication limits and methodological limitations to consider.

Limitations of VEPs include the inability to differentiate symptomatic from asymptomatic patients (de Blank et al., 2017), and the lack of standard testing parameters. As mentioned earlier, the method also does not allow us to determine the affected VF region, which is the ultimate goal of perimetry assessments. Thus, results indicate that, in these early phases of validation, the pattern specific ssVEP method cannot replace any of the currently used methods. However, it may prove to be a valuable tool in the future, particularly if we can find a way to stimulate the full VF while using steady-state stimulation frequencies.

There are various methodological limitations to consider when interpreting results of this thesis. First, the small sample size of patient's with OPGs is one important limitation that must be considered. Additionally, every patient's tumor was different in shape, size, and location along the optic pathway, but the results were analyzed as a whole, with all patients in one group. Thus, this kind of analysis does not account for tumor differences.

Secondly, although an experimenter was present with participants throughout the entire acquisition phase to interrupt the recording when the eye deviated from the central fixation dot, a better control strategy to ensure central fixation would be through an eye tracker system. The addition of an eye tracker would allow us to remove the parts of recordings where the child deviated his or her gaze and potentially increase the power

of results. However, the tradeoff of using an eye-tracker is the added cost and the diminished practicality for clinicians with limited budgets.

Another limitation of this study pertains to the peripheral VF analyses. The comparison of SNRs between groups was conducted even though there was a large proportion of VEPs that were not statistically greater than cortical noise levels. Thus, the SNR is essentially "noise/noise" instead of "signal/noise", which limits the interpretation of peripheral VF results. Nonetheless, this outcome remains informative, as it provides information about the method's limitations in measuring the peripheral VF. Essentially, the low peripheral signals indicate that the method is not effective in detecting the peripheral VF in most participants.

Another limitation of this study is the recruitment method, which was conducted through "snowball sampling" and may have resulted in greater sociodemographic advantages in the control group. However, snowball sampling is more or less concerning in EEG visual assessment protocols, as socio-economic status and other demographic advantages do not affect visual functions. Nonetheless, it is important to highlight this limitation as it may be an important consideration for study replications.

3.5 Future research

It is clear from this study and previous ones that VEP recordings could be a valuable complimentary way to measure visual functions and provide additional information that cannot be obtained from existing clinical tools. However, there is no doubt that the method needs adjustments and fine tuning to be effective in measuring the entire VF in a quick and efficient manner. Thus, it is important for future researchers to experiment with different presentation parameters and protocols, while using steady

state frequency presentations. Essentially, full-field and multi-focal presentation paradigms should be tested with high frequency stimulation rates.

Once the right parameters are identified, the next step should entail a longitudinal study, continuously monitoring tumor evolution over time and correlating data with other measures, including MRI, perimetry, and VA. These future research perspectives could also be validated in other clinical populations and improve the monitoring of various populations with visual deficits, and potentially result in treatment protocols being adjusted earlier, preventing further visual decline.

CONCLUSION

This thesis aimed to assess the feasibility and value of field-specific pattern ssVEPs to assess the integrity of the central and peripheral VF of children with OPGs. Results revealed significantly lower SNRs in patients with OPGs compared to the control group for the central VF stimulation in both eyes, regardless of the stimulus contrast level. This group difference in the central condition remained significant even when controlling for visual acuity. This finding indicates that ssVEPs assess visual functionning beyond visual acuity, which supports the usefulness of this tool in assessing and monitoring children with OPGs. Our protocol allowed us to obtain a functional and objective measure of central vision within three minutes of testing.

This study suggests that ssVEPs can be a complementary tool to quickly evaluate visual functions in preverbal and uncooperative children with OPGs. The proposed ssVEP approach might also be successfully applied to other pathologies affecting the central VF (i.e. macular degeneration, acute glaucoma, papilledema's, optic neuritis, hypoplasia of the optic nerve, etc.). Additional studies are needed to identify optimal testing parameters for ssVEP visual-field assessment, in particular for the peripheral VF. Even though the method is not yet optimal, it nonetheless provides valuable information about visual functions. This thesis supports the usefulness of ssVEPs to detect abnormalities in the visual pathway in patients with OPGs. We therefore recommend that this method be considered in the diagnostic protocol of children with OPGs together with MRI and perimetry.

ANNEX A

INFORMATION AND CONSENT FORM

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Pour l'amour des enfants
Université de Montréal

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

(POUR PARTICIPANTS MINEURS)

Projet de recherche

Utilisation des potentiels évoqués visuels stationnaires pour mieux évaluer l'intégrité du champ visuel d'enfants atteints de gliomes optiques

Chercheurs impliqués

Saint-Amour, Dave (PhD), chercheur, ophtalmologie
Perreault, Sébastien (MD), chercheur, neurologie/neuro-oncologie
Ospina, Luis (MD), neuro-ophtalmologiste
Carret, Anne-Sophie (MD), hémato-oncologue
Samson, Yvan (MD), hémato-oncologue

Source de financement

Ce projet est financé par le Fonds d'opération pour la recherche clinique du CHU Sainte-Justine accordé au Dr. Dave Saint-Amour et Dr. Sébastien Perreault.

Invitation à participer à un projet de recherche

En collaboration avec le Centre de recherche, les départements de neurologie et d'ophtalmologie du CHU Sainte-Justine ont mis sur pied une étude ayant pour objectif d'améliorer l'évaluation de la vision chez les enfants présentant une tumeur des nerfs optiques (gliomes des voies optiques). C'est pour cette raison que nous sollicitons aujourd'hui la participation de votre enfant. Nous vous invitons à lire attentivement ce formulaire d'information et de consentement afin de prendre une décision quant à la contribution de votre enfant à cette étude.

Quelle est la nature du projet?

Les gliomes des voies optiques sont un type de tumeurs fréquentes qui affectent les nerfs des yeux. Par conséquent, les patients présentent souvent une diminution de leur vision. Cependant, cette atteinte est souvent difficile à évaluer chez les enfants en raison de leur collaboration limitée aux tests standards. Afin d'améliorer leur suivi et éventuellement les thérapies, il est essentiel d'utiliser de meilleurs outils. Nous avons mis sur pied un test simple et fiable qui nous permettrait d'évaluer rapidement la vision des enfants. Nous invitons donc votre enfant à participer à ce projet de recherche qui vise à valider cette technique.

Comment se déroulera le projet?

La réalisation de ce projet implique la participation d'une dizaine d'enfants avec un gliome des voies optiques et d'une dizaine d'autres sans gliome en guise de témoins. Le groupe d'âge visé est entre 4 et 21 ans. L'étude auprès des enfants atteints d'un gliome comporte une série de visites d'environ 30 minutes chacune. Un total de 4 visites seront planifiées (environ une fois aux trois mois) et seront combinées dans la mesure du possible à vos rendez-vous déjà prévus dans le cadre du suivi clinique régulier de votre enfant. Plusieurs temps d'arrêt sont prévus lors de chaque évaluation.

Afin de recueillir l'information désirée, nous utiliserons un test de potentiels évoqués visuels (PEV). Il s'agit d'une méthode couramment utilisée en milieu hospitalier et universitaire. Elle permet de recueillir de manière non-invasive l'activité électrique du cerveau lorsque votre enfant regardera différentes images sur un écran d'ordinateur.

Les PEV sont captés par trois pastilles (électrodes) disposées à la surface de la tête, soit une à l'arrière de la tête, une à l'avant et une sur le front. L'installation implique d'abord le nettoyage de ces trois régions avec des tampons d'alcool et un gel exfoliant et s'effectue en quelques minutes. Les PEV permettent de vérifier l'intégrité du fonctionnement des régions du cerveau qui analysent les informations visuelles.

Dans le but d'interpréter correctement les informations obtenues à ces tests, un test de vision des couleurs sera également administré à votre enfant. Il vous suffira simplement de regarder des images colorées sur l'écran d'ordinateur pendant environ 10 min. De plus, nous récolterons aussi des données provenant de son dossier médical en collaboration avec les médecins traitants de votre enfant. L'équipe de recherche consultera donc le dossier médical de votre enfant seulement pour obtenir les informations pertinentes à cette recherche. Ces informations seront strictement confidentielles.

Avantages et bénéfices

Les participants à l'étude pourront recevoir l'information quant aux fonctions visuelles évaluées par l'électrophysiologie. La participation à l'étude signifie également la gratitude d'avoir participé à l'avancement des connaissances sur l'évolution et l'impact sur la vision des gliomes des voies optiques.

Inconvénients et risques

L'inconvénient réside principalement dans la pose d'électrodes. L'installation peut parfois être inconfortable, si toutefois elle apparaît trop désagréable, l'enfant ou son tuteur peut mettre fin à l'évaluation. Il importe de noter que cette partie de la participation ne représente aucun risque pour l'enfant.

Confidentialité

Sous la responsabilité du chercheur principal, Dave Saint-Amour (PhD), toutes les informations obtenues sur votre enfant dans le cadre de ce projet de recherche seront confidentielles et le demeureront pour des fins de recherche, à moins d'une autorisation de votre part ou d'une exception de la loi. Les noms des participants seront changés par un code afin de rendre confidentielles les informations. Les dossiers demeureront sous clé au CHU Sainte-Justine jusqu'en mars 2040, soit 25 ans après la fin du projet. Cependant, aux fins de vérifier la saine gestion de la recherche, il est possible qu'un délégué du Comité d'éthique de la recherche consulte les données de recherche et le dossier médical de votre enfant. Par ailleurs, les résultats de cette étude pourront être publiés ou communiqués dans un congrès scientifique mais aucune information permettant d'identifier votre enfant ne sera alors dévoilée. De plus, à des fins de protection, le Ministère de la santé des services sociaux pourrait avoir accès à votre nom et prénom ainsi que ceux de votre enfant, ses coordonnées, la date de début et de fin de sa participation au projet jusqu'à un an après la fin du projet.

Responsabilité des chercheurs

En signant ce formulaire de consentement, vous ne renoncez à aucun de vos droits prévus par la loi ni à ceux de votre enfant. De plus, vous ne libérez pas les chercheurs de leur responsabilité légale et professionnelle advenant une situation qui causerait préjudice à votre enfant.

Compensation prévue pour vos dépenses et inconvénients

Vous recevrez une somme forfaitaire de 20$ par visite en compensation des frais encourus (c.-à-d., frais de transport) et des contraintes subies.

Liberté de participation

La participation de votre enfant à cette étude est libre et volontaire. Vous pouvez retirer votre enfant de l'étude en tout temps et dans ce cas, les informations recueillies seraient détruites. Quelle que soit votre décision cela n'affectera pas la qualité des services de santé qui lui sont offerts.

Personnes ressources à contacter en cas de questions ou de difficultés

Pour de plus amples renseignements concernant le projet de recherche (déroulement de l'étude, incident ou dérogation au protocole, renseignements concernant mes droits, problème de santé, questions d'ordre médical, etc.), vous pouvez communiquer avec les chercheurs principaux : Dave Saint-Amour, Centre de recherche du CHU Sainte-Justine et Département d'ophtalmologie de l'Université de Montréal, tél.: 514-345-4931 (poste 3894), Courriel: d.st.amour@umontreal.ca. Sébastien Perreault, Service de neurologie, Département de pédiatrie du CHU Sainte-Justine tél: 514-345-4931 (poste 5019), Courriel: s.perreault@umontreal.ca. Pour tout renseignement sur les droits de votre enfant à titre de participant à ce projet de recherche, vous pouvez contacter le commissaire local aux plaintes et à la qualité des services du CHU Sainte-Justine au 514-345-4749.

Consentement et assentiment

On m'a expliqué la nature et le déroulement du projet de recherche. J'ai pris connaissance du formulaire de consentement et on m'en a remis un exemplaire. J'ai eu l'occasion de poser mes questions auxquelles on a répondu. Après réflexion, j'accepte que mon enfant participe à ce projet de recherche.

_____

Nom de l'enfant (Lettres moulées)

_____ _____

Assentiment de l'enfant (Signature) Date

Assentiment verbal de l'enfant incapable de signer, mais capable de comprendre la nature du projet : oui_____ non_____

_____
Nom du parent (Lettres moulées)

_____ _____
Consentement du parent ou tuteur (Signature) Date

Formulaire d'engagement du chercheur ou de la personne qu'il a déléguée

J'ai expliqué au participant et/ou à son parent/tuteur tous les aspects pertinents de la recherche et j'ai répondu aux questions qu'ils m'ont posées. Je leur ai indiqué que la participation au projet de recherche est libre et volontaire et que la participation peut être cessée en tout temps.

_____ _____ _____
Nom de la personne qui a obtenu le consentement (Lettres moulées) Signature Date

Le projet de recherche doit être décrit au participant et/ou à son parent/tuteur ainsi que les modalités de la participation. Un membre de l'équipe de recherche doit répondre à leurs questions et doit leur expliquer que la participation au projet de recherche est libre et volontaire. L'équipe de recherche s'engage à respecter ce qui a été convenu dans le formulaire de consentement.

_____ _____ _____
Nom du chercheur responsable (Lettres moulées) Signature Date

ANNEX B

RECEIPT TO PARTICIPANTS

Centre de
Recherche du
CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Université de Montréal

REÇU

Je, _____, soussigné(e), certifie avoir reçu la somme de 20$ pour la couverture de mes frais de déplacement liés à ma participation, avec mon enfant _____, au projet de recherche intitulé « Utilisation des potentiels évoqués visuels stationnaires pour mieux évaluer l'intégrité du champ visuel de personnes atteintes de gliomes optiques ».

Parent : _____

Date : _____

Responsable : _____

REFERENCES

Abdullah, S., Boon, M., & Maddess, T. (2012). Contrast-response functions of the multifocal steady-state VEP (MSV). *Clinical Neurophysiology*, *123*(9), 1865-1871.

Ammendola, A., Ciccone, G., & Ammendola, E. (2006). Utility of multimodal evoked potentials study in neurofibromatosis type 1 of childhood. *Pediatric neurology*, *34*(4), 276-280.

Aquilina, K., et al. (2015). Optic pathway glioma in children: does visual deficit correlate with radiology in focal exophytic lesions? *Child's Nervous System*, *31*(11), 2041-2049.

Astrup, J. (2003). Natural history and clinical management of optic pathway glioma. *British journal of neurosurgery*, *17*(4), 327-335.

Avery, R. A., Fisher, M. J., & Liu, G. T. (2011). Optic pathway gliomas. *Journal of Neuro-Ophthalmology*, *31*(3), 269-278.

Avery, R.A., et al. (2015). Longitudinal change of circumpapillary retinal nerve fiber layer thickness in children with optic pathway gliomas. *American journal of ophthalmology*, *160*(5), 944-952.

Bach, M. & Meigen, T. (1999). Do's and don'ts in Fourier analysis of steady-state potentials. *Documenta Ophthalmologica*, *99*(1), 69-82.

Bach, M. (1996). The Freiburg Visual Acuity Test-automatic measurement of visual acuity. *Optometry & Vision Science*, *73*(1), 49-53.

Balcer, L.J., et al. (2001). Visual loss in children with neurofibromatosis type 1 and optic pathway gliomas: relation to tumor location by magnetic resonance imaging. *American journal of ophthalmology*, *131*(4), 442-445.

Binning, M. J., Liu, J. K., Kestle, J. R., Brockmeyer, D. L., & Walker, M. L. (2007). Optic pathway gliomas: a review. *Journal of neurosurgery*, *23*(5), E2.

Brennan, S. & Sleightholm, M. (2006). Participation and Activity Limitation Survey 2006. *Facts on Seeing Limitations 3* (89-628-X). Ottawa: Statistics Canada. Retrieved from http://www.statcan.gc.ca/pub/89-628-x/89-628-x2009013-eng.pdf

Canadian Cancer Society. (2017). *Childhood Cancer Statistics*. Retrieved from http://www.cancer.ca/en/cancer-information/cancer-101/childhood-cancer-statistics/?region=on

Cappelli, C., Grill, J., Raquin, M., Pierre-Kahn, A., Lellouch-Tubiana, A., Terrier-Lacombe, M. J., ... & Hartmann, O. (1998). Long term follow up of 69 patients treated for optic pathway tumours before the chemotherapy era. *Archives of disease in childhood*, *79*(4), 334-338.

Chang, B. C., Mirabella, G., Yagev, R., Banh, M., Mezer, E., Parkin, P. C., ... & Buncic, J. R. (2007). Screening and diagnosis of optic pathway gliomas in children with neurofibromatosis type 1 by using sweep visual evoked potentials. *Investigative ophthalmology & visual science*, *48*(6), 2895-2902.

Chiappa, K. H. (1997). *Evoked potentials in clinical medicine* (3rd ed.). Philadelphia, PA: Lippincott-Raven Publishers.

Colenbrander, A. (2002). *Visual standards: aspects and ranges of vision loss with emphasis on Population Surveys. Report prepared for the International Council of Ophthalmology at the 29th International Congress of Ophthalmology, Sydney, Australia.* [San Francisco: International Council of Ophthalmology.]

de Blank, P.M., et al. (2017). Optic Pathway Gliomas in Neurofibromatosis Type 1: An Update: Surveillance, Treatment Indications, and Biomarkers of Vision. *Journal of Neuro-Ophthalmology*, *37*, S23-S32.

Dhermain, F.G., et al. (2010). Advanced MRI and PET imaging for assessment of treatment response in patients with gliomas. *The Lancet Neurology*, *9*(9), 906-920.

Dodge, H. W., Love, J. G., Craig, W. M., Dockerty, M. B., Kearns, T. P., Holman, C. B., & Hayles, A. B. (1958). Gliomas of the optic nerves. *AMA Archives of Neurology & Psychiatry*, *79*(6), 607-621.

Dotto, P., et al. (2018). Visual function assessed by visually evoked potentials in optic pathway low-grade gliomas with and without neurofibromatosis type 1. *Documenta Ophthalmologica*, *136*(3), 177-189.

Falsini, B., Ziccardi, L., Lazzareschi, I., Ruggiero, A., Placentino, L., Dickmann, A., ... & Di Rocco, C. (2008). Longitudinal assessment of childhood optic gliomas: relationship between flicker visual evoked potentials and magnetic resonance imaging findings. *Journal of neuro-oncology*, *88*(1), 87-96.

Fisher, M. J., Avery, R. A., Allen, J. C., Ardern-Holmes, S. L., Bilaniuk, L. T., Ferner, R. E., ... & Liu, G. T. (2013). Functional outcome measures for NF1-associated optic pathway glioma clinical trials. *Neurology*, *81*(21 supplement 1), S15-S24.

Fisher, M. J., Loguidice, M., Gutmann, D. H., Listernick, R., Ferner, R. E., Ullrich, N. J., ... & Hummel, T. R. (2012). Visual outcomes in children with neurofibromatosis type 1–associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. *Neuro-oncology*, *14*(6), 790-797.

Fisher, R. S., Harding, G., Erba, G., Barkley, G. L., & Wilkins, A. (2005). Photic-and pattern-induced seizures: a review for the Epilepsy Foundation of America Working Group. *Epilepsia*, *46*(9), 1426-1441.

Fortune, B., et al. (2007). Comparing multifocal VEP and standard automated perimetry in high-risk ocular hypertension and early glaucoma. *Investigative ophthalmology & visual science*, *48*(3), 1173-1180.

Fried, I., Tabori, U., Tihan, T., Reginald, A., & Bouffet, E. (2013). Optic pathway gliomas: a review. *CNS oncology*, *2*(2), 143-159.

Groswasser, Z., Kriss, A., Halliday, A. M., & McDonald, W. I. (1985). Pattern-and flash-evoked potentials in the assessment and management of optic nerve gliomas. *Journal of Neurology, Neurosurgery & Psychiatry*, *48*(11), 1125-1134.

Gutmann, D. H., Ferner, R. E., Listernick, R. H., Korf, B. R., Wolters, P. L., & Johnson, K. J. (2017). Neurofibromatosis type 1. *Nature Reviews Disease Primers*, *3*, 17004.

Harding, G. F. A., Robertson, K. A., & Holliday, I. (2000). Field specific visual evoked potentials for assessment of peripheral field defect in a paediatric population. *Supplements to Clinical neurophysiology*, *53*, 323-330.

Harding, G. F. A., Spencer, E. L., Wild, J. M., Conway, M., & Bohn, R. L. (2002). Field-specific visual-evoked potentials identifying field defects in vigabatrin-treated children. *Neurology*, *58*(8), 1261-1265.

Hébert-Lalonde, N., Carmant, L., Safi, D., Roy, M. S., Lassonde, M., & Saint-Amour, D. (2014). A frequency-tagging electrophysiological method to identify central and peripheral visual field deficits. *Documenta Ophthalmologica*, *129*(1), 17-26.

Holladay, J.T. (2004). Visual acuity measurements. *Journal of Cataract & Refractive Surgery*, *30*(2), 287-290.

Hood, D. C. & Greenstein, V. C. (2003). Multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma. *Progress in retinal and eye research*, *22*(2), 201-251.

Hood, D. C., Chen, J. Y., Yang, E. B., Rodarte, C., Wenick, A. S., Grippo, T. M., ... & Ritch, R. (2006). The role of the multifocal visual evoked potential (mfVEP) latency in understanding optic nerve and retinal diseases. *Transactions of the American Ophthalmological Society*, *104*, 71.

Hood, D.C., et al. (2004). Detecting early to mild glaucomatous damage: a comparison of the multifocal VEP and automated perimetry. *Investigative ophthalmology & visual science*, *45*(2), 492-498.

Horton, J.C. & Hoyt, W.F. (1991). The representation of the visual field in human striate cortex. A revision of the classic Holmes map. *Archives of Ophthalmology*, *109*(6), 816-24.

Horwich, A. & Bloom, H. J. G. (1985). Optic gliomas: radiation therapy and prognosis. *International Journal of Radiation Oncology • Biology • Physics*, *11*(6), 1067-1079.

Jahraus, C. D. & Tarbell, N. J. (2006). Optic pathway gliomas. *Pediatric blood & cancer*, *46*(5), 586-596.

Jasper, H. H. (1958). The ten twenty electrode system of the international federation. *Electroencephalography and Clinical Neurophysiology*, *10*, 371-375.

Jessen, K. R. & Mirsky, R. (1980). Glial cells in the enteric nervous system contain glial fibrillary acidic protein. *Nature*, *286*(5774), 736-737.

Kalin-Hajdu, E., Décarie, J. C., Marzouki, M., Carret, A. S., & Ospina, L. H. (2014). Visual acuity of children treated with chemotherapy for optic pathway gliomas. *Pediatric blood & cancer*, *61*(2), 223-227.

Kaufhold, F., Kadas, E. M., Schmidt, C., Kunte, H., Hoffmann, J., Zimmermann, H., ... & Paul, F. (2012). Optic nerve head quantification in idiopathic intracranial hypertension by spectral domain OCT. *PLoS One*, *7*(5), e36965.

Kelly, J. P. & Weiss, A. H. (2006). Comparison of pattern visual-evoked potentials to perimetry in the detection of visual loss in children with optic pathway gliomas. *Journal of American Association for Pediatric Ophthalmology and Strabismus*, *10*(4), 298-306.

Kelly, J. P. & Weiss, A. H. (2013). Detection of tumor progression in optic pathway glioma with and without neurofibromatosis type 1. *Neuro-oncology*, *15*(11), 1560-1567.

Kelly, J. P., Leary, S., Khanna, P., & Weiss, A. H. (2012). Longitudinal measures of visual function, tumor volume, and prediction of visual outcomes after treatment of optic pathway gliomas. *Ophthalmology*, *119*(6), 1231-1237.

Kiloh, L. G. & Osselton, J. W. (1966). *Clinical electroencephalography*. Washington, DC: Buttorworth.

Kuenzle, C. H., Weissert, M., Roulet, E., Bode, H., Schefer, S., Huisman, T., ... & Boltshauser, E. (1994). Follow-up of optic pathway gliomas in children with neurofibromatosis type 1. *Neuropediatrics*, *25*(6), 295-300.

Lacaze, E., Kieffer, V., Streri, A., Lorenzi, C., Gentaz, E., Habrand, J. L., ... & Grill, J. (2003). Neuropsychological outcome in children with optic pathway tumours when first-line treatment is chemotherapy. *British journal of cancer*, *89*(11), 2038.

Listernick, R., Charrow, J., & Gutmann, D. H. (1999). Intracranial gliomas in neurofibromatosis type 1. *American Journal of Medical Genetics Part A*, *89*(1), 38-44.

Listernick, R., Ferner, R. E., Liu, G. T., & Gutmann, D. H. (2007). Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Annals of neurology*, *61*(3), 189-198.

Matsumoto, C.S., et al. (2013). Liquid crystal display screens as stimulators for visually evoked potentials: flash effect due to delay in luminance changes. *Documenta Ophthalmologica*, *127*(2), 103-112.

Mcginn, C. & Tarbell, N. J. (1990). Definitive radiation therapy in the management of symptomatic patients with optic glioma. *Cancer*, *65*, 45-52.

Medlock, M. D. & Scott, R. M. (1997). Optic chiasm astrocytomas of childhood. 2. Surgical management. *Pediatric neurosurgery*, *27*(3), 129-136.

Meigen, T. & Bach, M. (1999). On the statistical significance of electrophysiological steady-state responses. *Documenta Ophthalmologica*, *98*(3), 207-232.

Naveh-Benjamin, M. & Kilb, A. (2014). Age-related differences in associative memory: The role of sensory decline. *Psychology & Aging*, *29*(3), 672-683.

Norcia, A.M., et al. (2015). The steady-state visual evoked potential in vision research: A review. *Journal of Vision*, *15*(6), 4.

Odom, J. V., Bach, M., Brigell, M., Holder, G. E., McCulloch, D. L., & Tormene, A. P. (2010). ISCEV standard for clinical visual evoked potentials (2009 update). *Documenta ophthalmologica*, *120*(1), 111-119.

Packer, R. J., Lange, B., Ater, J., Nicholson, H. S., Allen, J., Walker, R., ... & Needles, M. N. (1993). Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. *Journal of Clinical Oncology*, *11*(5), 850-856.

Parisi, V., Ziccardi, L., Stifano, G., Montrone, L., Gallinaro, G., & Falsini, B. (2010). Impact of regional retinal responses on cortical visually evoked responses: multifocal ERGs and VEPs in the retinitis pigmentosa model. *Clinical Neurophysiology*, *121*(3), 380-385.

Pilling, R. F., Lloyd, I. C., & Huson, S. (2010). Utility of optic pathway glioma screening in young children with neurofibromatosis type I: questions generated by a clinical audit. *Eye*, *24*(10), 1603.

Robert-Boire, V., et al. (2017). Clinical Presentation and Outcome of Patients With Optic Pathway Glioma. *Pediatric Neurology*, *75*, 55-60.

Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., ... & Javitt, D. C. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno-and parvocellular-selective stimuli in schizophrenia. *Clinical Neurophysiology*, *116*(9), 2204-2215.

Shapey, J., Danesh-Meyer, H. V., & Kaye, A. H. (2011). Diagnosis and management of optic nerve glioma. *Journal of Clinical Neuroscience*, *18*(12), 1585-1591.

Siatkowski, R. M. (2006). VEP testing and visual pathway gliomas: not quite ready for prime time. *Journal of American Association for Pediatric Ophthalmology and Strabismus*, *10*(4), 293-295.

Skottun, B. C. (2014). A few observations on linking VEP responses to the magno- and parvocellular systems by way of contrast–response functions. *International Journal of Psychophysiology*, *91*(3), 147-154.

Spencer, E. L. & Harding, G. F. A. (2003). Examining visual field defects in the paediatric population exposed to vigabatrin. *Documenta ophthalmologica*, *107*(3), 281-287.

Statistics Canada. (2017, May 3). Age and sex, and type of dwelling data: Key results from the 2016 Census. *The Daily* (11-001-X). Ottawa: the author. Retrieved from https://www150.statcan.gc.ca/n1/daily-quotidien/170503/dq170503a-eng.htm

Tobimatsu, S., Tashima-Kurita, S., Nakayama-Hiromatsu, M., & Kato, M. (1991). Clinical relevance of phase of steady-state VEPs to P100 latency of transient VEPs. *Electroencephalography and Clinical Neurophysiology*, *80*(2), 89-93.

Tomoda, Y., Tobimatsu, S., & Mitsudome, A. (1999). Visual evoked potentials in school children: a comparative study of transient and steady-state methods with pattern reversal and flash stimulation. *Clinical Neurophysiology*, *110*(1), 97-102.

Trick, G. L. (2003). Beyond visual acuity: new and complementary tests of visual function. *Neurologic clinics*, *21*(2), 363-386.

Trisciuzzi, M. T. S., Riccardi, R., Piccardi, M., Iarossi, G., Buzzonetti, L., Dickmann, A., ... & Falsini, B. (2004). A fast visual evoked potential method for functional assessment and follow-up of childhood optic gliomas. *Clinical neurophysiology*, *115*(1), 217-226.

Tudor, M., Tudor, L., & Tudor, K. I. (2005). [Hans Berger (1873-1941)--the history of electroencephalography]. *Acta Medica Croatica*, *59*(4), 307-313. Abstract in *PubMed*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16334737

Van Mierlo, C., Spileers, W., Legius, E., Casteels, I., & Cassiman, C. (2013). Role of visual evoked potentials in the assessment and management of optic pathway gliomas in children. *Documenta Ophthalmologica*, *127*(3), 177-190.

Vespignani, H. (2003). *L'EEG : de la technique à la clinique*. Montrouge, France: John Libbey Eurotext.

Vottonen, P., Kaarniranta, K., Pääkkönen, A., & Tarkka, I. M. (2013). Changes in neurophysiologic markers of visual processing following beneficial anti-VEGF treatment in macular degeneration. *Clinical ophthalmology (Auckland, NZ)*, *7*, 437.

Wan, M. J., Ullrich, N. J., Manley, P. E., Kieran, M. W., Goumnerova, L. C., & Heidary, G. (2016). Long-term visual outcomes of optic pathway gliomas in pediatric patients without neurofibromatosis type 1. *Journal of neuro-oncology*, *129*(1), 173-178.

Wolsey, D. H., Larson, S. A., Creel, D., & Hoffman, R. (2006). Can screening for optic nerve gliomas in patients with neurofibromatosis type I be performed with visual-evoked potential testing? *Journal of American Association for Pediatric Ophthalmology and Strabismus*, *10*(4), 307-311.

World Health Organisation. (2017). *Cancer Fact sheet*. Retrieved from http://www.who.int/mediacentre/factsheets/fs297/en/

Wu, J., Yan, T., Zhang, Z., Jin, F., & Guo, Q. (2012). Retinotopic mapping of the peripheral visual field to human visual cortex by functional magnetic resonance imaging. *Human brain mapping*, *33*(7), 1727-1740.