VISUAL PERCEPTUAL ABILITIES IN YOUNG CHILDREN DIAGNOSED WITH CEREBRAL VISUAL IMPAIRMENT VERSUS THOSE WITH OCULAR DISORDERS

A thesis presented to the graduate faculty of
New England College of Optometry in partial fulfillment
of the requirements for the degree of Master of Science

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VISUAL PERCEPTUAL ABILITIES IN YOUNG CHILDREN DIAGNOSED WITH CVI VERSUS THOSE WITH OCULAR DISORDERS

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ABSTRACT OF THE DISSERTATION

VISUAL PERCEPTUAL ABILITIES IN YOUNG CHILDREN DIAGNOSED WITH CEREBRAL VISUAL IMPAIRMENTS VERSUS THOSE WITH OCULAR DISORDERS

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New England College of Optometry, 2021

Visual impairment when present early in life can result in a significant negative impact on development and subsequently quality of life. [1] [2] [3] Cerebral visual impairment (CVI) is a brain-based visual dysfunction. It is the leading cause of pediatric vision impairment in the developed world. [4] [5] Sakki, et al (2018) [6] defined CVI as a verifiable visual impairment which is not attributed to anterior visual pathway pathology and/or ocular disorders. Currently, there is no available standard approach to diagnose CVI. Vancleef, et al (2019) [7] showed that the Children's Visual Impairment Test for 3- to 6-year-olds (CVIT 3-6) differentiated children with CVI from three groups: typically developing children, children with intellectual disorders, and typically developing children with simulated reduced visual acuity.

The CVIT 3-6 is an objective test which uses a simple matching paradigm to assess the child's visual perceptual abilities. We performed a prospective clinical study to assess the ability of the CVIT 3-6 to differentiate children with CVI, who often have some level of

intellectual disability and refractive error, from children with ocular and/or ocular motor disorders. In-person testing was not feasible due to the COVID-19 pandemic. We developed and tested a virtual model first in a small sample of typically developing young children. Success was defined as at least 75% of participants successfully completing all tasks required. Upon review of the pilot data, study participants were recruited from a pediatric low vision clinic. Our clinical cohort consisted of two groups, children with a previous diagnosis of CVI (N = 4) and children with ocular and/or ocular motor disorders only (N = 3). A validated parent questionnaire regarding CVI, the Flemish (Ortibus) CVI questionnaire, was also administered. [8]

Our virtual testing protocol was successful in the seven participants tested. Our results showed a small, non-significant difference in overall CVIT 3-6 scores between participants with CVI and those with ocular disorders. (mean = 56 ± 12.29 vs. 64.7 ± 3.06, respectively, mean difference = 8.67, p = 0.346). Participants in the CVI group had a significantly higher percent abnormal scores on average on the Flemish CVI questionnaire than those with ocular disorders (p = 0.004). In conclusion, the CVIT 3-6 did not differentiate between children with CVI compared to those without CVI. The Flemish questionnaire differentiated between children with CVI from children without CVI. Further studies with larger sample sizes are needed to confirm the results of this project.

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Table of Contents

Introduction *1*

The visual system *3*

The Retina 3

The LGN 3

Primary Visual Cortex 3

Higher Order Processing Areas 4

Clinical Presentation of children with CVI *6*

Visual Functions 6

Other Clinical Concerns/Findings 7

Oculomotor Disorders 8

Higher order-visual processing/Visual perceptual and visual motor dysfunctions 8

Global motion processing and global form processing 9

Ventral/object vision 9

Dorsal/vision for action 10

Crowding 11

Attention 12

Clinical Assessment and Diagnostic Criteria of CVI *13*

Study Rationale *16*

Methods *18*

Study design 18

Investigators and investigative site 18

Characteristics of the participants 19

Inclusion Criteria 19

Exclusion Criteria 19

Procedures 20

Test materials and procedures 20

CVIT 3-6 test 20

Vineland Adaptive Behavior Scales – 3rd Edition (Vineland-3) 22

Flemish CVI questionnaire 22

Visual Acuity 24

Medical History Checklist 25

Recruitment 26

Informed Consent and Assent 26

Study Procedures (Day of Assessment) 27

Data analysis/Hypotheses 28

CVIT 3-6 28

Flemish CVI Questionnaire 28

Results *30*

Discussion *34*

Bibliography *39*

Appendix *52*

Appendix A: Detailed description of CVIT 3-6 subtests.[121] 52

Appendix B 66

Statistical Analysis 66

Calculation of Flemish percent abnormal 66

LIST OF FIGURES AND TABLES

Figure 1: Example of the CVIT 3-6 subtest 'silhouettes' of the second domain; degraded object perception. 21

Figure 2: Visual function tests provided by the FrACT electronic software. Landolt C Acuity, highlighted in blue, was used in the study. A two-forced choice method (up and down orientations) was utilized to determine acuity levels. 24

Figure 3: Digital medical history checklist designed via Redcap. Caregivers filled out the checklist through link invites using smart 25

Figure 4: The percent abnormal scores on the Flemish CVI questionnaire are shown on the X-axis and the CVIT 3-6 scores on the Y-axis. 32

Figure 5: Developmental delay, is defined as the difference between age equivalent and chronological age. Age difference in months is shown on the y-axis and the Flemish percent abnormal score on the x-axis. *Negative values indicate developmental delay. 32

Figure 6: Data published by VanCleef, et al. (2019) [7] comparing CVIT3-6 total scores in children with CVI from three other groups.....35

Table 1: Results of the 5-factor model analysis in the Flemish CVI questionnaire 23

Table 2: Summary of individual data collected in the CVI group. 30

Table 3: Summary of individual data collected in the non-CVI group.....31

Introduction

Vision plays an essential role in the development of the child's sensorimotor and cognitive abilities. [1] [3] It comes with no surprise that children with visual impairment are more likely to experience developmental delays. [9] In fact, blind children are delayed in their self-initiated motor response. [2] [3] Delays are more marked in visually impaired children with intellectual disability and/or cerebral palsy. [10]

CVI describes damage to post-chiasmatic visual pathways and structures, including the lateral geniculate nucleus, the optic radiations, the occipital cortices, white matter and high-order visual processing areas, in any combination or degree. [11] [12] [13] This damage mainly occurs pre/perinatally or within the first few years of life. [14] [15]

Sakki, et al. (2018) [6] defined CVI as a verifiable visual impairment which can co-occur with but is not attributed to anterior visual pathway pathology and/or ocular disorders. CVI is the leading cause of pediatric visual impairment in developed countries. [4] [5] This is due in part to improved management of conditions of pediatric visual impairment (PVI) such as congenital cataract which previously was the most prevalent cause of PVI. The increase in CVI prevalence is primarily due to increased survival rate of infants born prematurely or those born with neurological disorders. [11] [16]

Causes of CVI can be categorized into: those associated with premature birth and those occurring in full term infants. The World Health Organization (WHO) defines prematurity as gestational age of less than 37 weeks. [17] In pre-term infants, the most common form of brain damage is periventricular leukomalacia (PVL). [18] [19] Damage to the periventricular white matter obstructs the communication between motor and sensory areas resulting in motor and cognitive impairments.

In infants born full term, perinatal hypoxia-ischemia encephalopathy (HIE) is the most common etiology of CVI. [20] [21] [22] The damage from HIE depends on the severity and duration of the hypoxic event and the infant's gestational age. It is also important to note that any inflammation of the developing brain can lead to CVI (e.g., meningitis and encephalitis). [14] [20] Other causes of CVI include hydrocephaly, traumatic brain injury, brain tumors, neurological maldevelopment or malformation, genetic or metabolic disorders, infections, seizures and drugs and toxins. [13] [22] [23] [24] CVI can be accompanied by other conditions such as cerebral palsy, hydrocephalus, autism spectrum disorder and William syndrome. [25] [26]

In order to gain a better understanding of the clinical characteristics and functional manifestations of CVI, the organization and function of the visual system must be first described.

The visual system

The visual system consists of a complex and highly specialized organization of interdependent and hierarchical structures. The first level of neural specialization starts at the retina. [27]

The Retina

Light sensitive photoreceptors (rods and cones) convert light signals into spatially organized neural signals and synapse with bipolar and horizontal cells. [28] [29] At this level, image brightness and color contrast are established. [30] The bipolar cells in turn make synapses with the ganglion and amacrine cells. [31] These connections encode for motion and directionality. [32] The captured visual information is passed along the ganglion cell axons to the optic nerve where the nasal retinal neurons decussate to the contralateral part of the brain at the level of the optic chiasm. [33]

The LGN

Visual information travels along the optic tract and terminates in different layers of the lateral geniculate nucleus (LGN) in the thalamus. [34] [35] The LGN consists of six primary layers: two magnocellular layers which are most sensitive to moving stimuli and four parvocellular layers which are sensitive to color and they form the basis of shape detection. In the LGN, there are thin layers inserted between the primary layers which are called koniocellular layers. [36] The axons from the layers of the LGN fan out forming the optic radiations. These neurons terminate in different layers of the primary visual cortex. [37]

Primary Visual Cortex

The primary visual cortex is also known as the striate cortex and is located in the occipital lobe. Visual input from the retina, specifically the retinal ganglion cells, converges in the occipital lobe. Initial processing of all visual information occurs in the occipital

cortex, which includes color, shape, motion and location. [38] Damage to the primary visual cortex results in vision loss in the contralateral hemifield. [39]

Higher Order Processing Areas

Visual input is then sent to other cortical areas for further processing. These areas are referred to as higher order processing areas. [40] Damage to such areas does not result in simple loss of vision but rather in deficits associated with complex interaction of vision, cognition and motor skills such as those seen in children with CVI. [41] [42] There are two types of higher order visual processing; the ventral stream known as the what pathway and the dorsal stream or the where pathway. [43] [25]

The ventral stream receives input from occipital cortical areas (V2 and V1), and other subcortical visual structures, and processes information in the inferotemporal cortex. This pathway is responsible for object identification and recognition by acting as a visual library of previous visual experiences. [44] Damage to the temporal cortex can result in object/form agnosia (inability to recognize objects) despite adequate visual acuity or the absence of cortical blindness. [45] The dorsal stream projects visual information from the occipital lobe to the posterior parietal lobe. This pathway creates a virtual three-dimensional map of the visual environment and ensures the integration of visually guided body, head, and eye movements. The dorsal pathway is also responsible for directing attention to objects or areas of interest in the visual field. [46] Dorsal stream dysfunction is associated with optic ataxia, gaze apraxia and simultanagnosia. Optic ataxia refers to impairment in visually guided hand movement towards an object, while gaze apraxia is the inability to make accurate shifts in fixational eye movements. It is important to note that optic ataxia and gaze apraxia are not attributable to motor deficits. Simultanagnosia refers to difficulty in

processing a complex visual scene comprising many items. This triad of optic ataxia, gaze apraxia and simultanagnosia is seen in Balint's syndrome. [47]

Clinical Presentation of children with CVI

Complete assessment of vision and visual related abilities involves the use of two terms; vision function and functional vision. [48] Vision function assessment evaluates basic visual abilities. whereas functional vision refers to the extent the child utilizes their visual function in vision-related activities. [49] [50]

Visual Functions

i) Visual Acuity (VA): VA in children with CVI ranges from near normal visual acuity to legal blindness, and in some cases, there is more severe visual acuity loss. [51] Complete blindness is rare. [13]

ii) Contrast sensitivity (CS): CS is defined as the lowest threshold or difference between two shades of grey that can be discerned. Children with CVI can have a significantly reduced CS. [52]

iii) Visual field (VF): VF defects arise from damage to neurons carrying visual input from the retina. [53] Pre-chiasmatic damage of neurons results in VF deficits confined to the eye of origin. While post-chiasmatic damage results in specific types of VF deficits involving the two eyes known as homonymous hemianopia. This is defined as a binocular same hemifield VF defect, affecting each eye, due to damage to the contralateral (opposite side) post-chiasmal visual pathway. [54] These defects can manifest in different ways. They can be absolute (no object or light is seen) or relative (small and/or dim-lighted objects are not seen but larger and brighter objects are seen). Severe constriction of the entire periphery of the visual field can also occur. [55]

Damage to the posterior parietal lobe in one cerebral hemisphere leads to relative inattention or neglect of the contralateral hemifield. This can be confused with homonymous hemianopia. However, there are two key differences between hemianopia

and hemifield neglect. The attentional neglect caused by damage to the right parietal lobe is likely to be greater when compared to left parietal lobe damage. Hemianopia does not differ between right and left if there is comparable contralateral structural damage. The second key difference is that the parietal lobe maps the visual field with respect to the body and not the head, therefore attentional neglect affects the contralateral side of the body.

Visual field deficits vary across individuals with CVI. Children with CVI can have normal VF function. This is commonly the case with early periventricular damage to the optic radiations. [56] Inferior field defects can occur as a consequence of PVL in infants born very prematurely.

iv) Color vision (CV): CV is generally unaffected in CVI. [57] Children with CVI may exhibit a preference to bright colors such as red and blue or an idiosyncratic color preference. [58] [59]

Other Clinical Concerns/Findings

Refractive Error: In refracting children with CVI, accommodative anomalies are not uncommon. (Accommodation refers to the ability to bring near objects into focus). [13] [60] The range of ametropia (refractive error, near to far sighted) among children with CVI is broad. [20] Refusal to wear spectacle correction is common. [13] In some cases in young children, the child's visual brain adapts to a certain quality of image such that it cannot tolerate the new, improved (to us) qualities. This implies that prescribing glasses should not be deferred until the child is older as potential improvement in vision may slowly occur. In addition, improvements in vision provide the brain with more detailed visual input which can be overwhelming to the child, causing discomfort. [13] Correction of low amounts of hyperopia should be considered to bring near objects into focus and provide

accommodative aid especially if supported by dynamic retinoscopy. [61] A large plus neutralizing lens in dynamic retinoscopy indicates an accommodation lag. [62]

Oculomotor Disorders

Eye movement disorders are frequently seen in CVI. Lower brain damage affects structures controlling eye movements such as strabismus and nystagmus. Meanwhile, damage to higher brain centers such as that seen in HIE, results in gaze difficulties involving fixation, inaccurate fast fixation eye movements (saccades) or impaired ability to follow a moving target smoothly (smooth pursuit). [57] [63] [64]

Such oculomotor dysfunction is also reported in children with CVI due to PVL. [65] Damage to higher order processing centers seen in CVI can interfere with various eye movements. For example, children with difficulty in perceiving multiple objects at once, can find it difficult to fixate on different areas of interest mimicking gaze paralysis or gaze apraxia. [66] [67] Children with CVI can also have binocular vision anomalies such as poor stereopsis, strabismus and/or amblyopia.

Higher order-visual processing/Visual perceptual and visual motor dysfunctions

The difficulties the child with CVI experiences with their daily living skills and tasks are more complicated than expected given their visual function deficits (VA, CS, VFs,) and ocular motor abnormalities. We label the visual abilities required in daily life skills/activities as functional vision. Damage to higher order visual processing areas substantially limits the child's functional vision. [10] [23]

Spatial vision encompasses many complex higher order visual processing areas related to spatial representations, objects in space, relative motion, location memory, reaching and attention. Dividing higher order visual processes into dorsal and ventral streams is artificial as everyday visual tasks involve complex interconnections between the two streams. [25] An

example of this is dissecting a task such as visual reach. In order to reach an object, it needs to be recognized (a process more dependent on the ventral stream). After recognition of the object, a coordinated eye-hand (and possibly body) reach needs to happen (a task more dependent on the dorsal stream).

Global motion processing and global form processing

Studies have compared the development of global motion processing (part of the dorsal stream) with global form processing (ventral stream function). These studies demonstrated that global motion develops earlier than global, static form. [68] Furthermore, infants born prematurely (> 33 weeks) showed similar responses in Visual Evoked Potential (VEP) for global form as compared to those born to term. On the other hand, Braddick, et al (2011) [69] showed that VEP responses to global motion differed between term-born and pre-term infants. Their findings indicate that pre-term infants, even those with only mild brain injury, are delayed in global motion (dorsal stream) development when compared to those born to term. [68] [69]These findings support the hypothesis coined 'dorsal stream vulnerability'. [70] [71] [72]

Ventral/object vision

Object recognition dysfunction: visual agnosia refers to impairment in visual object recognition. This in a general and broad perspective can affect recognition of object forms and shapes (inability to recognize familiar objects). [73] [74] Interestingly, individuals with visual agnosia can recognize objects that are moving against their background. This suggests that these individuals used depth cues provided by the dorsal stream to perceive form. This highlights the overlap in the functions of the ventral and dorsal streams. [75]

However, visual agnosia is very rare. More common types of visual agnosia are prosopagnosia (impaired recognition of faces) [76] [77] and alexia (impaired recognition in

words). The latter is very complex and can include, pure alexia (in which individuals can write but cannot read despite good vision function) [78]and secondary alexia (due to central vision loss) [79] Reading might also be affected due to attentional neglect. This is known as neglect dyslexia in which hemifield neglect from lesions to the parietal or frontal lobes results in same-side reading errors. [80]

Children with CVI can be impaired in recognizing certain features in the visual scene. These include visual agnosia, alexia and most notably prosopagnosia. Prosopagnosia typically results from damage to the right hemisphere or bilateral ventral occipito-temporal cortex. [81] [82]

Dorsal/vision for action

The dorsal stream is a complex and extensive set of interconnections of brain areas. Kravitz, et al. (2011) [83] reported that the dorsal stream has three distinct pathways. First, one connecting the pre-motor cortex with parietal areas and is associated with visuomotor batteries for guided action (i.e., reaching and grasping). Second, a pathway connecting pre-frontal areas (associated with spatial memory and attention) with the frontal eye fields (responsible for saccades and pursuits). Lastly, one connecting parietal areas with the temporal lobe and hippocampus which is responsible for integrating spatial information with information from the ventral stream to allow for navigation.

Children with abnormal development of dorsal stream processing reach motor milestones later than typically developing children. This delay involves both gross (learning to walk) and fine motor skills. [84] In addition, some motor-related problems continue into later in life. These include difficulties walking on uneven surfaces and difficulties in judging depth and negotiating stairs. [85] Dorsal stream dysfunction is also

associated with deficits and delays in visuomotor development and action planning. Impaired visual guidance of movement can be accompanied and therefore masked by motor difficulties. In the absence of gross motor difficulties, impaired visual guidance of movement may present as the principal problem. This is evident in a mismatch between the hand and the spatial location of interest.

Bilateral damage to the posterior parietal lobes, results in dorsal stream dysfunction. This leads to visual difficulties such as optic ataxia (impaired visual guided movement) which is often accompanied by simultanagnosia (the ability to simultaneously perceive two or more objects at a time) and gaze apraxia (inability or difficulty in gaze shifts). [66] [86] [67]

Crowding

Crowding refers to the inability to recognize objects in clutter. [87] It is related to dorsal stream dysfunction, which can result in difficulties extracting visual information in complex visual scenes. [88] Clinically, showing letters in isolation may improve VA levels in children with CVI due to crowding. Van Genderen, et al (2012) [89] reported that 41% of children with CVI have a Crowding Ratio (CR) of ≥ 2.00 as compared to only 2% of their normal counterparts. CR is the ratio of single optotype acuity to linear acuity. It is also postulated that due to crowding children with CVI prefer to view objects at a near distance. This consequently enlarges the retinal image of the object of interest therefore reducing or eliminating crowding altogether. [59] Zee, et al [90] recommended that low vision specialists add the CR to their routine diagnosis to distinguish children at risk of CVI from children with ocular pathology.

Attention

Visual attention describes the ability to attend or focus on certain aspects within the visual field. Attention primarily involves two areas of the brain, the dorsal stream and an execution center located in the frontal lobe. [91] Attentional deficits result from poor frontal lobe connections. Infants with either focal lesions or diffuse HIE exhibited sticky fixation (defined as inability to easily switch visual attention from one target to another) [92] [93] [94] This is linked to both right and left parieto-frontal areas which are necessary for the development of attention switching mechanisms. [92] [95] A child with CVI may only be able to perceive a very small area of space at a time in spite of being found to have a full visual field. [13] It is of note that attentional field defects relate to the body and may not be compensated by eye and head movements only.

Clinical Assessment and Diagnostic Criteria of CVI

Early diagnosis of CVI is critical to guide early habilitation strategies and thereby improve functional vision. Rigorous studies evaluating the quality of preschool and early childhood education reveal that children who received additional services had better educational outcomes. [96] [97] For example, one study concluded that every dollar spent on services provided early in life yielded approximately $13.00 in return. [96] Visual skills play a part in learning and cognitive processes. [66] Although no studies have specifically evaluated the effects of CVI on learning and educational outcomes, it is surmised that any form of early-onset visual impairment will adversely impact learning and cognitive development. [66]

Currently, there is no available standard and widely accepted method to diagnose children with CVI. [98] The examination typically starts with a detailed medical history. Here the examiner reviews the child's prenatal, neonatal and early postnatal history. This includes gestational age, abnormal events around birth, including anoxia i.e., HIE, evidence for PVL and any other abnormal findings. [99] [13] Other considerations include cerebral hemorrhage, hydrocephalus, epilepsy and central nervous system infections. [100] These are typically revealed upon review of medical records.

Over a number of years, Drs. Barry Kran, Luisa Mayer and Nicole Ross at the NECO Center for Eye Care at Perkins, developed a consensus approach in which they extensively (30 minutes to more than an hour) review medical reports, previous eye care reports, reports from preschool or school personnel (which include OTs, PTs, vision teachers, etc.) and communication and speech and language reports. Eye care providers may utilize validated questionnaires completed by the child's caregiver, (Flemish and Dutton). [101] [102] These questionnaires or inventories are used to aid with the history taking and are important in

leading to a directed examination. These surveys are limited, however, in that they do not reveal specific visual perceptual abilities, such as visual-visual matching, recognition of objects in line drawings or in different orientations, or when occluded, and finding objects in complex images. [7]

Ultimately, based on the review of medical history and other materials, and parent-based CVI questionnaires along with findings in the examination of the child as well as observations of the child during examination, the eyecare provider determines the probable cause of the child's visual difficulties. Are they explained by anterior pathway (ocular) pathology or other systemic issues, or whether there is a brain-based visual impairment? If the latter, then CVI is strongly suggested. Occasionally a definite diagnosis of CVI cannot be made, especially in initial assessment of the child and only a working hypothesis is formed.

Functional vision assessment during examination supports the diagnosis of CVI. This is often qualitative and aims to provide real-life assessment of the child's performance in daily life activities. This assessment consists of clinical tests of vision functions coupled with the use of tools and modifications to create an environment that allows the examiner to acquire information about the child's functional vision. [103]

Dutton, et al. (2010) [104] noted that functional vision can only be completely assessed in the child's home and school environments. This is not possible for clinicians. [105] Assessment of higher order visual perceptual difficulties and their impact on the child's functional vision is complicated and focuses on aspects that include visual attention, visual search and perceptual groupings. Zhil, et al. (2015) [106] investigated the performance of children, with and without dorsal stream dysfunction, to find a diamond present in a diagram along with an increasing number of dots. Their results showed that children with

dorsal stream dysfunction took longer search times and used random search patterns as compared to those without visual perceptual difficulties. This assessment of perceptual groupings and visual search is utilized at NECO Center for Eye Care at Perkins via the use of puzzles of increasing complexity.

McConnell, et al. (2020) [107] reviewed diagnostic assessment of CVI in literature. The most documented aspect of the diagnostic process was a detailed medical history of the child, which was documented in 93% of reviewed literature. However, not all articles reported a full picture of the child's medical history. This study postulated that standard clinical tests were carried out, however this has not been well reported or documented in literature. Almost all articles reported VA levels. However, only 43% of these articles reported measuring the child's refractive error. More than half the articles (56.5%) conducted visual field and ocular health tests. Only 11% reported assessment of contrast sensitivity. Approximately 9% of articles assessed accommodative status. Neuroimaging, most commonly MRI, was documented in 63% of articles. Most of which were obtained retrospectively through accessing the child's medical records.

Study Rationale

The clinician combines clinical findings with the child's medical history and school reports and in many cases with a CVI parent-based questionnaire. However, this may not be sufficient for a definite diagnosis of CVI. This approach is adopted by Drs. Kran and Ross and was used to determine the participant pool from which this study recruited.

While there is no standard approach to CVI diagnosis, similar approaches have been adopted by other clinicians dealing with a similar patient population. However, an objective assessment tool that is specific in diagnosing CVI would benefit less experienced clinicians.

Bennet, et al. (2019) [48] utilized virtual reality (VR) to assess functional vision in children with CVI. The use of VR allowed the researchers to evaluate functional vision in real life-based scenarios via simulation. They employed two virtual scenarios to assess the child's static and dynamic visual search. [48] One scenario consisted of a virtual toy box, where the child is asked to locate a favorite toy, while the other was a virtual hallway with a task to locate a familiar person in a crowd. [108] [109] Tasks' environment was manipulated through introducing distractors (presence of more elements in the virtual visual scene). Responses were collected in an objective manner via eye tracking which continuously monitored and recorded eye search patterns during both tasks. The output of the results is presented as a heat map where warm colors represent areas the child spent most time on and vice versa. The cohort consisted of neuro-typically developing children, children with ocular visual impairment (OVI) and children with CVI. Heat map patterns remained similar before and after the introduction of distractors in both tasks in the control and OVI groups. However,

participants in the CVI used a broader search pattern when more distractors were present. This is supported by literature in which the visual performance of children with CVI tend to decrease with increasing complexity of the visual scene.

The purpose of this study is to examine the ability of an objective visual perceptual-based test to differentiate between children with CVI and those with ocular and/or ocular motor disorders only. If the test does differentiate between CVI and ocular disorders, it can be utilized to aid in the diagnosis of CVI by other ophthalmic clinicians. We chose this test in our study because it is a normed objective test which is not limited by age (can be performed on children with developmental ages of as young as 3 years old) or intact verbal or motor skills. It is also cost-effective and only requires a computer with internet access which is readily available in almost all clinical practices.

Methods

Study design

An objective test that evaluates children's visual perceptual abilities was selected for this study. The Children's Visual Impairment Test for 3- to 6-Year-Olds (CVIT 3-6) was developed and normed by Vancleef, et al. (2019). [7] A detailed description of the test is provided below. In the 2019 paper, the CVIT 3-6 test differentiated children with CVI from three other groups: those with intellectual disability, those with simulated reduced visual acuity, and typical, normally developing children.

Investigators and investigative site

Principal investigators: Reem Almagati, BSc. & Barry Kran, OD.

Co-Investigator: D. Luisa Mayer Ph.D.

Investigative site: Virtual Zoom telehealth via necoeyecare.org.

To investigate the CVIT 3-6, we tested children seen in a pediatric low vision practice, the NECO Center for Eye Care at Perkins. Children recruited in this study were either previously diagnosed with CVI or had ocular and/or oculomotor disorders without CVI.

In order to confirm the clinical diagnosis of CVI, we also administered a parent-based questionnaire that has been shown to identify children with CVI. This questionnaire is called the Flemish CVI questionnaire. [8] We descriptively compared the results on the CVIT 3-6 with the Flemish questionnaire for evidence of agreement. Description of tests and procedures is provided below.

Characteristics of the participants

Participants were identified by a review of the database of patients seen at the NECO Center for Eye Care at Perkins in the interval January 1, 2016 - March 12, 2020. Two groups of potential participants were identified: children with a previous diagnosis of CVI and children with ocular and/or ocular motor disorders only.

Inclusion Criteria

A. Patients with completed examinations seen in the NECO Center for Eye Care at Perkins between January 1, 2016 - March 12, 2020.
B. Best corrected binocular visual acuity of 20/63 (0.5 logMAR) or better using symbols or letters.
C. Chronological age between 3 and 11 years for children with CVI and between ages 3 and 8 years for those without CVI. The rationale for this difference in chronological age between the two groups is based on the assumption that children with CVI are more likely to have developmental delay and therefore would have lower developmental ages. [110] [57]

Exclusion Criteria

A. Insufficient information in the database on the potential participant's ocular status.
B. Age equivalence (developmental age) outside the range 3 to 6 years.

Potential participants were first identified from the patient database using the inclusion criteria of diagnosis, chronological age and visual acuity. Thirty and fifty potential participants were invited to participate from the CVI and non-CVI groups, respectively.

Participation was solicited from parents using encrypted email invitations. These procedures were compliant with the Health Insurance Portability and Accountability

Act (HIPAA) regulations and the Helsinki guidelines. A total of three invitations per potential participant were sent.

Procedures

Due to the COVID-19 pandemic, we were unable to test subjects in person. To conduct the study, we developed and piloted a virtual model for testing with a small sample of typically developing young children. The procedures used in the pilot study were followed in testing the recruited subjects. Two Zoom visits were scheduled for each participant. The first Zoom visit consisted of visual acuity testing using the Freiburg Visual Acuity and Contrast Test (FrACT). Prior to the second visit, the parent/caregiver was asked to complete a medical history checklist, the Flemish CVI questionnaire and the Vineland-3 comprehensive parent questionnaires. These were completed asynchronously. The second Zoom visit included another testing of visual acuity and administration of the CVIT 3-6.

Neither the CVIT 3-6 results nor the Flemish CVI responses were used to aid with the initial diagnosis of CVI in this study population.

Test materials and procedures

CVIT 3-6 test

The CVIT 3-6 consists of four domains that are further divided into three to five subtests. Each subtest consists of two trial questions and five test questions. The first domain assesses object and scene perception. Three subtests are presented in this domain: object recognition, which serves as a control for the following subtests, context recognition and scene perception. The second domain is degraded object perception in which objects are degraded in different ways: silhouettes, full line drawings, fragmented outlines, objects in noise and unconventional viewpoints. The third domain evaluates the child's motion

perception which tests different forms of motion on each subtest: coherent motion perception, kinetic object segmentation, and biological motion. The fourth and last domain in the CVIT 3-6 is global-local processing. It has three subtests: overlapping figures, embedded figures and missing parts. Maximum CVIT 3-6 score is 70. The cut-off score for normal visual perception is 53 which represents the 10th centile of scores in typically developing children. [7] An example of one of the subtests is shown in Figure 1. Further information on the CVIT 3-6 with more examples of the test materials are provided in Supplementary Material as described by Vancleef, et al. (2019) (page 50-60). Because the CVIT 3-6 scores results based on a child's developmental age, we evaluated the children's developmental age using the vineland-3 comprehensive parent questionnaire [111]

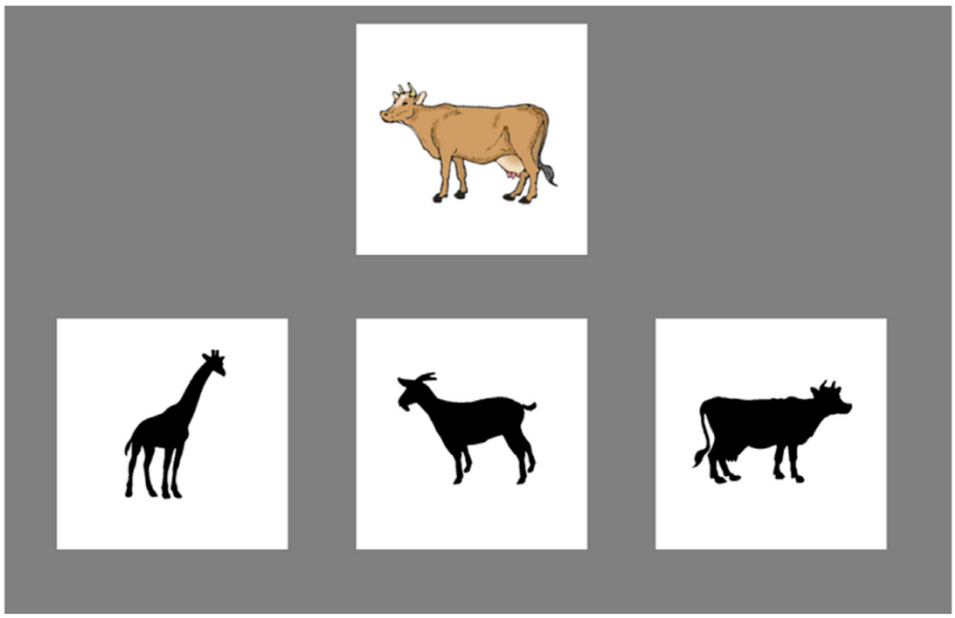


Figure 1: Example of the CVIT 3-6 subtest 'silhouettes' of the second domain; degraded object perception.

Vineland Adaptive Behavior Scales – 3rd Edition (Vineland-3)

The Vineland-3 is a standardized measure of adaptive behavior, that is, the things that people do to function in their everyday lives. Ability measures focus on what the examinee can do in a testing situation while the Vineland-3 focuses on what they actually do in daily life. The Domain Level tests four adaptive behavior domains, Communication, Daily Living Skills, Socialization and Motor skills. Because it is a norm-based instrument, the examinee's adaptive functioning is compared to that of others of their age. Age equivalent scores are derived from the subject's measured raw score in reference to the normative sample median. The electronic Vineland-3 was completed by the subject's parent via computer or smartphone prior to the second Zoom visit. Developmental age equivalence was derived from the Vineland-3 results to assign the participant to the appropriate age group. A report is autogenerated after completion of the questionnaire reporting 11 values of age equivalent under the aforementioned four basic domains. We utilized bootstrapping around the median (a resampling method) of the four adaptive behavior domains to obtain the developmental age.

Flemish CVI questionnaire

This is a validated questionnaire which consists of 46 binary closed-ended questions completed by the child's caregiver. [50] [101] [8] The information from this survey is useful for characterizing behavioral difficulties, particularly regarding vision for action, vision while moving, and spatial orientation, which provides evidence for the possibility of CVI. The parent checks the most appropriate response for each item. The possible responses are: agree, disagree or NA (not applicable). Under normal circumstances, the questionnaire is available as a hard copy and is filled by the

caregiver in the clinic/waiting area. Due to the pandemic and the virtual nature of this study, Redcap, a secure web forum for creating and managing online databases and surveys, was used to obtain a digital version of the questionnaire that can be accessed remotely. The finished online version of this questionnaire was approved by Dr. Els Ortibus and colleagues through email exchange.

In a recent paper published by Itzhak, et al. [8] the authors reviewed the records of 630 children to investigate the underlying factor structure of the Flemish CVI questionnaire to differentiate children with and without CVI. A 5-factor model was selected which explained 56% of the total variance in factor scores. This model was implemented here in scoring of our percent abnormal value. (See Table 1). Description of percent abnormal calculations is provided in appendix B (page 61).

Table 1: Results of the 5-factor model analysis in the Flemish CVI questionnaire

Factor 1: Object and face processing impairments	
Does not recognize everyday objects, such as an apple, bike, house, ball (no. 22)	0.78
Cannot focus on persons or objects (no. 2)	0.77
Manipulates an object rather than look at it (no. 40)	0.75
Cannot keep looking at objects or persons (no. 9)	0.75
Does not find way to the classroom and/or in the home (familiar environments) (no. 26)	0.78
Does not understand facial expressions (no. 25)	0.63
Recognizes familiar objects only when they are drawn in colour (no. 23)	0.59
Looks away when taking the chocolate spread from the table (no. 29)	0.56
Pays attention only to objects in the centre of the visual field (no. 8)	0.55
Does not find the chocolate spread on the table (no. 34)	0.50
Cannot play memory games (no. 42)	0.48
Eye contact is absent (no. 1)	0.48
Needs encouragement to look at an object, explore the room (no. 14)	0.45
Tries to compensate by talking a lot (no. 47)	0.44
Stops activity when there is too much to look at (no. 43)	0.44
Cannot find teddy bear (or equal) among other cuddly animals (no. 33)	0.43
Do not do their best for tasks where they need to look carefully (no. 45)	0.42
Recognizes persons by listening to their voice and watching their posture than by looking at their faces (no. 24)	0.41
Factor 2: Visual (dis)interest	
Abandons play activity quickly (no. 11)	0.77
Does not find/recognize familiar persons in a crowd (no. 35)	0.69
Do not find toy when they drop them (no. 6)	0.52
Sits right in front of the television (no. 17)	0.52
Factor 4: Moving in space impairments	
Bumps easily into something (no. 7)	0.75
Falls frequently over clearly visible objects (no. 5)	0.72
Cannot estimate distances (no. 36)	0.41
Factor 5: Anxiety-related behaviours	
Is scared or restless in unfamiliar environment (no. 18)	0.72
Clings to parents in an unfamiliar environment (no. 20)	0.59
Shows interest for complex pictures (no. 31)	−0.44
Is generally anxious (no. 44)	0.42
Needs encouragement to look at an object and/or explore the room (no. 14)	0.40

Visual Acuity

Each participant's binocular visual acuity was tested using their habitual distance correction. The acuity test optotypes are letters presented by a validated electronic software Freiburg Visual Acuity and Contrast Test (FrACT) (https://michaelbach.de/fract/). [112] [113] (See Figure 2)

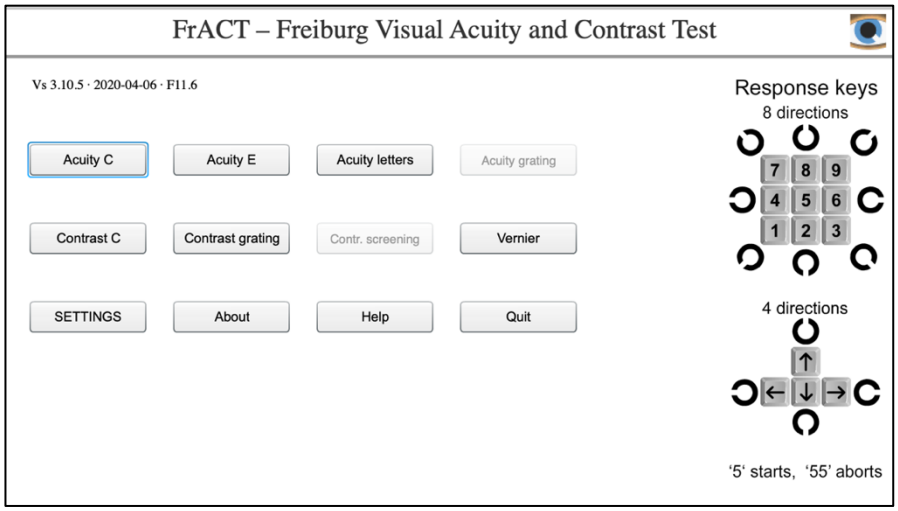
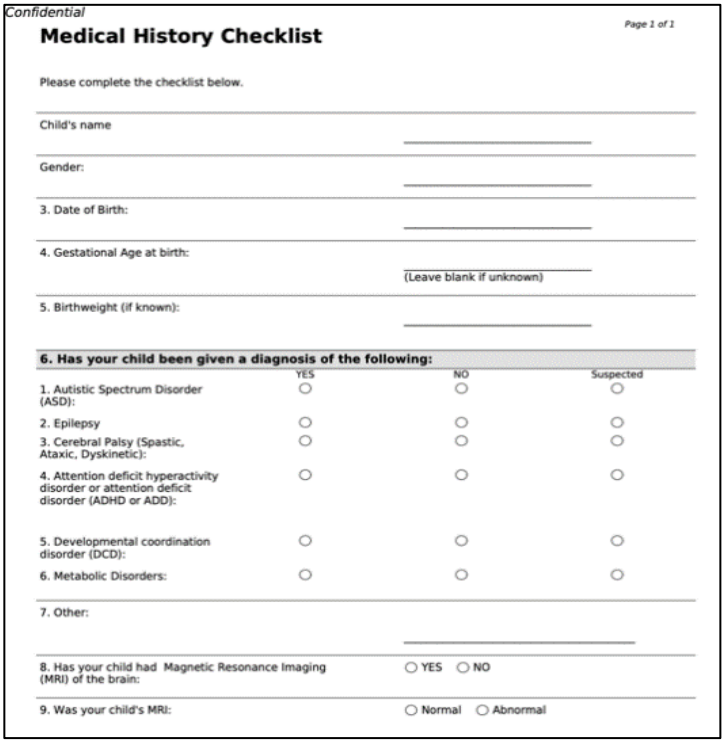


Figure 2: Visual function tests provided by the FrACT electronic software. Landolt C Acuity, highlighted in blue, was used in the study. A two-forced choice method (up and down orientations) was utilized to determine acuity levels.

Medical History Checklist

Information regarding the child's birth history was obtained from parents/caregivers via a simple digital checklist using Redcap. (See figure 3)



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Medical History Checklist

Page 1 of 1

Please complete the checklist below.

Child's name _____

Gender: _____

3. Date of Birth: _____

4. Gestational Age at birth: _____ (Leave blank if unknown)

5. Birthweight (if known): _____

6. Has your child been given a diagnosis of the following:

	YES	NO	Suspected
1. Autistic Spectrum Disorder (ASD):	○	○	○
2. Epilepsy	○	○	○
3. Cerebral Palsy (Spastic, Ataxic, Dyskinetic):	○	○	○
4. Attention deficit hyperactivity disorder or attention deficit disorder (ADHD or ADD):	○	○	○
5. Developmental coordination disorder (DCD):	○	○	○
6. Metabolic Disorders:	○	○	○

7. Other: _____

8. Has your child had Magnetic Resonance Imaging (MRI) of the brain: ○ YES ○ NO

9. Was your child's MRI: ○ Normal ○ Abnormal

Figure 3: Digital medical history checklist designed via Redcap. Caregivers filled out the checklist through link invites using smart

Recruitment

Emails were sent out to caregivers of potential participants. Invitation emails contained an overview of the study and the consent and assent forms. The letter explained the purpose and the methods of the study. The consent and assent forms were signed digitally. All information requested from the parent was approved by the Institutional Review Board (IRB) at NECO.

When all documents were signed, a zoom telehealth visit was scheduled to measure binocular visual acuity. After obtaining the child's visual acuity, emails were sent with a request to complete the Vineland and Flemish CVI questionnaires. Upon completion, a second zoom telehealth visit was scheduled during which visual acuity was measured again and the CVIT 3-6 was administered to the child via screen sharing.

The examiner was not involved in the identification of potential participants from the patient database nor was she involved in the solicitation of the identified CVI and non-CVI groups. The email invitations, sending of consent and assent forms and scheduling of visits were handled by the clinic manager at NECO Center for Eye Care at Perkins, Ms. Carol Bernazani. The examiner had access only to the child's first name and the caregiver's email address. Furthermore, caregivers were instructed not to share anything with the examiner that could potentially reveal the child's diagnosis. In this manner, the examiner was unaware of the diagnosis at the time of testing.

Informed Consent and Assent

The purpose and details of the experiment was explained to the parent/caregiver before the testing began. Once the parent's and the child's (as appropriate) questions were all answered to their apparent satisfaction, the parent and child were asked to read and sign the consent and assent forms respectively.

Study Procedures (Day of Assessment)

In order to conduct the virtual visits, caregivers were instructed to ensure a computer screen size is at least 13 inches diagonally and to have a functional camera. In order for the investigator to observe the child's responses during the test, an auxiliary smart device (e.g., cellphone or tablet) was utilized positioned appropriately by the child's caregiver for the examiner to have a view of the child during testing.

There were two Telehealth Zoom visits with the parent and the participant. In each visit, the visual acuity of the child was measured while the participant was wearing their habitual distance correction. The parent/caregiver was instructed to have a millimeter ruler and a tape measure to calibrate test distance for the FrACT Visual Acuity test. A printable millimeter ruler was attached to the invite email. (https://www.readers.com/blog/wpcontent/uploads/2016/07/ReaPrintableSizeRuler.pdf) This first visit in which visual acuity only was tested typically lasted for less than 20 minutes.

In the second Zoom telehealth visit, visual acuity was again measured prior to administering the CVIT 3-6. This test was accessed with an internet link (https://psytests.be/clinicians) and projected on the examiner's screen and shared with the participant's caregiver and the participant via Zoom screen sharing. The second visit lasted about 1 hour.

Following acuity assessment, the CVIT 3-6 was administered. The instruction to the participant was to match an object with the object in a set of three alternatives. Any indication of a response was accepted: simple pointing to the matching object, tapping on the object on the screen, or a verbal response, or using the computer mouse. The examiner ensured that the participant responded to all test trials by friendly

encouragement. Breaks were allowed after completion of the first domain and the number of breaks were recorded at the end of the test. Scores were recorded for participants who successfully completed the test. The highest possible score is 70. Scores lower than 53 are considered below normal and possibly indicative of CVI. The CVIT 3-6 automatically calculated the overall score and constructed a graphical representation of scores across the 14 subtests.

Data analysis/Hypotheses

CVIT 3-6

1. Null: CVIT 3-6 performance relative to age equivalent norms will be similar in the children diagnosed with CVI and those without CVI.
2. Alternative hypothesis: CVIT 3-6 performance will be abnormal in a larger proportion of the CVI group.

Flemish CVI Questionnaire

1. Null: The Flemish percent abnormal scores will not differ between the CVI and non-CVI groups.
2. Alternative hypothesis: The mean of the Flemish percent abnormal scores will be higher in children diagnosed with CVI compared to those without CVI.

The Shapiro-Wilk Normality test was performed on data from the two tests prior to data analysis. A p-value > 0.05 indicates that the sample is normally distributed. The normality tests for both CVIT 3-6 scores and Flemish percent abnormal scores showed $p > 0.3$, indicating that the data are normally distributed.

A two-sided t-test was used to compare CVIT 3-6 total scores between the CVI and non-CVI groups. A score of less than 53 was abnormal. A two-sided t-test was used

to investigate whether the Flemish percent abnormal scores were statistically higher in the CVI group.

Additionally, as an exploratory analysis, a two-sided t-test was done to evaluate whether children with CVI have developmental delays compared to the non-CVI group. Developmental delay was derived from the difference between age equivalent values measured by the Vineland-3 parent questionnaire and the participant's chronological age. We opted for two-sided t-tests because in the results published by Vancleef et al. (2019) [7], there was an overlap in the performance of children with CVI as compared to typically developing children. In addition, we chose to go with a more conservative statistical route due to the small sample size we were able to obtain.

Results

This research project yielded an n of 7 participants. The CVI group (4) had developmental anomalies, premature birth, hyperopia, amblyopia and binocular disorders. The Non-CVI group (3) had hyperopia and other oculomotor disorders.

Visual acuities of some of the participants did not meet the study inclusion criterion when the FrACT test was administered. This test differed from the tests used in the eye clinic in that Landolt-C optotypes were used vs. symbols, letters in lines, etc. used in the clinic. Tables 2 and 3 show VA levels in the clinic, as reported in the participants' files and the levels obtained via the FrACT for the CVI and non-CVI groups, respectively.

Table 2: Summary of individual data collected in the CVI group.

Subject	Flemish % Abnormal	CVIT 3-6 Score	Age Equivalent (Months)	Chronological Age (Months)	VA on File (logMAR)	FrACT VA (logMAR)
1	8.66%	42	73	40	0.42	1.2
2	11.36%	65	39	61	0.30	0.15
3	12.87%	NA	21	67	0.40	0.88
4	6.28%	61	66	69	0.30	0

* Note that subjects No. 1 & 3, did not meet the VA criteria. In addition, subject 3 had a developmental age of less than 3 years; 36 months.

One participant from the CVI group (#3, Table 2) could not complete the CVIT 3-6 subtests as the tasks became more difficult. This is not surprising since this child had markedly reduced age equivalent (21 months) vs. chronological age (67 months) and nystagmus. Moreover, the CVIT 3-6 is normed for the youngest subjects at age 3 years. This participant also had reduced VA and disinterest in TV and smart screens as noted

by the parent. Their data were analyzed for the Flemish percent abnormal results and for chronological age vs. age equivalent but not for the CVIT 3-6 results.

For the CVI group (N=3) the mean CVIT 3-6 score was 56 ± 12.29. The mean percent abnormal on the Flemish inventory (N=4) was 9.82% ± 2.9%. Chronological age of participants in the CVI group (N=4) had a mean of 59.25 months ± 13.28; the mean age equivalent was 49.75 months ± 24.13.

For the non-CVI group (N=3 for all analyses) the mean CVIT 3-6 score was 64.67 ± 3.06. The mean % abnormal score on the Flemish inventory was 0.63% ± 1.09%. Chronological age mean was 65.67 months ± 22.3 and mean age equivalent was 52.33 months ± 22.5. These results are shown in Table 3.

Table 3: Summary of individual data collected in the non-CVI group.

Subject	Flemish % Abnormal	CVIT 3-6 Score	Age Equivalent (Months)	Chronological Age (Months)	VA on File (logMAR)	FrACT VA (logMAR)
1	1.88%	68	75	91	0.18	0.15
2	0%	62	52	49	0.18	0.04
3	0%	64	30	57	0.18	0.18

To answer the research main question, (Is the CVIT 3-6 robust enough to differentiate children with CVI in a typical pediatric low vision clinical population?) we performed a two-sided Welch Two Sample t-test compared the mean CVIT 3-6 scores between the CVI and non-CVI groups (N = 3 in both groups). There was no significant difference between the means (difference = 8.67, t = -1.1855, df = 2.25, p= 0.346, 95% confidence interval: -37.04 - 19.7). The individual data are plotted in Figure 4 as CVIT 3-6 score vs. Flemish abnormal percentages.

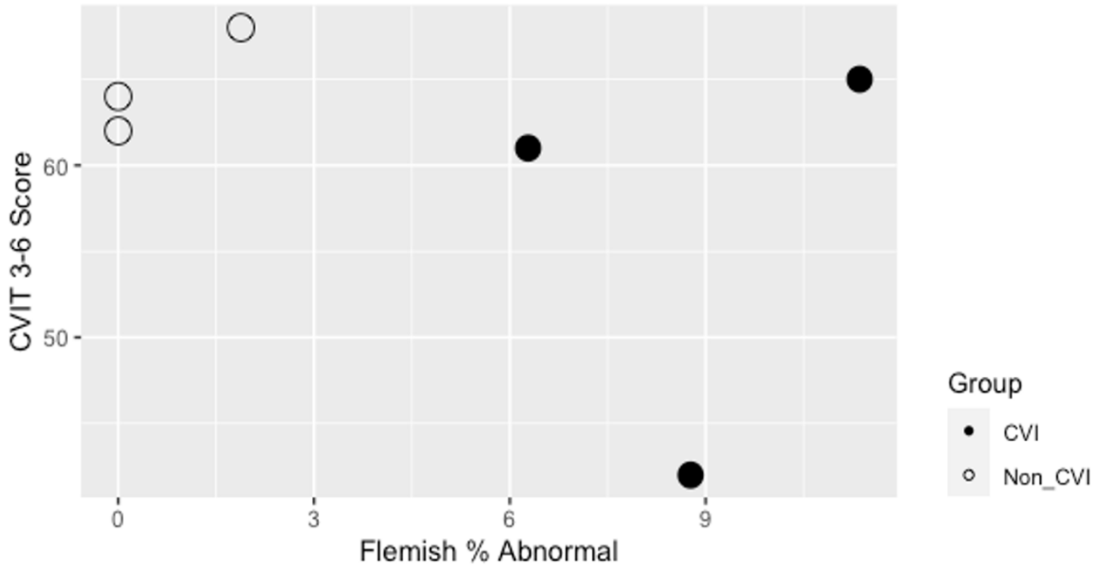

Figure 4: The percent abnormal scores on the Flemish CVI questionnaire are shown on the X-axis and the CVIT 3-6 scores on the Y-axis.

Regarding the difference in Flemish percent abnormal scores between the CVI and non-CVI groups (N=4 and 3 respectively), the two-sample t-test was statistically significant (mean difference = 9.19%, t = 5.8124, df = 4.0126, p = 0.004. Therefore, we rejected the null hypothesis and accepted the alternative hypothesis indicating that there is a true difference in the means with a 95% confidence interval: 4.80 - 13.58). That is, participants in the CVI group had significantly higher percent abnormal scores on the Flemish CVI questionnaire than those with ocular disorders. Figure 5 shows the individual data for developmental difference vs. Flemish subnormal percentages.

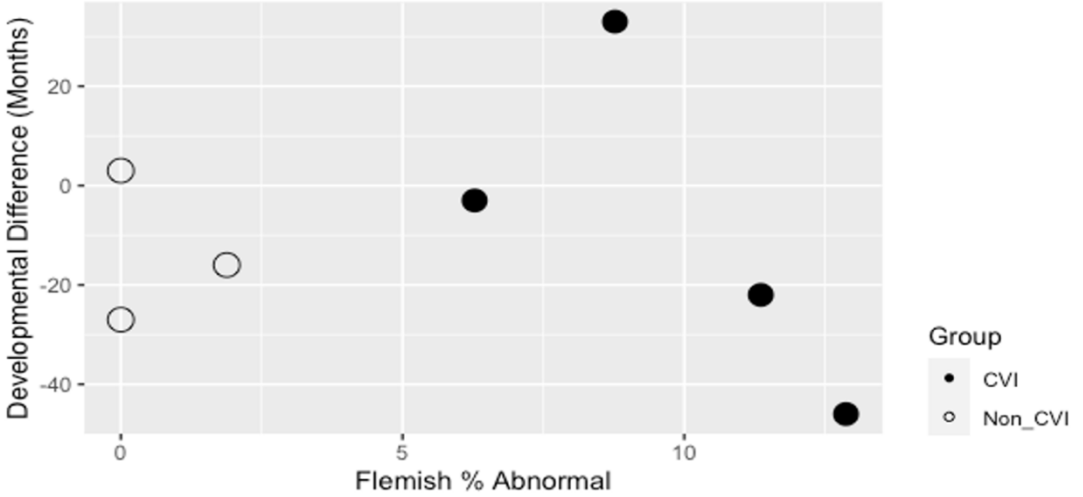

Figure 5: Developmental delay, is defined as the difference between age equivalent and chronological age. Age difference in months is shown on the y-axis and the Flemish percent abnormal score on the x-axis. *Negative values indicate developmental delay.

As part of our exploratory analysis, we performed the Welch Two Sample t-test to compare the difference between chronological age and age equivalent (based on the Vineland-3 questionnaire) between the two groups. There was no significant difference (N=4 for CVI and 3 for non-CVI group); $t = 0.20349$, $df = 4.384$, $p = 0.4239$). Fig. 5 shows the difference between chronological age and age equivalent as a function of the Flemish percent abnormal score for the 7 participants. This difference in age is taken to indicate developmental advance (plus values) or developmental delay (minus values).

Discussion

The CVIT 3-6 did not differentiate between the participants with CVI and those with ocular or ocular motor disorders only. Only one of the three participants in this study whose CVIT 3-6 score was below the abnormal cutoff of 53.[7] All three of the participants without CVI scored above the cutoff. This non-significant finding does not replicate the results of the VanCleef et al study. They conducted an ANOVA test to compare the performance of children with CVI (N=12), typically developing children (N= 25), children with intellectual disability (N=10) and children with simulated poor VA (N=12, VA no worse than 20/63) on the CVIT 3-6. The authors reported a signifi difference between groups ($F[3, 55]=5.2$, $p=0.003$). This difference was more pronounced between CVI and typically developing children ($p=0.009$, Sheffe correction). (Data shown in figure 6). This may be due to the small number of research participants in this study (only 3 in each group). Prior to conducting this study, we estimated that an N of 40 would be needed to reach statistical power of 0.80. The limited statistical power of this study due to the small sample size played a role in the significance of our findings. We conducted a post hoc power analysis based on the CVIT 3-6 mean values obtained in this study. This analysis revealed that the observed effect size in this study was 0.26. An N of approximately 13 subjects in each group (total of 26) would be needed to obtain a statistical power of 0.80.

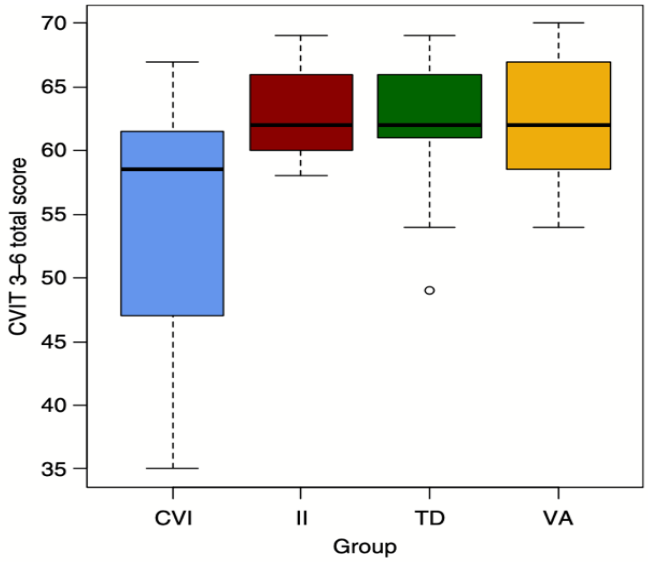

Figure 6: Data published by Vancleef, et al. (2019)[7] comparing CVIT3-6 total scores in children with CVI from three other groups.
*II: Children with intellectual impairment, TD: Typically developing children & VA: children with simulated poor visual acuity.

In our study, the scores on the Flemish percent abnormal assessment did differentiate between the CVI and non-CVI groups, with all 4 CVI participants scoring higher on the percent abnormal scale than the participants in the non-CVI group (see Tables 2 & 3).

For this study a new measure for percent abnormal score on the Flemish questionnaire was derived based on previous research with this tool.[8] This new score provides a summary measure for responses on the whole questionnaire. The scoring method differentiated children with CVI diagnosis vs. those without CVI in this study and thus the questionnaire and scoring may be useful for other clinicians to aid in diagnoses of their young patients.

An exploratory analysis on the discrepancy between chronological age and age equivalent in the two groups was conducted. Based on the experience from the children diagnosed with CVI in the NECO Center for Eye Care at Perkins, developmental delay (minus difference between chronological age and estimated age equivalent) would be expected for the CVI group. However, in this study, two participants in each group showed a developmental delay greater than 10 months. The average developmental age estimate was low for both groups and not statistically higher among the CVI group. Admittedly, the

sample in both groups was very small. Maline, et al. (2020) [115] compared the Vineland-3 comprehensive interview to the Pediatric Evaluation of Disability Inventory-Computer Adapted Test (PEDI-CAT) in identifying children in need of support. Their results suggested that the Vineland-3 was more sensitive than the PEDI-CAT in identifying functional difficulties. This could explain why both CVI and non-CVI groups showed a low average age equivalent.

Nevertheless, scoring the CVIT 3- 6 requires using an "age equivalence" and to do this we used a well-accepted tool, the Vineland-3 comprehensive parent questionnaire. Patients may be referred from a hospital or other facility to the NECO Center for Eye Care at Perkins where they have received a developmental assessment which could be used to estimate age equivalence (such as in the Vancleef, et al. study [7]). However, this is not universal and different examiners and tests are used. Therefore, relying on this method was not considered feasible.

Interestingly, one subject in the CVI group had a significantly higher age equivalent. This participant showed almost 3 years (33 months) developmental advancement as evident in Table 2. Developmental advancement is defined here as having a higher age equivalent as compared to the chronological age. The Vineland-3 comprehensive parent questionnaire reports 11 values for age equivalent. We used these values to bootstrap around the median to obtain a single value for age equivalent as noted earlier. This particular subject had a chronological age of three years but scored higher than 22 years on the interpersonal relationships subdomain of the socialization domain. Based on the examiner's subjective assessment of the child during the Zoom visits, the child did not reflect such advancement. Given that this value is an extreme outlier (participant's chronological age is 3 years and

the median of age equivalent values reported by the vineland-3 was 6 years) this value was replaced with the second highest value in the analysis.

While obtaining a larger sample size was not feasible, the clinical value of the CVIT 3-6 lies in its ability to identify children with CVI. The CVIT 3-6 identified only one subject as having CVI out of the three subjects who completed the test in the CVI group. Patients in the NECO Center for Eye Care at Perkins often have a combination of refractive, ocular, systemic and neurological conditions which can make the definitive diagnosis of CVI difficult. The need for a simple objective test is more pronounced in patients where CVI is further complicated and perhaps masked by other conditions such as poor refractive status. The CVIT 3-6 is normed for visual acuity levels of 20/63 or better. In practice, this level of visual acuity may not be achievable in children with CVI as we found in our visual acuity measurements at the time of the study. This visual acuity level required for the CVIT 3-6 limits the clinical application of this test to children who do not have significant VA deficits.

Our findings showed that the CVI group had a significantly higher percent abnormal On the Flemish questionnaire compared to the children who were not diagnosed with CVI. The digital version of the Flemish CVI questionnaire we developed in this study is easily accessible via any smart device. It has the potential of being a practical, convenient and inexpensive screening tool for CVI.

The results of our small study support the feasibility of adapting virtual models in data collection for various pediatric eyecare research projects. Certainly, a larger sample of patients is needed to confirm or disprove our findings with the CVIT 3-6. Although the CVIT 3-6 was performed remotely, it closely followed the same procedure suggested by Vancleef, et al. (2019)[7] with only one exception, which is that the child was observed via

cameras. That said, the child's attention may impact data collection. Since the child is in a familiar environment during their regular days, they might express less interest in following the clinician and in this case the investigator's instructions. This is especially because a digital screen is the sole means of communication. However, the findings of this study showed that the CVI group performed better than expected in regards to their visual perceptual abilities.

Patient recruitment occurred in the fall and early winter of 2020 and finally in January 2021. The low response to participation is postulated to be related to the combination of access to devices, stress of managing the household's access and use of devices for school and work and otherwise caring for their children while being employed. It is anticipated that as the pandemic wanes, there will be more flexibility to participate in remote studies such as this one.

This study shows that virtual testing of young patients using complex tools is feasible in pediatric eye research. The model we adapted is more convenient for many families. In a broader perspective, such a model can be scaled for larger studies of rare conditions such as CVI without being confined by proximity to the researcher. Furthermore, it is a cost-effective approach to improve timely access to care and early screening for CVI, especially in remote rural areas that might not have access to in-person care facilities. However, internet access automatically becomes an inclusion criterion. This approach may be discriminatory against people with low socioeconomic status who might not have access to digital devices or access to a stable internet connection which are both required in this model.

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Appendix

Appendix A:

Below is a verbatim detailed description of CVIT 3-6 subtests provided in an appendix by Vancleef, et al. (2019)[121]

*Note that appendix A, including the references below, are the work of Vancleef, et al.[121] There is a minor difference in the citations in appendix A from in the remainder of the thesis. Citations here come before the end of the sentence (i.e., followed by a period) vs after the sentence ends in the thesis.

Object and Scene Perception

The first of the four themes in CVIT 3-6 is highly influenced by clinical input and contributes to the ecological validity of the test. The theme includes three subtests (Figure S1).

In the first subtest, *Object Recognition*, the child has to recognize an image of an object presented in color on a white background. The alternatives to choose from are three words that can be read out loud by the examiner. This subtest is a control test for the third subtest *Object Recognition in Context* in which the same objects are presented within a scene. The two distractor alternatives are chosen to be plausible objects in the scene, but not essential objects in that scene. For example, a sand pit or beach scene will have as alternative answers: sand castle, swimming suit, cat. By comparing performance in both tasks, we assess whether a child can segregate an object from a background, a function that is often impaired in CVI[1]. In the second subtest*, Scene Perception*, the child has to choose the scene out of three scenes that contains the target object presented at the top of the screen and point to the target object in the scene. The target object is presented in color and on a

white background. The scenes are chosen to be similarly cluttered and the target object could plausibly appear in every scene, however the scene does not contain obvious clues for the presence or absence of the object. For instance, when the target is a bridge, the alternatives will all represent outdoor scenes.

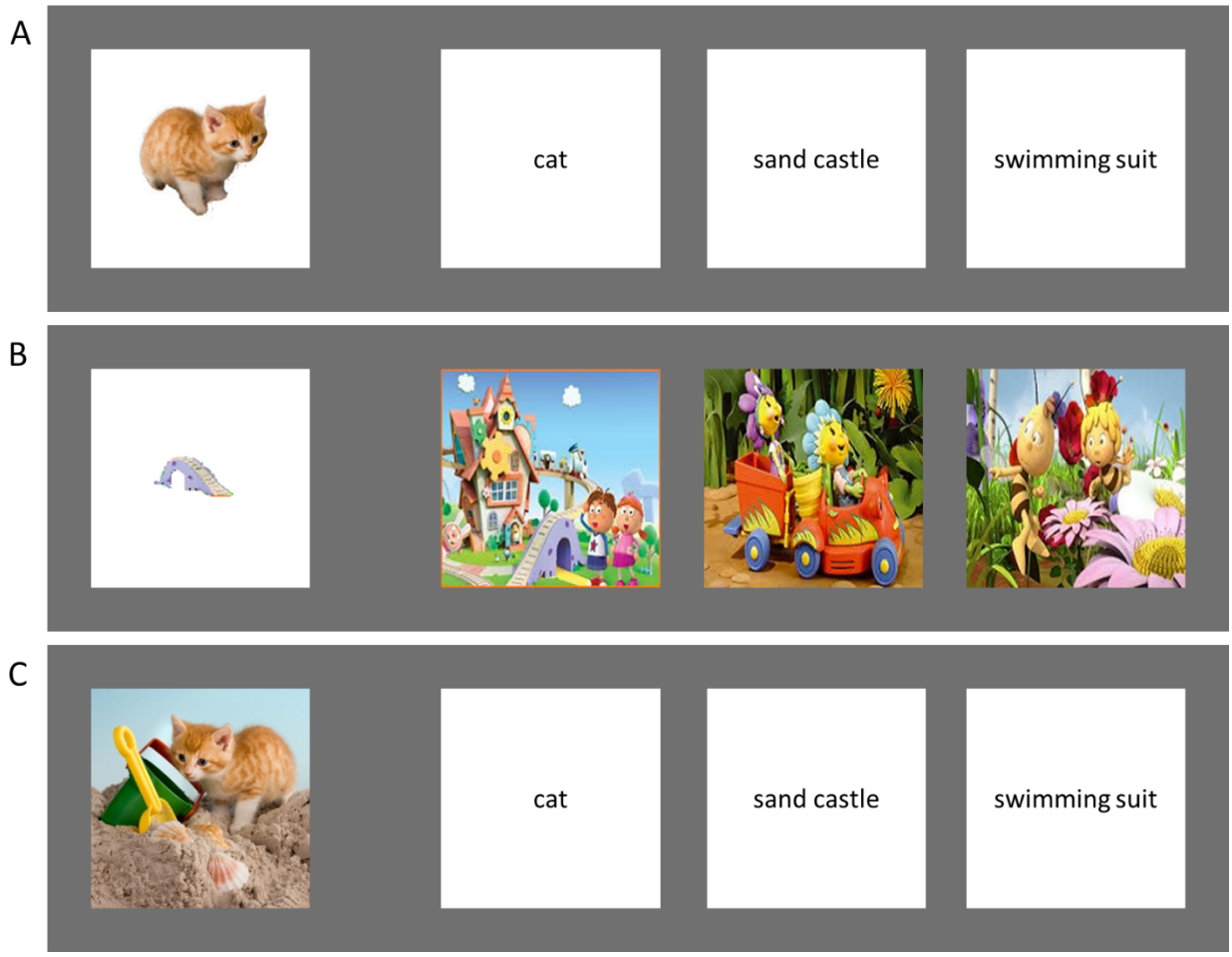

Figure S1. Example trials from the Object and Scene Perception subtests. Here, the target item is shown first, followed by three alternatives. The first alternative in each row is the correct alternative.

In CVIT 3-6 the target item is presented above the three alternatives and the order of the alternatives is randomly determined (see Figure 2). (A) Object Recognition (B) Scene Perception (C) Object Recognition in Context. Images reproduced from the following sources: scene with house: http://www.cartoonbrew.com/wp-

content/uploads/2012/09/Nick-Jr-Tickety-Toc-e1346898433862.jpg; scene with flowers in car: http://lh6.ggpht.com/_YwmWMOKujdE/SKSc7SEg3KI/AAAAAAAAS6U/-wCcr67cW58/fifi01.jpg; scene with bees: Maya the Bee

Degraded Object Perception

The first four out of five subtests (Figure S2) in this theme use the Snodgrass-Vanderwart stimulus set[2]. In the last decades several variations of this stimulus set have been developed and norm data for recognition and familiarity are available [2][3][4][5][6]. We have selected target and alternative stimuli with a previously reported identification rate of at least 90% in a normal adult population. In the subtests of this theme the target stimulus at the top is always an easy recognizable colored object on a plain white background from the study by Rossion and Pourtois[3]. The alternatives are degraded versions of the target object and two distractor objects. The way in which objects are degraded varies between subtests.

In *Full Line Drawings* objects are degraded by removing the color information and black-and-white line drawings are presented as the alternatives[2]. This subtest evaluates how much a child relies on color information to recognize an object[1]. In the *Silhouettes* subtest, the alternatives are silhouettes of the target object[6][7], removing information like texture and surface curvature. In the *Fragmented Outlines*, we show white object outlines on a black background. The outlines consists of small line fragments that need to be grouped and integrated to give rise to the percept of an object. This subset relies on perceptual organization principles of good continuation and closure identified by Wertheimer[8][9] and was studied in the context of fragmented outline object recognition by Panis et al.[4]. In the *Object in Noise* subtest, black and white versions of the stimuli[3] are

occluded by noise. The noise consists of grey-scale squares of 15 by 15 pixels. The position and the luminance of the squares was randomly determined. The average luminance levels of the three alternative stimuli was equalized before noise was added to the images. In this subtest, a child needs to group small patches of the object to create a coherent whole that can enter the object recognition pathway. Grouping can be done based on similarities in luminance and good continuation of object boundaries.

The last subtest in this theme, *Unconventional Viewpoints*, shows a target object from an unconventional viewpoint and three alternative objects from conventional viewpoints. This subtest relies on adequate mental rotation[10]. Stimulus images are courtesy of Michael J. Tarr (Center for the Neural Basis of Cognition and Department of Psychology, Carnegie Mellon University, http://www.tarrlab.org/). We present grey scale images of the objects that were equalized for average luminance to avoid any color or luminance cues. To exclude pixel by pixel matching strategies, the correct alternative is a mirror version of the target object in all the subtests of Degraded Object Perception. The distractor objects are chosen to have a similar shape or orientation and / or are semantically related to the target object (e.g., all four-legged animals).

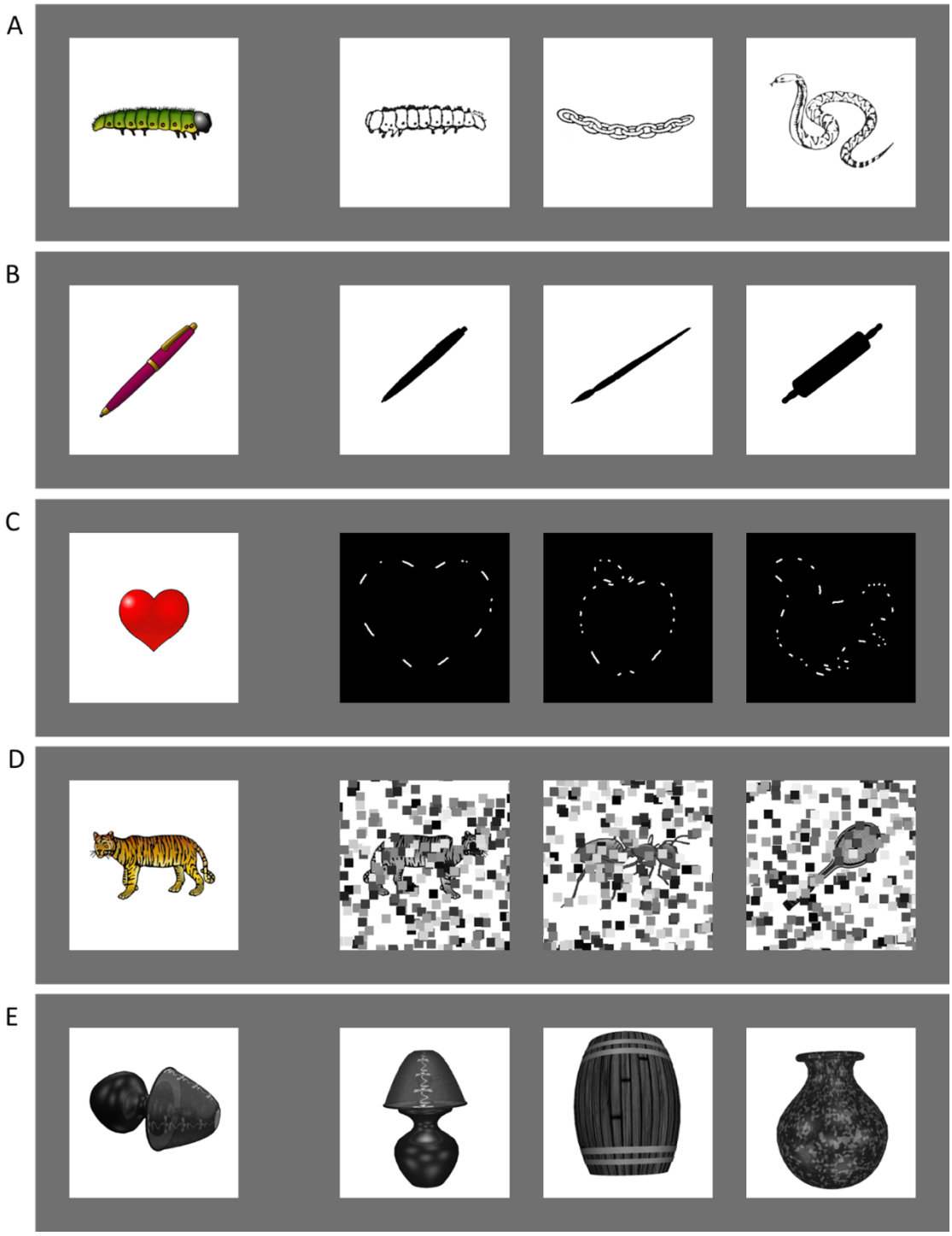

Figure S2. Example trials from the Degraded Object Recognition subtests. The target item is shown first, followed by three alternatives. The first alternative in each row is the correct alternative. (A) Full Line Drawings (B) Silhouettes (C) Fragmented Outlines (D) Object in Noise (E) Unconventional Viewpoints.

Motion Perception

The three Motion Perception subtests of CVIT 3-6 each tap into different levels of motion perception (Figure S3).

The most basic form of motion perception measured in CVIT 3-6 is *Global Motion Detection*. In this subtest the child needs to detect coherent motion in a set of moving dots by grouping the dots with the same motion direction (grouping principle of common fate, [8]). In the target random dot kinematogram 75% of the dots move in a coherent direction, either upwards or downwards. The distractor dots move in random directions. The alternative stimuli show arrows pointing and moving upwards, downwards, or sideways. Coherent motion detection has been associated with area MT and MST complex, located on the temporo-parietal-occipital junctions[11][12].

In the *Kinetic Object Segmentation* subtest, the child needs to extract the shape from the motion in addition to detection of overall coherent motion. The stimuli contain two areas that can be segregated based on motion direction. This creates the perfect outline of the shape or figure against a background with the motion segregation edge as the shape's contour. Neuroimaging studies have associated this task with specific activation of the Kinetic Occipital (KO) area[13][14]. Details about stimulus construction can be found in the following papers:[15][16].

In the subtest *Biological Motion*, the child's ability for dynamic grouping and integration of moving dots into human body-and-action representation is tested. The displays depict a moving human figure using isolated light points on the major joints. Naive observers spontaneously observe these dynamic dot patterns as representing a human figure[17]. Biological motion perception relies particularly on the Superior Temporal Sulcus (STS)[12][18]. The target stimulus in our subtest represents a walker to the left or the right.

The correct alternative shows a smaller sized version of the same walker, moving at a reduced speed[19]. For the distractor stimuli, the position of the dots is randomized to break up the grouping into a human figure. All stimuli are moving simultaneously. This spatial scrambling keeps the motion trajectories and speed of each dot intact, but disturbs the integration into a meaningful human figure. The five trials within this subtest differ in terms of the viewpoint, identity, and speed of the walkers.

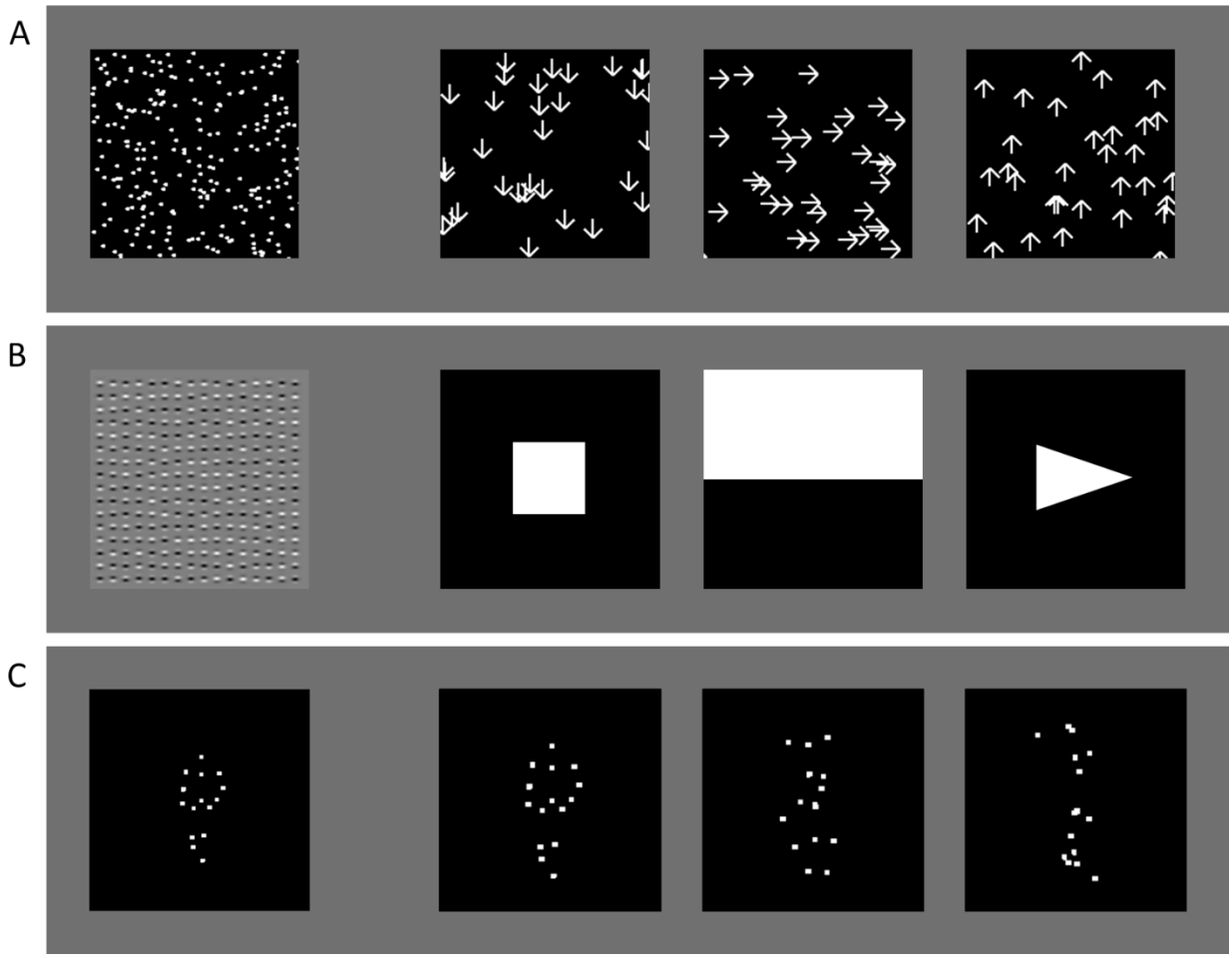

Figure S3. Example trials from the Motion Perception subtests. The target item is shown first, followed by three alternatives. The first alternative in each row is the correct alternative. (A) Global Motion Detection (B) Kinetic Object Segmentation (C) Biological Motion.

Global-Local Processing

Global versus local processing of information is a crucial part of visual perception. Our perception can either have a global or a local focus. For instance, when crossing the street, we pay attention to moving cars without necessarily noticing details like type of windscreens, tires, etc. while those details will be the focus of our attention when we are looking for a car to buy. Grouping local details or parts into a global coherent whole can be stimulus-driven (e.g., grouping parts that are similar in texture and color like leaves are spontaneously grouped into one coherent whole, a tree) or can be driven by top-down information like object knowledge, expectations or intentions (e.g., not spotting a spelling mistake in a very familiar word). Impairments in global processing have repeatedly been observed in preterm children and children with lower birth weight [20][21][22][23].

In the *Overlapping Figures* subtest (Figure S4), three contour outlines of everyday objects are presented on top of each other. For this subtest, we again make use of the Snodgrass-Vanderwart stimulus set to maximize experimental control[2][6]. The alternative stimuli show object outlines in isolation. Only one of these outlines is included in the overlapping target figure. To solve the task, the child needs to segregate the overlapping outlines from each other relying on the grouping principle of good continuation[8].

In the *Embedded Figures* subtest of CVIT 3-6, global integration is stimulus-driven[24]. The child is required to detect and extract a simple shape that is embedded in a more complex context. At the top we present a simple target shape, while the bottom alternatives show a more complex configuration of shapes. Only one of them includes exactly the same simple target shape. The overlapping contours of the simple shape and the shapes it is embedded in results in a strong stimulus-driven grouping that favors a global rather than a local processing of the stimulus. This long-established test evaluates

hierarchical part-whole encoding. Good performance has been associated with a local information processing style[25][26] and has been frequently observed in children with autism [27][28][29].

Attention to detail is also required to solve the *Missing Parts* subtest. This subtest is inspired by clinical observations that patients might perceive the global configuration and are able to recognize the object, but do not have access to local details. Similarly, healthy observers can often miss important changes in details of the environment when task demands are high[30]. The target stimulus shows an everyday object with a missing detail. The correct alternative shows an enlarged version of the object with the same specific part missing, while the incorrect alternatives either have another part missing or show the intact object with no missing parts. In this subtest the global percept is driven by top-down object knowledge. This means that children with an intact global processing but disturbed focus on structural details will have difficulties with this subtest.

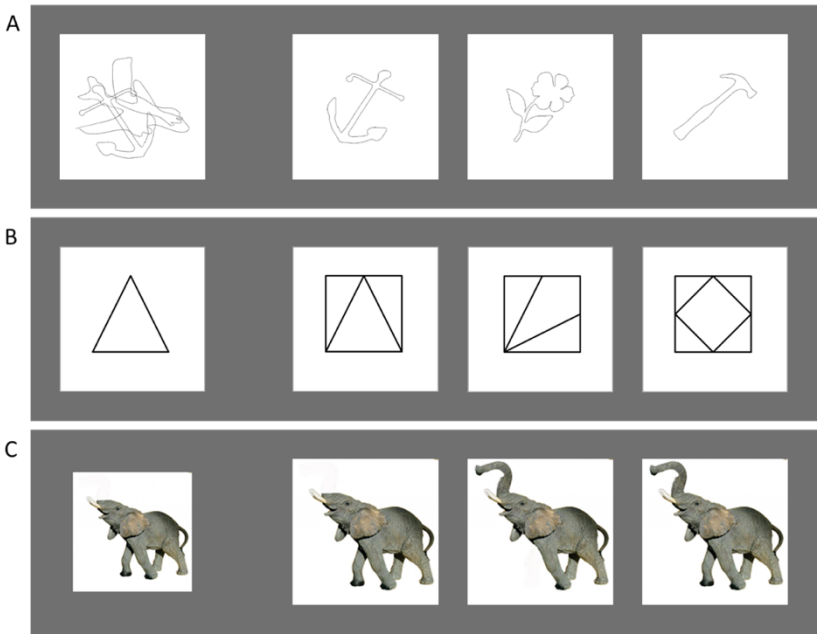

Figure S4. Example trials from the Global-Local Processing subtests. The target item is shown first, followed by three alternatives. The first alternative in each row is the correct alternative. (A) Overlapping Figures (B) Embedded Figures (C) Missing Parts (image source could not be confirmed).

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Appendix B

Statistical Analysis

Unfortunately, due to many reasons, primarily the COVID-19 pandemic, our sample size was much smaller than we had hoped. We acknowledge that in order to fully investigate the clinical value of both tools utilized (the CVIT 3-6 and the Flemish questionnaire), we need to evaluate their sensitivity and specificity as tools to diagnose CVI. We had aimed to achieve that via conducting a logistic regression on the diagnostic outcomes of both tools. E.g., zero for outcome normal (not having CVI) and one for abnormal (presence of CVI). The findings of such analysis would then be used for 2 X 2 table of four elements; true positive, true negative, false positive and false negative. We had also hoped to conduct further subsequent analyses on which subtests of the CVIT 3-6 contributed most to the outcome (total score) through regression analysis.

Calculation of Flemish percent abnormal

Table 1 shows the results of the 5-factor model analysis conducted to validate the Flemish questionnaire. [8] The items in the Flemish questionnaire are interactive with one another. This means that some items contributed more than others to the screening of CVI while others when checked by the caregiver lowered the sensitivity of the questionnaire. In Table 1, this is indicated as positive and negative values in the weight each item contributes to the final outcome. In this study, to efficiently and practically utilize the validated version of the questionnaire, we calculated for percent abnormal. This is a new measure that given the results of our small sample can be valuable in assessing children with CVI. Percent abnormal is simply calculated by dividing the algebraic sum of the weight of the items checked by the caregiver by the total sum of the weight of all items.