Early rehabilitation for children with visual processing dysfunctions from 1 year of age: a Randomized Controlled Trial protocol

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Abstract

Background

An increasing amount of children suffer from brain damage-related visual processing dysfunctions (VPD). At present, there is a lack of evidence-based rehabilitation methods that can be used early in development. We developed a visual rehabilitation protocol suitable from 1 year of age. The protocol contains objective, quantitative outcomes and is structured, comprehensive and individually-adaptive. Our aim is to investigate effectiveness of this first visual rehabilitation program for young children with (a risk of) VPD.

Methods

We conduct a single-blind, placebo-controlled trial that is embedded within standard clinical care. The study population consists of 100 children born very or extremely preterm (<30 weeks) of 1 year of corrected age (CA), of whom 50% are expected to have VPD. First, children undergo a visual screening at 1 year CA. If they are classified as being at risk of VPD, they are referred to standard care: an ophthalmic and visual function assessment and a (newly developed) visual rehabilitation program. This program consist of a general protocol (standardized and similar for all children) and a supplement protocol (adapted to specific needs of the child), and employs quantitative parameters of visual outcome. Children are randomly allocated to an intervention group (starting upon inclusion at 1 year CA), or a control group (postponed: starting at 2 years CA). The control group will receive a placebo treatment. The effectiveness of early visual rehabilitation will be examined with follow-up visual and neurocognitive assessments after 1 year (upon completion of the direct intervention) and after 2 years (upon completion of the postponed intervention).

Discussion

Through this RCT we will establish the effectiveness of a new and early visual rehabilitation program. Combining a general and supplement protocol enables structured comparisons between participants and groups, and custom rehabilitation that is tailored to the children’s specific needs. The design ensures that all included children will benefit from participation by advancing the age at which they start receiving rehabilitation. We expect results to be applicable to all children with (a risk of) VPD
early in life.

Background
Over the past decades, survival rates of children who experienced adverse perinatal events (e.g., preterm birth, hypoxia/ischemia; hemorrhages) have increased due to the intensive, high quality care that they receive. As a consequence, the number of children that sustains neurological damage has increased as well. Because about 40% of the brain is involved in processing visual information, there is a high chance that these children will develop problems in the visual domain.

Visual dysfunctions with a cerebral origin, i.e. cerebral visual impairment (CVI), have become common in children: conservative estimates range from 10–22 cases per 10000 births in developed countries, to 40 per 10,000 in developing countries(1). Brain damage-related visual dysfunctions are now the primary cause of low vision in children(2, 3).

Given the large underlying visual and oculomotor network, children with these impairments can suffer from a variety of problems, e.g. visual sensory, oculomotor or visual perception problems. What they have in common is dysfunctions with properly processing incoming visual information, i.e. visual processing dysfunctions (VPD). The problem is particularly urgent for young children, because early visual dysfunctions can severely delay or disrupt their neurocognitive, motor and behavioral development(4–6). To alleviate early-onset problems, prevent later growing-into-deficit and maximize developmental opportunities, detection and rehabilitation of VIP problems early in life is crucial(7, 8).

Early in development, high levels of cerebral plasticity enable recovery or take-over of function.

Therefore, it is assumed that the sooner visual rehabilitation programs start, the higher the chances are that they will enhance visual processing development. Although there are a large number of infant studies in the field of early detection that rely on this assumption, the effectiveness of early rehabilitation in the visual domain has never been proven.

Early rehabilitation starts with early detection of problems. Before the age of 4–5 years, it used to be challenging to assess the functional consequences of damage to the brain’s visual system. There have been advances in the early detection of (a risk of) visual problems, for example the early assessment of basic visual function in neonates as early as 31 weeks PMA in preterm infants(9), and a
functional vision battery with cognitive and integrative aspects, to use between one and four years of age(10). These batteries involve various aspects of visual function and rely on behavioral observations. In addition, more quantitative, computer-based methods have been developed, such as an eye tracking-based task for attention in toddlers(11). Building on these innovations, our group developed a method to quantify the efficiency of visual processing in a nonverbal manner in children, using an eye tracking-based approach(12, 13). We showed that children with (a high risk of) neurological damage (e.g. children with visual disorders or children born preterm) are prone to develop VPD(14–16). These VPD were particularly strongly correlated with brain damage-related visual problems (cerebral visual impairment; CVI)(17, 18).

These innovative early and nonverbal assessments can fulfill the need for scientifically strong psychometric tools to evaluate the effectiveness of early intervention. Hence, besides providing an early characterization of VPD that was previously unavailable, they also open up the possibility to monitor or rehabilitate VPD in these children at a young age. One can even argue that early detection of problems is only useful if it leads to advancing support and rehabilitation. Hence, the essential next step in the field of pediatric visual dysfunctions is to provide affected children with effective early rehabilitation programs.

A major problem is that there is no evidence-based rehabilitation for VPD from 1 year of age: this area is severely understudied(19) and quality of evidence is low(20–22). Available (visual) interventions lack a standardized approach and/or systematic objective evaluation(23–25), and ideas about their effectiveness merely stem from clinical impressions, not from randomized and carefully controlled studies. The available evidence has predominantly been found in older children, for a limited range of visual functions (i.e., visual acuity and/or contrast sensitivity)(26), without incorporation of functional vision measures, using only stimulation and no training(24, 26), and without objective outcome measures. Studies that did use a comprehensive and structured training approach had a small sample size(27, 28). Although these existing studies provide important information on approaches and possibilities to rehabilitate visual problems, the effectiveness of such visual rehabilitation programs for children younger than 4 years has not yet been investigated with an RCT.
VPD in children can arise from many different conditions, e.g. perinatal asphyxia or hypoxia, focal lesions, cranial trauma, infections, or hemorrhages. Therefore, the general population with VPD is a highly diverse group of children. In the present study, we focus on children born very or extremely preterm (i.e. born <30 weeks of gestation) from 1 year of corrected age (CA). In an ongoing longitudinal study we found elevated risks of visual attention and processing problems in this population(15, 16), driving the urgency for rehabilitation. However, we expect outcomes to be applicable to other young children at risk of brain damage-related VPD. After positive results have been obtained, the visual rehabilitation program can be investigated in other risk groups. The aim of this study is to investigate the effectiveness of early rehabilitation of VPD in children born very or extremely preterm from 1 year CA. To this end, we developed a structured yet tailored visual rehabilitation protocol and will test its effectiveness in enhancing visual development in a randomized controlled trial. Unique features of the present approach are the objective outcome measures that are assessed from a young age, broad quantitative and qualitative data collection to assess the full spectrum of visual and neurodevelopment, and its embedding within standard neonatal and visual clinical care. This protocol was written in accordance with the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines. Additional file 1 contains the SPIRIT checklist.

Methods

Study design

Randomized single-blind, placebo-controlled intervention study (RCT), embedded within standard clinical care.

Study setting

The study will be executed at the Neonatology department of an academic medical center, in collaboration with the department of Pediatric Ophthalmology and with four regional centers of a center of expertise for blind and partially sighted people that provides visual diagnostics and rehabilitation.

Participant characteristics & timeline
It is expected that 25–50% of the very/extremely preterm population is at risk of VPD at 1 year CA(15, 16). Therefore, all infants who have been born extremely or very preterm (i.e. before 30 weeks gestational age) and who participate in the clinical follow-up program of the dept. Neonatology, Erasmus MC-Sophia Children’s Hospital, will be available for inclusion around 1 year CA. We aim to include:

N = 100 children from 1 year CA, born very or extremely preterm (< 30 weeks of gestation). About 50% are expected to be at risk of VPD (and eligible for the intervention)
N = 100 children born at term without VPD from 1 year of age, to add to an existing database of typically developing children (healthy control group).

The study population can be divided in 3 groups:

Group 1: children born preterm from 1 year CA, without a risk of VPD
Group 2: children born preterm from 1 year CA, with a risk of VPD
Group 2A: 50% will receive direct visual rehabilitation (intervention group)
Group 2B: 50% will receive postponed visual rehabilitation (control group)
Group 3: children born at term without a risk of VPD

Eligibility criteria

Inclusion criteria
Born <30 weeks gestational age
Age at inclusion of 1 year CA (+/- 2 months)

Exclusion criteria
Visual acuity below 0.05 (Snellen equivalent)
The eye tracking-based exam is designed to be visible with a visual acuity of 0.05 or higher.
High chance of epileptic activity during assessment
More than 2 attacks in the previous year or when using the anti-epileptic Vigabatrin (which may lead to visual dysfunctions).
Retinopathy of prematurity (ROP) of grade 3 or higher, assessed by a pediatric ophthalmologist, as this will account for their visual dysfunctions.

Study procedures

Figure 1 outlines the general time schedule of the study. The separate components are:

Participant inclusion and baseline

Children born very or extremely preterm (< 30 weeks GA) will be recruited around the corrected age (CA) of 1 year at the department of Neonatology of an academic medical center. After obtaining
written informed consent (see Additional file 2), a visual assessment is performed to identify the prevalence and nature of visual processing problems. This assessment consists of an eye tracking-based test of visually-guided orienting behavior and a checklist for neurological dysfunction. The visual assessment results are compared to normative references to identify the children with a risk of visual processing dysfunctions (VPD). The children who are identified as being at risk of VPD will first undergo an orthoptic and ophthalmic exam (dept. Pediatric Ophthalmology). Next, they will be referred to a visual advisory and rehabilitation center in order to receive standard care, consisting of a visual function assessment (VFA) and a visual rehabilitation program. The VFA is used to evaluate visual sensory functions (e.g., visual acuity, visual field, contrast sensitivity, ocular motility), and observe the functional visual behavior of the child. This assessment is performed by experienced orthoptists/optometrists and behavioral therapists, and together they will determine the visual level of the child (these levels are adapted from earlier work)(5, 29):

A. Profound visual dysfunction/ legally blind (mainly responding to light)

B. Severe visual dysfunction, passive attentional system (reactions to stimuli do not reach normative levels, child does not actively search for visual stimulation, low recognition)

C. Moderate visual dysfunction/ basic perception (active visual attention system and basic visual recognition)

D. Mild visual dysfunction, subnormal visual function (functioning at the lower bound of normal)

**Intervention**

To reliably examine the effectiveness of this visual rehabilitation program with an RCT, children who are at risk of VPD will be randomly allocated to one of two groups:

1. *Intervention group (direct)*

   This group consists of preterm children who are at risk of VPD and who will start the visual rehabilitation program upon referral to the visual rehabilitation center (i.e. around 1 year CA). The
program consists of a general protocol (standardized across participants) and a supplement protocol (tailored to the child’s specific VPD), and lasts ~1 year.

2. Control group (postponed & sham/placebo)

This group consists of preterm children who are also at risk of VPD, but for whom the visual rehabilitation program will be postponed for the duration of 1 year. These children will be placed on a waiting list for the duration of the direct visual rehabilitation (i.e. ~1 year). However, during this first year they will receive a placebo intervention: general developmental support that is aimed at monitoring the child’s developmental progress without providing specific visual rehabilitation. As soon as the follow-up assessments of the direct intervention group are completed, children in the control group will start visual rehabilitation (i.e. around 2 years CA).

Importantly, this study design ensures that all children at risk of VPD will receive visual rehabilitation at an earlier age than is the case in current standard care (i.e. where only a small number of young will be referred based on obvious ocular disorders, and others will not receive rehabilitation before ~4y of age)), while the RCT design enables a reliable and controlled comparison of the effectiveness of visual rehabilitation within this group. For a detailed outline of the visual rehabilitation protocol we refer to Additional file 3; template visual rehabilitation protocol.

Follow-up after 1 year

One year after inclusion, the children at risk of VPD will repeat the visual function assessments, and all included children (with and without VPD risk) will repeat the eye tracking-based visual screening, and undergo a neurodevelopmental assessment (that is standard care at most Neonatology departments, from 2 years CA).

That way, the specific effects of early visual rehabilitation on visual processing and neurocognitive development are compared and evaluated.

Postponed intervention

After this first follow-up, the children in the postponed intervention group will start their visual rehabilitation program, which will also be evaluated 1 year later. In addition, the results of the visual screening are again evaluated for all children, to identify new cases with a risk of VPD who will then
also qualify to start visual rehabilitation. Differences in effectiveness of direct and postponed early visual rehabilitation are assessed. The intervention study will have a duration of either 1 year or 2 years, depending on the visual rehabilitation group.

**Data collection methods**

**Baseline (T0)**

*Medical information*

Medical and demographic information will be extracted from the medical records available at the hospital.

*Visual screening—A0*

All included children will be screened for a risk of VPD, which consists of 1) an eye tracking-based assessment, and 2) a neurological checklist.

The eye tracking-based assessment is used to measure visual processing functions. The assessment will be combined with an existing appointment for standard outpatient visits at the Neonatology department when the child is ~ 1 year CA (T0) and 2 years CA (T1). During this assessment, children sit in front of the eye tracker monitor at a distance of approximately 60 cm, either independently, on the lap of their parent or in a pram. They do not receive verbal instructions and their body and head position is not restricted. The assessments will be conducted in a quiet room with ambient light conditions. Visual stimuli (images and movies) are presented on the monitor to engage reflexive orienting eye movements of the child, while simultaneously the eye positions are recorded over time using infrared cornea reflection [Tobii T60 XL or Tobii X3, Tobii Corporation, Danderyd, Sweden]. That way, the child’s eye movement responses to various types of visual information (i.e. contrast, color, motion and form) are automatically recorded. From these responses, the reaction time to fixation (RTF) of a stimulus is calculated; a measure for the timing of detecting and processing visual information. This is the main study parameter (12, 13, 30, 31). Total test duration is approximately 15 minutes. The child’s orienting behavior parameters per visual stimulus are analyzed and compared with normative data (i.e. developmental trajectories of an existing database of healthy control children, born at term), and are classified as normal or abnormal.
Second, medical specialists examine the child’s medical history for the presence of neurological risk factors for VPD in the context of prematurity, i.e., moderate-severe damage on neonatal MRI scans; cerebral palsy; unilateral, bilateral, hemiplegia, diplegia infantile esotropia/convergent strabismus or nystagmus deviating head circumference (>1 SD in 12 months)

Inventories for daily life visual functioning—B0

The PAI-CY questionnaire (32) will be filled in by parents upon inclusion. This questionnaire assesses daily visual functioning and can be used to investigate and monitor rehabilitation needs of visually impaired young children. It is the only available questionnaire for young children and its psychometric properties are currently under investigation.

Determining the risk of VPD

Abnormal visual orienting behavior, indicated by abnormal RTF values on one or more visual stimuli AND/OR the presence of at least one neurological risk factor for VPD. The children at risk of VPD are referred to standard care for children with suspected visual dysfunctions, i.e.:

1. They will undergo an ophthalmic exam to evaluate eye and orthoptic function,
2. They will become clients of the visual advisory and rehabilitation center where they undergo a visual function assessment and are enrolled in the visual rehabilitation program.

Ophthalmic exam (standard care; group 2A and 2B)—C0

All children at risk of VPD will be referred to the Pediatric Ophthalmology department to evaluate visual acuity, refractive error and ocular alignment. This evaluation is performed by ophthalmologists and/or research orthoptists. Total time of the exam is approximately an hour.

Visual function assessment (VFA; standard care; group 2A and 2B)—D0

All children at risk of VPD will undergo an extensive VFA. This assessment is part of standard care and will be done by an experienced orthoptist or optometrist. All assessments will be performed according to a standardized protocol that ensures similar assessments, choice of tests, and scoring by the various examiners. The following functions will be assessed: ocular alignment and fixation preference,
binocular vision, presence of nystagmus, oculomotor function (fixation, saccades, pursuit, motility), convergence, visual acuity, visual field, contrast sensitivity and color vision. Performance per function is classified as normal or abnormal for the child’s (developmental) age.

First follow-up (T1):

Starting one year after inclusion, i.e., from 2 years CA, the following assessments are repeated:

**Visual screening (study-specific; all groups)—A1**

The visual assessment (eye tracking-based exams) will be repeated in all included children, and will be combined with an existing appointment for standard outpatient visits the Neonatology department.

**Inventories for daily life visual functioning (study-specific)—B1**

Will be given to, or sent to, parents around the first follow-up.

**Visual function assessments (VFA; standard care)—D1**

The VFAs will be repeated in the children at risk of VPD (independent of the visual rehabilitation group they are in), as part of standard care at the visual advisory center.

**Neurodevelopmental assessment (standard care Neonatology)—E**

From 2 years CA, all children will receive a neurodevelopmental assessment at the NICU as part of the standard care follow-up program. This assessment consists of the Bayley Scales of Infant and Toddler Development (Bayley-III-NL) and is performed by experienced (neuro)psychologists.

Second Follow-up (T2):

Two years after inclusion, i.e. from 3 years CA, all included children will repeat the eye tracking-based visual screening (A2) and the inventories for daily life visual functioning (B2). Since at 3 years CA there is no regular follow-up as part of standard care, study-specific appointments will be made at the academic hospital or in the form of home visits. In addition, the children at risk of VPD who have been referred to Visio will undergo the visual function assessment again (D2), as part of standard care.

By embedding this study within standard clinical care, close collaboration with involved medical and rehabilitation specialists, and planning participation together with regular appointments or in the form of home visits, we expect to maximize participants’ completion of the follow-up measurements.

**Intervention: visual rehabilitation protocol (Additional**
We developed a structured visual rehabilitation protocol using a two-stepped approach: 1) dissecting available scientific knowledge about visual interventions in young children, and 2) establishing other, clinically relevant, factors in close collaboration with experienced behavioral therapists and neuropsychologists.

First, based on available (visual) rehabilitation literature we extracted several key features the rehabilitation should contain, i.e. we made a protocol that:

a. starts well before school age to maximize experience-dependent neuroplasticity (33, 34)

b. involves the total spectrum of visual development, not restricted to only a few visual functions (35) or general neurodevelopment (36)

c. has quantitative and functional outcomes (23, 28)

d. employs two rehabilitation strategies that have complementary value (20, 27):
   Passive (bottom-up-feedforward) visual stimulation that is purposeful and specific (37–39)
   Active (top-down-modulated) visual perceptual training that is contingent on children’s abilities (28, 38, 40)

e. can be individually-tailored by adapting materials and activities to children’s preferences/capabilities (25)

f. incorporates children’s systems through active caregiver involvement (33, 41)

Second, we examined the clinical and practical requirements for a rehabilitation protocol by consulting professionals about, e.g., which types of rehabilitation, in which (developmental) domains, which elements, materials and objects, minimum duration and frequency, and how to deal with parental motivational and resistance issues. The answers to these questions were grouped and analyzed in order to extract common themes and the most important clinical features the protocol should contain.
The result of this two-step process is a visual rehabilitation program that consists of:

1. a general protocol that is identical for all children, and
2. a supplement protocol that is tailored to the specific VPD of the child.

Both parts are designed to adhere to the basic visual skills a child presents with, and to their cognitive, motor and socio-emotional developmental level. Importantly, the parent-child relationship will be taken into account in order to support, involve and stimulate the parents in executing the rehabilitation program at home.

The *general visual protocol* is adapted to the child’s age and developmental level and consists of exercises focused on the following functions: fixation, pursuit, visual attention, enhancing visual experiences and knowledge, perception of details and combining vision with motor action (visuomotor skills). The rehabilitation program consists of several steps that can be applied to all functions:

- Enhancing the diversity of training with different visual materials
- Enhancing the duration of visual training
- Developing increasingly complex visual skills and behavior that are ecologically valid, i.e. related to the child’s activities and daily environment.

Visual input is provided in the form of different visual materials of different visual modalities (colors, black-white, moving and static objects, light and dark). The nature of visual input will be adapted to the preferences and abilities of the child, and successful responses and behavior will be rewarded (based on operant conditioning). Visual training of more complex skills and behavior is done by teaching the child to use a specific visual skill, to expand its use to other tasks and to integrate it in everyday life.

The *supplement visual protocol* is designed around the specific VPD that are determined based on results of the visual screening and assessments (VFA and observation) performed at baseline. For example, children with abnormal processing of form and motion information, but with normal processing of contrast and color information, will get additional training for the processing of form and motion-related visual information that is integrated within the visual rehabilitation program itself; in order to comprehensively support the child.

*Additional components:*

Focus moments. These sessions with video feedback, evaluation with the parents and reporting
behavioral observations, are done three times throughout the intervention period to determine whether the program suffices or needs adaptations.

Stepping cards. An instruction for parents given after each session that contains a specific goal, instruction, observational points, and evaluation for their daily practice sessions.

Logbook for therapists (per session) and parents (to be completed weekly). The logbooks are used to keep track of the frequency/intensity and content of the therapy sessions and the daily practice sessions by parents.

Protocol for Activities & Materials to be used, based on chapter 5(29)

Criteria for discontinuing or modifying interventions

Modifying intensity of rehabilitation: after the second focus moment (around week 16), it is determined whether the child still benefits from sessions every week or every two weeks. If this rehabilitation intensity is no longer indicated/ no longer needed, the intensity is brought down to once every 4 or 6 weeks, to keep monitoring (visual) development, and to enable a frequency adaptation again when needed. This will be done until the end of the program.

Modifying the content/focus of rehabilitation: this is based on the evaluations with parents and the observations after each therapy session. If a modification is warranted, only the supplement protocol will be modified, the standard protocol remains as is.

Improving and monitoring intervention adherence

All rehabilitation activities are demonstrated and explained by the therapists to the parents, with the goal that they understand the content and the motivation, in order for them to practice daily with their child. Parents will participate in all therapy sessions: they do not only receive practice instructions but will also be educated on the visual development of their child. The parents are asked to log their daily practice session in order to evaluate them in the therapy sessions. These evaluations will give insights in improvements and/or changes in visual performance of the child, which is known to motivate parents and enhance intervention adherence.

Permitted concomitant care

Participating children will not be restricted in receiving care as usual. If applicable, they are allowed to engage in additional neurodevelopmental training programs during this study. However, participation in such programs will be carefully registered and monitored to take into account interference with the possible effects of the visual rehabilitation program. In addition, children in the control intervention
group will, in the first year, be provided with general developmental support and monitoring that does not include specific visual training components. This program consists of visits by a psychologist-in-training (under supervision of neuropsychologists from the academic hospital and visual advisory center) and aims at monitoring developmental achievements of preterm children from 1 to 2 years of corrected age. That way, we directly involve all parents in the study, and enable a structured and controlled investigation of the effectiveness of specific visual rehabilitation. After concluding the study, the children who are at risk of VPD and have been referred to the visual rehabilitation center will remain clients there. This means that their treatment does not necessarily stop, but that this depends on the indications and judgement of the therapists and psychologists.

**Outcome measures**

To answer our main research question about the effectiveness of early visual rehabilitation in young preterm children, we will compare visual outcomes between the intervention and control group. We will analyze results from the eyetracking-based visual assessment and the additional visual function assessments at baseline and at yearly follow-up measurements. Primary outcomes are the changes in visual parameters after the duration of the intervention study (i.e. from baseline to 1-year follow-up T1 and/or T2), i.e.:

- Quantitative visual parameters (viewing reaction times, fixation accuracy)
- Visual function assessment (visual acuity, contrast sensitivity, visual field, ocular motility)

Endpoints are the changes in these parameters after the visual rehabilitation program. These parameters are chosen since their combination provides both quantitative and objective results about functional viewing behavior (the eye tracking-based assessment), and clinically-relevant visual function outcomes (i.e. the visual function assessments). In addition, we will compare the effectiveness of direct (at 1 year CA) versus postponed visual rehabilitation (at 2 years CA); by comparing visual outcomes between these groups at T2.

Secondary outcomes are the neurodevelopmental level at the first follow-up (T1) and results from parental questionnaires about daily visual functioning at T1 and/or T2, i.e.:

- Total score, cognitive and motor sub scores of the neurocognitive assessment with Bayley Scales of Infant and Toddler Development (Bayley-III-NL)
- Total score and sub scores per visual domain of the PAI-CY Inventory (i.e. social visual behavior,
information processing, orientation, play, mobility, communication, sensory function)
These measures were chosen because Bayley-III-NL is the only available neurocognitive assessment for children at this age, and the PAI-CY Inventory is the only available parental questionnaire about daily (visual) behavior at this age.

**Sample size calculation**

Each year approximately 200 children are born before 30 weeks of gestation and admitted to the Neonatal Intensive Care Unit at Sophia Children’s Hospital, Rotterdam, the Netherlands. Based on previous experiences with research in this population we expect an inclusion rate of ~50%. Therefore, we expect to include at least 100 children at 1 year CA. There are no thorough estimates of the prevalence of VPD in preterm children. A previous study using the eye tracking-based assessment in extremely preterm children identified visual processing delays in 48% of preterm children without evidence for brain damage(16), and in 9 to 23% of children in a cross section of the preterm population at 1y CA(15). In addition, between 25% and 33% of children with CVI have prematurity as contributing factor(42). However, the prevalence of risk factors for VPD (brain damage, perinatal events) is much higher than 50% in our study population. Therefore, we expect that each year at least 50 newborn preterm children from the Neonatology department (i.e., 50%) are at risk of VPD and thus eligible for inclusion in the intervention study.

**Recruitment strategies**

Children will be recruited from the current medical follow-up program for children born preterm that is ongoing at the department of Neonatology. Children’s eligibility for inclusion will be screened by a multidisciplinary team (project leader and project members from Neonatology). The project leader and/or other investigators will approach their parents first by telephone, to ask for permission to send an information leaflet about the study. Two weeks after sending the study information, parents will be contacted again to ask for their permission to include their child in the study. The baseline assessment (i.e. the visual screening) and the 1-year follow-up assessment will be scheduled together with an existing appointment at Neonatology, to minimize burden for children and parents. Children in the control group (group 3) will be recruited through daycare centers. The parents will receive study
information by mail and are asked to contact the project leader if they are willing to participate. If they give their consent, an appointment for the visual assessment will be made.

**Randomization & treatment allocation**

Prior to recruitment of participants, a randomization scheme has been designed in which the order of visual rehabilitation groups (either direct or postponed) is randomized using an online tool (Sealed Envelope Ltd. 2016; https://www.sealedenvelope.com/simple-randomiser/v1/lists). Randomization is blocked, to ensure a balance in sample size across groups over time, and stratified, to control and balance the influence of covariates (43). Covariates in the current study are: the presence of brain damage and gestational age (<28 weeks or 28–30 weeks).

After this computer-generated randomization, preterm children who are classified as being at risk of VPD will be assigned a participant number and concurrently be allocated to one of the visual rehabilitation programs. The order of allocation corresponds with the date and order of inclusion. This allocation will be done by the principal investigator and remains concealed to all other investigators, the participating children, and their parents. All participant numbers will be separately placed in opaque envelopes that contain a note with the assigned visual rehabilitation group. Revealing the group allocation to parents will be done by opening the opaque envelopes in their presence.

**Blinding**

The study set-up is single-blind. Intervention allocation will be known by the project leader managing the contacts between all involved parties, and by the behavioral therapists of Visio who will execute the interventions. Parents cannot be blinded to intervention allocation either, as they will actively participate in the intervention programs. However, the allocation will be blinded for the researchers and/or master students and orthoptists who perform the baseline and follow-up visual assessments, and for the researchers performing data analyses.

Prior to analyzing results of the visual rehabilitation (i.e. analyzing results of the follow-up visual assessments), participant numbers will be converted into a new participant code and visual intervention group will be coded into a new variable (group A or B). That way, group allocation remains concealed and bias during data analysis will be prevented (44).
Data management

All data will be handled confidentially and anonymously. Communication about participating children between the various participating departments and organizations will only be done using codes, not names or other personal identifying information. All data will be coded, and only a separate coding list will link study data to personal identifying information of a specific subject. The coding list is password-protected and only accessible by the main investigator(s). Data files will be stored on a PC and will only be accessible with a password. This password is only known to the main investigator(s). Paper documents will be stored in a locked cupboard of which only the main investigator(s) have a key. The investigator(s) will remain blind to the participants’ outcomes during the course of the study. All data will be anonymized prior to analyses and publications. Group allocation and randomization will not be revealed until after the statistical analyses have been finished.

Withdrawal

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. When subjects withdraw from the visual rehabilitation program they will not be replaced, to ensure adherence to the randomization protocol for the RCT. Withdrawal of subjects will be taken into account during data analyses, by using intention-to-treat (ITT) analyses. Subjects withdrawn from the visual rehabilitation program will be followed-up with a short questionnaire (assessed by telephone) in which they are asked for their reasons and circumstances of their withdrawal.

Statistical analyses

Sample size calculation

To answer our primary research question about the effectiveness of early visual rehabilitation programs on visual processing functions in preterm children at risk of VPD, we use a repeated measures ANOVA for the parameter RTF as primary analysis. An a priori power analysis provided a recommended total sample size of 32 children (and an actual power of 0.81 and a critical F of 4.17).

Effectiveness of visual rehabilitation program

In children at risk of VPD who have been allocated to a visual intervention group, differences in
viewing behavior parameter RTF between T0 and T1 are analyzed with a Repeated Measures ANOVA. A p-value of 0.05 will be considered statistically significant. Covariates are the medical and demographic factors and the RM analyses will be done with and without them to obtain their contribution to the main effect. All analyses are done according to the intention-to-treat principle.

Other effects of visual rehabilitation on VPD (other parameters)

Secondary study parameters are the differences in other eye tracking-based parameters of viewing behavior and the outcomes of visual function assessments (e.g., visual acuity, contrast sensitivity, extent of visual field). RM ANOVAs with a p-value of 0.05 will be considered statistically significant. After finding a main effect of group on the viewing behavior parameters, post-hoc comparisons will be done to establish which of the 5 visual stimuli significantly differ from each other in parameter values. For these comparisons, Bonferroni’s correction will be applied to the viewing behavior variables to correct the p-value for the number of comparisons.

Effects of visual rehabilitation on neurodevelopment

At 2 years of age, parameters from Bayley-III-NL are used as indicators of neurocognitive development. First, the relation between the visual assessment parameters and Bayley-III-NL parameters of the cognitive composite score, the language composite score, and the motor composite score will be analyzed using Pearson and Spearman correlation analyses. Next, univariate ANOVA’s are used to analyze differences in Bayley-III-NL scores between preterm children without a risk of VPD and children at risk of VPD, and between preterm children at risk of VPD in the direct versus the postponed intervention group.

Monitoring

Data monitoring & auditing

The risks of our study for patients and for scientific quality have both been judged as negligible, based on the NFU risk classification (Netherlands Federation of University Medical Centers). This risk level implies that monitoring should be done once a year. Monitoring involves:

Study documents and agreements
Patient inclusion, consent, compliance and source document verification
Patient safety
Study procedures
Clinical data management system
Correct saving of raw data, corrected data, and backups

Harms
In accordance with section 10, subsection 4 of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC.

The investigator will take care that all subjects are kept informed.

Ethics & dissemination
The present study has been approved by Medical Ethical Testing Committee (METC) of Erasmus Medical Center, Rotterdam (MEC–2016–724) on April 19, 2017. Important protocol modifications have been and will be communicated with the METC (in the form of amendments to the original protocol), project employees/researchers, and participating parents. Written informed consent will be obtained by the researchers before the baseline assessment, based on a comprehensive information document that the potential participants have received. See additional file 2 for a model consent form.

Participant confidentiality will be protected through our data management policy (see section Data Management). The main investigator(s) and the participating medical and clinical specialists will have access to the final trial dataset. There are no contractual agreements that limit such access for investigators. During the course of the study the principal investigator will have no access to patient-identifying data and communication will only be done using participant codes.

The involved researchers and sponsors have no financial or other competing interests for the overall trial nor for each study site.

No harm is expected from trial participation, in particular since most study components are part of standard clinical care. Therefore ancillary and post-trial care are suspected to be non-applicable.

Nature and extent of the burden, risks and benefits associated with participation
The risks associated with participation are negligible and the burden for the children is minimal. Apart from the visual assessment from 1 year CA onwards, the total program is standard care for children with (suspected) visual problems. Only the age at which this care is applied is advanced for this study, and the visual rehabilitation protocol has been structured in order to enable comparisons between children. Benefits for all preterm children are earlier visual assessments, general developmental support and, if applicable, earlier rehabilitation of a risk of VPD than is the case in conventional pediatric care (i.e. from 1–2 years CA instead of ~4 years CA).

**Dissemination policy**

Dissemination of the results will include publications in peer-reviewed scientific journals and use of the visual assessments and the rehabilitation protocol in clinical practice. There are no restrictions in the publication policy. The investigators aim to publish all results obtained from the study unreservedly.

**Authorship guidelines**

Our study adheres to the Research Code of Erasmus MC in which guidelines for publishing and authorships are defined (https://www6.erasasmusmc.nl/cs-research/bijlagen/publiceren?reason = 404).

**Plans for granting public access to full protocol, dataset and statistical code**

Public access to the full protocol will be given through this paper. All results will be published open access. The dataset will not be made publicly available given the patient identifying information it contains. Statistical code will be made available upon request.

**Discussion**

The aim of this RCT is to investigate the effectiveness of an innovative and comprehensive visual rehabilitation program for children from 1 year of age. We have developed a visual rehabilitation protocol that adheres to recent scientific insights regarding rehabilitation and that conforms to standard clinical care for children at visual rehabilitation centers in the Netherlands. The present study provides a solution to some notorious problems in the (early) rehabilitation domain. Firstly, an underlying problematic paradox in the execution of rehabilitation studies is that the content
of visual rehabilitation has to be tailored to the individual child in order to exert effects, but that
establishing scientific evidence for effectiveness requires structured and controlled designs with
homogeneous groups. With this protocol, we can achieve visual rehabilitation that is not only
structured and evidence-based, but also individually tailored and adaptive to a child’s level of
functioning. Parts of the general visual protocol are currently used in visual practice but they have
never been structured into one comprehensive protocol, and have never been subject of scientific
investigation. Since there is a lack of evidence-based visual intervention or training programs(20, 22),
but clinical experiences are good, these programs are considered best clinical practice. In addition,
the supplement visual protocol and additional components were specifically designed for this study
and satisfy the need for individually adaptive programs.
Secondly, in order to obtain true evidence for the effects (does improvement occur as a result of the
rehabilitation or as result of ‘normal’ visual development?) an RCT is needed in which children with
visual dysfunctions are randomly allocated to an intervention or control group. However, a difficulty
with conducting RCTs in (young) patient groups is the ethical consideration with randomization of
treatment allocation, which means that one group is withheld treatment. Our RCT design circumvents
this problem. We start with providing rehabilitation to all participants a couple of years earlier than is
currently possible within clinical visual care (from about 4y of age). That way, both the intervention
(from 1y of age) and control group (from 2y of age) will receive earlier care than usual and are both
expected to benefit from participation in this study.
This study has the potential to satisfy a great clinical and scientific need for early and evidence-based
visual rehabilitation options. Up to now, several reviews of visual interventions in children mentioned
a lack of evidence-based programs. One showed some evidence for visual training as opposed to,
more passive, visual stimulation(20). Another focused on several strategies for visual improvement in
children with frequently co-occurring visual and neurodevelopmental problems(22). The strongest
evidence was found for visual aids (e.g. spectacles) and environmental modification to compensate
for visual loss. Less evidence was found for functional behavioral methods that focused on actually
improving visual function, and it was stressed that more information on this subject is needed. Given
the increasing prevalence of children with corrected low vision, i.e. for whom spectacles cannot provide more functional visual improvement, the availability of behavioral training programs is of the utmost importance.

It is important to note that the present study not only concerns early rehabilitation but also early screening of a VPD risk. A combined approach of detecting and rehabilitating VPD in children will benefit from the multidisciplinary collaboration of involved neuroscientists, neuropsychologists, and behavioral therapists. Upon achieving the study goals, this set-up also ensures immediate dissemination in the form of clinical implementation of the visual rehabilitation program. The proposed training programs contain a unique combination of elements that ensures incorporation of a widely-advocated system approach (33, 41). This will not only improve VPD and development, but also support the parent-infant relationship and improve infant self-regulation and later independence. With implementing this new program, we expect that more children will gain opportunities for learning, development, and daily independence earlier in development. These are invaluable and essential steps toward an inclusive society that maximizes children’s opportunities.

The broader scope of this new rehabilitation program lies in monitoring and supporting the development of children at risk not only in the visual domain, but also in behavioral, cognitive and social-emotional domains. Focusing our attention on the early development of children born preterm will help set the good circumstances for further learning and development up to school age. Ultimately, we expect the outcomes to be applicable in all types of pediatric patients at risk of visual processing dysfunctions/ VPD (e.g., comorbid with syndromes or developmental disorders). The possibility to train visual functioning brings us closer to enhancing neurodevelopment in prevalent neurological risk groups, and will optimize recovery or compensation on a functional and daily level.

**Study design challenges and limitations**

An important challenge is to determine the right age to start interventions: how early is too early?.

This is yet unknown, which is why we chose to start at 1 year CA when basic visual and neurodevelopment has completed and more elaborate development emerges. We expect that careful monitoring of visual assessment outcomes, not only related to interventions but also in the placebo
control group, and in the form of yearly follow-up measurements, will reveal the age(s) at which children start to show specific VPD. This will inform future clinical applications or new studies about the possible best developmental stages to start visual intervention programs. In addition, it was difficult to estimate the risk of VPD in this specific population of children born <30 weeks at 1 year CA. The precise number will determine the inclusion and sample size of the rehabilitation leg of the study. However, besides investigating effectiveness of visual rehabilitation in children born preterm, the present protocol provides a solid basis for other studies and/or applications in different pediatric populations at risk of VPD early in life. Lastly, the study population is a relatively vulnerable risk group, particularly because of their young age. Children born very or extremely preterm generally go through a rough first start in the neonatal period, putting a medical and psychological burden on both the children and their parents. Therefore we start recruiting at 1y of CA, when for the majority of children the most intense periods are behind them.

**Trial status**

Protocol version number and date: 5, 19 April 2017

Date recruitment began: 20 April 2017

Date recruitment for visual screening completed: 1 June 2018

Date recruitment for (direct and postponed) rehabilitation is estimated to be completed: 1 September 2019

**List Of Abbreviations**

ANOV A analysis of variance

CA corrected age

CVI cerebral visual impairment

GA gestational age

METC medical ethical testing committee

MRI magnetic resonance imaging

PAI-CY participation and activities inventory - children and youth

RCT randomized controlled trial
Declarations

Ethical approval and consent to participate

The present study has been approved by Medical Ethical Testing Committee (METC) of Erasmus Medical Center, Rotterdam (MEC–2016–724) on April 19, 2017. Written informed consent is obtained from parents or legal guardians of all participating children, prior to starting their participation in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author’s contributions

JVDS, SVDS, and IR conceived the study; MK and JP designed the study and procedures; YVDL, JVD, YVDZ and MK designed the visual rehabilitation protocol and procedures; YVDZ, RS, LS, SL, SVDS, JVDS and KK significantly contributed to study design, procedures and execution. MJGK drafted, revised and prepared the manuscript. All authors gave final approval for the submitted manuscript.
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Trial Registration
Netherlands Trial Register (https://www.trialregister.nl/trial/6622): NTR6952. Registered 19 January 2018.

Figures
| TIMEPOINT | Enrolment | Baseline visual screening | Random allocation | Intervention | 1st Follow-up | Intervention | 2nd Follow-up |
|-----------|-----------|---------------------------|-------------------|--------------|---------------|--------------|---------------|
| ENROLMENT: |           |                           |                   |              |               |              |               |
| Eligibility screen | X |                           |                   |              |               |              |               |
| Informed consent | X |                           |                   |              |               |              |               |
| Random allocation | X |                           |                   |              |               |              |               |
| INTERVENTIONS: |           |                           |                   |              |               |              |               |
| Direct visual intervention |   |                           |                   | X            |               |              |               |
| Placebo program (general support) |   |                           |                   | X            |               |              |               |
| Postponed visual intervention |   |                           |                   | X            |               |              |               |
| ASSESSMENTS: |           |                           |                   |              |               |              |               |
| A. Visual screening |   |                           |                   | X (A0)       | X (A1)        | X (A2)       |               |
| B. Visual behavior inventory |   |                           |                   | X (B0)       | X (B1)        | X (B2)       |               |
| C. Ophthalmic exam |   |                           |                   | X (C0)       |               |              |               |
| D. Visual function assessment |   |                           |                   | X (D0)       | X (D1)        | X (D2)       |               |
| E. Neurocognitive assessment |   |                           |                   |              |               | X (E)        |               |

Figure 1

Time schedule of enrolment, interventions, and assessments.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Kooiker et al_Trials_Additional file 3.docx
Kooiker et al_Trials_Additional file 2.docx
Kooiker et al_Trials_Additional file 1 - SPIRIT-Checklist.doc