2015•2016
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

OPTIMEYES: Oculomotor therapy for persons with progressive MS: a pilot randomised controlled trial

Promotor :
Prof. dr. Peter FEYS

Copromotor :
De heer Lieven VANBUEL

Copromotor :
Prof. dr. WERNER HELSEN
dr. ANN LAVRYSEN

Joren Lipkens

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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OPTIMEYES: Oculomotor therapy for persons with progressive MS: a pilot randomised controlled trial

Promotor: Prof. Dr. Peter Feys

Co-promotor: Msc. Lieven Vanbuel

Externe co-promotoren: Prof. Dr. Werner Helsen (KULeuven), Dr. Ann Lavrysen (KULeuven)

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Woord vooraf

Een eindwerk maken is een laatste stap van het behalen van een diploma en tegelijkertijd een eerste stap in de onderzoekswereld. Het is een unieke kans om na vijf jaar studeren theoretische kennis om te zetten in het onderzoeksveld en je kennis over een specifiek onderwerp uit te breiden.

Hoewel ik voor een andere afstudeerrichting koos dan de neurologische revalidatie, is mijn interesse in chronische problematieken zoals multiple sclerose erg toegenomen. Voornamelijk de stageperiodes, waarin ik de pathologie van nabij hebben mogen meemaken, hebben een grote indruk op mij nagelaten. Dit heeft me dan ook erg gemotiveerd om een bijdrage te leveren aan de wetenschappelijke kennis binnen dit domein.

Het schrijven van een thesis is een verhaal van vallen en opstaan. Uiteraard, alleen zou ik dit niet verwezenlijkt kunnen hebben en daarom zou ik graag een aantal personen bedanken. Ik richt graag een woordje van dank aan Prof. Dr. P. Feys, Dr. F. Van Halewyck, Prof. Dr. W. Helsen en Dr. A. Lavrysen. Zonder hun constructieve feedback en professionele ervaring was het me nooit gelukt.

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Ook wil ik alle vrijwilligers die deelnamen aan deze studie bedanken. Hun positivisme en gedrevenheid waren opmerkelijk en zorgden voor de nodige energie om deze thesis tot een goed einde te brengen.

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Tot slot wil ik nog graag mijn vriendin Anke Rubens, mijn ouders en mijn familie hartelijk bedanken voor hun onvoorwaardelijke steun gedurende de afgelopen vijf studiejaren.

Neerpelt, 16-06-2016 J. L.

Research context

Multiple sclerosis (MS) is one of the most prevalent neurological disease of adults around the world. However, in current literature, little is known about the effect of oculomotor training in persons with cerebellar ataxia, especially in patients with primary or secondary progressive MS. To the best of our knowledge, this study was the first that investigated the effect of a home-based training program on upper limb function.

The main objective of this proof of concept study was to investigate whether the eye-hand coordination of persons with multiple sclerosis (pwMS) can be improved using a home-based oculomotor training program. This would be provided by means of applications on an iPad during four weeks. Furthermore, changes in eye movement characteristics were assessed. Finally, the overall impact of the chronic neurologic disease was surveyed by use of standardised clinical tests and self-reported questionnaires.

The research described in this master's thesis was a collaboration between the Rehabilitation Research Centre (REVAL) of the Biomedical Research Institute of the university of Hasselt, the university of Leuven and the university of Plymouth (UK) as an international partner.

In order to achieve the master's degree of Rehabilitation Sciences and Physiotherapy at the University of Hasselt (J. Lipkens) and the University of Leuven (L. Christiaansen and C. Cuypers), the students L. Christiaansen, C. Cuypers and J. Lipkens were involved in the development of the training booklet, the pre- and post-intervention assessments of the participants and the statistical processing of the results. The research described in this master's thesis was supervised by promotors Prof. Dr. P. Feys, Prof. Dr. W. Helsen and co-promotors Dr. A. Lavrysen and Msc. L. Vanbuel. The protocol was designed in dialogue with their colleagues, Prof. Dr. J. Marsden and Dr. L. Bunn of the university of Plymouth, who simultaneously executed this randomised controlled trial in the United Kingdom.

Funding was provided by the Progressive MS Alliance. This is an international collaboration that encourages and financially supports research of treatment methods for persons with progressive MS (http://www.progressivemsalliance.org). All the necessary equipment and facilities were provided by the university of Hasselt, university of Leuven and the university of Plymouth.

OPTIMEYES: Oculomotor therapy for persons with progressive MS: a pilot randomised controlled trial

1 Abstract

Background Cerebellar ataxia is frequently observed in persons with progressive multiple sclerosis (MS), resulting in a wide range of oculomotor and locomotor abnormalities, leading to difficulties in both eye and hand coordination and the performance of activities of daily living (ADL).

Objective This study was a preliminary randomised controlled trial in which the effect of a 4 week home-based oculomotor training (OMT) program was examined primarily on eye-hand coordination. Secondary outcome measures concerning functions necessary for activities of daily living, were evaluated using a battery of clinical tests and self-completion instruments.

Methods A total of 15 persons with progressive MS were included after passing the selection criteria. They were randomised into an experimental (n = 7) and a control group (n = 8). In addition, a group of healthy controls (n = 8) underwent a selection of clinical tests to serve as reference for the baseline measurements. A four week during home-based training intervention was feasible for persons with MS (pwMS) without any drop-outs.

Results The selection of an age- and sex-matched healthy control for each pwMS and a good randomisation of pwMS in the experimental and control group were confirmed. The experimentally developed tests could not detect significant differences between pwMS and healthy controls for the hand movement parameters at baseline. Limited improvements in the experimental group were found at the post-intervention assessment. A trend towards significance was found for Time to peak velocity, suggesting an improvement in hand movement control in the experimental group after training.

Conclusion Improvements of oculomotor deficits in pwMS were expected after a targeted training of eye movements, leading to an improvement of goal-directed aiming movements. Despite the fact that this pilot study was not able to confirm the proposed hypothesis, a positive influence of the OMT on hand movement control was suggested.

Keywords oculomotor training, multiple sclerosis, cerebellar ataxia, home-based training, eye-hand coordination

Index of abbreviations and symbols

* = statistically significant ($p \leq 0.05$)

** = highly statistically significant ($p \leq 0.01$)

Δ = difference

± = standard deviation

ABC = Activities-specific Balance Confidence scale

BBT = Block and Box test

EDSS = Expanded Disease Status Scale

FRT = Functional Reach Test

HAI = Hauser Ambulation Index

INAS = Inventory for Non-Ataxia Signs

IVIS = Impact of Visual Impairment Scale

MAM-36 = Manual Ability Measure (36 items)

MFIS = Modified Fatigue Impact Scale

MSIS-29 = Multiple Sclerosis Impact Scale (29 items)

MSWS-12 = Multiple Sclerosis Walking Scale (12 items)

NHPT = Nine Hole Peg Test

ORT = Oculomotor Rating Test

SARA = Scale of the Assessment and Rating of Ataxia

SDMT = Symbol Digit Modality Test

SWM = Semmes-Weinstein Monofilament test

T25FW = Timed 25-Foot Walk

VAS = Visual Analogue Scale

2 Introduction

In daily life, tasks are performed in a seemingly automatic way, without conscious thinking, such as reaching for a glass of water, entering a security code in a bank terminal or avoiding obstacles during walking (Hayhoe & Ballard, 2005; Land, 2006). These movements all seem very straightforward. However, complex temporal and spatial control of two systems is needed to perform such tasks in a successful way. First, the oculomotor system continuously scans the environment for task-relevant information (Land & Furneaux, 1997). Secondly, the motor system is dependent on the efficient functioning of several cortical structures involved in movement planning (frontal eye fields, posterior parietal cortex, supplementary motor area, dorsolateral prefrontal cortex) (Hayhoe & Ballard, 2005; Moore & Fallah, 2001). Deficits in these two systems seem to contribute to an impaired movement control (Solaro et al., 2007; Ternes, Fielding, & Corben, 2014).

Multiple sclerosis (MS) is a chronic, inflammatory disorder of the nervous system (Spooren, Timmermans & Seelen, 2012). It is characterised by axonal loss and randomly located multifocal sclerotic plaques, arising from demyelination lesions (Trapp et al., 1998). There are four phenotypes of MS: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS) and recently added clinically isolated syndrome (CIS). In RRMS, relapses of an additional or increasing neurological dysfunction are alternated with full or partial recovery. CIS is considered to be part of the relapsing-remitting disease spectrum and is defined by clear-cut syndromes such as optic neuritis or cerebellar dysfunction. As the term suggested, progressive disease is characterised by steadily increasing neurological dysfunction without periods of recovery, including both PPMS and SPMS. In PPMS, a progressive accumulation of disability from onset is observed, while persons diagnosed with SPMS experience an initial relapsing course followed by progressive accumulation (Lublin, 2014). In this study exclusively patients with progressive MS were included. MS affects the motor, sensory, visual and autonomic systems (Compston & Coles, 2002; Trapp et al., 1998). Therefore, it is not uncommon that individuals with MS have motor impairments (e.g. disequilibrium) and experience difficulties in activities of daily living (ADL), resulting in an undeniable impact on the quality of life of the patient and his or her family (Kalron & Achiron, 2013; Miller & Dishon, 2006).

The cerebellum or cerebellar system plays an important role in the online control of both eye and hand movements, as well as in the coordination of these two effectors (Feys, Helsen, Buekers, et al., 2006; Feys, Helsen, Liu, et al., 2003; Feys, Helsen, Verschueren, et al., 2006).

Cerebellar dysfunction due to MS can present itself as a variety of clinical signs. Characteristic eye movement abnormalities are very common in MS and are often present in association with other signs of cerebellar dysfunction i.e. postural and kinetic tremor, dysmetria of arm movements, dysdiadochokinesia, impaired postural control and gait dysfunction (Bunn, Marsden, Giunti, & Day, 2015; Crowdy et al., 2002). This syndrome is often referred to as cerebellar ataxia and is more prevalent in individuals with PPMS compared to RRMS and controls (Anderson et al., 2011; Mills, Yap, & Young, 2009).

More than 75% of the persons with MS (pwMS) experience some visual deficits during the course of their disease (Barnes & McDonald, 1992). Some studies suggest that eye movement disturbances can be a useful tool for detecting MS (Chen & Gordon, 2005; Ventre, Vighetto, Bailly, & Prablanc, 1991). These disturbances of visual afferent or oculomotor systems can originate from both peripheral and central cerebellar neural dysfunction (Flipse et al., 1997). The most common eye movement disturbances in MS are bilateral internuclear ophthalmoplegia, pendular nystagmus and abnormalities compatible with damage to the cerebellum or its connections (Jozefowicz-Korczynska, Łukomski, & Pajor, 2008). Cerebellar eye movement disorders are observed in about one-third of the MS-patients, with saccadic undershoot or overshoot dysmetria, pendular nystagmus and fixation instability as the most prevalent disturbances (Barnes & McDonald, 1992). Impaired visual function can also be related to peripheral damage of the optic nerve as a result of MS, defined as optic neuritis (Buzaid, Dodge, Handmacher, & Kiltz, 2013). In practice, these deficits result in a delayed onset of eye movements, prolonged eye movements and other significant inaccuracies related to the eyes (Feys, Helsen, Liu, et al., 2003).

Unlike healthy individuals, pwMS with cerebellar ataxia have difficulties in the homing phase when fixating onto a target (Feys et al., 2005; Feys, Helsen, Lavrysen, Nuttin, & Ketelaer, 2003). According to Woodworth's two-component model (1899), the homing phase is the second phase of a goal-directed aiming task. Firstly, there is a ballistic, pre-programmed phase that brings the limb near the target area (transport phase). Secondly, there is a homing phase in which visual and proprioceptive feedback are used to reduce the discrepancy between limb and target position (target phase) (Elliott & Helsen, 2001; Elliott et al., 2010). The fixational issues are presumably due to nystagmus and the inability to suppress the vestibulo-ocular reflex (Prasad & Galetta, 2010). In current literature, a positive effect of oculomotor training (OMT) on eye movement control was reported in patient populations with acquired brain injury (Kapoor,

Ciuffreda, & Han, 2004; Thiagarajan & Ciuffreda, 2014a, 2014b), progressive supranuclear palsy (Zampieri & Di Fabio, 2009) and convergence insufficiency (Van Leeuwen et al., 1999). To the best of our knowledge, no studies have investigated the effect of OMT on individuals with MS.

As mentioned before, the coordination and online control of visually guided goal-directed aiming, is regulated through cerebello-cortical circuits. This has been mentioned in several MS-specific studies (Feys, Helsen, Buekers, et al., 2006; Feys, Helsen, Liu, et al., 2003; Feys, Helsen, Verschueren, et al., 2006). When MS-patients with cerebellar ataxia perform voluntary movements (e.g. reaching for a glass of water), noticeable disturbances, such as late movement onset and a delayed onset of antagonist activity of the arm movement can occur, resulting in dysmetric movements (Hore, Wild, & Diener, 1991). For this reason, pwMS often overshoot their target and are forced to perform corrective movements. Consequently, prolonged movement durations and abnormally curved movement paths occur (Diener & Dichgans, 1992; Feys, Helsen, Liu, et al., 2003; Sailer, Eggert, & Straube, 2005).

Given the notion that visual deficits and upper limb impairments are both present in MS, it is remarkable that only a few studies have investigated possible interactions. Disturbed eye movements lead to inaccurate visual information, which causes multiple corrections in the eye movements and affects the eye-hand coordination, causing cerebellar tremor (Crowdy, Hollands, Ferguson, & Marple-Horvat, 2000; Feys et al., 2008; Feys, Helsen, Lavrysen, Nuttin, & Ketelaer, 2003; van Donkelaar & Lee, 1994). The study of Feys et al. (2005) measured a series of parameters for quantitatively assessing both hand and eye movement disorders, as well as their interactions during a visually guided wrist step-tracking task. In healthy individuals, the spatial and temporal coupling ensure that the eyes stay in an optimal position to fixate on the target position to make adjustments during hand deceleration, reflecting in very small values of endpoint error. Despite the dysfunctional eye-hand coordination in pwMS, spatial and temporal coupling between the primary saccadic eye and hand movements was preserved. Moreover, both the primary saccade and peak velocity were significantly delayed and the amplitude of the primary hand movement always exceeded that of the preceding saccade respectively (Feys, Helsen, Liu et al., 2003). It is conceivable that the target overshoot in pwMS is partially related to the enlarged primary eye saccade, as saccadic amplitude is known to influence the hand pointing movements in healthy individuals (van Donkelaar, 1998). Without a preceding saccadic eye movement, the initial hand error and hand tremor amplitude are reduced, corresponding with smaller values of the additional path length, confirming the influence of the ocular system

on the hand movements. On the contrary, different levels in hand tremor severity do not affect eye movements (Feys et al., 2005).

Recent research suggests that OMT might have a positive impact on postural stability in people with cerebellar ataxia (Bunn et al., 2015), as well as a positive effect on gait in progressive supranuclear palsy (Zampieri & Di Fabio, 2008). In several studies, optokinetic stimulation and gaze stabilisation were used as elementary components in vestibular rehabilitation to improve static balance (Bunn, Marsden, Giunti, & Day, 2015; Chen, Hsieh, Wei, & Kao, 2012; Morimoto et al., 2011). Crowdy et al. (2002) investigated the effect of rehearsal of eye movements on locomotor performance in cerebellar patients. They reported an improvement of stepping regularity and accuracy in the two cases and a decrease in stance and double support phase durations in one patient only. Improved oculomotor control was shown by a reduced occurrence of saccadic dysmetria, measured as a significant increase in the ratio of single to multi-saccadic eye movements (Crowdy et al., 2002). An earlier study of Crowdy et al. (2000) showed that the amount of locomotor problems seen in cerebellar patients during visually guided stepping is linked to the severity of their oculomotor abnormalities. Despite the heterogeneity in level of dysfunction between the participants, a significant improvement in the accuracy of steps as a result of eye movement rehearsal, compared to repeated walking alone, was found.

All studies mentioned above investigated the effect of an OMT on balance and lower limb functionality. Since the relevance of visually guided goal-directed aiming in pwMS has been described above, it is remarkable that no research has been conducted on this topic, to the best of our knowledge. Therefore, this study aims to investigate the effect of a home-based eye movement training program on upper limb function in individuals with progressive MS. The primary goal was to determine the effect of OMT on the quality of a goal-directed aiming task. Secondly, through various clinical tests and self-reported questionnaires, the effect of the training program on ataxia and functions necessary for ADL (e.g. manual dexterity, balance, gait, cognitive function) was evaluated. After an intensive training period of 4 weeks, a better performance on goal-directed aiming tasks and an improvement in clinical outcomes related to upper limb functioning were hypothesised. Furthermore, to connect the objective experimentally developed measurements with the clinical practice, self-reported questionnaires were used to give insight into possible improvements of ADL.

3 Materials and Methods

3.1 Participants

A total of 15 persons with progressive MS were enrolled in this research. They were randomly allocated to an experimental group (EG) (n = 7) or a control group (CG) (n = 8) in such a way that an equal distribution of pwMS with score of the Scale of the Assessment and Rating of Ataxia (SARA) > 12 and < 12 was achieved in both groups. The SARA is an 8-item scale with the subcomponents gait, stance, sitting, speech, under-overshoot, intention tremor, alternating hand movements and heel-shin slide (Schmitz-Hubsch et al., 2006). Also, 8 age- and gender-matched healthy controls (HC) were included to serve as reference for the baseline measurements, to which the MS-group was compared. The EG received additionally an OMT intervention, while the CG continued their usual care.

PwMS were included in this study if they met all of following criteria: a) age between 18 and 70 years, b) diagnosed with primary or secondary progressive MS according to the McDonald's criteria (Polman et al., 2011), c) signs of cerebellar dysfunction as defined by the SARA (score of ≥4/40) (Schmitz-Hubsch et al., 2006), d) clinically detectable oculomotor deficits of cerebellar origin (two or more symptoms of; gaze evoked or vertical nystagmus, saccadic dysmetria, incomplete or broken smooth pursuit, impaired suppression of the vestibulo-ocular reflex) and e) able to perform the transfer from bed to chair. HC were matched for age and gender to a corresponding pwMS of the EG. However, HC had to be at least 18 years old and a difference in age of maximum 5 years compared to the pwMS was admitted.

Individuals with MS were excluded because of following reasons: a) diagnosed with relapsing-remitting MS, b) a relapse one month prior to recruitment, c) presence of neurological symptoms that are unrelated to MS, d) suffering from primary visual deficits (e.g. glaucoma, cataract, macular degeneration) and e) unable to follow study instructions. The HC were excluded when orthopaedic or neurological conditions that could impair oculomotor control or upper or lower limb function, were present.

A few anthropometric characteristics were gathered from all the participants: age, gender, height and weight. Some additional information was asked to the pwMS of both the EG and CG**:** date of diagnosis, type of MS, first symptoms related to MS, time of last relapse, medication, type and hours of rehabilitation per week. During the post-intervention assessment, participants were requested to note down any alterations in medication and hours of

rehabilitation during the last weeks. The score of the Expanded Disease Status Scale (EDSS) was inquired too (Kurtzke, 2008). In case the participant did not know his/her EDSS-score, it was received from the report of the neurologist.

Volunteers were recruited from the Rehabilitation and MS Centre at Overpelt and the Rehabilitation Research Centre (REVAL) of the Biomedical Research Institute of the university of Hasselt by handing out informational brochures to potential participants. Also, the neurologists and staff were informed about this research and provided a list of eligible pwMS. Subsequently, one of the research members contacted the persons on the list by phone and scheduled an appointment in their home environment. During this first consultation, the participants were screened for eye movement disorders by means of the oculomotor scoring system (Downey et al., 2002; Serra, Derwenskus, Downey, & Leigh, 2003). Subsequently, the SARA was administered to check for the presence of cerebellar ataxia. The HC-group consisted mainly out of family members, friends and acquaintances of the researchers, which were all age- and sex-matched with the MS patients of the EG.

Approval of the protocol was given by the Ethical Committee of the KU Leuven and the university of Hasselt, as well as those of the Rehabilitation and MS Centre at Overpelt. All potential participants signed the informed consent sheet prior to cooperating in the experimental study.

3.2 Procedures

All volunteers visited the Rehabilitation and MS Centre at Overpelt or the Research Rehabilitation Centre of the university of Hasselt for the first assessment. Considering that the complete test battery would consume approximately three hours, generally two persons were scheduled per day. During the tests, each participant was able to request a break or a drink at all times.

An extended sequence of outcome measures was assessed in this study. The testing was divided into three parts: experimental tests, clinical examinations and self-reported questionnaires. All participants had to take the experimental tests and five general clinical tests at baseline (BBT, T25FW, NHPT, SDMT, FRT) (cf. 3.5). PwMS, both the CG and EG, were asked to complete five additional clinical tests (SARA, INAS, ORT, HAI, SWM) (cf. 3.5) and six questionnaires (MSIS-29, ABC, MSWS-12, MAM-36, MFIS, IVIS) (cf. 3.5). Furthermore, a retrospective evaluation of the

number of falls during the past year and the VAS for pain were registered for each pwMS. After four weeks, both groups were invited for a post-intervention assessment. The entire test battery was repeated except for the INAS, SWM, fall risk and number of falls.

3.3 Task and apparatus

The participants were seated 40 cm away from a computer screen with their head supported in a chin rest and trunk supported by a chair. The chin rest prevented head movements, so only eye movements could be made. For the upper limb function and eye-hand coordination testing, the right forearm was inserted into an orthosis with a hinge at the wrist. Participants were instructed to track a moving target using a wrist-controlled cursor by making flexion/extension movements in the horizontal plane. The target and cursor were both projected onto the screen by a custom designed software from the KULeuven, named VisCon. The intertarget distance of 27.2 cm on the monitor corresponded to 40° of wrist flexion/extension. A high-precision shaft encoder with an accuracy of 0.0055° and sampling frequency of 250 Hz was attached to the axis of the orthosis. Simultaneously, eye and hand movements were recorded using respectively an electrooculogram (BlueGain EOG, Cambridge Research systems, UK) and an orthosis linked to the VisCon software. The room in the laboratory contained a minimal amount of distractions to minimise visual disturbances.

The EOG consisted of three electrodes, placed around the right eye (+ lateral, - medial, reference electrode on the forehead) and was plugged into a BlueGain device that was connected with a laptop via Bluetooth. Synchronisation between BlueGain and VisCon was done manually by placing a marker in the output of the EOG when the VisCon software was started. The sampling rate of the EOG was 1000 Hz.

The participants started the experiment with a calibration test for the EOG. During the calibration, the participants were asked to fixate their eyes on three different black squares: one left, one in the middle and one on the right side of the screen. Looking to the left corresponded with a negative potential difference on the EOG and looking to the right logically resulted in the opposite.

Secondly, different tests to assess upper limb and eye movement parameters were performed. Each distinct test was performed twice in order to have sufficient data. The upper limb paradigm started with the cyclical task with eyes alone. Two different cyclical tasks were

executed. They had to fixate their eyes on a red square that moved in linear or sinusoidal motion between the two black targets. As the term suggested, the target in linear motion moved at a constant speed over the entire range, whereas in the sinusoidal pattern the target followed a sinusoidal velocity profile, thus slowing down when reaching the turning points. In both cyclical tasks, the moving red square reached the other target in 1.2 seconds, so one cycle was completed in 2.4 seconds. Subsequently, the same cyclical tasks were carried out with a wrist orthosis. A cursor in the shape of a black circle was shown on the monitor. The goal was to keep this circle as close as possible to the red square by moving the wrist.

Next, a discrete task was performed first with eyes alone and secondly accompanied with hand movements. The discrete task consisted of making saccadic eye movements between two black fixed squares. Participants were instructed to look as quickly and accurately as possible to the other target when there was an auditory stimulus. There was alternately an intermission of 4 and 5 seconds between the stimuli, respectively when looking at the right and left target. In the eye-hand condition participants had to move the black circle between the red squares on an auditory stimulus.

The next block of tasks was composed exclusively of eye movements. Fixation, saccades, smooth pursuit and optokinetic responses in the horizontal direction were measured using an EOG in order to assess the oculomotor control. These four tasks were played by MATLAB clips, each repeated twice: a) fixate: the participant was instructed to fixate a stationary white dot on a moving grey background; b) saccade: the same white dot made saccadic jumps in the horizontal direction for a period of 90 seconds, with a variable amplitude across the screen; c) smooth pursuit: the white dot moved with a varying speed and amplitude in the horizontal direction on the screen for 105 seconds within one trial; d) optokinetic nystagmus: the participant was instructed to fixate the location of a stationary white dot on a grey background. This target disappeared as soon as horizontally moving black and white columns appeared on the screen, provoking an optokinetic reflex. The direction of the optokinetic stimulus was randomly generated each trial. Participants had to be able to suppress the optokinetic reflex in order to keep focus on the former position of the white dot. After a period of 20 seconds, the initial target reappeared for the participant to fixate again.

3.4 Intervention

Participants of the EG received a 4 week home-based OMT program. They were instructed to exercise for 15 minutes per day, each day of the week, on an iPad provided by the researchers. The training program consisted of three different apps: Focus Builder (NeurdSolutions, USA), Vision Tap (Kevin Sullivan, USA) and Eye Movement Training (Ebenezer international residential school, India). Focus Builder aims to train smooth pursuit eye movements, (anti-)saccades and eye fixation. Vision tap contains various exercises to train the eye-hand coordination, whereby participants tapped moving objects on the screen. Lastly, the Eye Movement Training application enhances smooth pursuit eye movements. A computer screen with a plug-in for the iPad was provided in order to enlarge the stimuli so that participants would see them clearly. At the end of the pre-intervention session, a researcher handed over the training booklet with all prescribed exercises, accompanied by a brief explanation about the settings and purpose of each application. The training program was presented in a day to day format, so participants could easily adjust and configure the iPad for every session. The exercises had an increasing difficulty level over time. In case exercises were not challenging enough, participants were allowed to adjust the settings of the applications to fit their own level. Additionally, contact details of the members of the research team were implemented in the training manual, thus participants were able to mail or call in case of problems. Moreover, at weekly intervals, the participants received a phone call from one of the investigators to follow-up possible difficulties and progress.

3.5 Clinical Outcomes

The spatial and temporal variables measured during the execution of different goal-directed eye-hand aiming movements, were the most important primary outcomes. The hand movements were explored in both discrete and cyclical tasks. The raw position data were filtered using a low-pass Butterworth filter (cutoff: 20 Hz). Subsequently, velocity and acceleration were calculated. As mentioned before, two distinct phases could be distinguished in a goal-directed aiming task: a transport phase and a target phase. The transport phase consisted of a ballistic, which is a pre-programmed movement that brings the limb near the target area. During the second movement phase, the so called target phase, visual and proprioceptive feedback were used to precisely home-in on the target (Elliott et al., 2010). The

intertarget distance was equal to 27.2 cm and corresponded to 40° wrist flexion/extension. The target phase had a fixed duration of 1200 ms starting from the end of the ballistic phase. The following variables were calculated for the discrete task: a) mean amplitude ballistic phase: the distance travelled between the beginning and end of the transport phase; b) mean time of the ballistic phase: the average time needed to travel the transport phase; c) initial error: the distance between the target position and the actual hand position at the end of the transport phase, which could result in an undershoot or overshoot, corresponding with a negative or positive value respectively; d) endpoint error: the mean distance between target position and the actual hand position at the end of the target phase; e) peak velocity: the highest velocity of the hand movement; f) time to peak velocity: the time needed to reach highest velocity in the primary submovement, expressed as a percentage of total hand movement duration; g) additional path length of the target phase: the amount of additional distance travelled by making corrective movements in the target phase, which was calculated by substracting the distance between the start and endpoint position of the target phase from the total length of the covered trajectory in this phase; h) zero crossings target phase: the number of directional changes in the velocity profile.

In the cyclical task, both linear and sinusoidal patterns were tested. As the objective was to track a moving target, the efficiency of the movement pattern was of main interest. The time between beeps of the cyclical task was 2.4 seconds. Both the duration of the transport phase and the target phase were defined to be 1.2 seconds. The target phase was defined as a period from 600 ms before to 600 ms after the target reversal point and the transport phase was defined as the time in between these moment. The following variables were calculated in both subcategories: a) additional path length of the transport phase: the length the participant covered in the transport phase minus the absolute distance between the starting and endpoint of the transport phase; b) additional path length of the target phase: this parameter was calculated as described above and its value was negative when the participant undershot the target; c) additional path length of the total movement: this parameter was calculated by summing both former parameters and reflects the overall amplitude of intention tremor of the total movement; d) zero crossings of the transport phase and e) zero crossings of the target phase corresponded both with the number of directional changes in the velocity profile in the transport and target phase respectively.

In addition to the eye- and hand measurements during the aiming task, a battery of clinical tests and self-reported questionnaires were used to obtain secondary outcome measurements. First, five general clinical tests concerning upper limb function, balance, gait and cognitive function were taken from both pwMS and HC to provide baseline statistics and to evaluate intervention effects between EG and CG. Furthermore, the pwMS completed six additional tests to give information about the level of ataxia, symptoms other than those related to cerebellar dysfunction, oculomotor dysfunction, gait impairment and peripheral sensory dysfunction.

With regard to upper limb functioning, more specific manual dexterity, the Block and Box Test (BBT) and the Nine Hole Peg Test (NHPT) were administered (Goodkin, Hertsgaard, & Seminary, 1988; Lamers & Feys, 2014; Platz et al., 2005). These quantitative tests demand the ability to repeatedly grasp an object as quickly as possible, transport it, and release it again. In particular, the type of unilateral manipulation and transportation needed for the NHPT, requires more advanced fine motor skills than the BBT, which evaluates the gross manual dexterity. Because balance could be compromised in pwMS due to sensory and motor impairments, the Functional Reach Test (FRT) was assessed. It was executed in stance with feet a fist width apart (Frzovic, Morris, & Vowels, 2000). Participants were instructed to lean forward as far as possible next to a wall with their arm extended at shoulder level and a closed fist, without taking a step. For wheelchair-dependent pwMS the modified FRT was performed in seated position. They had to perform this three times: forward, to the left and to the right. The average of these three distances was calculated (Katz-Leurer, Fisher, Neeb, Schwartz, & Carmeli, 2009; Lynch, Leahy, & Barker, 1998). The fourth clinical test was the Timed 25-Foot Walk test (T25FW), which served as a quantitative assessment of gait function (Larson, Larson, Baumgartner, & White, 2013; Phan-Ba et al., 2012). The Symbol Digit Modality Test (SDMT) was used to screen cognitive functioning, particularly the processing speed (Van Schependom et al., 2014). As the SDMT was tested orally, cerebellar ataxic deficits (e.g. disturbed eye-hand coordination, intention tremor) could not affect the outcome.

Following five additional tests, Scale of Assessment and Rating of Ataxia (SARA), Inventory of Non-Ataxia Signs (INAS), Oculomotor Rating Test (ORT), Hauser Ambulation Index (HAI) and the Semmes-Weinstein Monofilament test (SWM), were completed by the pwMS in the pre- and post-testing procedure. To assess the severity of cerebellar ataxia, the SARA was implemented (Kim et al., 2011; Schmitz-Hubsch et al., 2006; Weyer et al., 2007; Winser, Hale, Claydon, & Smith, 2013; Yabe, Matsushima, Soma, Basri, & Sasaki, 2008). It was taken during the initial visit

as it was one of the selection criteria for pwMS. The first three items of the SARA (gait, stance, sitting) were summed and defined as the SARA balance. Furthermore, the total score was also documented as SARA total. Additionally, symptoms other than those related to cerebellar dysfunction were surveyed by the INAS (Jacobi et al., 2013). To determine whether or not the pwMS had clinically detectable oculomotor deficits, the ORT was applied (Downey et al., 2002; Serra et al., 2003). Both authors reported that a brief clinical examination of dynamic eye movements (e.g. saccades, VOR) provides information about the involvement of brainstem and cerebellar circuits in pwMS. The HAI, a likert scale from 0 to 10, was used for assessing the extent of gait impairments (Cattaneo et al., 2002). Finally, the SWM was taken to assess the amount of peripheral sensory dysfunction by the use of 10 g tactile point pressure on both hands (SWM hand) and feet (SWM foot) (Bell-Krotoski & Tomancik, 1987; Tracey, Greene, & Doty, 2012).

In order to have a comprehensive understanding of the consequences of MS on the locomotor performance (walking ability, fall risk, balance problems), manual dexterity, visual and psychological functioning and fatigue, several disease-specific questionnaires were included. The twelve-item MS Walking Scale (MSWS-12) is a questionnaire that allows patients to subjectively rate the impact of MS on their walking ability (Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2003; Mcguigan & Hutchinson, 2008; Motl & Snook, 2008; Pilutti et al., 2013). Since MS-patients could experience some disequilibrium (Kalron & Achiron, 2013) the Activities-specific Balance Confidence scale (ABC-scale) was implemented (Cameron & Huisinga, 2013; Nilsagård, Carling, & Forsberg, 2012). To assess the self-reported impairment in manual dexterity by rating ADL that require some eye-hand coordination, the Manual Ability Measure with 36 items (MAM-36) was used (Chen & Bode, 2010; Chen, Kasven, Karpatkin, & Sylvester, 2007). Subsequently, the Impact of Visual Impairment Scale (IVIS), a five-item instrument that provides an assessment of difficulties with visual recognition tasks performed daily, without visual corrective aids, was assessed. The IVIS is part of the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Dilorenzo, Halper, & Picone, 2003; Marrie, Miller, Chelune, & Cohen, 2003; Ritvo et al., 1997). Furthermore, the MS Impact Scale (MSIS-29), a questionnaire with a 5-point likert scale that evaluates both the physical and psychological impact of MS from patients' perspective, was implemented (Hobart, Lamping, Fitzpatrick, Riazi, & Thompson, 2001; Riazi, Hobart, Lamping, Fitzpatrick, & Thompson, 2002). The hindmost MS-specific questionnaire included in this clinical trial, was the Modified Fatigue Impact Scale (MFIS). This scale consists of

21 physical, cognitive and psychosocial statements concerning how fatigue impacts the lives of pwMS (Larson, 2013; Learmonth et al., 2013; Mills, Young, Pallant, & Tennant, 2010).

Finally, fall risk, number of falls and Visual Analogue Scale (VAS) for pain were surveyed. PwMS who reported falls during the past year, were considered to have a fall risk. If this was reported, the number of falls in the past year were inquired. Self-reported pain was measured with the VAS, which is an instrument to visualise pain on a scale from 0 to 10.

3.6 Statistical analysis

Statistical processing of the data was accomplished using the statistical software IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY). First of all, normality was checked using a Shapiro-Wilk test for all variables. Despite that not all analyses showed normally distributed values and a relatively small sample size was included, a parametric analysis was performed. All data were analysed with an analysis of variance (ANOVA). This technique was assumed to be superior as it allowed to concurrently compare groups based on mean values, both between and within groups, ensuring there was only one chance of false-positive results. A one-way ANOVA between groups was utilised for the comparison of pwMS vs. HC (cf. table 1) and EG vs. CG (cf. table 2) by means of anthropometric characteristics, clinical tests and questionnaires (cf. table 2). A one-way ANOVA between HC, EG and CG was checked for the anthropometric characteristics and for the five general clinical tests, but did not result in additional information. The chosen statistical analysis was assumed to be superior since it allowed to give a more clarifying overview of the results of interest.

A one-way ANOVA between HC, EG and CG was used to compare the results of the experimental tasks (cf. table 3). 2 x 2 repeated-measures ANOVAs were applied to process the pre-and post-intervention results of the EG and CG to assess the training effect (cf. table 4a, table 5a). The Bonferroni procedure, which served as the post hoc analysis, was performed whenever a significant interaction effect was found, so it was possible to discover whether the significant effect was located in the within-group or between-group difference and in which session or group (cf. table 4b, table 5b). The significance level was set at 5% ($p \leq 0.05$) and values were indicated as highly significant if lower than or equal to 1% ($p \leq 0.01$).

The excluded data had to be explored more in detail. Firstly, the data of one participant from both the discrete as the cyclical task during the pre-training assessment, were retrospectively

eliminated due to a deviant pattern of movement. The tremor interfered with the movement in such way that most of the values differed by more than three standard deviations from the mean value. Two trials of the cyclical eye-hand linear task were considered unsuccessful due to reported difficulties with the orthosis, and were excluded for that reason. Further, an overview of missing data was provided. For the T25FW test, there were missing data of four participants. Three of them were unable to take the test because they were wheelchair bound. From the other, there was no record of the test during the initial session, so the score of the post-intervention assessment was excluded. Finally, one participant did not complete the MAM-36 correctly and was therefore unusable. For the data processing, the mean of the two trials was used. Missing data of one trial was expected to not greatly affect the outcomes.

4 Results

Table 1 outlines the anthropometric values and the results of five general clinical tests compared between the HC and all pwMS (EG + CG). With the exception of the NHPT, all clinical tests yielded statistically significant differences between groups. The performance of the FRT ($p \leq 0.05$) was significantly different, while the BBT, the SDMT and the T25FW were even indicated as highly significantly different ($p \leq 0.01$). No significant differences were found for the anthropometric values.

Table 1. Anthropometric characteristics and clinical tests (S1): pwMS - HC

PARAMETER	pwMS (N = 15)	HC (N = 8)	F-test	P-value
Sex: m (f)	7 (8)	5 (3)		
Age (yrs)	54.00 ± 7.45	56.00 ± 6.59	0.406	0.531
Height (cm)	173.73 ± 8.92	175.63 ± 9.68	0.221	0.643
Weight (kg)	70.47 ± 13.42	78.19 ± 10.63	1.972	0.175
BBT (# of blocks)	44.00 ± 9.89	64.69 ± 4.24	31.355	0.000**
NHPT (s)	41.06 ± 32.66	19.28 ± 1.26	3.476	0.076
SDMT (# of correct answers)	43.20 ± 11.63	56.63 ± 7.67	8.562	0.008**
FRT (cm)	31.19 ± 7.10	39.16 ± 8.01	6.039	0.023*
T25FW (s)	6.51 ± 2.74	3.61 ± 0.66	8.519	0.010**

A comparison of the pre-intervention assessment between the EG and CG is presented in table 2. All anthropometric characteristics and clinical tests were found not significantly different, except for the INAS ($p \leq 0.01$) and the SWM test of the feet ($p \leq 0.05$). The EG scored higher on the INAS compared to CG, which corresponded to more non-ataxia signs (e.g. spasticity, paresis) at baseline. Furthermore, the EG had more sensory deficits on the foot than the CG as suggested by the results of the SWM foot.

Table 2. Anthropometric characteristics, clinical tests and questionnaires (S1): EG – CG

PARAMETER	EG (N = 7)	CG (N = 8)	F-test	P-value
Sex: m (f)	4 (3)	3 (5)		
Age (yrs)	54.86 ± 8.55	53.25 ± 6.84	0.164	0.692
Height (cm)	176.14 ± 5.79	171.63 ± 10.94	0.954	0.347
Weight (kg)	72.86 ± 8.95	68.37 ± 16.76	0.398	0.539
Type of MS: PPMS (SPMS)	2 (5)	4 (4)	3.050	0.435
Disease duration (yrs)	11.71 ± 7.76	20.63 ± 11.35	0.650	0.104
EDSS (0 - 10)	5.50 ± 0.71	4.56 ± 1.76	1.726	0.212
BBT (# of blocks)	44.43 ± 11.57	43.63 ± 8.98	0.023	0.882
NHPT (s)	44.15 ± 41.68	38.35 ± 25.03	0.110	0.745
MAM-36 (36 - 144)	111.33 ± 32.10	127.87 ± 12.67	1.794	0.205
T25FW (s)	6.24 ± 1.76	6.84 ± 3.83	0.119	0.739
HAI (0 - 9)	2.50 ± 1.22	2.20 ± 1.79	0.109	0.749
MSWS-12 (12 - 60)	51.00 ± 7.26	41.12 ± 16.57	2.114	0.170
FRT (cm)	33.68 ± 6.13	29.01 ± 7.54	1.697	0.215
ABC (%)	46.25 ± 19.02	43.28 ± 30.12	0.050	0.826
Fall risk: Y (N)	6 (1)	5 (3)	0.957	0.346
# of falls	3.21 ± 3.41	6.94 ± 8.29	1.221	0.289
SARA balance: item 1-3 (0 - 18)	5.29 ± 1.11	6.13 ± 4.09	0.220	0.609
SARA total (0 - 40)	10.14 ± 2.72	11.31 ± 6.07	0.275	0.647
INAS (0 - 142)	16.57 ± 2.70	10.88 ± 3.36	12.847	0.003**
SDMT (# of correct answers)	43.57 ± 10.21	42.88 ± 13.45	0.012	0.913
SWM hand (0 - 6)	6.00 ± 0.00	5.44 ± 0.82	3.254	0.094
SWM foot (0 - 10)	9.36 ± 0.99	6.38 ± 2.57	8.263	0.013*
ORT (0 - 15)	3.71 ± 1.38	3.38 ± 0.95	0.314	0.585
IVIS (0 - 15)	2.86 ± 3.08	3.75 ± 3.65	0.257	0.620
MSIS-29 (29 - 145)	87.71 ± 22.63	72.50 ± 19.03	2.003	0.181
MFIS (0 - 84)	42.43 ± 24.51	47.25 ± 9.11	0.270	0.612
VAS pain (0 - 10)	4.43 ± 3.46	3.62 ± 3.25	0.215	0.650

Table 3 summarises results for the hand movement parameters in each of the conditions the EG, CG and the HC established at baseline. The additional path length of the total movement during the sinusoidal cyclical task ($F = 3.450$, $p = 0.053$) was borderline significant. Post hoc analysis revealed a difference between the CG and HC ($\Delta = -2.12$, $p = 0.050$), which means that the CG experienced more difficulties to adequately track the target, resulting in more additional movements throughout the movement.

Table 3. Results for the hand movement parameters in each of the conditions (S1): EG – CG – HC

PARAMETER	EG (N = 6)	CG (N = 8)	HC (N = 8)	F-test	P-value
Discrete task					
Mean amplitude ballistic phase (0°-40°)	38.52 ± 2.14	37.64 ± 1.77	390.09 ± 1.23	1.457	0.258
Mean time ballistic phase (ms)	264.15 ± 68.14	277.23 ± 103.66	239.89 ± 61.84	0.434	0.654
Initial error (°)	− 1.37 ± 2.01	− 2.02 ± 1.35	− 0.85 ± 1.22	1.200	0.323
Endpoint error (°)	− 0.09 ± 0.19	− 0.09 ± 0.09	− 0.06 ± 0.09	0.201	0.819
Peak velocity (°/s)	143.36 ± 38.34	142.51 ± 58.11	152.31 ± 40.77	0.102	0.904
Time to peak velocity (%)	14.19 ± 1.66	16.96 ± 2.79	16.32 ± 3.31	1.826	0.188
Additional path length target phase (°)	1.73 ± 0.79	2.88 ± 2.00	1.52 ± 1.23	1.914	0.175
Zero crossings target phase (#)	2.13 ± 0.41	2.87 ± 1.83	2.54 ± 1.06	0.563	0.579
Cyclical task: linear					
Additional path length transport phase (°)	1.69 ± 1.49	1.40 ± 1.31	2.04 ± 1.96	0.316	0.733
Additional path length target phase (°)	− 1.02 ± 3.62	− 1.23 ± 2.36	− 0.20 ± 1.78	0.351	0.709
Additional path length total movement (°)	6.07 ± 3.65	6.66 ± 4.42	6.28 ± 3.07	0.046	0.956
Zero crossings transport phase (#)	1.43 ± 1.19	1.15 ± 0.64	1.26 ± 0.96	0.161	0.852
Zero crossings target phase (#)	2.03 ± 1.20	1.80 ± 0.58	1.66 ± 0.45	0.412	0.668
Cyclical task: sinusoidal					
Additional path length transport phase (°)	0.54 ± 0.55	0.77 ± 0.70	0.33 ± 0.50	1.136	0.342
Additional path length target phase (°)	0.93 ± 1.94	0.59 ± 2.23	0.49 ± 1.11	0.110	0.897
Additional path length total movement (°)	2.45 ± 1.67	3.61 ± 2.15	1.50 ± 0.70	3.450	0.053
Zero crossings transport phase (#)	0.72 ± 0.64	0.86 ± 0.65	0.49 ± 0.54	0.735	0.493
Zero crossings target phase (#)	1.94 ± 0.96	1.92 ± 0.62	1.73 ± 0.33	0.241	0.788

The comparison of all experimental hand movement parameters during pre- and post-intervention between the EG and CG is displayed in table 4. To start, the mean time of the ballistic phase of the discrete task ($p \leq 0.05$) was statistically significant between pre- and post-intervention assessment. Both groups improved their performance of the discrete task because they needed less time to travel the transport phase. Also, a statistically significant difference between groups was found for the Endpoint error in the discrete task ($p \leq 0.05$). This means that the EG differed from the CG over both sessions. Furthermore, the analysis of Peak velocity showed a significant main effect between pre- and post-intervention assessment ($p \leq 0.05$). The peak velocity of the hand of both groups in the post-intervention assessment was higher than during the initial evaluation. For all significant within or between differences, no interaction effect was found. A borderline statistical significant interaction effect of the Time to peak velocity ($F = 4.580$, $p = 0.054$) was found. Post hoc analyses verified that this difference was located between the EG and CG during the pre-intervention assessment ($\Delta = – 3.330$, $p = 0.065$).

Table 4. Hand movement parameters (S1 & S2): EG – CG

PARAMETER		PRE (S1)	POST (S2)	Within-groups (S1 – S2)		Between-groups (EG – CG)		Interaction	
Discrete task									
Mean amplitude ballistic phase (0°-40°)	**EG**	38.52 ± 2.14	39.06 ± 1.07	F = 1.494	p = 0.245	F = 1.030	p = 0.330	F = 0.002	p = 0.968
	CG	37.64 ± 1.77	38.14 ± 2.01						
Mean time ballistic phase (ms)	**EG**	264.15 ± 68.14	231.13 ± 75.23	F = 6.920	p = 0.022*	F = 0.232	p = 0.639	F = 1.049	p = 0.326
	CG	277.23 ± 103.66	262.72 ± 90.24						
Initial error (°)	**EG**	− 1.37 ± 2.01	− 1.08 ± 1.15	F = 0.682	p = 0.425	F = 0.693	p = 0.422	F = 0.000	p = 0.989
	CG	− 2.02 ± 1.35	− 1.72 ± 1.68						
Endpoint error (°)	**EG**	− 0.09 ± 0.19	0.13 ± 0.26	F = 0.673	p = 0.428	F = 5.661	p = 0.035*	F = 2.736	p = 0.124
	CG	− 0.09 ± 0.09	− 0.16 ± 0.24						
Peak velocity (°/s)	**EG**	143.36 ± 38.34	169.06 ± 53.64	F = 4.990	p = 0.045*	F = 0.167	p = 0.690	F = 2.023	p = 0.180
	CG	142.51 ± 58.11	148.21 ± 48.69						
Time to peak velocity (%)	**EG**	14.19 ± 1.66	19.19 ± 2.94	F = 0.142	p = 0.713	F = 2.025	p = 0.180	F = 4.580	p = 0.054
	CG	16.96 ± 2.79	20.05 ± 2.71						
Additional path length target phase (°)	**EG**	1.73 ± 0.79	3.16 ± 2.30	F = 0.899	p = 0.362	F = 0.103	p = 0.754	F = 2.898	p = 0.114
	CG	2.88 ± 2.00	2.48 ± 1.21						
Zero crossings target phase (#)	**EG**	2.13 ± 0.41	3.19 ± 1.49	F = 3.557	p = 0.084	F = 0.259	p = 0.620	F = 1.076	p = 0.320
	CG	2.87 ± 1.83	3.18 ± 1.64						
Cyclical task: linear									
Additional path length transport phase (°)	**EG**	1.69 ± 1.49	1.48 ± 1.98	F = 0.002	p = 0.969	F = 0.015	p = 0.905	F = 0.171	p = 0.686
	CG	1.40 ± 1.31	1.58 ± 1.83						
Additional path length target phase (°)	**EG**	− 1.02 ± 3.62	− 0.10 ± 4.03	F = 0.846	p = 0.376	F = 0.002	p = 0.968	F = 0.022	p = 0.885
	CG	− 1.23 ± 2.36	0.03 ± 1.76						
Additional path length total movement (°)	**EG**	6.07 ± 3.65	5.64 ± 5.32	F = 0.141	p = 0.714	F = 0.286	p = 0.603	F = 0.662	p = 0.432
	CG	6.66 ± 4.42	7.82 ± 6.40						
Zero crossings transport phase (#)	**EG**	1.43 ± 1.19	1.74 ± 2.17	F = 0.675	p = 0.427	F = 0.318	p = 0.583	F = 0.037	p = 0.850
	CG	1.15 ± 0.64	1.33 ± 0.78						
Zero crossings target phase (#)	**EG**	2.03 ± 1.20	2.38 ± 1.97	F = 0.335	p = 0.573	F = 0.639	p = 0.440	F = 1.298	p = 0.277
	CG	1.80 ± 0.58	1.69 ± 0.44						

Cyclical task: sinusoidal		**PRE (S1)**	**POST (S2)**	**Within-groups (S1 – S2)**		**Between-groups (EG – CG)**		**Interaction**	
Additional path length transport phase (°)	**EG**	0.54 ± 0.55	0.47 ± 0.70	F = 1.257	p = 0.284	F = 0.216	p = 0.651	F = 0.380	p = 0.549
	CG	0.77 ± 0.70	0.52 ± 0.52						
Additional path length target phase (°)	**EG**	0.93 ± 1.94	1.90 ± 5.00	F = 0.117	p = 0.738	F = 0.758	p = 0.401	F = 0.264	p = 0.616
	CG	0.59 ± 2.23	0.39 ± 1.69						
Additional path length total movement (°)	**EG**	2.45 ± 1.67	3.05 ± 4.43	F = 0.119	p = 0.736	F = 0.074	p = 0.790	F = 1.676	p = 0.220
	CG	3.61 ± 2.15	2.55 ± 1.89						
Zero crossings transport phase (#)	**EG**	0.72 ± 0.64	0.60 ± 0.78	F = 2.124	p = 0.171	F = 0.117	p = 0.738	F = 0.013	p = 0.910
	CG	0.86 ± 0.65	0.71 ± 0.64						
Zero crossings target phase (#)	**EG**	1.94 ± 0.96	2.56 ± 1.99	F = 1.685	p = 0.219	F = 0.285	p = 0.603	F = 0.845	p = 0.376
	CG	1.92 ± 0.62	2.02 ± 0.53						

The pre- vs. post-training measurements of all clinical tests for each of the conditions are summarised in table 5. The within-group analyses resulted in a significant difference for the ORT ($p \leq 0.05$) and the ABC ($p \leq 0.05$). Both groups scored lower on the ORT and had a higher score on the ABC post-intervention, which corresponded with an improvement on both parameters. However, no interaction effect was found for these two questionnaires. Additionally, an interaction effect was detected for the FRT ($p \leq 0.05$). The post hoc analysis validated a decrease in performance of the EG on the FRT in the post-intervention assessment ($\Delta = -4.292$, $p \leq 0.05$).

Table 5. Clinical tests and questionnaires (S1 & S2): EG – CG

		PRE (S1)	POST (S2)	Within		Between		Interaction	
BBT (# of blocks)	**EG**	44.43 ± 11.57	42.93 ± 10.37	F = 1.887	p = 0.203	F = 0.009	p = 0.928	F = 1.589	p = 0.239
	CG	43.63 ± 8.98	44.63 ± 7.73						
NHPT (s)	**EG**	44.15 ± 41.68	41.48 ± 29.85	F = 1.887	p = 0.203	F = 0.901	p = 0.367	F = 0.109	p = 0.749
	CG	38.35 ± 25.03	36.92 ± 20.58						
FRT (cm)	**EG**	33.68 ± 6.13	29.36 ± 7.50	F = 1.019	p = 0.339	F = 0.009	p = 0.928	F = 5.760	p = 0.040*
	CG	29.01 ± 7.54	30.75 ± 9.15						
T25FW (s)	**EG**	6.24 ± 1.76	6.68 ± 1.67	F = 4.970	p = 0.053	F = 0.165	p = 0.694	F = 0.285	p = 0.606
	CG	6.84 ± 3.83	7.56 ± 4.39						
HAI (0 - 9)	**EG**	2.50 ± 1.23	2.67 ± 1.03	F = 0.818	p = 0.389	F = 0.190	p = 0.673	F = 0.818	p = 0.389
	CG	2.20 ± 1.79	2.20 ± 1.79						
SDMT (# of correct answers)	**EG**	43.57 ± 10.21	46.43 ± 10.95	F = 1.375	p = 0.271	F = 0.099	p = 0.760	F = 1.053	p = 0.332
	CG	42.88 ± 13.45	41.75 ± 14.23						
SARA balance: item 1-3 (0 - 18)	**EG**	5.29 ± 1.11	5.57 ± 1.51	F = 0.117	p = 0.740	F = 1.948	p = 0.196	F = 0.117	p = 0.740
	CG	6.13 ± 4.09	5.75 ± 4.23						
SARA total (0 - 40)	**EG**	10.14 ± 2.72	9.64 ± 3.50	F = 0.472	p = 0.509	F = 0.459	p = 0.515	F = 0.029	p = 0.867
	CG	11.31 ± 6.07	10.44 ± 6.56						
ORT (0 - 15)	**EG**	3.71 ± 1.38	2.93 ± 2.01	F = 9.378	p = 0.014*	F = 0.007	p = 0.934	F = 3.007	p = 0.117
	CG	3.38 ± 0.95	2.88 ± 1.36						
MSWS-12 (12 - 60)	**EG**	51.00 ± 7.26	47.57 ± 8.02	F = 0.229	p = 0.642	F = 1.888	p = 0.197	F = 0.561	p = 0.469
	CG	41.12 ± 16.57	41.88 ± 11.67						
ABC (%)	**EG**	46.25 ± 19.02	66.15 ± 19.86	F = 7.700	p = 0.018*	F = 0.001	p = 0.978	F = 0.089	p = 0.771
	CG	43.28 ± 30.12	60.65 ± 32.78						
MAM-36 (36 - 144)	**EG**	111.33 ± 32.10	115.86 ± 22.62	F = 1.911	p = 0.194	F = 0.847	p = 0.377	F = 1.336	p = 0.272
	CG	127.87 ± 12.67	128.50 ± 16.48						
IVIS (0 - 15)	**EG**	2.86 ± 3.08	2.86 ± 2.79	F = 0.887	p = 0.366	F = 0.402	p = 0.539	F = 1.594	p = 0.233
	CG	3.75 ± 3.65	2.38 ± 3.58						
MSIS-29 (29 - 145)	**EG**	87.71 ± 22.63	84.00 ± 19.43	F = 0.216	p = 0.651	F = 0.746	p = 0.406	F = 0.216	p = 0.651
	CG	72.50 ± 19.03	72.50 ± 28.81						
MFIS (0 - 84)	**EG**	42.43 ± 24.51	47.00 ± 19.43	F = 0.001	p = 0.980	F = 0.481	p = 0.502	F = 1.586	p = 0.234
	CG	47.25 ± 9.11	39.38 ± 26.37						
VAS pain (0 - 10)	**EG**	4.43 ± 3.46	4.29 ± 3.68	F = 0.123	p = 0.732	F = 0.095	p = 0.764	F = 0.287	p = 0.603
	CG	3.62 ± 3.25	3.75 ± 3.33						

5 Discussion

In this pilot study, a 4 week home-based OMT program was conducted to investigate whether or not training of eye movements could enhance visually guided step-tracking movements in individuals with progressive pwMS. To the best of our knowledge, this study was the first to investigate OMT in pwMS.

First, we take a closer look at the results of the statistical analysis. Genuine differences were present between pwMS and HC in all general clinical tests, which were assessed at baseline, except for the NHPT. Despite an expected difference in manual dexterity could not be detected, the mean value showed that pwMS needed more time to perform the test than HC. Perhaps a larger sample size would result in a significant difference. Given that anthropometrics did not differ significantly, it could be concluded that for each pwMS, a corresponding healthy individual was found. Consequently, selection criteria were formulated and applied accurately. The comparison of the pre-intervention assessments between EG and CG, by means of anthropometric characteristics and clinical tests, was not significantly different, with the exception of the INAS and the SWM of the feet. The EG had more non-ataxia signs (spasticity, paresis) and showed more sensory deficits on the foot than the CG. However, these two differences were considered not decisive for the results since the INAS and SWM test were exclusively used to see whether the EG and CG were comparable and did not serve as a post-intervention measurement. In conclusion, a well-performed randomisation of the pwMS in the EG and CG was obtained. With groups being homogenous, potential significant differences and improvements were assumed to be attributable to the intervention. Despite the expectation that pwMS had marked visual and locomotor deficits, no significant differences in hand movement parameters could be detected between pwMS and HC at baseline. A borderline significant interaction effect was found for the additional path length of the total movement during the sinusoidal cyclical task, meaning that the CG experienced more difficulties to adequately track the target than the HC. This could be a result of tremor and/or problems with eye-hand coordination. Because group differences could not be detected in a consistent way across various parameters, it should be noted that pwMS were included based on signs of ataxia (SARA of ≥ 4/40) and on detectable oculomotor deficits of cerebellar origin, not on arm movement dysfunction.

Although cerebellar ataxia could affect the arm movements, no values of the arm function were used for inclusion criteria. Therefore, the risk of a “too good“ hand function could not be excluded.

The comparison of pre- and post-intervention assessment between EG and CG of the experimental parameters of the hand movement revealed a borderline significant interaction for time to peak velocity. Post hoc testing verified a difference between the EG and CG during pre-intervention assessment, whereby the EG reached their peak velocity faster in the primary submovement than the CG. This means that the EG needed more time for corrective movements in the target phase corresponding to less control. However, the EG did no longer differ from the CG post intervention and therefore it could be concluded that the EG gained control due to training. The pre- vs. post-training measurements between EG and CG of all clinical tests revealed one significant interaction effect for FRT. When exploring this effect, a decrease in balance was suggested as the EG could reach significantly less far during the post-intervention compared to the initial assessment session.

A few limitations of this study have to be considered. First of all, expected differences in the results of the goal-directed aiming tasks between the EG, CG and HC could not be detected at baseline. It could be disputed whether or not these experimentally developed tests were sensitive enough to detect baseline and consequently short-term improvements in eye-hand coordination. It is also possible that there were more trials necessary to detect significant differences. However, the included sample size might have been too small to detect minimal clinically important differences in general. It had to be acknowledged that it was difficult to recruit a large number of pwMS who met the proposed selection criteria. Secondly, it was chosen not to use EOG data in this dissertation because of quality issues with the data and complex processing was needed. Reduced quality might have been the result of problems with the attachment of the electrodes as well as the occasionally poor connection between the laptop and the BlueGain device. For this reason, any objective enhancement in oculomotor control could not be confirmed. Crowdy et al. (2000), who made use of the EOG method in combination with reflectometry infrared, also reported issues to extract information from the data of the EOG. They decided to use these data only to verify the saccade identification detected with infrared. Recently, Stevenson, Jung, & Cauwenberghs

(2015) demonstrated that the EOG method is an inexpensive and proper way to assess eye movements. They did not report any difficulties and proposed the EOG method as a potential new approach for eye tracking movements. Unlike the experimental set-up in this study, they measured both eyes and made use of a known target stimulus moving in three-dimensional space to estimate eye movement direction and fixation depth. Moreover, they highlighted EOG as inexpensive, non-invasive and insensitive to environmental light. Since this dissertation did not use a known target stimulus moving in three-dimensional space, EOG data processing would only provide information for timing of saccades and not for spatial parameters. Although the assumption of an effective transfer from improved eye movements to the motor system could not be endorsed in the current study, Crowdy et al. (2002) showed that oculomotor and locomotor performance was improvable by eye movement rehearsal alone. In the study of Crowdy et al. (2002), eye movement rehearsal consisted of saccadic eye fixation on the irregularly placed stepping stones without performing the walking task. Therefore, the rehearsed eye movements were relatively task-specific. Additionally, they tested the participants immediately after the rehearsal. Assuming that the locus of improvement was cerebellar, some studies reported that improvements might be task-specific and rather short-lived (Martin, Keating, Goodkin, Bastian, & Thach, 1996a, 1996b; Thach, 1992)**.** The post-intervention assessment in this study was performed within four days after the last training. Despite the rather short time between training and post-intervention assessment, no improvements could be reported. Perhaps the applied intervention in the current study was not task-specific enough to detect enhancements in the experimentally developed tests.

In general, little knowledge and guidelines about an optimal OMT program is available. This study consisted of a 4 week home-based OMT of daily 15 minutes exercising. Some remarks about the proposed protocol could be made. To start, this study strived for high repetition of training, as the participants were requested to practise every day. Consequently, possible incidence of exercise-related fatigue on the outcomes was not taken into account. When participants indicated fatigue-related problems, they were authorised to split the training of 15 minutes into blocks of 5 minutes. This way, participants were more stimulated and motivated to continue training. The study of Bunn, Marsden, Giunti, & Day (2015) showed

that high intensity of training could be maintained without interfering individual lifestyles, by providing two rest days every week. Even though participants were asked to train for only 15 minutes per day, it could be questioned whether participants felt encumbered. This might have had a negative influence on compliance. Secondly, both this training protocol as well as those of Bunn, Marsden, Giunti, & Day (2015) had a duration of four weeks, resulting in no significant improvements. Perhaps this training period was too short to culminate statistically detectable improvements.

Therefore, it could be useful to compare other OMT programs concerning intensity and duration. The study of Bunn, Marsden, Giunti, & Day (2015) used a more or less similar intervention in patients with a pure cerebellar dysfunction. Balance tasks combined with OMT were practised 15 minutes per day, 5 times per week during 4 weeks. Although a tendency towards improvement was established by use of self-reports, no objective improvements could be documented. Also, Zampieri & Di Fabio (2009) investigated the effect of balance training with or without supplementary eye movements and visual awareness exercises. Participants received 3 training sessions of one hour weekly during 4 weeks. Post-intervention measurements suggested a better gaze control in the group that received balance training in combination with OMT. The study of Kapoor et al. (2004) applied a slightly different approach of OMT, as the two participants with acquired brain injury trained twice a week for 60 minutes, with 36 minutes of actually performing versional and reading-related eye movements. After 8 weeks of training, an improvement of ocular motility was objectively detected. However, it could be questioned whether the protocols used in previous studies could be generalised to pwMS. Moreover, since there was a great variability in the applied interventions, a lack of an unambiguous training protocol could be suggested. Further research in determining adequate guidelines for OMT in general as well as for pwMS in particular, is desirable.

A home-based OMT program provided a very easy and accessible way to improve eye movements, as the participants were not obligated to visit the research centre daily. On the other hand, it was more challenging to remain control of adherence. In the beginning of the intervention, a member of the research team went through all exercises together with each participant of the EG. A weekly telephone follow-up was made to resolve any difficulties and

participants were able to contact us at any time. Despite these efforts to enlarge control, this study design relied mainly on the integrity of the participants. Therefore, it might be designated to research the effect of supervised OMT first in future studies. As demonstrated in the study of Bunn, Marsden, Giunti, & Day (2015), a daily diary could easily enhance compliance. This could be a useful addition in future home-based studies to enlarge control.

Further, the standardisation of the intervention had to be considered. Although there was a training booklet composed with progressive exercises, participants were allowed to adjust the settings of the applications to their own level. In addition, participants were authorised to divide the training during the day. These adaptations might have been at expense of the standardisation.

Some final remarks about the test set-up should be mentioned, specifically a one-dimensional wrist orthosis and a simple chin-rest were used. The choice of the equipment was based on former literature (Feys et al., 2005; Feys, Helsen, Buekers, et al., 2006; Feys, Helsen, Verschueren, et al., 2006; Van Halewyck, Helsen, Elliott, & Levin, 2014). Because of these instruments, a simplification of an aiming movement was performed. It had to be acknowledged that this simplification might have had an influence on the external validity. On the other hand, this simplification ensures that parameters can be easily compared. Moreover, this set-up was only used for the pre- and post-intervention assessment. Since the intervention consisted of more natural and functional movement tasks, possible improvements were considered to be more generalizable to ADL.

The cost-effectiveness of this study has to be acknowledged as an important strength. Despite the rather extensive test battery, contact time was limited due to the home-based training design. Although rather expensive equipment was utilised for the intervention, costs were minimised by simultaneously training four participants whereupon equipment could be reused. Secondly, it had to be highlighted that there were no dropouts in this study. Even though more control was designated to reassure compliance, participants did not report any difficulties or disturbing factors during the training period.

As stated before, several suggestions for future research can be proposed. First of all, more knowledge has to be gathered about the optimal duration and intensity of OMT in general

and for pwMS in particular. Another general concern in this domain is the content of the intervention. More specifically, task-specificity has to be established in future research. Also, more studies that evaluate the validity, reliability and usability of eye-tracking devices as well as investigating other approaches or developing instruments for measuring both eye and hand movements concurrently, are desirable.

Unfortunately, this pilot study was not able to confirm our main hypothesis. The small sample size could be the key limiting factor in obtaining positive results. However, there was found one borderline significant training-effect for Time to peak velocity, which suggested that the EG gained more control following the intervention. Important to note is that the current dissertation is part of a larger project in collaboration with the university of Plymouth; the OPTIMEYES-project. The overall project, included a larger sample size of 28 people with progressive MS. This way, the likelihood to find significant results is expected to be greater. Furthermore, the overall study implemented extra data concerning balance activities and gait, and analysed the EOG data too. This could give more insight into the interaction between eye and hand movements and the extrapolation of eye movement improvements to other functional tasks.

Since more and more studies highlight the negative impact of eye movement deficits on locomotor functioning, one could suggest that training and improving eye movements is the key element to improve aiming movements. The present pilot study has provided a first impression of how OMT could be designed in the future. The use of an iPad could be a very easy, accessible and non-invasive way to improve functionality. Since this training protocol fits well in the current high-tech society, this OMT program could be easily added to general rehabilitation programs. A good eye-hand coordination is essential in performing numerous activities of daily living (e.g. reaching for a glass of water). Consequently, this training intervention might potentially have a greater impact on quality of life in pwMS than shown in this pilot study.

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