

Available online at www.sciencedirect.com**ScienceDirect**Journal homepage: www.elsevier.com/locate/cortex**Research Report****Efficacy and predictors of recovery of function after eye movement training in 296 hemianopic patients****Arash Sahraie^{a,*}, A. Matilda H. Cederblad^a, Sigrid Kenkel^b and Jose G. Romano^c**^a School of Psychology, University of Aberdeen, UK^b NovaVision GmbH, Magdeburg, Germany^c Department of Neurology, University of Miami Miller School of Medicine, USA

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ABSTRACT

Compensatory approaches to rehabilitation of vision loss as a result of brain injury are aimed at improving the efficacy of eye movements, enabling patients to bring the otherwise unseen stimuli into their sighted field. Eye movement training has shown promise in a large number of studies in small clinical populations. Nevertheless, there remain two problems; standardisation and wide accessibility. NeuroEyeCoach™ (NEC) has been developed to address both. The therapy is based on the visual search approach and is adaptive to the patient's level of disability and the task difficulty is varied systematically through a combination of set-size and target/distractor similarity. Importantly, the therapy can be accessed online or in clinical settings, to enhance accessibility. Here we have reported on the findings from the first 296 consecutive cases who have accessed and completed NEC online, the largest cohort of patients studied to date. Patients' performance on two objective (visual search times and errors) and one subjective (self-reported disability) measures of performance were assessed before and after therapy. The findings showed that patients improved in search time, had less errors and improved disability scores in 87% (255/294), 80% (236/294) and 66% (167/254) of all cases respectively. We examined factors age, sex, side of blindness, age at the onset of brain injury, and time elapsed between the brain injury and start of therapy as predictors of both objective and subjective measures of improvements. Age was a significant predictor of improved search errors with older patients showing larger improvements. Time between brain injury and intervention negatively influenced search reaction time, however, none of the factors could predict improved subjective reports of disability.

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Abbreviations: RT, Visual search reaction times; ER, Number of Errors; DS, self-reported disability score; NEC, NeuroEyeCoach™.

* Corresponding author. School of Psychology, William Guild Building, King's College Campus, University of Aberdeen, Aberdeen, AB24 3FX, UK.

E-mail address: a.sahraie@abdn.ac.uk (A. Sahraie).

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1. Introduction

Areas of blindness in the visual field could arise as a result of lesions along the visual pathways. Stroke is the main cause of brain injury, although trauma and elective surgery may also affect the visual pathways. There is a high incidence (60%) of visual impairments in stroke survivors (Rowe, Hepworth, Hanna, & Howard, 2016), with as many as half of those have been reported to have visual field loss (Fujino, Kigazawa, & Yamada, 1986; Zhang, Kedar, Lynn, Newman, & Biousse, 2006a). In post chiasmatic lesions, the resultant blindness is similar in extent within the same hemifield in both eyes, hence referred to as homonymous. Homonymous hemianopia is therefore blindness covering the entire one hemifield in both eyes.

The leading causes of sight loss such as age-related macular degeneration, cataracts, diabetic retinopathy and glaucoma, characteristically affect an individual over an extended period of time typically ranging from weeks to years (Groeneveld, Tavenier, Blom, & Polak, 2019; Rudnicka et al., 2015). Although the blindness is debilitating, there is scope for a period of adjustments to the gradual visual impairment. Sight loss due to brain injury on the other hand is sudden and often occurs over few hours and without prior warning. Some spontaneous recovery may take place in the acute stage of injury, but the probability of recovery diminishes rapidly with time and very little recovery of sight is expected 3–6 months post injury (de Haan, Heutink, Melis-Dankers, Tucha, & Brouwer, 2014; Zhang, Kedar, Lynn, Newman, & Biousse, 2006b).

There are three main approaches to rehabilitation of hemianopic patients, namely substitution, restitution or compensatory approaches. Substitution refers to methods where the damaged field is imaged onto a portion of the sighted field using spectacle prisms to enable patients to see the otherwise undetected objects (Bowers, Keeney, & Peli, 2008). The method can expand the field of vision, nevertheless a number of studies have shown low compliance (Bowers et al., 2008; Bowers, Keeney, & Peli, 2014). This may in parts be due to the reported difficulties that patients experience with the required shifts in attention and the distraction caused by rival information in the two eyes (Raz & Levin, 2017). Also, the benefits are of course contingent upon the use of optical devices. Hence the substitution techniques have not been widely adopted in clinical practice.

Restitution techniques are aimed at improving the visual sensitivity within the field defect. Post-geniculate lesions along the optic radiation and early cortical processing may lead to lack of conscious visual experience. However, there are numerous projections of visual information to subcortical and cortical sites that by-pass the usual retinogeniculo-striate route (Cowey, 2004; Sahraie & Treveltham, 2014). The premise of restitution techniques relies on the residual capabilities of the remaining pathways enhanced through perceptual learning. That is, with repeated stimulation over an extended period of time, learning can take place. Thus, associating visual stimulation with residual neuronal activity (Huxlin, 2008; Sahraie, 2007). The fact that neuronal activity associated with visual stimuli, confined to the blind visual fields, can influence behaviour in forced-

choice paradigms and in the absence of conscious perception is well established and is termed blindsight (Weiskrantz, 1986). Whilst there is an absence of any conscious experience in type I blindsight, some rudimentary awareness may be experienced in type II blindsight, often reported as a feeling that a visual event had taken place (Weiskrantz, 1998). Conscious visual experience lies on a continuous spectrum and systematic and repeated stimulation can lead behavioural performance from no detection ability to blindsight type I, type II, and eventually conscious vision (Sahraie, Treveltham, Macleod, Weiskrantz, & Hunt, 2013). Over the past two decades, a number of restitution techniques based on systematic stimulation have been developed. These include utilising repeated stimulation of the light flux channel in Vision Restoration Therapy (Kasten & Sabel, 1995; Poggel, Mueller-Oehring, Kasten, Bunzenthal, & Sabel, 2008; Romano, Schulz, Kenkel, & Todd, 2008). Active stimulation of motion sensitivity (Huxlin et al., 2009), spatial vision (Sahraie et al., 2006) and flicker sensitivity (Raninen, Vanni, Hyvärinen, & Näsänen, 2007) have also been used in restoration approaches. The time commitment for patients using restitution techniques is significant, often requiring adherence to the daily use of an intervention over a number of months.

Compensatory techniques rely on the patient's intact visual field for processing the otherwise unseen stimuli, by using eye movements to bring their image onto the intact field. Although such compensatory approach is intuitive, spontaneous adaptation and development of an effective eye movement pattern is seen in only 40% of hemianopic patients (Zihl, 1995) and the majority of cases shows inefficient eye movements years after the injury. The pattern of eye movements in affected cases can be characterised as having smaller amplitude saccades, leading to requiring a larger number of eye movements to explore a given portion of the field, hence slowing down in time to explore and identify targets within the field defect (Zihl, 2011). There is also a more disorganised search strategy in that patients make more frequent between hemifield saccades. Disturbances of eye movement patterns extend to both sighted and blind hemifields (Chokron, Perez, & Peyrin, 2016; Zihl, 1995; Zihl & Hebel, 1997). In a pioneering study (Zihl, 1988), demonstrated that hemianopic patients that undertook a visual search training (involving detection of a target item amongst distractors) had improved search times. These studies were extended by the use of computerised visual search paradigms in the same lab (Zihl, 1995, 2011) as well as others (Kerkhoff, Münßinger, Haaf, Eberle-Strauss, & Stögerer, 1992; Mannan, Pambakian, & Kennard, 2010; Nelles et al., 2009, 2001; Pambakian, Mannan, Hodgson, & Kennard, 2004; Roth et al., 2009); showing an overall improvement in detection time, a reduced scanpath and a smaller number of fixations prior to target detection (for a review see Sahraie, Smania, & Zihl, 2016). It is important to note that the improvements following compensatory therapies are domain specific. For example, reading disorders are also common following stroke and online therapies such as Read-Right (Ong et al., 2012; Woodhead, Ong, & Leff, 2015) can lead to improvements in reading abilities. However, performance improvements following specific training for eye movement scanning

behaviour and those for reading do not transfer (Schuett, Heywood, Kentridge, Dauner, & Zihl, 2012).

As eye movements play a crucial role in visual perception and in the interaction of an individual with their environment, it is assumed that improved eye movement efficiency could lead to a reduction in self-reported level of disability. Indeed, assessment of improvements in self-reported ratings of perceived disability, introduced by (Nelles et al., 2001) has been implemented and extended in a number of studies (Aimola et al., 2014; Lane, Smith, Ellison, & Schenk, 2010; Mannan et al., 2010; Pambakian et al., 2004). Evaluation of the functional improvement in quality of life and interaction with the environment after visual rehabilitation interventions has not been carried out in any large scale studies to date, and the reported subjective ratings in Activities of Daily Living (ADL) questionnaires remain the most widespread method for such assessments.

Recent systematic reviews of the evidence for the effects of visual rehabilitation interventions (Pollock et al., 2011, 2019) have suggested eye movement training to be the most promising approach to vision rehabilitation in stroke patients. There are however, two major issues that needs to be addressed if any eye movement-based intervention is to become the standard care. These include standardisation of approach and ease of access (Pollock et al., 2019). In a collaborative approach Sahraie et al. (2016) reported on development of NeuroEyeCoach™ (NEC), an eye movement intervention that was based on the original visual search task that had shown to be effective in improving search performance in hemianopia (Zihl, 1995) (also described below). NEC is a Class I CE marked medical device in the EU and is registered as an FDA 510(K) exempt medical device in the US. For the patient sample described in this paper, the cost of accessing NEC was approximately \$400US. The intervention was self-administered with in-built algorithms to adapt to the patient's level of disability and systematically train the affected individual to make effective eye movements. In addition, the intervention was deliverable over the internet, thus it could be accessed at home or in clinical settings. To further illustrate the stages involved in NEC, a demo version can be accessed here (<https://novavision.com/download-neuroeyecoach-demo/>).

Here, we report for the first time, on changes in performance of a large group of hemianopic patients who undertook NEC outside a clinic environment. We have obtained pre- and post-intervention self-reported assessment of ADL (referred to as disability score DS) as well as reaction time (RT) and errors (ER) on a specific search task. Improvements in RT, ER and DS have been analysed in relation to age, sex, side of blindness, age at the onset of brain injury, and time elapsed between the brain injury and start of therapy.

2. Materials and methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Participants

As NEC is web deliverable, patients directly accessed the therapy via internet. Patients' performance on pre- and post-intervention as well as results of their daily completion of therapy stages was automatically logged on a database. NEC database was accessed on 29th November 2018 and a comprehensive data download to that timepoint was obtained by staff at NovaVision Inc. The anonymised dataset was then made available to the authors, comprising of 296 (85F, 211M) consecutive cases that had completed the therapy. Patients were self-declared survivors of stroke or other brain injury; hence no access was possible to their clinical notes or brain scans. As a condition of ethical permission, we received limited patient identifier data and were provided with age at brain injury, date of injury, months elapsed between birth and injury onset and days elapsed between therapy start and injury onset, for each patient. There was a wide range for age at the onset of brain injury (range 9.82–89.83 years, $M = 54.42$, $SD = 17.76$), time elapsed between brain injury and start of NEC (range .03–43.08 years, $M = 1.84$, $SD = 3.78$) and age at the start of NEC (range 13.08–90.95, $M = 56.26$, $SD = 17.06$).

Patients also self-declared whether the blindness only affected their left, right or both visual fields. Out of 296 cases, there were 103 and 101 cases with left and right visual field loss respectively and 92 cases reported visual loss on both fields.

The ethical permissions were obtained for the retrospective analysis of de-identified data from University of Miami Institutional Review Board (IRB), USA as well as Psychology Ethics Committee, University of Aberdeen, UK.

2.2. Intervention

Intervention was performed with NEC and accessed online by patients. A full description of NEC has been outlined elsewhere (Sahraie et al., 2016). Commercial legal barriers prevent us from archiving the NeuroEyeCoach software and digital materials in a public repository. Readers seeking to replicate the procedures that produced the current dataset would need to purchase the software from the vendor (www.novavision.com). In brief, during the installation process screen resolution and dimensions are determined and a viewing distance is recommended to ensure a minimum of $\pm 20^\circ$ of visual angle in horizontal extent. Patients are encouraged to use both eye and head movement throughout, therefore no head stabilisation is required. All visual target dimensions are also systematically set to ensure clear visibility. NEC contains 12 levels, with 4 levels at each of pop-out, complex, and conjunction search categories, hence the task difficulty is systematically increased as therapy progresses. For each level, there are three sub-levels where set sizes are set to 8, 16 and 24 to obtain an additional way of manipulating task difficulty. Examples of pop-out search include searching for either a T or an X amongst Os; or an H amongst Cs. Complex searches include searching for an S amongst Cs; an O amongst Gs; or a B amongst Ds. Both target shape and colour are altered in conjunction searches (searching for green X, amongst blue Xs and green Rs; a green b amongst blue bs and green ps; or a green T amongst blue Ts and green upside-down Ts). Target

and distractors are equally distributed on the left and right half and the upper and lower parts of the screen. In order to reduce the cognitive load for the intervention, we have reduced the need to memorise the searched for target by always showing an example within an orange circle in the middle of the screen. As patients mainly access NEC at home settings, we have developed an algorithm to manipulate the task difficulty to ensure a systematic criterion for progression to the next level. Each sub-level contains 200 trials (100 target present and 100 target-absent trials) and having completed 3 sub-levels the progression to the next level is contingent upon achieving 80% or higher in accuracy in at least 2 of the 3 sublevels. The patient's task was to indicate whether or not a specific target was present by pressing one of two mouse buttons. The time allowed for each trial was limited (1500 msec) but increased by 500 msec, if a level had to be repeated (i.e., performance below 80% correct in 2 sublevels). Again, to reduce the cognitive demand, if a patient failed to achieve the 80% accuracy threshold in at least two sub-levels for the second time, they were provided with unlimited response time. To minimise fatigue, after completion of a sub-level patients were advised to take a break before continuing with the therapy. Patients were recommended to undertake visual training regularly with up to 3 episodes of 15 min training per day and for at least 5 days per week. Most patients completed the therapy in relatively short duration ($N = 296$, Median = 23 days, $M = 40$ days, $SD = 49$) such that half the participants managed to complete the intervention in approximately 3 weeks, with nearly $\frac{3}{4}$ of patients completing in 6 weeks.

2.3. Pre- and post-intervention assessments

To assess the effect of NeuroEyeCoach™, reaction time and accuracy in a visual search task as well as subjective ratings for an activity of daily living questionnaire was obtained before and after the therapy. The search task consisted of a practice session of 10 trials where the presence or absence of a black O amongst black Ts and Ls was reported using either of two mouse buttons. They then completed 4 blocks of 20 trials at set-sizes of 4, 8, 16, and 24 objects. The pre- and post-therapy reaction time was calculated as the mean of the median reaction times from all 4 blocks. The errors across all 4 blocks were summed to obtain pre- and post-therapy errors. Patients also reported their perceived disability on a 5-point scale for performing various activities of daily living. The nine questions were difficulties seeing obstacles; bumping into obstacles; losing their way; finding objects on a table; finding objects in a room; finding objects in a supermarket; crossing the road; using public transport; or using a computer. The rating scale ranged from no difficulty at all, to having occasional, sometime, often, or severe difficulties. Patients performed all the assessment tasks once again after completing the NeuroEyeCoach™.

2.4. Analysis plan and data access

Prior to the application for ethical approval for this study, a detailed plan of the analysis to be conducted was developed. This plan was saved to the wiki entry for the project on Open

Science Framework on 2018-11-08 (Sahraie & Cederblad, 2018). The wiki for this project "Analysis of NeuroEyeCoach data", can be found through this link: <https://osf.io/2hvdv/wiki/home/> and constitutes the totality of the pre-registration (Sahraie & Cederblad, 2018).

Pre-registration was completed without access to data and the only included analysis that were not part of pre-registration is highlighted below and labelled as an exploratory analysis. Data reported here is also available and can be accessed on Open Science Framework (Sahraie & Cederblad, 2018).

3. Results

3.1. Reaction time and errors in visual search

Two patients' datasets were partially corrupted, leading to missing cells for reaction time and errors and hence were excluded from this analysis, leaving 294 cases (85F, 209M) who had completed both pre- and post-therapy visual search tasks. The group mean for reaction time at post-therapy ($M = .977s$, $SD = .25$) was significantly shorter than at pre-therapy ($M = 1.162s$, $SD = .24$) (difference $M = .185$, $SD = .22$, $t(293) = 14.305$, $p < .001$, Cohen's $d = .834$). A scatter plot of post-vs. pre-therapy RT is shown in Fig. 1A. 87% of the cases (255/294) fell below the equal performance line indicating that the majority of patients had improved reaction times after completing the therapy compared to their baseline performance. Fig. 1B shows the overall reaction time data, broken down to those from 4 different visual search set-sizes and plotted for pre- and post-therapy for targets appearing in the sighted and blind field separately. The effect of training on RT in visual search task was analysed for blind and sighted fields in those subset of patients that reported unilateral sight loss only, using a $2 \times 4 \times 2$ repeated measure ANOVA with a within subject factor Training (2 levels: pre- and post-), Set size (4 levels: 4, 8, 16 & 24), and Hemifield (2 levels: sighted and blind). There were significant main effects of Training [$F(1,180) = 195.2$, $p < .001$, $\eta^2 = .52$], Set size [$F(3,540) = 57.8$, $p < .001$, $\eta^2 = .243$] and Hemifield [$F(1,180) = 108$, $p < .001$, $\eta^2 = .375$]. The interaction of Hemifield x Training did not reach significance [$F(1,180) = 3.27$, $p = .072$, $\eta^2 = .018$]. This further demonstrates that patients improved for target presentations in both sighted and blind field and that the improvements observed were not due to them performing faster only in their sighted field. It is of interest to point out that following training, the group data shows that their blind field performance reached those of their sighted field at the pre-therapy stage.

The accumulated errors during post-therapy search times were also significantly smaller ($M = 2.017$, $SD = 2.67$) than those at the pre-therapy ($M = 4.024$, $SD = 4.68$) [difference $M = 2.007$, $SD = 4.297$, $t(293) = 8.008$, $p < .001$, Cohen's $d = .467$]. The scatter plot of pre-post-therapy errors (Fig. 2A) shows that 80% of patients (236/294) had a smaller number of errors in the search task at post-vs. pre-therapy. To further investigate the relationship between errors and side of presentations, for those cases where the blindness was restricted to either left or the right hemifield, the average number of errors made during

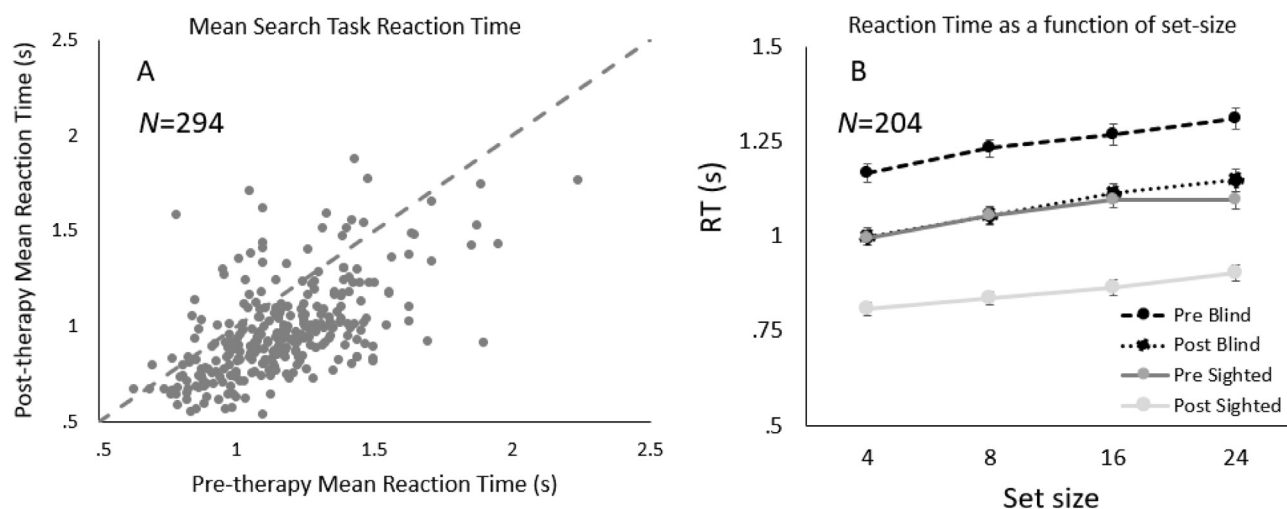


Fig. 1 – Post- and pre-therapy average reaction times for each patient is plotted in panel (A). The dashed line denotes equal performance at both sessions and 87% of cases fall below this line, indicating faster reaction times at post-therapy. Panel (B) plots the reaction time for targets appearing on the sighted and blind field separately, again indicating that improvements take place at both sides. Error bars denote \pm SEM.

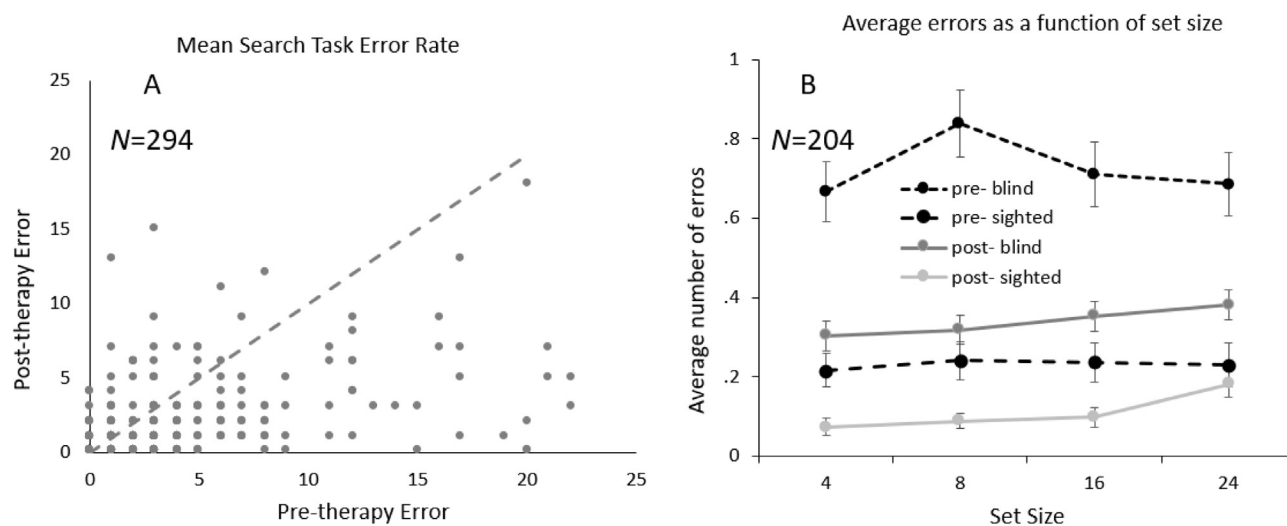


Fig. 2 – Total number of errors made across four blocks of trials (4 set sizes) are accumulated. Panel (A) shows a plot of pre- versus post-therapy values for all cases. The dotted line shows the locus for equal scores and 80% of cases fall below this line. For those with blind field restricted to one hemifield, the errors were subdivided into targets missed in the blind versus sighted field and plotted in panel (B). Patients initially performed poorly for blind field target presentations, but at post-therapy they performed more accurately than the pre-therapy performance in their intact field. Error bars denote \pm SEM.

pre- and post-therapy search task has been plotted in Fig. 2B. Errors were larger for target presentations within the blind field than the sighted field both before and after the therapy. However, there was a marked improvement in performance for blind field target presentations after the therapy to a level similar or better than those for the sighted field before the therapy. The effect of training on errors in visual search task was analysed for blind and sighted fields in those subset of patients that reported unilateral sight loss only, using a

$2 \times 4 \times 2$ repeated measure ANOVA with a within subject factor Training (2 levels: pre- and post-), Set size (4 levels: 4, 8, 16 & 24), and Hemifield (2 levels: sighted and blind). There were significant main effects of Training [$F(1,190) = 50.7$, $p < .001$, $\eta^2 = .211$], and Hemifield [$F(1,190) = 82.5$, $p < .001$, $\eta^2 = .303$] but not Set size [$F(3,570) = 1.28$, $p = .281$, $\eta^2 = .007$]. The interaction of Hemifield \times Training was also significant [$F(1,190) = 13.49$, $p < .001$, $\eta^2 = .082$]. A subsequent paired-sample comparison in those with self-reported left or right

sight loss only, showed that after training, change in number of errors in the blind field ($M = -1.53$, $SD = 3.65$) was significantly higher than the sighted field ($M = -.48$, $SD = 1.41$) [$t(203) = -4.22$, $p < .001$, Cohen's $d = -.295$]. The combined data of Figs. 1B and 2B shows that post-therapy patients not only were faster to detect targets in their blind field, they also made less errors (i.e., at post-therapy there was a lower chance of missing targets presented in the blind field). Altogether, the level of improvement was larger for blind compared to the sighted field.

3.2. Self-reported disability score

To assess the effect of visual field loss on patients' activity of daily living, subjective ratings of their disability were obtained using the same questionnaire as reported in previous studies (Mannan et al., 2010; Nelles et al., 2009, 2001; Pambakian et al., 2004; Roth et al., 2009). These ratings were then summed to obtain a Disability Score (DS). Although all patients had completed the pre-therapy questionnaire, a number of cases had terminated the programme after post-therapy visual search task and did not complete the post-therapy questionnaire. 254 cases had completed both sets and Fig. 3 shows the plot of post-versus pre-therapy scores. The disability score at pre-therapy ($M = 18.68$, $SD = 7.14$) was higher than that on post-therapy ($M = 15.47$, $SD = 6.14$) and this difference was significant [$t(253) = 8.70$, $p < .001$, Cohen's $d = .546$]. Overall 66% (167/254) reported a subjective improvement in their level of disability after the therapy. However closer inspection of the data shows that the proportion of those improving (falling below the oblique dashed line) depends on the level of baseline subjective report of disability. The vertical dashed-lines show the subdivision of disability to low (<10), moderate (≥ 10 and < 20) and high (≥ 20) levels. 80% (74/93) of those with high DS show improvements and as a group the reduction in DS from pre-training ($M = 26.44$, $SD = 4.77$) compared to post-training ($M = 19.70$, $SD = 6.3$) was significant [$t(92) = 9.623$,

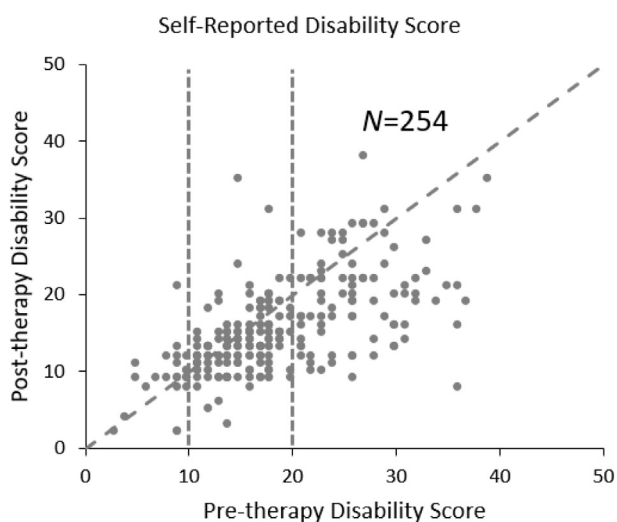


Fig. 3 – The total score for activity of daily living questionnaire is plotted showing the subjective post-versus pre-therapy reports. The dashed line denotes the equal reported disability.

$p < .001$, Cohen's $d = .998$]. 62% (89/144) with moderate disability report post-therapy improvement and the reduction in DS from pre-training ($M = 14.99$, $SD = 2.68$) to post-training ($M = 13.51$, $SD = 4.25$) was significant [$t(143) = 4.436$, $p < .001$, Cohen's $d = .37$]. In contrast, only 4/17 with low disability show any subjective improvement and the change in DS from pre-therapy ($M = 7.47$, $SD = 2.07$) to post-therapy ($M = 8.88$, $SD = 4.7$) was not significant [$t(16) = -1.31$, $p = .21$]. This is likely to be a floor effect as these cases appear to have adapted well to their disability. Therefore, 69% (163/237) cases with moderate to high disability report subjective benefit of eye movement training.

3.3. Relationship between subjective and objective measures of improvement

The time taken for a patient to identify a target amongst distractor items (RT) as well as the number of errors made, i.e., missed targets, (ER) are two objective measures of performance. In the above analysis we showed that a large proportion of patients were faster in detecting objects (87%; 255/294) and made less detection errors (80%; 236/294). The disability score, on the other hand, was a subjective assessment of perceived disability. In the following analysis we have attempted to establish whether the subjective and objective measures of improvement were concurrent. This analysis was not part of our pre-registration and therefore is included as an additional exploratory analysis. Fig. 4 shows the performance on the reaction time subdivided between those with a low/intermediate level of reported disability (<20 , $N = 161$) (Fig. 4A) versus those with high disability (≥ 20 , $N = 91$) (Fig. 4B, 2 cases with incomplete data on RT/ER excluded, leaving a total of 252 cases).

Of those with a low/intermediate DS, after therapy 58% (93/161) reported less subjective disability (improved DS), 74% (119/161) had faster reaction times and 60% (96/161) a lower error rate. An objective improvement after therapy could be that a patient is faster to detect targets and/or that they are less likely to miss targets. Of those with improved DS, 94% (87/93) also showed improvement on one or both objective measures (RT/ER).

Of those with a high DS, after therapy 79% (72/91) reported less disability 70% (64/91) had faster reaction times and 62% (56/91) had lower error rates. Similarly, of those with improved disability score, 88% (63/72) also showed improvement on one or both objective measures.

3.4. Predictors of recovery in objective and subjective measures

It is of interest to establish factors that can predict recovery of function in hemianopic patients as a function of both objective and subjective measures of performance. In order to do this, the changes in reaction times, errors and disability scores were determined for each patient. A multiple regression to predict changes in reaction time following therapy from age at therapy start, gender, side of blindness, age at the onset of brain injury, and time elapsed between the brain injury and therapy start showed significant results [$F(4,289) = 2.467$, $p = .045$, R square = .033]. The increase in time elapsed between the brain

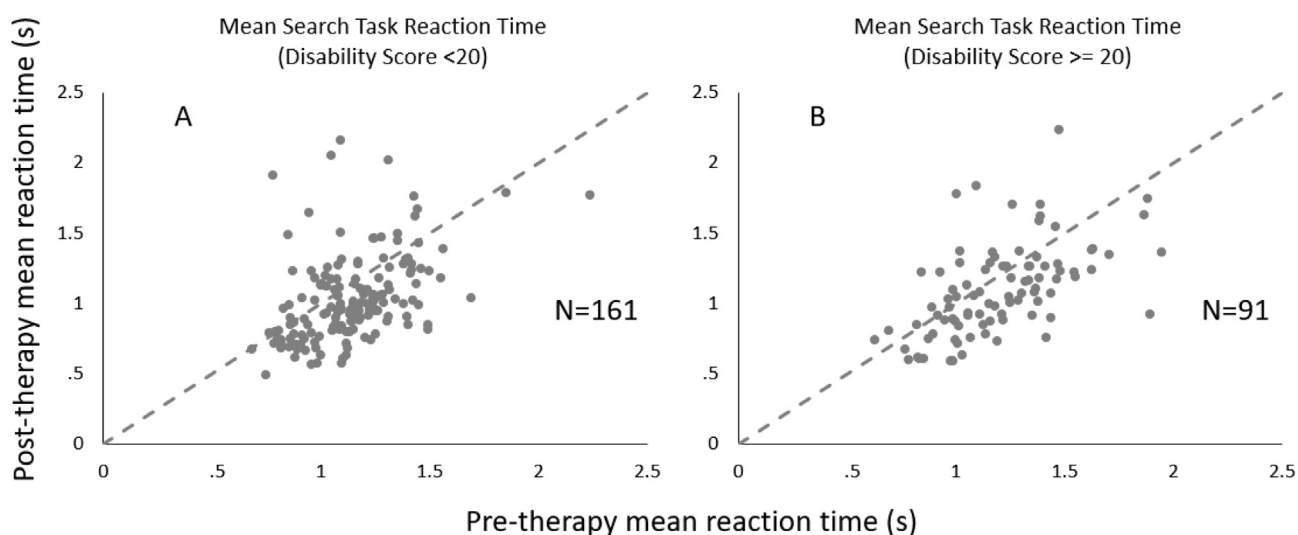


Fig. 4 – Patients’ performance on pre-post-therapy search task is plotted for those with low/intermediate (A) and high (B) subjective disability score. The dashed lines show equal pre-post-therapy performance.

injury and therapy start, predicted a lower reduction in RT (Standardised Coefficient Beta = $-.119$, $t = -2.046$, $p = .042$). A similar analysis for Error rate with the same predictors also showed significant results [$F(4,289) = 3.004$, $p = .019$, R square = $.04$], with Age at therapy start being the only significant predictor (Standardised Coefficient Beta = $.164$, $t = 2.806$, $p = .005$). That is, older patients were more likely to show a larger reduction in errors following therapy.

A final multiple regression to predict changes in self-reported disability also showed that none of the above were significant predictors [$F(4,249) = 1.689$, $p = .153$, R square = $.026$]. Fig. 5 depicts the scatter plots of changes in the three measures with age at brain injury onset and time elapsed between brain injury and therapy. Therefore, the results from this large cohort of patients undertaking a systematic compensatory therapy show that patients can improve in subjective and objective measures of performance.

4. Discussion

Sight loss following brain injury is a life changing event and highly detrimental to an individual’s personal and social life. Nevertheless, systematic provision of vision rehabilitation is limited to advice on coping strategies through Low Vision Clinics (MacIntosh, 2003). As the majority of brain injuries are caused by stroke, which is often lateralised in the brain, most patients have a sighted/intact field and only suffer partial sight loss in one hemifield. Therefore, eye movements can be utilised to bring the unseen images into the intact sight and to compensate for the visual deficit. In a systematic review, this compensatory approach has been flagged as a promising way forward to provide patients with an effective therapy (Pollock et al., 2011, 2019).

There is however a lack of systematic approach to large scale provision of compensatory therapies. A handful of

specialist laboratories in Europe can provide local patients with much needed help. Some online software has also been provided (for example, “. Eye-Search Therapy UCL Institute of Neurology | UCL Multimedia,” n.d.), nevertheless, most available programmes are not regulated devices and promoted as research tools with their use being subject to participation in clinical studies. NeuroEyeCoach™ also stemmed from a local clinic in Ludwig Maximilian University of Munich, is a Class I CE marked medical device in the EU and is registered as an FDA 510(K) exempt medical device in the US. It has been developed as an adaptive, internet deliverable medical device that can be accessed by patients throughout the EU and the US (Sahraie et al., 2016).

Clinical studies on compensatory therapies often have small sample sizes. The small sample size allows more resource intensive research to be conducted which would often include detailed investigations such as administration of a battery of cognitive tests in the form of questionnaires and observational studies of behaviour (Rowe et al., 2013). The wider accessibility of an online therapy allows for much larger sample sizes, however, it also imposes limitations on assessments that can be obtained. There is a balance to be struck between the robustness of laboratory based observations and the analytical power that comes with large scale studies that may be noisy but rely on large size of the dataset to overcome the variance. Here we have reported on the first 296 cases that had completed the therapy. NEC has in built functionality to assess performance pre- and post-therapy providing two objective (visual search reaction time and errors) and one subjective measure of performance (self-reported ratings of disability: Disability Score).

Use of NEC led to improved reaction time and error scores in 87% (255/294) and 80% (236/294) of cases respectively. Therefore, patients were faster and more accurate in visual search, but importantly, we have shown that this improvement applied to both sighted and blind field target

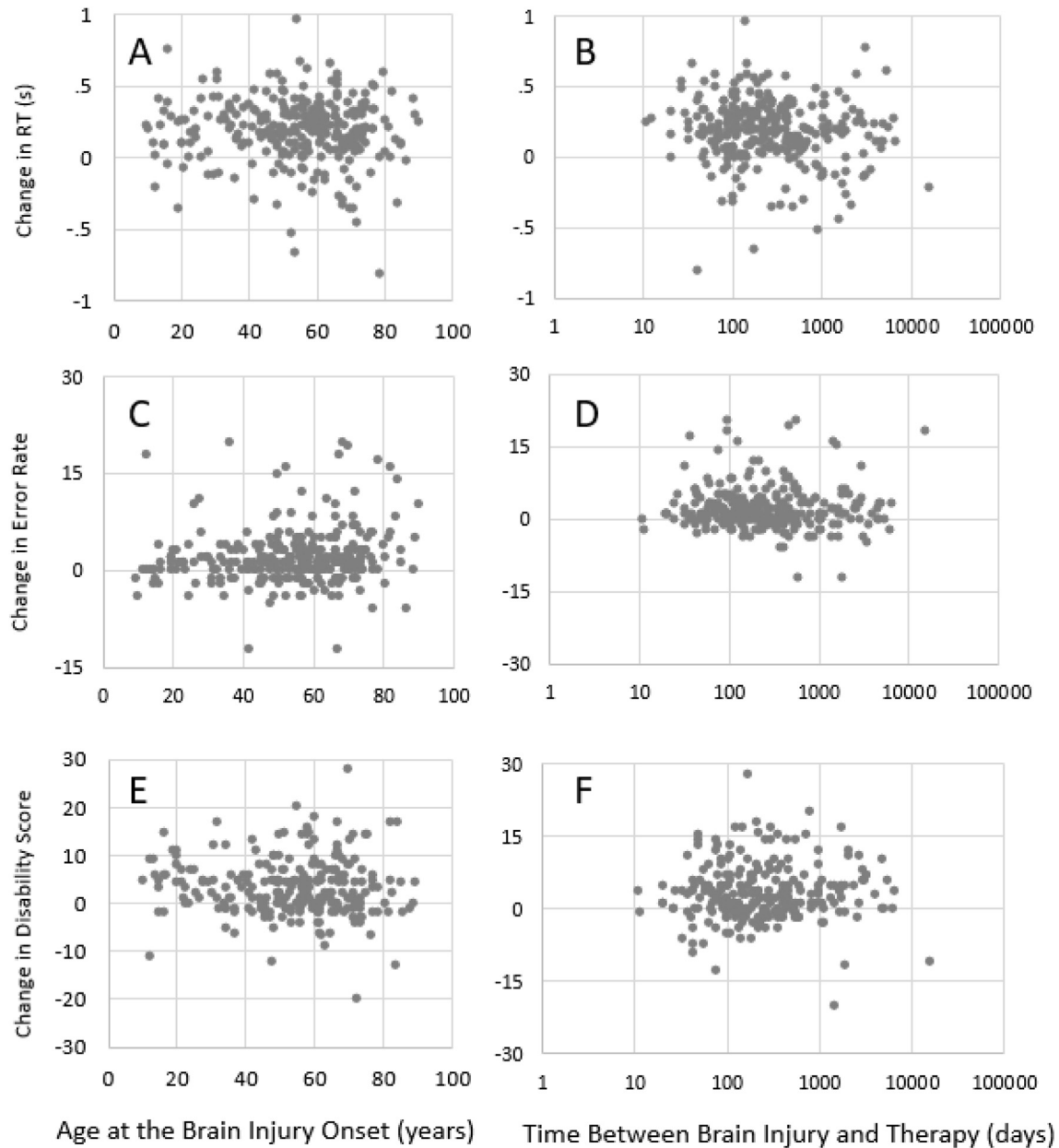


Fig. 5 – Scatter plots of change in reaction time, error rate and disability score as a function of age at brain injury and time between brain injury and therapy. Neither of the two parameters are significant predictors of recovery as measured by the objective (reaction time and error rate) and subjective (disability score) measures.

presentations. Also, their performance in their blind field either matched or was better than that of the sighted field prior to the therapy. In the only other reported study of an online visual search training programme, improvements were reported in the blind field only and no change in the sighted field performance (Ong et al., 2015). This is likely to be due to the limited duration of training (800 trials). We have shown that with more prolonged intervention, the overall performance can improve in both blind and sighted fields.

Devising reliable tasks to assess changes in behaviour, particularly when interventions are remotely administered is challenging. The ideal assessment would be an objective test

of functional vision that can be administered remotely (or performed in a clinical setting for inpatient interventions). In the absence of such assessments, we have developed a simple target search task conducted for 4 set sizes where target and distractor presentations were counterbalanced across trials. As compensatory training inevitably involves practicing target/distractor detection across the visual field, it remains a possibility that any improvements seen is simply due to a practice effect and does not reflect a functional change in oculomotor behaviour. Significant hemifield by training interactions observed in reduction of errors for targets presented in the intact and blind hemifield (and an

almost significant effect for RT) balances the explanation for a change in behaviour towards a more fundamental oculomotor dynamics explanation than a simple general (non-hemifield specific) practice effect. We do not have direct oculomotor data to establish which parameters of eye-movement controls have improved, however previous detailed examination of eye movements has shown a marked reduction in number of fixation and re-fixation as well as an increased in saccadic amplitude can take place, leading to better organised visual scanning behaviour (Passamonti, Bertini, & Ládavas, 2009).

Brain imaging data can provide definitive information on the site and extent of the brain injury and detailed neuropsychological testing can reveal other associated cognitive deficits. Due to inherent limitation of a large-scale online based study, we have relied on self-declaration to establish right or left sided blindness. Based on the data for reaction time and errors shown in Figs. 1B and 2B, we would argue that this self-declaration is largely reliable as they show lower performance in the self-declared blind hemifield compared to the sighted field. Executive and/or other visuo-spatial deficits could co-exist in this patient population (Chokron, Peyrin, & Perez, 2019), however, the current data is largely free of those with significant deficits as the task demands and threshold for progression to the next training levels were high and those with significant co-deficits were unlikely to progress in this task. Those with low level deficits should not be excluded as an effective intervention should be inclusive and applicable to as wide a population as possible.

Patient's subjective reports of vision-related disability showed improvements post-therapy in 66% (167/254) of all cases with the ratio being much higher for those with pre-therapy high level of self-reported disability (80%, 74/93). To explore the relationship between the subjective and objective measures of change, we have conducted further analysis that showed that subjective reports of improvement in those with low/moderate level of disability, were accompanied by faster RT and less errors in 94% of cases (87/93). For those with high reported disability this figure was 88% (63/72). This shows that when patients reported subjective improvements, they also performed better on objective measures.

A pertinent question as regards to effectiveness of any rehabilitation intervention is the generalisability of the improvements to other tasks. This is a controversial issue as far as the effect of compensatory approach to vision rehabilitation is concerned. Reports of generalisability depend on the choice of other eye-movement related tasks. Many studies use performance on a cancellation task, where the patient is required to cross out (often but not always using pen on paper) a particular target amongst distractor items (Bolognini, Rasi, Coccia, & Ládavas, 2005; Lane et al., 2010; Zihl, 2011). It is however possible to argue that these tasks are not widely different than those the patients trained on. Performance on reading tasks has also been used to investigate transferability/generalisability of learning. Previous studies using multi-sensory stimuli have shown that if not all, at least some reading parameters improve after multi-sensory stimulation (Bolognini et al., 2005; Passamonti et al., 2009) although the sample sizes in these studies were small. However, the findings from eye-movement interventions influencing reading

has been mixed with some showing a transfer (Aimola et al., 2014) and others showing no transfer of training (Schuett et al., 2012; Schuett & Zihl, 2013). On the subjective level, one may argue that person's perception of the level of disability in their interaction with activities of daily living is an appropriate measure of generalisability, since if the improvements on the trained task did not result in any subjective improvements, then the training would be of little practical value. Almost all studies on eye-movement training that have made use of these subjective reports, including this report, show such subjective improvements.

It is often stated or assumed that younger patients are more likely to recover from brain injury, attributed to higher likelihood of plasticity taking place at the younger age than in the older patients (Chang et al., 2015). Having a large sample size allowed us to investigate the predictors of recovery in both objective and subjective measures of performance. We found that none of the variables of age, gender, side of blindness, age at the onset of brain injury, and time elapsed between the brain injury and start of therapy were significant predictors of improvement is subjective reports of disability, although for those patients who have potentially adapted well to their disability and find little impact of the brain injury on their vision-related activities of daily living, the subjective benefits were lower. The time since brain injury was also a significant predictor for improved reaction times, that is, those who had adapted to the injury over longer periods, showed smaller improvements in reaction times. The patient's age at the start of therapy was a predictor of improved number of errors, with older participants showing larger improvements. However, there was also a significant correlation between the patient's age and the number of errors made at pre-therapy stage with older patients making more errors (Pearson Correlation .230, $p < .001$). It is likely that the predictive power of age on the level of improvements (less errors) may simply be due to older patients making more errors at pre-therapy. An advantage of having a large dataset is that the range of performances reported is more likely to be a fair representation of that of the patient population as a whole. This allows us to explore the parameters of interests that can be investigated in future controlled clinical trials. However, the downside of the large datasets is that statistically significant correlations and interactions can be found that may be of little clinical relevance. In these situations, reported effect sizes can be a good pointer to the probable relevance of the findings in clinical practice. The two significant predictors that we have reported for the objective measures of RT and Error both have small effect sizes. Indeed, the age and time since injury only explained 3–4% of the variance. This means that both findings may be of limited clinical relevance and a better summary of the findings is that the vast majority of patients benefited from the eye movement therapy irrespective of age, gender and side of brain injury. It is also important to note that those who underwent this therapy were aware of the procedures involved and the task demands, therefore they could devote the time and the attention needed for the duration of therapy. Therefore, the sample of patients reported here are those with little or no cognitive impairments or other stroke related disability that would impair task performance.

All analysis included in this paper were based on the data that was available to us and therefore reflect the changes that were observed between pre- and post-therapy stages, and the sustainability of improvement at long periods post therapy completion could not be assessed. Nevertheless, the findings reported here are in agreement with the benefit of compensatory therapies shown in randomised control trials (Carter, Howard, & O'Neil, 1983; Roth et al., 2009), as those trials were in a smaller sample of patients. The restitution techniques have also shown promise in improving sensitivity in the impaired visual field (Melnick, Tadin, & Huxlin, 2016), although the rate of recovery is slow and often takes place over many months (Sahraie et al., 2013). Compensatory approaches on the other hand are short in duration (few weeks rather than months). Ideally a rehabilitation protocol for hemianopic patients should include both restitution and compensatory approaches to enable the best use of existing sight and a reduction of lost sight. The most effective order in which an individual should take these therapies is yet unknown. It may be the case that an initial, short-period intervention by a compensatory therapy can provide patients with immediate strategies on how to compensate for their sudden vision loss on daily basis. This may then be followed by a longer restitution approach. To establish the efficacy of such protocols, further research is needed.

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Open practices

The study in this article earned Open Data and Preregistered badges for transparent practices. Materials and data for the study are available at <https://osf.io/2hvds/wiki/home/>.

Declaration of Competing Interest

AS and JR are on the Scientific Advisory board of NovaVision and SK is employed by NovaVision. AMHC is funded by an EastBio BBSRC Case Ph.D. studentship in collaboration with NovaVision.

CRediT authorship contribution statement

Arash Sahraie: Formal analysis, Methodology, Visualization, Writing - original draft. **A. Matilda H. Cederblad:** Data curation, Formal analysis, Writing - review & editing. **Sigrid Kenkel:** Data curation, Project administration, Validation, Writing - review & editing. **Jose G. Romano:** Methodology, Validation, Writing - review & editing.

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