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Combining fixation and lateral masking training enhances perceptual learning effects in patients with macular degeneration

Marcello Maniglia
UC Riverside, Riverside, CA, USA
Université de Toulouse-UPS, Centre de Recherche Cerveau et Cognition, Toulouse, France
Centre National de la Recherche Scientifique, Toulouse Cedex, France

Vincent Soler
Unité de rétine, consultation d'ophtalmologie, hôpital Pierre-Paul-Riquet, CHU de Toulouse, Toulouse Cedex, France

Yves Trotter
Université de Toulouse-UPS, Centre de Recherche Cerveau et Cognition, Toulouse, France
Centre National de la Recherche Scientifique, Toulouse Cedex, France

Macular degeneration (MD), a retinal disease affecting central vision, represents the leading cause of visual impairment in the Western world, and MD patients face severe limitations in daily activities like reading and face recognition. A common compensation strategy adopted by these patients involves the use of a region in the spared peripheral retina as a new fixation spot and oculomotor reference (preferred retinal locus, or PRL). Still, peripheral vision is characterized by poorer visual acuity, fixation stability, and larger crowding zones that further hinder processes like object recognition, visual search, and reading. Perceptual learning (PL) has been successfully used to improve visual acuity in mild visual conditions (e.g., presbyopia, amblyopia and myopia), but results in MD are less clear, often showing limited generalization of learning, unlike what is observed in a healthy population. A possible reason is the suboptimal fixation in the PRL that might prevent patients from processing the briefly presented training stimuli. Following this hypothesis, we trained five MD patients and four age- and eccentricity-matched controls with a protocol that combined contrast detection and a task previously used to train fixation stability. Results showed transfer of learning to crowding reduction, reading speed, and visual acuity in both MD patients and controls. These results suggest that in the case of central vision loss, PL training might benefit from the integration of oculomotor components to optimize the effect of training and promote transfer of learning to other visual functions.

Introduction

In recent years, research in the field of vision science has provided great insights into the clinical application of experimental paradigms: perceptual learning (PL), in particular, seems to be a promising technique for treating sensory, and particularly visual, pathologies by exploiting the neural plasticity of the brain. PL studies, based on the repetition of simple tasks such as contrast detection or orientation discrimination (Sagi, 2011), showed that a wide range of visual abilities can be improved after a sizable number of training sessions. Despite early evidence of location and orientation specificity (Karni & Sagi, 1991), more recent research showed that PL can transfer to untrained visual functions, and the degree of generalization might depend on the characteristics of the training (Maniglia & Seitz, 2018). The possibility of generalizing training features to other retinal locations, stimulus features, or even different visual abilities appears to be a key element for the successful applications of PL in clinical populations (Campana & Maniglia, 2015). Specifically, for common visual pathologies of a refractive nature

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such as myopia and presbyopia, contrast detection training managed to restore foveal visual acuity to the level prior to the onset of the pathology (Polat, 2009; Tan & Fong, 2008). In both cases, PL is thought to train the brain to overcome the optical limitation by sharpening the response of the neurons processing early optical input. Moreover, PL is effective in improving visual functions also in the presence of cortical abnormalities, as is the case in amblyopia (Levi and Li, 2009) and cortical blindness (Das, Tadin, & Huxlin, 2014). However, PL seems less effective in cases of more severe diseases compromising the structural integrity of the retina, such as macular degeneration (MD). MD is a progressive retinal disease currently representing the leading cause of visual impairment in the Western world (World Health Organization, 2015). Patients in the late stages of MD tend to compensate for the loss of central vision by developing an eccentric fixation spot outside the damaged retinal region to replace the fovea (preferred retinal locus [PRL]; Cummings, Whittaker, Watson, & Budd, 1985; Timberlake et al., 1986). The PRL often becomes the retinal region used for fixation and/or oculomotor reference (Crossland, Engel, & Legge, 2011) so that patients would describe themselves as looking straight ahead when fixating with their PRL (White & Bedell, 1990; Whittaker & Cummings, 1990). This re-referencing toward the PRL has been observed in a large majority of MD patients (White & Bedell, 1990).

Several reasons might contribute to the modest results of PL in MD, particularly the reduced plasticity usually associated with older adults (Smirnakis et al., 2005; Sunness et al., 2004). Moreover, elderly participants, often relying on others for transportation to training facilities, may show lower compliance for PL studies spanning several weeks. Because central vision in MD patients is lost, the strategy is to train a peripheral retinal spot, usually the PRL, to carry over the duties of the fovea, particularly oculomotor reference and fine vision. Thus, the neural plasticity-mediated changes induced by training need to be much greater than those observed in classic PL protocols.

Therefore, to transform the PRL into a functional substitute of the fovea, a visual training protocol should induce much greater neural plasticity with respect to classic PL protocols aiming at bringing the visual system back to its normal status. In these past years, a number of studies have tested different paradigms to improve residual vision in MD patients (see Maniglia et al., 2016): Specifically, Chung (2011) showed that reading training with rapid serial visual presentation (RSVP) reduces crowding in the PRL of MD patients. Crowding, the detrimental effect of flanking elements on target identification (Levi, 2008), is one of the trademark features of peripheral vision, and since MD patients rely on their peripheral vision, crowding reduction represents a valuable outcome in rehabilitation training (Chung, 2011). However, while the RSVP training successfully reduced crowding, it did not show transfer of learning to other visual functions such as visual acuity (VA) or critical font size. Similarly, MD patients undergoing oculomotor (Rosengarth et al., 2013) and texture discrimination (Plank et al., 2014) training showed small improvements in reading speed and Vernier acuity, respectively, and, in general, lack of transfer to other visual abilities. While acknowledging the complex interaction between the different factors that contribute to generalization of learning after training (task, paradigm, temporal characteristics of the stimuli, length of the blocks and sessions, etc.), one of the reasons for this reduced transfer might be due to the task used. Texture discrimination task (TDT) is known for its specificity (Karni & Sagi, 1991), while oculomotor training alone might not improve the neural networks subserving VA, contrast sensitivity (CS), and other typical transfer tasks. On the other hand, Maniglia et al. (2016) showed that a training protocol based on contrast detection with a lateral masking configuration, a paradigm that has been shown to induce transfer of learning in healthy participants, both in the fovea (Polat, 2009; Polat, Ma-Naim, Belkin, & Sagi, 2004) and in the near periphery (Maniglia et al., 2011), led to long-lasting improvements in VA and CS in a group of MD patients. Lateral masking training is thought to induce plasticity at the level of the horizontal connections in early visual areas (Darian-Smith & Gilbert, 1994; Gilbert, 1998); therefore, improving neuronal processing at these first stages would provide later stages of visual analysis with a better input signal, increasing, in turn, visual functions such as CS, VA, or crowding that rely on these early inputs. However, in contrast to what is observed in normal participants (Maniglia et al., 2011), lateral masking training, while effective in improving VA, did not reduce crowding in MD patients (Maniglia et al., 2016). A possible explanation lies in the unstable fixation in the PRL that characterizes this clinical population (Macedo, Crossland, & Rubin, 2011). Indeed, better control over fixation has been linked to improved processing of briefly presented visual stimuli (Denison, Yuval-Greenberg, & Carrasco, 2019; Fischer & Breitmeyer, 1987), potentially leading to greater learning and transfer. Therefore, the lack of crowding reduction observed in Maniglia et al. (2016) might be due at least partially to the patients' unstable fixation that masked or lessened the transfer of learning. To test this hypothesis, we combined lateral masking with fixation stability training in five MD patients and four age- and eccentricity-matched control participants. The fixation training task was based on the one used by Guzman-Martinez and colleagues (Guzman-Martinez, Leung, Franconeri, Grabowecky, & Suzuki, 2009) to train fixation stability in healthy participants by using flickering patterns that, under conditions of steady fixation, appear homogeneously gray.

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Of note, this fixation training is based on the subjective appearance of the flickering pattern and does not make use of eye tracker devices, whose calibration and implementation in clinical populations can be challenging (Leigh & Zee, 1980). While the lack of direct control of eye movements can be considered a limitation, this indirect evaluation of fixation stability based on visual percept proved quite reliable in the patients according to their verbal reports.

To summarize, in the present article, we explored the effect of PL in MD on a series of transfer tasks and tested whether fixation training might be beneficial in reestablishing the reduction in crowding previously observed in normal participants but not in MD patients. Moreover, to better map the progress of the training in terms of transfer of learning, we conducted a midterm evaluation, alongside posttraining tests. Results confirmed the VA improvements previously reported and showed an additional new result on crowding reduction and improved reading speed, suggesting that combining perceptual and fixation stability training might be crucial in developing an effective visual rehabilitation method for MD patients. Moreover, midterm tests showed that shorter trainings might be almost as effective as longer ones in improving some visual abilities in MD. While the present study does not provide definitive evidence on the role of the fixation training that we used, it does suggest that combining such training with lateral masking produces improvements that have not been observed in previous studies with MD patients using only perceptual training (Maniglia et al., 2016).

Method

Apparatus

Stimuli were displayed on a 17-in. (Dell, Inc., TX, USA) M770 CRT monitor with a resolution of 1,024 × 768 pixels and a refresh rate of 60 Hz. Stimuli were generated with MATLAB Psychtoolbox (Pelli, 1997). Each pixel subtended 2.14 arcmin. The minimum and maximum luminance of the screen were 0.98 cd/m^2 and 98.2 cd/m^2, respectively, and the mean luminance was 47.6 cd/m^2, as measured by a Minolta CS110 (Konica Minolta, Ontario, Canada). A digital-to-analogue converter (Bits#; Cambridge Research Systems, Cambridge, UK) was used to increase the dynamic contrast range (12-bit luminance resolution). A 12-bit gamma-corrected lookup table (LUT) was used to linearize the monitor. Experiments were carried out at the Centre de la Retine, PPR, Purpan Hospital, Toulouse (France).

Inclusion/exclusion criteria

To keep the patient sample homogeneous, we selected a number of inclusion and exclusion criteria. Specifically, inclusion criteria were absolute central binocular scotoma, age >65 years, residual vision in both eyes <3/10 (corresponding to 60/200 Snellen), and presence of a single PRL (as detected with optical coherence tomography (OCT) measurement, see "PRL location" section). Exclusion criteria were coexisting ophthalmic pathology, cognitive impairment (Mini-Mental State Exam (MMSE) <25), monocular MD, and presence of multiple PRL.

Participants

Participants' information is reported in Table 1. At the beginning of the study, MD patients were asked to indicate which eye they would consider their "best eye." This was the eye that was used for the training. Patients were asked to use their monocular PRL to fixate on a cross in the center of the screen and adjust their head on the chinrest to allow comfortable fixation. Control participants, each assigned to a patient of similar age and trained at the eccentricity corresponding to the PRL position of his or her paired MD patient (see Table 1), fixated on the central cross while the testing configuration was presented in peripheral vision. All participants gave written informed consent prior to their inclusion in the experiment and received payment for their participation in the experiment. The experimental protocol was approved by the relevant ethical committee at Centre National de la Recherche Scientifique with our institutional review board (CPP, Comité de Protection des Personnes, protocole 13018–14/04/2014) and in comformity with the Declaration of Helsinki (1964).

PRL localization

To localize each patient's monocular PRL, we used the procedure described in our previous study (Maniglia, Soler, Cottereau, & Trotter, 2018). A summary of PRL locations for the eye used in the study is shown in Figure 1.

Lateral masking training

Participants underwent a 24-session training on contrast detection with a lateral masking configuration in which a central Gabor patch, the target, was flanked above and below by two high-contrast, iso-oriented Gabor patches. Two consecutive displays, one containing the target and the flankers and the other showing the flankers only, were presented to the

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Participant	Sex	Age of onset (years)	Time since onset (years)	Age	Diagnosis	Scotoma size	PRL coordinates (*x*-axis)	PRL coordinates (*y*-axis)	Tested eye
MD1	M	61	7	68	AMD	18.4° × 15.8°	−8.15°	0.1°	OS
MD2	F	59	7	66	AMD	17° × 23.4°	−5.43°	1.15°	OS
MD3	F	74	3	77	AMD	12° × 16°	−0.61°	0.78°	OS
MD4	F	57	4	61	Macular atrophy	23.2° × 17.5°	−6.98°	1.78°	OS
MD5	F	82	4	87	AMD	25.3° × 20.2°	−2.62°	9.12°	OD
C1	F	—	—	67	**Control**	—	Same as MD1	Same as MD1	OS
C2	F	—	—	65	**Control**	—	Same as MD2	Same as MD2	OS
C3	F	—	—	73	**Control**	—	Same as MD3	Same as MD3	OS
C4	M			61	**Control**		Same as MD4	Same as MD4	OS

Table 1. Summary table with participants information. PRL coordinates are provided with respect to the fovea. OS = left eye; OD = right eye.

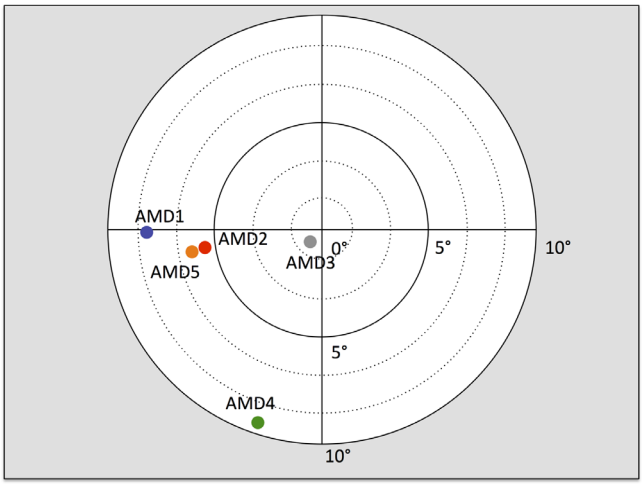

Figure 1. PRL position of the patients. Coordinates were averaged across three consecutive OCT measurements (see Maniglia et al., 2018).

participants, who were asked to report which interval contained the target. The two displays, presented for 133 ms each, were separated by a blank interstimulus interval (ISI) of 500 ms. MD patients were instructed to fixate with their PRL on the center of the screen, where a fixation point was always present. They were asked to adjust their head position in order to fixate as naturally as possible. To increase their fixation stability, three red disks were displayed on the screen to match the internal border of their scotoma, and patients were instructed to keep their fixation on the fixation point and use the disks' visibility as feedback: When the PRL was aligned to the center of the screen, the three disks would be invisible; conversely, one or more visible disks would indicate that the PRL was misaligned with the center of the screen (see Figure 2). The training configuration was presented in the center of the screen with a vertical global orientation (except for AMD5, for whom the configuration was presented horizontally) to ensure that all the elements in the triplets were presented outside the scotoma. Control participants were assigned to each MD, and their training location was selected accordingly. To minimize eye movements, the location of the training configuration was randomized along the *x*-axis. The contrast of the target was changed according to a 3:1 staircase, in which three consecutive correct responses decreased the target contrast by 0.1 log units while one wrong response increased the contrast by the same amount. Each daily session ended after 120 trials or 14 reversals, lasting roughly 30 min. Contrast thresholds, corresponding to 79% of correct detection, were estimated by averaging the value of the last six reversals. An acoustic signal (1,000 Hz) would indicate the onset of each interval, while a lower (500-Hz) tone would be provided as a feedback in case of wrong response. Each daily session consisted of four blocks, each with a different target-to-flanker separation (i.e., 3λ, 4λ, 6λ, and 8λ). Spatial frequency was kept constant at 1 cpd for the first 12 sessions and 2 cpd for the remaining 12 sessions. Both groups performed the task monocularly. Patients indicated their "better eye" that was then used in the study. Control participants' trained eye was matched to that of their corresponding patient. Before the start of the training, a practice block of 15 trials was run to ensure that the patients were able to see the three elements of the configuration while fixating on the fixation point with their PRL. Initial spatial frequency and target-to-flanker distances were chosen to optimize peripheral collinear facilitation and training (Maniglia, Pavan, & Trotter, 2015; Maniglia, Pavan, Aedo-jury, & Trotter, 2015). Similarly, a temporal 2 alternative forced choice (2AFC) paradigm was adopted following previous evidence that this procedure seems to lead to greater improvements and generalization of training with respect to a single-interval presentation (Maniglia et al., 2016).

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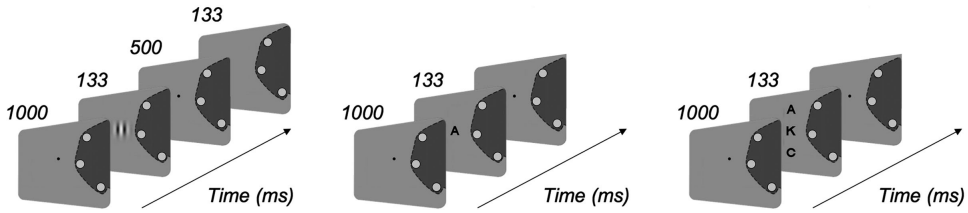

Figure 2. Examples of the test configuration for contrast detection (left), visual acuity (center), and crowding (right). For each patient, the position of the PRL with respect to the fovea and the border of the scotoma was measured with the OCT (see PRL localization). Three bright circles were placed within the border of the scotoma to help the patients align their PRL with the center of the screen. Patients were instructed to use the three circles as references for fixation (i.e., they were asked to fixate so that the bright disks were not visible).

Fixation training

Each lateral masking session was preceded by fixation training. The task was adapted from Guzman-Martinez et al. (2009) and consisted of the presentation of a rapidly flickering (37.5-Hz) pattern of random dots (50% black pixels and 50% white pixels), alternated with its contrast-reversed version (i.e., the white pixels turned black and the black pixels white). When fixation was stable, the image appeared as uniform gray. However, small eye movements led to the perception of black and white patterns, providing immediate feedback to the participant about involuntary eye movements. Participants were instructed to use this information as feedback and to try to reduce the perception of black and white dots in favor of a uniform gray display. Participants underwent five sessions of 30 s each.

Transfer tasks

Participants were tested on a number of transfer tasks at three different moments (before, halfway through, and after training). All tests were conducted at a viewing distance of 57 cm except for the Far VA test, performed at 3 m, and the reading speed test, performed at 40 cm. All the tests, except reading speed, were performed monocularly, one eye at the time.

Contrast thresholds

Participants were tested on four spatial frequencies in separate blocks. In each trial, participants were presented with two temporal intervals (2AFC), one containing a Gabor patch ($\sigma = 5$ deg) and one blank. Each interval lasted for 100 ms, with an ISI of 500 ms (see Figure 2, left). Targets were presented vertically in the center, and visual aids were used to help the patients align their PRL with the center of the screen. An acoustic cue indicated the onset of each interval.

Far (3 m) VA

To measure far VA, we used the Landolt C and the Sloan letter tests from the Freiburg Acuity and Contrast Test (FrACT). Participants were instructed to report the orientation of the C (in the Landolt C task) or the letter that appeared on screen (Sloan letter task). The stimulus remained on screen for 10 s, after which, if no response was provided, the trial was registered as a wrong response. The participants performed the task monocularly and were allowed to move their eyes during the test.

Near (57 cm) VA

Participants were presented with a single letter appearing on screen for 100 ms. The target was presented in the center and visual aids were used to help the patients to align their PRL with the center of the screen (see Figure 2, center). The size of the letter varied according to a 3:1 staircase (increasing after every error and decreasing after three consecutive correct responses). The step size was 1 font size, the character type was Sloan, and the starting font size was 20. Participants had to verbally report the letter while the experimenter registered the answer. The session terminated after either 100 trials or eight reversals. The threshold acuity, expressed as the font size corresponding to 79% correct identifications, was the mean of the last four reversals.

Crowding

The crowding task was similar to the VA task, with the difference that the target letter was flanked above and below by two different letters (Figure 2, right). The size of both the target and flanking letters was set 20% bigger than each participant's VA threshold. The interletter distance varied according to a 3:1 staircase. The initial distance between letters was set at 5 deg. The session terminated either after 100 trials or 16 reversals. The threshold was obtained by averaging the

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last eight reversals. The crowding configuration was presented vertically (except for MD5, for which the configuration was presented horizontally) to ensure that all the elements in the triplets were presented outside the scotoma.

Reading speed

Participants were asked to read aloud a printed text for 3 min. The number of words read and mistakes were then counted. All participants read the same text (*Le petit prince*, Antoine de Saint-Exupéry [1943]), but different passages of the same book during each assessment session, printed on a sheet of paper (font: Arial, font size: 36 pt, single spaced). Patients did not use magnification glasses.

Fixation display

In the absence of eye tracking or microperimetry devices to track the stimulus projection onto the retinal surface (Chung, 2011), we used visual aids to ensure stimuli presentation in the PRL of MD participants (see Figure 2). A fixation point was always present to indicate the center of the configuration, while three bright circles were placed within the borders of the scotoma. Patients were instructed to keep their fixation on the central dot with their PRL and to use the three disks to adjust their gaze on the central dot. A similar approach involving visual aids was adopted in previous studies that used visual aids to stabilize fixation in this clinical population (Astle, Blighe, Webb, & McGraw, 2015; Kasten, Haschke, Meinhold, & Oertel-Verweyen, 2010; Maniglia, Soler, Cottereau, & Trotter, 2018; Nilsson & Nilsson, 1986; Rosengarth et al., 2013). For chart-based tasks, far VA was measured with the FrACT software (Bach, 1996), and for reading speed, patients were free to move their eyes.

Data analysis

To assess the effect of training on patients and control participants, we conducted a mixed-model analysis of variance (ANOVA) with group as the between-subject factor and training as a within-subject factor. For the contrast sensitivity function (CSF), we conducted a mixed-model ANOVA with group as a between-subject factor and training and spatial frequency as within-subject factors. The alpha level was 0.05. In case of violation of sphericity (Mauchly test < 0.05), Greenhouse-Geisser correction was applied. When appropriate, we conducted post hoc tests with Bonferroni correction for multiple comparisons. To assess baseline differences, we conducted two-sample t tests between pretest MD and control performances.

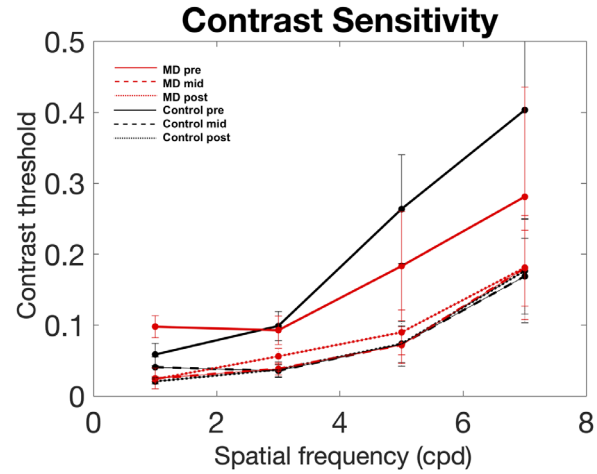

Figure 3. Contrast thresholds for different spatial frequencies for MD and controls before, midway, and after training. Bars indicate ± SEM.

Results

Fixation training

Given the nature of the task (subjective perception of a visual pattern) and the lack of eye tracking, we could not quantify changes in fixation stability. However, all patients subjectively reported that, throughout training, they perceived the pattern as homogeneous gray progressively more often than black and white checkerboard.

Contrast thresholds

Figure 3 shows the contrast threshold results for the two groups. The mixed-model ANOVA showed a main effect of training ($F_{1.04,\ 7.28} = 5.61$, $p = 0.048$, $\eta^2 = 0.445$) and spatial frequency ($F_{1.34,\ 9.41} = 20.85$, $p < 0.001$, partial $\eta^2 = 0.749$) and no significant main effect of group ($F_{1,\ 7} = 0.309$, $p = 0.596$, $\eta^2 = 0.042$). Overall, contrast thresholds decreased by $-47.77\% \pm -40.87\%$ in MD patients and $48\% \pm 29.92\%$ in controls.

Near VA

Figure 4 shows the results for visual acuity in patients and controls. The mixed-model ANOVA showed a main effect of training ($F_{1.09,\ 7.68} = 6.39$, $p = 0.035$, $\eta^2 = 0.477$) and group ($F_{1,\ 7} = 12.48$, $p = 0.01$, $\eta^2 = 0.641$). The interaction was not significant ($F_{1.09,\ 7.68} = 3.2$, $p = 0.093$, $\eta^2 = 0.341$). Comparing pretest and posttest, VA improved on average by $31.03\% \pm 8.9\%$ in MD patients and $17.2\% \pm 7.1\%$ in controls.

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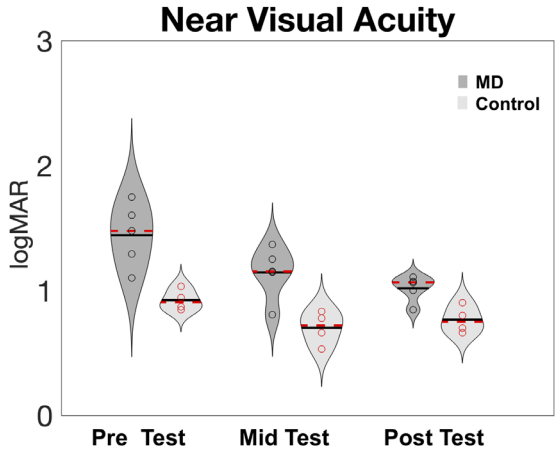

Figure 4. Near visual acuity results (expressed in logMAR) for the two groups before, halfway through, and after the training. Solid black lines within each violin plot represent the mean, while dashed red lines represent the median.

Far VA

Results are shown in Figure 5. The mixed-model ANOVA showed no significant main effect of training for either of the tests used (Sloan and Landolt from FrACT, $F_{2,\ 14} = 0.145$, $p = 0.867$, $\eta^2 = 0.02$ and $F_{2,\ 14} = 0.49$, $p = 0.952$, $\eta^2 = 0.007$, respectively), while both tests showed a significant difference between control and MD patients (main effect of group), with the latter exhibiting overall higher visual acuity thresholds ($F_{1,\ 7} = 18.11$, $p = 0.004$, $\eta^2 = 0.721$ and $F_{1,\ 7} = 8.99$, $p = 0.02$, $\eta^2 = 0.562$ for Sloan and Landolt, respectively).

Crowding

Results are shown in Figure 6. The mixed-model ANOVA showed a main effect of training ($F_{2,\ 14} = 12.21$, $p = 0.001$, $\eta^2 = 0.636$), while the main effect of group and the interaction were not significant ($F_{1,\ 7} = 2.27$, $p = 0.143$, $\eta^2 = 0.28$ and $F_{2,\ 14} = 1.14$, $p = 0.347$, $\eta^2 = 0.14$, respectively). Post hoc analyses showed that both midtest and posttest measurements were significantly lower than pretest ($p = 0.041$ and $p = 0.011$, respectively). The critical space of crowding was reduced by 63.35% ± 12.9% in MD patients and 54.8% ± 44.1% in controls.

Reading speed

Figure 7 shows the results for reading speed. The mixed-model ANOVA showed a main effect of training ($F_{2,14} = 13.345$, $p = 0.001$, $\eta^2 = 0.656$) and group ($F_{1,7} = 74.48$, $p < 0.001$, $\eta^2 = 0.914$). Post hoc analyses showed a significant difference between pretraining and midtraining ($p = 0.04$) and pretraining and posttraining ($p = 0.01$). ANOVAs conducted separately for the two groups showed a significant main effect of training for both MD patients ($F_{2,8} = 4.5$ $p = 0.049$, $\eta^2 = 0.53$) and controls ($F_{2,8} = 16.3$, $p = 0.004$, $\eta^2 = 0.94$), with post hoc analyses showing a significant difference between pre- and posttraining measurements in MD patients ($p = 0.01$) and between pre- and midtest in controls ($p = 0.043$). Overall, patients improved their reading speed by 47.7% ± 42%, while controls improved by 11.7% ± 7.8%.

Transfer of learning to the untrained eye

To measure transfer of learning and provide interpretation of the possible neural mechanisms involved in the training, we measured baseline, midtraining, and posttraining performance in the untrained eye as well. Results showed a significant reduction of crowding ($F_{2,\ 8} = 4.58$, $p = 0.029$, $\eta^2 = 0.396$, 28.25% ± 50.53% and 50.9% ± 41.57% reduction in MD patients and controls, respectively) and a significant improvement in VA ($F_{1.08,\ 7.61} = 5.8$, $p = 0.042$, $\eta^2 = 0.573$, VA improved by 39.35% ± 34.38% and 24.79% ± 15.95% for MD and controls, respectively), while no change was observed for the other assessments.

Baseline differences

To evaluate baseline differences between the two populations, we conducted two-sample t tests and a one-way ANOVA on the pretest score of each assessment. Results showed significantly worse thresholds in patients for near and far VA (near: $t_{4.1} = 2.65$, $p = 0.039$; far Sloan: $t_7 = 4.8$, $p = 0.002$; far Landolt: $t_7 = 3.45$, $p = 0.011$) and reading speed ($t_7 = 9.18$, $p < 0.0001$) but not for crowding and contrast sensitivity ($t_7 = 1.63$, $p = 0.147$ and $F_{1,\ 7} = 0.401$ $p = 0.547$, $\eta^2 = 0.054$, respectively).

Time course of learning

To test for the time course of learning, we conducted separate one-way ANOVAs with time as main factor with three levels (pre, mid, and post) to assess (a) whether more training leads to larger improvement in the assessment tasks, (b) whether learning distribution differs between early and late-stage training, and (c) whether improvements observed early on in the study might be lost by the end of the training (as previously observed in MD; see Rosengarth et al., 2013). Results

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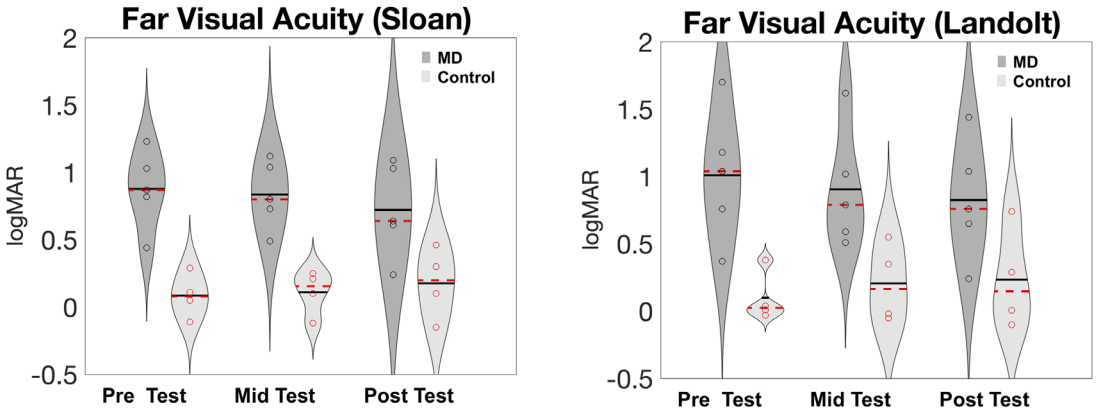

Figure 5. Far (3 m) visual acuity results (expressed in logMAR) for the two groups before, midway, and after training. Solid black lines within each violin plot represent the mean, while dashed red lines represent the median.

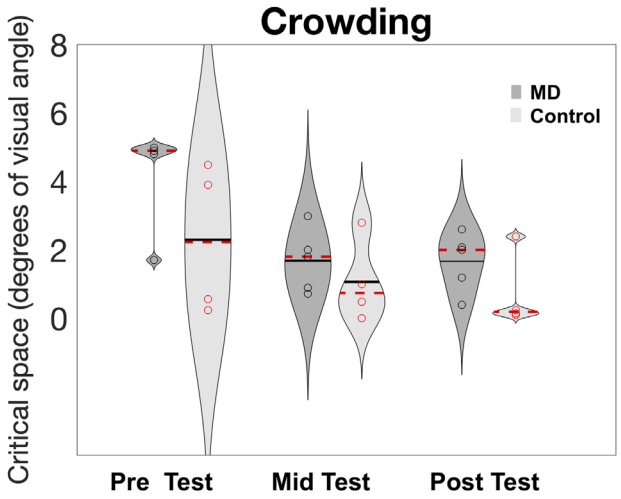

Figure 6. Crowding results (expressed in degrees of critical space) for the MD group before, midway, and after the training. Solid black lines within each violin plot represent the mean, while dashed red lines represent the median.

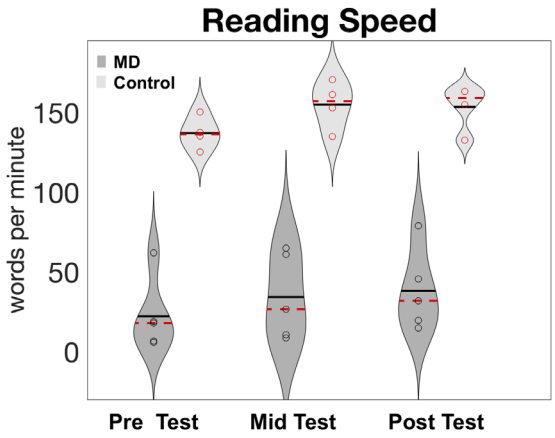

Figure 7. Reading speed (words per minute) results before training, midtraining, and at the end of the training. Solid black lines within each violin plot represent the mean, while dashed red lines represent the median.

showed an overall effect of training for contrast and visual acuity, while reading speed and crowding showed significant improvement already at midtest.

A comprehensive summary of training results for all the assessments is reported in Table 2.

Discussion

Moving outside the laboratory setting, PL is finding its way into rehabilitative practice with promising results in a number of visual pathologies that showed neural plasticity-induced improvements in visual processing (Campana & Maniglia, 2015; Lu, Lin, & Dosher, 2016; Polat, 2009). When compared with other types of interventions, its relative inexpensiveness, low invasivity, and ease of administration make PL a strong candidate for clinical interventions. However, while effective in cases of optical deficits (myopia, presbyopia) or cortical abnormalities (amblyopia), PL seems less convincing in more severe visual conditions affecting the structural integrity of the retina (Maniglia et al., 2016; Plank et al., 2014; Rosengarth et al., 2013). In particular, MD patients seem to exhibit less generalization of learning (Chung, 2011; Plank et al., 2014), a key aspect of the clinical application of PL. Indeed, MD patients require a different kind of intervention. Rather than restoring foveal vision, PL has to train a new peripheral spot (PRL) to carry over the duties of the fovea, both in terms of high-resolution vision and as a new oculomotor reference to plan saccades and stabilize images on the retina. Considering these issues, in the present study, we tested a combined approach in which

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Task	Baseline difference	Training effect	Time course effect	Transfer untrained eye	Pre-post improvement
Visual contrast	NS	Overall	NS	No	47.77+/40.9% (MD) 48+/29.9% (control)
Visual acuity (near)	Ctrl>MD	Overall	NS	Yes	31.03+/8.9% (MD) 17.2+/7.1% (control)
Sloan visual acuity (far)	Ctrl>MD	NS	NS	No	NS
Landolt visual acuity (far)	Ctrl>MD	NS	NS	No	NS
Crowding	NS	Overall and group-specific	Mid>Pre Post>Pre	Yes	63.3+/12.9% (MD) 54.8+/44.1% (control)
Reading speed	Ctrl>MD	Overall and group-specific	Mid>Pre Post>Pre	NS	47.7+/42% (MD) 11.7+/7.8% (control)

Table 2. Summary of training effects for each assessment. Overall = significant training effect; NS = not significant; Ctrl>MD = control performance significantly better than MD; Mid>Pre = performance at midtest significantly better than performance at baseline.

MD patients were trained using a classical PL paradigm (contrast detection with lateral masking) coupled with a flickering display to train fixation stability with their PRL. Since poor fixation stability is a common feature of MD, and unstable fixation might hinder PL effects, combining PL with fixation training might be effective in inducing the same improvements in visual abilities observed in healthy participants. Previous studies showed that MD patients with stable eccentric fixation perform better than patients with unstable fixation in tasks like reading (Tarita-Nistor, Brent, Steinbach, Markowitz, & González, 2014) while neuroimaging studies showed increased posttraining functional activation in perceptual areas correlated positively with fixation stability (Plank et al., 2014).

Results showed that monocular training on fixation stability and contrast detection with lateral masking not only improved contrast sensitivity and near visual acuity in MD patients and age-matched controls but also generalized to visual crowding and reading speed, unlike what has been previously reported for MD patients trained on contrast detection alone (Maniglia et al., 2016). Additionally, we observed transfer of learning to the untrained eye for visual acuity and crowding.

Generalization of learning to other visual functions

Improvements in crowding and reading speed following contrast detection training in MD are the main novel results of this study. Concerning crowding, while a previous study in healthy participants trained on lateral masking reported a similar result (Maniglia et al., 2011), this paradigm did not seem equally effective in MD patients (Maniglia et al., 2016). We believe that fixation training played a significant role in the reduction of crowding. Training fixation might have reduced crowding per se (Chung, 2013a) or enhanced the effect of the subsequent contrast detection training by stabilizing the image on the PRL, thus reestablishing the transfer of learning to crowding, as observed in healthy participants (Maniglia et al., 2011). Indeed, there is evidence that better control of eye movements leads to improved perception of briefly presented stimuli (Denison et al., 2019; Fischer & Breitmeyer, 1987), thus potentially enhancing the effects of training.

Additionally, there is evidence linking fixation stability and peripheral VA and reading, both in MD patients (Calabrèse et al., 2011; Crossland & Rubin, 2014; Tarita-Nistor, Brent, Steinbach, & González, 2011; Tarita-Nistor, González, Markowitz, & Steinbach, 2008; Timberlake et al., 2005) and participants trained with simulated scotoma (Chen et al., 2019), and with the hypothesis that reading difficulties may depend on unstable fixation (Falkenberg et al., 2007) and the suggestion of potential rehabilitative benefits of interventions based on fixation stability training (Falkenberg et al., 2007).

Generalization of learning to the untrained eye

As a further measure of transfer of learning, we tested the same assessment tasks in the untrained eye. Results showed that, overall, near visual acuity and crowding significantly improved in the untrained eye. These results are consistent with what observed in the trained eye and further suggest that training might have improved fixation stability, which, as mentioned in the previous subsection, seems to be related to both acuity and crowding (Calabrèse et al., 2011; Chen et al., 2019; Crossland & Rubin, 2014; Tarita-Nistor, Brent, Steinbach, & González, 2011; Tarita-Nistor, González, Markowitz, & Steinbach, 2008; Timberlake et al., 2005).

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Time course of learning

To better characterize the time course of learning, we measured midtraining performance after 12 training sessions (out of the 24 total). These midtraining tests results suggest that a significant improvement in reading speed and crowding was observed after the first 12 sessions. A possible explanation for this result lies within the framework of the time course of perceptual learning as previously suggested (Yotsumoto, Watanabe, & Sasaki, 2008). Lower visual areas, deprived of their retinotopic input, might be more plastic than higher, nonretinotopically specific perceptual areas not directly affected by retinal loss. Since early training effects are associated with plasticity-related changes in early visual areas, this is where the larger improvements might be expected to occur. Also, to further improve performance, higher-level perceptual regions might require a larger-scale reorganization that goes beyond fine-tuning of a perceptual unit's response. This is consistent with the suggested time course of PL (Sasaki, Nanez, & Watanabe, 2010) and stresses the importance of monitoring progress at different time points during the training, expanding over a classic baseline/posttraining design. In general, characterizing various phases of learning seems crucial in developing a training protocol for the clinical population, since a midterm testing can reveal improvements that, by the end of the training, might be reduced or lost (Rosengarth et al., 2013). These results seem to suggest that the training was mostly effective between pre- and midtest for both crowding and reading speed. This piece of evidence might help in designing an optimized training that would use a shorter number of sessions, alleviating the known recruitment and compliance issues in clinical populations.

On the other hand, contrast sensitivity and visual acuity showed an overall effect of training that did not seem to show clear early or late-stage training effects.

Control participants

The extent to which MD patients' visual cortex successfully adapts to the loss of central vision is still highly debated (Baseler et al., 2011; Dilks, Baker, Peli, & Kanwisher, 2009; Julian, Dilks, Peli, & Kanwisher, 2011; Masuda, Dumoulin, Nakadomari, & Wandell, 2008). Indeed, there is behavioral evidence both for (Chung, 2013b; Maniglia et al., 2018) and against (Haun & Peli, 2015; Van der Stigchel et al., 2013) the hypothesis that MD patients undergo functional use-dependent plasticity in their PRL and that this plasticity is reflected in their behavioral performance. To test whether MD patients would exhibit different training effects with respect to healthy participants, we recruited four age- and eccentricity-matched control participants in the study. Overall, control participants did not show significant differences in training effects with respect to MD patients. However, baseline measurements showed that control participants had significantly better reading speed and peripheral visual acuity. While the difference in reading speed can be clearly attributed to the fact that control participants were allowed to use their foveal vision during the task, the difference in visual acuity measured at PRL-matched eccentricities could be again attributed to poor fixation stability (Falkenberg et al., 2007).

Comparisons with previous studies

Previous studies using visual training in MD patients adopted different techniques, such as RSVP (Chung, 2011, Tarita-Nistor et al., 2014), oculomotor training (Rosengarth, 2013), texture discrimination (Plank et al., 2014), and contrast detection (Maniglia et al., 2016). The latter represents the closest reference to the present study, since it adopted a similar paradigm, but without the use of fixation training preceding the contrast detection sessions. Maniglia et al. (2016) reported a comparable improvement in visual acuity in MD (40% vs. 31% of the present study) but a smaller, more variable and nonsignificant reduction in crowding (40% ± 40.1% vs. 63.35% ± 12.9% here).

Reading speed improved by 47% in patients, similar to what was reported (53%) by Chung (2011) in MD patients using RSVP. However, the improvement in reading speed was not accompanied by significant changes in critical print size (i.e., the smallest print size at which patients can read with their maximum reading speed) or visual acuity. A more recent study (Astle, Blighe, Webb, & McGraw, 2014) showed an even larger improvement in reading speed (71%) in patients trained on a word identification task, but the authors did not train patients in their PRL but rather at the same arbitrary eccentricity (10°) .

Limitations of the study

It is important to point out some of the limiting aspects of the present study. First, in the absence of adequate instruments, we did not track the eyes of the participants during the training, nor did we measure fixation stability before and after training with devices like scanning laser ophthalmoscopes to perform microperimetry. Indeed, our training, based on the one developed by Guzman-Martinez et al. (2009), requested patients to adjust their behavior according to the feedback provided by a flickering pattern, in a sort of biofeedback-like paradigm, but it did not directly measure performance. Thus, we

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cannot directly and decisively assert that the present training improved fixation stability in our sample of MD participants. Another possible limitation of the present study concerns the ability of patients to actually perceive the flickering pattern in the case of an eye movement. However, we used high-contrast stimuli (pixels reversed from the highest luminance [white] to the lowest luminance [black] and vice versa) with a flicker rate well within the limits of resolution of the visual system (Davis, Hsieh & Lee, 2015). This allowed the participants to see the reversing pattern, as they confirmed verbally, even close to 10° of eccentricity (patients AMD1 and AMD5), consistent with previous studies in MD patients, in which dynamic microperimetry was measured up to 10° of eccentricity (Phipps, Dang, Vingrys, & Guymer, 2004).

Our hypothesis regarding the effects of fixation stability training on performance is then based on indirect evidence stemming from the results of the transfer tasks, particularly the generalization pattern (the improvements in reading speed and the reduction in crowding in both trained and untrained eyes seem highly linked to fixation stability). Comparing the present results with those of Maniglia et al. (2016), in which a similar paradigm was used, except for the fixation stability training, we could hypothesize that the latter did play a role in the observed improvements in crowding and reading speed with respect to Maniglia et al. (2016).

Concerning the task itself, most patients are familiar with exams and visual assessments requiring subjective responses (e.g., visual field test, microperimetries), and thus we believe they complied with the instructions, although once again we do not have a direct way to test it.

One last limitation of the present study is the small sample size. Unfortunately, this is a familiar restriction for those working with MD patients. Previous training studies in the MD population tested four (Chung, 2011), seven (Maniglia et al., 2016), four (Van der Stigchel et al., 2013), eight (Plank et al., 2014), and nine (Rosengarth et al., 2013) patients, often including patients with different clinical profiles and diagnoses. Studies with larger populations are usually meta-analyses or evaluations of efficacy of orthoptic protocols rather than controlled, single- or double-blind studies and often had a shorter duration than the current study, which had 24 sessions, with respect to the 12 sessions reported by Rosengarth et al. (2013) and the 4 sessions by Chung (2011) and Tarita-Nistor et al. (2014).

Conclusion

Despite the severe impact of MD on everyday life, recent breakthroughs in vision science are offering potentially effective solutions for the application of lab-based paradigms to help develop effective treatments. In this study, we showed that a group of five MD participants and age- and eccentricity-matched controls trained on contrast detection with lateral masking and fixation stability improved their contrast sensitivity and visual acuity, similar to previous reports with a similar paradigm (Maniglia et al., 2016), but also significantly improved reading speed and visual crowding. We suggest that in clinical populations characterized by central vision loss, an oculomotor training protocol aimed at improving peripheral fixation might enhance the effects of classical PL visual training, as similarly suggested by studies in healthy individuals trained with gaze-contingent displays to simulate central vision loss (Liu & Kwon, 2016). Future studies are needed to confirm this hypothesis by directly measuring fixation stability through eye tracking, quantifying fixation training outcomes and test a larger sample of patients. Additionally, MD patients might benefit from an integrated training approach that combines different procedures to engage perceptual, oculomotor, and cognitive systems (Maniglia & Seitz, 2018). Further, synergistically combining lab-based tests, such as crowding, VA, and reading speed, with clinical tests, such as microperimetries and OCT, would offer a more complete assessment of the visual functions of the patients and monitor their progress during the course of the training.

Keywords: macular degeneration, perceptual learning, neural plasticity, clinical neuroscience

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Corresponding author: Marcello Maniglia.
Email: mmanig@ucr.edu.
Address: 900 University Ave, Riverside, 92521 CA, USA.

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