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Perceptual learning leads to long lasting visual improvement in patients with central vision loss

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Abstract.

Background: Macular Degeneration (MD), a visual disease that produces central vision loss, is one of the main causes of visual disability in western countries. Patients with MD are forced to use a peripheral retinal locus (PRL) as a substitute of the fovea. However, the poor sensitivity of this region renders basic everyday tasks very hard for MD patients.

Objective: We investigated whether perceptual learning (PL) with lateral masking in the PRL of MD patients, improved their residual visual functions.

Method: Observers were trained with two distinct contrast detection tasks: (i) a Yes/No task with no feedback (MD: N = 3; controls: N = 3), and (ii) a temporal two-alternative forced choice task with feedback on incorrect trials (i.e., temporal-2AFC; MD: N = 4; controls: N = 3). Observers had to detect a Gabor patch (target) flanked above and below by two high contrast patches (i.e., lateral masking). Stimulus presentation was monocular with durations varying between 133 and 250 ms. Participants underwent 24–27 training sessions in total.

Results: Both PL procedures produced significant improvements in the trained task and learning transferred to visual acuity. Besides, the amount of transfer was greater for the temporal-2AFC task that induced a significant improvement of the contrast sensitivity for untrained spatial frequencies. Most importantly, follow-up tests on MD patients trained with the temporal-2AFC task showed that PL effects were retained between four and six months, suggesting long-term neural plasticity changes in the visual cortex.

Conclusion: The results show for the first time that PL with a lateral masking configuration has strong, non-invasive and long lasting rehabilitative potential to improve residual vision in the PRL of patients with central vision loss.

1. Introduction

Macular degeneration (MD) is the leading cause of visual impairment in elderly population (age-related macular degeneration; AMD) in Western developed countries (Liu, Chan, & Tuo, 2012). However, this pathology can also affect young population in the form of Juvenile Macular Degeneration (JMD), whose most common manifestations are Stargardt disease and Best's disease (Bither & Berns, 1988). This condition involves loss of central vision, including loss of contrast sensitivity and visual acuity, mostly caused by a foveal scotoma.

MD can manifest itself in wet (exudative) and dry (geographic atrophy [GA]) forms (de Jong, 2006; Zarbin, 2004). The most common type of MD is the wet form (Ferris, Fine, & Hyman, 1984),

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which develops quickly as a consequence of choroid neovascularization, whereas dry MD has a slower progression. Wet MD is also characterized by distortion of the retina and by the presence of fluid, haemorrhage, and scarring.

As a strategy to overcome visual loss, patients affected by MD usually learn to use a portion of the spare retina as a new fixation point, also known as preferred retinal locus (PRL) (Guez, Le Gargasson, Rigaudiere, & O'Regan, 1993; Timberlake, Peli, Essock, & Augliere, 1987). PRL has been defined in different ways, based on various tasks and techniques to measure its location (Crossland, Engel, & Legge, 2011). The most common procedures of PRL assessment include scanning laser ophthalmoscope (SLO) (Timberlake et al., 1986), Microperimeters (Tarita-Nistor, Gonzalez, Markowitz, & Steinbach, 2008), fundus camera, and ophthalmoscopes (Mackensen, 1966). In vision science, SLO and Nidek MP-1 are the current standard to measure PRL, identifying on the fundus of the retina the portion of the spared retinal tissue that the patient uses to fixate stimuli. The most common location of the PRL is in an area located to the left with respect to the scotoma; Guez et al. (1993) reported that the PRL was located to the left of the visual field scotoma in 60% of the sample, Sunness, Applegate, Haselwood, and Rubin (1996) in 63%, and Fletcher and Schuchard (1997) in 34% of the sample. On the other hand, a survey by Trauzettel–Klosinski and Tornow (1996) in a sample of young patients with macular degeneration found that 50% of the patients had a PRL located above the retinal scotoma (i.e., in the lower quadrant of the visual field).

The position of PRL can vary between young and old patients but it is generally located not far from the border of the scotoma, with some subjects using more than one PRL to perform different tasks (e.g., one for reading and one for visual exploration). In general, being the new retinal point that MD patients use to explore the external world, the quality of vision in this eccentric region is of crucial importance, especially considering that a recent survey showed that MD patients experience a reduction in quality of life compared to age-matched control observers in several categories of the Visual Function Questionnaire 25 (VFQ 25), including social functioning (Siaudvytyte, Mitkute, & Balciuniene, 2012). Consequently, rehabilitation protocols usually focus on improving visual functions in the PRL of MD patients.

Over the past few years, Perceptual Learning (PL) paradigms have been successfully employed to treat a series of visual conditions affecting central vision (see Campana and Maniglia (2015) for a recent research topic). Specifically, training observers for several weeks on basic visual tasks improved their visual abilities, such as visual acuity (VA) and the contrast sensitivity function (CSF) (Chung, 2011; Chung & Truong, 2013; Levi & Polat, 1996; Polat, 2009; Polat, Ma-Naim, Belkin, & Sagi, 2004; Tan & Fong, 2008). One of the most efficient approaches consists in a contrast detection task of a low contrast Gabor patch flanked above and below by high contrast Gabor patches (Casco et al., 2014; Maniglia et al., 2011; Polat, 2009; Polat et al., 2004; Sterkin, Yehezkel, & Polat, 2012). For foveal stimuli, it has been found that collinear flankers placed at a distance of 3-4 times the wavelength of the target Gabor's carrier (λ) enhance target detection (Polat & Sagi, 1993, 1994a, 1994b), thus producing facilitation (i.e., lower contrast detection thresholds). On the other hand, for shorter target-to-flankers distances (i.e., 1–2λ), the target contrast detection threshold is increased compared to the condition in which the target is presented alone, thus resulting in suppression (i.e., higher contrast detection thresholds) (Polat & Sagi, 1993). PL with collinear configuration increases facilitation, reduces suppression (Polat & Sagi, 1994b) and transfers to untrained, higher-level visual abilities such as VA and contrast sensitivity with improvement retained after one year (see Polat (2009) for a review). This training paradigm has also been demonstrated to improve visual functions in patients with blurred vision, such as myopia (Camilleri, Pavan, Ghin, Battaglini, & Campana, 2014; Camilleri, Pavan, Ghin, & Campana, 2014; Casco et al., 2014; Tan & Fong, 2008), presbyopia (Polat, 2009) and in individuals with amblyopia (Campana, Camilleri, Pavan, Veronese, & Lo Giudice, 2014; Levi & Li, 2009).

In addition, there is recent psychophysical evidence of collinear facilitation in the near periphery of the visual field (4° of eccentricity), at a target-to-flankers distance larger than in the fovea (between 7λ and 8λ) (Lev & Polat, 2011; Maniglia, Pavan, Aedo-Jury, & Trotter, 2015; Maniglia et al., 2011; Maniglia, Pavan, & Trotter, 2015), suggesting that the spatial range of facilitatory lateral interactions is increased in the near periphery. Peripheral collinear suppression appears to be modulated by PL. Specifically, PL reduces suppression but does not increase facilitation (Maniglia et al., 2011), transfers to untrained visual functions (e.g., Contrast Sensitivity Function; CSF) and reduces the crowding effect, i.e., the inability of discriminating peripheral objects or letters in clutter (Levi, 2008; Pelli & Tillman, 2008). This result is consistent with recent studies using different types of stimuli (i.e., collinear configuration, letters, trigrams), which have demonstrated that PL with eccentric presentation can transfer to untrained higher visual functions, improving visual acuity and recognition of crowded letters in normal sighted observers (Bernard, Arunkumar, & Chung, 2012; Chung, 2007; Hussain, Webb, Astle, & McGraw, 2012; Lev et al., 2015; Lev et al., 2014; Yu, Legge, Park, Gage, & Chung, 2010).

The aforementioned studies show a transfer of learning from one task to another. While this might be considered as a training-dependent reduction of spatial uncertainty, the specificity of PL for collinear configurations with respect to a (control) orthogonal condition, i.e., when flankers are orthogonally oriented with respect to the vertical target (Maniglia et al., 2011), suggest the involvement of cortical neural plasticity. This is consistent with previous studies in fovea showing that PL modulates lateral interactions rather than merely contrast sensitivity, thus reflecting neural plasticity in the primary visual cortex (Polat et al., 2004; Polat & Sagi, 1994b). Consequently, PL might be considered a non-invasive and inexpensive behavioural rehabilitative technique to improve vision in the PRL of patients with central vision loss. Few recent studies used PL with MD patients in order to improve their visual abilities (Chung, 2011; Plank et al., 2014; Rosengarth et al., 2013). Rosengarth et al. (2013) trained a group of nine AMD patients using an oculomotor training paradigm for 6 months, 12 sessions in total, and found improvements in reading speed and fixation stability between pre-tests and mid-tests, but not between pre-tests and post-tests. Moreover, no significant changes in blood-oxygen-level dependent (BOLD) signals were observed between pre and post training tests in early visual areas (V1, V2 and V3) or in associative areas (LOC, fusiform gyrus, ITG). Similarly, Plank et al. (2014) trained eight AMD patients to perform a texture-discrimination task at their PRL. After six training sessions over three weeks, patients showed somesmall improvements in Vernier acuity for an eccentric line-bisection task, a weak positive correlation between the increase of BOLD signals in early visual cortex and initial fixation stability, and a weak positive correlation between the increase in task performance and fixation stability. These improvements were accompanied by a small alteration in the BOLD response in early visual cortex. We argue that the small or short lasting improvements observed in these previous studies might depend on the training task and stimuli used. In the present study MD patients and controls were trained in a contrast detection task using a collinear configuration. This procedure has been shown to probe neural plasticity (Levi & Polat, 1996; Polat & Sagi, 1994b) and producing significant generalization to other visual abilities not previously trained (e.g., VA, CFS, crowding), both in fovea and in the near periphery of the visual field (Casco et al., 2014; Maniglia et al., 2011; Polat, 2009; Polat et al., 2004; Tan & Fong, 2008).

The aim of the present study was to investigate whether training contrast detection of a low-contrast target flanked by collinear high contrast flankers can improve untrained high-level visual abilities in MD patients. Seven MD patients were trained. Three MD patients performed a Yes/No task, and other four patients performed a temporal two-alternative forced-choice task (temporal-2AFC). There is psychophysical evidence that a temporal-2AFC procedure is more effective in controlling response bias and criterion shift than a Yes/No task (Green & Swets, 1974). Furthermore, one relevant difference that we introduced between the Yes/No task and the temporal-2AFC was that only during the temporal-2AFC task an auditory feedback for incorrect responses was provided. The rationale behind the choice of these procedures derives from recent literature on foveal and peripheral collinear facilitation. Two previous studies on peripheral collinear facilitation used a Yes/No task with feedback (Lev & Polat, 2011) and without feedback (Maniglia et al., 2011). In both studies peripheral (4° eccentricity) suppression was found for short target-to-flankers separations (2-3λ) and facilitation for larger separations (7-8λ), suggesting little effect of feedback when using a Yes/No task. Besides, two other studies used a temporal-2AFC task with feedback (Maniglia, Pavan, Aedo-Jury, et al., 2015; Maniglia, Pavan, & Trotter, 2015). In the present study we compared two procedures that we have previously employed (i.e., Yes/No task with no auditory feedback and temporal-2AFC with auditory feedback) in order to assess which task is more effective in improving visual functions. Although the auditory feedback constitutes a major difference between the two procedures, previous studies showed that a Yes/No task without feedback and a temporal-2AFC with feedback yield to the same results in terms of collinear facilitation, suggesting that the feedback has little effect on collinear facilitation (Lev & Polat, 2011; Maniglia et al., 2011).

The aim of the present study was also to assess the degree of generalization to different stimuli and tasks following perceptual training with a Yes/No task and a temporal-2AFC task. We hypothesized that being a temporal-2AFC a more robust procedure (Polat & Sagi, 2007), this method should produce generalization of the training to different stimuli and tasks. Participants performed before and after PL different visual tasks including VA, contrast sensitivity and crowding, both in their PRL and in a symmetrical, peripheral retinal location with respect to the PRL (i.e., Non-PRL). In addition, three patients trained with the temporal-2AFC task (Experiment 2) also performed follow-up sessions four to six months after the training.

In order to test whether the training modulated lateral interactions between the target and the collinear flankers, in Experiment 2 observers performed an additional transfer tasks in which the flankers were orthogonally oriented with respect to the central target. Lateral interactions are highly selective for the global orientation of the three elements, therefore orthogonal flankers should not produce any modulatory effect on target's detection by lateral interactions (Casco et al., 2014; Maniglia et al., 2011; Polat & Norcia, 1996; Polat & Sagi, 1993, 1994b). We argue that post-tests showing no changes in contrast sensitivity with orthogonal flankers would rule out a general effect of learning and would point towards a PL modulated by lateral interactions. Therefore, the training was not devised to specifically improve the target's detectability per se, but rather to probe the strengthening of neural connections that may lead to an improvement of untrained visual abilities (Polat, 2009; Polat et al., 2004).

To date this is the first study using a perceptual training of collinear facilitation in order to produce long lasting improvements of visual functions in patients with central vision loss.

2. Experiment 1: PL with Yes/No task

In Experiment 1 we investigated the effect of PL for collinear configurations using a single presentation interval with a Yes/No task (Amiaz, Zomet, & Polat, 2011; Polat & Sagi, 2007; Zomet, Amiaz, Grunhaus, & Polat, 2008). Previous studies used a Yes/No task with eccentric stimulus presentation and found collinear facilitation with and without auditory feedback (Lev & Polat, 2011; Maniglia et al., 2011). We attempted at replicating these findings in MD patients since this task may be advantageous when compared to a temporal-2AFC task. In fact, Klein (2001) reported some problems of the temporal-2AFC method when applied to target detection: (i) temporal-2AFC requires the observers to memorize the stimuli presented in the two temporal intervals and then compare the results of two subjective responses. Thus, the cognitive load in a 2AFC and Yes/No is different; it is cognitively easier to respond to a single stimulus presentation. This may be disadvantageous with patients, since they can make lapses simply becoming confused about the presentation order of the stimuli, (ii) temporal-2AFC methods make generally more difficult to model the effects of probability summation and uncertainty, this is because one has to average across all the possible response criteria, (iii) models that relate psychophysical performance to underlying neural processes or mechanisms require information about how the noise varies with signal strength. The method of constant stimuli (MCS) used in Experiment 1 measures *d*'s as a function of the stimulus contrast and provides an estimate of how the variance of the signal distribution increases with contrast. The temporal-2AFC method lacks such an information, (iv) though temporal-2AFC methods are supposed to eliminate the response bias, when the stimulus is near threshold there could be a bias favouring one interval instead of the other, potentially producing higher contrast thresholds, (v) temporal-2AFC methods may be limited by the requirement to maintain fixation between the two temporal intervals (Lev & Polat, 2011).

In order to compare the results with our previous findings (Maniglia et al., 2011), we did not provide an auditory feedback in the Yes/No procedure. Observers performed six blocks per day, three blocks with stimuli presented in the PRL and three with stimuli presented in the Non-PRL. Within each block the stimulus configuration was always presented either in the PRL location or in the Non-PRL location. Each block consisted of 48 trials. Only the retinal location was randomized across participants; that is, an observer could perform three blocks with stimulus presented in the PRL and then three blocks with stimulus presented in the Non-PRL, or vice versa. Fixation was maximally facilitated on the PRL since stimuli fell on this region of the peripheral (intact) retina, spontaneously chosen for fixation. We asked whether stimulus presentation in the PRL produces better or different PL outcomes with respect to a stimulus presentation in the Non-PRL.

Table 1

Details of the MD patients and control participants that performed the Yes/No task. Details include: type of deficit, gender, age, size of the scotoma (deg), location of the PRL (deg), tested eye and visual acuity (VA; logMAR)

Patients	Deficit	Gender	Age	Scotoma size (diameter°)	Position of PRL	Tested eye	Visua Acuit (logMAR)
MD1	Stargardt	Female	38	11	Left-down 5.0°–4.2°	LE	0.7
MD2	AMD	Female	64	6	Left-down 4.5°–3.2°	LE	1
MD3	JMD	Male	32	5	Left-down 5.8°–2.7°	RE	0.52
C1	none	Female	26	None	none	Non-dominant	0
C2	none	Female	28	None	none	Non-dominant	0.041
C3	none	Female	24	None	none	Non-dominant	0.079

3. Methods

3.1. Participants

Three MD patients (MD1-MD3) and three normal-sighted observers (C1-C3), performed a Yes/No contrast detection task of a vertically oriented Gabor patch (target) flanked above and below by two high contrast collinear Gabor patches (flankers). Training was conducted monocularly. MD patients' microperimetry is shown in Fig. 1 and observers' details are summarized in Table 1.

In order to assess the location of the PRL in MD patients we used a Nidek MP-1 microperimeter (Nidek Co, Japan) to measure fixation stability. Patients were requested to fixate (eccentrically) a red cross of 4 deg in diameter for approximately 30 s, whereas controls fixated the target with their fovea. The technique measures 25 samples per second, resulting in 750 fixation samples over 30 s. The Nidek software records the time period that was measured and the proportion of the time span that was effectively tracked. It also records the percentage of fixation points that fell in a range of 2 or 4 deg diameter around the center of the fixation target, based on the time spans effectively tracked. The Nidek MP-1 was also used to measure the PRL stability. Several recordings showed the preference of the patients for the same retinal locus (see Rosengarth et al., 2013 for a similar procedure).

All participants gave their informed consent prior to their inclusion in the study. The study was performed in accordance with the ethical standards laid down by the Declaration of Helsinki (1964). The study was approved by the Ethics Committee of the Department of General Psychology, University of Padova (Protocol 1449). We obtained written informed consent from all participants.

4. Apparatus and stimuli

4.1. PL stimuli

Participants sat in a dark room 57 cm from the screen. Stimuli were displayed on a 19-inch CTX CRT Trinitron monitor with a refresh rate of 75 Hz and a spatial resolution of 1024 × 768 pixels. Each pixel subtended 1.9 arcmin. The mean luminance of the display was 46.7 cd/m^2.

Horizontal and vertical stimulus eccentricity for MD patients corresponded to their PRL in the lower left visual quadrant (5.0° × 4.2° for MD1, 4.5° × 3.2° for MD2 and 5.8° × 2.7° for MD3) or to the Non-PRL in the upper left visual quadrant. In order to establish a reliable comparison, controls observers were instructed to fixate centrally and the stimulus

Fig. 1. Nidek MP-1 microperimetry of the left eye of MD1 (left panel), of the left eye of MD2 (central panel), and of the right eye of MD3 (right panel). The blue points represent the dispersion of monocular fixation pattern that indicates the location of PRL, i.e., the part of the retina that is used by the patients during fixation tasks.

Fig. 2. Stimulus configuration used in the learning sessions. Only one spatial frequency is shown (i.e., 3 cpd). A central target Gabor is flanked by two high-contrast Gabor patches of the same orientation and spatial frequency. Panels from left to right show the five target-to-flankers distances trained: 2λ, 3λ, 4λ, 6λ and 8λ.

eccentricity was approximated to that of MD patients: 4° × 4° in either the lower left (corresponding to PRL) or upper left visual quadrant (Non-PRL). Stimuli were generated with Matlab Psychtoolbox (Brainard, 1997; Pelli, 1997). We used a gamma-corrected lookup table (LUT) so that luminance was a linear function of the digital representation of the image.

Stimuli were Gabor patches consisting of a cosinusoidal carrier enveloped by a stationary Gaussian. Each Gabor patch was characterized by its sinusoidal wavelength (λ), phase (φ), and standard deviation of the luminance Gaussian envelope (σ) in the (x, y) space of the image:

$$G\left(x,\,y\right)=\cos\left(\frac{2\pi}{\lambda}x+\varphi\right)e^{\left(-\frac{x^2+y^2}{\sigma^2}\right)} \qquad (1)$$

with $\sigma = \lambda$ and $\varphi = 0$ (even symmetric). Gabors' spatial frequency was 2 and 3 cycles per degree (cpd) (corresponding to 1.18 and 1.0 logMAR) for MD patients and 3 cpd for controls. A vertical Gabor target (Fig. 2) was presented flanked, above and below, by two high-contrast Gabor patches (0.6 Michelson contrast).

5. Transfer stimuli

5.1. Peripheral visual acuity and crowding

Eccentric visual acuity (eccentric VA) and crowding effect were measured before and after PL sessions. Stimuli were generated using E-Prime software and presented at 57 cm from the same screen used for the perceptual training. The stimuli were SLOAN-letters (D, N, S, C, K, R, Z, H, O, V) (Sloan, 1959) randomly presented for 133 ms. In the eccentric VA test, the target letter was presented in separate blocks in the PRL and in the Non-PRL of MD patients, and at 4° eccentricity for controls. The size of the letters varied according to a 1-up/3-down staircase (Levitt, 1971). The step size was 1 font size corresponding to a stroke width of –0.72 logMAR. The starting font size was 20, corresponding to a stroke width of 0.57 logMAR. Participants had to report verbally the letter displayed and the experimenter registered the answer. The session terminated after either 100 trials or 18 reversals, with the acuity threshold estimated by averaging the last 8 reversals and corresponding to 79% correct identification.

For crowding, two different letters flanked horizontally the target. The triplets were presented in separate blocks in the PRL and Non-PRL of MD patients and at 4° eccentricity for controls. MD patients and controls performed one block for each retinal location. The MD patients were able to detect all the three letters at the largest spacing used. The size of both the target and flanking letters was set 30% higher than the VA threshold. We measured the critical spacing, i.e., the edge-to-edge inter-letter distance, for which observers could discriminate the target (i.e., the central letter) with 79% accuracy. The initial distance between letters was set at 1.98 logMAR, and the step size was constant at 0.28 logMAR. The stimuli were presented for 133 ms. Spacing was varied using a 1-up/3-down staircase (Levitt, 1971). The session terminated either after 100 trials or 18 reversals. Threshold was estimated by averaging the spacing values corresponding to the last 8 reversals.

5.2. Peripheral contrast sensitivity

We measured the peripheral contrast sensitivity functions (CSF) before and after PL by using sinusoidal gratings generated with a VSG2/3 graphics processor (Cambridge Research System Ltd, Rochester, Kent, UK). Gratings were displayed on a 17-inch Philips Brilliance 107P CRT monitor with a refresh rate of 70 Hz and a spatial resolution of 1024 × 768 pixels. The stimuli were vertical gratings displayed on the whole screen area (26 × 20 deg) with a central black circular window of the size of the patients' scotoma (diameter: ~8 deg). Contrast thresholds were estimated with both the ascending and descending method of limits. In the ascending method, the initial contrast of the grating was set at a low level so that the grating could not be detected, then its contrast was gradually increased until the participant reported that she/he could detect it. In the descending method this was reversed. In each case, the threshold was considered to be the contrast at which the grating was just detected. The ascending and descending methods were presented in separate blocks and contrast thresholds estimated from each block were averaged. Three spatial frequencies were tested: 1, 2 and 4.5 cpd (corresponding to 1.48, 1.18 and 0.82 logMAR) (Durbin, Mirabella, Buncic, & Westall, 2009). We measured the peripheral CSF for the PRL only.

5.3. Statistical analysis

In order to assess the effect of PL on the *d*'s (see the PL procedure section), we conducted a mixed ANOVA including as between-subjects factor the group (MD patients vs. controls) and as a within-subjects factors the training (pre- vs. post-training), retinal location (PRL vs. Non-PRL), and target-to-flankers distance.

For crowding and visual acuity, we conducted a mixed ANOVA including as between-subjects factor the group (MD patients vs. controls), and as within-subjects factors the training (pre-vs. post-training) and retinal location (PRL vs. Non-PRL). Where applicable, we performed separate repeated measures ANOVA for patients and controls.

For the CSF, we conducted a mixed ANOVA including as between-subjects factor the group (MD patients vs. controls) and as within-subjects factors the training (pre- vs. post-training) and spatial frequency. The alpha level was 0.05. *Post-hoc* multiple comparisons were corrected using the Bonferroni correction.

6. Procedure

6.1. Pre-and post-training evaluation

Participants performed a monocular eccentric-VA, crowding and contrast sensitivity (CSF). All these tests were repeated within five days from the last training session.

6.2. PL procedure

We used the psychophysical method of constant stimuli (Laming & Laming, 1992). In the method of constant stimuli, a series of contrast values of the stimulus are initially selected from pilot observations. Fixed contrast values are then repeatedly presented in random order while asking to the participant to report if they detect it or not. In our case we asked to the participants to report if they could detect or not the central target (i.e., Yes/No task). The task was performed with a vertical collinear configuration and target-to-flankers distances of 3λ, 4λ and 6λ presented in the left low (PRL) and upper (Non-PRL) visual quadrants (separate blocks). Stimuli were presented for 133 ms.

A daily session consisted of one hour of training divided in 12 experimental blocks. Each experimental block lasted approximately 5 minutes and consisted of 48 randomly presented trials that corresponded to 8 repetitions of 6 fixed contrast levels: two values above and two values below (in steps of 0.1 log units) the contrast threshold estimated before the training individually for each observer. In addition, we introduced catch trials in which the target was not present (Michelson contrast = 0). This was necessary to estimate individually for each observer the False Alarms rate, Criterion and *d*'*s*. The percentage of catch trials was 16%, i.e., 1/6 of the total number of trials. Initial contrast thresholds were estimated using a temporal-2AFC task and a 1-up/3-down staircase, leading to a 79% correct detection.

We trained two spatial frequencies (2 and 3 cpd), three target-to-flanker distances (2λ, 3λ and 6λ) and two retinal locations (PRL and Non-PRL). A standard daily session consisted of 576 trials separated in 12 blocks, in which the target-to-flankers distance was varied starting from the largest distance (6λ), and the spatial frequency was varied starting from the lowest value (2 cpd). In the first six blocks stimuli were presented in the PRL location, whereas in the last six blocks stimuli were presented in the Non-PRL location. This training regime was performed 3 times a week. Thus, each participant performed 24 sessions distributed over the course of 8 weeks. For each participant, and for each combination of spatial frequency, target-to-flankers distance and stimulus location, we obtained the probability of correct detection associated to each of the six contrast levels. *d*' were derived by the proportion of "yes" responses when the target was absent (i.e., False Alarm) and the proportion of "yes" responses for the second highest contrast value presented (corresponding approximately to the 90% of the observer's initial contrast threshold) (Maniglia et al., 2011).

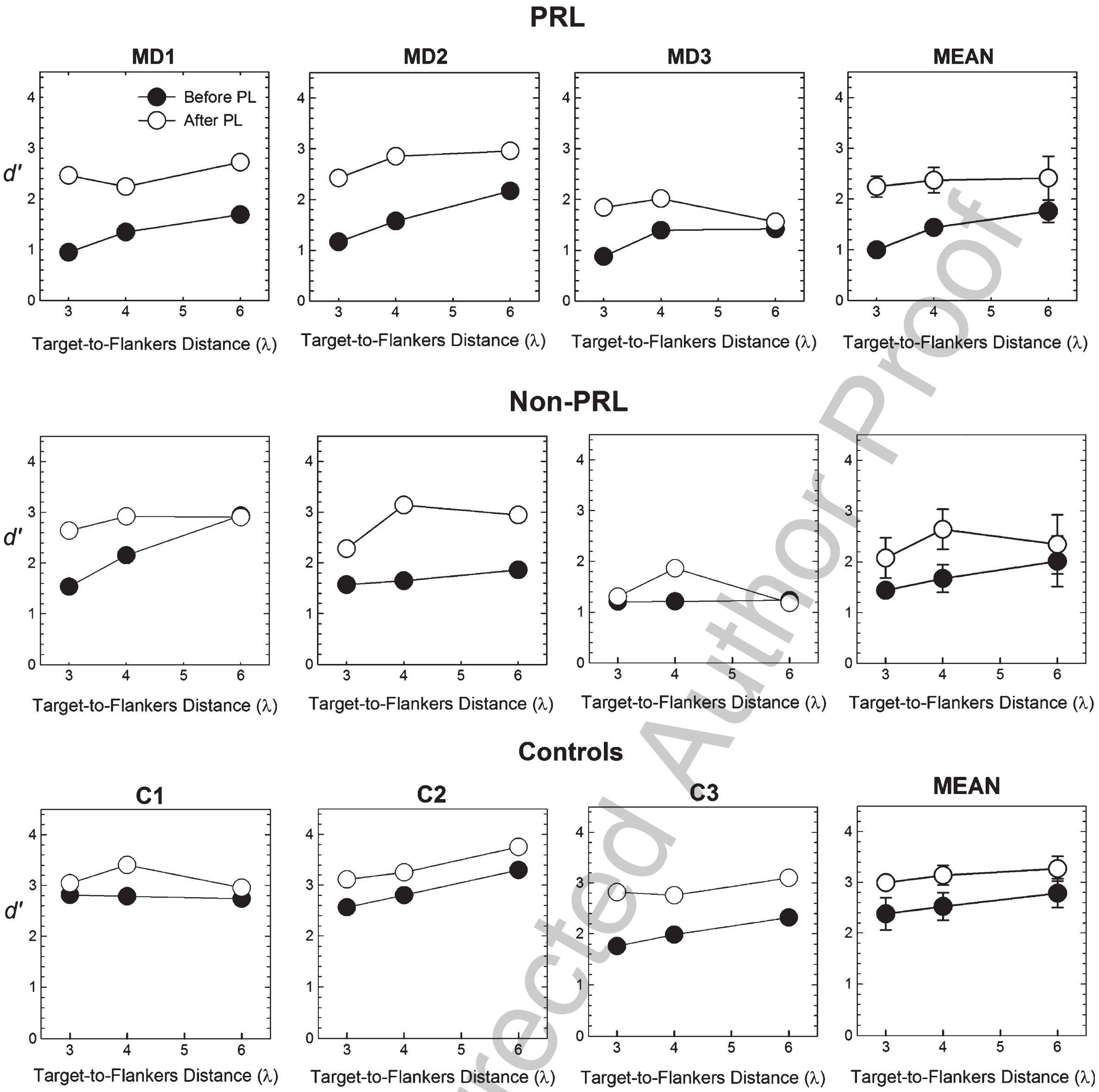

Fig. 3. *d*' estimated before and after PL as a function of the target-to-flankers distance for each MD patients and separately for the retinal locations trained (i.e., PRL and Non-PRL) (panels within the black frame). *d*' for controls are also reported (bottom row). Rightmost panels report average data for MD patients (separately for PRL and Non-PRL) and controls. Error bars ± SEM.

7. Results

7.1. The effect of PL on contrast sensitivity (d')

PL results are shown in Fig. 3. Data are divided for PRL and Non-PRL in patients and pooled for retinal location for the control group. A mixed ANOVA including as factors the group (MD patients vs. controls), training (before vs. after PL), retinal location (PRL vs. Non-PRL) and target-to-flankers distance (2λ, 3λ and 6λ), reported a significant effect of PL ($F_{1,4} = 16.6$, $p = 0.015$, *partial*-$\eta^2 = 0.8$), while the effect of group was not significant ($F_{1,4} = 7.37$, $p = 0.053$, *partial*-$\eta^2 = 0.65$). The interaction between training and retinal location only approached significance ($F_{2,8} = 7.01$, $p = 0.057$, *partial*-$\eta^2 = 0.98$). These results indicate that PL generally increased contrast sensitivity for the flanked target; that is, PL renders participants more sensitive to contrast variations in all conditions. Moreover, consistent

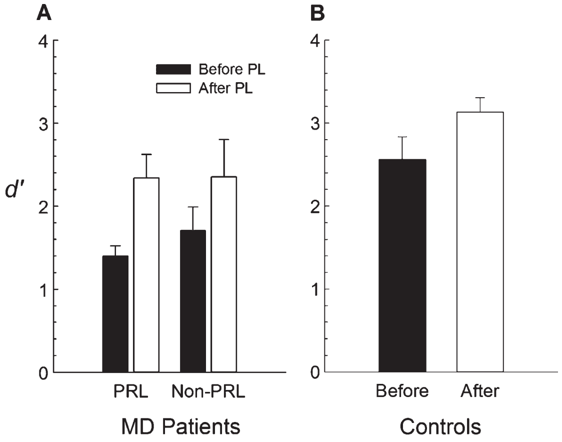

Fig. 4. A) Mean *d*'s estimated for MD patients before and after PL as a function of the retinal location (i.e., PRL and Non-PRL). Data are pooled across the spatial frequencies and the target-to- flankers distances used. B) Mean *d*'s estimated for controls before and after PL. Data are pooled across retinal location, spatial frequency, and target-to-flankers distance. Error bars ± SEM.

with previous studies (Lev & Polat, 2011; Polat & Sagi, 2007), we found lower d' for shorter target-to-flankers distances before training. This effect may be due to a higher FA rate for short distances (Polat & Sagi, 2007) and/or suppression from short target-to-flankers distances at the periphery.

A repeated measures ANOVA conducted separately for MD patients and controls showed no main effect of the training ($F_{1,2} = 15$, $p = 0.061$, *partial*-$\eta^2 = 0.88$, and $F_{1,2} = 13.39$, $p = 0.067$, *partial*-$\eta^2 = 0.87$, for MD patients and controls respectively).

We also assessed the effect of PL on Criterion and False Alarms rates. In signal detection theory (SDT), the Criterion (*C*) is the judgment each observer uses to produce a response in a detection task, and it can be liberal (when *C* is below zero) or conservative (when C is above zero). For MD patients, a repeated measures ANOVA including as factors the training, retinal location and target-to-flankers distance, reported only a significant effect of the target-to-flankers distance ($F_{2,4} = 7.62, p = 0.043$, *partial*-$\eta^2 = 0.79$). *Post-hoc* comparison showed a significant difference between 3λ and 4λ ($p = 0.033$), with C values being significantly lower at 3λ than at 4λ. For controls, a repeated measure ANOVA on C including as factors the training and the target-to-flankers distance did not report any significant effect or interaction. This is consistent with the results of MD patients.

Similarly, we conducted a repeated measures ANOVA on False Alarms (FA), separately for MD patients and controls. Results showed a significant effect of the target-to-flankers distance for the patients group ($F_{2,4} = 11.31$, $p = 0.023$, *partial*-$\eta^2 = 0.85$), with FA decreasing with increasing the target-to-flankers distance, but no significant effects for the control group. Table 2 reports C and FA for MD patients and controls.

Figure. 4A shows the effect of PL averaged across the spatial frequencies used and target-to-flankers distances. There was no effect of retinal location in either the patients or controls (Fig. 4B), for which training was not significant ($t^2 = 1.82$, $p = 0.2$).

7.2. *Transfer to CSF*

Figure. 5 shows the contrast sensitivity function (CSF) for MD patients and controls. A mixed ANOVA reported a significant effect of training ($F_{1,4} = 9.45$, $p = 0.037$, *partial*-$\eta^2 = 0.7$) and spatial frequency ($F_{2,4} = 5.72$, $p = 0.029$, *partial*-$\eta^2 = 0.59$), while the factor group was not significant ($F_{1,4} = 2.29$, $p = 0.2$, *partial*-$\eta^2 = 0.36$). Overall, there is a general improvement of contrast sensitivity in both groups, specifically MD patients improved by 25.8%±21%, while controls by 30.5%±30.1%.

7.3. *Transfer to VA*

Eccentric vision has higher optical blur and lower spatial resolution than central vision (Strasburger, Rentschler, & Juttner, 2011). Therefore, it is important to establish whether PL on collinear configurations transfers to the letter recognition task (eccentric VA), since contrast detection and letter recognition seem to be related (Chung, Legge, & Tjan, 2002; Chung, Mansfield, & Legge, 1998; Legge, Rubin, Pelli, & Schleske, 1985; Levi, Song, & Pelli, 2007; Majaj, Pelli, Kurshan, & Palomares, 2002; Patching & Jordan, 2005; Solomon & Pelli, 1994). Transfer of PL to eccentric VA is shown in Fig. 6, in which controls' data are pooled for retinal location and MD patients' data are shown separately for the two retinal locations.

A mixed ANOVA showed a significant effect of the group (i.e., MD patients vs. controls) ($F_{1,4} = 19.7, p = 0.011$, *partial*-$\eta^2 = 0.83$) and training ($F_{1,4} = 11.22$, $p = 0.029$, *partial*-$\eta^2 = 0.74$). Overall, MD patients have lower eccentric VA than controls, and the effect of training was the same in MD patients and normal controls. MD patients improved their VA of 0.19 ± 0.065 logMAR in their PRL and 0.16 ± 0.033 logMAR in the Non-PRL

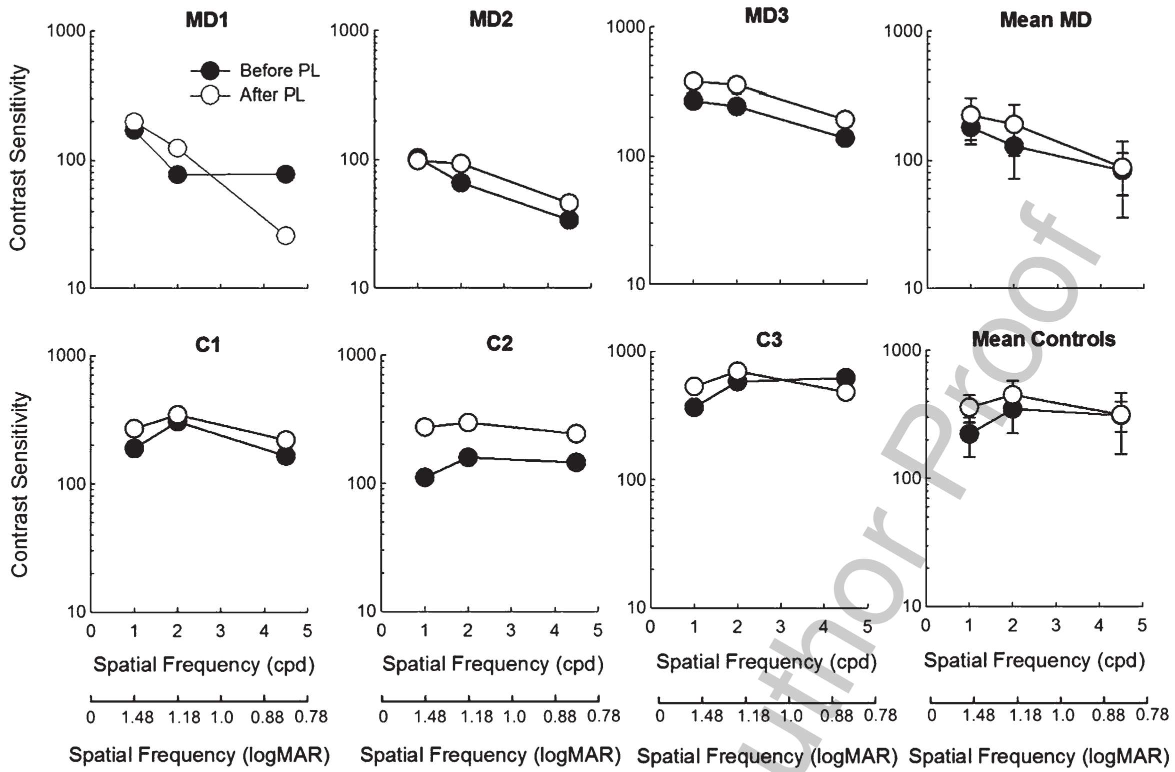

Fig. 5. Contrast sensitivity as a function of the spatial frequencies tested (1, 2 and 4.5 cpd) is shown separately for each MD patient and control observers. Mean contrast sensitivity is also reported for MD patients and controls (rightmost panels). The secondary abscissa reports spatial frequency values in logMAR. Error bars ± SEM.

(corresponding to an improvement of 19.7%±5.74% and 18.4%±3.2% in the PRL and Non-PRL, respectively). Controls improved their VA of 0.18 ± 0.18 logMAR, corresponding to an improvement of 31%±33.8%.

7.4. Transfer to crowding

Transfer of PL for crowding is shown in Fig. 7. A mixed ANOVA did not report any significant result. On average, critical spacing increased by 5.4%±10.3% in the PRL of MD patients, but decreased by 0.82%±31.6% in the Non-PRL. For controls on average critical spacing decreased by 35%±30.6%. However, all these differences were not statistically significant.

8. Discussion of Yes/No task results

Results with the Yes/No task showed that PL increased contrast sensitivity for the flanked target in both MD patients and controls. This improvement is associated with a reduction of FA in both groups. We also found that the improvement in target detection was independent of target-to-flankers distance, while in our previous study (Maniglia et al., 2011) we found a PL-induced decrement of contrast thresholds only for the shortest target-to-flankers distances tested, but no change in contrast thresholds was observed at 8λ.

Interestingly, the results showed a general improvement of contrast sensitivity at both retinal locations. One possibility is that it reflects, in addition to or instead of a PL-dependent improvement in contrast sensitivity, a PL-related increase of attentional resources to the target configuration. Indeed, in our previous study (Maniglia et al., 2011), the stimuli in each block were randomly presented in one of the two visual hemi-fields at 4° eccentricity. Therefore, attention had to be distributed across the two spatial locations instead of being focused to one fixed location, i.e., either the PRL or the Non-PRL. Reduced attentional demands may have produced a larger increase of *d*'s in the present study than that observed in Maniglia et al. (2011). To test for this possibility, that is, whether attention towards a smaller portion of the visual field would increase observers'

Table 2

The top table reports False Alarms (FA) for MD patients and controls. For MD patients FA are reported separately for PRL and Non-PRL, before and after the perpetual training (Pre/Post) and for each target-to-flankers distance (3λ, 4λ, and 6λ). For controls, data from the two retinal locations trained were pooled. The bottom table reports Criterion (C) values for MD patients and controls

FALSE ALARMS

	PRL			Non-PRL		
	3λ	4λ	6λ	3λ	4λ	6λ
	Pre/Post	Pre/Post	Pre/Post	Pre/Post	Pre/Post	Pre/Post
MD1	0.60/0.48	0,38/0.27	0 23/0.05	0.46/0.27	0.31/0.17	0.27/0.12
MD2	0.21/0.31	0.19/0.19	0.15/0.067	0.210.33/	0.19/0.11	0.15/0.01
MD3	0.15/0.07	0.048/0.029	0.048/0.029	0.11/0.21	0.029/0.08	0.01/0.07
	3λ	4λ	6λ			
	Pre/Post	Pre/Post	Pre/Post			
C1	0.21/0.19	0.18/0.15	0.23/0.07			
C2	0.12/0.2	0.11/0.1	0.04/0.07			
C3	0.56/0.06	0.27/0.01	0.12/0.01			

CRITERION

	PRL			Non-PRL		
	3λ	4λ	6λ	3λ	4λ	6λ
	Pre/Post	Pre/ Post	Pre/Post	Pre/Post	Pre/Post	Pre/Post
MD 1	–0 62/–0 63	–0.56/ –0.36	0 22/0 78	–0.97/0.39	–0.39/ –0.41	–0 21/–0 07
MD2	–0.098/ 0.43	0.16/ –0.19	0.41/0.18	0.03/ –0.83	0.07/ –0.14	0.24/0.84
MD3	0.92/0 43	1.20/1.32	0.86/1.36	I 3/0 32	1.43/1.20	1.54/ 1 06
	3λ	4λ	6λ			
	Pre/Post	Pre/Post	Pre/Post			
C1	–0.54/ –0.52	–0.28/ –0 33	–0.34/ 0 09			
C2	0.23/ –0.46	–0 04/ –0 12	0.09/ –0.17			
C3	–0.53/0.9	–0.03/0.85	0.37/0.57			

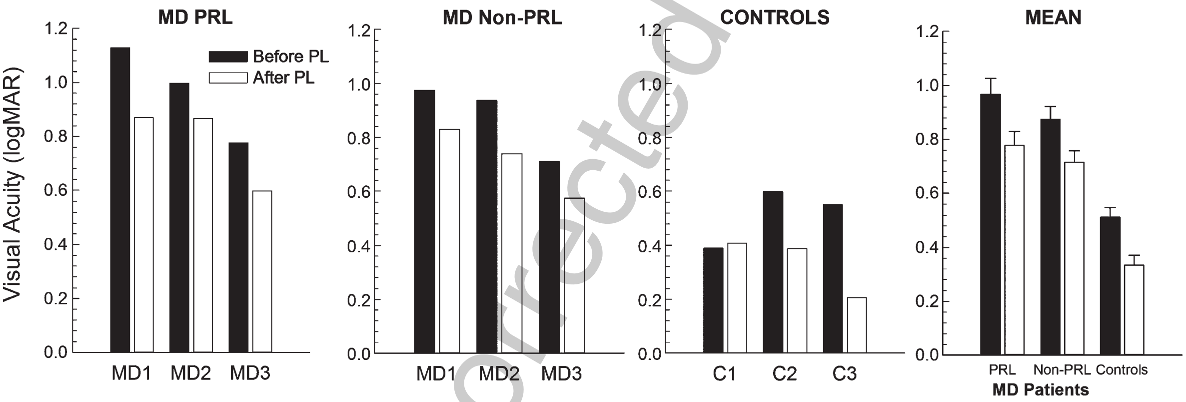

Fig. 6. Eccentric visual acuity (logMAR) for MD patients, separately for the two retinal locations (i.e., PRL and Non-PRL). Mean eccentric visual acuity (data pooled across the two retinal locations) is also shown for controls. The rightmost panel shows average data for MD patients and controls. Error bars ± SEM.

performance, we compared *d*'s ratios (i.e., *d*' after PL / *d*' before PL) obtained by MD and controls with those of the eight observers tested binocularly by Maniglia et al. (2011) in the same stimulus conditions (i.e., 3λ and 4λ for a spatial frequency of 2 cpd). The results of a Crawford *t*-test (Table 3) revealed no significant difference between the two groups, with except for the target-to-flankers distance at 3λ in only one MD patient (MD3).

Overall there are no differences between the *d*' ratios calculated in the present study and those calculated from our previous study (Maniglia et al., 2011), suggesting a little role of attention in producing the PL effect, that may rely on a flankers' induced

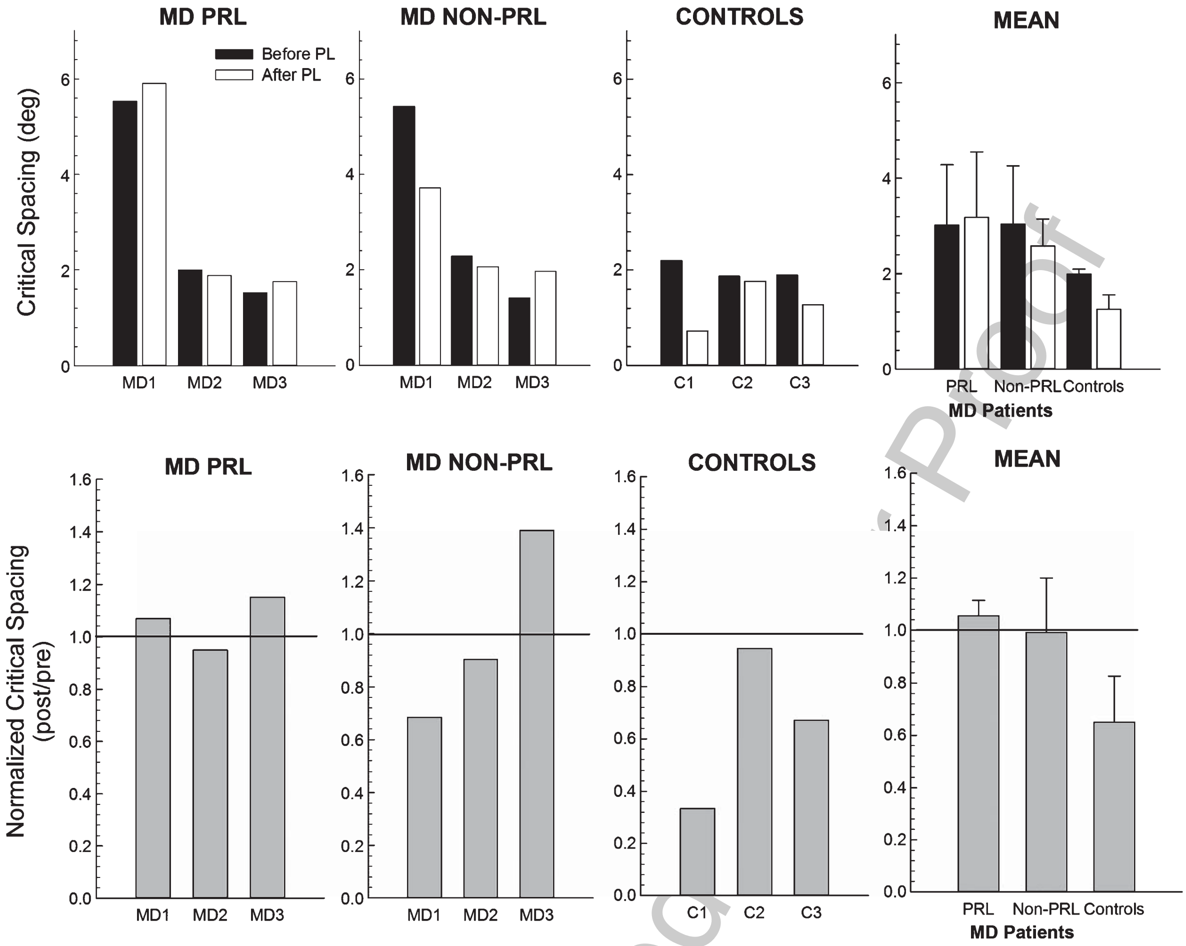

Fig. 7. (A) Critical spacing (deg) for MD patients in the PRL and Non–PRL. Critical spacing is also shown for each control observer. For controls, data were pooled across the two retinal locations. The rightmost panel shows group mean for MD patients (separately for PRL and Non-PRL) and controls. (B) Normalized critical spacing calculated as the ratio between post- and pre-training thresholds for MD patients (separately for PRL and Non-PRL) and controls. The rightmost panel shows group means. Values below one (continuous black line) indicate improvement after training, whereas values above one indicate no training-related improvement. Error bars ± SEM.

Table 3

The results of a Crawford *t*-test between the *d*'s ratio for MD and control participants (*d*'s after PL / *d*'s before PL) and the average *d*' ratio calculated on the data of Maniglia et al. (2011) across eight observers tested binocularly and in comparable experimental conditions (i.e., 3λ and 4λ for a spatial frequency of 2 cpd)

	3λ		4λ	
Observer	*t*	*p*	*t*	*p*
MD1	1.25	0.25	–0.371	0.72
MD2	0.526	0.62	1.299	0.231
MD3	2.893	0.02*	0.408	0.69
C1	0.25	0.81	–0.668	0.52
C2	0.107	0.92	–0.334	0.75
C3	–0.012	0.99	–0.037	0.97

modulation of contrast sensitivity (Polat, 2009; Polat & Sagi, 1994b; Tan & Fong, 2008). The reduction of the crowding effect was effective in only one patient out of three, but only in the Non-PRL location. The reason for the lack of PL effect on crowding in the other two MD patients might be due to several factors. First, the patients' sample was overall older than the controls, so the neural plasticity might have been reduced in the former group. Second, for MD patients those retinal regions might have reached a "plateau" due to a more constant use in everyday life. This hypothesis is further supported by the fact that the patient that improved in the crowding task had a larger pre-training critical spacing. Finally, several studies show that peripheral performance in MD patients can be worse than peripheral performance of normally sighted observers, even in a retinal area not affected by scotomas (Chung, 2011). For controls, on average, we found a small reduction in critical spacing after the training, though this effect was not significant. This may depend on the fact that critical spacing in controls was already small before training.

9. Experiment 2: PL with a 2AFC task

Four different MD patients and three controls performed a contrast detection task with collinear configurations using a temporal-2AFC task with feedback on incorrect trials (Maniglia, Pavan, Aedo-Jury, et al., 2015; Maniglia, Pavan, & Trotter, 2015; Polat, 2009; Polat & Sagi, 1993, 1994b). The temporal-2AFC procedure is considered to be effective in reducing response bias and criterion shift with respect to a Yes/No task (Green & Swets, 1974). Giorgi, Soong, Woods, and Peli (2004) showed that a temporal-2AFC task is a suitable procedure to measure collinear facilitation as a function of the target-to-flankers distance, and it is more effective than a spatial-2AFC. In addition, PL with a temporal-2AFC task combined with auditory feedback may reinforce learning by maximizing decision mechanism through internal reward (Kumano & Uka, 2013), which in turn may affect PL and promote generalization to untrained visual tasks.

On the other hand, temporal-2AFC may not be an adequate psychophysical procedure for several reasons. First, simulation studies showed that threshold estimation with a temporal-2AFC task are less efficient with respect to a Yes/No paradigm, using the same number of trials (Alcala-Quintana & Garcia-Perez, 2004; Garcia-Perez, 1998; Garcia-Perez & Alcala-Quintana, 2005; Garcia-Perez & Peli, 2001; Kershaw, 1985; Taylor, 1967). Second, when used with parafoveal stimuli, performance may be limited by the observers' ability to maintain fixation between the first and the second interval (Lev & Polat, 2011), a problem that becomes insidious in MD patients that have peripheral and often unstable fixation (Rosengarth et al., 2013). However, recent studies on peripheral collinear facilitation (Maniglia, Pavan, Aedo-Jury, et al., 2015; Maniglia, Pavan, & Trotter, 2015) showed that in normal sighted observers a temporal-2AFC task leads to consistent and stable effects.

The aim of Experiment 2 was to assess whether using a different procedure produces a different PL effect and a different amount of transfer to stimuli and tasks not previously trained. Moreover, differently from Experiment 1, MD patients were trained only in their PRL. Before and after the perceptual training we measured contrast detection thresholds for a vertical target flanked by orthogonally oriented flankers (orthogonal configuration) and flanked by vertically oriented flankers (collinear configuration). Using the orthogonal configuration we assessed whether PL was specific for the trained collinear configuration, since lateral interactions are specific for collinearly-flanked targets (Polat & Sagi, 1994b). Three MD patients trained with the temporal-2AFC task also performed follow-up tests in order to assess whether the effect of training was retained. Patient MD4 performed follow-up tests after four months, patient MD7 after five months, patients MD5 and MD6 after six months.

10. Method

10.1. Participants

Four MD patients (MD4-MD7) and three controls (C4-C6) participated. Patients' microperimetry is shown in Fig. 8 and observers' details are summarized in Table 4.

11. PL Stimuli

Apparatus and stimuli were the same as used for the Yes/No task. Gabor patches had a spatial frequency of 2 and 3 cpd for controls (corresponding to 1.18 and 1.0 logMAR). For MD4 Gabor patches had a spatial frequency of 1 and 3 cpd (i.e., 1.48 and 1.0 logMAR), for MD5 spatial frequencies were 4, 5 and 6 cpd (i.e., 0.88, 0.78 and 0.7 logMAR), for MD6 we used a spatial frequency of 3 cpd (i.e., 1.0 logMAR) and for MD7 the spatial frequency was 2 cpd (i.e., 1.18 logMAR). Two high contrast (Michelson contrast 0.6) collinear flankers were placed at various distances above and below the target (i.e., 2λ, 3λ, 4λ, and 8λ). The tests were conducted monocularly, either in the left eye (MD4 and MD6), or the in the right eye (MD5 and MD7). Patient MD5 was trained with both vertical and horizontal collinear configurations since for neither configurations the flankers fell in the scotomatous area.

12. Transfer stimuli

To assess whether training transferred to viewing conditions similar to those of everyday life, transfer stimuli were presented centrally (except for crowding) and observers were asked to use optimal fixation.

Table 4

Details of the MD patients and controls that performed the temporal-2AFC task. Details include: type of deficit, gender, age, size of the scotoma (deg), location of the PRL (deg), tested eye and visual acuity (VA; logMAR)

Patients	Deficit	Gender	Age	Scotoma size (diameter°)	Position of PRL	Tested eye	Visual Acuity (togMAR)
MD4	CRSC	Male	50	4	Left-up 2.0°–1.0°	LE	07
MD5	Macular hole	Female	49	3	Right-up 1.5°–1.0°	RE	0.15
MD6	Best disease	Male	58	8	Left-up 4.0°–2.7°	LE	0.7
MD7	CRD	Male	62	6	Left 4.5°	RE	07
C4	none	Female	54	none	None	Non-dominant	0
C5	none	Male	54	none	None	Non-dominant	0
C6	none	Male	64	none	None	Non-dominant	0

12.1. Visual acuity and crowding stimuli

We used the FrACT (Freiburg Visual Acuity and Contrast Test) Software (Bach, 1996) to measure visual acuity. Observers viewed the stimulus (Landolt-C) monocularly for a maximum of 30 s. The Landolt-C had four possible gap orientations. Observers had to discriminate the orientation of the gap (4AFC). Stimulus and gap sizes were varied according to the accuracy of the response. The viewing distance was 200 cm.

Crowding was measured as in Experiment 1, but only for MD patients and with stimulus presentation in the PRL. The stimulus duration was 133 ms.

12.2. CSF stimuli

CSF was measured using FrACT Software and only for MD patients. Stimuli were Gabor patches of 5 deg (full width at half maximum) with four different orientations (horizontal, vertical, diagonal at 45° and 135°). Observers performed monocularly an orientation discrimination task (4AFC). Stimulus disappeared immediately after the observer's response. Stimuli were displayed for a maximum of 30 s. The contrast of the stimulus was varied according to a BEST PEST procedure. The viewing distance was 200 cm and an acoustic feedback was provided for incorrect trials. Spatial frequencies tested were 1, 3, 5, 7, 9 and 11 cpd (corresponding to 1.48, 1.0, 0.77, 0.63, 0.52, 0.44 logMAR).

12.3. Orthogonal configuration

Before and after the training observers also performed, with the same presentation conditions used for the PL stimuli, a transfer condition in which they had to detect a central vertical target flanked by orthogonally oriented Gabor patches. In addition, patient MD5, who was trained with horizontal collinear configurations, after the training performed the contrast detection task on a horizontal stimulus configuration with a horizontal target flanked by vertically oriented Gabor patches (i.e., orthogonal configuration).

13. Procedure

13.1. Pre- and post-training evaluation

Before PL, we measured monocularly VA, crowding, CSF and the target contrast thresholds for the orthogonal configuration. All the tests were repeated after the training sessions.

13.2. Collinear facilitation

The amount of collinear facilitation was estimated by computing the threshold elevation (TE) as:

$$TE = \log^{10}\left(\frac{CT\ collinear}{CT\ orthogonal}\right) \tag{2}$$

Where *CT collinear* is the contrast threshold estimated in the collinear condition, whereas *CT orthogonal* is the contrast threshold estimated in the orthogonal condition. *TE* was calculated separately for each target-to-flankers distance (i.e., 2λ, 3λ, 4λ, and 8λ).

13.3. PL procedure

The contrast threshold of the target was varied according to 1-up/3-down staircase (Levitt, 1971). Participants performed a temporal-2AFC. The target was presented in one of the two temporal intervals whereas the flankers were always presented in both temporal intervals. Observers had to report in which temporal interval the target was presented. An acoustic feedback was provided for incorrect trials. Each

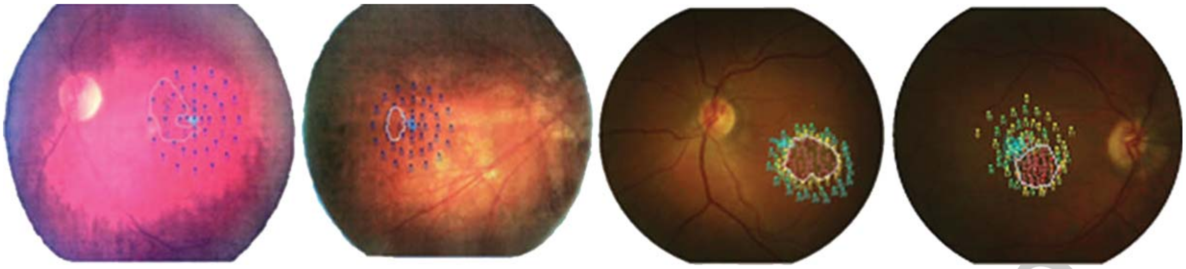

Fig. 8. Nidek MP-1 microperimetry of patients MD4 (left eye), MD5 (right eye), MD6 (left eye) and MD7 (right eye). The blue points indicate the part of the retina that is used by the patient during fixation tasks.

block terminated after 120 trials or 16 reversals. Contrast thresholds were estimated by averaging the contrast values corresponding to the last 8 reversals. In order to control for fixational eye movements, control observers were instructed to fixate the central fixation point while stimuli were randomly presented on the right or on the left visual hemi-field in each temporal interval.

During the training, the target-to-flankers distance was varied within a daily session, starting always with the largest distance, whereas the global orientation of the stimulus configuration (horizontal and vertical) was repeated twice across four daily sessions. Stimulus duration was 250 ms for MD4, MD6 and MD7, whereas for MD5 and controls it was 133 ms. Stimulus duration was longer than Experiment 1 because three of the four MD patients could not detect targets presented for 133 ms. Participants completed between 19 and 27 sessions in 6–8 weeks, with spatial frequencies adjusted according to performance, starting from the lowest one (Polat, 2009). Patients performed the training in their PRL.

14. Results

14.1. PL results on threshold elevation

Results for PL are shown in Fig. 9. We performed a statistical analysis of the effect of PL on *TE* values. This analysis was performed despite MD patients and controls were trained on a different range of spatial frequencies. A mixed ANOVA including as between-subjects factor the group (MD patients vs. controls) and as within-subjects factors the training (pre- vs. post-training) and the target-to-flankers distance (i.e., 2λ, 3λ, 4λ, 8λ) showed a significant effect of the group ($F_{1,5} = 51.53$, $p = 0.001$, $partial{-}\eta^2 = 0.91$), training ($F_{1,5} = 9.78$, $p = 0.026$, $partial\text{-}\eta^2 = 0.66$), a significant interaction between training and target-to-flankers distance ($F_{3,15} = 9.05$, $p = 0.05$, $partial\text{-}\eta^2 = 0.644$) and a significant interaction between group and target-to-flankers distance ($F_{3,15} = 4.05$, $p = 0.027$, $partial\text{-}\eta^2 = 0.448$).

A separate repeated measures ANOVA for MD patients including as factors the training and the target-to-flankers distance showed no significant effects or interactions.

A repeated measures ANOVA for controls including as factors the training and target-to-flankers distance showed a significant interaction between the two factors ($F_{3,6} = 17.01$, $p = 0.02$, $partial\text{-}\eta^2 = 0.89$).

PL substantially reduced the threshold elevation, and follow-up data on two MD patients (MD6 and MD7) show that the improvement was retained after six months for patient MD6 and after five months for MD7 (see Fig. 9, grey symbols). For controls the reduction only occurred at a target-to-flankers distance of 2λ (paired *t*-test corrected for multiple comparison: $t^2 = {}^{8.74}$, $p = 0.0125$ [critical $p = 0.0125$]). However, we cannot exclude an effect of PL for the other target-to-flankers distances since contrast thresholds were measured using low (8-bit) luminance resolution.

We also performed Bonferroni corrected one-sample *t*-tests (critical $p = 0.0125$) between estimated threshold elevation and zero. Values above zero reflect suppression whereas values below zero reflect facilitation. For MD patients, the *t*-tests showed significant collinear facilitation after training for target-to-flankers distances of 3λ ($t3 = 7.43$, $p = 0.005$) and 4λ ($t3 = 6.89$, $p = 0.006$).

Interestingly, the pattern of lateral interactions seems different between MD patients and controls. In particular, three out of four MD patients show collinear facilitation for target-to-flankers distances that in normal perifoveal vision leads to suppression (Maniglia, Pavan, Aedo-Jury, et al., 2015; Maniglia

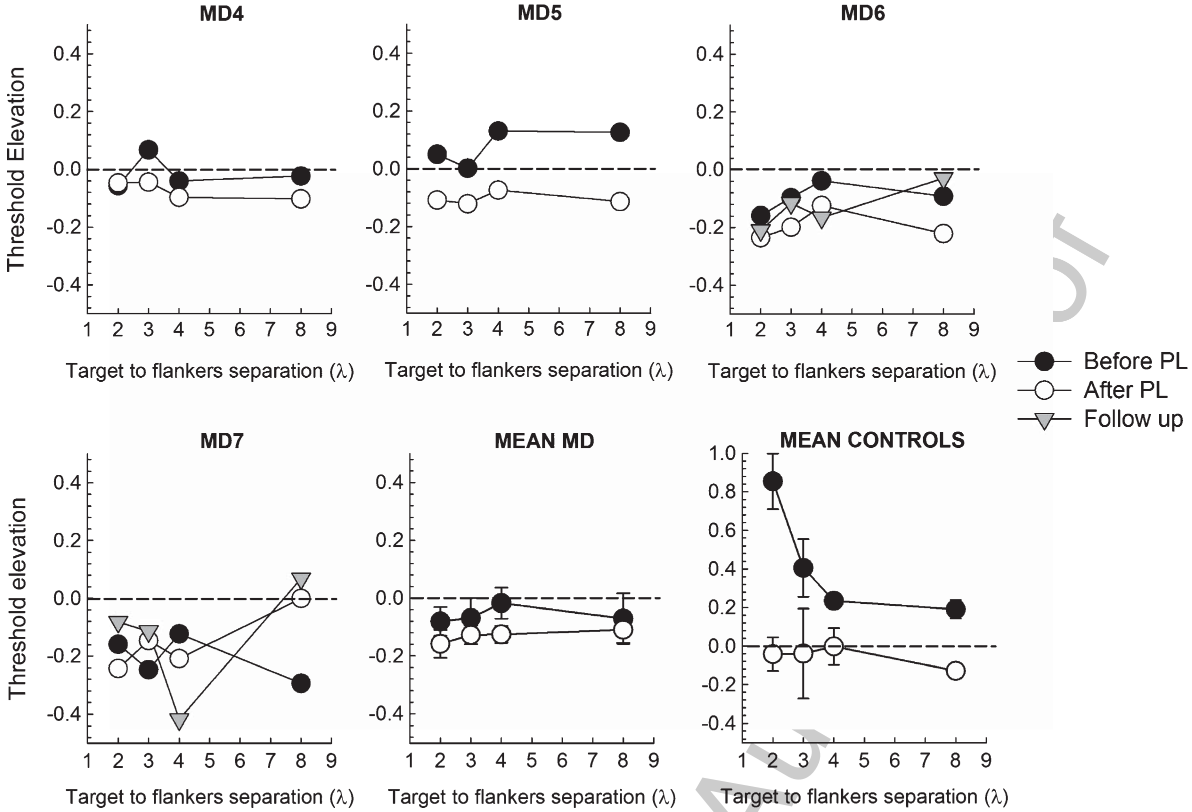

Fig. 9. Threshold elevation (*TE*) values (i.e, lateral interaction curves) as a function of the target-to- flankers distance for four MD patients and controls. *TE* is averaged across the two global configurations (horizontal and vertical) and spatial frequencies trained: 1 and 3 cpd (MD4); 4, 5 and 6 cpd (MD5), 3 cpd (MD6), 2 cpd (MD7) and 2 and 3 cpd (controls). Follow-up data are also reported for MD6 and MD7 (follow-up after 6 and 5 months, respectively). The dashed line represents the point of no modulation. Average data for MD patients and controls are also reported. Error bars ± SEM.

et al., 2011; Maniglia, Pavan, & Trotter, 2015). A possible explanation invokes neural reorganization of perceptive fields (PFs; the psychophysical correspondent of the classical receptive field in the visual cortex) (Jung & Spillmann, 1970) with recruitment of units formerly responding to foveal vision; consequently, the size of peripheral PFs is reduced and shorter target-to-flankers distances lead to facilitation rather than inhibition. This data is consistent with post facto analysis of crowding in AMD patients (Chung, 2011). Bonferroni corrected one-sample *t*-tests between threshold elevation values and zero were also performed for controls; the *t*-tests did not report any significant difference either before or after the training ($p > 0.05$).

Overall, *TE* values are modulated by PL. In MD patients PL generally increases collinear facilitation whereas in controls PL decreases suppression at 2λ. These results suggest a different pattern of lateral interactions in MD patients and controls which are both modulated by PL.

14.2. Transfer to VA

Figure. 10 shows visual acuity thresholds for discriminating the gap orientation in the Landolt-C test, obtained before and after PL for MD patients. Follow-up data were collected after six months for MD5 and MD6, and after five months for MD7.

A paired *t*-test (pre-vs. post-training) showed a significant improvement of visual acuity (i.e., reduced logMAR) ($t3 = 3.51$, $p = 0.039$). The average VA improvement was 0.29 ± 0.16 670 logMAR (corresponding to an improvement of 40.3%±19.3%). On average, follow-up data showed a VA improvement with respect to the pre-training sessions of 0.15 ± 0.09 logMAR, corresponding to a learning retention of 28.4%±23.7%.

14.3. Transfer to crowding

The transfer of PL to crowding is shown in Fig. 11. On average, critical spacing decreased after PL by

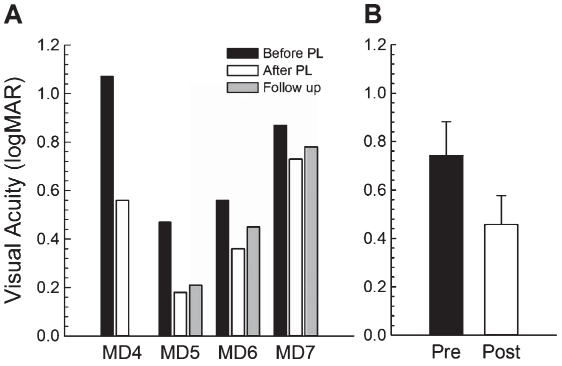

Fig. 10. (A) Visual acuity (logMAR) estimated in the Landolt-C test for MD patients before and after PL. Grey bars represent follow-up for patients MD5-MD7 (follow-up after 6 months for MD5 and MD6, and after 5 months for MD7). (B) Mean data for MD patients before and after the training. Error bars ± SEM.

40%±40.1%. Follow-up results revealed that after six months for MD5 and MD6, and after five months for MD7, the critical spacing was still 32%±47.4% lower than the spacing estimated in the pre-training sessions. However, a paired *t*-test did not reach significance, mainly because of the high variability.

14.4. Transfer to CSF

Figure. 12 shows the contrast sensitivity functions for MD patients. A repeated measures ANOVA including as factors training and spatial frequency did not show any significant effect. On average, contrast sensitivity improved by 213%±80.3% (this percentage increment was calculated only for spatial frequencies of 1, 3 and 5 cpd; see Mean panel of Fig. 12). Follow-up results indicated that the transfer was retained for patients MD5 (follow-up after six months) (CSF improvement from pre-test sessions to follow-up sessions 62.8%±40.6%) and MD7 (follow-up after five months) (CSF improvement from pre-test sessions to follow-up sessions 325.7%±427%) but not for MD6 (follow-up after six months) (–17.8%±31.7%). Importantly, after training, two of the four MD patients were able to perform the contrast detection task at higher spatial frequencies than those performed during the pre-test.

15. Discussion of temporal-2AFC results

In Experiment 2, MD patients and controls were trained using a temporal-2AFC task. For controls, PL mainly reduced suppression exerted by the flankers at the lowest target-to-flankers distance (i.e., 2λ), consistently with previous studies on PL and collinear facilitation in the near periphery of the visual field (Maniglia et al., 2011). Moreover, PL in patients MD4, MD5 and MD6 generally increased collinear facilitation. Most importantly in MD patients, as with the Yes/No task, PL transferred to VA, confirming that PL can generalize to higher level visual functions. Overall, these results suggest that PL with a temporal-2AFC task is an appropriate procedure to induce modulation of lateral interactions.

16. General discussion

16.1. Differences in PL effect between the two procedures (Yes/No vs. temporal-2AFC)

The effect of PL on contrast detection for a target flanked by high contrast collinear elements was assessed with a Yes/No task (Experiment 1) and a temporal-2AFC task with auditory feedback on incorrect trials (Experiment 2) for two distinct groups of patients with macular degeneration (MD) and normal controls. Overall, we found a noticeable variability in the observers' performance, probably due to the different characteristics of the sample (age, years of pathology, eccentricity of the scotoma, fixation stability etc.) and in general expected in PL studies when clinical population is involved (Chung, 2011). In the Yes/No task the results of PL on *d*'s showed that PL increased sensitivity at all target-to-flankers distances both in MD patients and controls, a result somehow different from a previous study we conducted in which a similar training led to an improvement in *d*' only for short and suppressory target-to-flankers distances (Maniglia et al., 2011). With the temporal-2AFC task, the reduction of contrast threshold was associated, for three MD patients (MD5, MD6 and MD7) to a PL-dependent increase in facilitatory lateral interactions and, for controls, with a reduction of inhibitory lateral interactions, consistently with our previous study (Maniglia et al., 2011). The transfer results indicate that PL with a low-level visual task yielded significant perceptual benefits to untrained, higher level visual functions. Both PL procedures (i.e., Yes/No and temporal-2AFC) improved VA, but PL with the temporal-2AFC task transferred to CSF. In Experiment 2, the contrast sensitivity of MD patients improved by 213%±80.3% after training, while in Experiment 1 the improvement was just 25.8%±21% (Casco et al., 2014; Maniglia et al.,

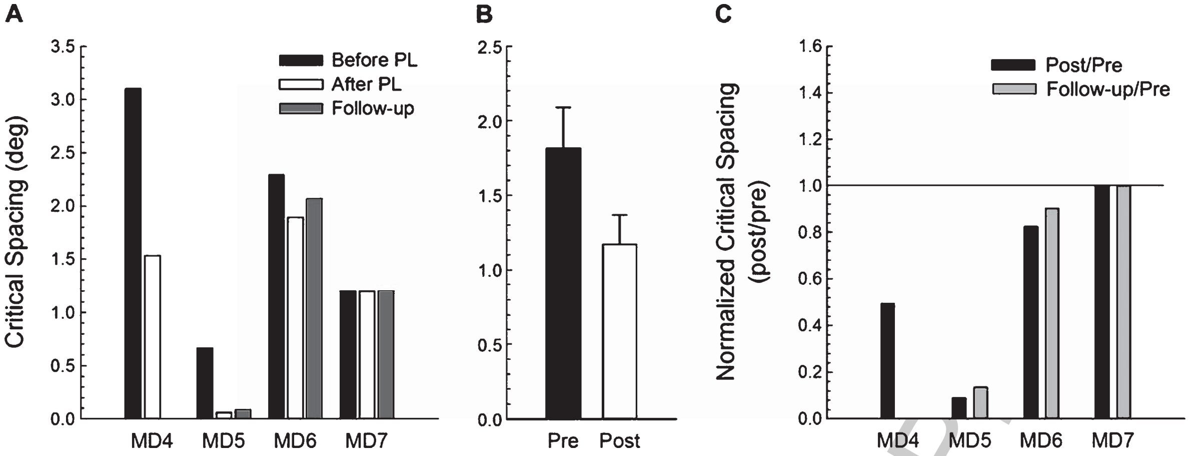

Fig. 11. (A) Critical spacing (deg) for MD patients before and after PL. Follow-up data are also reported for patients MD5-MD7 (follow-up after 6 months for MD5 and MD6, and after 5 months for MD7). (B) Mean critical spacing (deg) for pre- and post-training sessions. (C) Normalized critical spacing calculated as the ratio between post- and pre-training thresholds for MD patients. Follow-up normalized critical spacing thresholds are also reported and are calculated as the ratio between follow-up and pre-training thresholds. Values below one (continuous black line) indicate improvement after training. Error bars ± SEM.

2011; Polat, 2009; Polat et al., 2004; Tan & Fong, 2008). In Experiment 2, the focus of training on the PRL might have produced the larger improvement observed. In general, the PL-dependent modulation of lateral interactions with the temporal-2AFC task suggests more directly a refinement of lateral interactions between target and flankers.

16.2. Transfer of learning

The assessment of transfer of PL, in the framework of a rehabilitative protocol, was the main aim of this study. Transfer is relevant both for clinical and theoretical purposes, raising the question of the locus and specificity of PL (Polat, 2009; Sagi, 2011). Our transfer results suggest that perceptual training of a low-level visual task modulates visual processes at different levels of complexity, depending on the PL task. Visual acuity was improved by both PL procedures (i.e., Yes/No and temporal-2AFC), but the improvement found in the PRL of MD patients in Experiment 2 was larger than the improvement found in Experiment 1 (i.e., 0.19 ± 0.065 logMAR vs. 0.29 ± 0.16 logMAR for Experiment 1 and 2, respectively). Moreover, only PL with a temporal-2AFC task transferred to CSF, while PL with the Yes/No task did not show the same degree of generalization (i.e., 25.8% ± 21% vs. 213% ± 80.3% for Experiment 1 and 2, respectively). The greater generalization found with the temporal-2AFC seems to depend on the configuration used during the training, known to probe neural plasticity (Polat & Sagi, 1994b). However, we did not find any significant improvement of the critical spacing (i.e., reduction of the crowding effect) with the two procedures. Though not significant, the amount of the reduction of the crowding effect (35% ± 30.6% and 40% ± 40.1% in Experiments 1 and 2, respectively) seems closely related to reduction of lateral inhibition; in fact, it has been proposed that both effects rely on similar mechanisms (Lev & Polat, 2011; Maniglia et al., 2011). Pelli et al. (2004) suggested that crowding depends on an excessive features integration process, so it is possible that the modulation of lateral-interactions at low-level of visual processing may induce a balance between inhibitory and integration mechanisms at a higher level of visual processing.

It may be argued that the differences in the training effects found with the two tasks may depend on the auditory feedback used in the temporal-2AFC task rather than on neural plasticity mechanisms. We acknowledge that the auditory feedback during the temporal-2AFC task may have reinforced the transfer of PL. In particular, the transfer to untrained visual tasks (e.g., CSF and VA) may result from maximizing the read-out of visual channels selective to different spatial frequencies and orientations when training with a temporal-2AFC task. Indeed there is psychophysical evidence that inner reward/feedback can improve performance (Gibson & Gibson, 1955; Herzog & Fahle, 1998; Petrov, 2006; Sasaki, Nanez, & Watanabe, 2010; Shibata, Yamagishi, Ishii, &

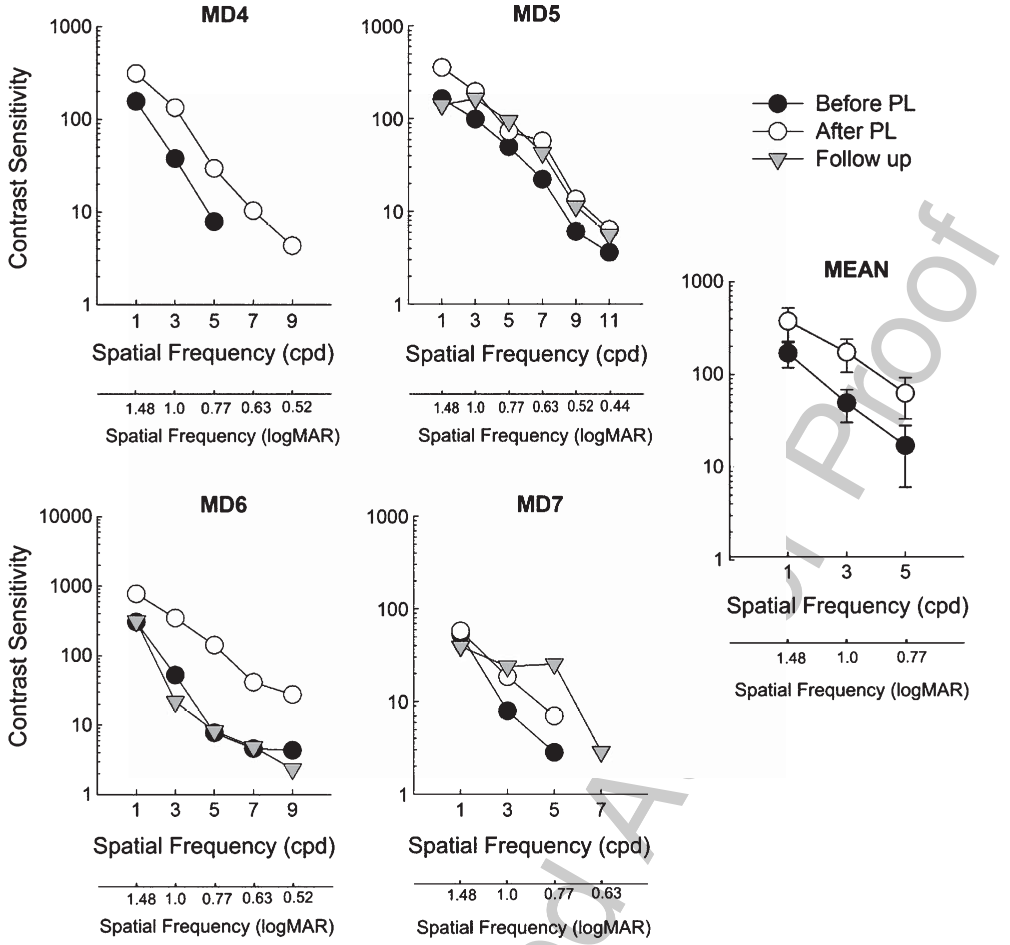

Fig. 12. Contrast sensitivity function (CSF) of MD patients measured for spatial frequencies ranging from 1 to 11 cpd. Follow-up data are also reported for patients MD5-MD7 (follow-up after 6 months for MD5 and MD6, and after 5 months for MD7). The Mean panel (rightmost panel) represents average data for MD patients only for spatial frequencies of 1, 3 and 5 cpd. The secondary abscissa reports spatial frequency values in logMAR. Error bars ± SEM.

Kawato, 2009). For example, Shibata et al. (2009) found that even a “fake” feedback, indicating a larger performance improvement, facilitated learning compared with genuine feedback. In addition, authors found that variance of the “fake” feedback also modulated learning, suggesting that feedback uncertainty can be internally evaluated biasing decision mechanisms. However, in the present study the modulation of lateral interaction by PL with the temporal-2AFC task suggests PL-dependent effects based on the task rather than on the auditory feedback.

16.3. Comparison with previous studies

In general, the use of PL to improve residual visual functions in MD patients is a recent field of research. Previous studies with patients with central vision loss (Chung, 2011; Plank et al., 2014; Rosengarth et al., 2013) aimed at improving a specific visual ability (e.g., texture discrimination, fixation stability, reading speed) by directly training it. In these studies, authors used perceptual tasks (guided saccades, texture discrimination, letter recognition, and reading) known in the literature for their high specificity of learning; consequently, transfer of learning to other visual abilities, as a product of neural plasticity, was not necessarily expected. For example, Chung (2011) found an improvement of 53% in reading speed after training on this specific task but no changes in critical print size (i.e., the smallest print size at which patients can read with their maximum reading speed) or visual acuity. Consistently, Rosengarth et al. (2013) reported an increase in patients’ performance only between pre- and mid-test measurements, but not between pre- and post-tests, showing that an oculomotor training alone might not be robust enough to produce long lasting changes. Moreover, functional neuroimaging data from Plank et al. (2014) and Rosengarth et al. (2013) showed no or small changes in early visual areas (V1, V2 and V3) and in higher visual areas (e.g., LOC, fusiform gyrus, ITG). More recently, Astle, Blighe, Webb, and McGraw (2015) reported an improvement in reading speed of 71% after a word identification training; however, authors trained all the MD patients at the same eccentricity, regardless of the location of their PRL and the size of their scotoma, making it difficult to compare the results.

Conversely, in the present study, learning transferred to other visual abilities. In particular, in Experiment 1 and for MD patients, VA improved by 19.7% ± 5.74% in their PRL and 18.4% ± 3.2% in their Non-PRL. In Experiment 2, learning transferred to VA in MD patients, and the transfer was greater than in Experiment 1. In particular, VA in MD patients improved by 0.29 ± 791 0.16 logMAR (i.e., 40.3%±19.3%). One of the reasons for such a high degree of transfer may lie in the type of training employed; in fact, Tarita-Nistor, Brent, Steinbach, Markowitz, and Gonzalez (2014), using the same paradigm as Chung (2011) but with words presented near the threshold for reading acuity, found an improvement in the trained task of 54%, similar to that found by Chung (2011), but they also found a transfer to binocular VA (on average from 0.54 to 0.44 LogMAR) and fixation stability (62% in the good eye and 58% in the worse eye). The rationale of Tarita-Nistor et al. (2014) was that PL is more effective when stimuli are around the observer's threshold and induce a greater focus on the task (Sagi, 2011; Seitz & Watanabe, 2005; Tsodyks & Gilbert, 2004), while previous studies on MD patients used exclusively above thresholds stimuli (Chung, 2011; Seiple, Grant, & Szlyk, 2011). Consistently, previous studies with amblyopic patients showed that PL can generalize to untrained visual functions (Polat, 2009), but not when stimuli are above threshold (Chung, Li, & Levi, 2008, 2012). Accordingly, the stimuli we used during perceptual training were always around the observer's threshold, and this may have induced the observed generalization of learning.

16.4. Challenges in the study of PL with MD patients

Perceptual training of MD patients represents a challenge for several reasons:

(1) When addressing the issue of whether PL can be used as a rehabilitative method for macular degeneration, the problem of eye movements control in MD patients must be considered. Our patients had one single and localized PRL but we found no difference between PRL and Non-PRL presentation. This aspect should be taken into account when planning a training protocol for MD patients who often have non-localized PRL or more than one PRL (Timberlake et al., 1987). However, since it is not always practical to record eye movements in MD patients, conclusions that are based on MD patients with more than one PRL or in which online recording of eye position through SLO or Nidek is not present, should be taken with care. Intuitively, we argue that it is easier for MD patients to fixate with their PRL, though this requires a full development of such peripheral spot.

(2) A main backdrop of the present study, and in general of most of the clinical literature, is the small sample size. This, coupled with the high variability of PL effects (Chung, Levi, & Tjan, 2005; Fahle & Henke-Fahle, 1996), makes it difficult to draw strong conclusions from the present study. Previous studies with MD patients did not test more than 10 patients (Chung, 2011; Plank et al., 2014; Rosengarth et al., 2013; Tarita-Nistor et al., 2014) and often the clinical profile and diagnosis differed among participants. Studies with larger populations are usually meta-analysis or evaluation of efficacy of orthoptic protocols rather than controlled, single- or double-blind studies, and often there is not an appropriate control group (Coco-Martin et al., 2013).

(3) Consistently with Chung (2011), we found high inter-individual variability, especially in Experiment 2, where our patient MD7 showed moderate improvement in VA between pre- and post-test sessions (and follow-up), whereas on the same task and after the training patient MD4 obtained a VA threshold that was halved with respect to the pre-training session. Accordingly, after the training the VA threshold of patient MD5 was 2.6 times lower than the VA threshold estimated in the pre-training session (Fig. 10). While this can be easily observed in normal sighted participants, variability in performance and PL effects are even greater in clinical populations where many

factors have to be considered. In the case of MD patients, the years since the offset, the size of the scotoma, the location of the PRL and the monocular vs. binocular diagnosis contributes in creating an inhomogeneous puzzle. For example, the process of development of the PRL is still not clear, and several aspects, such as residual visual acuity, size of the visual field, size of the scotoma and proximity of the fovea seem to play an important role (Altpeter, Mackeben, & Trauzettel-Klosinski, 2000; Schuchard & Fletcher, 1994). Moreover, there seems to be a difference in the retinal location of the PRL between juvenile MD and age-related MD (Crossland, Culham, Kabanarou, & Rubin, 2005). Besides, the gain through PL for clinical populations seems related to the initial level of deficit (Levi & Li, 2009).

As several studies pointed out (Polat, 2009; Tarita-Nistor et al., 2014), custom-tailoring the protocol on each patient's needs and possibilities seems to be the key to gain consistent and long lasting visual improvement. A higher flexibility and sensitivity of the protocol would be essential in developing an effective treatment, for example in taking into account the learning curve of each individual patients and training them on a challenging but not too difficult level. To this purpose, Hung and Seitz (2014) showed how PL with constant near-threshold trials gates transfer of learning. Moreover, Chung and Truong (2013) showed that the overall number of sessions is what matters in a PL training regime; consequently planning a sparser training-per-week schedule may be beneficial in those cases in which patients have to be accompanied to the training facility.

(4) Another concern is the feasibility of training. MD patients, unable to drive, are often dependent on other people to reach lab facilities. A primary goal in visual rehabilitation would be to reduce the minimum amount of training sessions needed to reach a significant improvement of performance. Recently, few studies showed how PL coupled with non-invasive electrical brain stimulation can be effective in improving visual abilities with a small number of training sessions (Campana et al., 2014; Fertonani, Pirulli, & Miniussi, 2011). Future directions of MD-oriented PL protocols should take into account the rapidly increasing role of online non-invasive electrical brain stimulation for visual restoration.

17. Conclusions

In this study we demonstrated for the first time that training on lateral interactions is effective in improving the residual visual functions in the periphery of the visual field of MD patients. Moreover, these improvements seem to be long lasting; a follow-up conducted between four and six months showed good retention of the PL and transfer effects for the temporal-2AFC group. Consequently, the perceptual training scheme presented represents a likely candidate for a non-invasive rehabilitative visual training regime for patients suffering of central vision loss.

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