LEARNING TO SEE (BETTER): IMPROVING VISUAL DEFICITS WITH PERCEPTUAL LEARNING

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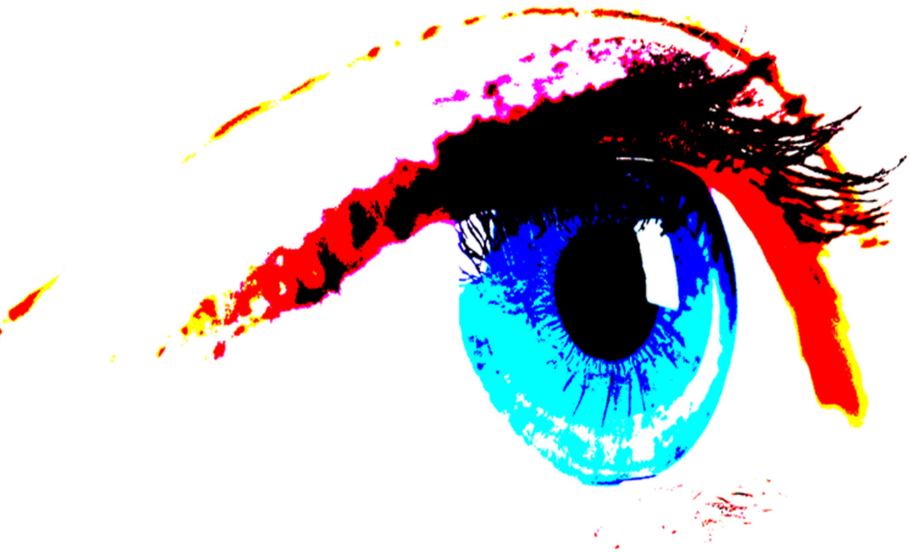

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LEARNING TO SEE (BETTER): IMPROVING VISUAL DEFICITS WITH PERCEPTUAL LEARNING

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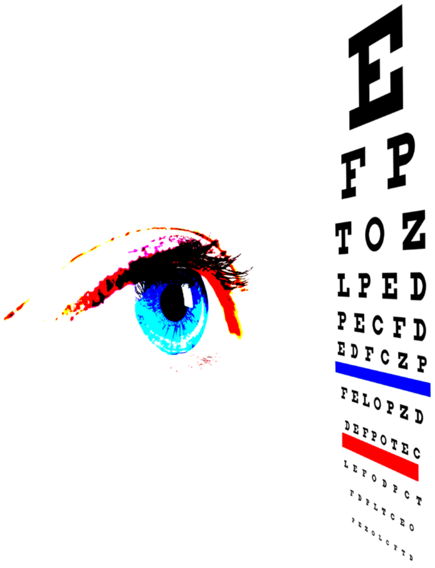

Image by Gianluca Campana

Perceptual learning can be defined as a long lasting improvement in a perceptual skill following a systematic training, due to changes in brain plasticity at the level of sensory or perceptual areas. Its efficacy has been reported for a number of visual tasks, such as detection or discrimination of visual gratings (De Valois, 1977; Fiorentini & Berardi, 1980, 1981; Mayer, 1983), motion direction discrimination (Ball & Sekuler, 1982, 1987; Ball, Sekuler, & Machamer, 1983), orientation judgments (Fahle, 1997; Shiu & Pashler, 1992; Vogels & Orban, 1985), hyperacuity (Beard, Levi, & Reich, 1995; Bennett & Westheimer, 1991; Fahle, 1997; Fahle & Edelman, 1993; Kumar & Glaser, 1993; McKee & Westheimer, 1978; Saarinen & Levi, 1995), visual search tasks (Ahissar & Hochstein, 1996; Casco, Campana, & Gidiuli, 2001; Campana & Casco, 2003; Ellison & Walsh, 1998; Sireteanu & Rettenbach, 1995) or texture discrimination (Casco et al., 2004; Karni & Sagi, 1991, 1993).

Perceptual learning is long-lasting and specific for basic stimulus features (orientation, retinal position, eye of presentation) suggesting a long-term modification at early stages of visual analysis, such as in the striate (Karni & Sagi, 1991; 1993; Saarinen & Levi, 1995; Pourtois et al., 2008) and extrastriate (Ahissar & Hochstein, 1996) visual cortex.

Not confined to a basic research paradigm, perceptual learning has recently found application outside the laboratory environment, being used for clinical treatment of a series of visually impairing conditions such as amblyopia (Levi & Polat, 1996; Levi, 2005; Levi & Li, 2009, Polat et al., 2004; Zhou et al., 2006), myopia (Tan & Fong, 2008) or presbyopia (Polat, 2009).

Different authors adopted different paradigms and stimuli in order to improve malfunctioning visual abilities, such as Vernier Acuity (Levi, Polat & Hu, 1997), Gratings detection (Zhou et al., 2006), oculomotor training (Rosengarth et al., 2013) and lateral interactions (Polat et al., 2004). The common result of these studies is that a specific training produces not only improvements in trained functions, but also in other, untrained and higher-level visual functions, such as visual acuity, contrast sensitivity and reading speed (Levi et al, 1997a, 1997b; Polat et al., 2004; Polat, 2009; Tan & Fong, 2008).

More recently (Maniglia et al. 2011), perceptual learning with the lateral interactions paradigm has been successfully used for improving peripheral vision in normal people (by improving contrast sensitivity and reducing crowding, the interference in target discrimination due to the presence of close elements), offering fascinating new perspectives in the rehabilitation of people who suffer of central vision loss, such as maculopathy patients, partially overcoming the structural differences between fovea and periphery that limit the vision outside the fovea.

One of the strongest point, and a distinguishing feature of perceptual learning, is that it does not just improve the subject's performance, but produces changes in brain's connectivity and efficiency, resulting in long-lasting, enduring neural changes.

By tailoring the paradigms on each subject's needs, perceptual learning could become the treatment of choice for the rehabilitation of visual functions, emerging as a simple procedure that doesn't need expensive equipment.

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EDITORIAL
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Editorial: Improving visual deficits with perceptual learning

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The capability of improving performance on visual tasks with practice has been a matter of intense investigation during the last 40 years (Fiorentini and Berardi, 1980; Sagi, 2011). This phenomenon, called perceptual learning, has been proven to occur with virtually any visual skill or stimulus characteristic (Fahle and Poggio, 2002), and to be long-lasting, thus involving neural plasticity at the level of perceptual or even sensory areas (Sagi and Tanne, 1994). Despite this, only recently has perceptual learning started to be considered a useful tool for improving visual functions in clinical populations. This delayed exploitation has possibly been caused by the common finding that learning was highly specific for the trained stimulus attributes (Fiorentini and Berardi, 1980; Ball and Sekuler, 1981; Ahissar and Hochstein, 1996; Schoups et al., 2001; Campana and Casco, 2003; Fahle, 2005), or even for the trained eye or retinal location (Karni and Sagi, 1991), thus resulting impractical for therapeutic purposes. More recently it has become clear that, under specific training conditions, perceptual learning could generalize to other stimuli, tasks and circumstances (McGovern et al., 2012), yielding potential benefits for various types of visual impairments. So far, perceptual learning has been shown to be effective in improving, among other dysfunctions, visual abilities in amblyopia (Levi and Li, 2009; Polat, 2009; Hussain et al., 2012), mild refractive defects (myopia: Tan and Fong, 2008; Camilleri et al., 2014a; presbyopia: Polat et al., 2012), central or peripheral vision loss and cortical blindness (Kasten et al., 1998; Sabel et al., 2005; Huxlin et al., 2009; Chung, 2011; Das et al., 2014), dyslexia (Gori and Facoetti, 2015), and has even been shown to improve the efficacy of other sensory modalities so that they can somehow replace vision (so called sensory substitution) in blind people (Bach-y-Rita and Kercel, 2003; Ortiz et al., 2011).

The goal of this Research Topic is to demonstrate the development of innovative methods, based on perceptual learning, for treating—or at least overcoming some of the deleterious effects of—various visual dysfunctions, from mild deficits such as myopia to complete blindness. New frontier methods should aim at finding the most effective procedures both in terms of perceptual learning and transfer to useful visual functions. This is made possible by combining different techniques aimed at boosting learning or its generalization, such as training with different stimulus features (Xiao et al., 2008; Harris et al., 2012), exploiting multisensory facilitation (Shams and Seitz, 2008) and reinforcement procedures (Seitz and Watanabe, 2009), or combining perceptual learning with non-invasive brain stimulation procedures (Fertonani et al., 2011). Also, in order to achieve the best possible compliance with the patients, shorter and/or more enjoyable trainings (possibly self-administered at home) should be preferred.

For example, while training on either off-the shelf video games (Li et al., 2011; Franceschini et al., 2013), or specifically designed video games involving detection of low contrast stimuli (Deveau et al., 2014a,b) has been shown to improve a range of visual functions (visual acuity, contrast sensitivity, reading skills and even sport performances) both in normally sighted people and people with developmental dyslexia or amblyopia, in the present Research Topic we see that the latter type of video games can also improve visual acuity in participants with refractive defects such presbyopia

(Deveau and Seitz, 2014) or reduce crowding (the deleterious effect of nearby elements on target's perception; Levi, 2008) in participants with cortical deficits such as amblyopia (Hussain et al., 2014). While negligible in normal foveal vision, crowding is an important issue also in children with visual impairment accompanied by nystagmus. Reduction of crowding in these children (besides an improvement of near visual acuity, see Huurneman et al., 2013) can be obtained with training on crowded letters, thus producing faster reaction times and an increase of fixation durations (Huurneman and Boonstra, 2014).

Visual functions in participants with mild refractive defects or amblyopia have also been shown to considerably improve with contrast detection trainings (with or without lateral masking) (Tan and Fong, 2008; Levi and Li, 2009; Polat, 2009; Polat et al., 2012; Camilleri et al., 2014a). Here we see how, both in mild myopia and amblyopia, combining a contrast detection training with non-invasive brain stimulation (specifically, transcranial random noise stimulation—tRNS) seems to yield to faster/more effective perceptual learning and transfer to visual acuity and contrast sensitivity (Camilleri et al., 2014b; Campana et al., 2014).

Perceptual learning can also be successfully applied to patients with loss of central vision. Indeed, past research has shown, in sighted participants, how perceptual learning on a contrast detection task with lateral masking was able to reduce crowding at eccentric retinal locations (Maniglia et al., 2011). Here we see how, in patients with macular degeneration, eccentric perceptual learning with a rapid serial visual presentation (RSVP) produces an improvement in reading speed mainly with supra-threshold word durations (above 200 ms) (Coates and Chung, 2014), while a texture discrimination training enhances temporal processing of eccentric stimuli (reflected in shorter stimulus onset asynchrony needed for discrimination), especially when fixation was stable (Plank et al., 2014).

In fact improved temporal processing in areas of residual vision (besides an extension of such areas) in patients with vision loss (hemianopia or quadrantanopia) can be also obtained with the so-called vision restoration therapy, an individualized program providing stimulation at the border of the dysfunctional visual field (Poggel et al., 2014).

Finally, perceptual learning could be useful even for blind people. Blindness often produces an impaired spatial representation in other sensory domains (e.g., Gori et al., 2014a). Here it is shown that blindfolded sighted participants can learn an auditory spatial bisection task, but improvements only occur when a tactile feedback is delivered, indicating that the tactile system can be used to recalibrate the spatial representation in the auditory domain (Gori et al., 2014b). This finding suggests that, also in blind people, auditory spatial representation can be improved via tactile feedback.

To sum up the findings of the present Research Topic, the studies collected here provide the frontline of behavioral and brain stimulation-coupled treatments of a heterogeneous ensemble of visual dysfunctions. Future studies are needed to define the best combination of approaches in order to improve vision with the shortest and most efficacious training, increasing patients' compliance and tailoring the training specifically for each patients' needs.

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Applying perceptual learning to achieve practical changes in vision

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Research of visual perceptual learning has illuminated the flexibility of processing in the visual system and provides insights into therapeutic approaches to remediating some components of low vision. A key observation from research of perceptual learning is that effects of training are often highly specific to the attributes of the trained stimuli. This observation has been a blessing to basic research, providing important constraints to models of learning, but is a curse to translational research, which has the goal of creating therapies that generalize widely across visual tasks and stimuli. Here we suggest that the curse of specificity can be overcome by adopting a different experimental framework than is standard in the field. Namely, translational studies should integrate many approaches together and sacrifice mechanistic understanding to gain clinical relevance. To validate this argument, we review research from our lab and others, and also present new data, that together shows how perceptual learning on basic stimuli can lead to improvements on standard vision tests as well as real world vision use such as improved reading and even improved sports performance. Furthermore, we show evidence that this integrative approach to perceptual learning can ameliorate effects of presbyopia and provides promise to improve visual function for individuals suffering from low vision.

Keywords: perceptual learning, presbyopia, visual therapy, applied vision, reading

INTRODUCTION

Vision is a highly beneficial sense that is paramount to social interactions, navigation of the world, and most workplace and leisure activities. As such, poor vision can have profound negative impact on peoples' ability to interact with the world around them. Acknowledging this problem there is a tremendous industry associated with optical devises, surgical procedures, specialized drugs, etc with a focus on improving the operation of the eye. However, our ability to see relies not only on a well-functioning eye with good optics, but also on how the brain makes use of this information. Many examples of poor vision, such as due to strokes, traumatic brain damage, or developmental disorders such as amblyopia, make clear that impaired brain processing is an important component of low vision. Furthermore, as we argue in the present paper, suboptimal brain processing of visual information is the norm and that there is a need to develop therapies that address the brain's contribution to poor vision. These "brain training" approaches have the potential to ameliorate impacts of retinal disease, potentially cure conditions of cortical dysfunction such as amblyopia, and unlock substantial gains for normally functioning individuals, across the life-span.

Key examples of the ability of the adult visual system to improve processing come from the field of perceptual learning (Sagi, 2011). Perceptual learning is often defined as improvements in performance on visual tasks following practice or experience with stimuli related to those tasks and has been a focus of substantial research over the last 40 years. By now, practically any visual skill that can be described has been the target of at least some study of perceptual learning (Fahle and Poggio, 2002) and collectively research of perceptual learning demonstrates that there is room for improvement in most aspects of vision. Furthermore, perceptual learning research is exemplified by the long-lasting improvement on simple but difficult perceptual tasks with benefits shown to last months, even years (Ball and Sekuler, 1981; Sagi and Tanne, 1994; Crist et al., 2001).

Given the demonstrated plasticity of the visual system and the longevity of benefits, one would assume wide-scale adoption of perceptual learning approaches in clinical settings. However, despite the plethora of research, perceptual learning research has had limited penetration into the clinic. While there are many reasons for this, such as most research of perceptual learning is from Psychology and Neuroscience, having limited interactions with Optometrists and Ophthalmologists, and with most perceptual learning research mostly involving normally seeing human subjects or animals, with limited research in low vision populations. In addition, research of perceptual learning has been dominated by, and in some case defined by, examples of learning that are specific to the particulars of the stimuli experienced during training; trained stimulus features (Fahle, 2005), such as orientation (Fiorentini and Berardi, 1980), motion direction (Ball and Sekuler, 1981; Watanabe et al., 2002), retinal location (Karni and Sagi, 1991) or even the trained eye (Poggio et al., 1992; Seitz et al., 2009). While such findings provide insights into the brain system that underlie perceptual learning, and help constrain models of perceptual learning, training that only manifests at a single retinal location, for a limited stimulus space, provides limited therapeutic benefit. As such specificity, which is a "blessing" to mechanistic studies of perceptual learning, is a "curse" to clinical viability.

However, there is increasing evidence that certain types of training yields beneficial learning that transfer beyond the trained context. Notable examples include vision training to improve reading (Chung et al., 2004), or hitting baseballs (Deveau et al., 2014b). Furthermore, numerous studies suggest that perceptual learning can lead to relatively broad-based improvements in visually impaired individual such as amblyopia (Levi and Li, 2009), peripheral vision loss (Chung, 2011), presbyopia (Polat, 2009), macular degeneration (Baker et al., 2005), stroke (Huxlin et al., 2009; Das et al., 2014), and late-life recovery of visual function (Ostrovsky et al., 2006) and other individuals with impaired vision (Huang et al., 2008; Zhou et al., 2012). These studies suggest the potential value of perceptual learning as a rehabilitative approach for individuals with low vision and that the curse of specificity can be overcome.

OVERCOMING THE CURSE OF SPECIFICITY

Specificity perceptual learning stems, at least in part, from research procedures that train participants on reduced stimulus sets (e.g., single orientation at single retinotopic location). Such training engages a limited neural population (Fahle, 2004), teaches participants to attend to this limited features space and to ignore other features (Zhang et al., 2013), and encourages decision policies/strategies that will be specific to this limited feature space (Fulvio et al., 2014). While there exists substantial debate regarding which neural mechanisms underlie specificity (Dosher and Lu, 1998; Fahle, 2004; Hung and Seitz, 2014), it is arguable that specificity occurs due to some form of overfitting of the training task (Mollon and Danilova, 1996; Sagi, 2011).

Training regimes that employ a broader stimulus space, such as those using multi-stimulus training (Xiao et al., 2008; Yu et al., 2010; Deveau et al., 2014a,b) and off-the-shelf video games (Green and Bavelier, 2003; Li et al., 2009) show greater generalization of learning than typically found in studies of perceptual learning. For example, Xiao et al. (2008) trained participants on a Vernier discrimination task at a specific orientation and retinotopic location, which classically leads retinotopic and orientation specific learning (Poggio et al., 1992), however, after training on a second orientation at a different spatial location, learning transferred across locations (although see Hung and Seitz, 2014). Taking this approach to clinical populations, Das et al. (2014) used a double training procedure where static and dynamic stimuli were presented to patients with cortical blindness in separate retinotopic locations. They found training with complex moving stimuli at one location transferred to improvements in a location only trained with static stimuli. Growing research shows how a diversity of factors can contribute to overcoming the curse of specificity; for example, the amount of training (Aberg et al., 2009; Jeter et al., 2010), and the difficulty/precision of the stimulus judgments training (Ahissar and Hochstein, 1997; Hung and Seitz, 2014) or testing (Jeter et al., 2009).

INTEGRATING MULTIPLE APPROACHES TO ACHIEVE GREATER LEARNING

We hypothesized that the greatest degree of learning and broadest transfer could be achieved by combining approaches from different research studies targeting different perceptual learning mechanisms. To test this hypothesis we combined multiple perceptual learning approaches, including training with a diverse set of stimuli (Xiao et al., 2008), optimized stimulus presentation (Beste et al., 2011), multisensory facilitation (Shams and Seitz, 2008), and consistent reinforcement of training stimuli (Seitz and Watanabe, 2009), which have individually contributed to increasing the speed (Seitz et al., 2006), magnitude (Seitz et al., 2006; Vlahou et al., 2012), and generality of learning (Green and Bavelier, 2007; Xiao et al., 2008) into a simple video game (for details see Deveau et al., 2014a,b) that trained a diverse set of stimuli (multiple orientations, spatial frequencies, locations, distractor types, etc).

Initial research using this integrated perceptual learning game provides support for our hypothesis of the effectiveness of this approach. In a first study (Deveau et al., 2014a), 14 participants (age 18–55) completed 24 training sessions and conducted tests of visual acuity and contrast sensitivity before and after training. Results showed significant improvements to central and peripheral vision (see **Figure 1**). Following up on this work, we investigated the extent to which such visual training could impact performance in the daily activities of study participants. To test this, we trained the position players of the UC Riverside baseball team for 30 sessions each with the integrated training game. Results showed both improvements in visual acuity (pre-training Snellen acuity of 20/13 ± 0.69 SE vs. post-training of 20/10 ± 0.59) with seven of the trained players reaching 20/7.5 Snellen acuity after training (Deveau et al., 2014b). Importantly, performance on the baseball field also improved, with trained players showing a significant reduction of strike-outs of 4.4% ± 2.0 SE, and an estimated increase of 41.2 runs created which led to an estimated 4–5 extra games won (over the 54 game season; Deveau et al., 2014b).

TRANSFER OF INTEGRATED TRAINING TO READING SKILLS

Notably, we also found that near vision was significantly improved in the baseball players after training (Deveau et al., 2014b). This led us to question whether visual abilities related to near vision were improved as well. Given that these were student athletes, we hypothesized that reading skills, which are highly important to the educational goals of the athletes, may also benefit from training.

To test this hypothesis, we measured reading acuity, speed, and critical print size before and after vision training in 44 UC Riverside undergraduates using MNREAD charts (see **Figure 2A**). The charts contain 19 English sentences (60 characters each) with print sizes ranging from 1.3 to −0.5 logMAR at a distance of 16 inches (0.41 m). Different charts were used for pre and post-tests, all tests were conducted in a well lit room. Charts were placed on a stand 16 inches (0.41 m) away from participants, who were instructed to read each sentence aloud as quickly and as accurately as possible. After each sentence participants would look to the left or right (away from the chart) until instructed to move on to the next sentence by the experimenter. A stopwatch was used to record the time taken to read each sentence to the nearest 0.1 s. The number of errors made in each sentence was also recorded. Reading acuity was calculated as the logMAR of the last sentence read, adding 0.01 logMAR for each reading error. Reading speed was measured in words per minute. Maximum reading speed was calculated as

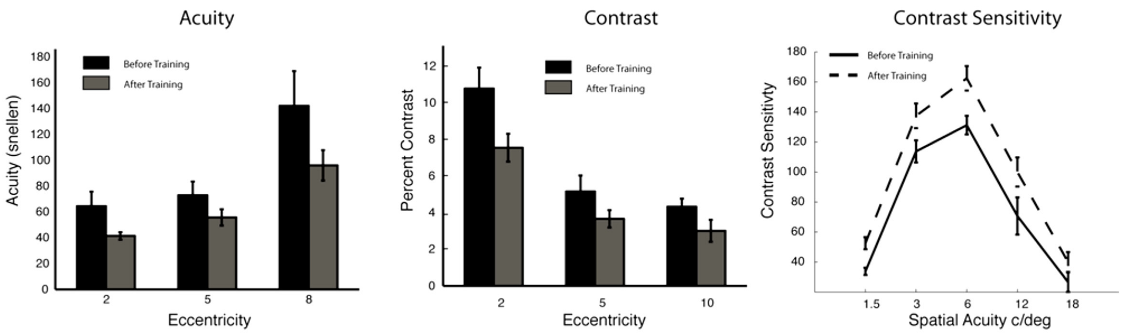

FIGURE 1 | Data from Deveau et al. (2014a). **Left**, for acuity, Landolt C size thresholds were measured at different locations in the visual field (with an eye-tracker to enforce fixation). **Middle**, contrast sensitivity thresholds were measured by varying the contrast of an "O" presented at visual field locations. **Right**, an Optec Visual Analyzer (Stereo Optical Company, Chicago, IL, USA) measured foveal visual acuity and contrast sensitivity. Data from pre-training tests (black) is shown against data of post-training tests (gray). In the left two graphs, lower values represent better performance. Acuity values **(left)** are based on standard 20/20 scores in the fovea (peripheral scores values are poorer). Weber Contrast **(middle)**. Contrast Sensitivity **(right)** shows contrast as a function of spatial frequency in central vision (higher values are better). Training-induced benefits are all significant at least to the $p < 0.05$ levels. Error bars represent SE of the mean.

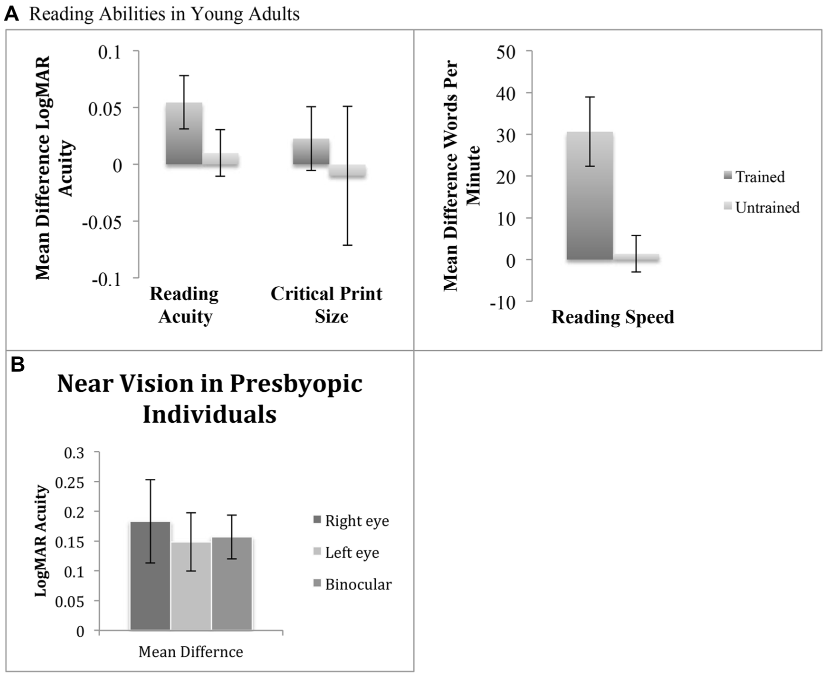

FIGURE 2 | (A) Mean difference of reading acuity, critical print size, and reading speed using MNREAD acuity charts in healthy young adults. Trained participants were tested binocularly before and after vision training. Untrained data reproduced from Subramanian and Pardhan (2006) where two different versions of the MNREAD acuity charts were used to measure learning effects. Error bars represent subject SE. **(B)** Mean difference in LogMAR acuity measurements taken in the right eye, left eye, and binocularly in presbyopic individuals. Participants were tested before and after vision training. Error bars represent within subject SE.

the fastest sentence read, regardless of logMAR. Critical print size was measured as the smallest print size participants can read close to their maximum reading speed.

Vision training consisted of video-game based custom software. The training procedure has been previously described (Deveau et al., 2014a,b). Briefly, the training stimuli consisted of Gabor patches (game "targets") at six spatial frequencies (1.5, 3, 6.3, 12.5, 25, and 50 cpd), and eight orientations (22.5, 67.5, 112.5, 157.5, 202.5, 247.5, 292.5, or 337.5°). Exercises alternated between static and dynamic types, in the static exercise an array of targets of a single spatial frequency, at a randomly determined orientation were presented randomly on the screen all at once. In the dynamic exercise targets of a randomly determined orientation/spatial frequency combination are presented one at a time, and faded in at a random location on the screen. The goal of the exercises was to click on all the Gabor targets as quickly as possible.

After training, reading acuity improved an average of 13% ($p = 0.02$), moving from a pre training mean logMAR acuity value of −0.06 to a post training value of −0.11, (mean difference SE ± 0.02). Reading speed improved an average of 13% ($p = 0.0004$), moving from a pre training mean value of 240.0 words per minute to a post training value of 270.6 words per minute (mean difference SE ± 8.28). However, critical print size did not improve after training (mean difference = 0.02 logMAR ± 0.03 SE; *t*-test, $p = 0.40$).

While we did not have an untrained control group in this study (see Discussion), previous research has found the MNREAD chart to be resistant to practice effects (**Figure 2A**, untrained). Subramanian and Pardhan (2006) used two different versions of the MNREAD acuity charts to measure learning effects of reading acuity, critical print size, and reading speed. Thirty college age participants conducted assessments in two separate sessions without a training intervention in between. These participants showed no significant differences in reading acuity, critical print size, and reading speed indicating the MNREAD is resistant to practice effects.

These data provide another example of real world benefits to normally seeing young individuals after integrated perceptual learning based vision training. These participants were young, with above average initial acuity. However, as we age near vision declines which can negatively impacting reading. Therefore we next sought to assess practical improvements from vision training in individuals with impaired near vision.

VISION TRAINING TO AMELIORATE PRESBYOPIA

Presbyopia refers to loss of vision associated with the aging eye and is primarily characterized by a gradual loss of accommodation and reduced elasticity of the lens (von Helmholtz, 1924). The result is the reduced ability to focus at a near distance, a requirement for many daily activities and hobbies such as reading, using a cell phone or tablet, or sewing, which can negatively affects one's quality of life (McDonnell et al., 2003). This accommodative decline is virtually universal, as of 2005 it is estimated over 1 billion people worldwide are presbyopic, with more than half of individuals without adequate treatment (Holden et al., 2008). The most common form of presbyopia correction is the use of spectacles, including multifocal (bifocal, trifocal, or progressive lens) or reading glasses. There are also several surgical treatment options for presbyopia, however side effects include reduced contrast sensitivity, increased glare, and poor night vision (Papadopoulos and Papadopoulos, 2014) that can negatively impact the overall quality of vision. Given that all other treatments for presbyopia have side-effects, a perceptual learning based approach to ameliorate the impact of presbyopia could have substantial benefits, especially for early stage or mild presbyopia.

Based on this research, here we applied our integrated training program to 13 presbyopic participants (seven male and six females; age range 40–78 years) over the course of 4–12 weeks (average of four sessions per week). Vision training procedures are the same as described in section "Transfer of Integrated Training to Reading Skills." After training, near vision in participants improved from mean logMAR values of 0.47–0.29 in the right eye (mean difference SE ± 0.07; *t*-test, $p = 0.01$, Pearson $r = 0.42$); 0.45–0.29 in the left eye (mean difference SE ± 0.05; $p = 0.009$, $r = 0.52$); and 0.31–0.15 binocularly (mean difference SE ± 0.04; $p = 0.0005$, $r = 0.46$; see **Figure 2B**). Binocular average initial visual acuity was 0.31 log units and improved to 0.15, a 43% benefit. Four individuals even reached non-presbyopic acuity levels similar to younger individuals, 0.0 logMAR or below.

These data show the promise of perceptual learning based therapies to improve near vision in adults with presbyopia. Our results are consistent with other recent studies showing that perceptual learning can improve contrast sensitivity and near visual acuity in presbyopic individuals (Polat, 2009; Polat et al., 2012). These improvements are unlikely to be the result of simple test–retest improvements, as these were not found in our other control groups and Polat (2009) found improvements in near acuity in presbyopic individuals after training on a contrast detection task, but not in untrained controls. These results provide intriguing potential for the many individuals with presbyopia, however, our current study and previous research (Polat, 2009; Polat et al., 2012) lack the appropriate control conditions to make substantial conclusion. Future studies with a double blind active control group are essential in determining the effectiveness of perceptual learning based vision training.

DISCUSSION

Classically, perceptual learning leads to learning effects that are specific to the training stimuli, hindering translational progress in alleviating low vision. Here, we suggest that the key to successful translation of perceptual learning research lies upon integrative approaches where the goal is not to achieve highly specific learning, but instead to achieve broad-based improvements to vision. To this end, we combined multiple perceptual learning approaches (including engagement of attention, reinforcement, multisensory stimuli, and multiple stimulus dimensions) that have individually contributed to increasing the speed, magnitude, and generality of learning into an integrated perceptual-learning video game. Training with this video game shows that the "curse of specificity" can be overcome and the perceptual learning based training can lead to improvements in central and peripheral acuity and contrast sensitivity, reading acuity, and speed, and even improved on-field baseball hitting statistics, in normally sighted young adults after training. We also find improvements in near visual acuity in adults with presbyopia; with many of these individuals reaching non-presbyopic acuity levels (0.0 logMAR or below) after training. These data provide evidence perceptual learning based vision training translates to real world skills used in daily life, which is of great practical importance.

While the presented data provide a proof of principle that the integrated vision training program is effective, the lack of a double-blind placebo controlled study raises the possibility of potential placebo effects (Boot et al., 2011). These placebo effects may even be greater in more complex experimental designs, like those used in the current study, where there are multiple factors that might lead participants to believe that their vision should be getting better. Thus while it is classically believed that acuity and contrast sensitivity are relatively robust to placebo effects, and benefits to contrast sensitivity typically require extensive and specialized training (Adini et al., 2002; Furmanski et al., 2004) further works will be required to confirm these results.

Still, the results are consistent with a growing body of research demonstrating improvements in visual abilities after perceptual learning training. For example, other recent successes applying perceptual learning show improvements in subjects with amblyopia (Levi and Li, 2009; Hussain et al., 2012), presbyopia (Polat, 2009), macular degeneration (Baker et al., 2005), stroke (Vaina and Gross, 2004; Huxlin et al., 2009), and late-life recovery of visual function (Ostrovsky et al., 2006) suggest great promise that perceptual learning can ameliorate effects of low vision.

Collectively these studies provide substantial promise for treatment of low vision and improved visual function in normally seeing individuals, alike. However, further research is needed to determine the optimal combination of approaches to improve vision and how these may differ for visual conditions and across individuals. A difficulty towards achieving this end is that most studies in the field, including ours, include small numbers of subjects, limited controls, and substantial individual subject variance. Thus to achieve greater impact in clinical settings the field needs to move towards conducting larger scale exploratory studies to further optimize procedures and clinical trials to further validate effects. While there is thus substantial work required to fully realize the positive impact of perceptual learning based training, we believe that the potential impact to society is substantial.

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The challenges of developing a contrast-based video game for treatment of amblyopia

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Perceptual learning of visual tasks is emerging as a promising treatment for amblyopia, a developmental disorder of vision characterized by poor monocular visual acuity. The tasks tested thus far span the gamut from basic psychophysical discriminations to visually complex video games. One end of the spectrum offers precise control over stimulus parameters, whilst the other delivers the benefits of motivation and reward that sustain practice over long periods. Here, we combined the advantages of both approaches by developing a video game that trains contrast sensitivity, which in psychophysical experiments, is associated with significant improvements in visual acuity in amblyopia. Target contrast was varied adaptively in the game to derive a contrast threshold for each session. We tested the game on 20 amblyopic subjects (10 children and 10 adults), who played at home using their amblyopic eye for an average of 37 sessions (approximately 11 h). Contrast thresholds from the game improved reliably for adults but not for children. However, logMAR acuity improved for both groups (mean = 1.3 lines; range = 0–3.6 lines). We present the rationale leading to the development of the game and describe the challenges of incorporating psychophysical methods into game-like settings.

Keywords: anisometropia, binocular, contrast sensitivity, development, perceptual learning, strabismus, visual acuity

1. INTRODUCTION

In this paper, we approach the challenge of creating a video game based on laboratory tasks shown to improve visual function in individuals with abnormal visual development (amblyopia). In amblyopia, monocular visual input is disrupted early in life due to misalignment of the ocular axes (strabismus), chronic blur in one eye (anisometropia), or a combination of the two. Visual acuity, contrast sensitivity and other visual judgments are reduced in the affected eye, and binocular function is degraded or absent (McKee et al., 2003; Levi et al., 2011). Amblyopia is a neural rather than optical disorder (Kiorpes and McKee, 1999; Barrett et al., 2004), and clinical treatment comprising occlusion of the non-amblyopic eye aims at strengthening the neural response to input from the amblyopic eye. This treatment is usually administered before 7 years of age, during the critical period of development when visual pathways in the brain are most malleable (Campos, 1995; Daw, 1998). Occlusion therapy can improve visual acuity in the amblyopic eye, but has issues of poor compliance (Holmes et al., 2003; Loudon et al., 2006; Wallace et al., 2013) and regression of improvements in up to a third of the cases (Hoyt, 2004). Therefore, supplementary treatments for amblyopia that surmount these issues continue to be of interest.

Practice of visual tasks can enhance visual function in amblyopic children and adults (Levi and Polat, 1996; Levi et al., 1997; Polat et al., 2004; Chen et al., 2008; Astle et al., 2011; To et al., 2011; Hussain et al., 2012b; Li et al., 2013). Such improvements in visual function after practice are classed under the phenomenon of "perceptual learning" and are attributed to residual plasticity in primary- and higher sensory cortices. In normally sighted individuals, perceptual learning is long-lasting and often specific to the trained task (for review see Sagi, 2011). In amblyopes, the improvements in addition to being long-lasting, generalize beyond the trained task to standard clinical measures of visual acuity and stereo acuity. The functional importance of perceptual learning for amblyopia has prompted a number of investigations into the task conditions that optimize improvements.

Visual acuity improves in amblyopia after practice on discrimination of single stimulus dimensions such as position, spatial frequency or contrast (Li and Levi, 2004; Polat et al., 2004; Astle et al., 2010, 2011), and after practice on commercial video games in which stimuli are far less constrained, but with which subjects are more likely to engage (Li et al., 2011; Jeon et al., 2012). Whilst psychophysical tasks help to isolate particular dimensions of improvement (e.g., resolution vs. contrast), video games provide more stimulating conditions that elicit the reward mechanisms associated with learning (Koepp et al., 1998; Suzuki et al., 2001; Dommett et al., 2005; Seitz et al., 2009; Rokem and Silver, 2010). From the psychophysical tasks tested to date, there is evidence that contrast sensitivity tasks are associated with the largest improvements on the trained task, and with the largest transfer of benefits to visual acuity (e.g., Polat et al., 2004; Chen et al., 2008; Astle et al., 2011, see Levi, 2012 for review). Practice need not be on contrast detection or discrimination *per se*, but on a visual judgment in which stimulus contrast is the dependent variable (e.g., Landolt C discrimination, Astle et al., 2011). There is also evidence that practice directed at the crowding problem in amblyopia (i.e., the inability to identify cluttered objects), improves visual acuity (Chung et al., 2012; Hussain et al., 2012b).

In all above studies, the task was practiced monocularly with the amblyopic eye. A different approach involves practice with both eyes open, each viewing an independent stimulus (i.e., dichoptic viewing), with the aim of balancing the combination of visual input between the eyes (Knox et al., 2012; Li et al., 2013; Ooi et al., 2013). We chose monocular training to extend to more naturalistic settings work showing the success of this method in improving amblyopic acuity. Monocular methods also have the advantage of few hardware or software requirements, and minimal intervention or supervision of experts, and therefore are more practical to implement at home. With the above factors in mind, we developed a video game that incorporated the following features:

1. Dynamic pursuit of moving targets to maintain subject engagement
2. Adaptively varying target contrast
3. Multiple (crowded) targets and distractors
4. Spatially broadband targets at suprathreshold size
5. Monocular play with the amblyopic eye

To evaluate the effectiveness of this approach, we tested children and adults, who played the game at home for a minimum of 12 sessions. A subset of participants played the game for an extended number of sessions. We monitored performance on the game, and tested LogMAR acuity and stereoacuity before and after training.

2. GAME CONCEPT

The game was called Pan's Remarkable Adventures, and can be accessed free of charge online at http://www.pangame.eu/beta. The game involves a central character, Pan, who travels across various destinations (or levels) in ancient Greece, collecting prizes, and avoiding enemies, with the goal of collecting as many coins as possible. We chose a collection-based game rather than a first-person shooter game to appeal to both genders, and to minimize violent content for younger age groups. Prizes and enemies varied across levels (**Figure 1**, bottom), as well as the configuration and motion of these objects. In each level, the player had 90 s to collect as many coins as possible, and to win stars that unlocked the next level. Progression across levels was visualized on a map showing each level as a destination (**Figure 1**). Players used a mouse to control Pan and pursue moving targets, and avoid colliding with moving enemies, both of whose contrast varied adaptively within each level. Players therefore had to discriminate and respond swiftly to targets and enemies of decreasing contrast. During an initial training phase, players were guided through a fixed sequence of levels on the map (Trial, Troy, Crypt, Milos, and Labyrinth of Minos). After three training runs, every training session always included the level Trial, which was used to track performance across sessions. The player was free to choose the remaining levels provided they had unlocked that level before. Free access to levels was designed to increase engagement with the game.

2.1. REWARD

There were two types of reward. The first, a motivational reward, was a coin score directly linked to target and enemy collisions. Subjects won coins if they caught targets, and lost coins if they collided with enemies. When the player caught a target, high contrast gold coins materialized near that object and swept toward a score displayed at the top of the screen. More coins accumulated when targets and enemies were at low contrast, related to a second, contrast sensitivity score (see below). A progress bar on the left side of the screen increased as coins accumulated, and decreased when coins were lost. In addition to coins, auditory feedback and a number of bonus features (e.g., animated helpers, targets, and enemies slowing down) were included to maintain interest in the game.

The second type of reward was a performance-based score displaying contrast sensitivity on a scale of 1–100. This score was calculated from target contrast, which was adjusted continuously using a method described below. Whereas the coin score was derived from the absolute number of target and enemy collisions, the contrast score was based on the relative proportion of collisions, and provided a measure of target visibility. Subjects were told that when they were performing well, the targets would be difficult to see, and that they should try to improve both their coin score and their contrast sensitivity score. At the end of each 90 s level a graph was displayed to subjects showing changes in contrast sensitivity during that level.

Thus, good performance on the game was associated with a high coin score and with a high contrast sensitivity score, and the player's goal was to maximize both scores during each level. Bonus features affected only the coin score and not the contrast score. The top coin scores and contrast scores were saved for each subject and displayed on a "Top 10" page that subjects could access from the menu to view their past performance (**Figure 1**).

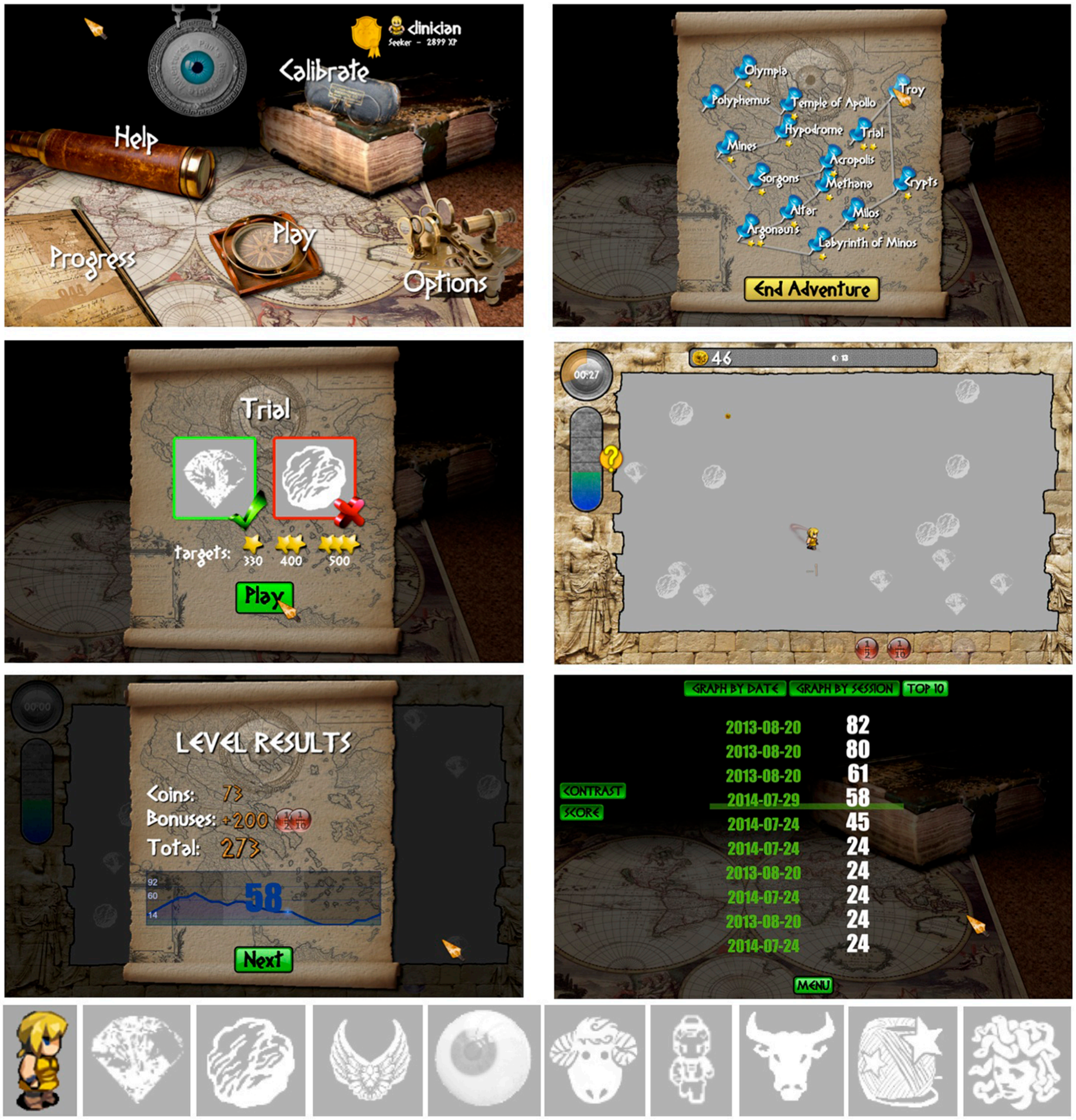
3. MATERIALS AND METHODS

3.1. SUBJECTS

Ten amblyopic children (mean age = 9.3 years; *SD* = 2.4 years), and 10 amblyopic adults (mean age = 41 years; *SD* = 8.1 years) participated in the study. All subjects except one had at least a two-line (0.2 logMAR) difference in acuity between the amblyopic and the non-amblyopic (i.e., fellow) eye. One adult subject (*SD*) was bilaterally amblyopic and had equally poor acuity in both eyes. Six of ten children and six of ten adults had received patching treatment previously. **Tables 1**, **2** provide clinical details of the subjects. All subjects were informed of the purpose and procedure of the study, which was conducted under ethics approval from the School of Psychology at the University of Nottingham. All subjects provided a detailed ophthalmic history and were refracted by an optometrist before testing. LogMAR acuity (ETDRS) and Stereo acuity (TNO) were measured before and after training. Four adults obtained these measures from their local eye-care specialist before and after playing the game, and sent us the details through email. Two children were tested at Glasgow Caledonian University by a registered optometrist. Subjects who were not tested at the University of Nottingham are marked with an asterisk in **Tables 1**, **2**.

3.2. APPARATUS AND SOFTWARE

The game was written in HTML5 and JavaScript by Ilixa, a software development company (www.ilixa.com). Ilixa participated



2013-08-20	82
2013-08-20	80
2013-08-20	61
2014-07-29	58
2014-07-24	45
2014-07-24	24
2013-08-20	24
2014-07-24	24
2013-08-20	24
2014-07-24	24

FIGURE 1 | Top left: Main menu of game with links to all features. **Top right:** Each level in the game was shown as a destination on a map. **Middle left:** Screen showing the prize and enemy for the upcoming level. **Middle right:** Example of a game in progress. **Bottom left:** Summary of coin score and contrast sensitivity at the end of a level. **Bottom right:** Top 10 scores across multiple sessions. **Bottom:** Player's icon (Pan) and examples of prizes and enemies in different levels.

in discussions about the design of the game, created all stimuli and the game interface, and devised the algorithm for contrast adjustment based on adaptive staircase procedures (see Section 3.4.3). Subjects were given a demonstration of the game on an Apple G5 iMac computer, on Google Chrome. The monitor was a Trinitron Dell P1130 with a screen width of 40 cm and resolution of 1280 × 1024 pixels. A subset of subjects were also given the demonstration on their laptop computers, which they used to play the game at home. The training sessions were always on subjects' home computers, and included a variety of LCD displays ranging from large-screen television displays to smaller, laptop displays. No iOS devices (e.g., iPhone, iPad) were used. The game was always played with an external computer mouse.

3.3. STIMULI

The targets and enemies were broadband, suprathreshold size, gray-scale objects whose contrast varied adaptively against a uniform rectangular gray background (details on contrast follow). All other items in the display besides targets and enemies were colored objects shown at high contrast (see **Figure 1**, middle panels).

3.3.1. Target size

Target size was set to 4.7% of the screen width in pixels, which ensured a constant number of targets and distractors on the screen across displays. On the laboratory display, target size at a viewing distance of 1 m subtended approximately 1° of visual

Table 1 | Amblyopic children clinical details.

Initials	Age (yrs.)	Sex	Amb. eye	Type	Refractive error	Alignment (Diopters)	Patched	LogMAR PRE	LogMAR POST
AB	8	M	L	Aniso+Micro	OD +1.50/−0.50 × 180			0.06	−0.10
					OS +3.50/−0.50 × 175	L Micro	Yes	**1.02**	**0.98**
BK	9	M	R	Strab	OD +7.00 DS	8∆ RSOT	Yes	**0.86**	**0.78**
					OS +5.50/−1.25 × 70			−0.10	−0.08
DP*	6	M	R	Strab	OD NA	18∆ RSOT	NA	**NA**	**NA**
					OS NA			NA	NA
LE	7	M	R	Strab	OD +7.75/−0.25 × 135	8∆ RSOT	Yes	**0.50**	**0.34**
					OS +8.00/−0.25 × 45			0.12	0.02
LG	9	M	L	Aniso	OD PL/−0.25 × 7			−0.10	−0.10
					OS +4.00/−4.50 × 170	–	No	**0.14**	**0.06**
MH	9	M	R	Strab	OD +1.00/−2.00 × 180	4∆ RSOT	Yes	**1.18**	**0.86**
					OS +2.00/−2.00 × 177			0.12	0.10
NJ	9	M	R	Aniso +Micro	OD +2.00/−0.50 × 125	R Micro	No	**0.20**	**0.08**
					OS PL			−0.10	−0.08
OD*	8	F	L	Strab	OD +3.50/−0.50 × 90			0.02	0.02
					OS +3.50/−0.50 × 90	18∆ LSOT	NA	**0.36**	**0.36**
SR	10	M	R	Aniso +Micro	OD+4.50/−2.50 × 100	R Micro	Yes	**0.42**	**0.22**
					OS +0.50/−0.75 × 85			0.00	0.00
WS	14	M	R	Aniso +Micro	OD +6.75/−1.75 × 165	R Micro	Yes	**1.36**	**1.32**
					OS +0.25 DS			0.02	0.00

LogMAR acuity was measured using the ETDRS chart. Acuity of amblyopic eye shown in bold. Subjects marked with an asterisk were tested by an optometrist at Caledonian University.

Table 2 | Amblyopic adult clinical details.

Initials	Age (yrs.)	Sex	Amb. eye	Type	Refractive error	Alignment (Diopters)	Patched	LogMAR PRE	LogMAR POST
AA*	42	M	L	Aniso	OD +1.00/−0.25 × 170			0.00	−0.08
					OS +3.00 DS	–	No	**0.22**	**0.18**
BM	36	F	R	Aniso +Micro	OD −0.75/−0.50 × 105	R Micro	No	**0.50**	**0.30**
					OS −4.00/−0.50 × 120			0.06	0.04
IB	44	M	L	Strab + Aniso	OD +0.25/−0.25 × 110			−0.14	−0.18
					OS +4.50 DS	10 ∆ LXOT	Yes	**0.52**	**0.36**
IT	42	M	L	Micro	OD +1.75/−0.75 × 90			−0.14	−0.08
					OS +3.25/−1.50 × 30	L Micro	Yes	**0.14**	**0.04**
JA*	24	F	L	Strab	OD +3.00 DS			−0.08	−0.08
					OS +4.50DS	12 ∆ LSOT	Yes	**0.44**	**0.24**
JJ*	53	M	L	Micro	OD +4.00/−0.25 × 90			0.00	0.00
					OS +4.25/DS	Small LXOT	Yes	**0.30**	**0.24**
JL*	41	F	R	Aniso	OD +3.50/−0.25 × 45	–	Yes	**0.18**	**0.00**
					OS +0.75/−0.25 × 150			−0.08	−0.08
RC	46	M	R	Micro	OD +6.25/−1.75 × 10	R Micro	Yes	**0.42**	**0.22**
					OS +6.00/−2.50 × 175			−0.06	−0.06
RM	44	M	L	Aniso +Micro	OD −0.50/−0.50 × 120			−0.16	−0.14
					OS +6.50/−6.25 × 85	L Micro	No	**0.16**	**0.12**
SD	37	F	B	Bilat.	OD +5.00/−0.50 × 100		Yes	**0.32**	**0.26**
					OS +3.00/−0.50 × 75			0.34	0.32

LogMAR acuity was measured using the ETDRS chart. Acuity of amblyopic eye shown in bold. Subjects marked with an asterisk were tested by their local eye-care specialist, and received the game instructions through email.

angle. For the purposes of the game, it was important that target size was set above the acuity limit of the amblyopic eye, rather than being set to one size for all subjects. Hence, the viewing distance (and target size) was adjusted in the laboratory and in subjects' homes, to ensure that targets and distractors were discriminable. Subjects were given one meter as a rule of thumb for viewing distance, and were instructed to adjust this distance if needed to make the targets as discriminable as during the demonstration, and to maintain the same viewing distance across sessions.

At the above viewing distance and size, most subjects could discriminate targets from distractors during the demonstration and practice session. The experimenter ensured this was the case by monitoring performance during the practice run. A few subjects (e.g., AB, WS; **Table 1**), could not perform the task even after the viewing distance was decreased, therefore a two-alternative forced choice (2AFC) task that was included within the game was used to determine the size threshold for target-distractor discrimination for those subjects. A sample target and a sample distractor were shown at maximum contrast in adjacent positions on the screen for an unlimited duration, and the subject's task was to click on the target item. A three-down-one-up staircase was used to find the size discrimination threshold. For AB and WS, this procedure confirmed that targets could not be discriminated from distractors at the default size at the nearest viewing distance, and target size was increased to 1.25× and 1.8× the default in these subjects' game settings.

3.3.2. Target-distractor configuration and motion

The motion, configuration and identity of targets and enemies on the screen varied from level to level. Targets were often diamond shaped objects and enemies were either spherical rock-like objects, or other objects that varied with the level (**Figure 1**). An example of the target and enemy for each level was shown at the start of each level. Target-distractor configurations ranged from being randomly intermingled on the screen (e.g., Trial), and forming mixed clusters (e.g., Olympia) to being placed in orderly, separated arrays (e.g., Milos). Target-distractor motion ranged from smooth translation in random directions across the screen, and bouncing movements, to situations in which targets eluded and/or enemies pursued the player.

3.4. CONTRAST

3.4.1. Display calibration

Displays were calibrated using an observer-based procedure developed for LCD displays (Xiao et al., 2011). In this procedure, the observer matches a patch of uniform luminance to a half-tone background using the method of adjustment. Matches are repeated for eight luminance levels, and judgments of relative luminance are interpolated to correct for the display nonlinearity (i.e., the opto-electronic transfer function, analogous to the gamma function in CRT displays). This procedure was completed through the "Calibration" option on the game home page. Subjects matched the brightness of a central eye-shaped pattern to that of the background by pressing on "+" or "−" buttons displayed on the screen, until the pattern blended into the background (**Figure 2**). Calibration was done in a lit room under the same conditions in which the game was played, and the entire procedure took about 5 min. Subjects were instructed to perform the calibration once prior to their first session, and to ensure that the display position and settings were unchanged across sessions. **Figure 2** shows the adjustments obtained for eighteen subjects using this method. Gray values of the central image (rescaled from 0–255 to 0–1.00) selected by observers to match the background are plotted for each of eight background luminances. The background comprised black and white pixels (i.e., pixels set to zero and 255), and luminance was varied by increasing the proportion of white pixels (see Xiao et al., 2011). Thus, the curves are analogous to the inverse gamma function applied to correct for display non-linearities in CRT displays. The calibration settings were stored locally on subjects' computers and loaded each time the game was played.

3.4.2. Contrast resolution and formula

Contrast resolution was increased beyond eight bits using an image dithering algorithm (Floyd and Steinberg, 1976), which is equivalent to adding imperceptible pixel noise to the target. Target pixels vary slightly around a mean value, rather than being set to a single value. These spatial fluctuations cannot be resolved by the eye, but change the effective contrast of the target against the background.

Contrast ranged between 0.00 and 1.00, and was defined as:

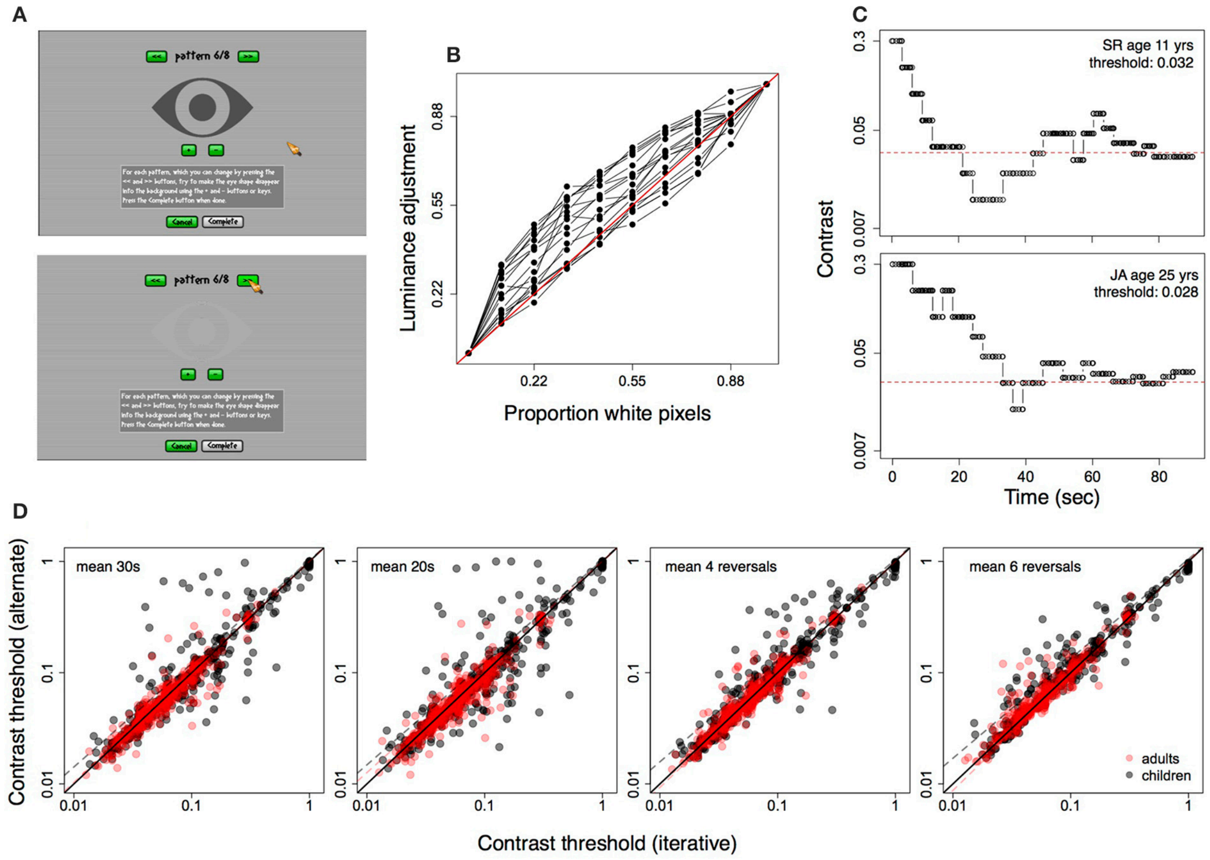
$$c = \frac{L_{\text{target}} - L_{\text{min}}}{L_{\text{min}}} \tag{1}$$

where, L_{target} was the luminance of the target objects, and L_{min} was the minimum or background luminance, which was approximately 0.50. This formula for contrast is the same as Weber contrast.

3.4.3. Contrast adjustment

Adjustment of contrast was modeled on standard staircase methods used in psychophysical experiments, and based on performance within successive 3-s time windows, each of which constituted a trial. Target contrast was adjusted using a probabilistic estimate of the subject's proportion of target collisions to total target and enemy collisions within the trial window. In a scenario where contrast must change adaptively based on events within a time window, it is more feasible to use a probabilistic estimate of performance than the actual number of collisions within each window. This is because the total number of target-distractor collisions within a short period may not be large enough to provide a precise measure of performance (e.g., zero hits, or 1/1 hit = 100% performance within 3 s), leading to large variations in contrast over time. Therefore, the method below was used to estimate the proportion of target collisions for the subject at a given contrast:

Let p be the number of targets collected, e be the number of enemies, and n the total number of collisions ($p + e$). Further, let P_p be the probability that any collision is a target, p. Two criteria, T_1 and T_2 were set, with T_1 equal to 0.7 and T_2 equal to 0.5. A contrast adjustment rule may be defined as:



For each pattern, which you can change by pressing the << and >> buttons, try to make the eye shape disappear into the background using the + and − buttons or keys. Press the Complete button when done.

FIGURE 2 | (A) Calibration screen showing central pattern matched to half-tone background using method of adjustment. Top: before adjustment, Bottom: adjusted pattern. **(B)** Calibration data for 18 displays, showing luminance adjustments (scaled from 0 to 1) against actual luminance increments (see text for details). **(C)** Contrast staircase from one level of the game for a child (top) and adult (bottom). **(D)** Correlation between contrast threshold calculated using iterative method (see text) and four other methods. From left to right: average contrast shown in final 30 s and final 20 s of the level, average of final four and final six contrast reversals.

- If $P_p > T_1$, contrast decreases
- If $P_p < T_2$, contrast increases

P_p cannot be estimated directly, therefore p and e were used to estimate the probability P_1 (the probability that P_p is in range $[T_1, 1.00]$) and P_2 (the probability that P_p is in range $[0.00, T_2]$).

These probabilities are estimated from the function:

$$f_{\mathrm{p,e}}(x) = x^p \cdot (1-x)^e \cdot \binom{p+e}{p} \tag{2}$$

where, x is the probability of a target collision.

From the above,

$$P_1 = \frac{\sum_{T1}^{1} f_{\mathrm{p,e}}(x).dx}{\sum_{0}^{1} f_{\mathrm{p,e}}(x).dx} \tag{3}$$

and

$$P_2 = \frac{\sum_{0}^{T2} f_{\mathrm{p,e}}(x).dx}{\sum_{0}^{1} f_{\mathrm{p,e}}(x).dx} \tag{4}$$

Now, if P_1 is high and P_2 is low, contrast decreases. Conversely, if P_1 is low and P_2 is high, contrast increases. This formulation was implemented discretely by setting dx to 0.001, and a stochastic variable was added to the contrast rule to smooth any sharp changes in contrast. Let r be a random number from a uniform distribution between 0 and 1.00:

- If $P_1 > 0.3$ and $r < P_1$ and $p > 0$, decrease contrast
- If $P_2 > 0.3$ and $r < 1 - P_2$ and $n = 0$ or $e > 0$, increase contrast
- Otherwise, keep contrast unchanged

Contrast was changed by multiplying or dividing by a multiplier (step size) to increase, or decrease contrast. The multiplier itself was adjusted based on performance in the previous three time windows (i.e., previous 12 s), with the starting (maximum) value set to 1.7, reaching a minimum of 1.12. **Figure 2C** shows examples of staircases constructed using the above method for one child and one adult subject during a single 90 s level.

3.4.4. Contrast threshold calculation

The contrast threshold for each level was calculated using an iterative procedure from 30% of target contrasts nearest to the average target contrast over the 90 s duration. The threshold estimate included target contrasts from 27 s (though not necessarily contiguous) of the 90 s period. We compared this threshold measure with measures approximated from psychophysical procedures (i.e., average of the final four and six contrast reversals within the level) and with the average of all contrasts displayed in the final 20 and 30 s of the level. **Figure 2D** shows the above four measures of threshold plotted against the iterative measure for all subjects, from all sessions, on one level of the game. Thresholds from the iterative method were strongly correlated with the other measures (Pearsons's $r > 0.80$, $p < 0.0001$ for all tests).

3.5. PROCEDURE

Subjects were refracted and a full ophthalmic history obtained. Subjects were fitted with their best optical correction for the demonstration and an initial practice run on the game, and were instructed to use their best correction when they played the game at home. The game was always played monocularly, with a patch over the fellow eye. Demonstration of the game included subject registration (setting up an ID and password that was used each time the subject played the game), use of the game menu, display calibration, ensuring that target size was set above the acuity limit of the amblyopic eye, and a practice run on the game. During the practice run, the experimenter confirmed that target contrast decreased adaptively from its starting point, indicating that subjects understood how to play the game. Detailed instructions were given on how to set up the game at home. Subjects were told to download the browser Chrome if it did not already exist on their computers, to set their computer monitors to a fixed viewing distance (1 m was suggested, but also see stimulus size section above) for all sessions, and to calibrate their display using the demonstrated method prior to the first session. For children, parents set up the game and confirmed that the instructions were being followed. For subjects who did not attend a demonstration at the University of Nottingham or Glasgow Caledonian University (i.e., four adults), detailed instructions of all steps were provided in a separate document sent through email. Subjects were instructed to play the game every day, for at least 25 min a day. Visual acuity was re-measured after at least 2 weeks of training. A subset of subjects (six children and four adults) continued to play the game after the first acuity re-test, and returned for a second re-test some weeks later.

3.6. DATA STORAGE

Each subject had a unique ID, which they used each time they played the game. Their data from each session were stored on a server, which could be accessed by the experimenters at the University of Nottingham. The data for each subject included date of session, duration of session, number of levels played at each session, names of the levels played and the contrast threshold for each level. Hardware and software details were also stored, including the OS, browser name and version, window size (in pixels), and monitor refresh rate. Thus, the experimenter was able to keep track of whether subjects were playing the game regularly, and for a minimum duration each session.

3.7. CONTRAST THRESHOLDS

Contrast thresholds from the Trial level, which was obligatory on each run, were used to measure improvement on the game. Contrast thresholds were always measured for the amblyopic eye, with a patch over the fellow eye. For each subject, outlying threshold values (i.e., thresholds more than two standard deviations greater than or less than the mean threshold over all sessions of that subject), were removed from the analyses. Five percent of the children's thresholds and four percent of the adults' thresholds were removed using this criterion. The number of training days between the pre- and post-training acuity tests ranged from twelve to thirty-two (mean = 23.4; $SD = 7.21$). Thresholds from the very first day (open symbols, **Figures 3**, **4**), were discarded from the analyses as they were measured during the initial demonstration, on a different display than the display used for the remaining sessions. The second day's threshold was considered as the initial threshold value. We measured the amount of improvement as the difference between thresholds on the initial and final training day (i.e., initial threshold minus final threshold). We also calculated learning slopes from linear regression of threshold against day for each subject. According to this measure, improvement is associated with a negative slope significantly different from zero. Improvement on perceptual tasks has also been suggested to increase as a power- or exponential function of the amount of practice (Dosher and Lu, 2007). We compared the fit of a linear model and a decaying exponential model of threshold against session number for each subject using the Akaike Information Criterion (AIC). This criterion produced better exponential fits than linear fits for three of ten adult subjects, and one of ten children (child: DP; adults: BM, IB, JO). For the analyses that follow, we report the linear fits for all subjects.

4. RESULTS

4.1. CONTRAST THRESHOLDS

Performance of amblyopic children and adults on all training days is shown in **Figures 3**, **4**. **Figure 5A** summarizes the threshold data. The average contrast threshold of children changed from 0.15 ($SE = 0.05$) on the initial day to 0.09 ($SE = 0.02$) on the final day. This change in threshold between days was not significant [$t_{(9)} = 1.021$, $p = 0.33$]. As seen in **Figure 3**, there was substantial variability in children's performance across days, and the learning slope did not differ from zero for any individual child. Contrast thresholds decreased from the initial to final measurement for the adults [**Figures 4**, **5A**, from 0.07 ($SE = 0.01$) to 0.045 ($SE = 0.005$)]. This change in threshold was significant [$t_{(9)} = 4.20$, $p = 0.002$]. **Figure 4** shows that the improvement in adults was more reliable than in children, with the learning slope for six of ten adults significantly different than zero. Overall these data suggest that for the adults, but not for children, the contrast

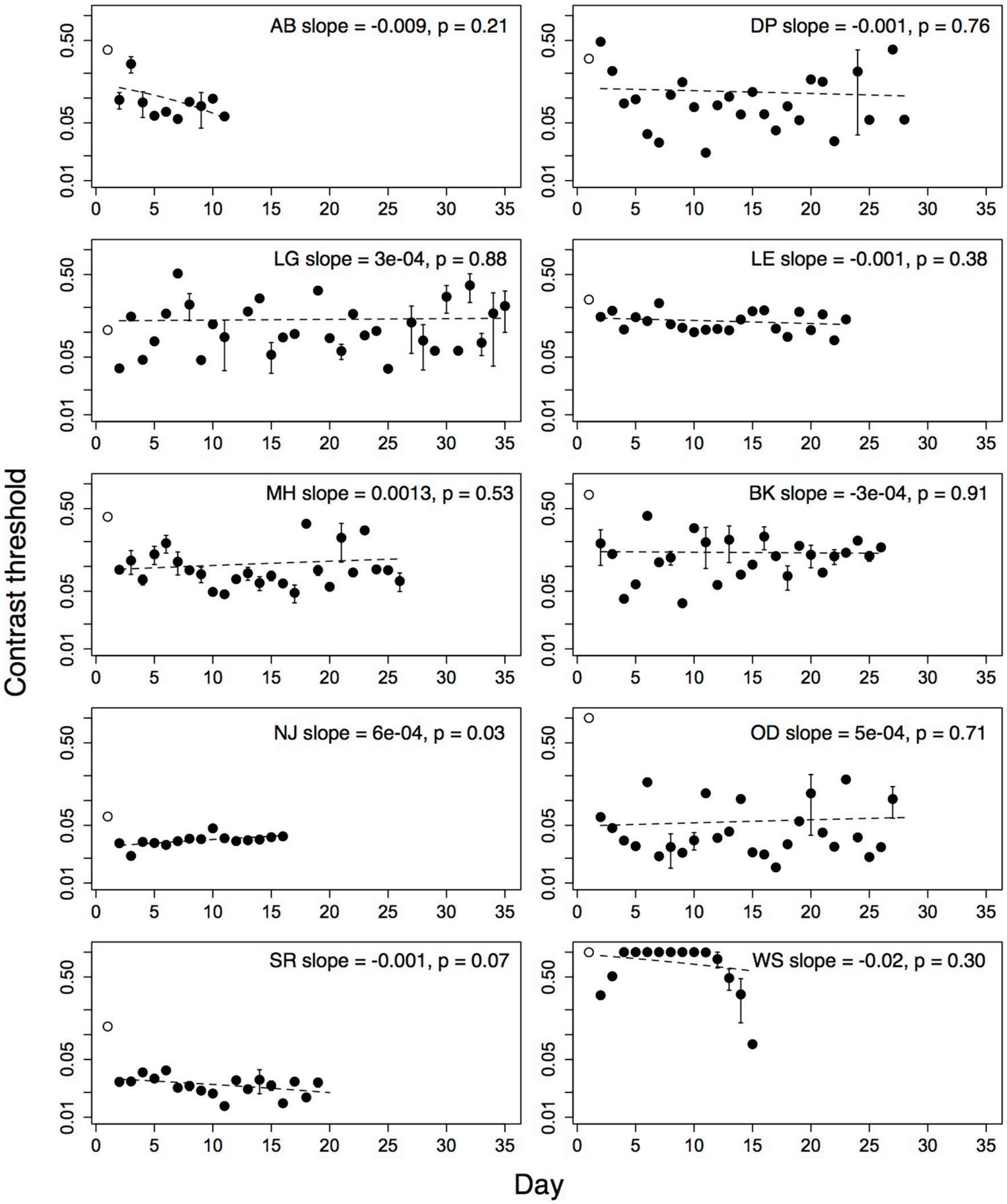


FIGURE 3 | Performance of 10 amblyopic children on level Trial over multiple days. Open symbol shows performance on first demonstration session. Error bars show standard error of the mean (s.e.m.), where the subjects played more than one run. Dashed line shows regression fit of threshold on day. Open symbol not included in fit. Subject initials, slope of the regression fit and associated *p*-value given in each plot.

threshold was a reliable measure of performance on the game. Potential explanations for this difference are discussed later.

4.2. LogMAR ACUITY

LogMAR acuity of the amblyopic eye and the fellow eye of the nineteen subjects is shown in **Figure 5B** (acuity data were not available for one child participant who was tested outside Nottingham). Acuity of the amblyopic eye improved by 0.12 logMAR both for children [$t_{(8)} = 3.51, = 0.008$], and adults [$t_{(9)} = 5.57, p = 0.00034$]. Acuity of the fellow eye did not change significantly after training either for children [$t_{(8)} = 1.43, p = 0.19$] or adults [$t_{(9)} = 0.6882, p = 0.51$]. **Figure 5C** plots the improvement in acuity of the amblyopic eye against the change in acuity of the fellow eye for all subjects. Improvement in the amblyopic

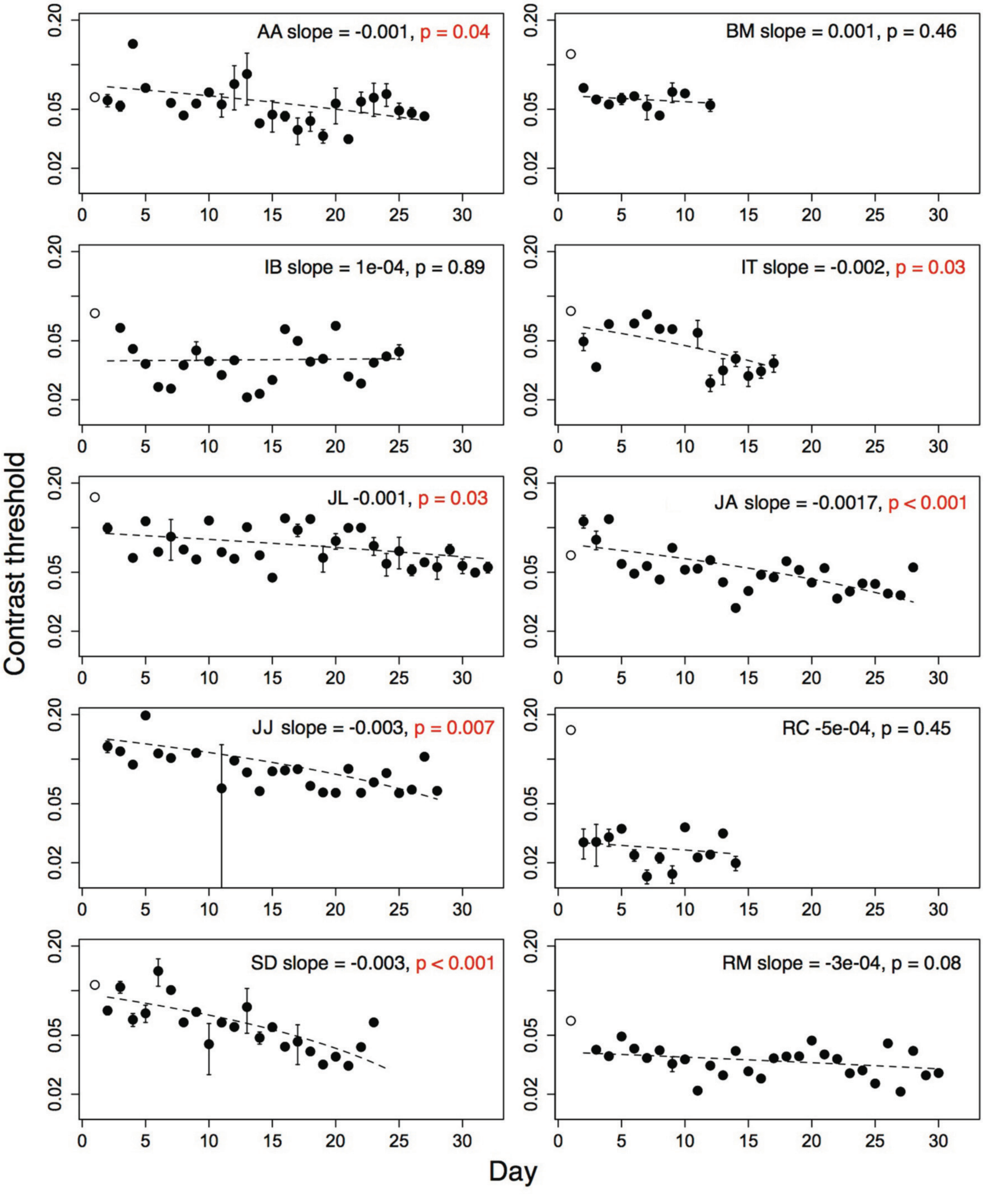


FIGURE 4 | Performance of ten amblyopic adults on level Trial over multiple days. Open symbol shows performance on first demonstration session. Significant improvement indicated by *p*-values in red. Error bars show standard error of the mean (s.e.m.), where the subjects played more than one run. Dashed line shows regression fit of threshold on day. Open symbol not included in fit. Subject initials, slope of the regression fit and associated *p*-value shown.

eye outweighed improvement in the fellow eye for all but three subjects, and improvements in the acuity of the amblyopic eye were not correlated with the change in acuity of the fellow eye. Therefore, subjects were not merely improving at reading the letter acuity chart. For four mild amblyopes (children: LG and NJ, initial acuity: 0.14 and 0.20, **Table 1**; adults: IT and JL, initial acuity: 0.14 and 0.18, **Table 2**), the difference in visual acuity between the eyes was reduced to less than two lines, rendering them no longer amblyopic according to the criterion of the study. **Table 3** gives the correlation coefficient (Pearson's *r*), and *p*-values for

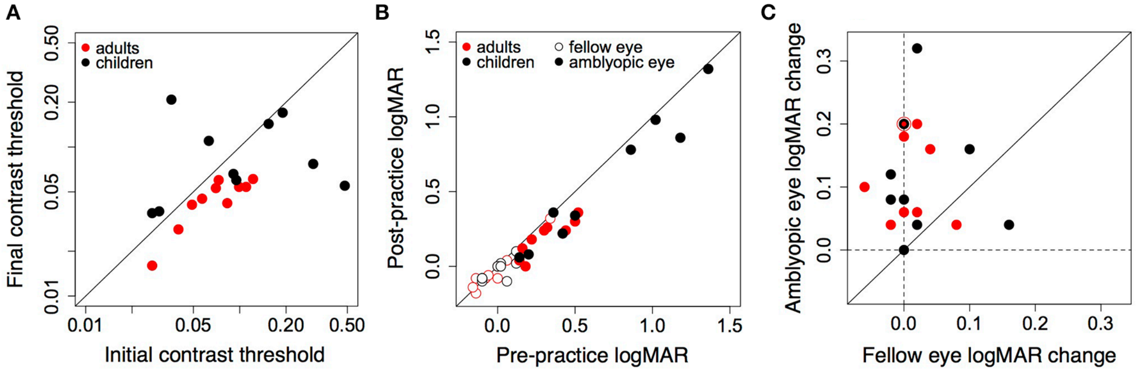


FIGURE 5 | (A) Initial and final contrast thresholds measured on the game for adults and children. Points below the diagonal show improvement. **(B)** Pre- and post-training LogMAR acuity of the amblyopic eye (closed symbols) and fellow eye (open symbols) of 9 amblyopic children and 10 amblyopic adults. Points below the diagonal show improvement. **(C)** Improvement of the amblyopic eye against improvement in the fellow eye. Dashed vertical and horizontal lines show zero change. Points above the diagonal show greater improvement in the amblyopic eye than fellow eye. The black and red symbol shows data for two adults and one child. Sixteen of nineteen points lie above the unity line.

Table 3 | Correlation between change in LogMAR acuity and other variables.

	Children	Adults
Threshold improvement	−0.05 (0.90)	0.26 (0.47)
Initial LogMAR acuity (amblyopic eye)	0.12 (0.76)	**0.63 (0.05)**
LogMAR improvement in fellow eye	−0.09 (0.81)	−0.08 (0.82)
Number of training sessions	0.11 (0.78)	−0.40 (0.26)
Median minutes per session	**0.61 (0.08)**	−0.15 (0.67)
Total hours played	0.53 (0.15)	−0.37 (0.28)
Total hours after extended practice	**0.66 (0.05)**	−0.04 (0.91)
Age	−0.05 (0.89)	−0.39 (0.26)

Correlation coefficient r, and p-value shown. Acuity tested multiple times for extended practice subjects. Values in parentheses are p-values.

correlations between absolute amount of logMAR improvement and threshold change, initial logMAR acuity, logMAR improvement in the fellow eye, number of sessions, session duration, total hours played and the age of the participant. Improvements in logMAR acuity were not correlated with most measures, except for a marginally significant positive correlation between initial logMAR acuity and logMAR improvement of the adults (suggesting that poorer starting acuity was associated with larger improvement), and marginally significant associations between improvement and session duration, and improvement and total hours played in children (see below).

4.3. EXTENDED TRAINING, SESSION DURATION, AND TOTAL AMOUNT OF PRACTICE

A subset of subjects (six children and four adults) played the game for additional days and returned for a second acuity re-test. Performance of these subjects on the game is shown in **Figure 6**. For these subjects, contrast thresholds did not change significantly between the logMAR pre-test and the first post-test [mean difference $= 0.02$; $t_{(8)} = 0.82$, $p = 0.44$], or between the first post-test and the second post-test [mean difference $= 0.009$; $t_{(8)} = 0.52$, $p = 0.61$]. For all subjects except subject WS, learning slopes did not differ from zero. Between the pre-test and first post-test, logMAR acuity of these subjects improved by 1.5 lines [mean $= 0.15$; $t_{(8)} = 4.6904$, $p = 0.002$]. After additional practice, logMAR acuity improved further by a small amount for children [mean $= 0.05$, $t_{(5)} = 3.02$, $p = 0.02$; post-test1 minus post-test2], but did not change for adults [mean $= -0.02$, $t_{(5)} = 2.45$, $p = 0.09$]. The total improvement in thresholds from the initial to the final session of these subjects was not correlated with their improvement in logMAR acuity from pre-test to the second post-test [$r = 0.46$; $t_{(7)} = 1.40$, $p = 0.20$]. These data suggest that extended play of the game produced slight additional improvements in logMAR acuity only for the children, and that the improvements in logMAR acuity of both groups were maintained over the testing period.

Did the duration of each session affect the amount of improvement? **Figures 7A,B** show histograms of session duration (in minutes), and and the time of day at which subjects played the game, for all sessions of all subjects. Adults played the game for approximately 24 min on average per session, which was significantly longer than children, who played for an average of 15 min per session [$t_{(462.249)} = 12.05, p < 0.0001$]. Therefore, adults, but not children, complied with the suggested duration of practice on the game. Both groups played the game during the latter part of the day, and adults played later than children (median hour: 20:28 vs. 18:52; Wilcoxon rank sum test; $W = 32311.5$, $p = 0.00026$). **Figure 7C** shows the relationship between median session duration for each subject and their logMAR acuity improvement. The correlation between improvement in logMAR acuity and duration was marginally significant for children [$r = 0.61$, $t_{(7)} = 2.01$, $p = 0.08$], but not adults [$r = -0.15$, $t_{(8)} = 0.44$, $p = 0.67$]. Note that median duration for adults always exceeded 15 min, and that the range of durations was fairly narrow (**Figure 7C**).

We examined whether larger amounts of practice, as measured by the total number of hours played by each subject, were associated with larger improvements in logMAR acuity. **Figure 7D**

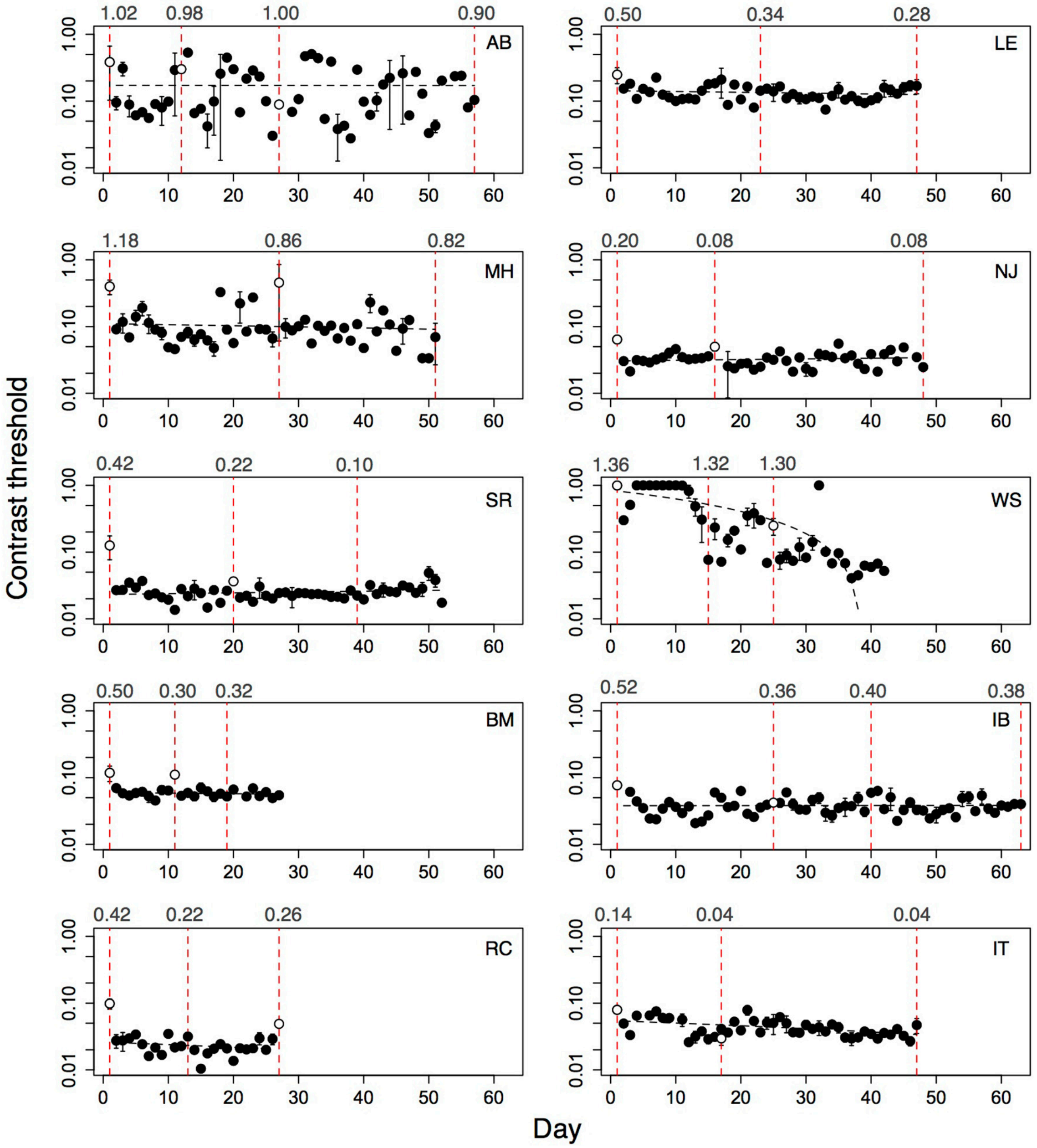


FIGURE 6 | Performance of ten amblyopic subjects who played for an extended number of days, and whose acuity was re-tested more than once. Top six panels show children, bottom four panels show adults. Closed symbols represent thresholds from subjects' home computers. Dashed black line: regression fit of threshold over day. Open symbols show thresholds measured in the laboratory and are not included in the fit. Vertical red dotted lines: days on which logMAR acuity was tested. Numbers at top of dashed lines: logMAR acuity. See text for analyses.

shows logMAR improvement for all subjects against the total number of hours played. These data include the extra hours played by subjects who trained for additional sessions after their first acuity post-test, and whose acuity was tested more than once (final acuity and number of hours shown for every subject). **Figure 7D** suggests that larger improvements in logMAR acuity were associated with more hours played; this correlation was marginally significant across all subjects [$r = 0.41$, $t_{(17)} = 1.87$, $p = 0.08$]. When considered for each group separately, the correlation between hours played and logMAR improvement was not significant for adults [$r = -0.04$, $t_{(8)} = -0.11$, $p = 0.91$], and marginally significant for children [$r = 0.66$, $t_{(7)} = 2.34$, $p = 0.05$]. Subjects whose acuity was re-tested more than once are indicated in **Figure 7D** (large symbols), and span the range of logMAR improvements, suggesting that this relationship was not based on acuity re-tests alone. Furthermore, a similar pattern was evident (but not significant) when the number of hours between pre-test and first post-test were considered (see **Table 3**, Total

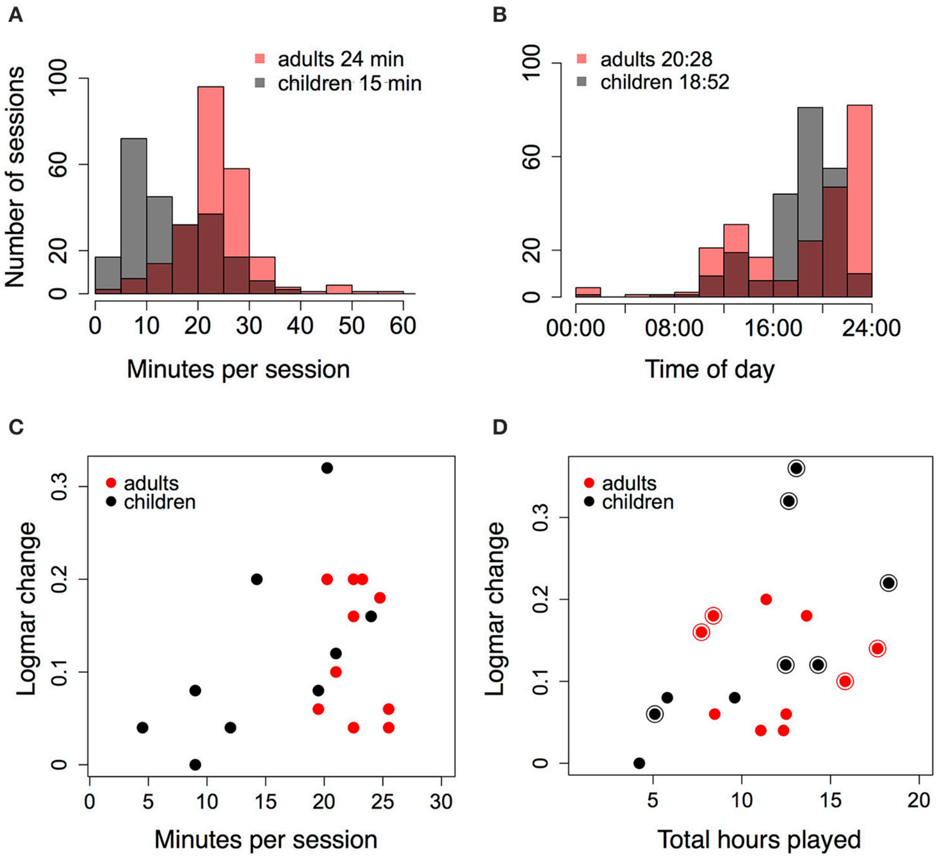


FIGURE 7 | (A) Histogram showing the amount of time played per session by children and adults. Legend shows mean number of minutes played each session. **(B)** Histogram showing time of day at which children and adults played the game. Legend gives median time. **(C)** Change in logMAR acuity for each subject (at first acuity post-test) against median minutes per session. **(D)** Change in logMAR acuity for each subject against total hours played over all sessions. Large symbols show subjects who played for an extended duration, and whose acuity was re-tested more than once.

hours played, Total hours after extended practice), suggesting that the total amount of practice did matter.

Overall, the data suggest that for children, clinically significant improvements in logMAR acuity may depend on a minimum amount of practice per session, and on the total amount of practice across all sessions. The number of sessions was not a good predictor of acuity improvement in children because it was uncorrelated with session duration and total hours played. The relationship between acuity improvement and session duration was less clear in adults, possibly because of the narrow range of durations across subjects. Large improvements in adults also may require far greater amounts of practice than are needed for children, greater than the maximum amount measured in this study. Additionally, the improvement in adults may be limited by other factors than the amount of practice, such as the depth of amblyopia and the properties of the training task. More data including a broader range (and manipulation) of session durations and total amounts of practice are needed to clarify this issue.

4.4. STEREOACUITY

Stereoacuity was measured using the TNO test for stereoscopic vision before and after training. Stereoacuity improved from 60 to 30 s of arc for one child, from 120 to 60 s of arc for two children, and from more than 30 min of arc (No Stereo) to 30 min of arc (Gross Stereo) for two children. There was no change in stereoacuity in the other five children. Stereoacuity changed from No Stereo to 480 s of arc for one adult, from No Stereo to Gross Stereo for another adult, and did not change in the other adults. We grouped subjects according to whether their stereo acuity changed (Group 1, $N = 7$) and did not change (Group 2, $N = 11$) after game play. There was no difference between these groups in amount of change in logMAR acuity [$t_{(14.98)} = 0.43$, $p = 0.67$], median minutes per session [$t_{(15.496)} = 0.40$, $p = 0.69$], hours played on the game [$t_{(15.37)} = 0.49$, $p = 0.62$], and number of sessions played [$t_{(10.1)} = 0.1.27$, $p = 0.23$]. These results suggest that improvements in stereo acuity could not be predicted from changes in letter acuity, or the amount of practice.

4.5. LEVEL DIFFICULTY AND PREFERENCE

Figure 8A shows average performance on each of the fifteen levels of the game for children and adults. Thresholds were higher for children than adults in all levels, and varied consistently across levels for both groups. These data illustrate the variation in difficulty across levels, which arose from the dynamics of the moving objects on the screen. The level Trial was always played during each session, after which subjects played a subset of the other

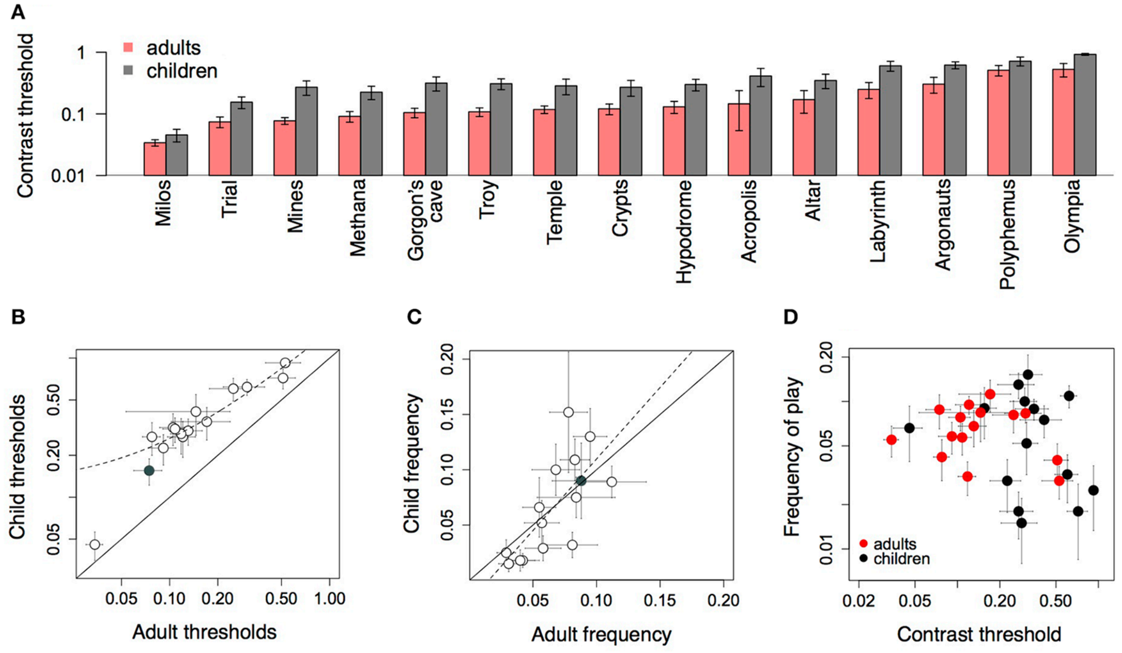


FIGURE 8 | (A) Average performance of children and adults on each level of the game. **(B)** Children's thresholds on each level of the game plotted against adult thresholds for that level. Filled symbol shows the level Trial. **(C)** Proportion (of all levels) that each level was played across all training sessions, children vs. adults. Filled symbol shows Trial. **(D)** Average frequency that each level was played against average threshold for that level.

levels, the choice of which varied across subjects. **Figure 8B** shows that children's thresholds across all levels were uniformly larger than adult's thresholds, and correlated across levels [$r = 0.95$, $t_{(13)} = 10.99$, $p < 0.0001$]. On average across all levels, children's thresholds were twice adult thresholds [mean $= 0.39$ vs. 0.18; $t_{(24.152)} = 2.89$, $p = 0.009$].

Figure 8C shows the preference for different levels by adults and children. Each symbol shows the average proportion that a given level was played, of all levels played across all sessions. With fifteen levels in the game, if subjects were choosing all levels equally, the frequency for each level would be approximately 0.07 (i.e., 1/15). However, certain levels were more popular than other levels, and this preference was consistent across adults and children [$r = 0.72$, $t_{(13)} = 3.71$, $p < 0.002$]. The gray symbol shows the level Trial, which was obligatory on each run, and which was played equally often by both groups.

Was level preference predicted by level difficulty? **Figure 8D** shows the average proportion that each level was played (across all levels and sessions) against the average contrast threshold on that level, separately for adults and children. The frequency that each level was played was uncorrelated with difficulty as measured by the average threshold, both for adults [$r = -0.32$, $t_{(13)} = -1.22$, $p = 0.24$], and children [$r = -0.27$, $t_{(13)} = -1.05$, $p = 0.31$].

5. DISCUSSION

Our aim was to create an engaging video game based on psychophysical tasks that achieve the largest acuity improvements in amblyopia. Contrast-based tasks (i.e., tasks in which the dependent measure is target contrast), have been linked to the largest benefits for visual acuity in amblyopia (Levi and Li, 2009; Astle et al., 2011; Levi, 2012). Therefore, targets that varied adaptively in contrast were a key aspect of the game. We tested both adults and children, who played the game for multiple sessions. The game provided reliable estimates of contrast thresholds for the adults, whose thresholds decreased with game play; thresholds were much more variable and did not change significantly after training for children. The absence of improvement in contrast thresholds of children may be related to a number of other factors discussed below. Threshold improvements notwithstanding, there was a significant improvement in logMAR acuity for both groups after training. For four subjects with mild amblyopia (initial acuities ranging from 0.14 to 0.20), the difference in acuity between the eyes decreased to less than 0.20 logMAR such that they could no longer be classified as amblyopic after training. The improvements in acuity were specific to the trained eye, and were retained when measured several weeks later for a subset of individuals who returned for a second post-test.

There are now a number of studies suggesting that playing of video games, whether off-the-shelf or customized, can improve visual acuity in amblyopia (Li et al., 2011, 2013; To et al., 2011; Hess et al., 2012; Jeon et al., 2012; Knox et al., 2012; Herbison et al., 2013). Across these studies, an improvement of approximately 1–2 lines (0.10–0.20 logMAR) was obtained after 5–40 h of training. We obtained an average logMAR improvement of 1.3 lines (range 0–3.6 lines; across both groups, and including the improvements obtained after extended practice), after an average of 11 h of training distributed over multiple sessions. An improvement in logMAR acuity of 1.3 lines within this duration compares favorably with the above reports, but it is not clear that further training would have produced more improvement. We consider below factors that may constrain improvement in game-like settings, the mechanisms of improvement in such settings, and the caveats of this study.

5.1. AMOUNT OF PRACTICE

An improvement of 1.5–2 lines in logMAR acuity emerges as the standard effect size from a number of studies on perceptual learning in amblyopia (see Levi and Li, 2009; Levi, 2012, for reviews). This effect size is fairly stable despite the considerable variety of tasks and practice durations used. Prolonged practice does confer additional benefits on the trained task in certain cases, (e.g., Li et al., 2007, 2008), but reports of complete resolution of amblyopia (based on the criterion of equivalent visual acuity in both eyes), are confined to cases of mild amblyopia (e.g., Li et al., 2011, and the present study). In the present case, the total number of hours played was positively correlated with logMAR improvement in children but not adults (**Figure 7**), and visual acuity improved slightly after additional practice only for children and not adults (**Figure 6**). This difference between children and adults may have arisen due to a longer initial period of procedural learning in children, due to differences in the amount of time played per session (i.e., the distribution of total practice across sessions), or simply due to differences in the maturity of sensory, cognitive and motor skills of the two groups. The maximum duration of game play here was 18.3 h, less than the 50–100 h reported to produce asymptotic performance in amblyopes on a positional discrimination task (Li et al., 2007, 2008). However, the relationship between total hours played and improvement in logMAR acuity was independent of performance on the game, which varied considerably and did not improve for children, but was more reliable, and improved in adults. In Li et al. (2007) as well, asymptotic performance on the trained task after an extended amount of practice was not accompanied by full resolution of the acuity difference between eyes. Hess et al. (2012) also have reported the absence of a correlation between total hours of play on a dichoptic video game and outcome measures including improvement on the game, improvement in logMAR acuity, and stereoacuity. This pattern of results suggests that for severe amblyopia, there may be a ceiling on the functional benefits of practice-based approaches that currently are being tested, and that the sheer amount of practice whilst beneficial for task performance *per se*, may only go so far toward improving visual acuity.

5.2. TASK- AND STIMULUS-RELATED FACTORS

5.2.1. Pursuit of low contrast targets in a video game

Pursuit of moving objects mimicked the engaging aspects of action video games that are thought to activate the reward mechanisms of learning (Rokem and Silver, 2010; Baroncelli et al., 2011; Levi, 2012). First person-shooter games such as Medal of Honor most frequently linked to improved visual function in amblyopia (e.g., Li et al., 2011), involve rapid responses to salient targets. Psychophysical tasks on the other hand, call for sustained focus on a single attribute of a stimulus, which although not as stimulating, may evoke types of learning that are absent or diffuse in video games. Contrast-based laboratory tasks that thus far have produced improvement in acuity in amblyopia, have required discrimination of foveated, static targets in clearly defined spatial or temporal intervals, that is, in stimulus conditions optimized for producing low thresholds (Polat et al., 2004; Zhou et al., 2006; Chen et al., 2008; Huang et al., 2008; Astle et al., 2011). Insofar as dynamic target pursuit remains an objective of a game, threshold tasks (and especially contrast-based tasks) are not easily adapted to video games because pursuit of targets is difficult or impossible near threshold. Furthermore, smooth pursuit eye movements in strabismus are abnormal, and biased toward certain parts of the visual field and directions of motion (Schor and Levi, 1980; Tychsen and Lisberger, 1986; Demer and von Noorden, 1988; Lions et al., 2013). This asymmetry in eye movements could affect performance on a large proportion of targets presented in these conditions. In other words, certain characteristics of videogames that are optimal for learning may be incompatible with those of psychophysical tasks, curtailing the overall benefits when both methods are combined. Note however, that as far as video games go, it is not crucial that the game be an action video game, or that contrast be manipulated. Improved visual function was shown after practice of a non-action video game (SIMS), involving no manipulation of contrast (Li et al., 2011).

5.2.2. Target size and other attributes

All stimulus attributes except contrast (e.g., size, speed), were above threshold and held constant across all sessions. This was done intentionally to isolate contrast as the training variable, and to minimize uncertainty associated with the other variables. However, there is evidence that near-threshold stimuli generate larger improvements than stimuli that are above threshold (Zhou et al., 2006; Huang et al., 2008). Larger improvement may have resulted here if stimulus size for instance, had been set exactly to, rather than above the acuity limit of subjects' amblyopic eye, and if this size were adjusted at the start of each session (and not just the first session).

5.2.3. Monocular vs. dichoptic training

Some studies suggest that interocular suppression (i.e., inhibition of the amblyopic eye by the fellow eye), plays a large role in the acuity deficit in amblyopia, and that treatments targeted at reducing suppression may be more successful in improving the acuity of the amblyopic eye (To et al., 2011; Hess et al., 2012; Li et al., 2013). To re-establish the balance between the two eyes, these studies have used dichoptic training methods, in which visual input to the two eyes is separated, and the contribution of inputs is recalibrated with training. Using a dichoptic version of the popular game Tetris, the above studies have shown significant recovery of stereo function and improvements in visual acuity, which in certain instances exceed the improvements found with monocular methods within an equivalent duration of practice (e.g., Li et al., 2013, N.B. Due to the asymmetric crossover design used in this study, an enhancement of the dichoptic effect from prior monocular training cannot be ruled out). Given evidence for the recovery of stereo function and acuity after monocular video game play (including full recovery for a subset of mild amblyopes, e.g., Li et al., 2011), it appears that techniques aimed at reducing suppression may be sufficient, but are not necessary to improve visual function in amblyopia. The relative advantages of these two approaches remain an area of investigation.

5.3. GAME DESIGN

What are the ingredients for a compelling video game? Features such as the stopping rule, for instance, may influence subjects' engagement over multiple sessions, or within a single session. These features are especially relevant for younger age groups less motivated by the functional benefits of game playing.

5.3.1. Stopping rule

Subjects played out each 90 s level regardless of whether stimulus contrast was near threshold, and then proceeded to the next level of their choice. Achievement was based on the total number of coins earned within the 90 s period, rather than on reaching a contrast-defined target. This scenario was created to give subjects the best chance at achieving a low threshold within the specified period. On the other hand, a performance-limited stopping rule rather than a time-limited stopping rule may have better guided subjects toward achieving lower thresholds. For instance, one rule might require the player to remain at a particular low contrast for a fixed duration, or to achieve a particular target contrast before progressing to the next level. Indeed, in many popular commercial video games, players must achieve well-specified targets or else they must re-play that particular level.

5.3.2. Feedback

Two sources of feedback were provided to subjects through a coin score and a contrast sensitivity score. Dual feedback may have been less effective than a single score based entirely on performance and more closely linked to the type of stopping rule described above. Various other mechanisms were included to boost subjects' interest in the game, including bonuses, auditory feedback and graphs at the end of each level showing contrast sensitivity over the 90 s period. Based on subjects' comments, we suspect that this some of this feedback was only partially effective, and not always meaningful. The link between bonuses and visual performance was sometimes not clear, and the bonuses may have distracted subjects from the targets.

5.3.3. Treatment of contrast

In a time-limited game with contrast changing adaptively, there were periods when the stimuli were not visible on the screen. During such periods, we observed that subjects tend to pause or to move the mouse randomly across the screen, resembling guessing in standard 2AFC tasks. The challenge lies in minimizing the duration of such guessing periods, which reduce engagement in the game, whilst keeping stimuli at near-threshold contrast. This might be achieved through algorithms that smooth the window over which contrast changes are calculated, and by setting an artificial floor for each session that does not allow contrast to decrease beyond a certain point.

5.3.4. Progression through levels

Each level in the game was a variation of target-distactor configuration and motion. Certain levels were more difficult and/or compelling than others, but were not ordered by difficulty. Subjects were free to choose which levels they played during a session, provided they had completed one run on Trial. Access to all levels was intended to keep subjects interested in the game, but guided or forced progression through levels of increasing difficulty may have created a larger sense of achievement in subjects.

5.4. AGE, MOTIVATION, AND ATTENTION OF PARTICIPANTS

Higher contrast thresholds for children than adults have elsewhere been attributed to the immaturity of the sensory system rather than non-visual, attentional factors (Liu et al., 2014). Here however, a number of factors could have contributed to childrens' larger variability in thresholds across sessions. The adult subjects were motivated by the visual benefits of the game and played the game regularly and for longer periods than the children (**Figure 7**). Keeping the children on task was more challenging. Several parents reported difficulty in motivating their children to play the game after the initial week. As with patching, even video games may carry issues of compliance when prescribed for children. Enhanced game design could address this issue to increase the attractiveness of the game, for instance by varying some other stimulus attribute than contrast, adding narrative elements, and changing the features described above. In the present case although motivational issues may have affected performance on the task, improvement in acuity did not differ between adults and children. Furthermore, although children's thresholds were generally higher than adults', they were strongly correlated with adults' thresholds across the different levels (**Figure 8**), suggesting that the variability in performance across levels was not due only to differences in motivation or skill. Children also tended to prefer the same levels as adults, suggesting that certain aspects of the game appealed to both age groups equally.

5.5. MECHANISM OF IMPROVEMENT AND CONSTRAINTS ON PLASTICITY

The mechanisms of learning of basic sensory tasks and of video games continue to be investigated. Learning may reside in plasticity of low-level representations (Jehee et al., 2012), decoding or decisional rules (Law and Gold, 2008; Gold and Ding, 2013), attentional sharpening (Otto et al., 2010), or in some combination of these. Perceptual learning has also been attributed to increased sampling efficiency (Gold et al., 1999), reduced internal noise (Lu et al., 2006), or a combination of both (Dosher and Lu, 1998; Lu and Dosher, 2009). Stimulus specific learning, a characteristic of perceptual learning in the normal visual system, was until recently interpreted as evidence for plasticity of sensory representations in primary cortices (see Karni and Bertini, 1997, for an earlier review). It is now clear that stimulus specificity depends on a number of factors including task difficulty (Wang et al., 2013), the axis of generalization (Webb et al., 2007), and attributes of the training regimen (Xiao et al., 2008; Zhang et al., 2010; Hussain et al., 2012a; Hung and Seitz, 2014). Therefore, stimulus specificity (or generalization) in itself cannot isolate the neural mechanism of learning. The broader-than-normal generalization of learning found in amblyopia on contrast sensitivity tasks (Huang et al., 2008; Astle et al., 2010) and the generalization of improvements from the trained tasks to logMAR acuity could reflect higher order learning, but also may reflect the greater capacity for improvement in low-level representations in developmentally impaired visual systems. Overall, the exact mechanisms of improvement after practice of sensory tasks are not yet clear, but the scope for improvement does appear larger in the amblyopic- than in the normal visual system. Improvements in visual function through perceptual learning can be enhanced through pharmacological and environmental interventions (e.g., fluoxetine, dark exposure) that relax the constraints on neural plasticity (Baroncelli et al., 2011; Montey and Quinlan, 2011). Due to the limited practicality of these interventions, other methods of enhancing the functional benefits from perceptual learning remain an area for future work.

5.6. CAVEATS

We tested the game on a small number of subjects (10 adults and 10 children), and found a positive effect on visual acuity after playing the game for 12 or more sessions. We compared improvements in acuity between the amblyopic and the fellow eye to rule out test-retest effects, and learning on letter-based measures of visual acuity. A more comprehensive study would have included a no-training group, a no-training group that was patched for a similar duration each day as the target group, and groups that played variations of the game to isolate its relevant components. All subjects in this study played the game at home, outside the supervision of the experimenters. Children may or may not have been supervised by their parents. In the above respects, the improvements in visual acuity cannot unequivocally be attributed to game play or to sensory plasticity. We also note a number of recent studies that call into question whether perceptual and cognitive benefits truly arise from practice on video games (Boot et al., 2011; Oei and Patterson, 2014; van Ravenzwaaij et al., 2014). Larger-scale studies, using randomized controlled trial methodology are needed to establish whether video game playing improves perceptual or cognitive skills in the normal population more generally, and in clinical populations specifically.

6. CONCLUSIONS

This study was designed to investigate the merits of combining psychophysical methods with video games for the purpose of treating amblyopia. We found a modest improvement in logMAR acuity of the amblyopic eye after subjects played a video game in which the contrast of targets changed adaptively over time. Future work will address more effective ways of combining the above methods to enhance the total amount of improvement.

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Training shortens search times in children with visual impairment accompanied by nystagmus

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Perceptual learning (PL) can improve near visual acuity (NVA) in 4–9 year old children with visual impairment (VI). However, the mechanisms underlying improved NVA are unknown. The present study compares feature search and oculomotor measures in 4–9 year old children with VI accompanied by nystagmus (VI+nys [$n = 33$]) and children with normal vision (NV [$n = 29$]). Children in the VI+nys group were divided into three training groups: an experimental PL group, a control PL group, and a magnifier group. They were seen before (baseline) and after 6 weeks of training. Children with NV were only seen at baseline. The feature search task entailed finding a target E among distractor E's (pointing right) with element spacing varied in four steps: 0.04°, 0.5°, 1°, and 2°. At baseline, children with VI+nys showed longer search times, shorter fixation durations, and larger saccade amplitudes than children with NV. After training, all training groups showed shorter search times. Only the experimental PL group showed prolonged fixation duration after training at 0.5° and 2° spacing, *p's* respectively 0.033 and 0.021. Prolonged fixation duration was associated with reduced crowding and improved crowded NVA. One of the mechanisms underlying improved crowded NVA after PL in children with VI+nys seems to be prolonged fixation duration.

Keywords: perceptual learning, fixation duration, visual impairment, visual search

INTRODUCTION

Evidence is accumulating that perceptual learning (PL) can have a beneficial impact on a range of visual perceptual skills, from contrast sensitivity (Polat et al., 2009) to visual acuity (Hussain et al., 2012) and depth perception (Uka et al., 2012). However, the mechanisms underlying PL often remain unclear (Fiorentini and Berardi, 1980). Fiorentini rightfully questioned: "Where does this learning occur?" A review on the neural basis of PL reported that training has no effect on, or only weakly alters, sensitivity of neurons in early visual areas, but instead constitutes to long-term changes in high level decision making stages that read out sensory signals (Kumano and Uka, 2013). We recently demonstrated that PL not only induces specific learning effects on the trained task in children with visual impairment (VI), but also transfers to improvements in near visual acuity (NVA) (Huurneman et al., 2013). The majority of children involved in our intervention study showed nystagmus (33 out of 45). An important question is whether NVA improvements and reduced crowding ratios after PL are related to oculomotor changes in children with nystagmus. The present study investigates the influence of PL on feature search performance and oculomotor measures.

Our study was not the first to report improvements in NVA after PL. Two earlier studies presented NVA improvements in individuals with myopia (Durrie and McMinn, 2007), and individuals with presbyopia (Polat et al., 2012). The underlying mechanism thought to be responsible for the NVA improvements was more efficient and effective neural processing, which enhances the image quality by compensating for blurred retinal images due to optical defocus caused by a low degree of myopia or presbyopia (Durrie and McMinn, 2007; Polat et al., 2012). The authors found no changes in optical performance of the eye, i.e., accommodation, pupil, size or depth of focus that could explain the observed NVA improvements (Polat et al., 2012). This remarkable finding that NVA can be improved after PL in individuals with substantial vision loss due to aging, myopia, or VI deserves further investigation into the underlying mechanisms.

Nystagmus, i.e., involuntary ocular oscillations, can be the sole cause of reduced visual acuity (as in idiopathic infantile nystagmus syndrome), but can also be associated with congenital visual abnormalities such as albinism, congenital cataract or optic atrophy (Abadi and Bjerre, 2002). Nystagmus characteristics are usually captured in the following parameters: amplitude, frequency, intensity (i.e., amplitude × frequency), foveation characteristics and waveform types (Kumar et al., 2011). Longer foveation periods, i.e., the time during which a stable foveal image is present, are related to better visual acuity (Dell'osso and Daroff, 1975; Abadi and Worfolk, 1989; Bedell and Currie, 1993). Subjects with infantile nystagmus syndrome (INS) show reduced nystagmus amplitudes and frequencies when target size is at visual threshold, which illustrates that increased visual task demand can have a favorable impact on the nystagmus waveform (Wiggins et al., 2007). Others found that the foveation periods in subjects with INS are unrelated to optotype size (Tkalcevic and Abel, 2005). In contrast, task-induced stress and motivation appear to decrease foveation periods and increase nystagmus amplitude and intensity (Cham et al., 2008, 2013).

Neural operations underlying visual cognition take place mostly during fixations, since visual signal processing is limited during the execution of saccades, due to saccadic suppression, and therefore the bulk of visual analysis occurs during fixation (Volkmann, 1962; Volkmann et al., 1968). The nystagmus parameter that correlates best with visual acuity is fixation duration (Sheth et al., 1995; Abadi and Bjerre, 2002). Mean fixation durations typically vary between 200 and 500 ms in individuals with NV (Jacobs, 1986), but have been mentioned to lie between 20 and 150 ms (or as much as 400 ms) in individuals with INS (Sheth et al., 1995). Characteristics of infantile nystagmus are amplitudes between 0.3 and 15.7°, and frequencies have been reported to range between 0.5 and 10 Hz (Abadi and Bjerre, 2002). Peak velocities of the eye range between 20 and 180°/s (Abadi and Worfolk, 1989). Some report that nystagmus cannot be diminished voluntary, and attempts to fixate only counteract by exacerbating the nystagmus (Sheth et al., 1995). In adults with normal vision, adjustment of fixation duration is determined by the difficulty of previously presented trials (McPeek, 1995; Hooge and Erkelens, 1998).

Three training tasks were used in this study: a crowded/experimental magnifier training, a crowded/experimental PL training, and an uncrowded/control PL training. The two experimental training tasks were designed with the aim to reduce crowding effects in children with VI. The rationale behind the design of these two experimental training tasks is that training tasks with small element spacing would eventually result in an improved ability to identify objects in clutter.

In order to find out whether oculomotor parameters change after PL, we recorded eye movements during visual feature search before and after 6 weeks of training. Four hypotheses were evaluated. The first is that there are baseline differences in fixation duration between children with normal vision (NV) and children with VI accompanied by nystagmus (VI+nys). The second is that search times of children with VI+nys are longer than search times of children with NV. The third is that training induces shorter search times in all training groups. Finally, it is hypothesized that there are no changes in fixation duration after training in children with VI+nys.

MATERIALS AND METHODS

PARTICIPANTS

Thirty-three children with VI+nys and 29 children with NV participated. Inclusion criteria for both groups were: age between 4 and 9 years and a normal developmental level. Additional inclusion criteria for children with VI were: distance visual acuity (DVA) between 20/400 and 20/40, normal birth weight (at least 3000 grams), birth at term (at least 36 weeks), no perinatal complications, no additional impairments, and an intact visual field. **Table 1** presents the average age and DVA of the children with VI and with NV. The supplemental Table presents clinical diagnosis and characteristics of the children in the VI+nys group. Informed consent was obtained from the parents of all children after explanation of the nature and possible consequences of the study. The local ethics committee approved the study before the assessments were conducted (CMO Arnhem-Nijmegen). The study was conducted in accordance with the Declaration of Helsinki (1969).

OPHTHALMOLOGICAL EXAMINATION

All children underwent ophthalmological examination before the start of the experiment. Distance visual acuity was measured mono- and binocularly at 6 m with the tumbling E chart (Taylor, 1978) and the Landolt *C*-test at 5 m (Haase and Hohmann, 1982) under controlled lighting conditions. NVA was determined binocularly with the LH-version of the *C*-test (Huurneman et al., 2012) and the LH line 50% crowding chart (Hyvarinen et al., 1980) at 40 cm. The eye-to-chart distance during NVA measurements was monitored with a ruler. The LH-version of the *C*-test contains two chart versions with absolute spacing: a crowded chart with interoptotype spacing of 2.6′, and a single chart with interoptotype spacing of ≥30′ at 40 cm. Children were asked to identify the first five symbols in a row, which were pointed out with a pencil, and could progress to the next line if they correctly identified 3 or more out of the 5 symbols. If there were fewer than 5 symbols in a row, children could progress if they could correctly identify at least half of the symbols.

Visual field was estimated by using confrontational techniques. In case of retinal disease children were tested on central or peripheral scotomas with dynamic perimetry (Goldmann). Objective refraction was obtained after cycloplegia and if necessary spectacle correction was prescribed or changed before the experiment and training period started.

Table 1 | Characteristics of children with normal vision (NV) and children with visual impairment accompanied by nystagmus (VI+nys) with age presented in months and distance visual acuity (DVA) presented in logMAR notation for the crowded version of the *C*-test [mean, (SD)].

	NV			VI+nys		
	M[a]	PLc[b]	PLu[c]	M	PLc	PLu
N	9	10	10	9	15	9
Age	78.3 (18.1)	81.6 (16.3)	83.9 (16.9)	76.9 (13.3)	81.80 (19.0)	87.8 (18.2)
DVA	0.04 (0.16)	0.00 (0.10)	−0.04 (0.08)	0.82 (0.17)	0.77 (0.27)	0.74 (0.31)

[a] *M, magnifier group.*

[b] *PLc, perceptual Learning crowded group.*

[c] *PLu, perceptual learning uncrowded group.*

TRAINING TASK

Children were divided into one of three training groups matched on age and distance visual acuity (see **Table 1**). There were two experimental groups and one control group (Huurneman et al., 2013). The first experimental training paradigm was a visual search training in which children had to search for the smiley in a grid of E's sized 145 × 145 mm and an edge-to-edge element spacing of 0.3 mm (consistent with the interoptotype spacing of the crowded version of the C-test described above, which is 2.6′ or 0.04° at 40 cm). This group was called the PL crowded group (PLc group). When the children found the smiley, they had to follow the path of inversed E's (leftward pointing E's). The E's were initially sized 7.0 mm, consistent with 1.0 logMAR at 40 cm. If the children did not make any errors, they could proceed to training material with smaller E's (two subsequent steps: 0.5 logMAR [3.5 mm] and 0.25 logMAR [1.75 mm]). As can be imagined, this task puts a strong demand on oculomotor and on interference control, as it was inspired by the Eriksen flanker task (Eriksen and Eriksen, 1974). The control training task was essentially the same task, but element spacing was 3.6 mm instead of 0.3 mm (consistent with the interoptotype spacing of the uncrowded *C*-test, which is at least 30′ or 0.5° at 40 cm). Therefore, the control group was the PL uncrowded group (PLu group).

The third training paradigm was a magnifier training in which children had to search for the inversed Landolt C within a 191 mm long search strip consisting of Landolt C's sized 0.5 mm (or −0.10 logMAR) with element spacing of 0.3 mm (the M group). The optotypes were too small to inspect with a bare eye, so an electronic handheld magnifier was used to find the inversed C. A game element was included to provide feedback and engage the children. Each training consisted of a maximum of 12 trials and these trials were coupled to tiles that could be placed on answer boxes. If all tiles were placed correctly, they formed a pattern that matched with the pattern in the upper right corner of the page. During training, children worked at a self-chosen distance.

PROCEDURE

Training

The training tasks are described in the section Training Task. Children with NV were seen once as a reference group at baseline. For children with VI, this baseline performance counted as their pre-test score. Training started within 2 weeks after the pre-test. During the training, children with VI were seen 2× a week for a period of 6 weeks (a total of 12 training sessions). Each training session consisted of 30 min of practice on the training task described in the section above. Trainers visited children at their schools. Within 2 weeks after the last training session children performed the post-test.

Visual search task

Children sat at a distance of 60 cm from the monitor wearing their best available optical correction. Viewing was binocular. Sixteen trials were presented to the children (4 (orientation) × 4 (spacing), see **Figure 1**). Four practice trials preceded the experiment in order to familiarize children with the task. Trials were presented in a randomized order to avoid measuring influences of learning effects. The target subtended 2° × 2° and the stimulus was screen-wide (29° × 25°). The instruction was to identify the unique E or, in case the E was absent, press the right pointing E (target absent trial). The location of the E was randomly varied in each quadrant of the screen to make sure the child actively searched for the target. Before the trial commenced a fixation cross of 2° × 2° was presented for 500 ms after which an intertrial-interval of 1000 ms followed. The influence of crowding was measured by manipulating spacing, with edge-to-edge element spacing of 0.04°, 0.5°, 1°, and 2°. There was no time limit for performing the search task. A new trial was presented after the child pressed the response button matching the target.

APPARATUS

Stimuli were presented on a 17″ monitor with integrated eyetrackers (Tobii T120, Tobii Corporation, Danderyd, Sweden). Stimulus presentation was driven by Delphi software. Eye movements were analyzed using MATLAB (MathWorks, Inc., Natick, MD). We did not fix the head positions of the children, because the Tobii has a large head movement box which means that it has a good ability to compensate for head movements (44 × 22 cm at 70 cm). Children stayed well within these limits, so head movements are not likely to cause data distortions. A rule was incorporated into the stimulus-presentation software, in order to assure that the children were seated at a proper viewing distance. When children came closer to the monitor than 60 cm, the stimulus disappeared from the screen, and reappeared if they were seated at 60 cm or more again. This rule was included to prevent children from reducing their viewing distance and to standardize our measurements. Eye movements were registered at a sampling rate of 60 Hz. Before the visual search task commenced a standard 5-point calibration procedure was performed. Fixations were detected offline and were defined as periods in which eye velocity remained below 50°/s for at least 50 ms. The velocity threshold was recalculated as 3.5× the standard deviation of the calculated noise of the eye velocity for each session. This recalculation is necessary, because of the diversity of the eye movements of our participants. For example, eye movement velocity might be seriously elevated in children with nystagmus and we might need a higher threshold than 50°/s to detect fixations. Data files with less than 35% valid data points were excluded from analysis.

STATISTICAL ANALYSIS

There were 2 main outcome categories: visual search performance measures (accuracy and search time) and oculomotor measures (number of fixations, fixation duration, and saccade amplitude). Accuracy measures were compared between children with NV and children with VI+nys with nonparametric tests (Mann–Whitney test and Friedman's test), because of skewed distributions and unequal variances. A correction for pairwise comparisons was used for the Friedman's test by reporting the adjusted *p*-value in which the K refers to the number of groups ($p_{\text{adj}} = p^*K(K-1)/2$).

Search time showed near-normal distribution and oculomotor measures were distributed normally. These measures were analyzed with a Repeated Measures ANOVA. Group was entered as the between-subjects factor and spacing as the within-subjects factor. Training effects in children in the VI+nys group were evaluated by conducting a 2 (pre-post) × 4 (spacing) Repeated

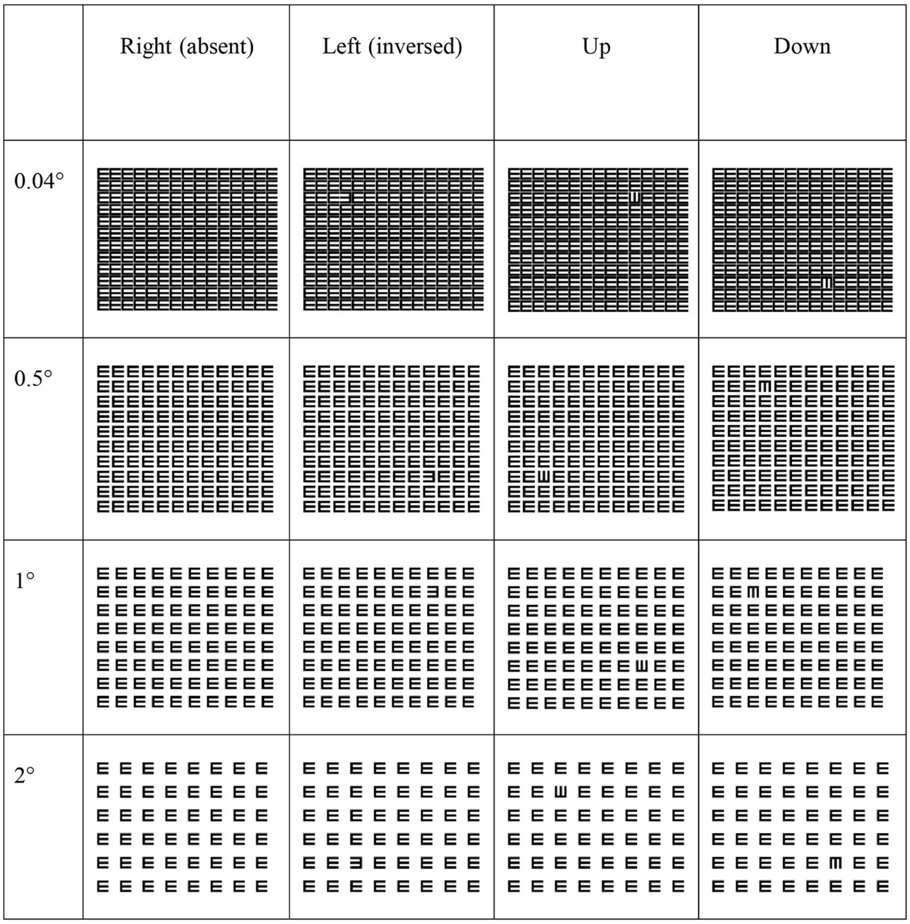

FIGURE 1 | Examples of the stimuli used in our experiment.

Measures ANOVA. Training group was then entered as the between-subjects variable. In case of pre-post × training group interactions, we conducted paired *t*-tests for each training group to see under which condition changes in performance occurred. In case pre-post × spacing interactions were found, separate Repeated Measures ANOVA's were conducted to evaluate how spacing affected performance before and after training. *Post-hoc* tests were performed using the Bonferroni method to correct for multiple comparisons (familywise Type I errors). Alpha was set on 0.10 to enable the detection of trends in our data set and because of the small sample sizes.

RESULTS

GROUP DIFFERENCES AT BASELINE

Figure 2 presents group differences in search time at baseline, **Figure 3** presents distributions of oculomotor measures, and **Figure 4** presents group differences in oculomotor measures at baseline. Valid oculomotor measures were collected in 20 children with NV, and 24 children with VI+nys.

Performance measures

Accuracy. No group differences were found in accuracy (see **Table 2**). There was a main effect of spacing on accuracy in both groups [NV: $\chi^2_{(3)} = 22.25, p < 0.001$; VI+nys: $\chi^2_{(3)} = 11.68, p = 0.009$]. Children with NV showed lower accuracies at 0.04° and 0.5° (75%) than at 2° spacing (100%), resp. $p = 0.026$ and $p = 0.005$. Pairwise comparisons in the VI+nys group were non-significant (see **Table 2**).

Search time. There was a group difference in search time [$F_{(1,\ 60)} = 3.71, p = 0.059$, partial $\eta^2 = 0.06$]. Children with NV showed shorter search times (3.7 s) than children with VI+nys (5.2 s; see **Figure 2**). No spacing effect or spacing × group interaction was found.

Oculomotor measures

Number of fixations. Groups did not differ with respect to the number of fixations made ($p > 0.1$, see **Figure 4A**). Children showed an average of 10.3 fixations ($SE = 0.7$). No spacing or interaction effect was found.

Fixation duration. There was a group × spacing interaction, $F_{(3,\ 126)} = 2.57, p = 0.057$, partial $\eta^2 = 0.06$. At 0.04°, children with VI+nys showed shorter fixation durations (255 ms) than children with NV (361 ms), $F_{(1,\ 42)} = 13.31, p = 0.001$, partial $\eta^2 = 0.24$. At 0.5°, children with VI+nys showed shorter fixation durations (268 ms) than children with NV (325 ms), $F_{(1,\ 42)} = 3.34, p = 0.075$, partial $\eta^2 = 0.07$. At 1°, children in the VI+nys

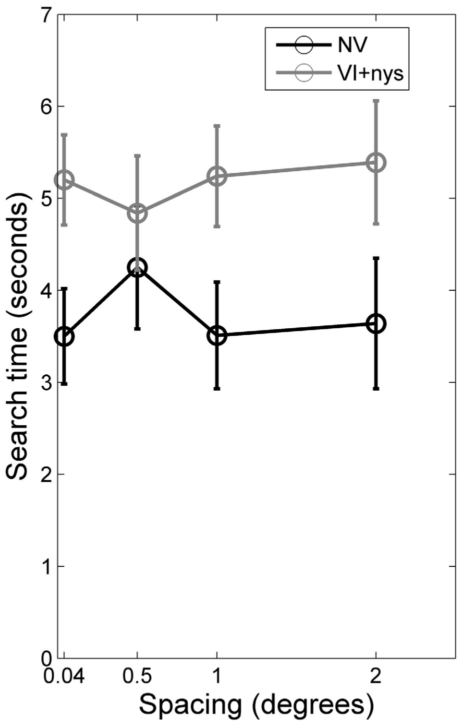

FIGURE 2 | Search times for children with normal vision (NV) and children with visual impairment accompanied by nystagmus (VI+nys). Children with NV showed shorter search times than children with VI+nys. Error bars indicate standard error of the mean (s.e.m.).

group showed shorter fixation durations (245 ms) than children in the NV group (304 ms), $F_{(1,\ 42)} = 7.21$, $p = 0.010$, partial $\eta^2 = 0.15$. At the largest spacing (2°), no group differences were found. Children with NV adjusted their fixation durations to spacing, $F_{(3,\ 57)} = 7.45$, $p < 0.001$, partial $\eta^2 = 0.28$. Children fixated longer at 0.04° than at 1° and 2° spacing, p's 0.037 and 0.002 (see **Figure 4B**). Spacing did not affect fixation duration in children in the VI+nys group.

Saccade amplitude. Saccade amplitudes differed between groups, $F_{(1,\ 42)} = 8.22$, $p = 0.006$, partial $\eta^2 = 0.16$. Children in the VI+nys group made larger saccades (9.2°) than children with NV (8.4°: see **Figure 4C**). Spacing influenced saccade amplitude, $F_{(3,\ 126)} = 5.09$, $p = 0.002$, partial $\eta^2 = 0.11$. Saccade amplitudes were larger at 0.5° (9.3°) than at 2° (7.9°), $p = 0.001$. No interaction was found.

DIFFERENCES AFTER 6 WEEKS TRAINING (VI CHILDREN)

We collected 17 valid eye movement recordings (magnifier, $n = 4$; PLc, $n = 9$; PLu, $n = 4$). **Figure 5** displays search times and **Figure 6** displays oculomotor measures before and after training. Supplemental Figures 1–3 display histograms with raw pre- and post-training oculomotor measures.

Performance measures

Accuracy. At 0.5°, the M and PLc group showed higher accuracies after training (median before training 75% and 100% after training: M: $\chi^2_{(1)} = 5.00$, $p = 0.025$; PLc: $\chi^2_{(1)} = 5.00$, $p = 0.025$). Children in the PLu group did not show improved accuracy; they already showed a median accuracy of 100% at pre-test. At 0.04°, 1° and 2°, none of the groups showed improved accuracy after training.

Search time. There was a spacing × training group interaction, $F_{(6,\ 90)} = 2.14$, $p = 0.057$, partial $\eta^2 = 0.13$. In the M group, a training effect was found, $F_{(1,\ 24)} = 10.31$, $p = 0.012$, partial $\eta^2 = 0.56$. Mean search time was 4.8 s before and 3.3 s after training (see **Figure 5A**). In addition, spacing influenced search times, $F_{(3,\ 24)} = 3.78$, $p = 0.024$, partial $\eta^2 = 0.32$. However, *post-hoc* tests were not significant. No pre-post × spacing interaction was found. In the PLc group, we also found a training effect, $F_{(1,\ 42)} = 4.99$, $p = 0.042$, partial $\eta^2 = 0.26$. Mean search times were 5.2 s before and 4.0 s after training (see **Figure 5B**). No spacing or pre-post × spacing interaction was found. A pre-post × spacing interaction did occur in the PLu group, $F_{(3,\ 24)} = 2.37$, $p = 0.096$, partial $\eta^2 = 0.23$. Paired t-tests showed that children did not show reduced search times at 0.04°, but did show reduced search times at all other spacings [0.5°: $t_{(8)} = 2.15$, $p = 0.064$, 1°: $t_{(8)} = 1.88$, $p = 0.097$, 2°: $t_{(8)} = 1.98$, $p = 0.083$; see **Figure 5C**].

Oculomotor measures

Number of fixations. There was no main training effect on the number of fixations, but there was a pre-post × spacing interaction, $F_{(2,\ 14)} = 3.83$, $p = 0.071$, partial $\eta^2 = 0.22$. Children made more fixations before (10.0) than after training at 2° (7.1), $t_{(16)} = 2.23$, $p = 0.041$. All other t-tests were non-significant.

Fixation duration. There was a three way pre-post × training group × spacing interaction, $F_{(1,\ 42)} = 2.24$, $p = 0.058$, partial $\eta^2 = 0.24$. Paired t-tests were conducted for each spacing and training group to disentangle interaction effects. In the M group, no changes were found in fixation duration (see **Figure 6B**). In the PLc group, children fixated longer after training at 0.5° and 2° (at 0.5°: $t_{(8)} = -2.58$, $p = 0.033$; at 2°: $t_{(8)} = -2.87$, $p = 0.021$, see **Figure 6B**). In the PLu group, prolonged fixation duration was found at 1°, $t_{(3)} = -2.49$, $p = 0.089$ (see **Figure 5B**). No spacing or interactions were found in any of the training groups.

Saccade amplitude. There was a spacing × training group interaction, $F_{(6,\ 42)} = 2.12$, $p = 0.071$, partial $\eta^2 = 0.23$. *Post-hoc* analysis showed that in the M-group, spacing affected saccade amplitude, $F_{(3,\ 9)} = 4.21$, $p = 0.040$, partial $\eta^2 = 0.58$. Children tended to make larger saccades at 0.5° (10.4°) than 2° (8.7°), $p = 0.055$ (see **Figure 6C**). In the PLc group, no main or interaction effects were found. In the PLu group, spacing affected saccade amplitude, $F_{(3,\ 9)} = 4.51$, $p = 0.034$, partial $\eta^2 = 0.60$. However, *post-hoc* tests were non-significant.

RELATIONS BETWEEN ACUITY, FIXATION DURATION AND PERFORMANCE MEASURES

A correlational analysis was conducted to investigate the relations between changes in visual and oculomotor measures for children in the VI+nys group. As can be seen in **Table 3**, the increase in fixation duration was related to a reduction of the crowding ratio and improved crowded NVA, *r's* 0.65 and 0.52, *p's* 0.002 and 0.016.

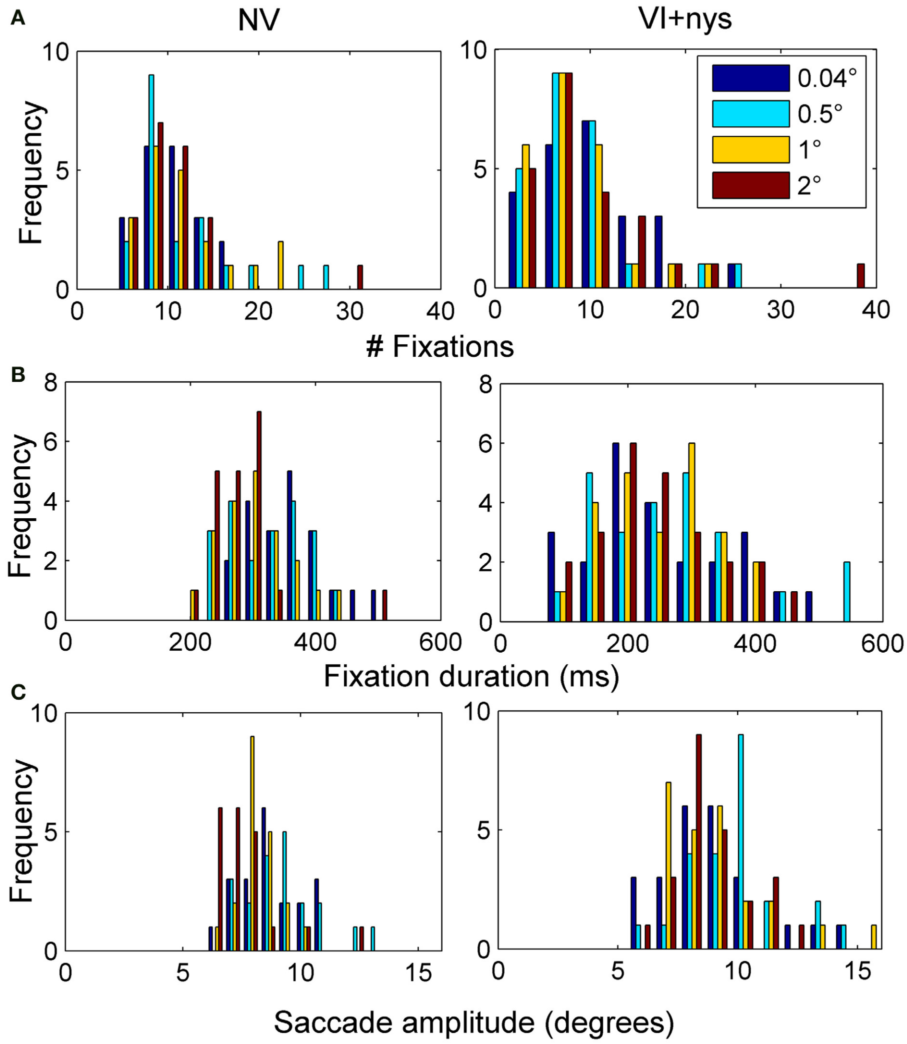

FIGURE 3 | (A) Distribution of the number of fixations made by children with normal vision (NV) and children with visual impairment accompanied by nystagmus (VI+nys). **(B)** Distribution of fixation durations. **(C)** Distribution of saccade amplitudes.

DISCUSSION

The goal of this study was to evaluate the effect of PL on visual feature search performance and oculomotor measures in children with VI+nys. Different from what we expected, we found evidence that oculomotor parameters in children in the VI+nys group can be altered after a 6-week period of PL. We only observed significant increases in fixation duration in the PL groups. In the next sections our findings are discussed in the light of the postulated hypotheses.

GROUP DIFFERENCES IN FIXATION DURATION BETWEEN GROUPS AT BASELINE

Our first hypothesis was that there were group differences in fixation duration at baseline. Children with NV showed longer fixation durations (278–361 ms) than children in the VI+nys group (242–268 ms). This finding is in line with results from a previous study from our group which reported shorter fixation durations in children in the VI+nys group compared to children with NV during serial visual search (Huurneman et al., 2014). A second difference between groups occurred with regards to the adjustment of fixation duration to element spacing. Children with NV showed an adjustment of fixation duration to stimulus properties and fixated longer on stimuli when element spacing was smaller (346 ms at 0.04° and 292 ms at 2° spacing). This finding is consistent with oculomotor behavior observed in adults with NV (Vlaskamp et al., 2005; Vlaskamp and Hooge, 2006). Children in the VI+nys group showed no adjustment of fixation durations to element spacing, neither before or after 6 weeks of PL.

In addition to group differences in fixation duration, a group difference in saccade amplitude was found. Mean saccade amplitude of children in the NV group was smaller (8.4°) than the saccade amplitude of children in the VI+nys group (9.2°). Saccade amplitudes were calculated by measuring the distance from one fixation point to a following fixation point. The finding

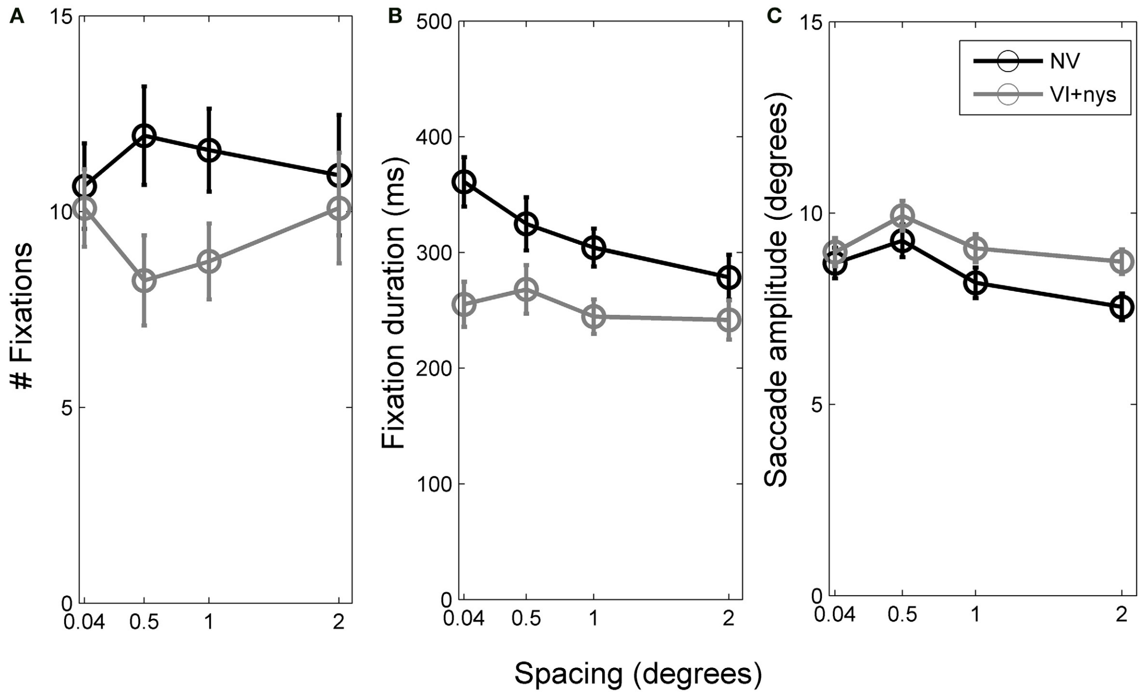

FIGURE 4 | (A) Number of fixations per trial made by children with normal vision (NV) and children with visual impairment accompanied by nystagmus (VI+nys). **(B)** Fixation durations of children with NV and children with VI+nys. **(C)** Saccade amplitudes of children with NV and children with VI+nys. Error bars represent s.e.m.

Table 2 | Median accuracies and statistics for accuracy.

Spacing	Accuracy medians		Group difference [standardized test statistic (z)]	Within-subjects effects	
	NV (%)	VI+nys (%)		NV	VI+nys
0.04°	75	75	$z = 0.23$, $p = 0.821$	$\chi^2_{(3)} = 22.25$	$\chi^2_{(3)} = 11.68$
0.5°	75	75	$z = 0.96$, $p = 0.337$	$p < 0.001$	$p = 0.009$
1°	75	100	$z = 0.39$, $p = 0.694$	0.04° < 2°***	*Post hoc* n.s.
2°	100	100	$z = -0.88$, $p = 0.380$	0.5°< 2°**	

**p < 0.1, **p < 0.05, ***p < 0.01.*

that children with VI+nys make larger saccades than those with NV is a replication of what was reported in an earlier study (Huurneman et al., 2014). We did not control for the influence of cases when children were looking away from the screen during search. If the child looks off screen during a trial and returns to the screen to initiate a new fixation, the "decision" to look at a certain location is based on the visual information that has been analyzed before, so we do not expect saccade amplitudes to be influenced by this behavior.

There were no differences in the number of fixations made by children with NV and children with VI+nys. An explanation for the absence of a group difference in number of fixations could be the lower percentage of valid data points recorded with the eye-tracker for children with VI+nys. The average percentage of valid data points in a whole session was 62.7% for children with NV and 44.7% for children with VI+nys. An explanation for the low percentage of valid data points in children with VI+nys is that eye movement velocity in these children might often be above 50°/s and above the fixation detection threshold. Characteristics of infantile nystagmus are amplitudes between 0.3 and 15.7°, and frequencies have been reported to range between 0.5 and 10 Hz (Abadi and Bjerre, 2002). Peak velocities of the eye range between 20 and 180°/s (Abadi and Worfolk, 1989). Therefore, less fixations might have been detected in these children, because the algorithm did not find a fixation (i.e., at times when eye movement velocity was above 50°/s). Furthermore, factors such as photophobia, long eye lashes and/or glasses might also cause signal loss during eye-tracking in children with ocular disorders.

LONGER SEARCH TIMES FOR CHILDREN WITH VI THAN CHILDREN WITH NV AT SMALL SPACINGS

Our second hypothesis was that search times of children with VI+nys are longer than search times of children with NV. We did observe longer search times for children in the VI+nys group than

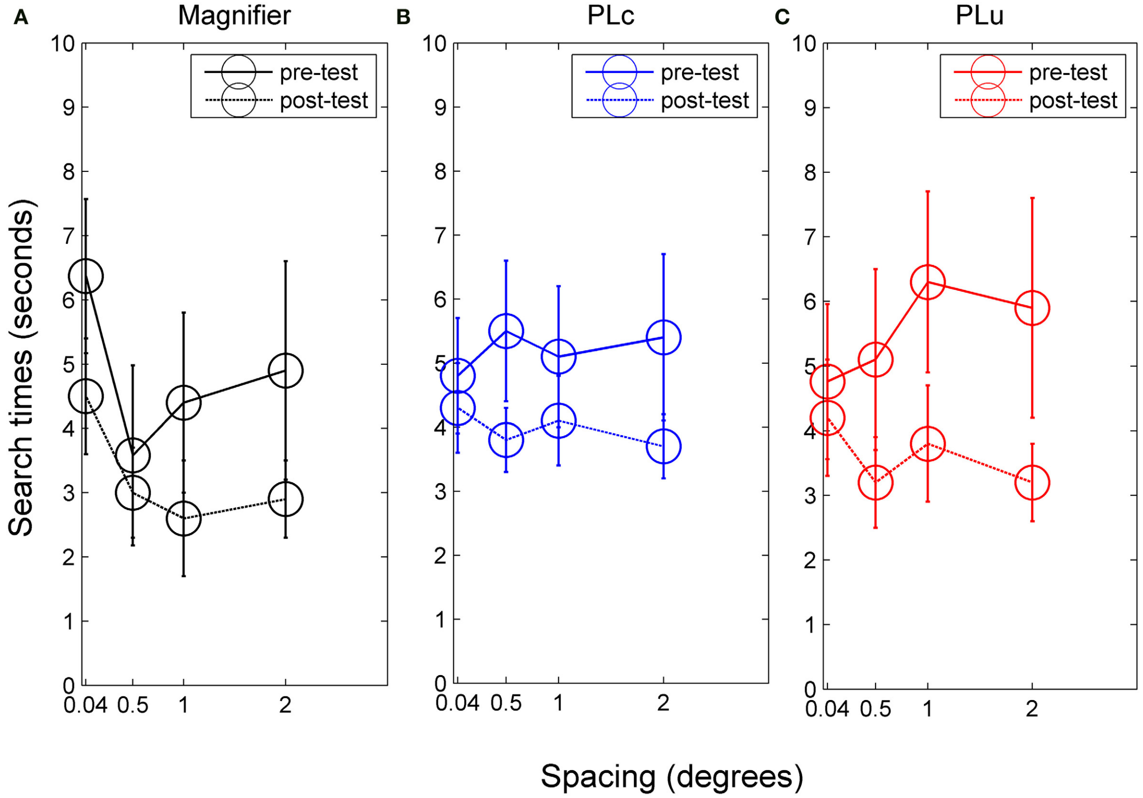

FIGURE 5 | Search times for (A) children in the magnifier group, (B) children in the PLc group before and after training, and (C) children in the PLu group before and after training. Error bars represent s.e.m.

children in the NV group (5.2 s for children in the VI+nys group and 3.7 s for children in the NV group).

The group differences reported in the present study are much smaller than previously reported differences in search time between children with NV and children with VI. For example, in an earlier study where children had to search for a unique target in a grid with elements sized 2 times their threshold acuity, we found up to 5-fold slower search times for children with VI compared to children with NV (Huurneman et al., 2014). Search times for 9–18 year old children with low vision have been reported to be 3-fold compared to that of normally sighted age-matched peers for search in naturalistic wide-field 58 × 45° displays (Tadin et al., 2012). Two explanations might account for the less pronounced group differences in search time in the present study.

A first explanation is that the size of the stimuli was 2 × 2°, which is obviously larger than the average symbol size of 0.67° used in a previous study (Huurneman et al., 2014). Children in the VI+nys group therefore seem to benefit from working with large stimuli. A second explanation might be that the present task is more structured than a naturalistic wide-field display (Tadin et al., 2012). The grid consisted of E's presented in our feature search task might be perceived as a pattern and poses only a little demand on precise eye movements. Some studies indicate that patterns with discriminable elements in close proximity can be segregated more easily than patterns in which the same elements are more widely spaced (Nothdurft, 1985, 1993; Scolari et al., 2007). Deviances, or unique features, within a pattern consisting of homogeneous distractors can be found easily, and this process has been said to be even easier with small element spacing. However, in the present study we observed, for the second time, that during matrix search in children small element spacing does not facilitate search (Huurneman et al., 2014). Search times were unaffected by spacing. The absence of an increase in search time with increasing number of distractors indicates that the search task was conducted in a parallel manner (Treisman and Gelade, 1980).

SHORTER SEARCH TIMES IN CHILDREN WITH VI AFTER TRAINING

The third hypothesis was that we expected training to induce shorter search times in all training groups. Children with VI accompanied by nystagmus did show shorter search times after training. Only the two experimental groups showed reduced search times for all spacings. The control PL group did not show a reduction in search time at small spacings. An explanation for the absence of a training effect at small spacings for the PLu group might be that children in this training group did not work with closely spaced elements. In our previous study we also observed differences in the amount of improvement children made with regards to their crowded NVA. All children showed an improvement in single NVA, but only children in the PLc group showed

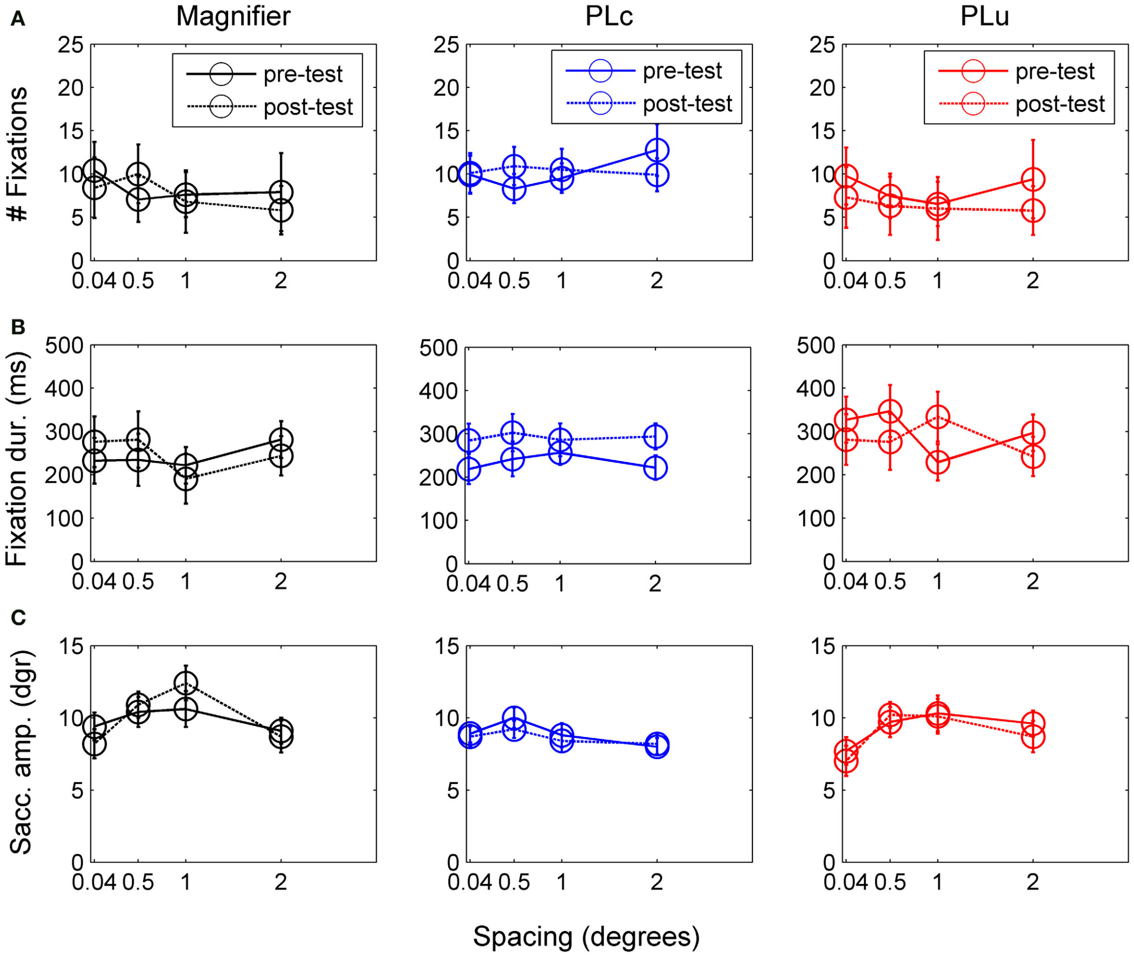

FIGURE 6 | (A) Number of fixations before and after training. **(B)** Fixation duration before and after training. **(C)** Saccade amplitude before and after training. Error bars represent s.e.m.

Table 3 | Correlation matrix displaying the relations between visual and oculomotor measures.

	Gain logMAR single	Gain logMAR crowded	Fixation duration gain at 0.5°	Reduction search time at 0.5°	Improvement accuracy at 0.5°
Gain logMAR crowded	0.61*				
Fixation duration gain at 0.5°	−0.41	0.52*			
Reduction search time at 0.5°	−0.05	0.52*	0.03		
Improvement accuracy at 0.5°	0.19	0.35	−0.03	0.14	
CR reduction	−0.77**	0.62**	0.65**	0.30	0.11

CR reduction, crowding ratio reduction (CR pre-test–CR post-test).

$^{*}p < 0.05$.

$^{**}p < 0.01$ (one-tailed p-test).

an improvement on the crowded NVA chart (Huurneman et al., 2013).

CHANGES IN OCULOMOTOR MEASURES AFTER TRAINING

Our fourth hypothesis was that fixation duration could not be changed by training in children with VI+nys. In contrast to our hypothesis, the results did show changes in fixation duration after training. The children in the PLc group showed prolonged fixation durations at 0.5° (from 242 to 303 ms) and 2° element spacing (from 222 to 294 ms). In addition, the PLu group showed prolonged fixation duration at 1° spacing, but the effect was not observed at other spacings in this training group and seemed to be less consistent than the increase in fixation duration in the PLc group.

The prolongation of fixation durations in the PLc group is an unexpected and exciting finding, because individuals with nystagmus are considered to be unable to voluntary diminish their nystagmus and attempts to prolong fixation periods usually have a negative impact on nystagmus (Sheth et al., 1995). Earlier research has reported the beneficial impact of interventions other than surgery on prolonging fixation duration in individuals with INS, e.g., afferent stimulation by providing vibratory neck stimulation (Sheth et al., 1995). To our knowledge there have not been studies reporting the positive impact of PL on fixation characteristics in individuals with nystagmus. As might be expected from the large body of literature emphasizing the relation between acuity and foveation periods, prolongation of fixation duration indeed was significantly related to a reduction of crowding ratios ($r = 0.65$) and improvements in crowded NVA ($r = 0.52$). In an earlier study, we found that nystagmus frequency was positively related to mono- and binocular crowding ratios in children with idiopathic nystagmus (Huurneman and Boonstra, 2013).

Three explanations may account for changes in fixation duration after training. The first is maturation of the nervous system, which may alter the sinusoidal and jerk nystagmus so that foveation time increases and vision improves (Van Vliet, 1982). A second explanation for the prolonged fixation periods is that increased visual task demand and visual attention can also alter nystagmus movements (Wiggins et al., 2007). When adults with nystagmus were looking at a threshold sized target, they demonstrated longer foveation duration and reduced nystagmus frequency than when looking at a larger target sized 3 log steps above their threshold acuity. This finding indicates that increased visual demand or visual attention may dampen oscillatory eye movements in nystagmus. We think that the observed improvements are probably due to improved visual attentional processing, because during training children worked with small densely packed optotypes which required focused visual attention. A third explanation is that the prolonged fixation durations after training might be due to familiarity with the test display (Cham et al., 2008, 2013). However, reduced stress does not explain the differences in fixation duration gain between training groups. We therefore conclude that more than one explanation might be applicable for the more extended improvements in the experimental PL group.

The mechanism responsible for the extended fixation durations after training is not known, since we only recorded eye movements. A combination of psychophysiological and brain imaging techniques would be required to find out whether changes on a behavioral level have a specific neural origin. One might expect that the reticular formation is involved, a brain structure responsible for arousal, alertness and awareness (Role and kelly, 1991; Sheth et al., 1995), the frontal eye fields, an area responsible for the control of voluntary eye movements (Braddick and Atkinson, 2011) and covert shifts of attention (Ronconi et al., 2012), the superior colliculus (controlling head orientations and adjusting eye movements in response to retinal slip), and/or the cerebellar vermis (Leguire et al., 2011). The presence of ocular torticollis, referring to compensatory head turns made in order to fixate the eyes at the null-point, should also be monitored, because it could also be possible that convergence or gaze angles caused prolonged fixation durations (Abadi, 2002). Future research is needed to investigate the physiological mechanisms underlying extended fixation periods.

CONCLUSIONS

The present study indicates that PL in children with VI showing nystagmus does not only transfer to improvements in NVA, but also induces improvements in feature search performance and oculomotor measures. The most striking finding observed in this study is that children with VI prolonged their fixation duration after training. This prolongation of fixation duration is significantly related with improvements in crowded NVA and reduction of crowding ratios.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fpsyg.2014.00988/abstract

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Improvement of uncorrected visual acuity and contrast sensitivity with perceptual learning and transcranial random noise stimulation in individuals with mild myopia

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Perceptual learning has been shown to produce an improvement of visual acuity (VA) and contrast sensitivity (CS) both in subjects with amblyopia and refractive defects such as myopia or presbyopia. Transcranial random noise stimulation (tRNS) has proven to be efficacious in accelerating neural plasticity and boosting perceptual learning in healthy participants. In this study, we investigated whether a short behavioral training regime using a contrast detection task combined with online tRNS was as effective in improving visual functions in participants with mild myopia compared to a 2-month behavioral training regime without tRNS (Camilleri et al., 2014). After 2 weeks of perceptual training in combination with tRNS, participants showed an improvement of 0.15 LogMAR in uncorrected VA (UCVA) that was comparable with that obtained after 8 weeks of training with no tRNS, and an improvement in uncorrected CS (UCCS) at various spatial frequencies (whereas no UCCS improvement was seen after 8 weeks of training with no tRNS). On the other hand, a control group that trained for 2 weeks without stimulation did not show any significant UCVA or UCCS improvement. These results suggest that the combination of behavioral and neuromodulatory techniques can be fast and efficacious in improving sight in individuals with mild myopia.

Keywords: visual acuity, contrast sensitivity, myopia, perceptual learning, tRNS

INTRODUCTION

Perceptual learning has been found useful in improving visual abilities such as visual acuity (VA) and contrast sensitivity (CS), both in participants with deficits in visual cortical processing such as amblyopia (Polat et al., 2004; Levi and Li, 2009; Astle et al., 2011) and in participants with optical defects such as myopia or presbyopia (Tan and Fong, 2008; Polat, 2009; Polat et al., 2012). The mechanisms subtending such improvements involve neural plasticity. The link between neural plasticity and visual improvements is better defined in the context of amblyopia and is thought to be due to abnormal interactions between neurons tuned to specific orientations and spatial frequencies (Polat et al., 1997) and inter-ocular suppression at early cortical levels (Li et al., 2011). Mechanisms of improvement in participants with non-corrected refractive defects on the other hand is more puzzling and has been ascribed to an increase in neuronal signal-to-noise ratio able to buffer the blurred (noisy) images due to optical defocus (Tan and Fong, 2008). Improvements of uncorrected VA (UCVA) following perceptual learning in participants with mild myopia ranges from 0.16 (Camilleri et al., 2014) to 2.2 LogMAR (Durrie and McMinn, 2007), whereas improvements in uncorrected CS (UCCS) ranges from no improvements (Camilleri et al., 2014) to an improvement of 2.6 times respect to baseline UCCS at high spatial frequencies (Tan and Fong, 2008). These variations in improvements may be attributed to the different training procedures used in different studies (e.g., simple contrast detection vs. contrast detection under lateral masking conditions).

Although many studies support the view that a high degree of specificity of perceptual learning for simple stimulus attributes (Fiorentini and Berardi, 1981; Karni and Sagi, 1991; Poggio et al., 1992; Schoups et al., 1995; Campana and Casco, 2003; see Sagi, 2011 for a review) points to plasticity at early cortical sites (Schoups et al., 2001; Pourtois et al., 2008; Hua et al., 2010; Sale et al., 2011), more recent studies have demonstrated that, under appropriate conditions, perceptual learning is generalizable to other stimulus characteristics and other visual tasks altogether, suggesting that plasticity could also involve changes in the read-out of sensory neurons by higher-level neurons, or be distributed across multiple levels of the visual cortical hierarchy (Liu and Weinshall, 2000; Ahissar and Hochstein, 2004; Zhou et al., 2006; Webb et al., 2007; Xiao et al., 2008; Jeter et al., 2009; McGovern et al., 2012; Kumano and Uka, 2013). Despite this, the levels of processing where plasticity takes place when learning transfers to different tasks such as VA and CS continues to be a matter of debate (Zhai et al., 2013; Bonaccorsi et al., 2014; Zhang et al., 2014).

Neuromodulation techniques such as transcranial magnetic stimulation (TMS) or transcranial electrical stimulation (tES) have also been tested for the restoration of visual functions in people with abnormal cortical processing and are also considered useful in the understanding of visual functions at the cortical level. While TMS has been found useful in increasing CS up to 1 Log CS on medium–high frequencies, both temporarily (Thompson et al., 2008) and for extended periods (Clavagnier et al., 2013), tES (e.g., transcranial direct current stimulation, tDCS) has only shown a transient improvement of CS (Spiegel et al., 2013).

Online transcranial random noise stimulation (tRNS, a type of tES using alternating current with random frequencies and delivered during task execution) has recently been proven to be the most efficacious type of electrical stimulation for boosting perceptual learning in healthy participants (Fertonani et al., 2011; Pirulli et al., 2013).

To date, no techniques of neuromodulation have been used in an attempt to improve visual functions in participants with optical defects such as myopia. Thus, in the present study a short perceptual training regime in a contrast detection task using a single Gabor patch joined with tRNS was administered in order to investigate the effects of this combined approach on UCVA and UCCS in participants with mild myopia.

MATERIALS AND METHODS

PARTICIPANTS

Sixteen participants with mild myopia were recruited from the University of Padova (mean age of 24.12, ranging between 19 and 27). The first group of eight participants carried out a 2-week (eight sessions) behavioral training using a contrast detection task combined with online high-frequency tRNS (hf-tRNS). The second group of eight participants (control group) underwent the same training protocol but without tRNS. This was done in order to compare the effect of the combination of behavioral training + tRNS with the effect of the behavioral training alone (without tRNS) on UCVA and UCCS.

The participants fit the following inclusion criteria: refractive error up to −2 diopters (D) in either eye (minimum was −0.75 D), with astigmatism not exceeding −0.5 D in either eye. All tests as well as the training were administered binocularly and with no optical corrections. The participants had a stable refractive index for the 6 months prior to training. Exclusion criteria included any other ocular condition or cause for reduced VA other than simple myopia and/or mild astigmatism; these include diabetes mellitus, pregnancy, presence of myopia-related ocular complications and any previous ocular surgery. To ensure the inclusion and exclusion criteria, prior to training the participants carried out a detailed assessment by an optometrist. This assessment was repeated at the end of the training. Additionally, each participant in the tRNS group also filled in a questionnaire ensuring that all were eligible to undergo non-invasive brain stimulation. Any participant with a history of seizures, internal metal objects, or previous traumatic brain injury was excluded from our study. This study was approved by the local ethics committee.

EXPERIMENTAL PROCEDURE

Before (pre-tests) and after the training (with tRNS; post-tests), UCVA and UCCS were assessed for each participant by using Landolt C and Grating tests of the Freiburg Visual Acuity Test (FrACT; Bach, 1996). After 3 months from the post-test, in a follow-up session, UCVA was tested again in order to see whether any UCVA improvement was maintained over time.

Stimuli (UCCS assessment) consisted of sinusoidal gratings presented in a circular window with a narrow Gaussian taper. Size of the gratings was 3°. Grating orientations used were 0°, 45°, 90°, or 135°. The task of the participant entailed discriminating the orientation of the grating at different spatial frequencies, ranging from 1 to 15 cpd, in separate blocks.

The Landolt C test was used to assess UCVA. The task of the participants was to indicate, in every trial, the orientation of the gap of the Landolt C out of eight possible orientations.

For both FrACT tests, the Best-Pest adaptive procedure was used to calculate the absolute threshold for each of these tests. Stimulus duration lasted until the participants' response. An auditory cue was presented upon stimulus presentation and a different auditory cue was implemented as feedback for error responses.

The following behavioral paradigm described was used in an earlier study by Camilleri et al. (2014) in a 2-month perceptual training regime in individuals with mild myopia. It consisted of a two-interval forced choice (2IFC) task where the participants had to detect the presence of a single Gabor Patch, which changed in contrast according to the performance of the participant. The threshold corresponding to 79% of correct detection was determined by using a 1up/3down staircase procedure (Levitt, 1971). Stimuli used in the training comprised Gabor patches consisting of a cosinusoidal carrier enveloped by a stationary Gaussian. Standard deviation of the luminance Gaussian envelope (σ) was equal to the sinusoidal wavelength (λ); that is, the size of the Gabor patch covaried with its spatial frequency. Additionally, the spatial phase of the cosinusoidal carrier equalled to 0 (evenly symmetric Gabor patch). Stimulus duration lasted 200 ms. Participants underwent eight training sessions over 2 weeks (four consecutive sessions each week) and trained on four different orientations of the stimulus with a single spatial frequency, chosen according to the individual's cut-off performance in the pre-test UCCS measurement, defined as the spatial frequency at which the estimated contrast threshold from pre-training UCCS measurements was 0.50 (Michelson contrast; Zhou et al., 2006). Since interleaving different stimulus conditions (roving) has been shown to hinder perceptual learning (Kuai et al., 2005; Herzog et al., 2012), in order to increase the efficacy of perceptual learning, participants were trained on the same orientation for two consecutive days. Three participants were trained with a spatial frequency of 11 cpd, two participants with 7 cpd, and the remaining three participants with a spatial frequency of, respectively, 5, 9, and 15 cpd. Each session consisted of eight blocks each containing 60 trials, which lasted for approximately 45 min. Participants were administered hf-tRNS (1.5 mA) during the first five blocks on each session (Fertonani et al., 2011). In order to reduce spatial and temporal uncertainty both an auditory and a spatial cue were implemented. On each trial a central fixation point preceded the presentation of each interval, and an auditory cue indicated when the stimulus (if present) appeared. Performance feedback was also provided to the participants in the form of an auditory beep following an incorrect response.

APPARATUS

Stimuli were displayed on a 22-in Philips Brilliance 202P4 monitor with a refresh rate of 60 Hz. The monitor was luminance-calibrated with gamma = 1 by means of a professional monitor calibrator (Datacolor Spyder 4 Elite). The stimuli used in the training were generated with the Matlab Psychtoolbox (Brainard, 1997; Pelli, 1997), whereas stimuli for measuring UCVA and UCCS were generated using the Freiburg Acuity and Contrast Test (FrACT 3.8, Bach, 1996). Spatial dithering (Bach, 1997) and color bit stealing (Tyler, 1997) for increasing the depth of contrast resolution (12 bit) were enabled on the FrACT, thus allowing precise CS measurement. All stimuli were presented centrally. The screen resolution was 1280 × 1024 pixels, each pixel subtended 0.33 arcmin at a viewing distance of 3 m, and 0.67 arcmin at a viewing distance of 1.5 m. Viewing distance was equal to 3 m for pre- and post-tests, whereas the training was administered from 1.5 m (Durrie and McMinn, 2007; Tan and Fong, 2008). Both the tests and training were carried out in a dark, silent room. Background screen luminance (corresponding to mean luminance of Gabor stimuli) was 31.5 cd/m^2.

tRNS

High-frequency tRNS was delivered using a battery-driven stimulator (BrainSTIM, EMS) through a pair of saline-soaked sponge electrodes. The tRNS consisted of an alternating current of 1.5 mA intensity with a 0-mA offset applied at random frequencies. The frequencies ranged from 100 to 640 Hz.

The stimulations were applied for approximately 5 min during each of the first five training blocks (Fertonani et al., 2011). The total duration of stimulation was ~25 min. The active electrode had an area of 16 cm^2 and was placed over the occipital cortex measured at ~3 cm above the inion. The reference electrode had an area of 60 cm^2 and was placed extracephalically on the upper right arm. The current density was maintained well below the safety limits (always below 1 A/m^2; Poreisz et al., 2007). The electrodes were kept in place with bandages.

RESULTS

Pre-test, post-test, and follow-up measurements of the training + tRNS group were compared with a Friedman's ANOVA, followed by two Bonferroni-corrected Wilcoxon signed-rank test. Friedman's ANOVA revealed a significant UCVA difference between pre-test, post-test, and follow-up measurements ($\chi^2_2 = 10.57$, $p < 0.005$): participants trained on a contrast detection task for eight sessions with concurrent tRNS significantly improved their UCVA by 0.15 LogMAR ($Z = -2.521$, $p < 0.05$), that is from 0.33 to 0.18 LogMAR, and this improvement was maintained at the follow-up, where VA (0.15 LogMAR) was still significantly different from pre-test ($Z = -2.37$, $p < 0.05$; **Figure 1**, black columns). Across participants, the size of improvement ranged from virtually no change (only one participant, with an improvement <0.05 LogMAR; Camilleri et al., 2014) to an improvement of 0.33 LogMAR. UCCS (**Figure 2A**) also improved significantly at the following spatial frequencies: 3 cpd ($Z = -2.521$, $p < 0.01$), 5 cpd ($Z = -2.38$, $p < 0.05$), 7 cpd ($Z = -2.24$, $p < 0.05$), 9 cpd ($Z = -2.521$, $p < 0.01$), and 11 cpd ($Z = -2.521$, $p < 0.01$). The largest improvements were seen

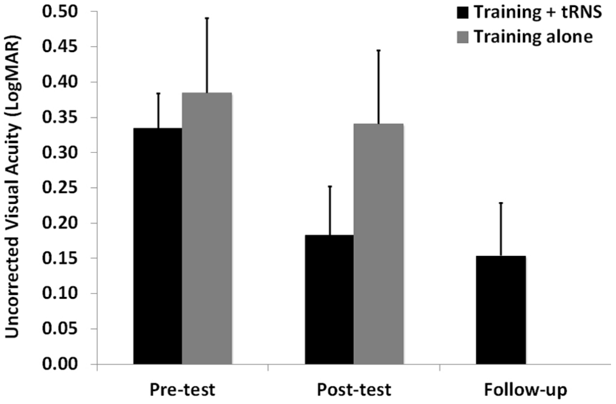

FIGURE 1 | Mean UCVA before (pre-test), after (post-test), and at 3 months follow-up (follow-up) of an eight-session contrast detection training, either coupled with online tRNS (black columns) or alone (gray columns). Error bars represent one SEM.

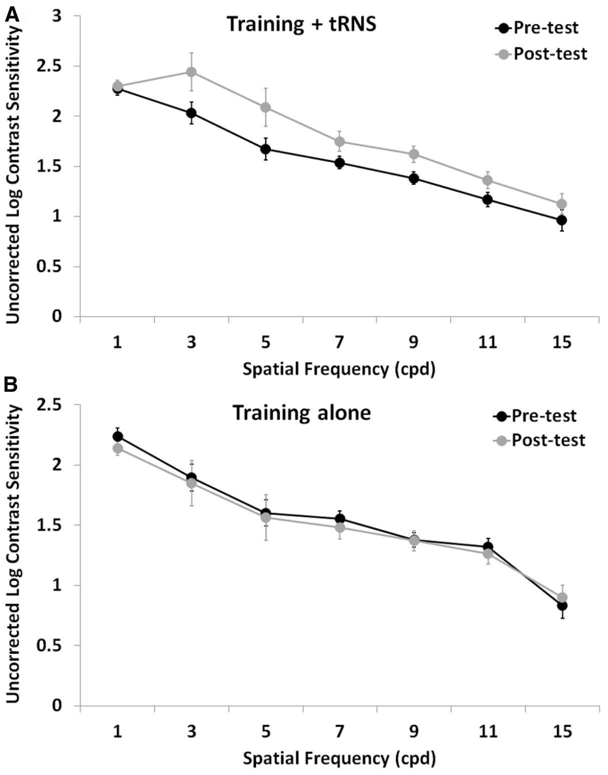

FIGURE 2 | Mean UCCS as a function of spatial frequency before (pre-test, black symbols) and after (post-test, gray symbols) an eight-session contrast detection training, either coupled with online tRNS (A) or alone (B). Error bars represent one SEM.

at intermediate spatial frequencies (3 and 5 cpd), where UCCS increased, on average, by five to six times at the post-test, with respect to the pre-test. Given that participants were mainly trained at higher spatial frequencies (just one participant was trained with 5 cpd, and none with 3 cpd), this means that learning mainly generalized from higher to lower spatial frequencies, consistently with previous studies (Astle et al., 2010). No significant improvement was seen at the lowest (1 cpd) and highest (15 cpd) tested spatial frequencies.

The control group (training alone) did not improve neither in UCVA (pre-test: 0.38 LogMAR; post-test: 0.34 LogMAR; $Z = -0.098$, $p > 0.05$; **Figure 1**, gray columns), nor in UCCS, in any of the tested spatial frequencies (all $Z \leq 1.4$, $p > 0.05$; **Figure 2B**). Across participants and across spatial frequencies there was no substantial change in performance in post- with respect to pre-tests, except for two subjects who had a twofold increase in UCCS at 3 cpd.

DISCUSSION

In a recent study, Camilleri et al. (2014) found that 24 sessions of contrast detection training in mild myopic participants produced a UCVA improvement of 0.16 LogMAR, but no UCCS improvement. In the present study, by using just eight sessions of training with a similar procedure but with the concurrent administration of tRNS, we found a comparable UCVA improvement (0.15 LogMAR), as well as a conspicuous improvement of UCCS at intermediate and high spatial frequencies (3–11 cpd). On the other hand, the same eight sessions of training with no tRNS did not produce any change in UCVA nor any substantial change in UCCS in any of the tested subjects. These results suggest that the application of tRNS during a perceptual training is able to boost perceptual learning (Fertonani et al., 2011; Pirulli et al., 2013), that is then transferred to other visual functions such as UCVA or UCCS at different spatial frequencies respect to the trained ones, under conditions of blurred vision due to optical defocus. The improvement in UCVA is smaller than that reported by other studies on myopia (Durrie and McMinn, 2007; Tan and Fong, 2008), and this is probably due to the use of a more efficacious training paradigm based on lateral masking (see Camilleri et al., 2014 for a discussion on this issue). However, the improvement in UCCS found in the present study (UCCS increased up to five to six times) is larger than that found in previous studies (up to 2.6 time of UCCS increase; Tan and Fong, 2008), and more pronounced at intermediate spatial frequencies, despite most participants were trained at higher spatial frequencies. These results, together with the striking difference in UCCS improvement respect to the study of Camilleri et al. (2014) where a similar training (yet longer and with no brain stimulation) was used, suggest that tRNS is particularly efficacious in boosting perceptual learning of UCCS, and its transferring of this learning to untrained spatial frequency channels.

The mechanisms mediating improvement of visual functions by perceptual learning in individuals with optical defects have not been completely understood. It has been suggested that refractive defects, often arising after the critical period, might produce a mismatch between an abnormal visual input due to optical defocus and a "normal" neural processing and connectivity developed (with focused input) in early childhood. Such a mismatch would decrease the perceived contrast, especially at high spatial frequencies, thus degrading UCVA (Tan and Fong, 2008). Learning to detect low contrast stimuli with no optical correction increase CS, thus improving the efficiency of neuronal responses to the abnormal (defocused) visual input, that in turn increases UCVA. However, learning of contrast detection requires a high number of training sessions (e.g., compare the results of Camilleri et al., 2014 with the present results). tRNS over the visual cortices could boost learning of (low) contrast detection. Being a repetitive and random sub-threshold stimulation, tRNS could induce temporal summation of small depolarizing currents that could interact with the ongoing activity of cortical neurons tuned to specific orientations and spatial frequencies and engaged in a contrast detection task, thus enhancing performance and inducing synaptic potentiation (Fertonani et al., 2011).

Since eight sessions of perceptual training with no tRNS does not seem to induce any improvement, it could be argued that perceptual learning here is not playing a role at all, and that the observed improvements are solely due to tRNS. In fact, previous studies found that anodal tDCS over the visual cortex can improve CS even in the absence of perceptual training (Kraft et al., 2010; Spiegel et al., 2013). It must be pointed out that the effects of tDCS and tRNS seem to be mediated by different neural mechanisms (Terney et al., 2008): while tRNS seems to act by increasing the activity of ion (sodium) channels and therefore by a temporal summation of small membrane potentials induced by consecutive openings of these channels (Terney et al., 2008), tDCS directly modulates the transmembrane potential (thus the firing rate) of individual neurons with a continuous flux of current that produces an initial facilitation often followed by adaptation to rebalance the modulation of ion channel conductance (Bindman et al., 1964; Fertonani et al., 2011), and that in turn could produce unpredictable results. In fact the effects of anodal tDCS on perceptual learning are conflicting: when administered over the visual cortex before a perceptual task (offline), it produced an improvement of learning within the same day (Pirulli et al., 2013), but it blocked consolidation of learning on a subsequent day (Peters et al., 2013). On the other hand, Pirulli et al. (2013) showed that perceptual learning in a visual discrimination task was increased only when hf-tRNS was administered concurrently (online) with the task, while no improvement was seen when it was administered alone (offline, with no concurrent task). This finding makes it very unlikely that the improvements in UCVA and UCCS were due to tRNS alone without any effect of the concurrent behavioral training.

Future studies are needed to assess whether more efficacious training protocols (e.g., those based on lateral masking) can also benefit of a concurrent tRNS for improving visual abilities in participants with cortical (such as amblyopia) or non-cortical visual deficits (e.g., refractive defects), and whether the improvement is long-lasting, as found with longer trainings without brain stimulation (Polat et al., 2004; Tan and Fong, 2008). Additionally, although tRNS does not result in any superficial skin sensations and thus participants are not directly aware that they are undergoing stimulation, making it unlikely that unspecific effects of stimulation occur, incorporating a sham tRNS group in subsequent studies is deemed necessary in order to account for any possible placebo effects. Although it has been demonstrated in healthy participants that hf-tRNS is more effective when administered during a perceptual learning task (Pirulli et al., 2013), it would also be worthwhile investigating whether hf-tRNS in the absence of any behavioral training could also bring about improvements in UCVA and UCCS in refractive defects.

In sum, these preliminary findings suggest that coupling a short contrast detection training with tRNS in participants with mild myopia results in an increased UCVA and UCCS, similar to or even larger than that seen with no tRNS and with a longer training using a similar training paradigm and stimuli parameters, but in the absence of brain stimulation.

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Improving visual functions in adult amblyopia with combined perceptual training and transcranial random noise stimulation (tRNS): a pilot study

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Amblyopia is a visual disorder due to an abnormal pattern of functional connectivity of the visual cortex and characterized by several visual deficits of spatial vision including impairments of visual acuity (VA) and of the contrast sensitivity function (CSF). Despite being a developmental disorder caused by reduced visual stimulation during early life (critical period), several studies have shown that extensive visual perceptual training can improve VA and CSF in people with amblyopia even in adulthood. With the present study we assessed whether a much shorter perceptual training regime, in association with high-frequency transcranial electrical stimulation (hf-tRNS), was able to improve visual functions in a group of adult participants with amblyopia. Results show that, in comparison with previous studies where a large number sessions with a similar training regime were used (Polat et al., 2004), here just eight sessions of training in contrast detection under lateral masking conditions combined with hf-tRNS, were able to substantially improve VA and CSF in adults with amblyopia.

Keywords: amblyopia, visual acuity, contrast sensitivity, perceptual learning, lateral masking, tRNS

INTRODUCTION

Amblyopia, sometimes referred to as "lazy eye," is a developmental visual disorder characterized by several functional impairments in spatial vision (even with the best optical correction) in absence of any organic defects of the eye besides the refractive ones (Ciuffreda et al., 1991; McKee et al., 2003; Robaei et al., 2006). Impairments range from a reduction of visual acuity (VA), contrast sensitivity function (CSF) and Vernier acuity, to abnormal spatial interactions (Polat et al., 1997; Levi et al., 2002) or deficiencies in stereopsis (Wallace et al., 2011). It is believed to be due to an anomalous pattern of functional connectivity within the primary visual cortex, in particular of neurons selective for orientation and spatial frequency (Polat, 1999), thus causing abnormal processing of visual information coming from one or both eyes (but typically only one eye is involved). Until recently, amblyopia was thought to be untreatable after the "critical period" spanning up to the first decade of life (Epelbaum et al., 1993; Greenwald and Parks, 1999; Loudon et al., 2002), due to diminished neural plasticity within the visual cortex that would limit any anatomical, physiological or functional changes (Berardi et al., 2003).

Numerous studies, however, have reported large and stimulus-specific performance improvements (perceptual learning) in normal adults following training in various visual tasks (Fiorentini and Berardi, 1980; Karni and Sagi, 1991; Poggio et al., 1992; Schoups et al., 1995; see Sagi, 2011 for a review), pointing to neuronal plasticity at early levels of the adult visual system (Schoups et al., 2001; Pourtois et al., 2008). In fact, over the past 15 years, marked improvements of various visual functions in adults with amblyopia, following extensive sessions of perceptual learning, have been reported (see Levi and Li, 2009 and Polat, 2009; Astle et al., 2011a,b for recent reviews). Different authors used different training tasks, ranging from Vernier acuity (Levi and Polat, 1996; Levi et al., 1997), stereo acuity (Astle et al., 2011a), to position discrimination in noise (Li and Levi, 2004; Li et al., 2005, 2007), identification of luminance-defined letters in noise (Levi, 2005) or contrast-defined letters (Chung et al., 2006, 2008), contrast detection, either with Gabor stimuli or letters in isolation (Zhou et al., 2006; Huang et al., 2008; Astle et al., 2011c), or when Gabors were flanked by similar collinear patches (i.e., lateral masking; Polat et al., 2004). Analysing the amount of improvement as a function of the task used in different studies, Levi and Li (2009) pointed out that in most studies the ratio of improvement between post- and pre-training contrast sensitivity (CS) thresholds is between 0.4 and 0.8 for both VA and CSF. The task that obtained the largest improvement ratio on both measurements (~0.35) was a contrast detection task using the lateral masking procedure (Polat et al., 2004). Focusing on the abnormal spatial interactions in amblyopia, Polat et al. (2004) used a training procedure that allowed a strengthening of facilitatory lateral interactions and a weakening of inhibitory lateral interactions between detectors tuned to specific orientations and spatial frequencies, thus obtaining a large and consistent improvement in VA (78% gain, equal to 0.25 LogMAR improvement) and CSF (improvement ranging from 2.05 to 4.23 times) in adults with amblyopia.

A drawback of this and similar training paradigms, however, is their duration: the large number of sessions required to achieve such improvements (from 30 to 80 sessions) could either prevent amblyopic patients from starting the training or lead to a high number of dropouts.

Recent studies have pointed out how non-invasive transcranial brain stimulation techniques are able to boost perceptual learning in normal observers. In particular, it has been shown that online transcranial electrical stimulation using random frequencies in the high-frequency range (high-frequency transcranial random noise stimulation, hf-tRNS), is the most efficacious type of electrical stimulation for enhancing and accelerating within-session perceptual learning (Fertonani et al., 2011; Pirulli et al., 2013).

In this study we assessed the extent of VA and CSF improvement in a small sample ($N = 7$) of patients with anisometric amblyopia, following a brief training (eight sessions) in contrast detection of a central Gabor patch (target) flanked by two high contrast Gabor patches of the same spatial frequency (i.e., lateral masking; Polat et al., 2004), in conjunction with online hf-tRNS.

MATERIALS AND METHODS

PARTICIPANTS

Seven participants with anisometric amblyopia were recruited at the San Paolo Ophthalmic Center of San Antonio Hospital (Padova, Italy) during routine ophthalmological assessment (mean age of 39.20, ranging between 26 and 52). The participants were enrolled in a 2-week (eight sessions) behavioral training program using a contrast detection task under lateral masking conditions (Polat et al., 2004; Polat, 2009) combined with online high frequency tRNS (hf-tRNS).

All pre/post tests were administered monocularly on either eye and with the best optical correction. Perceptual training was also administered monocularly on the amblyopic eye with the best optical correction. Exclusion criteria included any other ocular condition or cause for reduced VA other than amblyopia, myopia, presbyopia, hypermetropia and/or astigmatism; these include diabetes mellitus, pregnancy, presence of myopia-related ocular complications and any previous ocular surgery. Exclusion criteria also included incompatibility with transcranial electrical stimulation, as assessed with a questionnaire (e.g., history of seizures, skin problems, migraine, etc.). This study has been approved by the local Ethics Committee.

EXPERIMENTAL PROCEDURE

Before (pre-tests) and after the training (with tRNS; post-tests), VA and CSF were assessed for each participant by using, respectively, Landolt C of the Freiburg Visual Acuity Test (FrACT, Bach, 1996), and the CRS Psycho 2.36 test (Cambridge Research Systems Ltd, Rochester, UK) from a viewing distance of 1.5 m.

Visual acuity was measured with an orientation discrimination task (eight possible orientations of the gap of the Landolt C). The Best-Pest adaptive procedure was used to calculate the threshold corresponding to 62.5% of correct discrimination. Stimulus duration lasted until the participants' response. An auditory cue was presented upon stimulus presentation and a different auditory cue was used as feedback for incorrect responses.

Contrast sensitivity was measured with the method of adjustment by asking the participant to adjust the contrast of a vertical sinusoidal grating covering the whole screen (21.3 × 16°), with four ascending (from lower to higher grating contrast) and four descending (from higher to lower grating contrast) series. The initial contrast on the first descending series was set according to pilot experiments, ranging from −15 dB (17.78% contrast) at intermediate spatial frequencies, to 0 dB (100% contrast) at high spatial frequencies. On successive series the starting contrast for each tested spatial frequency was set as the contrast threshold obtained in the previous series, plus (in descending series) or minus (in ascending series) a factor between 6 and 10 dB (randomly selected). Increments/decrements were equal to 1 dB. The resulting contrast threshold was the arithmetic mean of the last selected contrast for each of the eight series, independently for each spatial frequency. Each tested spatial frequency (ranging from 0.8 to 14.5 cpd) was presented sequentially starting from the lower spatial frequency and progressively moving on to the higher spatial frequencies; five different spatial frequencies were tested. For each participant, CS at each tested spatial frequency was calculated by averaging across series.

The behavioral training consisted of a two-interval forced choice (2IFC) task where the participants had to detect the presence of a central Gabor, which changed in contrast according to the performance of the participant, surrounded by two high-contrast (0.6 Michelson contrast) collinear Gabors (flankers; **Figure 1**). Gabors were made of a cosinusoidal carrier enveloped by a stationary Gaussian. Standard deviation of the luminance Gaussian envelope (σ) was equal to the sinusoidal wavelength (λ); that is, the size of the Gabor patches covaried with their spatial frequency. Additionally, the spatial phase of the cosinusoidal carrier equalled to zero (evenly symmetric Gabor patch). Center-to-center distance between target and flankers was varied across blocks (1.5, 3, 4, and 8λ). On each session two blocks were administered with the same center-to-center distance. The order of presentation always started with the largest distance and ended with the smallest distance. Stimulus duration lasted 200 ms. Contrast threshold, corresponding to 79% of correct responses, was determined by using a 1up/3down staircase procedure on the last eight reversals (Levitt, 1971). Participants underwent eight training sessions during 2 weeks (four consecutive sessions per week), and trained on four different orientations of the stimulus (that changed every 2 days) with a single spatial frequency, chosen according to the individual's cut-off performance in the pre-test CS measurement, defined as the spatial frequency at which the estimated contrast threshold from pre-training CS measurements was 0.50 (Michelson contrast; Zhou et al., 2006). Trained spatial frequencies ranged from 3 to 15 cpd. Each session consisted of eight blocks each containing 60 trials, which lasted for approximately 45 min. The total training time for each participant, across the 2 weeks was approximately 6 h.

Participants were administered hf-tRNS (1.5 mA) during the first five blocks on each session (Fertonani et al., 2011). In order to reduce spatial and temporal uncertainty both an auditory and a

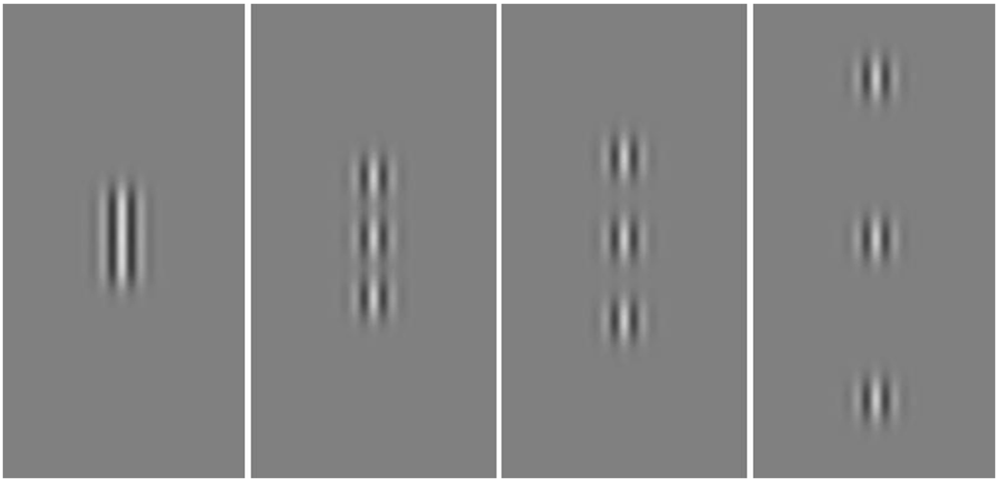

FIGURE 1 | Example of stimuli used in the training. The central Gabor was the target varying in contrast according to a staircase. Flanking Gabors had a fixed contrast of 0.6 Michelson contrast. The target-to-flankers distance was varied across blocks (i.e., 1.5, 3, 4, and 8λ; from left to right). The contrast of the target was increased for demonstrative purposes.

spatial cue were implemented. On each trial a central fixation point preceded the presentation of each interval. Performance feedback was also provided to the participants in the form of an auditory beep following an incorrect response.

The main differences between the training procedure used in the present study with respect to that of Polat et al. (2004), besides the use of online tRNS and a smaller number of sessions, are: the use of a range of durations (80–320 ms) vs. a fixed duration (200 ms) for stimulus presentation in our study; the alternate use of target with or without flankers vs. a constant use of flankers in our study; the use of an automated and computerized decision-maker algorithm for deciding the parameters (spatial frequency, orientation) to be used in subsequent sessions vs. a relatively fixed sequence of parameters in our study.

APPARATUS

Training and VA tests were displayed on a 22-inch Philips Brilliance 202P4 monitor with a refresh rate of 60 Hz and a resolution of 1280 × 1024 pixels. The monitor was luminance-calibrated (gamma-corrected with $\gamma = 1$). The stimuli used in the training were generated with the Matlab Psychtoolbox (Brainard, 1997; Pelli, 1997), whereas stimuli for measuring VA were generated using the Freiburg Acuity and Contrast Test (FrACT 3.8, Bach, 1996). All stimuli were presented centrally. Viewing distance was equal to 3 m for VA tests, whereas the training was administered from 1.5 m. Background screen luminance (corresponding to mean luminance of Gabor stimuli) was 31.5 cd/m^2.

Contrast sensitivity tests were displayed on a 17-inch CRT monitor (Brilliance 107P; Philips) with a refresh rate of 70 Hz and a resolution of 1024 × 768 pixels. The monitor was luminance-calibrates with $\gamma = 1$. The stimuli were generated with the CRS Psycho 2.36 test (CRS Psycho 2.36; Cambridge Research Systems Ltd, Rochester, UK) on a computer equipped with a 12-bit resolution graphics card (Cambridge Research Systems Ltd VSG2/3). Viewing distance was equal to 1.5 m. Background screen luminance (corresponding to mean luminance of the gratings) was 48.5 cd/m^2. All tests and the training were carried out in a dark and silent room.

tRNS

High frequency transcranial random noise stimulation was delivered using a battery-driven stimulator (BrainSTIM, EMS) through a pair of saline-soaked sponge electrodes. The tRNS consisted of an alternating current of 1.5 mA intensity with a 0 mA offset applied at random frequencies. The frequencies ranged from 100 to 640 Hz.

The stimulations were applied for approximately 5 min (equalling the duration of a training block) during each of the first five training blocks (Fertonani et al., 2011); thus, the total duration of the stimulation was ~25 min. This stimulation protocol has been demonstrated efficacious in boosting perceptual learning in previous studies (Fertonani et al., 2011; Pirulli et al., 2013). The active electrode had an area of 16 cm^2 and was placed over the occipital cortex measured at ~3 cm above the inion. The reference electrode had an area of 60 cm^2 and was placed on the forehead. The current density was maintained well below the safety limits (always below 1 A/m^2; Poreisz et al., 2007). The electrodes were kept in place with bandages.

RESULTS

Visual acuity and CS data were analyzed with a repeated measures ANOVA with Time (pre- vs. post-test), and Spatial Frequency (only for CS: 0.8, 2.9, 5.8, 9.7, and 14.5 cpd) as within-subjects factors, and Eye (amblyopic/trained vs. non-amblyopic/untrained) as a between-subjects factor. When data violated the assumption of sphericity, as assessed with the Mauchly's test, we applied the Greenhouse-Geisser correction of the degrees of freedom. Following eight sessions of a contrast detection training with lateral masking, VA significantly improved in both trained and untrained eye ($F_{1,12} = 35.4$, $p = 0.0001$, $\eta_p^2 = 0.75$). The interaction between Training Time and Eye was not significant ($F_{1,12} = 2.47$, $p = 0.14$, $\eta_p^2 = 0.17$), indicating a similar improvement on both trained and untrained eyes. Overall mean improvement was equal to 0.14 LogMAR, with a mean improvement close to 2 LogMAR lines (0.18 LogMAR, corresponding to 50% improvement, that is from 0.35 LogMAR to 0.17 LogMAR), in the trained (amblyopic) eye, and equal to 0.1 LogMAR, that is from 0 LogMAR to −0.1 LogMAR in the untrained eye (**Figure 2**). The VA in the trained and untrained eye was also significantly different ($F_{1,8} = 22.12$, $p = 0.001$, $\eta_p^2 = 0.65$).

Contrast sensitivity significantly improved after training ($F_{1,12} = 11.7$, $p = 0.005$, $\eta_p^2 = 0.49$), regardless the eye (interaction Time by Eye: $F_{1,12} = 0.03$, $p = 0.87$, $\eta_p^2 = 0.02$; **Figure 3**). As expected, there was also a large CS variation across the different spatial frequencies tested ($F_{1.5,18} = 29.7$, $p = 0.0001$, $\eta_p^2 = 0.71$), a significant difference in CS between the two eyes ($F_{1,12} = 8.8$, $p = 0.012$, $\eta_p^2 = 0.42$), and a significant interaction Time by Spatial Frequency ($F_{4,48} = 2.7$, $p = 0.043$, $\eta_p^2 = 0.18$), suggesting that the CS improvement could have occurred only at certain spatial frequencies.

In order to test this hypothesis, we performed further analysis separately for each spatial frequency. Repeated-measures ANOVA with Training Time (pre- vs. post-test) as a within-subject factor, and Eye (trained vs. untrained) as a between-subjects factor showed a significant difference between pre- and post-test at all tested spatial frequencies (0.8 cpd: $F_{1,12} = 7$, $p = 0.021$, $\eta_p^2 = 0.37$; 2.9 cpd: $F_{1,12} = 11.2$, $p = 0.006$, $\eta_p^2 = 0.48$; 5.8 cpd: $F_{1,12} = 11.5$, $p = 0.005$, $\eta_p^2 = 0.49$; 9.7 cpd: $F_{1,128} = 5.8$, $p = 0.03$, $\eta_p^2 = 0.33$; 14.5 cpd: $F_{1,12} = 5.4$, $p = 0.04$, $\eta_p^2 = 0.31$), regardless the eye (interaction Time by Eye was not significant in any of the tested spatial frequencies). In terms of percentage improvement with respect to pre-test, CS in the trained eye had nearly a twofold improvement (averaged across participants and spatial frequencies), ranging from 74% at the lowest tested spatial frequency to 435% at the highest tested spatial frequency, whereas CS in the untrained eye had a mean CS improvement of 60% (averaged across participants and spatial frequencies), ranging from 21% at intermediate spatial frequency (2.9 cpd) to 165% at the lowest tested spatial frequency.

FIGURE 2 | Mean visual acuity before (Pre-test) and after (Post-test) the lateral masking training with concurrent hf-tRNS, separately for the trained amblyopic eye and the untrained fellow eye. Error bars represent 1 SEM.

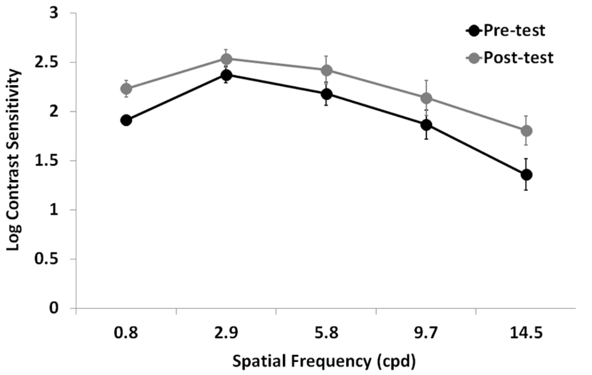

FIGURE 3 | Mean Log-CSF (average of the two eyes) before (Pre-test) and after (Post-test) the lateral masking training with concurrent hf-tRNS. Error bars represent ± 1 SEM.

DISCUSSION

In our small sample of participants, a short (eight sessions) contrast detection training under lateral masking conditions and concurrent hf-tRNS was able to increase mean VA by 0.18 LogMAR (53% improvement, ranging from 25 to 111%) in the trained amblyopic eye. An improvement between 2 and 3 LogMAR lines was achieved in four participants out of seven. This could be considered a smaller improvement in comparison to the results obtained by Polat et al. (2004), where a similar training procedure was used, but with a training regime of 48 sessions on average (VA increased by 0.25 LogMAR, 78% improvement). However, if we compare our results with the improvement attained by Polat et al. (2004) after eight sessions (0.13 LogMAR, 35% improvement), and considering that in our study the mean best-corrected VA reached 0.18 LogMAR (better than 6/9, the upper limit for normal vision), we can state that a marked and clinically relevant improvement in VA was obtained in a relatively short time frame.

The CSF also resulted in strong improvements following training, both in the trained amblyopic eye and in the untrained fellow eye. CSF in the trained amblyopic eye increased at all tested spatial frequencies by a factor of 1.05, 0.74, 1.13, 1.35, and 3.21 for spatial frequencies of 0.8, 2.9, 5.8, 9.7, and 14.5 cpd, respectively. Compared with the results of Polat et al. (2004) obtained with 48 sessions of training (CSF improved by a factor of 2.21, 2.12, 2.93, 4.23, and 2.05 for spatial frequencies of 1.5, 3, 6, 12, and 18 cpd), we also see that for the CSF the improvement we estimated appears smaller, although obtained this with 1/6th of the total amount of sessions. Most importantly, the largest improvement in our participants was at a similar high spatial frequency (14.5 cpd) compared to the largest improvement obtained by Polat et al. (2004, 12 cpd), and with a relatively similar improvement factor (3.21 vs. 4.23). On the other hand, a smaller improvement (by a factor of 2.05) was found by Polat et al. (2004) at 18 cpd. Although it is still possible that the results obtained with the present study with respect to that of Polat et al. (2004) were due to the slightly different conditions used, besides the different training duration and the use of tRNS (e.g., different target durations, the use of a computerized decision-maker algorithm to decide the parameters to be used in subsequent sessions), we believe that the conditions used by Polat et al. (2004) could in fact be more efficient in producing perceptual learning and transfer to related and unrelated visual functions. For example, training lateral interactions with a variable and faster stimulus presentation has been shown to improve not just CS but also processing speed, thus increasing the "improvement of other functions that are processed either at the same or at later stages" (Polat, 2009), and the use of computerized decision-maker algorithms should always supply the participant with the most effective stimulation parameters.

Although the present study lacks a Sham group and therefore the effects of tRNS cannot be isolated, the underlying mechanisms as to how tRNS administered over the visual cortices could boost learning of CS that would transfer onto unrelated tasks such as VA. Being a sub-threshold stimulation, which is repetitive and random in nature, whilst engaged in a contrast detection task, tRNS could be inducing temporal summation of small depolarizing currents that interact with the concurrent activity of cortical neurons which are tuned to specific orientations and spatial frequencies, thus enhancing performance on the task and inducing synaptic potentiation (Fertonani et al., 2011). In fact, Pirulli et al. (2013) showed that perceptual learning in a visual discrimination task only improved when the hf-tRNS was administered during task execution (online stimulation), while no improvement was found when it was administered with no concurrent task (offline).

Taken together these data suggest that a short perceptual training combined with online hf-tRNS can induce brain plasticity and can considerably improve visual functions in the amblyopic eye. Further studies are needed to confirm the present results on a larger sample of participants, and to estimate the best ratio between extent of improvements of visual functions and duration of the perceptual training combined with hf-tRNS. While the contribution of hf-tRNS on perceptual improvements has already been shown both in participants with normal sight (Fertonani et al., 2011; Pirulli et al., 2013) and in participants with uncorrected myopia (Camilleri et al., 2014), future studies with sham controls are needed to determine the precise contribution of hf-tRNS on such improvements in amblyopia.

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Changes across the psychometric function following perceptual learning of an RSVP reading task

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Several recent studies have shown that perceptual learning can result in improvements in reading speed for people with macular disease (e.g., Chung, 2011; Tarita-Nistor et al., 2014). The improvements were reported as an increase in reading speed defined by specific criteria; however, little is known about how other properties of the reading performance or the participants' perceptual responses change as a consequence of learning. In this paper, we performed detailed analyses of data following perceptual learning using an RSVP (rapid serial visual presentation) reading task, looking beyond the change in reading speed defined by the threshold at a given accuracy on a psychometric function relating response accuracy with word exposure duration. Specifically, we explored the statistical characteristics of the response data to address two specific questions: was there a change in the slope of the psychometric function and did the improvements in performance occur consistently across different word exposure durations? Our results show that there is a general steepening of the slope of the psychometric function, leading to non-uniform improvements across stimulus levels.

Keywords: perceptual learning, reading, rapid serial visual presentation, central vision loss, psychometric functions

1. INTRODUCTION

Performance for a variety of visual tasks improves with practice. This improvement is often termed *perceptual learning* and can be observed in the normal fovea (e.g., McKee and Westheimer, 1978; Ball and Sekuler, 1982, 1987; Karni and Sagi, 1991; Poggio et al., 1992; Fahle and Edelman, 1993; Li et al., 2004; Lu and Dosher, 2004) and the periphery (e.g., Chung et al., 2004, 2005; Chung, 2007). The effectiveness of perceptual learning in improving visual performance in the periphery is particularly important in relation to visual rehabilitation because it is commonly believed that the properties of vision in people with strabismic amblyopia resemble those of the normal periphery (Levi, 1991; Levi and Carkeet, 1993), and that people who lose their central vision due to macular disease must use their peripheral vision for seeing. Indeed, perceptual learning has been used as a remedy to improve functional vision for people with amblyopia for over two decades (for reviews, see Levi, 2005, Levi and Li, 2009 or Astle et al., 2011). Only recently have we observed an intense interest in applying perceptual learning to improve functional vision in people with central vision loss. Enhancing reading performance is a central goal, likely because the majority of patients seeking low vision rehabilitation services had central vision loss and most of them complained of reading difficulties (Owsley et al., 2009).

Previously, we tested the feasibility of using perceptual learning to improve reading speed for a group of six participants with long-standing macular disease: age-related macular degeneration (AMD) or Stargardt disease (Chung, 2011). Our task involved presenting sentences one word at a time using the rapid serial visual presentation (RSVP) paradigm and measuring reading accuracy as a function of word exposure duration. The advantage of using RSVP to train people with macular disease is that RSVP minimizes the need to make intra-word saccades during reading (Rubin and Turano, 1994), thus the training is not contaminated by any potential deficiency in eye movements, as has been reported for these individuals (White and Bedell, 1990). As such, the RSVP paradigm also allows us to independently test whether eye movement training or reading training would be more beneficial to people with macular disease, as in the study of Seiple et al. (2011). For example, it is hypothesized that "crowding" between letters in the periphery limits reading speed, and it has been shown previously that peripheral letter crowding can be reduced with perceptual learning (Chung et al., 2004; Chung, 2007).

Using our method, we defined reading speed based on the word exposure duration that yielded 80% correct on the psychometric function (PF) relating reading accuracy with word exposure duration. Our result showed that reading speed improved by an average of 53% following 6 weekly sessions of training using an RSVP reading task. Nguyen et al. (2011) trained a group of Stargardt disease patients also using an RSVP reading task and reported an increase of 25% of the median reading speed of the group following training. More recently, Tarita-Nistor et al. (2014) reported a 54% improvement in reading speed following training with a print size close to the threshold print size. In all these studies, reading speed was the primary measurement during training, and was used to gauge the effectiveness of the training paradigm. Besides the improvement in reading speed, which often was defined based on the shortest amount of time to read at a given level of accuracy, little is known about whether or not, and how, perceptual learning alters other properties of the participants' reading responses. Did the improvement in reading speed occur only at a specific testing duration, or did it generalize to other durations?

To further probe the effects of perceptual learning on the properties of participants' reading responses, we need to be able to fully characterize participants' reading performance at different stimulus levels (reading durations) and/or accuracy levels. The approach in our previous paper, measuring reading performance using the method of constant stimuli for multiple word durations, and fitting a psychometric function of reading accuracy vs. stimulus duration to describe the data (Chung, 2011), offers us the opportunity to explore the statistical characteristics of the response data beyond the defined reading speed thresholds. Other approaches have also been used to measure RSVP reading performance, most commonly using adaptive methods (Nguyen et al., 2011; Seiple et al., 2011; Tarita-Nistor et al., 2014). These approaches target at trials around a given accuracy criterion (the "threshold") and do not lend themselves readily for analyses beyond giving us the threshold values. In this paper, we are specifically interested in two questions: (1) was there a change in the slope of the psychometric function as a result of perceptual learning, and (2) were the performance improvements uniform across different word exposure durations?

To address our questions, we performed detailed analyses on the dataset of Chung (2011), with data from an additional new participant, also with age-related macular degeneration (AMD). Because a psychometric function was used to fit the data from each training block, we could evaluate if the slope of the psychometric functions change over the learning process (Question 1). An understanding of changes in the slope of the psychometric function is critical for at least two reasons. First, assumptions about the slope are the theoretical basis of adaptive methods such as QUEST (Watson and Pelli, 1983; Kontsevich and Tyler, 1999). Second, changes in the slope of the underlying psychometric function with learning may provide information about the underlying mechanism of the learning process or the specificity of the learning effect.

The predictions of how a psychometric function relating reading accuracy and stimulus duration may change as a result of perceptual learning are shown in **Figure 1**. The blue and red curves in each panel represent the psychometric function before and after training, respectively. Here, we make two general assumptions of the effects of perceptual learning on reading performance: (1) reading speed improves, which means that at the same level of accuracy, words can be read at shorter durations after training than before; and (2) the slope of the psychometric function either remains the same or becomes steeper after training, but will not become shallower. The three scenarios in **Figure 1** summarize how these effects may combine to produce the observed changes in the psychometric function following training. Panel A shows the scenario in which the slope of the psychometric function (sensitivity of responses) does not change. In this case, improvements in reading performance appear as a mere leftward shift of the psychometric function toward shorter durations (corresponding to faster reading speeds), yielding similar magnitudes of improvements across all durations, except at the very low and high end of the psychometric function. Panel B represents the case in which only the slope of the psychometric function becomes steeper (improvement in response sensitivity) following training. Because the slope of a psychometric function is defined with respect to the mean of the function (the 50% point), a steepening of the psychometric function (without any horizontal shift) would appear as an improvement in reading speed for accuracy levels above the mean of the psychometric function. However, this scenario predicts that there will be a drop in reading speed corresponding to accuracy levels below the 50% point. In Panel C, the steeper psychometric function is also accompanied by a leftward shift, resulting in improvements in reading speed that differ depending

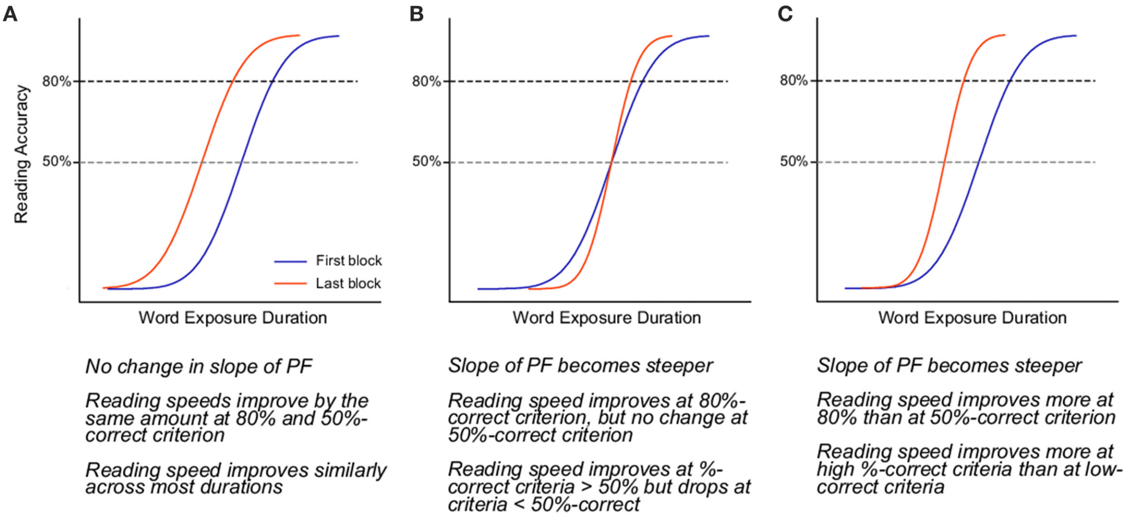

FIGURE 1 | Panels A–C illustrate the three possible outcomes of perceptual learning.

on the accuracy levels. For instance, reading speed defined at an 80% correct accuracy would yield a larger improvement than at 50% correct.

2. MATERIALS AND METHODS

2.1. EXPERIMENTAL PROCEDURES

Details of the experimental procedures are provided in Chung (2011). In brief, seven participants with macular disease practiced reading for six training sessions. Participants S1–S6 were from the study of Chung (2011), while data from S7 has not been reported previously. Visual characteristics of these seven participants are given in **Table 1**. Before and after training, participants were tested on a battery of tests that included the measurements of visual acuity, the location of the preferred retinal locus for fixation, fixation stability, the critical print size for reading and the maximum reading speed (when print size is not a limiting factor). The post-pre changes of these tests, if any, were reported previously in Chung (2011). In this paper, we focus on reporting the changes of the psychometric functions as a result of perceptual learning.

Reading performance was assessed using oral reading speed for single sentences presented in the RSVP format (Chung et al., 1998; Chung, 2002, 2011). On each trial, a single sentence was chosen randomly from a pool of 2630 sentences, containing between 8 and 14 words (mean = 10.9 ± 1.7 [SD]). All the words used were among the 5000 most frequently used words in written English, according to word-frequency tables derived from the British National Corpus (Kilgarriff, 1997). Words were rendered in Times-Roman font and were presented left-justified on a computer display, one word at a time in rapid succession, each for a fixed exposure duration. Participants were asked to read the words as quickly and as accurately as possible. The number of words read correctly was recorded after each trial. Feedback as to the number of words read correctly or the correct words (if read incorrectly) was not provided. In each block of trials, we used the method of constant stimuli to present sentences at five word exposure durations. The durations were chosen such that participants' reading accuracy spanned a range from 0–10% to 90–100% correct. Six sentences were tested at each duration, with a total of 30 sentences tested in each block and in a random order. With the exception of S6, all participants completed 10 blocks of trials (30 trials, or an average of ∼330 words presented per block) in each of the six training sessions, for a total of 60 blocks. S6 completed only seven blocks in the first training session, and eight in each of the subsequent sessions, for a total of 47 blocks. Training sessions were scheduled once a week for six consecutive weeks for participants S1–S5. Due to unexpected illness and personal issue, there was a three-week gap between sessions 3 and 4 for S6, the rest of his training sessions also occurred on a weekly basis. S7's training occurred on a daily basis (due to availability of the participant). Previously we have reported that the improvements due to perceptual learning are similar whether training took place on a daily or a weekly basis (Chung and Truong, 2013). With the exception of the frequency of training sessions (daily vs. weekly), the training protocol was identical for all participants.

Table 1 | Participant demographics.

Participant	Sex	Age	Diagnosis	LogMAR Acuity (RE, LE)		In 2011 study?
S1	F	82	AMD	0.50	0.52	Yes
S2	M	85	AMD	0.70	0.74	Yes
S3	M	84	AMD	0.56	0.70	Yes
S4	F	73	AMD	0.66	0.48	Yes
S5	F	62	Stargardt	0.58	0.58	Yes
S6	M	57	Stargardt	1.10	1.10	Yes
S7	M	72	AMD	0.78	0.78	No

All characteristics listed refer to the values during participation in the study.

3. RESULTS

3.1. STATISTICAL MODELING

To perform the statistical analyses subsequently described, we used the free software R (R Core Team, 2014). Additional analysis and plotting routines were written in Python, using the IPython (Pérez and Granger, 2007) environment and the NumPy/SciPy mathematics libraries (Millman and Aivazis, 2011).

There are several ways to analyze how the parameters of the psychometric function change over the course of training. The traditional approach (widely used, including in our own previous study), is to fit a psychometric function in each block as the first step, and then compare (i.e., with ANOVA, *t*-tests, etc.) or otherwise process the results of the fits (such as smoothing, fit an exponential, etc.) This two-step procedure is called the *Parameter-As-Outcome Model* (PAOM) in a recent article (Moscatelli et al., 2012) which serves as a tutorial to an alternative method comprising a principled one-step approach.

Using the one-step technique, psychometric functions are *simultaneously* fit to data and processed over time in a single step, permitting more robust statistical analyses. Since the change in performance over time is best described by an exponential function (Dosher and Lu, 2007; Chung, 2011), a non-linear mapping of the parameters vs. training block must be employed. No hypotheses exist about the change in slope over training, so non-parametric, assumption-free methods must be used. There are several possibilities, such as "additive models" (Wood, 2006), which have advantages over other non-parametric approaches such as LOESS or kernel regression (Knoblauch and Maloney, 2012). In a similar vein, we employed orthogonal polynomial fitting, where the change over time is modeled using sums of polynomials of increasing powers of the predictor variable (block number). Using R, this method can be incorporated as described above with simultaneous fitting of the psychometric function at each block, with the typical assumptions of a cumulative Gaussian psychometric function and binomial variance, such as in traditional probit analysis.

Two variants of this model were tested. The more general model (denoted M_{var}) models both the slope and 50% point as arbitrary functions of the block number. An alternative model (M_{fixed}), lets only the 50% point vary with the block; the slope is fixed. The sole free parameter when using orthogonal polynomials is the highest order of polynomial to utilize in fitting. Higher orders always yield a better fit to the data, but the risk is overfitting noise. To account for this, when choosing an order, a statistic such as BIC (Bayesian Information Criteria) is computed that penalizes the model likelihood by the number of parameters (Knoblauch and Maloney, 2012), here the highest order of polynomial. We summed the BIC across participants and evaluated all possible orders (1–60) of model M_{var}. The minimum BIC occurred at order 2, meaning the slope and 50% point are best approximated by the sum of a linear term and a quadratic term. A third model (M_{exp}) extended the traditional analysis (such as Dosher and Lu, 2007; Chung, 2011), modeling the change in performance as an exponential that reaches an asymptote, combined with a potential change in slope modeled as an arbitrary function, again using orthogonal polynomials.

3.2. PARAMETER ESTIMATES: CHANGES IN SLOPE AND 50% POINT

Figures 2, **3** depict the estimated values for the 50% point and slope, respectively. Each line shows the fit based on the method indicated in the figure legend. Several qualitative observations can be made about **Figure 2**. First, despite the difference in the constraints of each of the three models, the 50% point estimates are remarkably consistent between models. Most participants show a decrease in stimulus duration corresponding to the 50% point over the duration of training. The decrease is generally asymptotic, resulting in a function that is concave upward. S1 shows little improvement, however, and S4 may not have reached asymptotic performance. **Figure 3** demonstrates a general increase (steepening) in the slope of the psychometric

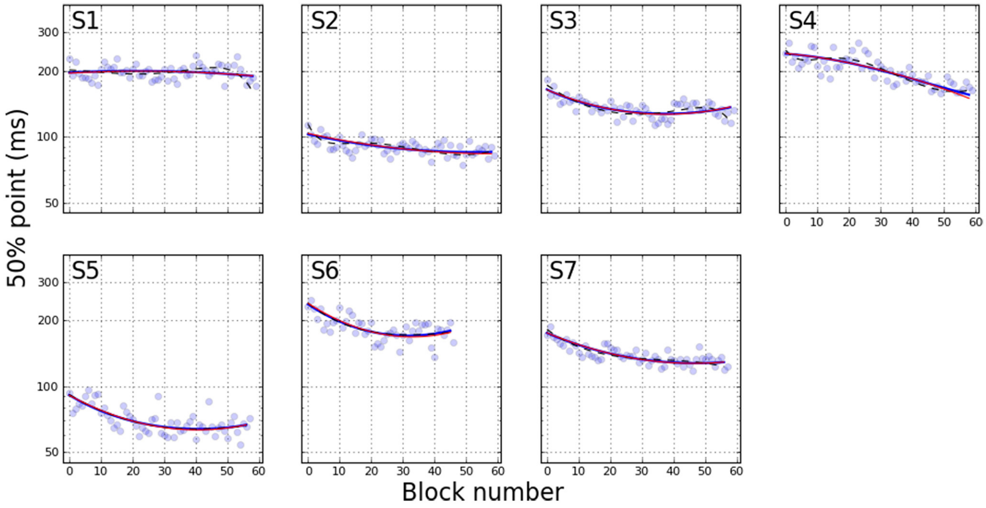

FIGURE 2 | 50% point on psychometric function as a function of training block. Blue curves are estimated using the variable slope model, while red curves indicate fixed slope. These curves are nearly indistinguishable. Dashed black lines show exponential fit. Pale blue dots represent PFs fit independently to each individual block.

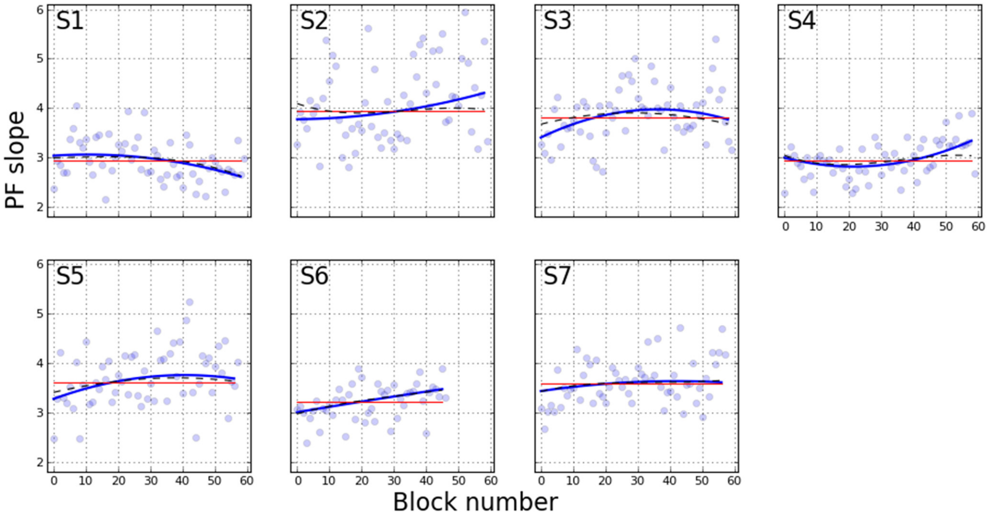

FIGURE 3 | Slope of PF across training blocks. Curves are colored as in **Figure 2**, with the estimated slope parameter as the variable of interest.

functions, either asymptotic (S3, S5, S7), or increasing (S2, S4, S6). S1 is the only participant showing a decrease (shallowing) of the slope. These trends are generally consistent between the two models that let the slope vary, while the slope for model M_{fixed} is flat, by definition.

To compare with Chung (2011), **Figure 4** plots the "reading speed" that is calculated from the estimated PFs. Reading speed is defined as the duration yielding 80% correct, converted to words-per-minute (wpm) by dividing the duration into 60 × 1000. This graph can be compared directly to **Figure 1** of Chung (2011). For the present study, the only real divergence between the three models can be observed with S4. Here the orthogonal polynomials estimate the change in reading speed as an upward concave function, whereas the exponential fit models the change as a shallow linear curve. Another difference between the exponential fit and the other smoothing approaches is that S1 does not show an improvement in reading speed except for a steep rise in the first few blocks, which is best captured by the exponential.

The improvements due to perceptual learning can be quantified by comparing the fitted values from the first and last blocks, as shown in **Tables 2–4**. These tables demonstrate the similarity of the predictions of the three models, as well as indicating the ratio of improvement from first to last block. **Table 4** further demonstrates the reasonable agreement in reading speed measurement with Chung (2011), despite the difference in methods.

Until now, we have reported the changes in 50% point and the slope of the psychometric functions as separate entities, but since both parameters progressively change with training, are these values related? **Figure 5** shows the corresponding changes to both the 50% point and psychometric function slope for all 7 participants on a single plot, as estimated using M_{var}. Each marker indicates the value of the two PF parameters on one training block, with color indicating participant and symbol size going from small to large to indicate the progression of training blocks. For most participants, it is clear that a steepening of the psychometric function accompanied the observed decrease in 50% point, though there are significant individual differences.

3.3. ESTIMATED CHANGE IN PERFORMANCE ACROSS THE PF

Changes in RSVP reading speed with training has been reported previously, but to our knowledge, whether or not the slope of the psychometric function changes with training has not been established. To confirm that the slope change is indeed significant, we performed statistical model comparison of the M_{var} and M_{fixed} models. Since M_{fixed} is a nested model of M_{var},

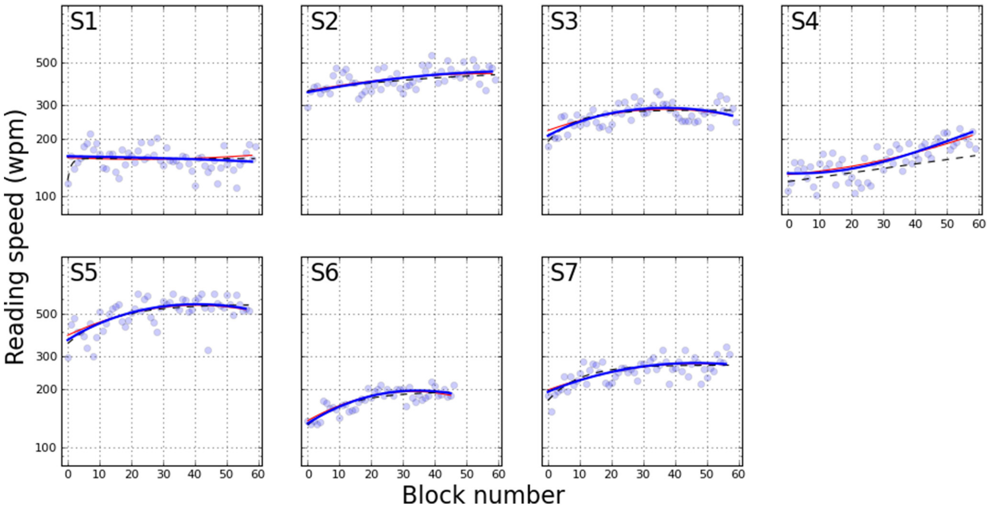

FIGURE 4 | Reading speed across training blocks. The data is derived from **Figures 2**, **3**, with conversion specified as reading speed $= \frac{60\times1000}{80\%\ \text{accuracy level}}$.

Table 2 | Estimated first and last PF 50% points.

Participant	First block			Last block			Ratio $\left(\frac{First}{Last}\right)$		
	M_{var}	M_{fixed}	M_{exp}	M_{var}	M_{fixed}	M_{exp}	M_{var}	M_{fixed}	M_{exp}
S1	196.23	194.94	201.56	188.94	189.57	160.79	1.04	1.03	1.25
S2	102.58	103.40	113.95	85.16	83.58	85.85	1.20	1.24	1.33
S3	164.16	163.61	171.99	136.07	136.64	117.09	1.21	1.20	1.47
S4	239.02	239.86	247.82	155.30	149.64	162.96	1.54	1.60	1.52
S5	91.31	91.14	91.83	66.76	66.75	65.72	1.37	1.37	1.40
S6	237.02	239.22	239.57	179.43	176.35	176.26	1.32	1.36	1.36
S7	175.30	175.51	182.05	128.99	129.13	123.17	1.36	1.36	1.48

a straightforward χ^2 difference test can be used. With this analysis, the addition of the two slope terms (the linear and quadratic coefficients), was statistically significant for all participants except S7. (For this participant, note the flatness of the estimated slope in **Figure 3**). **Table 5** lists the results of this test for each participant.

The change in slope is consistent amongst observers except for S1 (opposite sign of slope change) and S7 (not statistically significant). It is well known that there is substantial individual variability in the effects of perceptual learning (Fahle and Henke-Fahle, 1996), therefore we are not surprised that not all participants showed the same effects. In fact, the percentage of our participants not showing the effect as the other participants (∼28%) is comparable to the values reported for the percentage of participants not showing any improvement following perceptual learning (Fahle and Henke-Fahle, 1996; Chung et al., 2005).

To clearly illustrate the change in performance across the psychometric function, **Figure 6** shows the first and last PF for each participant. The full PFs are shown (estimated using model M_{var}), as well as the empirical data for the two blocks. From the PFs, the expected ratio of performance improvements can be estimated for any arbitrary criteria, as shown in **Figure 7**. Clearly, the more similar the slopes are, the flatter the ratio curve at different points of the psychometric function. In the case where the slope does not change (**Figure 1A**), the improvement curve will be completely flat (uniform improvements across PF), whereas for the steepening slope case (**Figure 1C**), the curve shown in **Figure 7** will increase for higher performance levels (larger × values). Finally, the case of **Figure 1B** would result in a curve with lower performance levels worsening (ratio <1), and higher performance levels improving (ratio >1). For our participants, S2–S6 exhibited a pattern consistent with **Figure 1C**, in agreement with the slope ratios shown in **Table 3**. S1 showed a negative pattern, while S7's pattern was flat, more consistent with **Figure 1A**.

4. DISCUSSION

In this paper, we performed detailed analyses of the rich data set of Chung (2011), with additional data from another participant

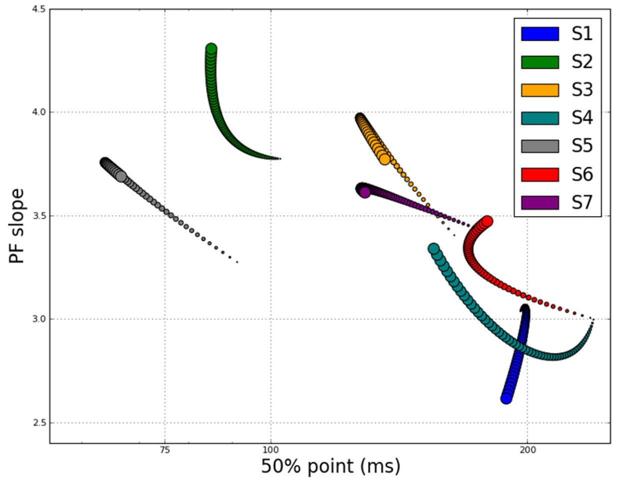

FIGURE 5 | Slope of PF vs. 50% point for each block of each participant, showing evolution throughout training. Color indicates participant, with circle size going from small to large over course of training.

Table 3 | Estimated first and last PF slopes.

Participant	First block			Last block			Ratio $\left(\frac{First}{Last}\right)$		
	M_{var}	M_{fixed}	M_{exp}	M_{var}	M_{fixed}	M_{exp}	M_{var}	M_{fixed}	M_{exp}
S1	3.04	2.93	3.00	2.62	2.93	2.63	0.86	1.00	0.88
S2	3.77	3.94	4.09	4.31	3.94	3.97	1.14	1.00	0.97
S3	3.40	3.81	3.67	3.77	3.81	3.68	1.11	1.00	1.00
S4	3.00	2.94	3.04	3.34	2.94	3.04	1.11	1.00	1.00
S5	3.28	3.61	3.41	3.69	3.61	3.63	1.13	1.00	1.07
S6	3.01	3.22	2.97	3.47	3.22	3.45	1.16	1.00	1.16
S7	3.43	3.58	3.43	3.61	3.58	3.65	1.05	1.00	1.07

Table 4 | Estimated first and last reading speeds, calculated as estimated 80% point on PF converted to WPM using WPM = $\frac{60 \times 1000}{duration}$. Columns marked (2011) show results of Chung (2011) study, which used a different method of fitting.

Participant	First block				Last block				Ratio $\left(\frac{First}{Last}\right)$			
	M_{var}	M_{fixed}	M_{exp}	(2011)	M_{var}	M_{fixed}	M_{exp}	(2011)	M_{var}	M_{fixed}	M_{exp}	(2011)
S1	161.55	158.96	155.91	118.52	151.38	163.46	178.50	172.81	0.94	1.03	1.14	1.46
S2	350.03	354.81	327.89	341.92	449.22	438.94	428.87	458.19	1.28	1.24	1.31	1.34
S3	206.87	220.43	205.83	189.08	263.77	263.94	302.67	285.91	1.28	1.20	1.47	1.51
S4	131.49	129.49	128.07	126.88	216.24	207.58	194.48	195.17	1.64	1.60	1.52	1.54
S5	363.64	385.03	369.99	349.78	531.45	525.69	535.64	595.51	1.46	1.37	1.45	1.70
S6	132.85	137.50	130.50	125.13	191.36	186.53	194.20	201.94	1.44	1.36	1.49	1.61
S7	194.64	198.87	187.18	n/a	271.99	270.30	286.43	n/a	1.40	1.36	1.53	n/a

with AMD, to address questions of whether there is a change in the slope of the psychometric function as a result of perceptual learning. With respect to this question, we had *a priori* reason to hypothesize that the slope of the psychometric function should either remain the same (but this should be accompanied by a shift of the psychometric function to reflect improvements in performance) or become steeper following perceptual learning. Here, the slope of a psychometric function represents the magnitude of the word duration that needs to be changed in order to alter the participant's reading accuracy by a certain amount. With perceptual learning, it is expected that participants would require a smaller change in word duration to produce the same amount of change in reading accuracy. With respect to our analysis, we found that the slope of the psychometric function became measurably steeper with training for 5 out of 7 participants (see **Figures 4**, **5**), although we acknowledge that there are individual variabilities.

The change in the slope of the psychometric function is interesting, and may be able to account for some improvements in reading performance. However, if the psychometric function simply becomes steeper but does not exhibit a shift toward shorter durations, then the function would be pivoted at the 50% point (as shown in **Figure 1B**), and we should observe a *decrease* in reading speed for reading accuracy below 50%. Therefore, we also analyzed the data to determine if the improvements in reading performance occurred similarly across all durations, or only for some specific durations. As shown in **Figure 7**, the improvements in reading performance are not the same across all durations, ruling out scenario A in **Figure 1** as the outcome of perceptual learning for most of the participants (S2–S6). The improvements are slightly larger near the high-end (performance close to 100% accuracy) of the psychometric function than the low-end (performance close to 0% accuracy). This finding, combined with the steepening of the psychometric function, identify scenario C as the effect of perceptual learning on the psychometric functions for our reading data.

In summary, following an RSVP training task to train participants with macular disease, we found that in addition to the previously reported improvement in reading speed, defined at the 80% accuracy, there is a steepening of the psychometric function relating reading accuracy with word exposure duration, accompanied by a shift of the psychometric function toward shorter duration. The shift is such that the psychometric function now appears to be pivoted at the low-end of the function. As such, the

Table 5 | χ^2 difference test of model M_{fixed} vs. model M_{var} for each participant. The nested model (M_{fixed}) has two fewer degrees of freedom: linear and quadratic coefficients for the modulation of slope over the course of training.

Participant	ΔDeviance	*p*-value	Significance
S1	12.034	0.002	**
S2	7.997	0.018	*
S3	14.002	0.001	***
S4	11.777	0.003	**
S5	10.879	0.004	**
S6	7.617	0.022	*
S7	2.226	0.329	

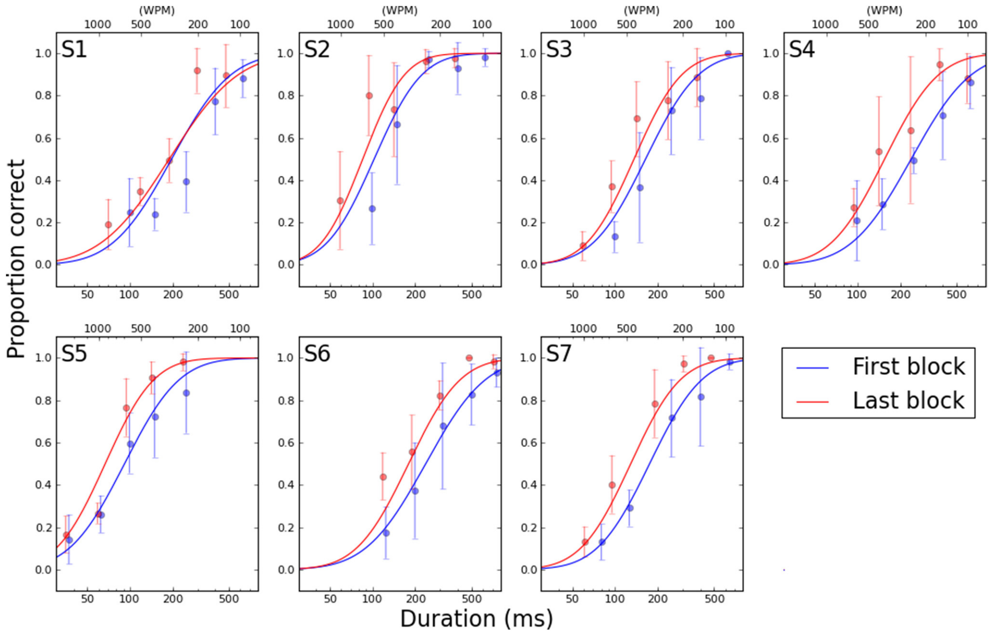

FIGURE 6 | First (blue curve) and last (red curve) psychometric functions for each participant, interpolated from model M_{var}. Abscissa is word duration, shown in milliseconds on the bottom axis and equivalent reading speed in words per minute on the top axis. Points show the mean and standard deviation of the six repetitions of each word duration in the specified block.

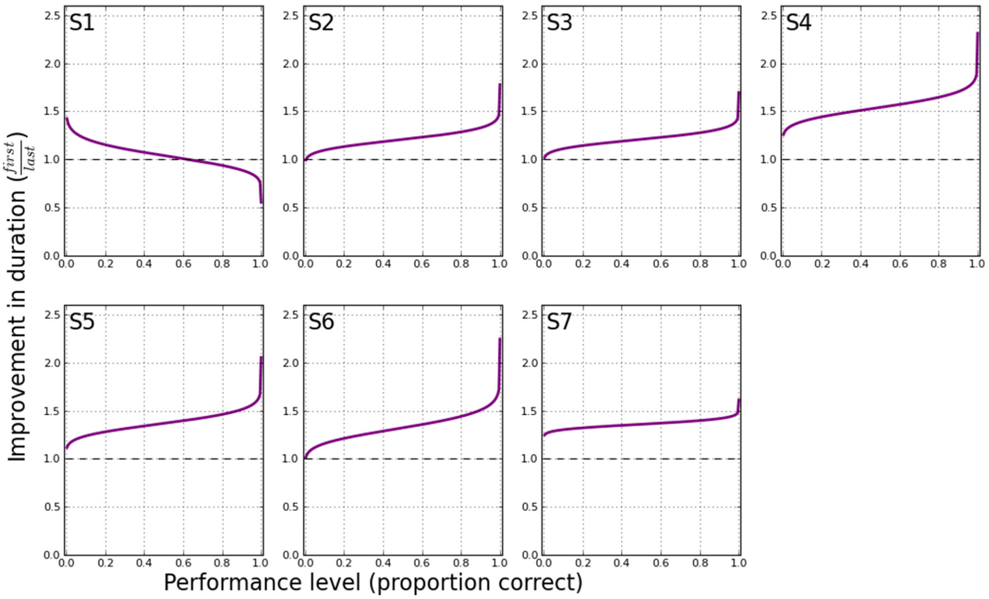

FIGURE 7 | Schematic improvement in performance (duration) at all points on the psychometric functions shown in Figure 6. At a given performance level (proportion correct), the corresponding stimulus durations are determined that yield the specified performance. The ratio of these durations (first/last) is then plotted on the ordinate, at the performance level indicated by the abscissa.

magnitude of improvement in reading speed would depend on the criterion to define reading speed. For example, the improvement is generally slightly greater when reading speed is defined at 80% accuracy than at 50%. This point is important for studies that use adaptive methods such as staircases for training, where reading performance is determined for more or less a similar accuracy level. Depending on the criterion accuracy level chosen, a larger or a smaller magnitude of improvement may be observed, and comparisons across studies would need to ensure that the accuracy levels are comparable.

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Perceptual learning in patients with macular degeneration

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Patients with age-related macular degeneration (AMD) or hereditary macular dystrophies (JMD) rely on an efficient use of their peripheral visual field. We trained eight AMD and five JMD patients to perform a texture-discrimination task (TDT) at their preferred retinal locus (PRL) used for fixation. Six training sessions of approximately one hour duration were conducted over a period of approximately 3 weeks. Before, during and after training twelve patients and twelve age-matched controls (the data from two controls had to be discarded later) took part in three functional magnetic resonance imaging (fMRI) sessions to assess training-related changes in the BOLD response in early visual cortex. Patients benefited from the training measurements as indexed by significant decrease ($p = 0.001$) in the stimulus onset asynchrony (SOA) between the presentation of the texture target on background and the visual mask, and in a significant location specific effect of the PRL with respect to hit rate ($p = 0.014$). The following trends were observed: (i) improvement in Vernier acuity for an eccentric line-bisection task; (ii) positive correlation between the development of BOLD signals in early visual cortex and initial fixation stability ($r = 0.531$); (iii) positive correlation between the increase in task performance and initial fixation stability ($r = 0.730$). The first two trends were non-significant, whereas the third trend was significant at $p = 0.014$, Bonferroni corrected. Consequently, our exploratory study suggests that training on the TDT can enhance eccentric vision in patients with central vision loss. This enhancement is accompanied by a modest alteration in the BOLD response in early visual cortex.

Keywords: perceptual learning, fMRI BOLD, cortical plasticity, visual cortex, macular degeneration

INTRODUCTION

Visual performance in a variety of tasks, for example in the detection or discrimination of certain stimulus patterns, has been shown to improve with training. The results of this perceptual learning appear to have long lasting effects (e.g., Gibson, 1963; Goldstone, 1998; Fahle and Poggio, 2002; Seitz and Watanabe, 2005; Sagi, 2011; Frank et al., 2014). At the same time it often takes only hours or days of practice to enhance perceptual abilities dramatically. This has been shown for texture discrimination (Karni and Sagi, 1991), orientation discrimination (Schoups et al., 2001), spatial frequency discrimination (Fiorentini and Berardi, 1981; Sireteanu and Rettenbach, 1995), Vernier discrimination tasks (Poggio et al., 1992), and the discrimination of motion direction (Ball and Sekuler, 1982), among others.

Perceptual learning thus appears to provide an ideal approach to be used in clinical settings as well, in the attempt to improve the abilities of visually impaired persons. Recent studies have focused on amblyopia, where perceptual learning proved to improve vision in the amblyopic eye (e.g., Polat et al., 2004; Zhou et al., 2006; Levi and Li, 2009; Astle et al., 2010, 2011; Levi, 2012; Chung et al., 2012; Hussain et al., 2012). Other applications include applying perceptual learning in myopia and presbyopia (Polat, 2009; Polat et al., 2012), in adults with impairments in stereopsis (Ding and Levi, 2011) and in children with visual impairment (Huurneman et al., 2013) and developmental dyslexia (Gori and Facoetti, 2014). In patients with central vision loss, Chung (2011) used rapid serial visual presentation (RSVP) in an oral sentence-reading task to improve patients' reading ability, a paradigm that has already been shown to improve reading speed in the peripheral visual field in both younger (Chung et al., 2004; Yu et al., 2010b) and older (Yu et al., 2010a) normally sighted adults. In Chung's (2011) study, RSVP reading speed improved on average by 53%.

Central vision loss is often caused by atrophy of photoreceptor cells in the macula, as can be observed in age-related macular degeneration (AMD) or hereditary retinal dystrophies (juvenile form, JMD) like Stargardt's disease or cone-rod dystrophy. Patients with central scotoma often develop eccentric viewing to cope with visual tasks like reading. The so-called "preferred retinal locus" (PRL) is a location in the eccentric visual field that is habitually used by MD patients as a pseudo-fovea (Bäckman, 1979; Timberlake et al., 1987; Whittaker et al., 1988; Guez et al., 1993; Fletcher and Schuchard, 1997). In this study, we trained AMD/JMD patients to perform a TDT (Karni and Sagi, 1991) with the target located at or near the PRL, with the aim to improve patients' visual abilities at this specific location in their visual field. To investigate possible transfer effects to other tasks or abilities, we used the Freiburg Visual Acuity and Contrast Test (FrACT; Bach, 1996) before and after training. Possible effects on quality of life issues were assessed with the Visual Function Questionnaire VFQ-25 (Mangione et al., 2001).

We were also interested in the neural correlates of training using functional magnetic resonance imaging (fMRI). The neural correlates of perceptual learning are still not well understood. Results so far indicate an increase of the BOLD signal in primary visual cortex (Schwartz et al., 2002) with the training of a TDT. But it was also shown with fMRI that with repeated training learning is accompanied by an initial increase followed by a decrease in response (Yotsumoto et al., 2008). We observed a similar development in a recent study on the effect of trial-by-trial feedback on a challenging coherent-motion discrimination task (Goldhacker et al., 2014). In the initial phase of training we observed an increase in the fMRI-BOLD signal in primary visual cortex. With repeated training the BOLD signal in early visual cortex decreases. At the same time the performance of participants increases further or remains constant at a high level. We interpret this development in the BOLD signal over several measurements and days as an indication for neuroplastic changes in visual cortex as a consequence of intensive training. In the initial training phase, additional neural resources are recruited to learn the new perceptual task. After the task has been well practiced, neural processing becomes more automatic with equivalent high performance, thus less neural resources are needed. As suggested by Yotsumoto et al. (2008), the increase of brain activation in early visual cortex in the initial phase of learning could be mediated by an increase in the number or strength of synaptic connections, while the drop in activation at a later stage could be explained by synaptic downscaling after performance becomes saturated. This pattern is also in line with reports of participants, suggesting that they only guess at the beginning of training, while later they claim to "see" the differences in the stimuli clearly and almost without any effort (Goldhacker et al., 2014). Further studies show that perceptual learning can even lead to a parallelization of a visual conjunction search task which can only be solved in a serial manner initially (Frank et al., 2014).

In this study we explored the effects of perceptual learning in patients with central visual field loss. We investigate whether repeated intensive training can improve performance on the TDT, while altering the response of neurons in early visual cortex responsible for the processing of peripheral information. To test for the visual-field specificity of training, during fMRI we tested patients for targets located at their PRL or at a location opposite of the PRL (OppPRL). Comparison with an age-matched control group should indicate the extent to which this form of learning is specific for persons with central vision loss.

MATERIALS AND METHODS

PATIENTS AND CONTROL SUBJECTS

Eight patients with diagnosed AMD and five patients with juvenile macular dystrophy (JMD; i.e., three patients with cone-rod dystrophy and two patients with Stargardt's disease) participated in the study (8 males, 5 females; mean age 63.8 years, range 47–79 years). Additionally twelve healthy age-matched control subjects took part in the experiment (4 males, 8 females; mean age 62.1 years, range 47–78 years). All participants signed an informed consent form prior to participating in the study and received modest monetary compensation for their participation. The study was approved by the Ethics Committee of the University of Regensburg and conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

CLINICAL CHARACTERISTICS AND VISUAL FIELD MEASUREMENTS

Table 1 presents details on demographic characteristics of patients and controls, including the gender, age, diagnosis, duration of disease at time of study, study eye, scotoma size, visual acuity, position of PRL, and fixation stability in the study eye. The dominant eye was chosen as the study eye. Eye dominance was determined by a modified version of the A-B-C Vision Test (Miles, 1930; Porac and Coren, 1976), by aiming a distant target through an opening formed by their hands. The study eye of the controls was always the eye corresponding to the study eye of their age-matched patient. Since some of our measures were conducted in the Eye Hospital, fixation stability, and visual acuity could only be determined at the start of the study.

Best-corrected visual acuity was determined by using a Vision Screener (Rodenstock Rodavist 524/S1) and Eye Charts for distant visual acuity (Oculus Nr. 4616). Scotoma size was measured using kinetic Goldmann perimetry with the isopters III/4e, I/4e, I/3e, I/2e, and I/1e in all patients except patients P8, P10, and P11. Defined as edges of the scotomata, those points were marked, where isopter III/4e were no longer detected. Scotoma size is reported in **Table 1** as scotoma diameter in degrees of visual angle as an average and approximation of rounded vertical and horizontal dimensions. Reliability of the Goldmann perimetric measures depends on fixation stability. For patients P8, P10, and P11 no Goldmann perimetry was available. Scotoma size was inferred from fundus photography (autofluorescence imaging as described in Rosengarth et al., 2013) instead. Controls did not undergo Goldmann perimetry. **Figure 1** depicts the shape of each patient's scotoma in the respective study eye as inferred from fundus photography. The techniques differ in principle as Goldmann perimetry provides direct visual field measures based on measures of visual function while fundus photography provides indirect evidence based on changes to fundus morphology.

As described in Rosengarth et al. (2013), 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° visual angle 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. During the measurement the camera sometimes lost track of the subject's eye. This can be due to eye blinks or fixation instability in the form of large saccades. The Nidek software records the time period that was measured and the proportion of the time span that was effectively tracked, as well as the percentages of fixation points that fell in a range of 2 or 4° diameter visual angle around the center of the fixation target, based on the time spans effectively tracked. Thus fixation stability can be overestimated by long or frequent time spans where the camera had lost track of eye position due to large saccades. To compensate for this we corrected the given fixation stability in the following way

Table 1 | Characteristics of patients (P1–P13) and controls (C1–C12) according to age, gender, diagnosis, duration of disease in years, study eye, decimal visual acuity, scotoma size (diameter in degrees visual angle), position of PRL (in degrees visual angle in x,y -coordinates with 0,0 put at central vision), and fixation stability (percentage of fixation in 2 and 4° visual angle around fixation target; patients fixated with their PRL, controls fixated with their fovea); m, male; f, female; Stargardt, Stargardt's disease; OS, oculus sinister; OD, oculus dexter.

Patient Nr.	Age	Gender	Diagnosis	Duration of disease (in years)	Study eye	Decimal visual acuity (study eye)	Scotoma size in study eye (diameter in ° visual angle)	Position of PRL (in ° visual angle)		Fixation stability in study eye	
								x	y	2°	4°
P1	64	M	AMD	6	OS	0.1	10	−8	1	74	95
P2	64	M	AMD	7	OS	0.08	25	−4	−1.5	76	95
P3	79	M	AMD	9	OD	0.2	10	−6	3	89	100
P4	47	F	Stargardt	13	OD	0.05	15	−1.5	−6	95	100
P5	63	M	Cone-rod dystrophy	19	OD	0.1	15	0	−5	22	22
P6	57	M	Stargardt	18	OD	0.05	15	0	−6	33.7	66.7
P7	58	M	AMD	5	OD	0.02	20	−13	−0.5	10.6	28.3
P8	61	F	AMD	8	OS	0.3	10	−6	−3	60	100
P9	72	F	AMD	12	OS	0.1	10	5	0	88	98
P10	74	F	AMD	20	OS	0.2	10	4	−4	83	100
P11	63	F	AMD	8	OD	0.1	20	−6	3	90	99
P12	59	M	Cone-rod dystrophy	13	OS	0.1	10	−9	0	90	100
P13	69	M	Cone-rod dystrophy	59	OD	0.1	10	0	−4	100	100
C1	64	F	–	–	OS	0.9	–	–	–	100	100
C2	67	M	–	–	OS	1.0	–	–	–	100	100
C3	71	M	–	–	OD	1.0	–	–	–	100	100
C4	47	F	–	–	OD	1.0	–	–	–	100	100
C5	78	M	–	–	OD	0.9	–	–	–	100	100
C6	52	F	–	–	OD	1.6	–	–	–	100	100
C7	63	F	–	–	OS	0.8	–	–	–	100	100
C8	51	F	–	–	OS	1.4	–	–	–	100	100
C9	64	F	–	–	OS	1.2	–	–	–	99	100
C10	54	F	–	–	OD	1.0	–	–	–	99	100
C11	56	F	–	–	OS	1.4	–	–	–	100	100
C12	78	M	–	–	OD	0.9	–	–	–	85	97

(see Plank et al., 2011): First we calculated the mean time span for which the camera lost track of eye position in the normally sighted control group, who fixated with their fovea. The resulting mean value of 9 s (SE = 3.0 s) yielded an estimate of the time that could be attributed to eye blinks. In a second step we subtracted this amount from the measured time, in which the camera had lost track of the eye of each patient. The individual difference between the measured time remaining and the effectively tracked time we attribute to large saccades. This time span was added to the effectively tracked time in each patient. On this basis we recalculated the percentages of fixation points falling in a range of 2 and 4° visual angle around the target for the patient group.

The Nidek MP-1 was also used to measure a microperimetry of 30° diameter around the patients' PRL, for all patients except P8 and P11. Patients fixated a central cross with their PRL on intact retina and were instructed to press a button as soon as they perceived a target. We used "strategy-fast" with static light points of intensity 16 and 8 dB, maximal brightness of 127 cd/m^2, that were presented for 200 ms each on a grid comprising the 30° of the visual field centered around the PRL.

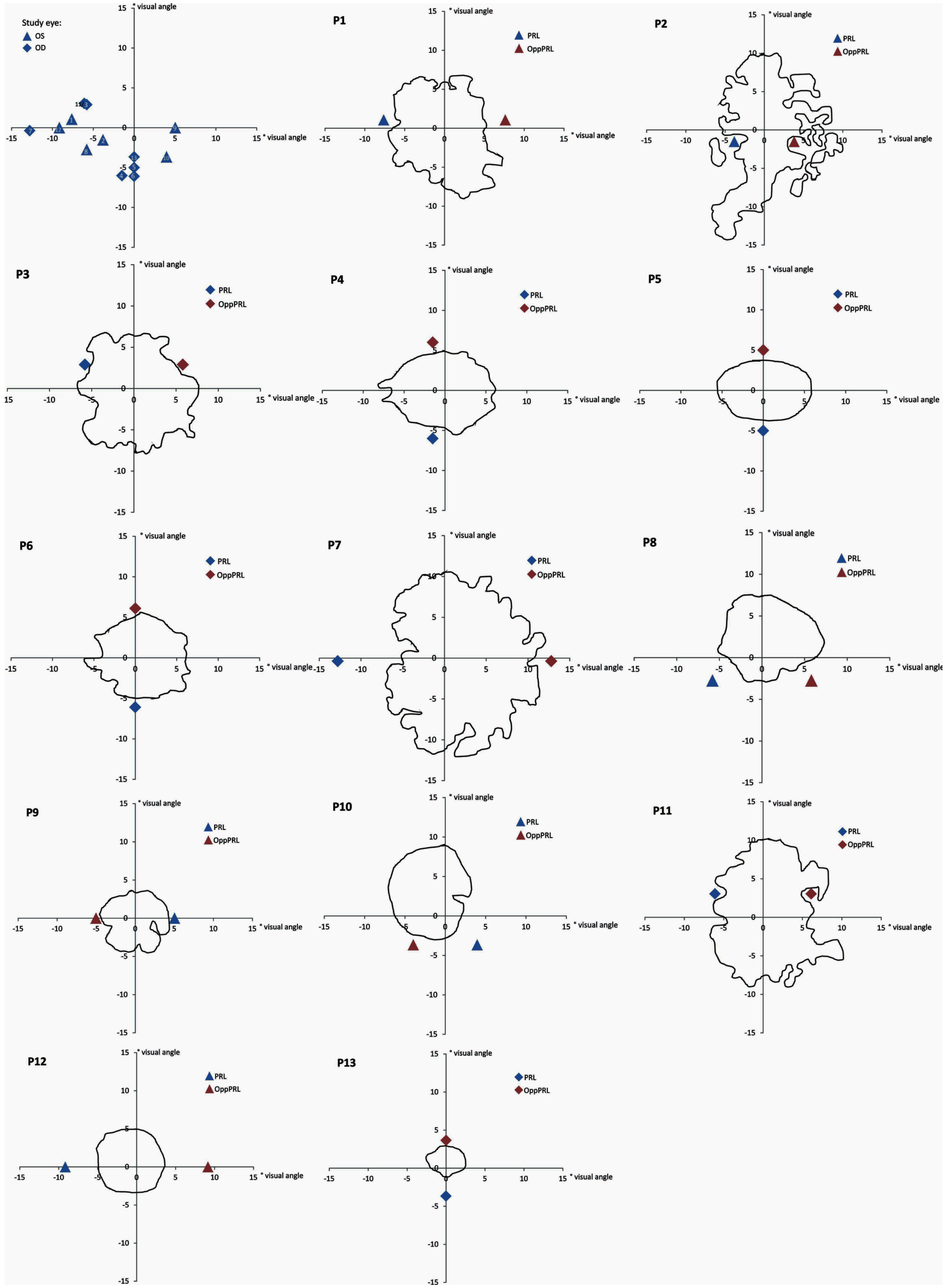

FIGURE 1 | Continued

FIGURE 1 | Continued
Schematic depiction of positions of PRLs for all patients (upper left; blue triangles mark the left eye as study eye, blue diamonds mark the right eye as study eye, labeled with patient numbers 1–13) and schematic depictions of the shape of each patient's scotoma as inferred from fundus photography (autofluorescence (P2, P3, P4, P5, P6, P8, P10, P11, P12, P13) or infrared reflection imaging (P1, P7, P9; blue symbols code the trained PRL position, red symbols code the untrained OppPRL position). The x- and y-axis of the plots give the eccentricity in degrees of visual angle.

The positions of PRLs were also assessed via the Nidek fundus images. They were later verified using a video eyetracker (High Speed Video Eyetracker Toolbox, Cambridge Research Systems, UK), while the patients fixated a target on a computer monitor. The distribution of positions of patients' PRLs in the visual field is given in **Figure 1**.

STIMULI AND TASK

Patients and controls were trained in a modified version of the TDT described by Karni and Sagi (1991). During training subjects were positioned with a distance of 60 cm in front of a 19-inch screen with a refresh rate of 75 Hz, while the luminance for black was 0.93 cd/m^2 and for white 106 cd/m^2. We used Matlab (version 7.12.0) and the Psychophysics Toolbox (Brainard, 1997) for programming the stimuli and the experimental design. Subjects were instructed to fixate with their individual PRL while controls had to hold their fixation in the center of the screen. To support patients' fixation a white dot (0.75°) was placed at their individual PRL position. Controls fixated at a white circle (0.5° visual angle) at the center of the screen. During a trial, participants had to discriminate the global orientation (horizontal/vertical) of three tilted lines, located in their PRL, against a uniform background of horizontal lines (see **Figure 2**).

Stimulus size was increased in comparison to the original paradigm (Karni and Sagi, 1991), with a line length of 2° and line width of 0.3° visual angle. We did not scale the target elements nor the distractors in the background for different eccentric locations, since stimulus displays had to fit into a 30-degree diameter display. Target position was individually adjusted according to each patient's PRL position. Each control subject was assigned to one particular patient and adopted that patient's PRL position as target position in the task. On each trial, the target stimulus was shown for 13.3 ms, followed by a blank screen with variable stimulus onset asynchrony (SOA) and a mask stimulus (106.4 ms duration), after which the participants responded with a button press (two buttons on a standard keyboard; see **Figure 2**). In each block the SOA was adjusted by using an adaptive procedure (two–down, one-up), starting with a SOA of 492.1 ms, to determine the 70.7% correct threshold (Levitt, 1971). Initial step size was 53.2 ms, which was decreased by 13.3 ms (i.e., the duration of one frame on the display) after each turning point. A block stopped after 32 trials and the last measured SOA was taken as the 70.7% threshold of this block. In a pre-training session the initial individual SOA threshold was determined by running five experimental blocks. This initial SOA threshold was then used in all fMRI sessions. All patients and controls performed six training sessions on separate days over a period of approximately 3–4 weeks. Each session consisted of 20 blocks, each with 32 trials. One block took about 2 min, depending on individual SOA and reaction times, and each session lasted approximately 45 min.

EYETRACKING DURING PSYCHOPHYSICAL MEASUREMENTS

A trial only could be evoked if fixation was stable, which was assured by an eye tracking system (resolution 0.05°, 250 Hz, High-Speed Video Eye-Tracker Toolbox, Cambridge Research Systems, Rochester, UK), thus the onset of trials could be delayed in case of unstable fixation. Calibration was done by controls with their fovea and by patients with their PRLs, resulting in a constant shift with respect to the position of the fovea. This constant shift, in coordinates of the individual PRL, was added as a correction factor to the tracked position of the eye.

STIMULI AND TASK DURING fMRI

During the fMRI sessions, visual stimuli were projected onto a circular screen (31° visual angle in diameter at a distance of 60 cm) placed behind the head of the participant at the end of the scanner bore and visible via a mirror placed within the MRI head coil. Subjects underwent an fMRI session before training, after three training sessions and again after another three training sessions. The stimuli as described above appeared in a distance of 60 cm on the screen (luminance of the dark background was 1.7 cd/ m^2, luminance of the white line elements was 193 cd/m^2). The fMRI sessions differed somewhat from the

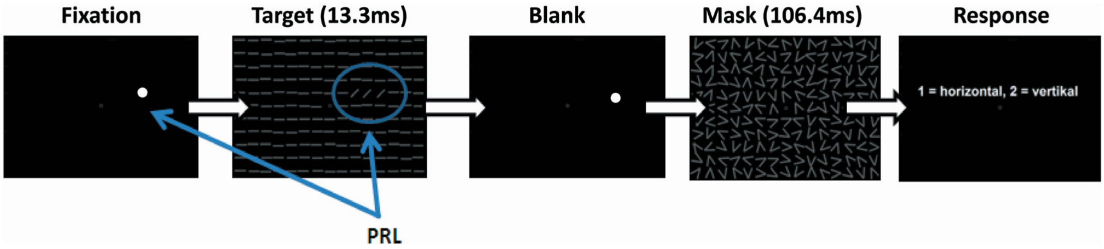

FIGURE 2 | Schematic depiction of a single trial in the training sessions. While subjects were successfully fixating with their PRL (white dot) the target stimulus appeared for 13.3 ms followed by a mask, which was shown for 106.4 ms. The time between stimulus and mask (SOA) was adjusted to provide a constant hit rate of 70.7%. At the end of each trial subjects had to indicate by button press whether the three lines of the target formed a horizontal or vertical array.

training sessions, since the target stimulus was presented randomly in half of the trials in the PRL position and in half of the trials in the opposite hemifield (OppPRL), leading to slightly lower performance (see below). This was indicated by a brief color change of the white fixation dot before appearance of the target stimulus. In most subjects the fixation dot at the target location turned to red at the PRL or blue to indicate that the target would appear at the OppPRL. In some patients the color of the dot only changed when the target was to appear in the OppPRL because those patients had problems in differentiating the colors red and blue. This color cueing was kept constant for the matched control subjects. As in the training session patients fixated with their PRL, while control subjects kept fixation in the center of the screen. No eyetracker was used during fMRI, but fixation stability could be estimated from psychophysical test sessions. The SOA achieved before training sessions served as fixed SOA for all three fMRI sessions. At the beginning of a trial the dot changed its colour for 505.4 ms, followed by the target for 13.3 ms. After an individual SOA the mask was presented for 106.4 ms. Then a fixation pause with temporal jitter of 3–4 s succeeded before a new trial started. Each block consisted of 100 trials (50 PRL, 50 OppPRL), lasting for, on average, 8 min, again depending on individual SOA and reaction times. Three blocks were conducted in one fMRI session. The participants viewed all test stimuli in all training and testing situations monocularly with their study eye.

FREIBURG VISUAL ACUITY AND CONTRAST TEST

Before and after training subjects' visual acuities and contrast sensitivity at the trained position in the visual field were assessed by applying the FrACT[1] (Bach, 1996) to monitor for possible improvements induced by training. Thereby the Landolt C contrast sensitivity test with 100 and 50 arcmin diameter, the contrast grating test and the Vernier test were chosen. Luminance linearization was applied as implemented in the software.

VISUAL FUNCTION QUESTIONNAIRE

To assess the patients' own perception of their visual function before and after perceptual learning we used the National Eye Institute's VFQ-25 (Mangione et al., 2001) in its German translation.

BEHAVIORAL DATA ANALYSIS

According to stimulus onset asynchronies obtained in the training sessions a 2 × 6 ANOVA for the factors group (patients, controls) and session (training session 1–6) was performed. To test explicitly for group differences in SOAs between training sessions 1 and 6, we applied two t-tests. For the fMRI sessions we conducted 2 × 2 × 3 ANOVAs related to the factors group (patients, controls), location (PRL, Opposite PRL) and session (before, during and after training) with respect to the dependent variables hit rate and reaction time. Additionally, we performed two 2 × 3 ANOVAs with the factors location (PRL, OppPRL) and session (before, during and after training), separately for each group, with respect to the dependent variables hit rate and reaction time. To test explicitly for group differences in hit rates between fMRI session 1 (before training) and 3 (after training), at the PRL and OppPRL, we applied four t-tests.

Additionally we performed correlation analysis between initial fixation stability, assessed before training started, and the development of hit rate and BOLD percent signal change in the PRL and OppPRL associated area in the early visual cortex.

For all ANOVAs, we corrected for violation of sphericity assumption if necessary by using Greenhouse–Geisser correction ($p < 0.05$). All statistical tests were performed using PASW 21 for Windows.

One patient (P13) was not able to participate in the fMRI sessions for physical reasons. We only included his behavioral values for the group analysis of the SOA measurement (see below). In total, data from 13 patients and 12 control subjects entered the SOA analysis of the behavioral data acquired during the training sessions. During the fMRI sessions, hit rate and reaction time were recorded in 11 patients and 10 control subjects. Behavioral data from one patient (P12) and two control subjects (C4 and C12) were lost due to technical problems with the response box.

According to the subtest of the FrACT and the VFQ a possible impact of training was assessed by paired t-tests (before and after training). Data from the FrACT were acquired in 13 patients and 12 control subjects. Data from one patient (P7) was excluded from the analysis of Landolt C contrast sensitivity, because he was not able to do the test. The data from another patient (P2) was excluded from the analysis of the Vernier test, owing to his inability to execute the Vernier test before training. Data from all 13 patients were available for the VFQ analysis.

STRUCTURAL AND FUNCTIONAL MRI MEASUREMENTS

Magnetic resonance imaging scanning was performed with a 3-Tesla Allegra head scanner (Siemens, Erlangen, Germany) and a one-channel head coil. Functional whole-brain images were acquired interleaved with a T2*-weighted gradient echo planar imaging (EPI) sequence (time-to-repeat, TR = 2 s; time-to-echo, TE = 30 ms; flip angle, FA = 90°) consisting of 34 transverse slices (voxel-size = 3 mm × 3 mm × 3 mm; field of view, FOV = 192 mm × 192 mm). In addition, we collected a high-resolution structural scan (160 sagittal slices each) with a T1-weighted, magnetization prepared rapid gradient echo (MP-RAGE) sequence (TR = 2.25 s, TE = 2.6 ms, FA = 9°, voxel size = 1 mm × 1 mm × 1 mm, FOV = 240 mm × 256 mm). The sequence was optimized for the differentiation of gray and white matter by using parameters from the Alzheimer's disease Neuroimaging Initiative project[2].

MRI DATA ANALYSIS

Magnetic resonance imaging data analysis was performed with Statistical Parametric Mapping 8 (Wellcome Center of Neuroimaging, London[3]). First a temporal interpolation of the functional data using the slice time function in SPM8 was conducted. Afterward a motion correction over all sessions was applied to the

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[1] http://www.michaelbach.de/fract/download.html

[2] http://adni.loni.ucla.edu/

[3] http://www.fil.ion.ucl.ac.uk/spm/

functional images followed by co-registering each participant's structural brain scan of the first session (before training) to the functional images. Then images were normalized to the MNI space, re-sampled to a 2 mm × 2 mm × 2 mm resolution and smoothed with a three-dimensional Gaussian kernel (full-width at half-maximum = 8 mm).

In the first-level statistical design the possible positions of the PRL and the OppPRL as prediction variable for each session were modeled separately and then convolved with the hemodynamic response function.

For a region-of-interest (ROI) analysis the SPM toolbox Marsbar was applied (Brett et al., 2002). A functional localizer was used to assess the individual representation area of the PRL, the OppPRL, and the fovea in the early visual cortex of the patients. Accordingly, during a separate fMRI scan contrast reverting checkerboard disks (size: 9° × 9° visual angle, presented with a reversal rate of 8 Hz) and chromatic images of everyday objects (e.g., animals, tools, vehicles, musical instruments; 7.3° × 7.3° visual angle) were visually presented on the individually determined position of the PRL, a location of the same eccentricity OppPRL and the fovea (corresponding to the scotoma region in the patients). For the control subjects the PRL/OppPRL coordinates of their age-matched patient were used. The PRL localizer scans were also conducted monocularly with the same study eye. The photographs used in the PRL localizer paradigm were collected from free Internet databases or taken by the authors. Stimuli were presented blockwise on a gray background, together with a baseline condition (gray background of medium luminance). The blocks were presented in four repetitions. Contrast reverting checkerboards and meaningful pictures were presented in the center, the PRL or the opposite PRL in separate blocks of 13 s each, the baseline condition (blank screen) in blocks of 18 s. In a block with meaningful pictures, the picture changed every 2.2 s without a gap, so that six different pictures were presented sequentially in each object block (for a detailed description see Rosengarth et al., 2013).

In a GLM analysis we modeled six regressors for the two types of stimuli (checkerboards, everyday objects) and the three locations (fovea, PRL, OppPRL) while the baseline condition (blank screen) served as an implicit baseline for the analysis to avoid an overspecification of the statistical design. Individually weighted T-maps for contrasts PRL > OppPRL and OppPRL > PRL were calculated. A sphere of 5-mm radius was placed on the voxel with the highest t-value of the resulting cluster in striate and extrastriate visual cortex. ROIs were always located in the hemisphere contralateral to the PRL/OppPRL location in the visual field. Since no explicit retinotopic mapping of visual area borders was conducted, we cannot separate these activations into the respective visual areas. These spheres served as ROIs for calculation of the individual percent signal changes in projection zones for the PRL and OppPRL in the visual cortex by applying these ROIs for the individual GLMs applied to the data of the main experiment.

The individual percent signal changes were integrated in a 2 × 2 × 3 factorial ANOVA with the factors group (patients, controls), location (PRL, OppPRL) and sessions (before, during, after training).

We also tested for the existence of a linear or quadratic trend in the factor session, with one-factorial ANOVAs, separately for each location (PRL, OppPRL) and group (patients, controls).

Because of technical issues two control subjects (C4 and C12) had to be excluded from the analysis of the fMRI data resulting in 12 patients and 10 controls for that analysis.

We also correlated patients' fixation stability with the development of percent signal change of the BOLD response with the training.

RESULTS

BEHAVIORAL DATA

In agreement with the original results of Karni and Sagi (1991), during training patients and controls showed a training-induced improvement in performance, as reflected in a significantly decreasing SOA over the six training sessions [$F(1,23) = 14.47$; $p = 0.001$; see **Figure 3**). No significant effect of group was observed, suggesting that both patients and controls learned the task equally well. Although not significant, there was a trend toward an interaction between the factors group and session [$F(1,23) = 3.5$; $p = 0.074$]. This trend in the results appears to be due to the fact that patients started generally with higher SOAs, which were followed by a steeper decrease of SOAs over training compared to control subjects. Differences in SOAs in training session 1 between the patient and control group just failed to reach significance [$t(23) = 2.2$; $p = 0.08$, Bonferroni corrected for multiple comparisons]. SOAs in training session 6 were indistinguishable between patient and control group [$t(23) = 0.46$; $p = 1.00$].

During the fMRI sessions there was a significant effect of session [$F(1,19) = 13.6$; $p = 0.002$] for the dependent variable hit rate, but there was no effect of location nor group in the omnibus ANOVA (**Figure 4**, upper panel). Additionally hit rates exhibited a significant interaction between target location (PRL, OppPRL) and group [$F(1,19) = 4.6$; $p = 0.045$]. As can be seen in **Figure 4**, and was also tested by additional ANOVAs separately for patients and controls, there was a significant effect of target location (PRL,

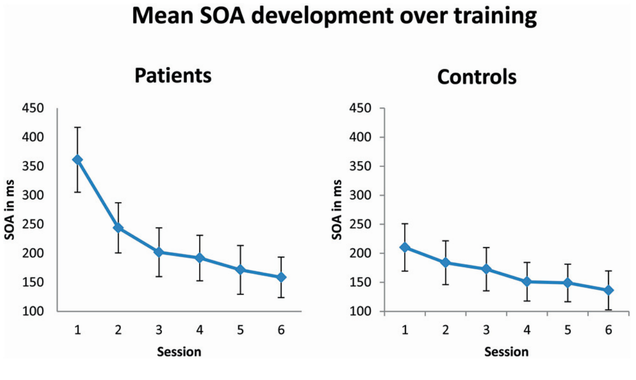

FIGURE 3 | Mean of stimulus onset asynchrony (SOA in ms) over six training sessions. The SOA decreases significantly ($p = 0.001$) from the first to the last training session in both patient ($n = 13$) and control ($n = 12$) groups. Error bars show ±1 SE of the mean.

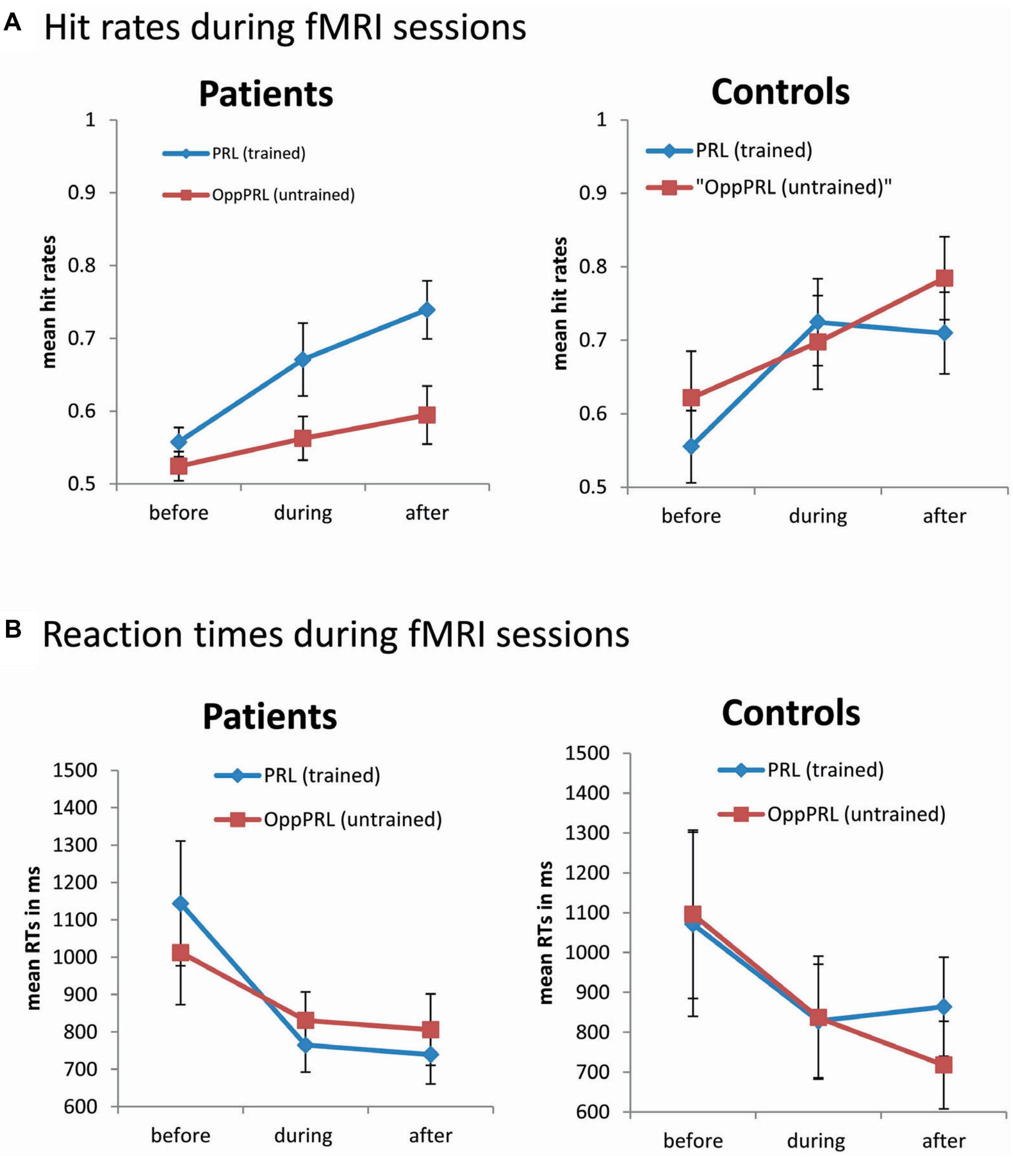

FIGURE 4 | Mean hit rates (A) and reaction times (B) in the PRL (trained location, blue symbols) and the OppPRL (untrained location, red symbols) for the patient (n = 11, left panel) and the control groups (n = 10, right panel) before the first, fourth and after the sixth training session. Error bars show ±1 SE of the mean. Data were collected during the fMRI sessions, with individually fixed SOA. An omnibus ANOVA revealed a significant effect of session [$F(1,19) = 13.6$; $p = 0.002$] for the dependent variable hit rate, but no main effect of target location nor group. Additionally hit rates exhibited a significant interaction between target location (PRL, OppPRL) and group [$F(1,19) = 4.6$; $p = 0.045$]. For reaction times an omnibus ANOVA revealed again a main effect of session [$F(2,38) = 6.6$; $p = 0.003$], but no main effect for location nor group. Also no significant interactions were apparent.

OppPRL) in the patient group [$F(1,10) = 8.78$; $p = 0.014$]. Accordingly, the hit rate was significantly higher when the TDT target was located in or near the PRL compared to when it was located in the opposite visual hemifield. The control group showed no significant location effect. Both groups, patients [$F(2,20) = 9.5$; $p = 0.001$] and controls [$F(1,9) = 5.7$; $p = 0.04$], showed a significant session effect, but no significant interactions.

For reaction times during the fMRI sessions we observed again a main effect of session [$F(2,38) = 6.6$; $p = 0.003$], indicating a decrease of reaction times with training, but no effect for location nor group (see **Figure 4**, lower panel). No significant interactions were apparent.

TRANSFER OF TDT TRAINING

The results of the FrACT, analyzed with paired t-tests, showed a trend toward improvement of the Vernier task [$t(11) = 2.22$; $p = 0.048$, not corrected for multiple comparisons; otherwise $p = 0.2$, Bonferroni corrected] in the patient group (see **Figure 5**). Here it has to be noted that an additional patient (P2) was not able to perform the task before the perceptual training, but achieved a

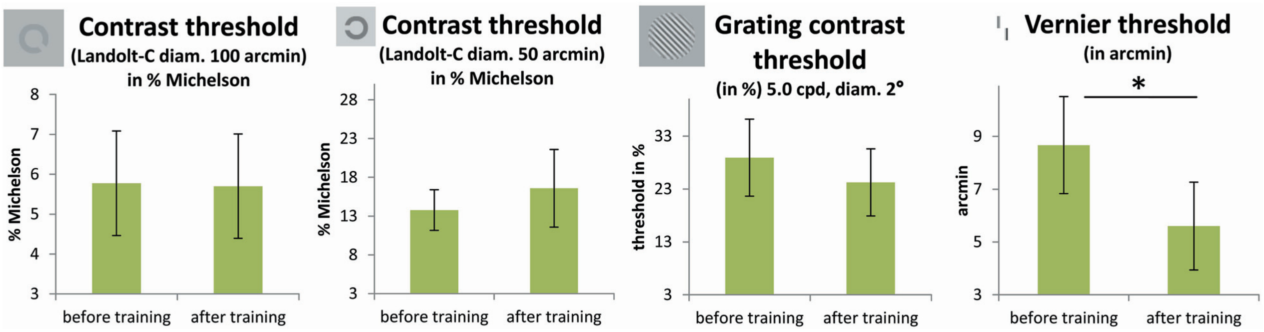

FIGURE 5 | Results from the FrACT (Bach, 1996). Two Landolt-C tests (with 50 and 100 arcmin optotypes, in % Michelson contrast), a grating contrast test and a Vernier test were conducted. Improvements in patients' performance with training were only apparent in the Vernier task [$t(11) = 2.22$; $p = 0.048$, not corrected for multiple comparisons; $p = 0.2$ Bonferroni corrected]. One patient (P2) was not able to perform the task before the perceptual training, but achieved a threshold of 5.58 arcmin in the task after the perceptual training. One patient (P7) was not able to perform the Landolt-C contrast sensitivity test, neither before nor after TDT training. Error bars show ±1 SE of the mean.

Table 2 | Correlation coefficients (*r*) and *p*-values (*p*; not corrected for multiple comparisons) between initial fixation stability (percentage of fixations within 2° of fixation target) and difference in mean percent signal change (upper rows) before the first and fourth training session, as well as before the first and after the sixth training session for PRL and OppPRL target locations.

Delta % signal change	Difference "during–before"		Difference "after–before"	
	r	***p***	***r***	***p***
PRL	0.155	0.629	0.531	0.075
OppPRL	0.042	0.896	0.444	0.148
Delta Hit rate				
PRL	**0.730**	**0.007**	0.361	0.275
OppPRL	−0.145	0.652	0.015	0.966

Significant values are shown in bold font. These values are based on patient data only (n = 12).

threshold of 5.58 arcmin in the task after the perceptual training. Contrast sensitivity measures did not differ before and after training, neither for Landolt-C with 100 arcmin diameter [$t(11) = 0.05$; $p = 0.96$] nor with 50 arcmin diameter [$t(11) = -0.5$; $p = 0.62$], nor for the contrast grating test [$t(12) = 0.85$; $p = 0.41$, all *p*-values not corrected for multiple comparisons]. One patient (P7) was not able to perform the Landolt-C contrast sensitivity test, neither before nor after TDT training. The control group did not improve significantly with training in any subtests of the FrACT.

Compared to values acquired before TDT training, patients yielded higher scores in the VFQ in the category of social functioning [$t(12) = 2.79$; $p = 0.016$, not corrected for multiple comparisons; otherwise $p = 0.18$, Bonferroni corrected] after training. All other scales showed no significant differences before and after training.

EFFECT OF FIXATION STABILITY IN BEHAVIORAL DATA

When we correlated fixation stability before training (percentage of fixations around 2° visual angle of the fixation point) and the development of hit rate in the patient group, separately for the trained PRL and the untrained OppPRL, we found a significant positive correlation with difference in hit rate between before and during training, but only for the trained PRL ($p = 0.007$, not corrected for multiple comparisons; otherwise $p = 0.014$, Bonferroni corrected; see **Table 2**; **Figure 6**). A correlation between fixation stability and development of reaction times in the patient group, separately for PRL and OppPRL, revealed no significant results.

fMRI DATA

Patients exhibited a trend for increased percent signal changes from the second to the third fMRI session which was similar for the PRL and OppPRL projection zones in the early visual cortex, but which failed to reach statistical significance (see **Figure 7**, upper panel). While patients showed no obvious change in percent signal change from the first to the second fMRI session control subjects revealed an increase of percent signal change from the first to the second fMRI session in both the trained and untrained projection zones in the early visual cortex. From the second to the third fMRI session, patients exhibited a modest increase in BOLD signal, whereas controls showed a decrease for the signal in the trained PRL associated area and a stabilization of the OppPRL associated area.

A repeated-measures ANOVA revealed no significant effect of session [$F(2,40) = 1.7$; $p = 0.20$], nor an effect of location [$F(1,20) = 0.02$; $p = 0.89$] or group [$F(1,20) = 2.09$; $p = 0.16$] in the omnibus ANOVA. Also no interactions were significant. One-factorial ANOVAs for the factor session for the patients and controls separately with target locations either PRL or OppPRL indicated a marginally significant quadratic trend (blue line in **Figure 7**, upper right panel) for the control group [$F(1,9) = 5.05$; $p = 0.05$, not corrected for multiple comparisons; otherwise $p = 0.1$, Bonferroni corrected]. Moreover, a non-significant linear trend (blue line in **Figure 7**, upper left panel) was apparent for the patient group [$F(1,11) = 3.04$; $p = 0.11$, not corrected for multiple comparisons; otherwise $p = 0.22$, Bonferroni corrected] with respect to the effect of training (sessions performed before,

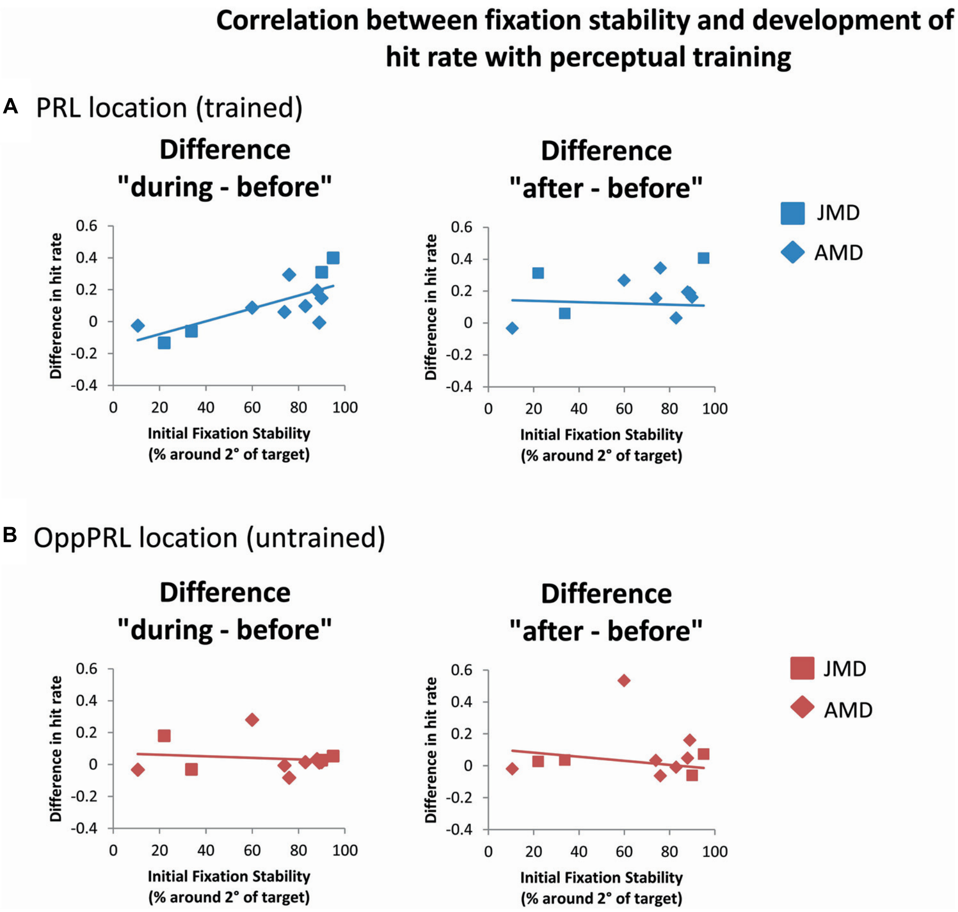

FIGURE 6 | Correlations between the difference in hit rate (before the first and fourth training session ("during"), left panel, as well as before the first and after the sixth training session ("after"), right panel, and initial fixation stability for the trained PRL location (A) or the untrained OppPRL location (B) for patient data only. Squares correspond to values from JMD patients, diamonds to those from AMD patients. Correlation coefficients for the trained PRL location are $r = 0.730$ ($p = 0.007$; $p = 0.014$, Bonferroni corrected) for the difference in hit rate "during–before," and $r = 0.361$ ($p = 0.275$) for the difference in hit rate "after–before." For the untrained OppPRL location correlation coefficients are $r = -0.145$ ($p = 0.652$) for the difference in hit rate "during–before," and $r = 0.015$ ($p = 0.966$) for the difference in hit rate "after–before."

during and after) on percent signal change in the PRL projection zone in the early visual cortex. For the OppPRL condition (red lines in **Figure 7**, upper left and right panel), no such trends were observed ($p = 0.42$ and $p = 0.35$, respectively, not corrected for multiple comparisons).

EFFECT OF FIXATION STABILITY IN FMRI DATA

When we correlated fixation stability (percentage of fixations around 2° visual angle of the fixation point) and the development of BOLD signal in visual cortex, we found a positive correlation between fixation stability and difference in percent signal change before and after training that just failed to reach significance ($p = 0.075$, not corrected for multiple comparisons; otherwise $p = 0.15$, Bonferroni corrected; see **Table 2**; **Figure 8**).

As becomes evident from **Figures 6** and **8**, a gap in fixation stability could be observed between three patients (P5, P6, and P7) with fixation stability <40% and the remaining patients, who exhibit more stable fixation (≥60%). After excluding the data from these three patients with fixation stability <40%, an ANOVA of BOLD percent signal change revealed a significant effect of training session [$F(2,16) = 4.1$; $p = 0.038$; see **Figure 7**, lower panel] within the patient group.

DISCUSSION

In this study we investigated whether patients with central vision loss can benefit from perceptual learning. We wanted to determine whether patients with central vision loss can be efficiently trained at their eccentric PRL to perform a challenging TDT and if such a learning effect might be reflected in fMRI-BOLD signal changes in the respective projection zone in early visual cortex. Further we investigated whether the gains accruing via TDT training at the PRL could generalize to other aspects of visual performance and vision-related aspects of quality of life.

Both patients and control subjects exhibited a typical learning effect on the TDT which was indicated by a significant reduction in SOA in both groups. This result is consistent with the classical findings of Karni and Sagi (1991), Schwartz et al. (2002), or Yotsumoto et al. (2008). Behavioral data acquired during fMRI

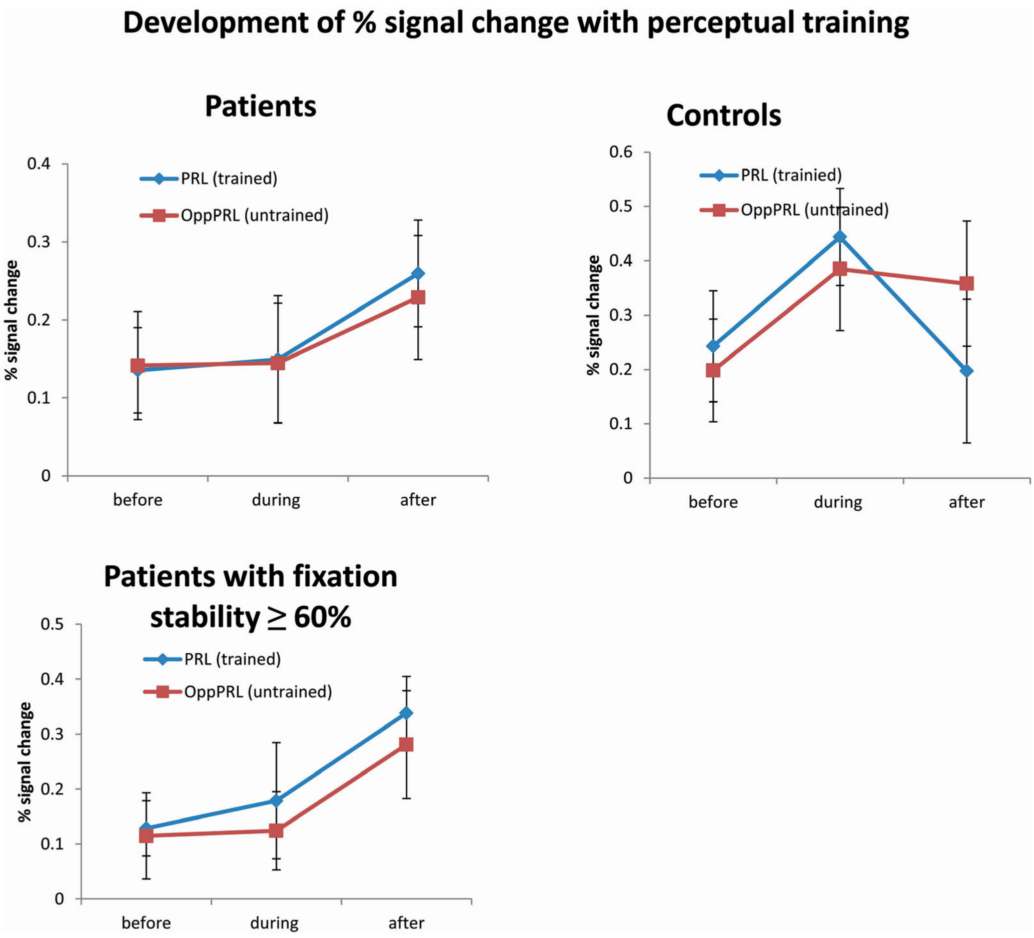

FIGURE 7 | Mean of percent signal change in the projection zones in the early visual cortex of the PRL (trained location, blue symbols) and the OppPRL (untrained location, red symbols) for patients ($n = 12$) and controls ($n = 10$; upper row) before the first, fourth and after the sixth training session. An omnibus ANOVA revealed no significant effects. The lower row shows these values for those patients who exhibited fixation stability over 60% ($n = 9$). Here, a repeated-measures ANOVA within the patient group revealed a significant effect of training session ($p = 0.038$). Error bars show ±1 SE of the mean.

indicated a significant effect of training on hit rates and reaction times. Considering the two groups (patients, controls) separately there was a significant effect of training in the patient group for the factor location (PRL, OppPRL), which was not the case for the control group. We further observed a significant interaction between target location and group with respect to hit rates (see **Figure 4A**). Before training patients showed similar hit rates for targets presented at the PRL and OppPRL locations in the visual field. During training their hit rate increased for targets presented at the PRL compared to when they were presented at the location OppPRL. In contrast control subjects showed also an increase in hit rates with training but no difference between the trained and untrained locations. One explanation for this finding could be that patients use their PRL additionally in their daily life which could influence the training procedure and efficiency. Therefore it might also be more intuitive for the patients to train on targets presented in their PRL since the PRL functions as a pseudo fovea, which is not the case for the control subjects.

In the fMRI results, we found neither a significant effect of session, nor of location nor of group in the omnibus ANOVA. We could observe a linear trend for the factor "training session" at the signal in the PRL projection zone in early visual cortex in the patient group while the control group seemed to exhibit a quadratic trend in that area. McGovern et al. (2012) claim that the low signal change which is sometimes found in studies dealing with perceptual learning in early visual areas (e.g., Ghose et al., 2002) might not be associated with the increase of performance directly. This suggestion also seems to hold here, since we could find clear learning effects according to SOA, hit rates and reaction times but only subtle changes of the amplitude of the BOLD signal with training. McGovern et al. (2012) argue that probably more brain areas than the early visual cortex might be involved in perceptual learning. The linear trend in patients of the signal in the PRL associated area in early visual cortex according to training is expressed in an increase of signal from the second to the third fMRI session. When we restricted our analysis to the subgroup of patients with high fixation stability (≥60%), we found a

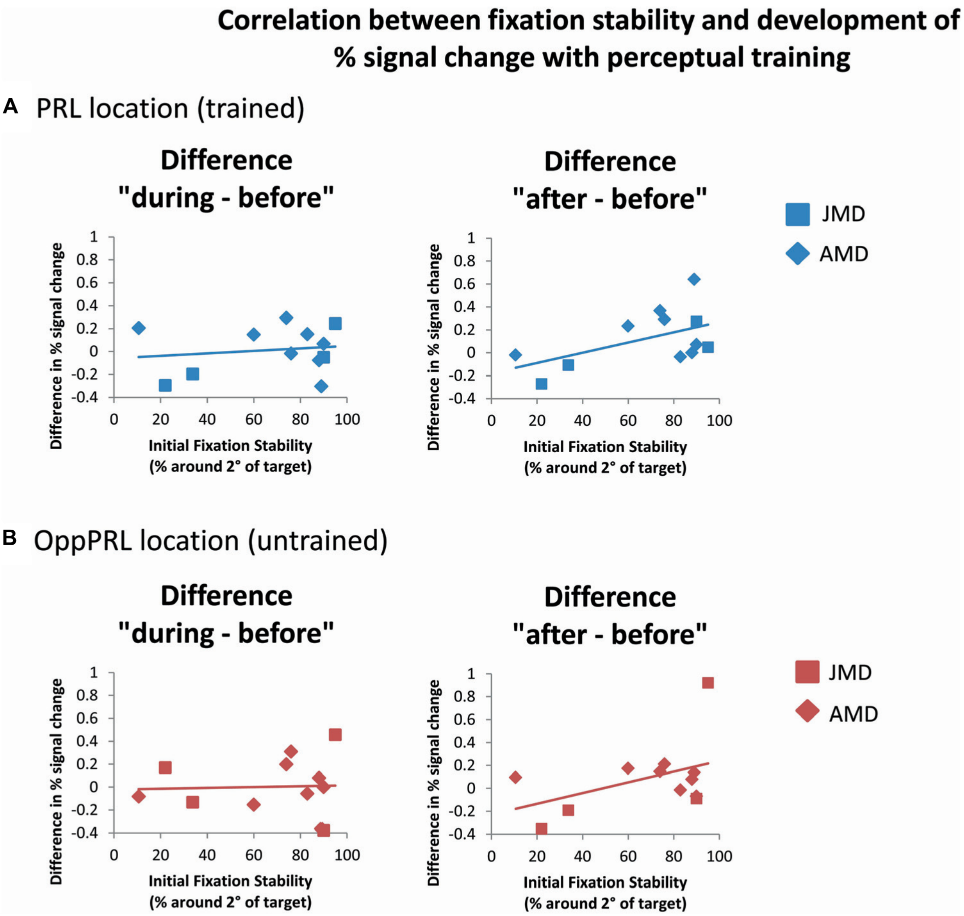

FIGURE 8 | Correlations between the difference in percent signal change (before the first and fourth training session ("during"), left panel, as well as before the first and after the sixth training session ("after"), right panel, and initial fixation stability for the trained PRL location (A) or the untrained OppPRL location (B) for patient data only ($n = 12$). As in **Figure 6**, squares correspond to values from JMD patients, diamonds to those from AMD patients. Correlation coefficients for the trained PRL location are $r = 0.155$ ($p = 0.629$) for the difference in percent signal change "during–before," and $r = 0.531$ ($p = 0.075$) for the difference in percent signal change "after–before." For the untrained OppPRL location correlation coefficients are $r = 0.042$ ($p = 0.896$) for the difference in percent signal change "during–before," and $r = 0.444$ ($p = 0.148$) for the difference in percent signal change "after–before."

significant increase of BOLD response in early visual cortex with training. This result is consistent with several other studies which report an increase in neural signal in early visual cortex with training. Frank et al. (2014) show also an increase of percent signal change over learning sessions while subjects trained in a challenging perceptual learning task. The time course of the neural signal referring to the trained location in early visual cortex in the control group follows the pattern observed in the study by Yotsumoto et al. (2008) who also used a TDT. Similar to the trend of the present results for the control group, they found an increase of signal from the pre-training session to the second fMRI session followed by a slight decrease of signal in the post-training session. Interestingly this was only the case for the PRL associated area in early visual cortex where subjects received training and not for the untrained OppPRL associated area. As described in the Introduction, the increase in BOLD signal observed in the initial phase of learning suggests the recruitment of respective brain areas in early visual cortex (Yotsumoto et al., 2008). The decline in the BOLD signal would accordingly correspond to a consolidation process. In our study the control subjects appeared to have reached the consolidation phase already after the first post-training session, while patients still showed an increase in BOLD-signal up to the second post-training session.

Considering the patients' fixation stability there was on the one hand a significant positive correlation between fixation stability and hit rate (difference during and before training) if the target appeared at the position of the PRL and on the other hand a positive correlation between fixation stability and percent signal change (difference after and before training) if the target was located in the PRL projection zone in early visual cortex, that just failed to reach significance. There was further a significant effect of session when three patients, who exhibited extremely poor fixation stability, were omitted from analysis. This finding suggests that fixation stability might be a prerequisite for a successful learning curve in perceptual learning. Moreover, other visual tasks seem to be affected by fixation stability. Plank et al.

(2013) reported that patients suffering from hereditary macular dystrophies (JMD) with stable eccentric fixation performed better in a visual search task than patients with less stable eccentric fixation. Interestingly this was also the case, if the target stimuli were not in or near the position of the PRL. Fixation stability has also usually been shown to be positively correlated with reading speed in patients with central vision loss (e.g., Sunness et al., 1996; Trauzettel-Klosinski and Tornow, 1996; Nilsson et al., 1998; Nilsson et al., 2003; Crossland et al., 2004; Rubin and Feely, 2009). Please note that, since eye movements were not recorded during fMRI sessions, we had to assume that the level of fixation stability measured during psychophysical testing was also evident during fMRI testing.

The FrACT sensitivity (Bach, 1996) revealed a training associated improvement in the patient group for the Vernier subtest. However, it should be noted that the significance level of this effect does not survive correction for multiple testing, suggesting that caution must be exercised here and that further studies are warranted. The other tasks seemed not to be influenced by the training intervention. The reason for the marginal improvement in the Vernier task might be due to the similarity among the stimuli in the TDT and the Vernier task.

With respect to the transfer of TDT training the findings reported above suggest that caution should be exercised when interpreting their implications with respect to potential application in visual rehabilitation. Obviously studies with larger patient samples are required that assess the amount of transfer of perceptual training at the PRL to other visual functions. The addition of a “sham” training group would establish the extent to which placebo effects influence perceptual learning in select patient groups. With respect to the effects of oculomotor and eccentric-fixation training in a similar patient group, we could recently rule out that the beneficial effects of training could be explained by a general placebo effect (Rosengarth et al., 2013).

Earlier studies have pointed to a persistence of perceptual learning effects. Polat et al. (2004) found a two to fourfold increase in contrast sensitivity in the amblyopic eye of trainees 12 months after training on a flanker-task had ended. Our group has recently shown that in healthy participants the effects of perceptual learning of a difficult conjunction visual search task are still evident at 9-month follow-up (Frank et al., 2014). We are currently retesting the patients and controls of the present study with respect to this aspect of the results (Plank et al., unpublished observations).

With respect to the results of the VFQ, patients exhibited higher scores after training on the category of social functioning, which considers personal contact und communication with other people. Šiaudvytytė et al. (2012) report differences in quality of life of AMD patients compared to age-matched control subjects in several categories of the VFQ including social functioning. Possible implications of these trends require further investigation in larger patient samples.

CONCLUSION

In this study we trained patients with central vision loss in a TDT, with the target appearing on their respective PRL, and compared their results to an age-matched normal sighted control group. We were also interested in the neural correlates of the learning process in the visual cortex. Although the task appeared to be more difficult for the patient group than for the control group, patients were able to do the task and showed significant learning effects. Patients with stable eccentric fixation showed better performance accompanied by a larger increase in BOLD-signal in the PRL projection zone of the early visual cortex. Owing to our strict inclusion and exclusion criteria with respect to disease manifestation in the study and companion eye of our patients, our results are limited to the present patient sample, thereby demanding further verification of beneficial effects of perceptual training in patients with different forms of macular disease. Nevertheless, the present results support the idea that perceptual learning can improve the efficient use of the PRL location in patients with central vision loss.

ACKNOWLEDGMENTS

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A matter of time: improvement of visual temporal processing during training-induced restoration of light detection performance

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The issue of how basic sensory and temporal processing are related is still unresolved. We studied temporal processing, as assessed by simple visual reaction times (RT) and double-pulse resolution (DPR), in patients with partial vision loss after visual pathway lesions and investigated whether vision restoration training (VRT), a training program designed to improve light detection performance, would also affect temporal processing. Perimetric and campimetric visual field tests as well as maps of DPR thresholds and RT were acquired before and after a 3 months training period with VRT. Patient performance was compared to that of age-matched healthy subjects. Intact visual field size increased during training. Averaged across the entire visual field, DPR remained constant while RT improved slightly. However, in transition zones between the blind and intact areas (areas of residual vision) where patients had shown between 20 and 80% of stimulus detection probability in pre-training visual field tests, both DPR and RT improved markedly. The magnitude of improvement depended on the defect depth (or degree of intactness) of the respective region at baseline. Inter-individual training outcome variability was very high, with some patients showing little change and others showing performance approaching that of healthy controls. Training-induced improvement of light detection in patients with visual field loss thus generalized to dynamic visual functions. The findings suggest that similar neural mechanisms may underlie the impairment and subsequent training-induced functional recovery of both light detection and temporal processing.

Keywords: blindness, temporal resolution, reaction time, visual restoration, training, plasticity, visual field, topography

INTRODUCTION

Visual signals contain information on many different aspects of our environment. Most prominently, intensity (or contrast), spatial configuration, and temporal aspects are important dimensions of visual perception. Traditionally, research on temporal aspects of perception was either concerned with higher cognitive mechanisms, for instance the estimation of interval duration—which we term "time perception"—or it examined basic psychophysical aspects of temporal parameters and their connection with basic perceptual functions (Wittmann, 1999, 2009)—which we term "temporal processing." In the study presented here we are exclusively concerned with the latter.

The two major aspects of temporal processing are the speed of visual perception as such—which can be measured, for instance, by simple visual reaction times (RTs; as explained in the methods section)—and the temporal resolution of visual perception—which can be measured for example by flicker resolution tasks. These two aspects in the temporal domain ("*when* do I perceive?" and "*how fine-grain* is the perception?") correspond basically to analogous concepts in the spatial domain ("where do I perceive?"—i.e., localization tasks—and "how fine-grain is the spatial resolution?"—i.e., can the perceiver discriminate between location A and B and what is the minimal distance between A and B that still allows that discrimination).

So far, there is no agreed-upon theoretical framework that may explain how different dimensions of visual processing (intensity, space, time) are related on the neural level: for example, it is not fully understood how they are integrated into a coherent percept, though neural synchronization seems to be involved (e.g., Singer and Gray, 1995). Particularly, the mechanisms underlying processing of time-related information in the brain and their interactions with early sensory processes are still poorly understood

(Ivry and Spencer, 2004; Mauk and Buonomano, 2004; Poggel and Strasburger, 2004; Poggel et al., 2012a,b; see Wittmann, 1999, 2009 for a review).

Numerous studies have provided evidence for close connections between visual stimulus intensity and temporal visual functions, e.g., using RTs or flicker detection (Kelly, 1972; Ulrich et al., 1998). However, most of these studies suffer from methodological shortcomings: in many cases, measurements were limited to the fovea and thus neglected the spatial dimension of vision and characteristics of the peripheral visual field (Poggel and Strasburger, 2004; Strasburger et al., 2011; Poggel et al., 2012a,b). Moreover, the employed flicker detection tasks were dependent on adaptation and modulation depth (Tyler, 1985, 1987; Treutwein, 1989; Tyler and Hamer, 1990; Treutwein and Rentschler, 1992).

In a normative study with a large sample of healthy subjects (Poggel et al., 2012a,b), we therefore took all three dimensions into consideration: stimulus intensity (by measuring perimetric luminance thresholds), spatial aspects (by performing measurements across the visual field), and temporal aspects (by measuring RTs and temporal resolution independently of the modulation depth). Interestingly, there was a clear dissociation between perimetric thresholds, RTs, and temporal resolution thresholds: not only did the maps of these three variables show different topographies, but there was also dissociation across the life span, i.e., the three variables showed different topographical patterns of aging. It thus seems that, as explained above, RTs and temporal resolution are based on different neural mechanisms: while (simple) RTs mainly depend on the speed of neural transmission (through the visual system and subsequently the motor system), temporal resolution can be assumed to depend on a read-out mechanism for separating two bursts of action potentials (corresponding to the two light pulses), the success of which depends on the degree of overlap between the first and second burst and thus on the signal-to-noise ratio rather than on the speed of transmitting the activation along the visual pathway (see Figure 6 in Poggel et al., 2006). Furthermore, the relationship between intensity measures (like light detection thresholds and contrast thresholds), and RTs or temporal resolution in the periphery of the visual field is not predicted by their relationship when measured solely in the fovea (as is done in most studies in the literature).

To further investigate potential connections or dissociations between visual and temporal functions, we looked at patients with vision loss resulting from lesions of the visual pathway. Experimental evidence (Strasburger and Rentschler, 1996; Gothe et al., 2000; Bola et al., 2014) as well as subjective complaints of patients (Poggel, 2002) had pointed earlier to a topographic mismatch between perimetric thresholds (the gold standard in clinical testing) and other visual and temporal functions, e.g., RTs, that do not play a role in standard clinical testing. When we investigated a patient sample (Poggel et al., 2011) with the same methods as in the normative study mentioned above (Poggel et al., 2012a,b), we found deficits of temporal processing (RTs and temporal resolution thresholds) across the entire visual field, i.e., even in areas that were perimetrically intact. Furthermore, performance of temporal processing within the defective visual field depended on the degree of intactness (or defect depth) of the respective visual field location. Thus, damage to the visual pathway also affects temporal processing of visual stimuli, and to a certain extent those deficits do not correspond with maps of perimetric light detection performance.

The overlap or dissociation of visual function maps is not only of interest for elucidating basic mechanisms of visual integration or for the planning of diagnostic procedures, but it is also clinically relevant with respect to processes of visual brain plasticity and treatment of vision loss. Studies on perceptual learning in healthy populations (Fine and Jacobs, 2002; Seitz and Watanabe, 2005; Jüttner and Rentschler, 2008; Gilbert et al., 2009; Fahle, 2009) and also clinical studies with visually impaired patients (van der Wildt and Bergsma, 1997; Kasten et al., 1998; Kerkhoff, 1999; Sabel, 1999, 2008; Poggel, 2002; Julkunen et al., 2003; Poggel et al., 2004; Sahraie, 2007; Huxlin, 2008; Bergsma and van der Wildt, 2010; Sabel and Gudlin, 2014) have demonstrated training-induced improvement of function, particularly of light detection performance (see Sabel et al., 2011, for a review). Perceptual learning experiments in healthy subjects have shown that the observed improvements are often specific to a visual function or to the visual field region targeted by the training (Fine and Jacobs, 2002; Fahle, 2009; Strasburger et al., 2011). Similarly, although previous light-detection training studies with patients showed some generalization to other functions like color and form discrimination (Kasten and Sabel, 1995; Kasten et al., 2000), a specific training of that particular function had a much more pronounced effect (Poggel, 2002).

The findings of an overlap as well as dissociations between light detection and temporal processing functions in healthy populations and in patients—but also previous evidence for at least some generalization in perceptual learning and training-induced recovery of visual function—led us to ask whether and to what extent vision restoration training (VRT) targeted at recovery of light detection would also have beneficial effects on temporal processing in patients with visual field loss. The potential benefits of this study would be twofold: on the one hand, finding "positive side effects" of light-detection training on dynamic visual functions would be of direct use to patients complaining about difficulties with dynamic vision; on the other hand, from a basic science perspective, the findings would provide a basis for investigating whether or not the intensity and the temporal aspect of vision may have a common neural basis.

MATERIALS AND METHODS

PATIENT SAMPLE AND HEALTHY CONTROL GROUP

Nine patients with visual field loss participated in the study (three female; mean age 42 years ± 4.5 years, range 22–62 years; **Table 1**).

Exclusion criteria for the study were dementia, hemispatial neglect, severe attentional deficits (especially reduced vigilance), depression and other psychiatric disorders, as well as visual impairment resulting from ophthalmic diseases. All subjects gave their informed consent for participation in the study. The experimental design had been approved by the local ethics committee and was in accordance with the guidelines of the Declaration of Helsinki.

Patients' performance was compared to normative data from 95 healthy participants who had been tested with the same set of

Table 1 | Patient characteristics.

Patient number	Age (years)	Gender (female/male)	Lesion age (months)	Hemisphere (left/right)	Location of lesion	Cause of lesion	Vision loss
2	35	Female	60	Right	Posterior artery	Aneurysm clipping	Hom. hemianopia left
3	62	Female	27	Right	Medial artery (?)	Infarction	Hom. hemianopia left
4	49	Male	36	Optic nerve	Optic nerve	Tumor surgery	Bilateral, heteronymous
5	43	Male	11	Right	Optic radiation	Infarction	Hom. quadrantanopia
6	22	Female	8	Right	Posterior artery	Infarction	Hom. quadrantanopia
7	44	Male	87	Right	Posterior artery	Infarction	Hom. hemianopia
8	23	Male	42	Left	Medial artery	Trauma	Hom. hemianopia
9	51	Male	10	Left	Posterior artery (?)	Bleeding	Hom. hemianopia
12	44	Male	27	Right	Posterior artery (?)	Infarction	Hom. hemianopia

methods in the Tölz Temporal Topography Study (Poggel et al., 2012a,b).

Patients served as their own control group: only patients with chronic, stable vision loss were included in this study. Stability of visual field size was ascertained by repeated visual field testing over a period of several weeks or months before and after training. Since the effectiveness of the training program had been shown earlier in two randomized, placebo-controlled trials (Kasten et al., 1998; Sabel and Gudlin, 2014), we did not include a placebo control group here.

DOUBLE-PULSE RESOLUTION

For assessing temporal resolution in the visual field, we measured double-pulse resolution thresholds (DPR; Treutwein, 1989, 1995, 1997; Treutwein and Rentschler, 1992). Participants were sitting in a darkened room (illuminance 1.5 lx), their head positioned on a chin rest at 30 cm viewing distance in front of a test screen. Stimuli were presented with microsecond accuracy on a 17-inch *x-y-z* monitor (HP 1310) that was controlled by D/A converters ("point plot buffer"; G. Finlay, Edmonton, Canada) connected to a PC.

A cross-hair was displayed before each trial. During a trial, nine rectangular white light stimuli (luminance: 215 cd/m^2, size: 1.15°) were presented simultaneously on the screen, one in the center, and the others on a circle around it at the intersections with the main horizontal, vertical, and 45° meridians. Eight of the nine stimuli within a trial served as distracters and were presented continuously, while the target was interrupted by a temporal gap which resulted in the perception of a short flicker of that stimulus for gap durations above threshold. For each trial, the participant verbally indicated the target position, and the experimenter entered the response using the computer keyboard so that the participant could keep their eyes fixated at the center of the screen. Fixation was controlled with an eye tracking device (IViewX, Sensomotoric Instruments, Teltow, Germany) and by the experimenter observing the subject's eye position via a mirror. The new trial was started when the subject was ready with stable fixation at the center of the screen.

The YAAP maximum-likelihood algorithm (Treutwein, 1995, 1997) controlled the gap duration between the two light pulses of the target stimulus. The starting point was set to 80 ms which was well above threshold for intact positions in the visual field. DPR thresholds were determined independently of each other in an interleaved fashion; target positions varied randomly from trial to trial. For stabilizing the adaptive procedure, the first 10 trials were non-adaptively presented according to the method of constant stimuli and an *a priori* distribution was created by calculating the likelihoods for these responses. These responses were included in the final estimates. Guessing resulted in an *a priori* ceiling value of >100 ms at the blind locations in the visual field. The first light pulse of the target stimulus had 80 ms duration, the second (after the gap) 280 ms (see Treutwein, 1989; Treutwein and Rentschler, 1992, for details on stimulus parameters). The distracters were presented simultaneously with the target so that their duration matched that of the complete target stimulus including the gap. Note that targets and non-targets appeared equal in brightness since they were well above the summing duration in Bloch's law (Treutwein, 1989; Treutwein and Rentschler, 1992).

A test block was ended when all nine thresholds were determined to a pre-specified confidence interval containing the threshold at 85% probability which took approximately 140–280 trials (between 10 and 20 min test duration). Eight blocks of trials were performed per subject. Within a block, the eccentricity of the peripheral stimuli, i.e., the ring radius, was constant. Four blocks were carried out with ascending ring radius of 2.5°, 5°, 10°, and 20°, respectively, followed by another four blocks in reverse order of eccentricities to balance series effects. Each eccentricity block thus occurred twice. DPR threshold maps were created by combining the results from test blocks of four eccentricities into an interpolated map (see below).

LIGHT DETECTION AND REACTION TIME MAPS

Visual field maps were acquired for each eye separately using conventional static perimetry (Octopus 101 Perimeter, Interzeag/Haag Streit, Koeniz-Berne, Switzerland). Subsequently, a high-resolution computer-based campimetric test (HRP, Nova Vision GmbH, Magdeburg; see Kasten et al., 1997) was used for the acquisition of detailed light detection maps and RT maps under the same standardized conditions described above for DPR testing. A PC with a 17′ screen (horizontal size: ±29°, vertical size: ±23°, background luminance: 26 cd/m^2) was used for presentation of the stimuli (circular white, luminance: 96 cd/m^2, size: 0.76° visual angle, duration: 150 ms). Viewing was binocular in all patients except in the subject with optic nerve lesion who was tested on his left eye only. Stimuli were presented in random sequence at 474 positions on the screen. The fixation mark was positioned on the screen such that about half of the stimuli were situated in the blind field. The subject pressed the space bar on the computer keyboard whenever a stimulus was detected. Feedback of correct responses and false alarms, respectively, was provided by a high vs. low tone following the response. Stable fixation was ascertained by requiring the subject to detect a change of the fixation point's color from equiluminant green to yellow (Kasten et al., 1997). Additionally, the eye position was recorded with an eye-tracker (see above), and it was monitored by the experimenter via a mirror.

Detected and missed stimuli were both registered by the test and mapped by the software. For detected stimuli, the RT was recorded. Results from five high-resolution campimetric tests were superimposed. This allowed computing detection probabilities at each location so that areas of residual vision near the border of the blind area with a stimulus detection rate between 20 and 80% could be mapped (see Poggel, 2002; Poggel et al., 2004). Subregions of areas of residual vision with 20, 40, 60, and 80% detection rate, respectively, were further outlined to reflect the defect depth or degree of impairment. RTs were averaged separately for each subregion. The same categorization was also used for comparison of DPR thresholds between regions with varying degree of lesion.

TRAINING PROCEDURE

Based on the size and location of the areas of residual vision, each patient received an individualized training program (VRT, Nova Vision, Magdeburg, Germany) that provided stimulation focused on the border of the defect, i.e., on the areas having the largest probability of training-induced improvement (Kasten et al., 1998; Poggel et al., 2004, 2008). Stimulus size, fixation control, and response procedures were identical to those of the HRP visual field test described above. Training stimuli appeared on the computer screen, increasing in brightness over a period of 2000 ms. Each training session lasted approximately 15–20 min and comprised 250 training stimuli. The patient performed three training units of 56 sessions each, so that one training unit was completed in about one calendar month if the patient complied with the recommended two sessions per day. The training software provided feedback on the number of stimuli detected after each session. After each training unit, the patient returned to the laboratory for a control examination consisting of a short interview, a visual field test, and the analysis of the training data, followed by an adjustment of the training area to accommodate any progress the patient had made. After the third training unit, post-training measurements were performed which were essentially identical to the pre-training baseline examinations described above.

DATA ANALYSIS

Each DPR test block with a specific eccentricity of the peripheral test location was presented twice: once in a sequence of ascending eccentricities and the second time in a sequence of descending eccentricities over test blocks. There was no significant difference between the DPR threshold values from the first and second test at the corresponding eccentricities. Therefore, the respective test results were averaged to increase reliability.

Raw data from DPR, campimetric, and perimetric tests, respectively, were entered into statistical software for data analysis (Microsoft Excel and SPSS Version 15, Chicago, IL, USA) and subsequently plotted with a Matlab script (see Gothe et al., 2000), with linear interpolation between average values at all target positions (Matlab Version 5.3, The MathWorks, Natick, MA, USA).

To determine the influence of eccentricity on performance, we calculated the averages over all test positions for a specific ring (i.e., test eccentricity). For a global comparison between subjects, the overall average over all visual field positions was determined per subject, as well as individual performance in the defective and intact hemifield (note that there were some intact or partially intact positions remaining in the defective hemifield so that these values could be calculated). For the topographical comparison of DPR and RTs, we matched the less densely sampled DPR positions to those in campimetric tests, and selected for analysis only the RT values at corresponding positions. These values were averaged and imported into Matlab for plotting. For a topographical comparison between DPR and RTs within subjects, we calculated, for each patient, the correlations between the two variables at corresponding visual field locations, and these topographical correlations were then averaged across subjects.

For each of the subregions of areas of residual vision (20–80% detection rate in five campimetric tests), we next calculated average DPR thresholds and average RTs. RT values of all five campimetric tests were averaged. Note that any variation of RTs across the visual field reflects the sensory component only (including decisions on sensory data), since motor requirements are invariant, i.e., contribute only to the absolute level of RTs (Teichner and Krebs, 1972; Schiefer et al., 2001). Patient DPR and RTs were further compared to normative data of the respective age group of each patient.

Non-parametric tests were used to compare average values (Kruskal–Wallis test, Mann–Whitney *U*-test, Wilcoxon test) and to test for the significance of correlations (Spearman's Rho). With the small sample size of our patient group and for the comparisons between healthy participants and patients with differences in sample size, we preferred non-parametric statistics as the more appropriate way of testing in these cases. For the within-subjects comparisons between different eccentricities and between areas with different defect depth (i.e., detection probability at baseline), we used parametric testing with caution to be able to compare the averages, e.g., in the *post hoc* comparisons. RT data were analyzed with parametric methods (t-test for comparison of averages and Pearson's coefficient (r) for correlations). For multiple comparisons between or within subjects, ANOVAs were employed. All statistical testing was done with SPSS (Version 15.0, Chicago, IL, USA). The alpha-level was set to 0.05, two-tailed.

RESULTS

IMPROVEMENT OF LIGHT DETECTION PERFORMANCE

During the 3-month training period, the patient group improved slightly but significantly in their average light detection performance. The average number of detected light stimuli in the computer-based campimetric visual field test (HRP) increased from 247.5 (±25.8 SEM) to 272.9 (±26.5) stimuli (Wilcoxon test: $Z = 1.96$, $p = 0.05$; t-test: $t = 2.49$, $p = 0.01$; **Figure 1**). In the conventional perimetric test (Oculus), the overall number of absolute defects (no detection) and relative defects (detection

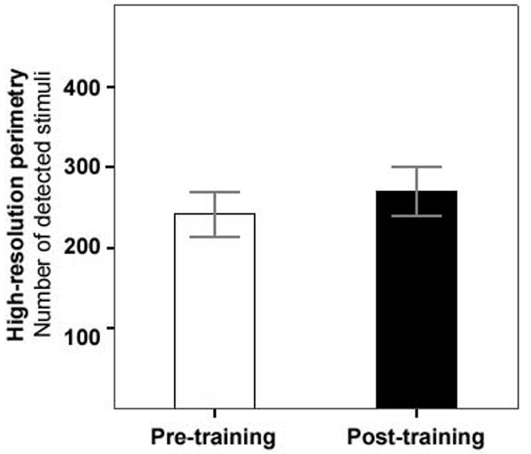

FIGURE 1 | Increase of light detection performance before vs. after training. Mean number of detected stimuli (out of 474) in computer-based high-resolution perimetry before (white bar) and after training (black bar), across the patient group (error bars represent SEM).

with increased threshold) in the visual field decreased over treatment, which was significant for the average number of absolute defects on the right eye only, however (before training: 44.8 ± 6.2, after training: 34.3 ± 7.1, Wilcoxon test: $Z = 2.52$, $p = 0.01$).

As expected from earlier studies, the variation of improvement between patients was large: several patients showed no improvement at all whereas others showed a strong treatment effect and a marked increase of intact areas. Patient 7 with a complete hemianopia and almost no areas of residual vision, for example, showed an unchanged visual field border before vs. after training. Patient 4 showed an intermediate (but statistically significant) success of visual field increase. Patient 9 with an incomplete quadrantanopia and large areas of residual vision had an almost intact visual field after training with respect to light detection (**Figure 2**).

IMPROVEMENT OF TEMPORAL RESOLUTION (DPR THRESHOLDS)

The group-mean DPR threshold over the entire visual field showed high variance and did not significantly change over the training period (DPR pre-training: 66.8 ± 6.6 ms, DPR post-training: 65.3 ± 7.4 ms; Wilcoxon test: $Z = 0.84$, $p = 0.40$; **Figure 3A**). However, when DPR thresholds in just the defective parts of the visual field (the hemifield or quadrant(s) containing the blind area) were compared, we found highly significant improvements (pre-training: 81.4 ms ± 2.4, post-training: 66.5 ms ± 3.7, Wilcoxon $Z = 2.64$, $p = 0.008$; **Figure 3B**).

The improvement of DPR thresholds did not depend on eccentricity (MANOVA: df = 4, $F = 0.32$; $p = 0.86$) but was instead influenced by the *degree of intactness* (or defect depth) of the respective position stimulated during treatment (MANOVA: df = 5, $F = 14.80$; $p < 0.001$). Particularly partially lesioned visual field areas (i.e., with pre-training detection rates between 20 and 80%)—which were at the same time the regions with the most prominent increase of light detection performance—showed the most pronounced reduction of DPR thresholds (**Figure 4A**).

Again, the variation of training effects between patients was considerable. Interestingly, the effects on temporal resolution and their topography were related to those of light detection, i.e., patients who improved in light detection typically also showed a decrease of DPR thresholds, and the improvements took place in roughly the same visual field locations (**Figure 2**). Conversely, patient 7 who showed no change of light detection performance (see **Figure 2**) also did not improve with respect to DPR thresholds (DPR pre: 46.9 ± 2.4 ms, DPR post: 49.9 ± 2.5 ms; Wilcoxon test: $Z = 0.95$, $p = 0.34$). Accordingly, there was no change in his DPR performance map as a result of training. Compared to healthy subjects of his age group he had normal DPR thresholds before and after training in his intact area. In contrast, patient 4 had markedly elevated DPR thresholds compared to his healthy age-matched control group, both before and after training. He improved only slightly (but not significantly) with respect to temporal resolution over the training period (DPR pre 92.1 ± 0.8 ms, DPR post: 90.9 ± 0.9 ms; Wilcoxon test: $Z = 1.40$, $p = 0.16$), i.e., there was a considerable dissociation of light detection and DPR threshold maps after training. Patient 9, who showed a strong improvement of light detection in the lower right quadrant (**Figure 2**) also improved significantly with respect to DPR thresholds (DPR pre: 48.2 ± 2.2., DPR post: 44.7 ± 2.1; Wilcoxon test: $Z = 2.20$, $p = 0.03$). DPR thresholds for this patient reached a normal level after training, both in the intact and in the previously defective visual field.

Before training, mean DPR thresholds (i.e., averaged across all visual field positions) were significantly higher for patients than for a sample of healthy subjects of all age groups (DPR-pre patients: 62.2 ± 1.7 ms, DPR healthy: 50.4 ± 0.9 ms, Mann–Whitney test: $Z = 9.53$, $p < 0.001$). Compared to the normally sighted controls, particularly, DPR thresholds were elevated in the patients' defective region of the visual field, but several patients also had increased thresholds even in perimetrically intact areas (see Poggel et al., 2011). After training, the difference of DPR thresholds between the patients and the healthy controls was significantly reduced. However, even after treatment, patients' DPR thresholds were still elevated compared to the healthy sample, although to a lesser extent (DPR-post patients: 61.7 ± 1.8 ms; Mann–Whitney test: $Z = 7.89$, $p < 0.001$). Again, the individual response varied: while several patients did not reach normal levels of temporal resolution even after training, other patients were within the range of their age-matched healthy controls even before training.

IMPROVEMENT OF SIMPLE VISUAL REACTION TIMES

RTs to simple light stimuli presented in the high-resolution campimetric test decreased by ~30 ms on average in the patient group over the period of training, although the difference missed significance due to the high variance between patients (RT pre-training ± SEM: 484.8 ± 37.6 ms, RT-post: 452.4 ± 26.5 ms; Wilcoxon test: $Z = 1.68$, $p = 0.093$; **Figure 3C**). Again, the improvement of RTs was much more pronounced (82 ms) and highly significant in the defective parts of the visual field (RT-pre: 531.7 ± 13.4 ms, RT-post: 449.9 ± 19.5 ms; Wilcoxon test: $Z = 2.90$, $p = 0.004$; **Figure 3D**). RT improvements were most pronounced in areas of residual vision.

As was the case for DPR thresholds, the reduction of RTs during training was independent of the eccentricity in the visual

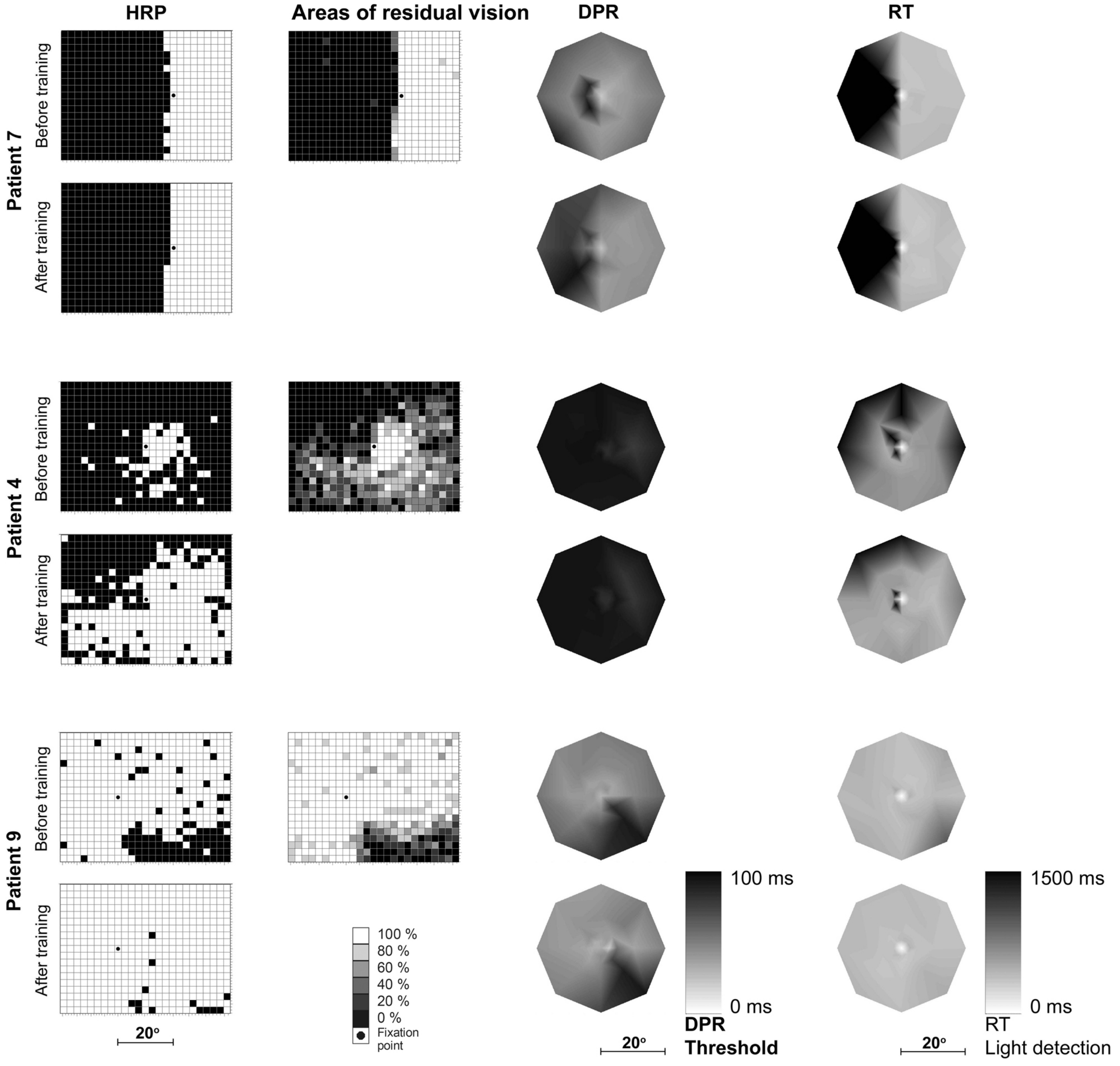

FIGURE 2 | Topography of light detection, DPR, and RTs before and after training. Typical examples of three patients with different magnitudes of change: no improvement (patient 7; first two rows), intermediate success (patient 4; middle two rows), and strong recovery (patient 9; bottom two rows) over 3 months of vision restoration training. For each patient, light detection performance in high-resolution perimetry (HRP; leftmost column) is shown before and after training. Black: blind field, white: intact field. The second column shows areas of residual vision (or transition zones) before training: shades of gray represent the probability of stimulus detection at each location. Double-pulse resolution (DPR) thresholds (third column) are plotted for the inner 20° radius of the visual field, before and after training (lighter areas represent better temporal resolution, i.e., lower thresholds). RTs in response to simple light stimuli in HRP before and after training (right column) are shown for the same visual field positions as for DPR measurements (lighter areas represent faster responses). Note that DPR and RT plots are shown in central fixation perspective while the visual field (detection) maps in the first two columns show the fixation position on the screen as presented in the original test.

field (MANOVA: df = 4, $F = 0.58$; $p = 0.98$). However, the pre-training light detection performance of the respective visual field position largely predicted the amount of improvement (**Figure 4B**), i.e., like in DPR thresholds the improvement was influenced by defect depth (MANOVA: df = 4, $F = 12.79$; $p < 0.001$).

Patient 7 who did not have a large transition zone showed no significant improvement of RTs over the treatment period (RT-pre: 391.0 ± 3.8 ms, RT-post: 375 ± 8.1 ms; Wilcoxon test: $Z = 1.48$, $p = 0.138$, **Figure 2**), and his RTs were not significantly different from those of the healthy sample, neither before nor after training. Patient 4, in contrast, was significantly

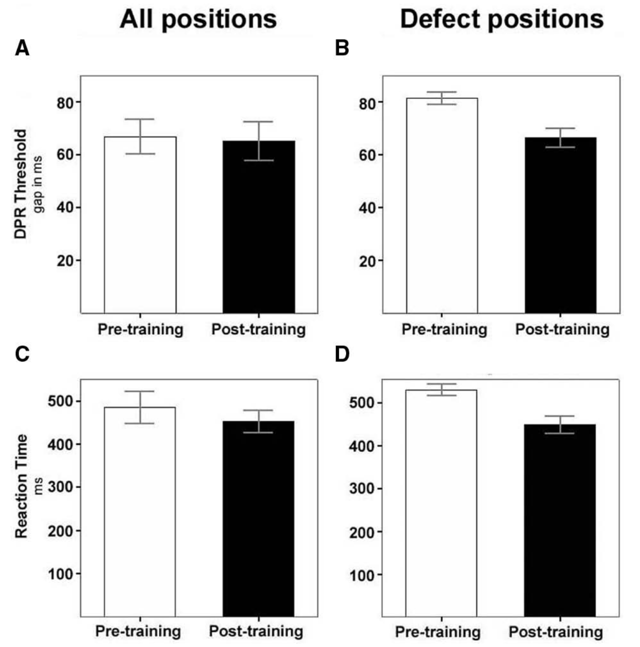

FIGURE 3 | Decrease of DPR thresholds and of RTs over training. White bars, before training; black bars, after training. **(A)** Mean DPR thresholds (±SEM) of the total patient sample for all visual field positions, including intact areas; **(B)** mean DPR thresholds (±SEM) of the total patient sample for positions in the defective field only. **(C)** Mean RTs (±SEM) of the total patient sample for all visual field positions, including intact areas; (**D**) mean RTs (±SEM) of the total patient sample for positions in the defective field only.

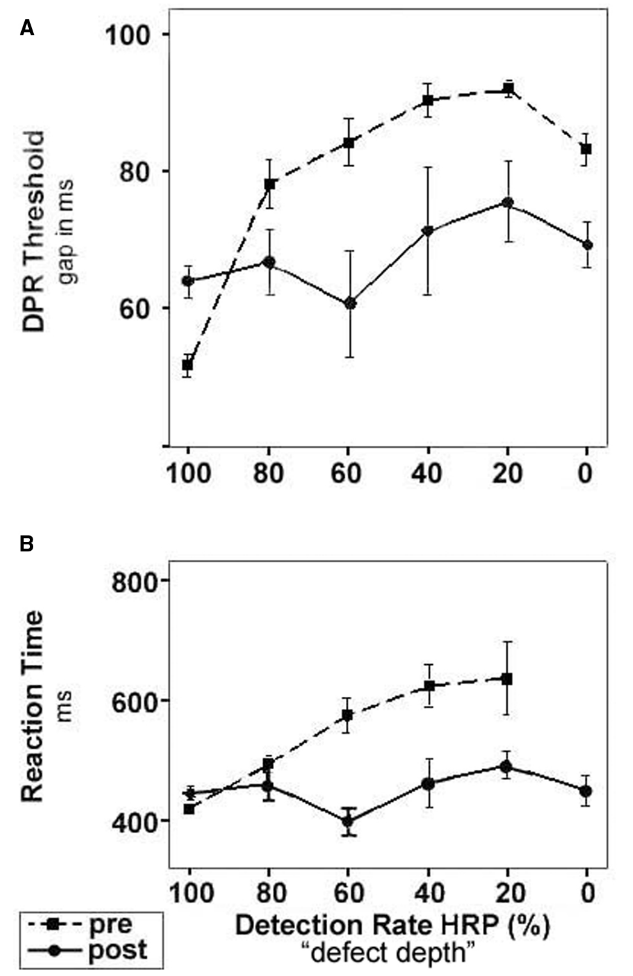

FIGURE 4 | DPR threshold and RT improvement depends on defect depth of visual field region. Dashed lines with square symbols: before training; solid lines with circle symbols, after training. Categorization of visual field regions was based on pre-training baseline measurements: areas with 100% detection rate were considered intact; areas of 0% detection probability were considered blind. Regions of intermediate detection performance of 20–80% were defined as areas of residual vision. **(A)** DPR thresholds before and after training plotted as mean (±SEM) over visual field regions with different defect depth. The most intense improvement of DPR thresholds was found in areas of residual vision. **(B)** RTs before and after training plotted as mean (±SEM) over visual field regions with different defect depth. The largest reduction of RTs was observed in areas of residual vision. Note that RT cannot be determined in blind areas. After training, RTs could be measured in areas which had been blind at baseline and which had partially recovered.

slowed in his reaction to simple light stimuli when compared to age-matched subjects with normal vision. Performance remained lower than normal after the training, although his RTs significantly improved during treatment (RT-pre: 682.6 ± 32.8 ms, RT-post: 527.0 ± 8.4 ms; Wilcoxon test: $Z = 2.02$, $p = 0.043$, **Figure 2**). Patient 9 who improved considerably in his light detection performance during training also showed a pronounced reduction of his RTs by 45 ms (RT-pre: 423.8 ± 20.2 ms, RT-post: 379.1 ± 6.8 ms; Wilcoxon test: $Z = 3.15$, $p = 0.002$). The RTs in the previously blind field reached the level of the intact field before training (**Figure 2**). Overall, however, patient 9's RTs were much longer than those of age-matched healthy controls which may be due to an impairment of the motor component of reacting to the light stimuli which did not improve as a result of the treatment.

Before training, the mean RTs of all patients were significantly longer than in the healthy sample (RT patients/pre: 484.8 ± 37.6 ms, RT healthy: 362.3 ± 3.5 ms; Mann–Whitney test: $Z = 12.37$, $p < 0.001$). RTs were slightly longer in the defective region of the visual field than in the patients' intact regions, though the difference was not significant due to the high variance. Even RTs in the intact area of the patients were significantly longer than in the healthy group, which may also be due to a general slowing of RTs due to the brain lesion (see Discussion; RT patient/intact: 448.2 ± 83.6 ms; RT healthy: 362.3 ± 67.1 ms; $Z = -9.58$, $p < 0.001$) After treatment, patients' RTs were, on average, still significantly longer than those of the healthy age-matched controls (RT patients/post: 452.4 ± 26.5 ms, RT healthy: 362.3 ± 3.5 ms; Mann–Whitney test: $Z = 9.57$, $p < 0.001$), but a few patients reached the level of normal subjects or even had normal RTs before training (see patient examples above and **Figure 2**).

Before training, DPR thresholds and RTs were highly correlated in the patient sample (Spearman's Rho = 0.98, $p < 0.001$). This correlation was much reduced after training (Rho = 0.64, $p = 0.09$).

DISCUSSION

Based on previous studies with healthy subjects and patients suffering from partial blindness, we wished to learn whether a restorative treatment designed to improve light detection would also change temporal perceptual performance in patients with visual field loss after brain lesions. In case we would find such a generalization of training effects, the question further was whether the level of improvement would reach that of age-matched healthy controls.

The study presented here was based on a solid body of psychophysical measurements of light detection and temporal processing with high spatial detail and the opportunity to do point-by-point comparisons in the visual field. Moreover, since our methodology was identical to our previous studies, the patient data could be directly compared to normative data of a healthy sample from the same age group.

LIGHT DETECTION AND TEMPORAL PROCESSING

How temporal processing of visual signals is achieved, and how light detection and other basic visual functions are connected with temporal variables, is largely unknown. Evidence from studies with healthy participants points to apparently close connections between visual stimulus intensity on the one hand, and temporal visual functions (e.g., RTs, flicker detection) on the other hand (e.g., Kelly, 1972; Ulrich et al., 1998). However, these findings are based on single-point, often exclusively foveal, measurements which are not representative of the whole visual field (Poggel and Strasburger, 2004; Strasburger et al., 2011; Poggel et al., 2012a,b), i.e., the spatial dimension of vision is mostly neglected. In addition, flicker detection tasks suffer from various methodological problems like dependence on adaptation and on modulation depth (Tyler, 1985, 1987; Treutwein, 1989; Tyler and Hamer, 1990; Treutwein and Rentschler, 1992).

In more recent years, methods have been developed that allow topographical testing of temporal variables in patients with vision loss. For example, component perimetry (Bachmann and Fahle, 2000) simultaneously presents stimuli of a certain category (e.g., dynamic patterns) across the visual field and tests subjective perception in the defect area. This method is well suited for a rapid detection of visual field defects but does not provide a detailed map of visual thresholds. Various approaches of flicker perimetry (Rota-Bartelink, 1999; McKendrick, 2005) also allow detailed topographical threshold testing. Their clinical application is mostly targeted at retinal or other eye diseases, but they have not yet been systematically applied for the examination of patients with post-geniculate defects.

In the present study, we employed measurements of DPR and of RTs in a topographical fashion and directly compared their topographical patterns to those of perimetric and campimetric measures of light detection performance. DPR thresholds are more reliable than flicker detection thresholds because (a) the technique avoids dependence on adaptation and on modulation depth (Tyler, 1985, 1987; Treutwein, 1989; Tyler and Hamer, 1990; Treutwein and Rentschler, 1992), and (b) targets and non-targets appear equally bright since they are well above the summing duration in Bloch's law (Treutwein, 1989; Treutwein and Rentschler, 1992). DPR thresholds also have the advantage of being independent of motor responses, in contrast to RTs (Schiefer et al., 2001; Poggel and Strasburger, 2004).

While forced-choice measurement of thresholds is more time-consuming and puts higher demands on the patient than do conventional clinical methods, the resulting measures are much more robust, free of observer bias, and allowed us to show—for the first time—in detail in how far the topographical patterns of variables of light detection and temporal processing overlap. In addition, the use of two different temporal variables (RTs and DPR thresholds) is useful to disentangle motor and visual components of processing speed.

To examine potential overlap or dissociations of light detection and temporal processing performance across the visual field, we had earlier used the tools described above to characterize a large sample of healthy subjects between 10 and 90 years of age (Poggel et al., 2012a,b). Unexpectedly, we had found that the visual field maps of perimetric thresholds, of RTs, and of DPR thresholds not only showed quite different topographic patterns, but also that the three variables showed different topographic patterns of aging. Hence, there is a dissociation of light detection and temporal variables both across the visual field and across the life span.

Another strategy to elucidate connections or dissociations between visual functions is their measurement in the damaged visual system. Here it is possible to check if loss of one function (detection) is associated with or dissociated from loss of another function (temporal processing). Patients with lesions of the visual pathway typically suffer from visual field defects, i.e., a loss, or reduction, of light-detection performance in a circumscribed region of the visual field. There is some evidence for a dissociation of perimetric thresholds and the topography of letter-contrast thresholds as well as RTs in patients with visual field loss (Strasburger and Rentschler, 1996; Gothe et al., 2000; see also Bola et al., 2013b, for a review). Hence, a topographic mismatch between different visual functions might explain why some forms of visual impairment remain undetected in clinical testing. In fact, many patients with visual field defects complain about difficulties of visual perception that escape detection with perimetric testing or other common measures of visual function. Frequently, these complaints are simply discarded as groundless (Poggel, 2002). While standard visual diagnostics are mainly concerned with the intensity aspect of vision (as assessed by perimetric luminance thresholds), the temporal dimension is usually neglected. Thus, some of the patients' subjective complaints may be the result of temporal processing deficits which are not included in routine clinical testing.

To achieve a detailed comparison of light detection and temporal variables across the visual field in patients with damage to the visual pathway, we previously investigated a patient sample (Poggel et al., 2011) with the same methods described above (Poggel et al., 2012a,b). Compared to healthy subjects, DPR thresholds turned out to be elevated, and RTs were increased in the patients' entire visual field, including areas that were perimetrically intact. Performance on temporal variables within the defective visual field depended on the degree of intactness of the respective visual field location. However, whereas DPR thresholds were increased around blind regions relative to the intact field, this was not the case for RTs. Thus, temporal processing in patients with cerebral vision loss is also impaired, but to a certain extent temporal processing appears to happen independently from perimetric light detection performance. This may partly explain reported subjective perceptual problems. The increased RT level in perimetrically intact areas was also confirmed in other samples of patients with pre- and post-geniculate damage to the visual system (Bola et al., 2013a; Sabel and Gudlin, 2014).

PERCEPTUAL LEARNING AND VISION RESTORATION TRAINING

The overlap or dissociation of visual functions is of considerable interest for several reasons: the findings of studies with normally sighted and visually impaired populations are important for explaining basic mechanisms of visual processing in the healthy and the damaged visual system, i.e., how visual and temporal processing are connected (or disconnected) in the brain. Secondly, the results provide important information on the usefulness of diagnostic procedures, e.g., the fact that perimetric measurements are often not sufficient for obtaining a complete picture of the patient's visual problems. A third important aspect concerns the therapeutic domain and processes of visual brain plasticity.

Human studies on perceptual learning in healthy subjects (Fine and Jacobs, 2002; Seitz and Watanabe, 2005; Jüttner and Rentschler, 2008; Fahle, 2009; Gilbert et al., 2009; see Strasburger et al., 2011 for review) showed that visual performance and hence visual brain areas are plastic throughout the life span. The observed improvements are usually specific to a visual function or to the visual field region targeted by the training (Fine and Jacobs, 2002; Fahle, 2009; Strasburger et al., 2011) and show only little, if any, generalization.

Similarly, clinical studies with patients suffering from vision loss after lesions to the visual pathway (for example van der Wildt and Bergsma, 1997; Kasten et al., 1998; Kerkhoff, 1999; Sabel, 1999, 2008; Poggel, 2002; Julkunen et al., 2003; Poggel et al., 2004; Sahraie, 2007; Huxlin, 2008; Bergsma and van der Wildt, 2010) have demonstrated training-induced improvement of function, particularly of light detection performance (see Sabel et al., 2011, for review). Despite earlier criticism (Pambakian and Kennard, 1997; Reinhard et al., 2005), there is substantial evidence that a partial restoration of visual function is possible in quite a number of patients (about one third showing either large, small, or no improvement, respectively) and that the training effect cannot be simply explained as being artifactual, like stemming from eye movements (Sabel et al., 2005; Kasten et al., 2006) or observer criterion shift (Poggel, 2002; Poggel et al., 2004). Similar to perceptual learning experiments with normally sighted samples, training studies targeting the improvement of light detection in patients with vision loss showed only little generalization to other functions like color and form discrimination (Kasten and Sabel, 1995; Kasten et al., 2000): a specific training of that particular function had a much more pronounced effect (Poggel, 2002).

IMPROVEMENT OF LIGHT DETECTION PERFORMANCE AND TEMPORAL PROCESSING VARIABLES

Improvement of Light Detection Performance

The results presented in this study replicated earlier studies with respect to campimetric light detection improvement, i.e., increase of intact visual field size in patients with cerebral vision loss (Kasten and Sabel, 1995; van der Wildt and Bergsma, 1997; Kasten et al., 1998; Poggel et al., 2004; Sahraie, 2007; Huxlin, 2008; Bergsma and van der Wildt, 2010; but see Reinhard et al., 2005; Schreiber et al., 2006; for review see Sabel et al., 2011) and patients with pre-chiasmatic lesions of the visual system (Kasten et al., 1998; Sabel and Gudlin, 2014). Despite shorter daily training sessions (15 instead of 30 min) and a shorter treatment period of 3 instead of 6 months in the current study, the average extent of visual field increase was comparable to that of earlier studies, as was the considerable variability of training outcome in individual patients. These findings had been expected based on an earlier analysis of predictors of training outcome (Poggel et al., 2008).

Improvement in the high-resolution computer-based visual field test (HRP) was also confirmed by a significant decrease of the number of absolute defects in conventional perimetry, the established standard of visual field measurement.

Improvement of Temporal Resolution (DPR Thresholds)

For the first time we have now shown that a training regime designed to improve light detection generalizes in its effects to an improvement of temporal-resolution thresholds, i.e., to a function not specifically trained during treatment. Importantly, DPR thresholds are independent of motor responses, i.e., neither the elevated DPR thresholds nor their improvement during the training period can be explained by the patient's motor function.

Interestingly, the improvement of DPR thresholds was significant only in transition zones, i.e., the areas between intact and blind visual field regions. These areas of residual vision are the crucial regions where the increase of light detection takes place, and their size has been shown to be the best predictor for training success out of a large number of relevant parameters that were tested (Kasten et al., 1998; Poggel et al., 2004, 2008). The findings suggest that basic visual processes like simple light detection and temporal resolution may be closely connected functionally and also in terms of neural-network connectivity and plasticity. This view is also supported by some topographical similarity of DPR and perimetric threshold maps in healthy subjects (Poggel et al., 2012a,b). We argued earlier that the detection of a temporal gap between the two light pulses during DPR threshold measurement requires a (possibly early cortical) readout mechanism that would detect and encode the drop in luminance within the double-pulse stimulus (Poggel et al., 2006). Thus, DPR thresholds seem closely linked to early levels of light perception (Fain and Cornwall, 1993) and may be improved when light detection thresholds are restored in a particular region of the visual field. This account is also supported by the observation that DPR improvement depended on the functional status (i.e., light detection probability or degree of impairment) of a particular region before training. Those areas with the greatest potential for an increase of light detection also exhibited the largest decrease of DPR thresholds over the training period.

The inter-individual variability of DPR training effects was considerable, however: some patients showed practically unchanged levels of temporal resolution before and after treatment, while others improved significantly. Of the latter, not all reached the level of healthy subjects in their age group and retained some residual impairment (see examples in **Figure 2**).

Hence, in some patients the topographical improvement of DPR and light detection was almost entirely overlapping, while in others there was a clear topographical dissociation between functional restoration of those two parameters. From studies with patients suffering from right-parietal lesions (e.g., Battelli et al., 2003), one might conclude that an influence of higher visuo-cognitive functions on temporal processing (e.g., onset and offset detection of flickering stimuli) might be an explanation for the differences found between our patients. However, in our—admittedly small—sample we could not find systematic effects of the hemisphere affected by the lesion, the lesion size (as estimated by the size of the blind area), or the location of the lesion in the region perfused by the posterior or middle artery. Furthermore, both visuo-spatial neglect and higher-order visual or cognitive deficits were exclusion criteria. A detailed lesion analysis in larger patient groups needs to be carried out to test the assumption that in patients with a dissociation of light-detection and temporal-performance measures, additional brain areas are affected that would normally coordinate performance (and possibly also functional recovery). Here we can only conjecture that connections to fronto-parietal networks may play a role in top-down coordination of light detection and temporal visual performance. Recent evidence points to changes in brain connectivity taking place during vision restoration (Bola et al., 2014).

Improvement of Simple Reaction Times

In several studies, elevated levels of RTs both in the intact and in the defective parts of the visual field in visually impaired patients have been confirmed (Poggel et al., 2004; Mueller et al., 2007; Bola et al., 2013a). This effect is found both in patients with pre-geniculate as well as with post-geniculate damage to the visual pathway. The increase of RTs depends both on local factors (the proximity to the scotoma in the individual patient's visual field) and on global factors (the size of the blind area, with longer RTs found in patients with larger scotoma; Bola et al., 2013a). While RT to simple light stimuli (as measured here using high-resolution campimetric testing, HRP) depend not only on visual temporal processing but also on the speed of the motor response, this is only true for the average RT value in a patient's result: the variation of RTs across the visual field reflects the sensory component only since motor requirements are invariant, i.e., contribute to the absolute level of RT only (Teichner and Krebs, 1972; Schiefer et al., 2001).

As already shown in previous research (Poggel, 2002; Poggel et al., 2004; Mueller et al., 2007), simple RTs to the detection of light stimuli also improved significantly during restoration training. This was recently also shown in patients with glaucoma (Sabel and Gudlin, 2014). Very likely, the improvement of RTs (and also of DPR thresholds) in response to restoration training is not specific for VRT, but should be a "positive side effect" of any method suitable for improving light detection performance. Although in our sample the improvement of RTs was small across the whole of the visual field, it was pronounced and highly robust in areas of residual vision around the blind parts of the visual field. Again, the functional status of a specific visual field position mainly determined whether, and to what extent, RT improvement was observed during treatment. The overall decrease of RTs in transition zones was closely connected to each patient's pre-training performance. Still, many patients remained at a level of severely increased RT compared to normal subjects even after training. Regions of elevated RTs remarkably included the perimetrically intact areas. Therefore, most of this residual impairment was likely due to unspecifically longer motor RT resulting from the cerebral damage. Since perimetric testing included contrast threshold measurements which were normal in the patients' intact visual field regions, increased RT levels in the perimetrically intact parts of the visual field could not be explained by deficits of contrast perception in intact areas (Plainis and Murray, 2000).

CONCLUSION

In summary, our findings show that the examination of temporal parameters of visual perception, in addition to spatial information processing, helps explain residual visual impairment that cannot be detected by exclusively using standard perimetric testing. Moreover, using our detailed maps of temporal functions, the improvement of dynamic characteristics of vision can be followed during recovery of vision, either spontaneous or induced by training. Further research on the relationship of basic visual functions and temporal functions will be required to more fully understand their interactions. In the current study we only show the relation between detection and temporal-processing performance, but it would be interesting to test cross-modal effects to obtain insight into potential supra-modal aspects of temporal processing or changes of temporal processing during perceptual learning. Also, an investigation of a larger sample of patients allowing for a detailed lesion analysis would be necessary to be better able to understand the influence of lesion size and location on temporal deficits and their recovery during training. An important question arising from our findings is whether, and to what extent, patients with selective impairments in the temporal domain of vision can be helped using a specific training for temporal aspects of vision. Hence, by gaining more knowledge about the interaction of light detection and temporal functions of vision we will be able to design more efficient techniques of vision restoration.

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Tactile feedback improves auditory spatial localization

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Our recent studies suggest that congenitally blind adults have severely impaired thresholds in an auditory spatial bisection task, pointing to the importance of vision in constructing complex auditory spatial maps (Gori et al., 2014). To explore strategies that may improve the auditory spatial sense in visually impaired people, we investigated the impact of tactile feedback on spatial auditory localization in 48 blindfolded sighted subjects. We measured auditory spatial bisection thresholds before and after training, either with tactile feedback, verbal feedback, or no feedback. Audio thresholds were first measured with a spatial bisection task: subjects judged whether the second sound of a three sound sequence was spatially closer to the first or the third sound. The tactile feedback group underwent two audio-tactile feedback sessions of 100 trials, where each auditory trial was followed by the same spatial sequence played on the subject's forearm; auditory spatial bisection thresholds were evaluated after each session. In the verbal feedback condition, the positions of the sounds were verbally reported to the subject after each feedback trial. The no feedback group did the same sequence of trials, with no feedback. Performance improved significantly only after audio-tactile feedback. The results suggest that direct tactile feedback interacts with the auditory spatial localization system, possibly by a process of cross-sensory recalibration. Control tests with the subject rotated suggested that this effect occurs only when the tactile and acoustic sequences are spatially congruent. Our results suggest that the tactile system can be used to recalibrate the auditory sense of space. These results encourage the possibility of designing rehabilitation programs to help blind persons establish a robust auditory sense of space, through training with the tactile modality.

Keywords: recalibration, auditory localization, spatial perception, tactile feedback

INTRODUCTION

Many studies show that vision is fundamental for space perception. For example, when vision and sound are in conflict, vision usually dominates, causing the so-called "ventriloquist effect" (Warren et al., 1981; Mateeff et al., 1985). Vision not only dominates sound in spatial location (under most conditions: Alais and Burr, 2004), it can also affect audition over longer periods. For example, owls reared with distorting prisms show systematic and persistent biases in auditory localization (Knudsen and Knudsen, 1985), that persist after removal of the lenses. Comparable (but transitory) effects have also been demonstrated in humans, after relatively short periods of adaptation to systematically non-aligned auditory and visual stimuli (Recanzone, 1998; Zwiers et al., 2003).

It has been shown that in absence of vision it is possible to develop some auditory spatial skills. For example studies show that blind individuals have enhanced auditory skills for static sound localization or for discriminating the relation between two sounds in the horizontal axis (e.g., Lessard et al., 1998; King and Parsons, 1999; Roder et al., 1999; Gougoux et al., 2004; Doucet et al., 2005; Lewald, 2007). This enhancement can reflect changes in the auditory pathway (e.g., Korte and Rauschecker, 1993; Elbert et al., 2002) or the recruitment of visual cortex (e.g., Weeks et al., 2000; Gougoux et al., 2005; Poirier et al., 2005; Renier and De Volder, 2005; Striem-Amit and Amedi, 2014).

On the other hand, concerning the understanding of the relationship between three sounds during a space bisection task, it has been recently shown that congenitally blind humans show specific deficits (Gori et al., 2014). This result is in agreement with the fact that vision plays an important role in auditory space calibration. It is also in agreement with neurophysiological studies showing that vision guides the maturation of auditory spatial response properties of neurons of superior colliculus (e.g., King et al., 1988; Knudsen and Brainard, 1991; King and Carlile, 1993; Wallace and Stein, 2007).

These studies raise the question of whether it may be possible to develop strategies to help reconstruct the auditory sense of space in the congenitally blind, via a different sensory modality, such as touch or audition. Evidence from blind echolocators supports this idea. Echolocation is the extraordinary ability to represent the external environment by using reflected sound waves from self-generated auditory pulses. Some blind humans who echolocate by making mouth clicks and listening to the echoes demonstrate excellent spatial acuity (Thaler et al., 2011, 2014; Teng et al., 2012). Unfortunately this is a rare ability that only few people naturally develop. Technology has also tried to move in this direction proposing different kinds of sensory substitution devices (SSDs) for visually impaired individuals. The empirical and experimental results deriving from the use of these devices shows that it is possible, to some extent, to signal visual information to the blind using haptic or auditory modalities (see Bach-y-Rita and Kercel, 2003 for a review). Interestingly, it has been shown that in some cases the substitution devices produce direct effect on cortical plasticity (e.g., Striem-Amit and Amedi, 2014). Interestingly, the most popular sensory displays substitute vision with tactile signals, applied to various surface areas to provide electro- and vibrotactile-vision sensory substitution (see Bach-y-Rita and Kercel, 2003 for a review). However, the neural mechanisms underlying these sensory substitutions are poorly understood.

That the tactile signal can successfully substitute vision in SSD suggests that this modality could be used to recalibrate the auditory sense of space in the absence of vision. To test this hypothesis we measured auditory spatial perception in 48 blindfolded sighted subjects, before and after audio-tactile feedback. Subjects' performance improved significantly after tactile feedback, but only when the sound and the tactile stimulations are spatially coherent. This result supports the idea that direct tactile feedback can interact with auditory spatial representation, possibly via a recalibration mechanism.

MATERIALS AND METHODS

We tested 48 sighted subjects (age: 24.8 ± 0.6 years). Participants were blindfolded before entering the room, so they had no notion of the room or speaker layout. They were sat at the center of a bank of nine speakers, spanning ±17.5° of visual angle, aligned with the fifth speaker (at the center of the array), 90 cm away. In order to decrease auditory precision (to allow for more improvement), we positioned the array obliquely with respect to the subjects (see **Figure 1**). Subjects were assigned at random to one of five groups: tactile feedback ($n = 11$); verbal feedback ($n = 11$); no feedback ($n = 14$); rotated ($n = 5$); rotated–reversed ($n = 7$).

Auditory spatial precision was measured by a bisection technique. Three brief sounds (500 Hz, 75 ms duration, 60 dB SPL at the subject) were presented successively at 500 ms intervals in three different positions. The first sound was always positioned at –17.5°, the third at +17.5°, and the second at an intermediate position determined by the QUEST adaptive algorithm (Watson and Pelli, 1983), which estimates point of subjective equality (PSE) after each response, and places the next trial near that estimate. To ensure that a wide range of positions was sampled, that estimate was jittered by a random amount, drawn from a Gaussian distribution of space constant 17.5°, and the nearest speaker to that estimate chosen. Subjects reported verbally whether the second sound was closer to the left (speaker 1 at –17.5°) or right sound (speaker 9 at +17.5°). To ensure that a wide range of positions was sampled, that estimate was jittered by a random amount, drawn from a Gaussian distribution of space constant 17.5°, and the nearest speaker to that estimate chosen. Each subject performed 100 trials for each measure of threshold. The proportion of rightward responses was plotted as a function of the speaker position, and the data fit with a cumulative Gaussian function (see **Figure 2**) by means of the maximum likelihood method to estimate both PSE (given by the mean) and threshold (SD). The space constant (σ) of the fit was taken as

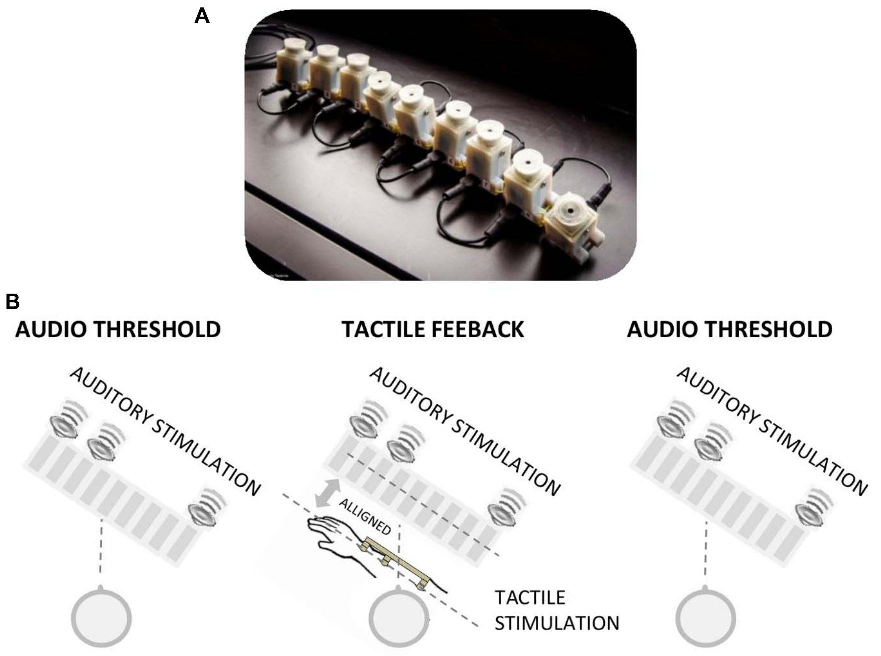

FIGURE 1 | (A) Image of the vibrotactile devices used for the tactile feedback. The device comprises a series of vibrotactile units (on the underside), each of which can be driven individually. **(B)** Image representing the tactile feedback condition. The audio spatial threshold was first measured by the bisection technique. They were then given a first session of audio-tactile feedback, the spatial audio threshold was measured again, a second session of audio-tactile feedback and the spatial audio threshold was then repeated.

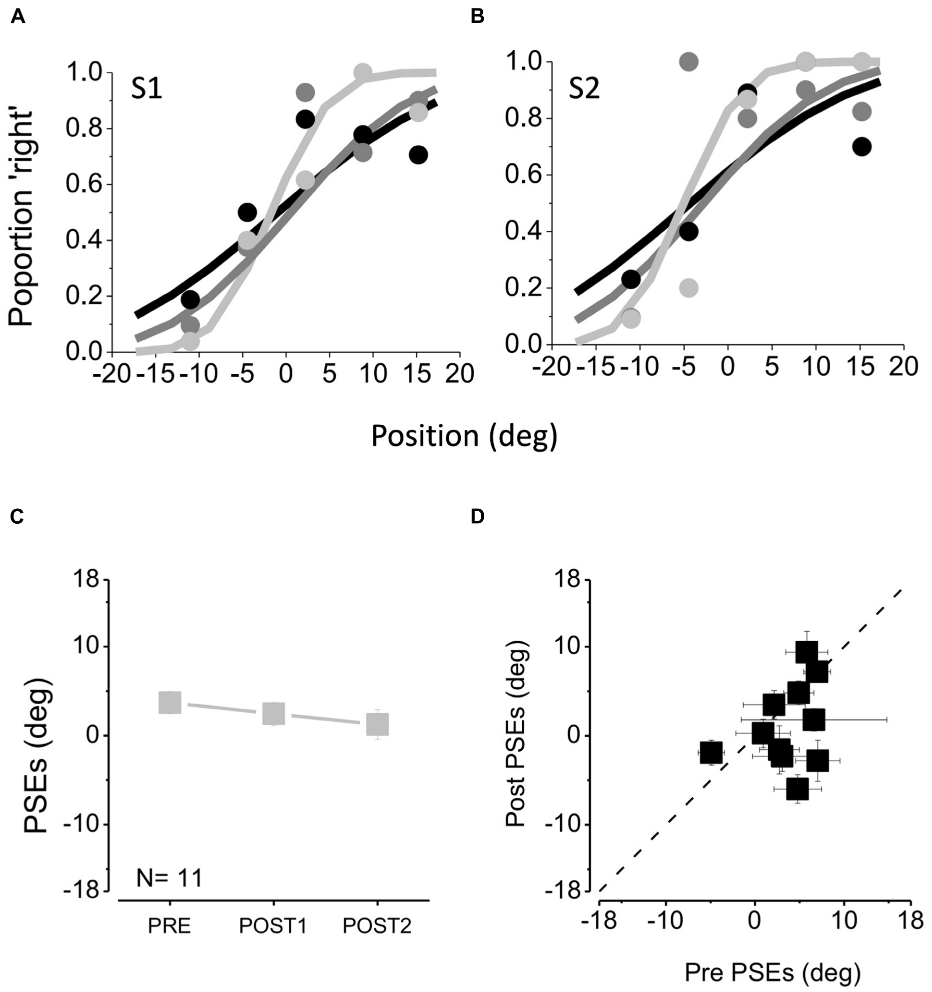

FIGURE 2 | (A,B) Psychometric functions of two example subjects, plotting proportion of trials where the middle sound is judged closer to the right-hand one, as a function of the position of this sound. The data were fit with cumulative Gaussian error functions, whose mean (50% point) gives the "point of subjective equality" (PSE) and steepness (SD) the estimate of threshold. Black data and curve are taken before feedback, the dark gray symbols after the first tactile feedback session and the light gray after the second tactile feedback session. Steeper psychometric functions suggest higher auditory precision. **(C)** Average PSEs measured before any feedback (PRE), after the first feedback session (POST1) and after the second feedback session (POST2). **(D)** PSEs after the second feedback session (POST2) against the initial PSEs (PRE).

the estimate of threshold indicating precision for the bisection task.

The paradigm comprised five phases: initial measurement of bisection threshold; first feedback phase; second measurement of bisection threshold; second feedback phase; final measurement of bisection threshold. During the feedback phases, subjects were presented a sequence of three sounds like the testing sequence. However, during this phase the subject did not respond, but merely paid attention to the sound sequence in order to associate this with the following feedback. To monitor attention, we randomly presented 10 higher tones within the 100 trials which subjects had to detect.

Feedback was either *tactile* or *verbal*, with 100 feedback trials in each feedback phase. In the tactile feedback condition, each of the nine speakers was associated with one of nine aligned vibrotactile stimulators (**Figure 1A**) positioned in the forearm of the subjects, and aligned spatially with the speakers (i.e., the arm of the subject was positioned parallel with respect to the speaker array with the middle tactile stimulus positioned in front of the middle speaker: **Figure 1B**). Each auditory three sound sequence was followed by the same tactile spatial sequence on the subjects' arm, after 200 ms delay. As the subject was positioned facing the speaker array, the audio and tactile spatial positions were coherent, in the same line of sight. In the verbal feedback condition, the positions of the sounds were verbally reported to the subjects by the experimenter after each presentation. The experimenter verbally reported the sequence of the speakers that produced the sound (e.g., "number 1, 3, 9" as represented in **Figure 1B**). Before testing, also in this experimental condition, the subject was informed that the first sound was always produced by the first speaker (number 1) and the last sound by the last speaker (number 9). In the no feedback condition, only the three testing phases were performed, with no feedback sessions.

Two further conditions were run to examine the importance of spatial coherence. One we refer to as the *rotated* condition, where tactile feedback was provided, but with the subjects rotated 180° so the speakers were positioned behind the subject. In this condition the position of the sounds and of the tactile stimulations were reversed in space. Another condition we refer to as *rotated–reversed*, where the subjects were rotated 180° with respect to the speakers, but the order of the tactile stimulators was reversed so they were aligned with the order of the speakers.

At the beginning of the testing session, all subjects (blindfolded before entering in the room) were described the setup, the stimuli presentation and the number of speakers. In the tactile, verbal, and no feedback conditions the arm of the participants was in the same position of the tactile feedback condition (see **Figure 1B**), even if the tactile device was not positioned on the arm. In the rotated and rotated–reversed conditions, the arm of the subject was reflected with respect to the speaker array. To check that the tactile precision was similar between groups in the tactile, rotated, and rotated–reversed group we also measured tactile bisection threshold at the end of the entire sessions. The task was identical to the auditory one with the only exception that the stimulation was provided by the vibrotactile devices positioned in the subject arm (**Figure 1A**). All participants gave informed consent prior to testing. The study was approved by the ethics committee of the local health service (*Comitato Etico, ASL3, Genova*).

RESULTS

Figures 2A,B show the psychometric functions for two example subjects (S1 and S2) at the beginning of the session (black line), after the first tactile feedback block (dark gray line) and after the second tactile feedback block (light gray line). The curves plot the proportion of trials where the middle sound is perceived closer to the third sound. The data have been fit with cumulative Gaussian functions, whose mean (50% point) gives the "point of subjective equality," or PSE, the perceptual midpoint of the speakers.

Figure 2C plots the average points of subjective equality as a function of tactile feedback session, showing that tactile feedback had very little effect on PSE, causing only a slight tendency to reduce the small positive bias. **Figure 2D** plots the individual PSEs after two session of feedback against the pre-feedback values. The points cluster around the equality line, with no significant difference with respect to the pre-training session after the first (one tailed paired t-test, $t_{10} = 0.90$, $p = 0.19$) and between the first and the second training sessions (one tailed paired t-test, $t_{10} = 1.01$, $p = 0.16$).

Inspection of the curves shows that the psychometric functions become steeper after the tactile feedback sessions, suggesting that precision increases after auditory-tactile spatial association. We take the steepness of the curve (given by the SD) as the estimate of thresholds. **Figure 3** plots thresholds for the tactile, no feedback and verbal conditions. The graphs at left show average results, and those at right individual thresholds. Tactile feedback (**Figure 3A** on the left) caused a clear and significant improvement with feedback [repeated measures multi-comparison one way analysis of variance (ANOVA) $F(2,30) = 5.18$, $p = 0.011$]. Thresholds decreased from $14.3 \pm 3.5°$ before feedback to $7.4 \pm 1.1°$ after the first session (two tailed paired t-test, $t_{10} = 2.3$, $p = 0.04$), and to $6.0 \pm 1.0°$ after the second session (two tailed paired t-test, $t_{10} = 2.63$, $p = 0.02$). **Figure 3A** on the right shows that thresholds improved for almost all subjects, with all except one data point falling below the equality line.

Improvement was specific to the tactile feedback condition. It did not occur spontaneously (**Figure 3B**), nor with verbal feedback (**Figure 3C**). Neither showed significant improvement (repeated measures multi-comparison one way ANOVA $F(2,30) = 0.03$, $p = 0.97$ for no feedback and ANOVA $F(2,39) = 0.34$, $p = 0.71$ for verbal feedback). In both cases the individual data points are scattered around the equality line, with no tendency to fall below it.

We then examined the importance of spatial coherence for the tactile feedback: in one condition (*rotated*) we rotated the subject, but left the ordering of the speakers as before (so it was reversed with respect to the direction of sound); in the other we rotated the subject but reversed the order of tactile stimulators so they corresponded with the direction of sound (*rotated–reversed*). The results are shown in **Figure 4**, in the same format as **Figure 3**. In the *rotated* condition (**Figure 4A**), the feedback has no effect [repeated measures multi-comparison one way ANOVA $F(2,14) = 0.24$, $p = 0.79$] after the first (one tailed paired t-test, $t_4 = 0.34$, $p = 0.37$) and nor after the second training (one tailed paired t-test, $t_4 = 0.53$, $p = 0.3$). However, in the *rotated–reversed* condition (**Figure 4B**), there was a significant improvement (repeated measures multi-comparison one way ANOVA $F(2,20) = 3.38$, $p = 0.056$) after the first (one tailed paired t-test, $t_6 = 2.17$, $p = 0.036$) and after the second training (one tailed paired t-test, $t_6 = 2.3$, $p = 0.03$), although less than when subjects faced the speakers (an average factor pre/post of 1.7 was obtained for the rotated and reversed condition while an average factor pre/post of 2.4 was obtained for the tactile condition). Also in this condition no change was observed for PSEs [repeated measures multi-comparison one way ANOVA $F(2,20) = 0.87$, $p = 0.437$] after the two feedback sessions (one tailed paired t-test, $t_6 = 1.23$, $p = 0.13$ for the first feedback session and one tailed paired t-test, $t_6 = 1.5$, $p = 0.09$ for the second feedback session). In order to check for tactile precision differences between groups we also measured the bisection task in the tactile modality (**Figure 4C**). No difference was found between subjects [repeated measures multi-comparison one way ANOVA $F(2,20) = 0.49$, $p = 0.62$]. Overall these results suggest that spatial correspondence is essential for the tactile feedback to improve auditory spatial localization.

DISCUSSION

Audition, vision, and touch encode spatial information in different ways, from different sensor platforms. How our brain interprets these spatial cues within a common framework is still unclear. One possible way to keep the different sensory signals in alignment may be to use one system to *calibrate* the others. It has been suggested that best system to calibrate the others should

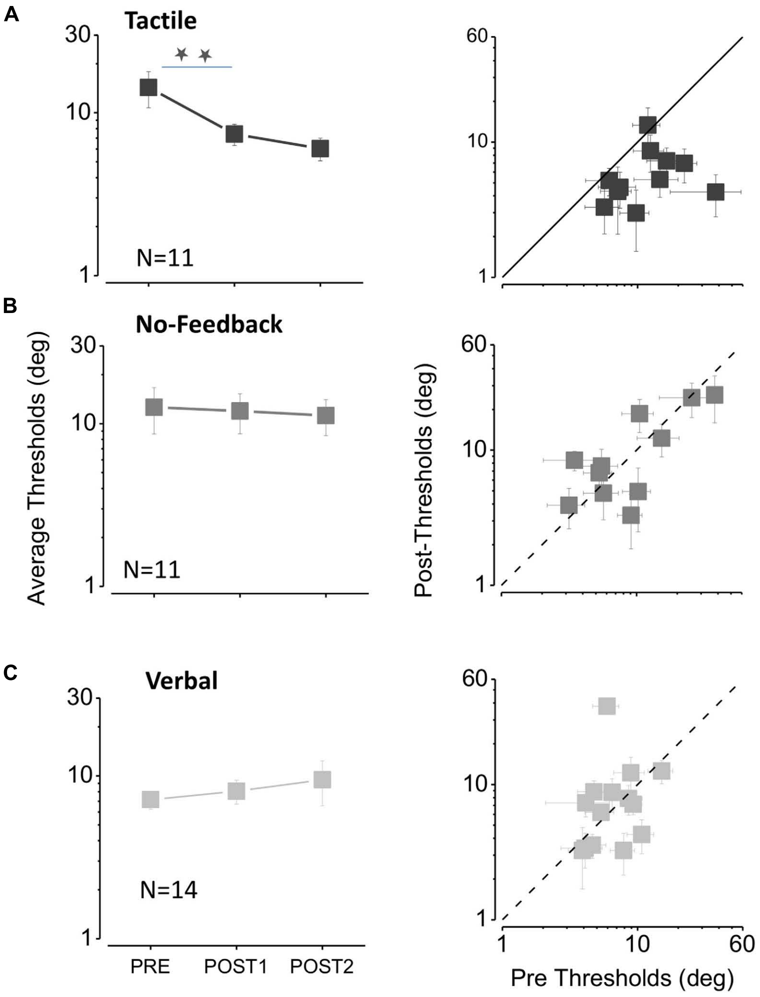

FIGURE 3 | The effect of feedback on auditory bisection thresholds. **(A)** Tactile feedback. The three data points in the left-hand graph plot average thresholds measured before the feedback sessions (PRE), after the first feedback session (POST1) and after the second session (POST2). The stars indicate a significant difference level of $p < 0.05$ (one tailed *t*-test, $p = 0.02$ after the first feedback; one tailed *t*-test, $p = 0.01$ after the second feedback). The plot at right shows the thresholds for all subjects, plotting the thresholds after the second feedback (POST2) against the initial thresholds (PRE). All points fall below the equality line, showing that all subjects improved after feedback sessions. **(B)** Same as **(A)** for the no feedback condition. **(C)**. Same as **(A)** for the verbal feedback condition.

be the more robust one, with the more accurate signals (Gori et al., 2008; Burr and Gori, 2011). For the perception of space, much evidence suggests that the visual system calibrates the others (Knudsen and Knudsen, 1985; Knudsen and Brainard, 1991; King and Carlile, 1993; Recanzone, 1998; Zwiers et al., 2001, 2003; Gori et al., 2008, 2010, 2012a,b; Burr and Gori, 2011). Vision seems to impact directly on the development of spatial aspects of other sensory systems (Gori et al., 2014).

In this study we showed that tactile feedback can improve auditory spatial discrimination in blindfolded sighted individuals. Auditory spatial precision improved by a factor of 2 after a brief feedback session. A second feedback session produced significant further improvement to a factor of 2.4 after the second training. We suggest that the improvement may reflect calibration (Burr and Gori, 2011) of the auditory sense of space, by tactile signals.

To control that the improvement in precision did not merely result from experience at the task, or from generic feedback, we incorporated two controls: one group received no feedback, and the other verbal feedback. Neither of these groups improved in performance, pointing to the importance of the feedback being of a sensory nature, rather than just being informative. Furthermore, to be effective, the feedback had to be spatially coherent with the sound source. When subjects were rotated by 180° so the spatial order was inverted on the arm, the feedback was ineffectual. However, when the order of the stimulators on the arm was reversed (restoring spatial coherence), the feedback became effective again. Clearly, to be effective, the feedback needs to be sensory. The lack of improvement observed in the verbal condition suggests that sensory, rather than cognitive mechanisms are involved. More interestingly, the feedback needs to have a spatial correspondence with the sound

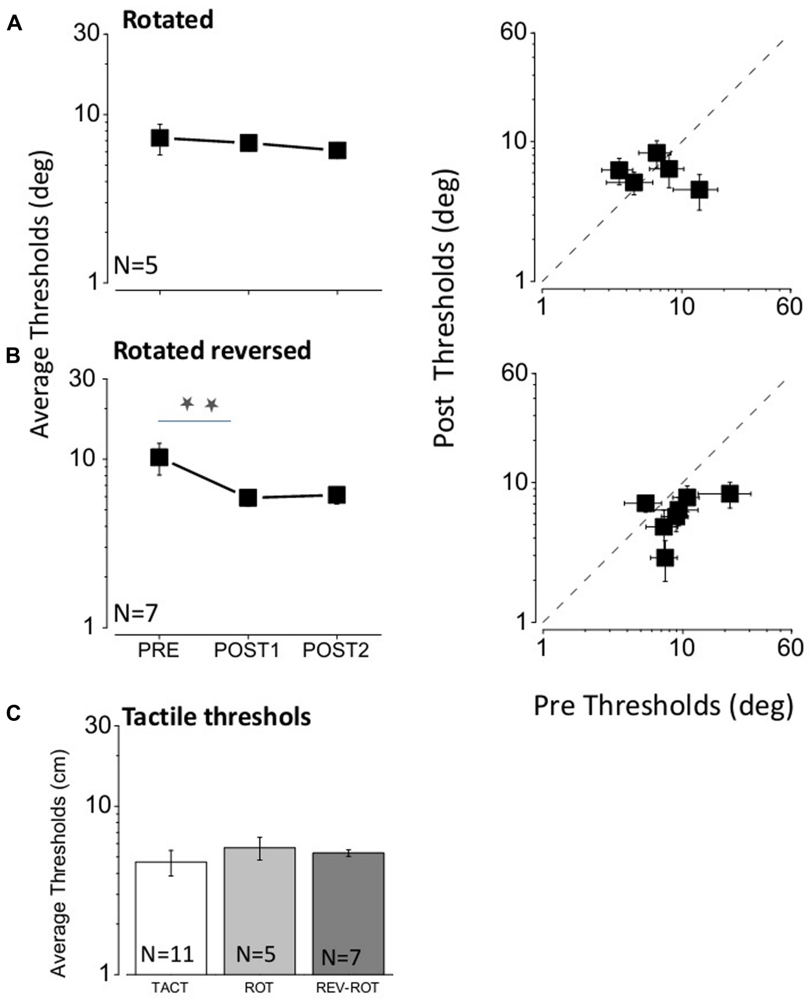

FIGURE 4 | (A) Results for the rotated feedback condition. The three data points in the left-hand graph represent the average results for the three bisection thresholds measured: the first one before any feedback (PRE), the second after the first feedback (POST1) and the third after the second feedback (POST2). The plot at right shows the thresholds for all subjects, plotting the thresholds after the second feedback (POST2) against the initial thresholds (PRE). **(B)** Same as **(A)** for the rotated–reversed feedback condition. Two stars represent a significant difference level of <0.05 (one tailed *t*-test, $p = 0.04$ after the first feedback; one tailed *t*-test, $p = 0.03$ after the second feedback). Also in this case all points, with the exception of one, fall below the equality line, showing that all subjects improved after feedback session. **(C)** Average tactile thresholds for the group of subjects with tactile, rotated and reverse–rotated feedback.

source to promote calibration between the tactile and the auditory system.

Cross-comparison between senses is clearly an effective strategy to establish and to maintain calibration, as each sense has access to different sources of information, differently affected by noise and distortions. Interestingly, our results suggest that in absence of one calibration modality, such as vision, for space, another modality can substitute it, and serve to calibrate the less robust modality (in this case audition).

The number of people with visual impairment worldwide in 2002 was over 161 million, of whom about 37 million were legally blind (Resnikoff et al., 2002). To date many technological solutions have been developed for visual disability. Several devices (both academic and commercial) available today are based on visual tactile substitution (e.g., Kaczmarek and Bach-Y-Rita, 1995; Bach-y-Rita et al., 1998; Kajimoto et al., 2003); and other on auditory-visual substitution (e.g., Meijer, 1992; Capelle et al., 1998). Our results suggest that stimulation of tactile modality can provide important information to recalibrate the sense of space in the absence of vision, and support the idea that both rehabilitation programs and SSD could provide tactile stimulation to substitute for vision. Further studies will be necessary to understand how these signals should be provided to produce the better effects in the everyday life of the visually impaired population.

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