Improving visual function through concomitant use of perceptual learning and brain stimulation : the case of macular degeneration

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THÈSE

En vue de l'obtention du

DOCTORAT DE L'UNIVERSITÉ DE TOULOUSE

Délivré par l'Université Toulouse 3 - Paul Sabatier

Cotutelle internationale : Université de Padoue

Présentée et soutenue par

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Le 9 mars 2020

Amélioration de la fonctionnalité visuelle par l'utilisation concomitante de l'apprentissage perceptif et de la stimulation cérébrale: le cas de la dégénérescence maculaire.

Ecole doctorale : **CLESCO - Comportement, Langage, Education, Socialisation, Cognition**

Spécialité : **Neuropsychologie**

Unité de recherche :
CERCO - Centre de Recherche Cerveau et Cognition

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Unité de recherche: CERCO Centre de Recherche Cerveau et Cognition

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Ph.D. COURSE IN: PSYCHOLOGICAL SCIENCES
SERIES XXXII°

ECOLE DOCTORALE: CLESCO - Comportement, Langage, Education, Socialisation, Cognition
DOCTORAT: NEUROPSYCHOLOGIE - 1ere inscription en thèse: 1 octobre 2016

IMPROVING VISUAL FUNCTION THROUGH CONCOMITANT USE OF PERCEPTUAL LEARNING AND BRAIN STIMULATION: THE CASE OF MACULAR DEGENERATION

Thesis written with the financial contribution of Fondazione Cariparo and Bando Vinci (Cap II) of Università Italo-Francese

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Abstract

Macular degeneration (MD) is a common visual disorder in the aging population characterized by a loss of central vision, reduced visual acuity contrast sensitivity, and increased crowding. This impairment strongly affects the quality of life and personal autonomy. There is currently no cure for AMD, available treatment options are only able to slow down the disease, and even palliative treatments are rare. After the emergence of the central scotoma, patients with MD develop one or more eccentric fixation areas - preferred retinal loci (PRLs) - that are used for fixation, reading, tracking, and other visual tasks that require finer ocular abilities. The final goal of the project was to investigate and to improve the residual visual abilities in the PRL. Four studies were conducted in total. Study 1 was conducted in MD patients to investigate whether after the emergence of the scotoma, the PRL acquire enhanced abilities in the processing of the visual information through spontaneous or use-dependent adaptive plasticity. Study 2 aimed to assess the effects of a single administration of transcranial random noise electrical stimulation (tRNS), a subtype of non-invasive transcranial electrical stimulation, on the spatial integration in the healthy visual cortex. Study 3 aimed to assess the between session effect of daily repeated tRNS coupled with perceptual training. The objective of study 4 was to translate the previous findings into a clinically applicable treatment approach by combining tRNS and perceptual training in adult patients with MD.

Contrary to previous results, we found neither a phenomenon of spontaneous nor use-dependent cortical plasticity undergoing in the PRL before the training. We also found that the tRNS was able to modulate the visuospatial integration in the early visual processing, promoting plastic changes in the stimulated network. Its effects were not limited to the short-term modulation but also produced a boosting of the learning in a crowding task. The final experiment showed that a combination of tRNS and perceptual training could result in greater improvements and larger transfer to untrained visual tasks in adults with MD than training alone. Overall, our results indicate that tRNS of the visual cortex has potential application as an additional therapy to improve vision in adults with bilateral central blindness.

Résumé

La dégénérescence maculaire (DM) est une pathologie visuelle fréquente dans la population vieillissante, qui se caractérise par une perte de la vision centrale, une diminution de la sensibilité au contraste et de l'acuité visuelle. Cette déficience affecte fortement la qualité de vie et l'autonomie . Il n'existe actuellement aucun traitement curatif de la DMLA, les options thérapeutiques disponibles ne permettant que de ralentir l'évolution de la maladie, avec de rares traitements palliatifs. Après l'apparition du scotome central, les patients atteints de DM développent une ou plusieurs zones de fixations excentrées - les lieux rétiniens préférentiels (PRLs) - qui sont utilisées pour la fixation, la lecture, et d'autres tâches visuelles qui nécessitent des capacités oculaires plus fines. L'objectif principal du projet était d'étudier et d'améliorer les capacités visuelles résiduelles dans les PRL. En tout quatre études ont été menées L'étude 1 a été menée chez des patients atteints de DMLA afin de déterminer si, après l'apparition du scotome, le PRL acquiert des capacités accrues dans le traitement de l'information visuelle grâce à une plasticité adaptative spontanée ou dépendante de l'utilisation. L'étude 2 visait à évaluer les effets d'une seule stimulation électrique transcrânienne à bruit aléatoire (tRNS), une variante de stimulation électrique non-invasive, sur l'intégration spatiale dans le cortex visuel sain. L'étude 3 visait à évaluer chez des sujets sains l'effet d'une répétition quotidienne du tRNS associée à un entraînement perceptif entre les séances.

L'objectif de l'étude 4 était de traduire ces résultats en une approche clinique en combinant la tRNS et l'entraînement perceptif chez des patients adultes atteints de DMLA. Nous n'avons trouvé aucun phénomène de plasticité corticale spontanée ou dépendante de l'utilisation dans la PRL avant l'entraînement contrairement à ce qui avait été montré dans d'autres études. Nous avons cependant constaté que le tRNS était capable de moduler l'intégration visuospatiale dans le traitement visuel précoce, en favorisant les changements plastiques dans le réseau stimulé. Les effets de la tRNS ne se sont pas limités à la modulation à court terme, mais ont également produit un renforcement de l'apprentissage dans une tâche d'encombrement spatial. L'expérience finale a montré chez les adultes atteints de DMLA qu'une combinaison de la tRNS et de l'apprentissage perceptif pouvait induire des améliorations plus importantes et un transfert accentué vers des tâches visuelles non entrainées que le seul apprentissage perceptif. Dans l'ensemble, nos résultats indiquent que la tRNS du cortex visuel peut être utilisée comme thérapie supplémentaire pour améliorer la vision chez les adultes atteints de cécité centrale bilatérale.

Riassunto

La degenerazione maculare (MD) è una patologia visiva che si verifica per lo più nell'età adulta ed è caratterizzata da una perdita della visione centrale, una riduzione della sensibilità al contrasto, una riduzione dell'acuità visiva, e un aumento dell'affollamento visivo. Questo deterioramento compromette in maniera significativa la qualità della vita e l'autonomia dell'individuo. Attualmente non esistono cure per l'MD ed anche le opzioni di trattamento palliativo sono scarse, tuttavia esistono alcuni trattamenti che permettono di rallentare il decorso della malattia. Con l'insorgenza di uno scotoma centrale, i pazienti con degenerazione maculare sviluppano una o più aree eccentriche di fissazione – loci retinici preferenziali (PRLs)– usati per compiti che richiedono fini abilità oculari e stabilità di fissazione quali ad esempio la lettura, la ricerca visiva, ed il riconoscimento di volti o oggetti. Gli obiettivi principali di questo progetto erano due: investigare le abilità visive residue nel PRL e verificare l'efficacia di un nuovo protocollo di riabilitazione visiva nei pazienti affetti da MD. Il progetto si è sviluppato attraverso quattro differenti studi. Il primo è stato condotto in pazienti con MD per analizzare se dopo lo sviluppo dello scotoma, il PRL acquisisca rafforzate abilità nel processamento dell'informazione visiva attraverso processi di plasticità corticale spontanea o uso-dipendente. Il secondo studio era atto a determinare gli effetti sull'integrazione spaziale nella corteccia visiva, di una tecnica di promozione della plasticità neurale basata sulla stimolazione elettrica transcranica non-invasiva a frequenza casuale (tRNS). Con il terzo studio, abbiamo

testato l'efficacia della tRNS nell'accelerare l'apprendimento percettivo ed il trasferimento dell'apprendimento nella periferia del campo visivo. Infine, l'obiettivo del quarto ed ultimo studio è stato quello di testare la fattibilità e l'efficacia di un protocollo di riabilitazione visiva per i pazienti affetti da MD che prevedesse l'uso combinato della tRNS e del training percettivo. Contrariamente a studi precedenti, nessun fenomeno di plasticità corticale spontaneo o uso-dipendente è stato trovato nei PRL prima del training. Inoltre, la tRNS si è dimostrata capace di modulare l'integrazione visuo-spaziale nel processamento visivo precoce, promuovendo cambiamenti nella plasticità della popolazione neurale stimolate. Gli effetti della stimolazione non si sono limitati alla modulazione a breve termine, ma hanno prodotto anche un aumento dell'apprendimento in compiti di affollamento visivo. L'ultimo studio ha mostrato come la combinazione tra tRNS e training percettivo nei pazienti affetti da MD produca un incremento dell'apprendimento e – parzialmente – del trasferimento verso compiti visivi non allenati. In generale, i nostri risultati indicano che la tRNS sulla corteccia visiva potrebbe avere possibili applicazioni come terapia aggiuntiva al training neuro-comportamentale nel trattamento della cecità centrale bilaterale. Questi risultati hanno inoltre potenziali ricadute anche per altre popolazioni cliniche che soffrono di bassa visione.

Acknowledgments

Firstly, I would like to express my gratitude to my supervisor, Professor Clara Casco, for her priceless continuous guidance.

I would also like to sincerely thank my co-supervisor, Professor Yves Trotter, for his immense help.

Sincere thanks to all members of the NeuroVis.US Laboratory, with particular gratitude to Dr. Luca Battaglini and the former member Dr. Marcello Maniglia, who have been great friends and colleagues.

Sincere thanks to Tania, Elena, Evelin, Max, and all the people at the DPG for sharing with me this valuable experience.

Sincere thanks to the CerCo members for sharing with me a healthy, pleasant, and stimulating working environment.

Sincere thanks to all my participants, the one with low vision, they are the real protagonists of this work.

Sincere thanks to my friends for forcing me to have a normal social life even in the darkest time.

Sincere thanks to my family, no expression of thanks can be sufficient for your love, care, patience, wisdom, and support you have given me during my whole life.

Lastly, but most importantly, I would like to thank my other half for the patience she always demonstrated during these three years.

Foreword

This project stems from the experience gained during my master's internship and the post-graduate Erasmus internship. Without these previous experiences, there would not have been the network of international collaborations that allowed the realization of the project. This thesis conveys my interest in translational research and goes through a multidisciplinary research field that ranges from optometry, and neuropsychology, to psychophysics. Many are the knowledge learned, and the people met along this path. I thank you all who will read this work of mine, science is a silly game if there is no dissemination.

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Glossary of Abbreviations

2AFC – Two-alternative forced choice

2IFC – Two-interval forced choice

AMD – Age-Related Macular Degeneration

AR – Augmented reality

CPD – Cycles per Degree

CS – Contrast sensitivity

CSF – Contrast sensitivity function

CRF – Cell's receptive field

dMRI – diffusion-weighted imaging

EEG – Electroencephalography

ETDRS – Early Treatment Diabetic Retinopathy Study logMAR chart

fMRI – Functional Magnetic Resonance Imaging

HF-tRNS – High-frequency transcranial Random Noise Stimulation

LF-tRNS – Low-frequency transcranial Random Noise Stimulation

LGN – Lateral Geniculate Nucleus

LTP – Long Term Potentiation

LTD – Long Term Depression

MD – Macular Degeneration

MT – Medio-temporal area

NMDA – N-methyl –D- Aspartate

NIBS – Non-invasive Brain Stimulation

PET – Positron Emission Tomography

PL – Perceptual Learning

PRL – Preferred Retinal Locus

rTMS – Repetitive Transcranial Magnetic Stimulation

RF – Receptive Field

SNR – Signal to Noise Ratio

tACS – Transcranial Alternating Current Stimulation

tDCS – Transcranial Direct Current Stimulation

TES – Transcranial Electrical Stimulation

TMS – Transcranial Magnetic Stimulation

tRNS – Transcranial Random Noise Stimulation

TVA – Tachistoscopic Visual Acuity

TVC – Tachistoscopic Visual Crowding

V1 – Primary Visual Cortex

VA – Visual Acuity

VAS – Visual Acuity with Sloan letters

VR – Virtual Reality

VWFA – Visual Word Form

Chapter I.

Introduction

The continued increase in average age in developed western countries has transformed macular degeneration (MD) into the main cause of visual impairment in the modern age. This condition involves the loss of central vision, including loss of contrast sensitivity and visual acuity, mainly caused by a foveal scotoma. The current treatment options available are limited and mostly aim only to slow progression rather than restore vision. People with MD to cope with the loss of the sharp central vision, begin to retrain their visual habits so that they can fixate with a peripheral preferred retinal locus (PRL) instead of the impaired macula. PRL is usually found in a region near the scotomatous retina (Klaver, 1998; Klein, Klein, & Linton, 1992). So far, current efforts to monitor and treat the macular disease have focused on the retina, and no therapy has been able to restore patients' vision as it was before the onset of the disease. Pharmacological treatments can slow down or even stabilize the formation of the visual defect; once it has manifested, treatment and rehabilitation must face its irreversibility. In the absence of a restorative treatment, the use of optical aids and compensative strategies might help to reduce the impact of the visual impairment (Calabrèse et al., 2018; N. X. Nguyen, Weismann, & Trauzettel-Klosinski, 2009; Rohrschneider, 2013; Romayananda, Wong, Elzeneiny, & Chan, 1982), on the other hand it is also possible to focus on enhancing the preserved visual functions (Maniglia, Cottereau, Soler, & Trotter, 2016; Pijnacker,

Verstraten, Van Damme, Vandermeulen, & Steenbergen, 2011). The main categories of vision-enhancing training are eccentric viewing training, eye movement training, and Perceptual Learning [PL] training (M. Li, Zhu, & Sun, 2015). PL is an improvement in a perceptual task resulting from the fine-tuning of sensory neurons through experience-dependent plasticity (Gilbert, Sigman, & Crist, 2001). PL has been proven effective in improving a wide series of visual dysfunctions, ranging from cortical blindness to mild refractive defects (Campana & Maniglia, 2015a; Das & Huxlin, 2010; M. Li et al., 2015). However, PL requires many sessions to be effective, and this represents a practical difficulty for patients that are not autonomous. In order to achieve a faster and larger improvement, recent studies combined PL with other techniques that have the ability to increase brain plasticity like brain stimulation (Camilleri, Pavan, Ghin, Battaglini, & Campana, 2014; Campana, Camilleri, Pavan, Veronese, & Giudice, 2014; Gall et al., 2015; Rufener, Ruhnau, Heinze, & Zaehle, 2017) and drug administration (Grieb, Jünemann, Rekas, & Rejdak, 2016; Kang, Huppé-Gourgues, Vaucher, & Kang, 2014; Rokem & Silver, 2013). Recently, non-invasive brain stimulation has been used, alone or coupled with PL, to enhance visual abilities (Camilleri, Pavan, & Campana, 2016; Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Campana et al., 2014; A. Fertonani, Pirulli, & Miniussi, 2011; Pirulli, Fertonani, & Miniussi, 2013; Thompson, Mansouri, Koski, & Hess, 2008). In particular, transcranial random noise electrical stimulation (tRNS), in which a weak current is delivered through the scalp on a cortical region at random frequencies, has shown promising results in boosting PL and reducing the number of sessions needed to observe significant improvements (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; A. Fertonani et al., 2011). Specifically, Camilleri et al. (2014) and

Campana et al. (2014) showed that when tRNS is repeatedly applied during a contrast-detection training it induced greater transfer (the post-training improvement observed in an untrained task) to visual acuity (VA) with respect to PL alone in both amblyopic and myopic patients (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Campana et al., 2014). In general, tRNS appears to boost both the early (within-session (A. Fertonani et al., 2011) and late (between sessions/days (Camilleri, Pavan, Ghin, Battaglini, et al., 2014) components of PL. The research presented in this thesis aimed to evaluate the therapeutic potential of tRNS in the treatment of human adults with bilateral central vision loss. The results presented in the thesis also contributed to increase our knowledge of the effects of tRNS on the visual cortex.

Conceptually this thesis has been divided into two parts. The first part is a review on the MD whose purpose is to critically review the evidence of adaptive neural plasticity in central vision loss. Based on the most recent literature, I will propose new interpretations of old results in this field. The second part will focus on my experimental activity.

The first part of the literature review (CHAPTER II) introduces the MD and its clinical features. Particular relevance has been given to the structural and functional alterations that accompany the ocular disease at the level of the central nervous system. I have also discussed how some of the results that were previously interpreted as evidence of adaptive reorganization can be reinterpreted in an alternative more conservative way. I have concluded exposing the importance of developing an effective rehabilitative protocol for MD patients. In CHAPTER III, PL is presented as a tool to improve visual functions. The concepts of learning, transfer, and specificity are discussed. CHAPTER IV

provides an overview of the action mechanisms proposed for the tRNS, the main results of previous studies, and some safety considerations. Finally, the possibility of extending the use of tRNS as a therapeutic intervention for other visual disorders is discussed. This thesis presents the data of four experiments, two of these were carried out on patients affected by bilateral maculopathy while the other two involved normal-viewing subjects. Each experiment was a necessary step to understand the interaction mechanism of tRNS and perceptual learning on the visual cortex of adults. Each subsequent study represented a further advancement from the basic scientific results towards the clinical application of the tRNS in MD. My hypotheses were:

- The spontaneous and use-dependent cortical adaptations in the region around the scotoma produces as perceptual consequences some alterations in the early spatial integration that would be measurable through psychophysical methods (CHAPTER V).
- tRNS modulates early visual-spatial integration by altering the balance between excitatory and inhibitory lateral interactions. (CHAPTER VI)
- tRNS boosts between session perceptual learning and transfer (CHAPTER VII)
- tRNS enhances and accelerate the outcomes of perceptual training in adults with bilateral macular degeneration (CHAPTER VIII).

CHAPTER IX combines datasets from different studies to further test the hypotheses presented in CHAPTER V.

The first study is presented in CHAPTER V. This experiment aimed to evaluate the presence of spontaneous or use-dependent plasticity in the patients' PRL. In the previous literature about plasticity in MD (D. D. Dilks, Baker, Peli, & Kanwisher, 2009;

Maniglia, Soler, Cottereau, & Trotter, 2018; Plank et al., 2017), there is debate whether the spared periphery undergoes a general process of adaptation triggered by the presence of the scotoma ("use-dependent reorganization" hypothesis) or whether the preferential use of the PRL for active high demanding tasks triggers a more specific use-dependent adaptation (D. D. Dilks et al., 2009; Maniglia et al., 2018; Plank et al., 2017). Knowing the type of adaptation process to which the PRL is subject is important to avoid damaging any compensatory mechanisms in place and instead to try to maximize them with the training. In this study, we tried to investigate this issue psychophysically by comparing spatial integration in the PRL, in a symmetrical retinal position (non-PRL) and a region with matched eccentricity in a control group. To do this, we probed the contextual influences by measuring the contrast gain for a vertical Gabor target, flanked by two high-contrast collinear masks compared to the orthogonal baseline condition. In line with previous literature (Maniglia et al., 2018), our prediction was to find evidence for plasticity, in the form of reduced collinear inhibition. Moreover, we expected the reduction of inhibition to be stronger in the PRL.

CHAPTER VI includes the results of a study that aimed at investigating whether the contextual influences are modulated by tRNS applied to the occipital cortex of human observers during task performance. Given that the tRNS main effect is to increase cortical excitability, it could expand the sensitivity of the neurons to weak stimuli and thus lowering the contrast threshold for the target. At the same time, this increased excitability could also modulate how the target is integrated with its context by altering the relative strength of excitatory (E) or inhibitory (I) influences from the flanking elements,

depending on which is weaker. In this case, we might expect an effect of tRNS even if tRNS shows no effect at all on target perceived contrast.

The study presented in CHAPTER VII investigated whether tRNS can effectively boost PL on a peripheral visual task over a small number of daily training sessions. Additionally, we tested whether learning transferred to untrained spatial location and task variation. We expected the tRNS to be able to increase both the learning rate and the transfer of learning.

The final study presented in CHAPTER VIII and CHAPTER IX brought together the findings of the experiments presented in this dissertation, investigating the combined effect of tRNS and perceptual learning in a visual rehabilitation protocol in MD patients.

This thesis explores a new path for visual improvement in MD and opens new possibilities for other clinical population.

Chapter II.

Macular Degeneration: Clinical Presentation

Macular degeneration [MD] can lead to severe visual impairment and blindness. Throughout the disease, the central retina responsible for our sharp vision undergoes a series of irreversible changes that endangers visual acuity.

The consequences of a bilateral central scotoma are severe visual impairments, especially in reading, face recognition, and visual search. Patients with central scotoma develop one or more eccentric fixation areas - preferred retinal loci (PRLs) - that are used for fixation, reading, tracking, and other visual tasks that require fine ocular abilities. This area, the preferred retinal locus (PRL), is a useful adaptation to central visual loss, but its function is weaker than that of the fovea because of the relatively poor visual resolution and the fixation instability.

There are different types of MD corresponding to different aetiology and progressions. Juvenile macular degeneration (JMD) is a quite rare type and includes several inherited eye diseases like Stargardt's disease, Best disease, and juvenile retinoschisis. In these cases, loss of central vision may begin in childhood or young adulthood. Unfortunately, there is no treatment available for these diseases, which are caused by gene mutations passed down in families. Early age-related macular degeneration (AMD) consists of retinal or subretinal drusen, yellow or white accumulations of extracellular material, and retinal pigment abnormalities. It is not known whether drusen promote AMD or if they are common results of an underlying process. Late AMD is divided into neovascular AMD and geographic atrophy (GA). Early AMD and GA are called dry AMD as a differentiation from the so-called wet AMD

that is a result of neovascularisation within the retina with leakage of fluid in the macula. There are different outcomes for the three type of AMD: patients with early AMD can retain some visual functionality, on the contrary, GA patients have no residual visual function in the affected area due to permanent loss of photoreceptors. In wet AMD, retinal scarring and deterioration can lead to blindness. No curative treatments are available until now for any of the diseases, but there are therapies able to slow down or freeze the progression. For wet AMD, treatment consists mainly of inhibitors of vascular endothelial growth factor (VEGF) repeatedly injected into the eye. AMD has been identified as the third leading cause of blindness in the world, and the first considering only the developed part (Wong et al., 2014). Current efforts for tracking and treating macular disease have focused on the retina, for instance, quantification of drusen distributions, photodynamic therapy (Wormald, Evans, Smeeth, & Henshaw, 2007), and even retinal prostheses for degenerations of the entire retina (Lohmann et al., 2019; Roux et al., 2016; Weiland & Humayun, 2013).

Moreover, the impact of degeneration is not limited within the scotoma, but it may also compromise the peripheral retinal region generally considered as "spared". Some studies have reported a higher frequency of peripheral lesions such as drusen, atrophy, and changes to the retinal pigment epithelium, in the retina outside the scotoma when compared to control eyes. (Domalpally et al., 2017; Johansen Forshaw, Minör, Subhi, & Sørensen, 2019; Laíns et al., 2018; Lengyel et al., 2015). This is in line with psychophysical studies reporting reduced visual acuity and contrast sensitivity in MDs in respect to age-matched controls at the same eccentricity (Fletcher & Schuchard, 2006; Maniglia, Pavan, et al., 2016). The indication that patients might show some impairments

even outside the scotoma has also to be considered when discussing results from experimental protocols that match normal viewers and MD patients.

So far, no therapies able to restore patients' vision as it was before the onset of the disease are available. Drug treatments can slow down or even stabilize the formation of the visual defect, but once formed, treatment and rehabilitation must face against its irreversibility. In the case of visual impairment, in the absence of Restorative approaches, it is possible to adopt other types of rehabilitations based on Compensatory and Substitutive techniques (Bouwmeester, Heutink, & Lucas, 2007; Lane, Smith, & Schenk, 2008). In particular, to ensure a better outcome in the daily life activities, the treatment of MD often require combined approaches that reckon on optical aids (N. X. Nguyen et al., 2009; Rohrschneider, 2013) and multiple kinds of training. Some possible training options are reading training (Seiple, Grant, & Szlyk, 2011), scotoma awareness training (Verghese & Janssen, 2015), oculomotor training (Rosengarth et al., 2013) and Microperimetric biofeedback training (Vingolo, Cavarretta, Domanico, Parisi, & Malagola, 2007; Vingolo, Salvatore, & Limoli, 2013). What I will focus on in this thesis is a training based on a perceptual learning paradigm whose purpose is to reshape the way in which visual information relating to multiple concomitant elements is integrated to form a single percept (Uri Polat, 2009). We will see this technique in more detail in CHAPTER III.

The PRL

It is still unclear how the PRL develops and if it acquires over time, particular processing ability with respect to the other quadrants of the functional periphery. Since it may be found in every direction around the scotoma, it is difficult to predict where the PRL might develop. Possibly would be the region with the best-spared sensitivity outside the scotoma (Timberlake, Peli, Essock, & Augliere, 1987) but this idea has been challenged recently since in average the PRL doesn't seem the absolute best retinal spot for visual acuity (Bernard & Chung, 2018; Shima, Markowitz, & Reyes, 2010) or contrast sensitivity and crowding (Contemori, Battaglini, & Casco, 2019). Some other factors known to play a role are the form and density of the central scotoma, the distance from the dysfunctional macula, and also the distance from the scotoma border (Crossland, Culham, Kabanarou, & Rubin, 2005; Erbezci & Ozturk, 2018; S N Markowitz & Aleykina, 2010; Riss-Jayle, Giorgi, & Barthes, 2008a, 2008b). Sometimes, multiple PRLs may co-exist, and they could be interchanged depending on the viewing distance, the task, or the luminance (Crossland et al., 2005; Déruaz, Whatham, Mermoud, & Safran, 2002; González, Tarita-Nistor, Mandelcorn, Mandelcorn, & Steinbach, 2018; Lei & Schuchard, 1997). Probably it is worthy of thinking of the PRL as the best region in terms of functional efficiency instead of best sensitivity. Shima and colleagues (2010) have proposed that the oculomotor efficiency is likely the driving force for the functional adaptive changes in MD. They suggest that the spot with the best sensitivity and the one with the best fixational abilities are not necessarily the same but that they are often nearby each other and functionally linked (Samuel N. Markowitz & Daibert-Nido, 2019;

Shima et al., 2010). Moreover, Kabanarou et al. (2006) showed that there is a shift in fixation in one or both eyes when comparing monocular versus binocular viewing conditions. Since the two monocular PRLs often fall on noncorresponding areas (Kisilevsky et al., 2016) one or both might switch to another position, to facilitate conjugation in binocular tasks (Kabanarou et al., 2006; Verezen, Hoyng, Meulendijks, Keunen, & Klevering, 2011). In general, visual acuity, eye movement, and fixation stability are driven by the better eye (Kabanarou et al., 2006; Schneider et al., 2013; Tarita-Nistor, Brent, Steinbach, & González, 2011) but the overall binocular oculomotor efficiency is still disrupted in patients who have a low correspondence between the two PRLs. As we might expect, the lower the difference in quality of vision between the two eyes end the better the oculomotor efficiency. In fact, the best predictors for the oculomotor efficiency are the contrast sensitivity ratio between the two eyes and the amount of stereoacuity – if measurable – not the absolute visual acuity (Shanidze, Heinen, & Verghese, 2017). The same concept holds also for the reading speed, in this case binocular integration and acuity gain have a stronger impact than absolute visual acuity. Indeed patients with interocular inhibition are reading significantly slower than those with no inhibition or summation (Tarita-Nistor, Brent, Markowitz, Steinbach, & González, 2013). It has been reported that some patients also show characteristics of binocular inhibition at low and medium spatial frequencies (Valberg & Fosse, 2002) but surprisingly in average binocular acuity gain is not different from that of age-matched control participants (Tarita-Nistor, González, Markowitz, & Steinbach, 2006). A better understanding of how the PRLs develop and how people with bilateral MD conjugate the two eyes is fundamental to design accurately any visual rehabilitation protocols that aims

at improving the residual visual ability in MD, but this requires ad hoc tools with different characteristics from those generally used in clinical evaluation and rehabilitation (Tarita-Nistor et al., 2015). As we will see later in CHAPTER III, the rehabilitative protocol discussed in this thesis partially overcomes this limitation. In fact, even if carried out monocularly, PL obtained with the lateral masking paradigm is able to transfer to the untrained eye with consequent benefit in binocular vision (Dorais & Sagi, 1997; C. Yu, Klein, & Levi, 2004).

As we will see in CHAPTER VII and VIII, one of the thesis aims is to improve PL outcome by maximizing the transfer through the concomitant use of the tRNS.

Plasticity in the Adult Visual System

Macular degeneration is the most frequent, but not the only cause of central scotoma. Regardless of aetiology, the onset of the central blindness generally occurs in adulthood. (Ferris, 1983).

To date it has been established, that once the critical period for the development of the visual system is over, there is still a certain level of residual plasticity that allows for adaptative changes of the system even in advanced age (C Darian-Smith & Gilbert, 1995; Kaas et al., 1990; Knudsen, 2004). It is also known, however, that this ability is slowly declining with time and that it is subject to the limits given by the functional equilibrium of the entire system (Haak, Morland, & Engel, 2015; Knudsen, 2004; Morishita, Miwa, Heintz, & Hensch, 2010). Any change in the network must be compatible with the subsequent, and previous stages of processing, otherwise perceptive distortions due to maladaptive plasticity may arise (Rosa, Silva, Ferreira, Murta, & Castelo-Branco, 2013). In some cases, visual hallucinations are a necessary step during visual recovery and tend to disappear when the plastic adaptive process matures, but if their presence persists, they could be functionally invalidating (Burke, 2002; C. S. H. Tan, Sabel, & Goh, 2006). When visual cortical neurons in adult mammals are deprived of their normal afferent input from retinae, they can acquire new receptive fields by modifying the effectiveness of existing intrinsic connections, a basis for topographic map reorganization. If the retinal lesions are relatively small (< 5 degrees), after long periods, the lesion projection zone (LPZ) shows partial recovery and exhibit normal receptive field properties for high contrast stimuli. However, their maximum response amplitude

and the contrast sensitivity is notably reduced (Y. M. Chino, 1995; Avinoam B. Safran & Landis, 1996; Sur, Nagakura, Chen, & Sugihara, 2013). Some other experience-dependent mechanisms may overlap on top of this spontaneous cortical plasticity, for example by prolonged practice it is possible to trigger a perceptual learning mechanism (PL) that benefits from reinforcement-dependent plasticity (Manfred. Fahle & Poggio, 2002; Karmarkar & Dan, 2006). Recent studies have shown how it is possible to take advantage of this residual plasticity to obtain significant improvements during rehabilitation protocols although with great limitations (M. Li et al., 2015; Maniglia, Cottereau, et al., 2016). Wandell & Smirnakis (2009) in their fundamental review state: "...it can be no serious debate as to whether the brain is plastic or not: it is both. A better question is to investigate distinct systems and understand the conditions under which each system is plastic or stable". More recently Haak and colleagues by reviewing contrasting results about cortical remapping in MD suggest that differently from animal studies, evidence for extensive reorganization in the adult human primary visual cortex is just limited. According to their model, this could be due to the costs associated with making changes at the very root of the visual processing hierarchy (Haak et al., 2015). A retinal lesion during (or before) the sensitive period can modify the architecture of the visual system radically, but after the development is completed, the patterns of connectivity become highly stable. At this point, the higher visual areas for their correct functioning rely on the retinotopic and functional organizations of the lower-level visual areas. Huge alterations of the low-level structures could have negative consequences in the readout of the upper areas. After the end of the sensitive period, the residual plasticity could be able to alter the connectivity patterns exclusively if the change respects the

architectural constraints established during development. In case of retinal damage, it would make more sense for the visual system to make slow structural adjustments at later stages of visual processing than a fast and extensive remapping at a lower-level, because the later stages have fewer dependencies that may be adversely affected (Merav Ahissar & Hochstein, 2004; Haak et al., 2015; Hochstein & Ahissar, 2002; Lillard & Erisir, 2011). It is important to note that this constraint would be less strict in the case of a simpler brain with less processing nodes such as mice or cats that are the main non-primate models for the study of retinal lesions.

According to the previous literature, a necessary factor for an extensive cortical reorganization might be the presence of a dense bilateral scotoma rather than a monocular scotoma or a bilateral scotoma with some spared islands of vision (Y. M. Chino, Kaas, Smith, Langston, & Cheng, 1992; Daniel D. Dilks, Julian, Peli, & Kanwisher, 2014; Schumacher et al., 2008). Also, the presence of a stable eccentric PRL seems to be relevant (Daniel D. Dilks et al., 2014; Plank et al., 2017; Schumacher et al., 2008). Undoubtedly if the central vision in one of the two eyes is preserved, there is no need for a re-referencing of the oculomotor activity, much less a cortical remapping, with the result that the mechanism of suppression of the best eye with respect to the defective one could be activated (Wiecek, Lashkari, Dakin, & Bex, 2015). This suppressive mechanism could be based on the consolidation of pre-existing inhibitory networks that are also transiently activated in normal viewers, for example during binocular rivalry (Holopigian, 1989; V. A. Nguyen, Freeman, & Wenderoth, 2001). Possibly it could easily be reversed with perceptual learning or dichoptic training, in the same way as of clinical suppression

(Barollo, Contemori, Battaglini, Pavan, & Casco, 2017a; R. F. Hess, Mansouri, & Thompson, 2010; Robert F. Hess, Mansouri, & Thompson, 2010).

Also, the re-activation at the level of the LPZ that is found in patients with bilateral partially overlapping scotoma could indicate a strengthening of a pre-existing feedback network already active in normal vision rather than an extensive cortical reorganization. This interpretation of the BOLD activity in the LPZ was originally suggested by Masuda, but to date it has not been confirmed (Masuda, Dumoulin, Nakadomari, & Wandell, 2008). We will discuss this possibility extensively in the 'Functional changes' section of this review.

The idea that the reorganization relies more on slow structural adjustments at later stages rather than extensive remapping at lower-levels undoubtedly re-launches the role of visual PL – and the active training in general – in the rehabilitation of visual deficits. Later, we will see how the major evidence of cortical reorganization in MD can be explained as the product of short-term non-specific spontaneous plasticity mechanisms. This form of plasticity contrasts with the one promoted by the perceptual training whose changes are slow but stable over time. (Maniglia, Cottereau, et al., 2016; Sabel, Henrich-Noack, Fedorov, & Gall, 2011; Trauzettel-Klosinski, 2011).

Is there a remapping process for the neurons inside the lesion projection zone (LPZ)?

Retrograde (presynaptic) degeneration of retinal ganglion cells and retinal nerve fibers following damage to the occipital lobe has been documented extensively (Beatty, Sadun, Smith, Vonsattel, & Richardson, 1982; Cowey & Stoerig, 1989; Dinkin, 2017). On the other hand, evidence for anterograde (postsynaptic) degeneration are not as prevalent, but the phenomenon is nonetheless accredited (You, Gupta, Graham, & Klistorner, 2012) as well as the fact that retinal degeneration could lead to secondary brain damage to the visual pathways through a trans-synaptic degeneration mechanism (Ito, Shimazawa, & Hara, 2010).

On the other hand, we also know that the adult visual system has residual plasticity that can counterbalance this phenomenon through the functional reorganization of neurons whose afferences have been suppressed (Gilbert & Li, 2012; Karmarkar & Dan, 2006). In this regard, the long-term visual deprivation might work as a trigger for the replacement (loss and formation) of spines in the deafferented cortex favouring the formation of new networks (Keck et al., 2008). One might wonder what the changes at a structural and functional level after a long period of adaptation to the loss of central vision are and whether these changes lead to compensation for the damage. Over the last two decades, a growing body of research has used magnetic resonance imaging (MRI) to answer these questions (Prins, Hanekamp, & Cornelissen, 2016). We will try to summarize the main findings in the following paragraphs.

Structural Changes

In MRI research that studies alterations following the loss of central vision, it is a common practice to compare patients with a corresponding age-matched control group.

The body of evidence that has gradually accumulated over time shows a reduction in the grey matter of the lateral geniculate nuclei, and of the visual cortex as well as in the white matter of the optic radiations (Boucard et al., 2009; Hernowo et al., 2014; Plank et al., 2011; Prins, Hanekamp, et al., 2016; Yoshimine et al., 2018). Grey matter loss in the visual cortex appears to overlap with the retinotopic region corresponding to the retinal lesion (Boucard et al., 2009) and to be correlated with scotoma size (Plank et al., 2011). Also, differences between JMD and AMD have been evidenced, with JMD showing more marked signs of grey matter loss (Prins, Plank, et al., 2016) and white matter loss in the optic nerves and the chiasm (Hernowo et al., 2014). If the long-term visual deprivation would be the mechanism behind those structural changes, we should see alterations in higher-level visual areas as a consequence of specific functional deprivation in the absence of damage in the early visual cortex. This is precisely what has been found in the case of late monocular blind patients where a volumetric decrease in the superior lateral occipital cortices is present in the absence of a decrease in the early visual cortex (Prins, Jansonius, & Cornelissen, 2017). On the contrary, in MD, observed data are consistent with a transsynaptic degeneration propagating from the degenerated retinal axons to the central visual system (Malania, Konra, Jägle, Werner, & Greenlee, 2017; Ogawa et al., 2014; Yoshimine et al., 2018).

Some very recent studies based on tractography and diffusion-weighted imaging (dMRI) have provided strong support to the existence of transsynaptic anterograde degeneration in case of damage to the peripheral visual nervous system (Balk et al., 2015, 2014; Malania et al., 2017; Ogawa et al., 2014; Tur et al., 2016; Yoshimine et al., 2018). In 2014 Ogawa and colleagues showed a reduction in fractional anisotropy – a measure of fiber integrity – in the optic tract and the optic radiation of patients with central vision loss. Other two studies have later corroborated their main finding. Malania et al., (2017) found a correlation between photoreceptors loss, atrophy of the ganglion cell axons, and diffusivity in the optic tract fibers. Moreover, they found that retinal nerve fiber layer thinning and the lower fractional anisotropy in the optic radiation was not limited to the foveal afferent fibers but also extended to the peripheral fibers (Malania et al., 2017). This is in agreement with the psychophysical and physiological finding showing that the "spared" periphery outside the scotoma maybe not so spared (Domalpally et al., 2017; Fletcher & Schuchard, 2006; Johansen Forshaw et al., 2019; Laíns et al., 2018; Lengyel et al., 2015; Maniglia, Pavan, et al., 2016). Despite this, it is clear that the main driver of the degeneration is the loss of central vision. Yoshimine and colleagues (2018) also found a reduction in fractional anisotropy along the optic radiation, but it affected fascicles primarily projecting to the central visual field in respect to the one projecting to mid or far-periphery. Contrary to the previous study, they did not find an alteration in the optic tract, but they found a positive correlation between the integrity of the optic radiation and the visual acuity (Yoshimine et al., 2018). Although the results of these studies have some minor inconsistencies, they provide convergent evidence that cell death within the retina causes significant alterations along the visual pathways to the cortex. This finding

challenges the understanding that macular degeneration is confined within the retinal tissue and questions the effectiveness of many restorative treatments (Lemos, Pereira, & Castelo-Branco, 2016a). The structural changes listed above are not, however, the only ones that have been found. Alongside with anterograde degeneration, another more general degenerative mechanism could be related to the etiopathology of AMD. For instance, Hernowo and colleagues (2014) have also found that AMDs but not JMDs show a reduction of white matter volume in frontal areas that are not strictly linked with visual processing. This could suggest a link with other forms of neural degeneration such as mild cognitive impairment and Alzheimer disease (AD). Indeed this hypothesis is corroborated by some studies that evidenced some common histopathologic features found in AD and AMD that might be led back to a common pathogenic mechanism (Lynn et al., 2017; Ohno-Matsui, 2011; Ong et al., 2019; Peiretti et al., 2014). Nevertheless, AD and AMD don't have a strong association with each other (Keenan, Goldacre, Goldacre, & Hyman, 2014; Michael A. Williams, Silvestri, Craig, Passmore, & Silvestri, 2014). In fact, the hazard ratio for developing probable or possible AD for people with established diagnoses of AMD (more than 5 years) is quite low, approximately 1.50 (C. S. Lee et al., 2019). A ratio of 1.50 does not surprise if we consider that there might be some common risk factors linked to lifestyle habits (Klaver et al., 1999).

Not all the structural alterations found in AMD have a negative connotation. Some studies have also reported changes that can be traced to a positive adaptation to the presence of the scotoma. For example, Plank et al. (2011) found increased grey matter volume in a region slightly anterior to the frontal eye fields, and this increase was

correlated positively with fixation stability. They proposed that this could be a consequence of oculomotor learning. Other evidence for structural changes linked to functional adaptive plasticity comes from the studies of Sabbah et al., (2017) and Sanda et al., (2018). In this second study, they provided evidence of structural modification linked to enhanced peripheral visual field processing in associative visual areas that compensate for the central visual field loss. In fact, despite a thinning of the visual cortex, they found an increase in synaptic complexity in some regions of the lateral occipital cortex (hOc4la) and the fusiform gyrus (FG1) that are involved in shape, place, object, and face processing (Lorenz et al., 2017; Malikovic et al., 2016). This is in agreement with the previous study of Sabbah (2017) that found increased resting-state functional connectivity between the peripheral early visual cortex and the fusiform gyrus in patients with central visual field loss. If we consider the results presented so far, we can imagine two mechanisms that act oppositely: an anterograde degeneration that spreads from the retinal lesion to the visual cortex and a compensatory mechanism that enhances the connections between the preserved peripheral visual field and the visual associative areas. In this context, the use of PL as a way to bolster activity-dependent plasticity during visual rehabilitation could have the dual purpose of reducing the effects of anterograde degeneration and guiding the strengthening of connections between the cortical projection of the PRL and the higher-level visual areas (Crair & Mason, 2016; Ganguly & Poo, 2013). PL might also work in combination with genetic or pharmacological strategies that reintroduce conditions for reorganization in the adult brain by promoting homeostatic rescaling and synaptic remodelling (Crair & Mason, 2016).

Functional Changes

The use of neuroimaging techniques in the study of central vision loss was not limited to structural investigations, and there are functional anomalies that have also been reported (for review on the topic see (Haak et al., 2015; Lemos et al., 2016a; Wandell & Smirnakis, 2009a). Given the retinotopic structure of the visual system, one of the most interesting questions is what happens to the deafferented part of the visual cortex. One hypothesis is that the neurons coding for the diseased part of the retina that is still functional could be recruited in the processing of stimuli outside the scotoma (Daniel D. Dilks et al., 2014; Masuda et al., 2008; Morland, Baseler, Hoffmann, Sharpe, & Wandell, 2001). By responding to stimuli originally outside the retinotopic area of their competence, these neurons would, therefore, undergo a functional remapping. This type of extensive reorganization is documented in animal models (Corinna Darian-Smith & Gilbert, 1994; U T Eysel & Schweigart, 1999; Ulf Th Eysel, Gonzalez-Aguilar, & Mayer, 1980; Keck et al., 2008) as well as in other domains such as the somatosensory cortex (Flor, 2003; Gaetz et al., 2018; Rigato, Begum Ali, Van Velzen, & Bremner, 2014; Winship & Murphy, 2009). In the human vision, this has been found in early partial blindness (Baseler et al., 2002; L. Muckli, Naumer, & Singer, 2009) and recently also in adults suffering from degeneration of the peripheral retina (Ferreira et al., 2017). In case of central vision loss, some authors observed a stimulus-related activation in the lesion projection zone (LPZ) (Chris I. Baker, Dilks, Peli, & Kanwisher, 2008; Masuda et al., 2008; Schmid, Panagiotaropoulos, Augath, Logothetis, & Smirnakis, 2009). There are two competing explanations for the activation in the LPZ: it could indicate structural

reorganization of the visual cortex or unmasking of previously silent cortico-cortical connections (Masuda et al., 2008). Although the first hypothesis finds support in animals and juvenile lesions, there are valid reasons to think that this activation does not represent an index of cortical reorganization in adults with MD. First of all the reactivation of the LPZ seems to be present only under some conditions (Masuda et al., 2008, 2010) and only for some patients (Chris I. Baker et al., 2008) and it has not been reported in all the studies (T. Liu et al., 2010; Sunness, Liu, & Yantis, 2004). Moreover, such an extensive reorganization could cause dysfunction at higher visual areas that rely on that input. The input could be misinterpreted as producing distortion or illusions (D. D. Dilks, Serences, Rosenau, Yantis, & McCloskey, 2007). In the case of extensive central vision loss, a huge rearrangement could prevent the long-term stabilization of the initial short-term plasticity (Haak et al., 2015). Based on the recent literature, here we propose a more conservative version of the second hypothesis based on the concept of reinforcement of already existing (and active) cortico-cortical connection instead of the unmasking of silent connection. Only about 20% of V1 activity comes from excitatory projections from the lateral geniculate nucleus (LGN) (Carandini, 2005), while most activity in V1 receives major contributions from top-down, feedback and lateral input (Budd, 1998). In particular, if it is true that collicular input drives the earliest spiking activity that is linked with local processing it is also true that there is a prolonged later response that is more influenced by contextual feature of the stimuli (T. S. Lee, Mumford, Romero, & Lamme, 1998). Recent research shows that feedback from higher-level areas plays more than a modulatory function in V1 but can drive a task-related activity that can spread to non-stimulated regions (Lars Muckli & Petro, 2013). For example activation in V1 carries

information of task-dependent and position-independent representations of imagined (Thirion et al., 2006), remembered (Serences, 2016), or compared stimuli (Mark A. Williams et al., 2008). Baseler and colleagues (2011) in analysing the population receptive fields centre location in MD and controls with artificial scotoma, found the presence of ectopic receptive fields that were not restricted to the LPZ and were equally present in both the patient and control group. They also hypothesized that feedback or lateral connections could be the source of this ectopic signal and that it could be more active in the absence of feedforward signals as in the patient group. The fact that the visual processing in V1 might not be strictly retinotopic plays against the interpretation of this "re-activation" of the LPZ as a sign of extensive cortical reorganization. Moreover, reactivation in the LPZ has been proven to be absent during passive viewing but present during an active task like a discrimination task (Masuda et al., 2008, 2010). This type of task is indeed difficult for the patient given the central scotoma, the instability of fixation and the narrowness visual field stimulated in the scanner. However, why the reactivation of the LPZ can be measured only with difficult active task and not during the classic retinotopic mapping? A possible explanation comes from the paper of Williams et al. (2008), in fact they have found a foveal activation during a peripheral matching task in normal viewers. This activation was related to task difficulty and performance and was stronger after practice. A series of psychophysical (Fan, Wang, Shao, Kersten, & He, 2015; Weldon, Rich, Woolgar, & Williams, 2016; Q. Yu & Shim, 2016) studies have later demonstrated that delayed foveal feedback is critical for peripheral perception in fine details processing. Moreover, this feedback has a precise time course, altering the processing of the feedback utilizing a foveal mask or a TMS pulse at around 350ms that

produces a decrease in the peripheral task performance (Chambers, Allen, Maizey, & Williams, 2013). This feedback seems to be activated "on-demand" only for active peripheral task that requires processing of the details of the image. It has been suggested that since the foveal region has higher spatial resolution and small receptive fields, it might act as a sort of "enhancing software" that reconstruct and solve the details of the blurry peripheral image (Shim, Jiang, & Kanwisher, 2013; Mark A. Williams et al., 2008). Is seems very plausible that the AMD take advantage of this foveal feedback even more than normal viewers. We might also expect a strengthening of this feedback connection, but this is far away from the concept of cortical remapping as found in the sensorimotor system or case of early visual impairments. However, where this feedback comes from? There is consistent literature about a "frontoparietal control system" active during a wide range of cognitive tasks including perceptual discrimination (Cole & Schneider, 2007; Duncan & Owen, 2000) that code for a range of different types of task-relevant information and that is sensitive to changing task demands (Duncan, 2010). Woolgar, Williams, & Rich (2015) showed that during a peripheral task, representation of visual stimuli in the frontoparietal cortex was stronger when stimuli were hard to perceive, and coding in early visual cortex was weak. On the contrary, coding in higher visual areas was sensitive to the allocation of attention but robust to changes in perceptual difficulty. This result is consistent with a feedback process that reinforces the visual percept at an early stage of visual processing. For the patients with central vision loss the possibility of reinforcing such feedback loop seems more probable than the possibility of an extensive rearrangement occurring at lower-order visual areas (Haak et al., 2015). Increased prefrontal and parietal activation in AMD patients compared to controls might

be a sign of increased top-down involvement in basic visual processing to compensate for the sensory loss (Szlyk & Little, 2009). However, some visual and non-visual high-level areas could be affected by the trans-synaptic anterograde degeneration which in turn could weaken the feedback to the lower-level areas. Ramanoël et al., (2018) testing AMD patients with low-pass, high-pass and nonfiltered scenes, found that in respect of controls patients had a much worse performance with high-pass scenes than low-pass. In patients, this was associated with reduced BOLD activity in the cortex corresponding to both the central and the peripheral visual fields. Moreover, they found reduced activation in the parahippocampal place area, a cerebral region specialized for scene perception. Increasing the contrast of the scene produced a benefit in the processing of high-pass images but surprisingly only the activation in the occipital cortex was spurred by the increase in contrast, while the BOLD signal in the parahippocampal place area was not significatively increased (Ramanoël et al., 2018). This could mean that the prolonged decreased sensitivity for high spatial frequencies, and therefore for details, has produced a long-term impoverishment in the area specialized in perception which becomes less responsive.

In contrast, motion sensitivity seems to be improved in MD. It is relevant to mention the case of a monkey who developed juvenile MD. Interestingly the animal showed limited reorganization and no remapping in V1 and V2, but area V5/MT showed increased spread of activation compared to controls (Shao et al., 2013). This finding has been further supported by another animal study that found enhanced peripheral vision as a result of the sensitization for motion processing relying on feedback from V5/PMLS and area 7 to area 17 (Burnat, Hu, Kossut, Eysel, & Arckens, 2017). The idea of

improved motion sensitivity in MD is partially corroborated by a human behavioural study which shows increased effect of large moving visual fields display in the vection of MD patients than controls (Tarita-Nistor, González, Markowitz, Lillakas, & Steinbach, 2008). While in the central visual field the geniculate inputs to the striate cortex are predominantly parvocellular the Parvo to Magno ratio progressively decreases as a function of eccentricity (Azzopardi, Jones, & Cowey, 1999). Moreover, the receptive field size of magnocellular neuron is, on average, much larger compared to the parvocellular one (Croner & Kaplan, 1995). If we consider these assumptions together, we might expect increased sensitivity to motion stimuli due to a compensatory mechanism that in the absence of the foveal input rely mostly upon the spared peripheral abilities. Future studies should better address the modification in motion sensitivity in patients. Moreover, the study of a possible dissociation in the performance of MD patients when tested with stimuli that are selective for the Magnocellular pathway (low spatial frequency and fast motion) or the Parvocellular pathway (high spatial frequency and slow motion) could have potentials implication for rehabilitation.

Receptive Field Expansion

In animal research it is well established that neurons in the border of and inside the LPZ after a given period of recovery display an enlarged receptive that might also be shifted outside the scotoma (Y. M. Chino et al., 1992; Y. Chino et al., 2001; U T Eysel et al., 1999; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1991; Kaas et al., 1990). In adult mammals, this reorganization occurs within hours of the lesion, but only if associated with the absence of input from the fellow eye (Y. M. Chino et al., 1992). The receptive field enlargement can be measured non-invasively by means of a functional MRI method that estimate the neuronal population receptive field size and location (pRF) (Dumoulin & Wandell, 2008; Harvey & Dumoulin, 2011). Results of this measurement in normal human subjects have been found to be in agreement with electrophysiological measurements in the corresponding areas in monkeys (Dumoulin & Wandell, 2008). Shao et colleagues (2013) in a monkey affected by MD found an average increase in the pRF size of non-deafferented V1 voxels of about 20%. Similarly to the MD monkey, even MD patients show increased pRF sizes when compared to healthy controls, but unexpectedly the same effect was also present when healthy controls were tested with an artificial central scotoma (Baseler et al., 2011a). Recent studies with the artificial scotoma suggest that the receptive field enlargement is part of a transient mechanism of homeostatic disinhibition that leads to increased cortical response in the cortical zone deprived of the visual stimulation (Haak, Cornelissen, & Morland, 2012; Papanikolaou, Keliris, Lee, Logothetis, & Smirnakis, 2015; Parks & Corballis, 2012). The fact that this expansion is very rapid and present also in case of artificial scotoma lets us think of a

reversible, spontaneous and automatic mechanism which has nothing to do with the retinal damage in the strict sense, but which instead comes into play whenever there is a significant decrease in the levels of visual activity in a given part of the visual field, and that is partly modulated by feedback signals from extrastriate visual areas (Haak et al., 2012).

This short-term plasticity comes at the expense of the neural response tuning as it causes a reduction in the inhibitory shaping of selectivity (Gannon, Long, & Parks, 2017). Even if it cannot be considered a reorganization process in itself, the increase in receptive field size together with the transient increase in cortical response might be the starter for a long-term topographical reorganization (Gannon et al., 2017).

At the same time, it could produce behavioural effects that in some cases might be detrimental. In AMD patients, some studies have shown a specific impairment for the elaboration of precise details transmitted from high spatial frequencies in the scenes, while the perception of global forms transmitted by low spatial frequencies remains relatively well preserved. (Musel et al., 2011; Peyrin, Ramanoël, Roux-Sibilon, Chokron, & Hera, 2017). This could be a consequence of the widening of the receptive fields that leads to a greater spatial summation, but also to a loss of neural tuning. Improving the sensitivity specifically to the medium and high spatial frequencies is one of the objectives of the neural-based perceptual learning that will be discussed in CHAPTER VIII of this thesis.

In the next section, I will discuss how, through the use of psychophysical methods it is possible to investigate the mechanisms of adaptation to the presence of the central scotoma.

Psychophysical Evidence of Cortical Plasticity in MD

We have previously seen what are the main visual deficits that emerge following the presence of bilateral central scotomas, we then saw what are the structural and functional alterations that ensue at the level of the central nervous system. Now we will focus on the psychophysical studies that have investigated the presence of cortical reorganization. Patients with retinal scotomas experience perceptual filling-in for scotomas as large as 6 degrees (Gerrits & Timmerman, 1969; Zur & Ullman, 2003). According to the classification in Weil & Rees (2011), this completion process falls under Stimulus-independent and instantaneous type. The exact mechanism through which this process takes place is still uncertain. There can be three possible mechanisms that can act independently or combined. First, there might be active lateral propagation of the visual information from the border to interior of the scotoma (Weerd, Gattass, Desimone, & Ungerleider, 1995); alternatively there might a be a remapping of receptive fields (Y. Chino et al., 2001). Lastly this completion might be driven by the activity of some location-independent large receptive fields like the one found in the lateral occipital and inferior temporal cortex that are activated even in case of partial visual stimulation as in the presence of an occluder (Hegdé, Fang, Murray, & Kersten, 2008; Weigelt, Singer, & Muckli, 2007). How much of this process can be attributed to a permanent and slow adaptive reorganization (long-range rewire) and how much is part of transient plastic mechanisms (receptive field enlargement and shift) is not given. Crossland and Bex (2009) in a Vernier task found an advantage when stimuli were presented across the physiological blind spot than over equally eccentric temporal retina, but the same

advantage was not present over pathologic retinal scotomas than more intact, equally eccentric retina. This result suggests that the filling-in in the pathological scotoma does not have a functional implication and is not the result of a low-level reorganization. With more complex stimuli De Stefani and colleagues (2011) found perfect discrimination of the curvature of the illusory contours over the pathological retinal scotoma that is usually not found over the physiological blind spot. A more recent study found that MD patients had higher sensitivity to mirror symmetry for configuration displayed at the two sides of the scotoma than controls at the same eccentricity. The same was not true for translational symmetry (Clara, Elisa, Luisa, Giovanni, & Luca, 2015). In respect of the Vernier stimuli, detection of illusory contour and mirror symmetry rely on a higher-level cortical representation as they provide stronger cue in Gestalt processes mediating object recognition. Those stimuli are likely coded in the lateral occipital cortex (Bona, Herbert, Toneatto, Silvanto, & Cattaneo, 2014) one of the visual areas that despite the anterograde degeneration shows an increase in synaptic complexity after central vision loss (Lorenz et al., 2017; Malikovic et al., 2016; Sabbah et al., 2017). The dissociation in the detection between low- and high-level visual stimuli in MD is further corroborated by other studies. When tested within their PRL, patients do not show any improved ability to recognize ladder contours, which suggests that there is no use-dependent improvement in contour integration or crowding undergoing (Haun & Peli, 2015). But at the same time, some patients display a spontaneous reduction of impairment over time (Avinoam B. Safran & Landis, 1996). Sunness, Applegate, and Gonzalez-Baron (2000) found that patients with bilateral scotoma have a slow improvement in their visual acuity after the initial drop. Casco and colleagues also reported a case of a patient who presented normal

acuity for crowded letters and better performance than controls in a lexical decision task and visual search (Casco, Campana, Grieco, Musetti, & Perrone, 2003).

Maniglia et al. (2018) using a lateral masking paradigm (I will discuss in depth this paradigm in CHAPTER III) measured the extent of the contextual effect of the two collinear flankers over the central target at the PRL of five MD patients. In this paradigm, depending on the reciprocal distance between flankers and target, we might have a facilitatory or inhibitory effect of the flankers over the target.

Each patient was matched with a control subject tested at the same eccentricity. What they found was a reduction of the inhibition that is generally found at the shortest target-to-flanker distance that was present only in the MD group. They interpreted this result as a sign of spontaneous cortical reorganization that might be related to the receptive field enlargement found in electrophysiological (Y. M. Chino et al., 1992) and MRI studies (Baseler et al., 2011a)

In the previous literature, the amount of lateral inhibition has been linked with the amount of crowding (Maniglia et al., 2011). This link is still controversial, but when MDs are tested with a crowding task at the PRL they display some unusual characteristic that might be in line with the reduction of inhibition. Firstly, despite having a worse visual acuity than controls at the same eccentricity, Md patients nominal critical spacing (the smaller target-to-flanker distance at which they can recognize an object when surrounded by similar flanking elements) is comparable with that of the normal fovea (Susana T.L. Chung, 2014). Secondly, they do not show the radial-tangential anisotropy that is typical when normal viewers are tested in the periphery (S. T. L. Chung, 2013). Interestingly, the similar reduction in the radial-tangential anisotropy has been observed in normal viewers

after a small practice with an artificial central scotoma. Moreover, this effect was correlated with a reduction in the crowding-related suppression measured with fMRI (N. Chen et al., 2019). The authors of this study suggest that this might be due to a reorganization in the local connections that alters the way in which the context is integrated (or segmented) with the target. It is tempting to make a link between this result and the previous ones that have shown a widening of the receptive fields and an increase of the cortical activity following the adaptation to a simulated central scotoma (Baseler et al., 2011a). It is not yet clear how these two results relate to each other, what seems clear is that both are the product of a spontaneous mechanism of adaptation to the absence of central input that acts quickly and is easily reversible. At the basis there might be an attempt by the system of maintenance of the homeostasis that tries to balance the absence of input by increasing the local activity (Ganguly & Poo, 2013).

Macular Degeneration: Final Consideration

Up to this point, I have discussed in detail many of the clinical features of MD. Particular emphasis was given to the theme of neural plasticity with reference to more recent work in the field. It is undoubtedly difficult to unify all the results in a coherent picture; in this section, I will try to summarize systematically the salient points:

- There are currently no restorative treatments for macular degeneration.
- The best option is the combined use of training and visual aids.
- MD patients develop one or more PRLs that are used in the tasks usually performed by the fovea.
- In MD, the visual deficits are not limited to central blindness but also partly involve the peripheral vision.
- For rehabilitation, it is important to also consider binocular visual skills and not just the best eye.
- The adult brain is still plastic, and in the event of injury, spontaneous compensatory mechanisms are activated.
- Retinal degeneration could lead to secondary brain damage to the visual pathways through trans-synaptic degeneration.
- There is little evidence of long-range cortical reorganization in MD patients.
- While the early visual areas show signs of degeneration, those of higher-level show use-dependent functional adaptations.

- The reactivation of the LPZ in V1 is largely due to the strengthening of feedback connections from the higher visual areas already present in normal viewers and not to an extended cortical remapping.
- The sensitivity for high spatial frequency in patients is reduced; on the contrary the sensitivity for low spatial frequency moving stimuli is increased.
- Converging evidence supports the presence of a spontaneous and rapid adaptation to the scotoma that can be the trigger for more complex slow changes.
- The homeostatic mechanisms already present in subjects with healthy vision are sufficient to explain the rapid initial adaptations to the scotoma.
- Visual training can be a useful tool to reduce the effects of transsynaptic degeneration and to guide spontaneous plasticity.

In the next CHAPTER, we will look at the features of perceptual learning in detail and how it can be used in visual rehabilitation. In particular, I will discuss the use of a paradigm based on lateral masking as a means to enhance residual vision in the PRL.

Chapter III.

Perceptual Learning as a Tool to Improve Visual Functions

Perceptual learning consists of a practice-dependent improvement in a task that may persist for months; it is specific to the stimulus, to the type of task, to the eye, to the retinal location, to the spatial frequency and the orientation used during the training process (Manfred Fahle, 2005; Goldstone & Byrge, 2013). This specificity of perceptual learning has been explained because of a long-term practice-dependent structural modification that alters response properties of neurons in the primary visual cortex (M Ahissar & Hochstein, 1993; Merav Ahissar & Hochstein, 1996, 1997; Manfred Fahle, 2005; Avi Karni & Sagi, 1991, 1993; KUFFLER, 1952). PL seems to occur even in the absence of an explicit task for the subject (Ghose, 2004; Guzzon & Casco, 2011; Herzog & Fahle, 1998; Presentation, 2011; Watanabe, Nẫez, & Sasaki, 2001), but the degree of acquisition, generalization, and retention are strongly related with task difficulty (Merav Ahissar & Hochstein, 1997; DeLoss, Watanabe, & Andersen, 2014; J. Liu, Lu, & Dosher, 2012; X. Wang, Zhou, & Liu, 2013), involvement of the subject (T. H. Lee, Itti, & Mather, 2012; T. H. Lee, Sakaki, Cheng, Velasco, & Mather, 2013) and attentional resources allocated on the stimulus (Donovan & Carrasco, 2015; Paffen, Verstraten, & Vidnyánszky, 2008; Roelfsema, van Ooyen, & Watanabe, 2010; Tsushima & Watanabe, 2009). Recent results suggest that if the sustained attention is involved, only the processing of characteristics that are relevant to the task is object of learning, while

reward-related reinforcement signals promote both non-relevant and task-relevant learning (Huang & Watanabe, 2012; Sasaki, Nanez, & Watanabe, 2010; R. Wang, Zhang, Klein, Levi, & Yu, 2012). As Yotsumoto and Watanabe (2008) suggest, different levels of processing are involved during PL depending on trained feature and training procedure. In general, we can distinguish between three primary levels where learning can take place, and for each of them, there is a particular model that tries to explain the mechanisms:

(A) Early-stage, local network model: (Yael Adini, Sagi, & Tsodyks, 2002; Tsodyks, Adini, & Sagi, 2004) learning may occur intracortically at low-level, and therefore we do not have to assume interactions between cortical areas at different levels in the visual processing hierarchy.

(B) Mid-level stage, reweighting: (B. A. Dosher, Jeter, Liu, & Lu, 2013; Barbara Anne Dosher & Lu, 1998), learning occurs by changing the strength of neural connections specific for a given task between the early processing stage and a decision unit. This reweight can account for transfer to very similar tasks that share the same processing network

(C) Higher-to-lower stages, Reverse hierarchy theory (RHT): (Merav Ahissar & Hochstein, 2004) top-down modulation influences the signal to noise ratio during the task, the sustained attention repetition after repetition drives learning triggering a structural change in the whole system. The three models should work as guidelines to achieve the best training procedures. Indeed, a clinical procedure needs feasibility, reliability, and should produce a long-lasting gain in the quality of life of the patients. Thus, it is possible to combine a task with increasing difficulty that ensures top-down

modulation (Ahissar & Hochstein, 1997; Wang, Song, Qu, & Ding, 2010) with a stimulus tuned according to low-level perceptual features of the system to target fundamental visual abilities, such as contrast sensitivity. Increasing task difficulty is necessary to engage the participant in the task and is known to positively affect the training results (S. C. Hung & Seitz, 2014; Y. Wang et al., 2010). This is usually achieved by the use of an adaptive procedure like a Levitt staircase procedure with nalternative forced choices (nAFC) (García-Pérez, 1998; Levitt, 1971). A virtue of this procedure is that of being predictable since it follows a staircase pattern that converges towards the threshold. In this way, the implicit statistical learning of the target variation helps the subject in building up an internal representation of expected target making the task more effective (Fiser, 2009; Fiser, Berkes, Orbán, & Lengyel, 2010; Neger, Rietveld, & Janse, 2014). This also provides a progression in the difficulty of the task that is supposed to increase learning gain (DeLoss et al., 2014; J. Liu et al., 2012; X. Wang et al., 2013) and reduce participants' frustration. Through this procedure, it is also possible to take advantage of the positive effect of the feedback that strengthens the stimulus-response association (task rule) through positive by maximizing decision mechanism through reward (Kumano & Uka, 2013; Z. L. Lu, Liu, & Dosher, 2010; Petrov, Dosher, & Lu, 2005). Using our previous knowledge, it is possible to refine the training procedure in such a way as to exploit the low-level plasticity and to foster transfer at higher-level untrained visual function. As Chung states in “The Glenn A. Fry Award Lecture 2012: Plasticity of the Visual System Following Central Vision Loss (2013): “The presence of this experience-dependent plasticity offers us an exciting opportunity to adopt PL as an alternative

rehabilitative strategy for improving visual functions for people with central vision loss" (Atchison, 2012).

Specificity vs. Generalization

One of the characteristics necessary for PL to become a useful tool for visual rehabilitation is undoubtedly a high degree of generalization. Without this, the definite improvement that is achieved hardly affects the everchanging activities of daily life. Very consistent literature shows the specificity of perceptual learning to many low-level visual features and training characteristics which are encoded in early visual areas such as V1 and V2 or MT. Some examples are orientation and spatial frequency (Fiorentini & Berardi, 1980), texture (Avi Karni & Sagi, 1991), retinal position (M. Fahle, Edelman, & Poggio, 1995), motion direction (Ball & Sekuler, 1982), motion speed (Saffell & Matthews, 2003), and the trained eye (Manfred Fahle, 2004) but under some conditions it is possible to allow transfer to slightly different stimuli or to totally untrained tasks (Merav Ahissar & Hochstein, 1997; Manfred Fahle, 2005; Z. Liu & Weinshall, 2000; Uri Polat, 2009). For example, Harris, Gliksberg, & Sagi, 2012 and Harris & Sagi, 2015 found that complete generalization to a new location can be observed by introducing "dummy" trials with task-irrelevant stimuli counteracting sensory adaptation. Following this research line, Mastropasqua, Galliussi, Pascucci, & Turatto in 2015 showed that transfer of learning was complete and mutual between two tasks ant different retinal locations when the alternation between the two tasks was implemented on a trial-by-trial basis. However, when the amount of additional training was significantly reduced (second task only in 20% of the trials) or the exposure to the second stimuli was passive, then PL remained confined to the trained location (no transfer). With double training, an active task is more likely to transfer to another retinal location, but the frequency of the

second task has to be higher than the 20% of the total trials. This study shows that the characteristics that can influence the level of generalization are many and peculiar. Many other studies found evidence of generalization, but the general rule is still unclear. Experiments with many repetitions and with stimuli that are very difficult to discriminate (high similarity between them) are more prone to produce specific learning (Harris et al., 2012) while more transfer has been observed with a small number of trials (Avi Karni & Sagi, 1993), with shorter training sessions (Kristoffer C. Aberg, Tartaglia, & Herzog, 2009), with easy tasks (Merav Ahissar & Hochstein, 1997) with coarse discrimination (Jeter, Dosher, Petrov, & Lu, 2009), or with interleaved double training (J.-Y. Zhang et al., 2010). It has been suggested, for instance, that sensory adaptation due to repeated visual stimulation is the main causes of specificity. When adaptation is removed, complete generalization to a new location can be observed (Harris et al., 2012). According to this view, perceptual learning would involve a low-level visual network that processes simple stimulus features and a higher-level readout network used to learn how to perform the task based on the output of the lower-level network. Sensory adaptation occurring during training could hinder learning at the level of the low-level network so that the readout higher-level network will not be able to successfully apply the experience previously gained to new conditions (transfer) (Harris & Sagi, 2015). Stimuli and task choice strongly influence the level at which we might expect the transfer, and as a consequence, the degree of generalization. Performing training on a fundamental visual feature with stimuli able to match the selectivity of the early visual cortex is very likely to drive a neural improvement at early stages of processing. A low-level stimulus with a restricted set of alternatives may lead to over-specificity of learning, significantly

reducing the transfer to other stimuli, but strongly increasing the signal-to-noise ratio for the input to all the subsequent processing modules (Sagi, 2011a). On the contrary, using complex stimuli or tasks might push the locus of learning at a higher stage of processing, making learning more generalizable but also less efficient (C. S. Green, Kattner, Siegel, Kersten, & Schrater, 2015). It has been suggested that the level a which learning occurs in the brain may change from time to time to achieve the greatest improvement possible, for the peculiar task, and stimuli at hand (Sasaki, Nanez, & Watanabe, 2010). Optimizing PL for clinical purposes, require to train the entire chain from the coding of the stimulus to the decision-making process and even beyond, up to the backward feedback propagation to the coding areas. A means to achieve this, is by providing a feedback to the subject. The feedback is a key factor that could influence both, the learning (Holloway, Tsushima, Nanez, Watanabe, & Seitz, 2010; Shibata, Yamagishi, Ishii, & Kawato, 2009) and the generalization (Herzog & Fahle, 1997; J. Liu, Dosher, & Lu, 2014). Using two different task, one orientation discrimination and one motion discrimination Holloway and colleagues (2006) found learning only in the trial-by-trial feedback conditions in respect to the no-feedback. Aberg & Herzog (2012) demonstrated that criterion and sensitivity are affected both by feedback delivered trial-by-trials while feedback delivered across block affects only the sensitivity. In an fMRI based study, Goldhacker, Rosengarth, Plank, & Greenlee (2013) find that feedback influenced behavioural performance and, even if to a lesser extent brain activation in areas responsible for monitoring PL, suggesting a top-down influence. In an ERP study, Zhang, Cong, Song, & Yu (2013) investigated electrophysiological correlate linked with location specificity and transfer in a Vernier PL paradigm. Results show that transfer is associated

with P1 reduction and N1 enhancement whereas location specificity is only associated with N1 suppression corresponding to the untrained retinal location. These results are consistent with the proposal of top-down modulatory influences at the untrained location. Moreover, Kahnt and colleagues (2011) acquiring fMRI data during a training in an orientation discrimination task involving feedback, found that activity in the ACC tracked changes in decision variables during learning. These results provide strong evidence for PL-related changes in higher order areas and suggest that perceptual and reward learning are based on a common neurobiological mechanism.

The Lateral Masking Paradigm

Among the various PL paradigms that have been proposed one, in particular, seems to have high potential in promoting neural plasticity from the lowest coding freedom to the highest decision-making process. The lateral masking paradigm consists in a contrast detection task for a low contrast Gabor patch flanked by two high contrast Gabor patches (Camilleri, Pavan, Ghin, & Campana, 2014; Casco et al., 2014; Maniglia et al., 2011, 2018; Maniglia, Pavan, et al., 2016; U. Polat, Ma-Naim, Belkin, & Sagi, 2004a; Uri Polat, 2009; Tanaka & Sagi, 1998). Among others approaches, contrast detection with lateral masking is one of the leading training paradigms adopted to treat a series of visual diseases such as amblyopia (Barollo et al., 2017a; U. Polat et al., 2004a), presbyopia (Uri Polat, 2009), myopia (Camilleri, Pavan, Ghin, & Campana, 2014; D. T. H. Tan & Fong, 2008) and Age-Related Macular Degeneration (AMD) (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). Although the method and parameters used are not always the same, all these studies have found an improvement in visual functions following training, in particular in visual acuity and contrast sensitivity. Tan & Fong (2008) trained myopic subjects with Gabor stimuli manipulating many different parameter such as the presence of flankers, the global and local orientation, the Gabor-flanker separation, the exposure time, the contrast and spatial frequency. At the end of the training they found an improvement in visual acuity with the Early Treatment Diabetic Retinopathy Study logMAR chart (ETDRS) (2.1 logMar lines) that was greater in subjects with lower visus. They found also an improvement in the contrast sensitivity for all the spatial frequencies tested and transfer to the contralateral eye. Moreover, follow up

after 6 and 12 months showed that the learning was largely maintained. Later, Durrie & McMinn (2007) replicated these positive results in a group of myopic and presbyopic subjects. Recently, Polat and colleagues (2012), after a training paradigm based on a "backward masking" with flankers, found a significant improvement in contrast sensitivity and visual acuity.

At this point a doubt arises, since training the neurons in V1 increase their tuning and thus their selectivity (Manfred Fahle, 2005; U Polat & Sagi, 1994), how is it possible to achieve transfer to complex stimuli and to the untrained eye after PL? Li and coworkers (2011) suggest that the transfer of the lateral masking paradigm could be unidirectional from the high spatial frequencies that represent the limit of acuity towards low spatial frequencies. It is also possible that since the task trains a low-level neuronal network all the higher lever module that readout from the trained one will benefit from the training allowing for a cascade of improvements (Maniglia et al., 2011).

This task also offers the advantage of allowing to study how early spatial integration of the target and its context occurs. Having been intensely studied, the predictions regarding the contextual effects of flankers are well detailed. From the previous literature we know that when collinear flankers are placed at a distance of 3-4 lambdas – the wavelength of the target Gabor's carrier (λ) – they are able to enhance the detection of the target if compared to the threshold for the single Gabor or the orthogonal neutral conditions (Polat & Sagi, 1993, 1994a, 1994b). On the contrary, for very short target-to-flankers distances (i.e., 1–2λ), the contrast threshold is increased. The mechanism behind this dissociation is not entirely understood, but there is a general agreement between neurophysiological and psychophysical data (Grinvald, Lieke,

Frostig, & Hildesheim, 1994; Uri Polat & Norcia, 1996). Lower contrast detection thresholds than the orthogonal are generally considered to be a sign of facilitation between receptive fields that are contiguous in space and that code for the same visual feature.

On the other hand the increase in contrast threshold could be explained by a within receptive field inhibition indicating that the flankers are falling in the proximity of the OFF zone of the receptive field (Y. Adini, Sagi, & Tsodyks, 1997; Uri Polat & Sagi, 1993; Zenger & Sagi, 1996). The spatial range of the lateral interactions is also known to increase with eccentricity, in agreement with what is known about the cortical magnification and the spatial integration in the periphery (Maniglia et al., 2011; Maniglia, Pavan, & Trotter, 2015). The last important factor to consider is that extensive training can "reshape" the range and the strength of collinear lateral interactions in both, the fovea and the periphery (Maniglia et al., 2011; Uri Polat, 2009; D. T. H. Tan & Fong, 2008). In particular, PL in the periphery reduces suppression that in turn reduces the critical space necessary to discriminate objects or letters in clutter, a phenomenon usually referred as visual crowding that is particularly critical for MD patients (Maniglia et al., 2011). The advantages and possibilities linked to the use of this technique as a visual rehabilitation technique for macular degeneration will be discussed in the next section.

Visual Crowding

Compared to central vision, the peripheral vision has limited performances in contrast sensitivity (CS), orientation discrimination, VA and word identification (Strasburger, Rentschler, & Jüttner, 2011). Moreover, the identification of a target among neighbouring similar elements, an effect known as visual crowding (Whitney & Levi, 2011), is much less efficient in the periphery in respect to the foveal vision. Crowding is usually quantified by the critical space, the minimal distance between the target and the surrounding elements (flankers) that leads to correct target identification. While not hindering healthy foveal vision (Huurneman, Boonstra, Cox, Cillessen, & Van Rens, 2012), crowding represents a major difficulty in letter recognition and reading for clinical populations suffering from central vision loss (Mansfield, Legge, & Bane, 1996). Recent literature on PL showed that training could reduce crowding effect, however it requires a large number of sessions in order to get significant improvements (Astle, Blighe, Webb, & McGraw, 2015; S. T L Chung, 2007; Susana T.L. Chung & Truong, 2013; Zahra Hussain, Webb, Astle, & McGraw, 2012; Yashar, Chen, & Carrasco, 2015a). Chung (2007) after training participants on crowded letter identification at 10° of eccentricity found a reduction in crowding extent of 38%. Yashar and colleagues (2015) showed that a short (600 trials) training could reduce the critical space of about 32%, with partial retinal transfer and a long-lasting effect. It is possible to obtain a reduction of the critical space even through indirect routes, for example by training lower-level abilities as demonstrated by Maniglia and colleagues (2011). After a long training based on a lateral masking paradigm, they found that the improvement in contrast sensitivity transferred

also to the visual acuity and to the crowding, the latter had a reduction of 16% after training. This encouraging evidence of improved peripheral visual abilities in normal sighted participants seem to indicate a way in which PL can be effectively used in patients suffering from central vision loss, similar to what reported for amblyopia, presbyopia, and myopia (Campana & Maniglia, 2015a; Levi & Li, 2009; Uri Polat, 2009; Woo & Wilson, 1990).

From Basic Experiments to Clinics

We have seen how patients with macular degeneration following the central scotoma appearance begin to use a peripheral region of the retina to perform tasks that require high visual skills usually performed by the fovea. This peripheral region, the PRL, is very sensitive to movement and low spatial frequencies but does not have a high visual resolution and is strongly affected by the phenomenon of visual crowding. This, together with the lousy stability of fixation, strongly compromises the reading and the ability to recognize faces and places, which in turn undermines the patient's autonomy.

Recent literature on PL showed that training could improve contrast sensitivity, visual acuity and reduce crowding (Casco et al., 2014; Chung & Truong, 2013.; Chung, 2011; Polat, Ma-Naim, Belkin, & Sagi, 2004; Polat, 2009; Tan & Fong, 2008). Few recent studies used PL with AMD patients in order to improve their visual abilities (Susana T L Chung, 2011; Maniglia, Pavan, et al., 2016; Maniglia et al., 2018; Plank et al., 2017, 2014; Rosengarth et al., 2013), however results are generally unsatisfactory and no standard rehabilitation protocol exists to this date (see Maniglia, Cottereau, Soler, & Trotter (2017) for a review). Rosengarth and colleagues (2013), trained eight MD patients in an oculomotor task, and found improvements in both reading speed and fixation stability between pre-tests and mid-tests, but not between pre-tests and post-tests. test. Furthermore, they did not find significant changes in the BOLD signals between the pre- and post-training tests in the striate or extrastriate visual cortex. Also, Plank et al. (2014) trained eight AMD patients in a texture-discrimination task. After six training sessions spread over three weeks, patients began to show improvements in Vernier acuity.

Moreover, they showed a weak positive correlation between the increase in performance and fixation stability. These improvements were also accompanied by a modest change in the BOLD response in early visual cortex. The limited benefit of classic PL in patients with central vision loss might depend on the reduced plasticity typical of the elderly population, but also on the different goal that a visual training must accomplish respect to myopia, amblyopia or presbyopia. While in the latter the aim of a rehabilitative training is to restore the foveal vision to its optimal state, in case of permanent retinal damage, the goal of PL would be to train a retinal region different from the retina to achieve tasks for which it is not supposed to, and that would require to unlock extra plasticity. The aim is to ensure that this retinal region assumes processing abilities like those of the normal fovea. The principal limit is given by the size of the receptive fields that are larger in the periphery together with the increased spatial range of the lateral interactions. If a high spatial integration is a desirable feature in the healthy periphery, in the PRL of patients this becomes an essential limit to the visual acuity since adjacent stimuli might be "packed together". In this context, perceptual learning based on lateral masking able to improve contrast sensitivity and selectivity for orientation appears to be the perfect tool for remodelling spatial integration in the cortex that codes for PRL. Maniglia and coworkers in 2016 explored this possibility and showed that with this task in MD subjects, PL effect was pronounced at the ʎs at which the flankers facilitate target detection. Moreover, they found reduced crowding and improved contrast sensitivity to untrained spatial frequencies for patients that had been trained with the two alternatives forced-choice task, but not for the yes/no task using the same stimuli. The ability for the lateral masking paradigm to modulate lateral interaction in the PRL of the MD patients

has been later confirmed with a second study from the same first author published in 2018. In this work they found that before training MD patients exhibited significantly reduced collinear inhibition. This was then interpreted as a sign of spontaneous neural plasticity triggered by the presence of the scotoma and consistent with the hypothesis use-dependent cortical reorganization in the PRL. Moreover, they showed that three AMD patients from the same group after training further reduced the inhibition exerted by the flankers at the shortest target-to-flankers distance. The same was not found in controls where the amount of inhibition before and after training was substantially unchanged. This result suggests that PL might be acting on top of the spontaneous adaptive change in the PRL further boosting neural plasticity, opening promising perspectives for the development of rehabilitation protocols for MD patients. However, similarly to other standard PL procedures this training still presents some drawbacks: First, as most visual PL studies pointing towards structural modification in the early visual cortex the degree of generalization might not be optimal (M Ahissar & Hochstein, 1993; Merav Ahissar & Hochstein, 1996, 1997; Manfred Fahle, 2005; A Karni & Sagi, 1993; Avi Karni & Sagi, 1991; KUFFLER, 1952). While in this and some similar cases training basic features have been proven to transfer to higher-level visual functions (Deveau, Lovcik, & Seitz, 2013, 2014; Maniglia et al., 2011; U. Polat et al., 2004a; Uri Polat, 2009), specificity of learning seems generally more common (Casco et al., 2014; Barbara Anne Dosher & Lu, 2005; Manfred Fahle, 2005; Z. Liu & Weinshall, 2000; Uri Polat, 2009). Alongside specificity, another back draw is the need for long periods of training to observe significant improvement (Susana T.L. Chung & Truong, 2013; R. W. Li, Provost, & Levi, 2007). For clinical populations, a lengthy training can be a reason

enough to prevent them from participation, especially in cases of serious visual diseases, such as AMD, that render patients not independent and force them to rely on others for transportation. Consequently, it is paramount for a clinical application of PL to reduce the length of the training and to define a better ratio between specificity and generalization. This is where electrical stimulation comes into play. Previously, tRNS has been proven useful to boost PL both between blocks and between sessions and also to increase its generalizability (Campana et al., 2014; Conto` & Battelli, 2017; A. Fertonani et al., 2011; Moret et al., 2018; van der Groen & Wenderoth, 2016). By modulating the firing rate of the target neurons tRNS is believed to be able to reduce the sensory adaptation during a perceptual task (Campana, Camilleri, Moret, Ghin, & Pavan, 2016). This thesis aims to push the accelerator of perceptive learning by using a neuromodulatory technique such as transcranial random noise electric stimulation to obtain a significant increase in learning rate. Secondly, we set ourselves the objective of verifying whether this increase in the learning rate turns into an increase in the transfer to tasks and stimuli different from those trained. Reducing the number of sessions required to achieve significant improvement would allow more straightforward application of mass perceptual training in clinical and hospital settings. It should also be taken into consideration that given the recent developments in retinal implantation techniques; perceptual learning becomes a fundamental tool for reducing the effects of trans-synaptic anterograde degeneration that could compromise the effectiveness of the implant in patients with long-standing retinal degeneration. Furthermore, even after the implantation, the use of a paradigm like the one proposed in this thesis could facilitate the adaptation of the central nervous system to artificial input, accelerating it and making it more effective.

Chapter IV.

Non-invasive Brain Stimulation Techniques: The tRNS

Among the non-invasive brain stimulation techniques [NIBS] the transcranial magnetic stimulation [TMS] and the transcranial direct current stimulation [tDCS] are the most exploited as a therapeutic intervention for cortically based disorders (Coslett & Hamilton, 2011). Both have been proven useful in the rehabilitation for motor, visual, somatosensory, attentional, cognitive and emotional function (Clayton, Kinley-Cooper, Weber, & Adkins, 2016; Dionísio, Duarte, Patrício, & Castelo-Branco, 2018; Martin et al., 2003; Solomons & Shanmugasundaram, 2019; Utz, Dimova, Oppenländer, & Kerkhoff, 2010; Wessel, Zimerman, & Hummel, 2015). During transcranial direct current stimulation (tDCS), a homogenous electric field is induced in between the electrodes to elicit polarity-specific modulation of cortical excitability, in particular an increase of cortical excitability by the means of sub-threshold depolarization for anodal stimulation and a decrease of cortical excitability for cathodal stimulation as a consequence of hyperpolarization, with effects lasting beyond the stimulation period (M. A. Nitsche & Paulus, 2000; Paulus, 2011; Radman, Ramos, Brumberg, & Bikson, 2009; Reato, Rahman, Bikson, & Parra, 2010). Through the tDCS, a homogeneous electric field is induced between the electrodes. This electric field is able to modulate the cortical excitability of the stimulated zone by increasing or decreasing it depending on the direction of the field. The anodic stimulation produces an increase in cortical excitability

through sub-threshold depolarization while the cathodic stimulation produces hyperpolarization. The effect of the stimulation lasts for a period of about an hour even after its interruption. The duration of this after-effect varies depending on the stimulation parameters and the stimulated area (M. A. Nitsche & Paulus, 2000; Radman et al., 2009; Rahman et al., 2013). The current is delivered through electrodes positioned on the scalp. In order to improve the flow of the current and reduce the impedance, conductive gel or sponges soaked in saline solution are used. This causes the focus of the stimulation to be limited, and therefore it is advisable to evaluate the actual intensity and extension of the electric field generated for each assembly through simulations on anatomically and physiologically plausible models. The direct current is caused by a battery-driven stimulator. The stimulator is a medical device, and thus in Europe it has to be certificated for the use. An electrode is placed over the target cortical region and the second electrode, usually larger to reduce current density, is placed on a non-target area. The two positions can be identified through neuronavigational tools or more simply by using the international EEG system 10-20 (Chatrian, Lettich, & Nelson, 1985). This approach, however, is susceptible to individual variations in the anatomy of the skull and the grooves that reduce the consistency of the technique (Jurcak, Tsuzuki and Dan, 2007). Not infrequently in fact unexpected effects of the stimulation are observed that can be attributable to the differences in response to stimulation between the subjects (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015). One way to explain the apparent inconsistencies of the polarity effect among previous studies is considering that the tES effect might be different in (sub)clinical population compared to healthy participant (Hill, Fitzgerald, & Hoy, 2016), but also that the task-induced activity is more critical than the

polarization to predict the stimulation effect on a participant's behaviour (Bortoletto, Pellicciari, Rodella, & Miniussi, 2015). Furthermore it must be considered that the same stimulation acts differently on different neural subpopulations producing a globally non-linear effect in some cases (Remedios et al., 2019). Recently, non-invasive brain stimulation has been used, alone or coupled with PL, to enhance visual abilities (Camilleri et al., 2016; Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Campana et al., 2014; A. Fertonani et al., 2011; Pirulli et al., 2013; Thompson et al., 2008). In particular, transcranial random noise stimulation (tRNS), in which a weak current is delivered through the scalp on a cortical region at random frequencies, has shown promising results in boosting PL and reducing the number of sessions needed to observe significant improvements (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; A. Fertonani et al., 2011). Specifically, Camilleri et al. (2014) and Campana et al. (2014) showed that tRNS during contrast-detection training-induced higher transfer (the post-training improvement observed in a new task) to visual acuity (VA) with respect to PL alone in both amblyopic and myopic patients. In general, tRNS appears to boost both the early (within-session - Fertonani et al., 2011) and late (between sessions/days - Camilleri et al., 2014) components of PL. So far, PL studies used tRNS coupled with lower-level perceptual tasks, such as contrast detection or orientation discrimination, rather than training directly higher-level visual abilities, such as VA or crowding. As we have seen, sensory adaptation occurring during training could hinder learning at the level of the low-level network, so that the readout higher-level network will not be able to successfully apply the experience previously gained to new conditions (transfer) (Harris & Sagi, 2015). hf-tRNS has been proven useful to boost the transfer of perceptual learning to untrained

visual tasks (Moret et al., 2018), a highly desirable outcome when perceptual learning is used for clinical purposes. A possible explanation of this result could rely on the effect of hf-tRNS in limiting sensory adaptation. This hypothesis is corroborated by a study from Campana et al. 2016 showing that the application of online hf-tRNS over the medial-temporal area (V5/MT) diminished the perceived duration of the motion after-effect. From a physiological point of view, tRNS might induce by temporal summation of small depolarizing currents, an increase in the activity of the engaged neurons (Cash & Yuste, 1998). In fact, stimulation between 100 and 1000 Hz may be optimal for affecting neuronal communication as it could interact with the activity of the cell body and dendrites whose the time constant is between 1 and 10 ms, s. The repetitive activation of the sodium channels and the consequent influx of Na+ ions inside the membrane (A. Fertonani et al., 2011; K.-A. Ho, Taylor, & Loo, 2013) may interfere with the depressed state of the adapted neurons repolarizing the membrane near to its resting state (Campana et al., 2016). The mechanisms underlying tRNS are still not completely understood: co-occurrence of stimuli in close succession and the temporal summation of small depolarizing currents induced by the random sub-threshold stimulation (D. Terney, Chaieb, Moliadze, Antal, & Paulus, 2008) might therefore facilitate the depolarization of cortical neurons, producing Hebbian LTP-like changes in the network that processes the task (Cappelletti et al., 2013; A. Fertonani et al., 2011; Miniussi, Harris, & Ruzzoli, 2013; Snowball et al., 2013), improving in turn performance over time (D. Terney et al., 2008). An alternative hypothesis is that the high fluctuating frequency of stimulation (100-640 Hz) prevents the homeostasis of stimulated neurons (A. Fertonani et al., 2011). Actually, tRNS seems to induce greater improvements than anodal tDCS, where the current flows

constantly along the same direction (A. Fertonani et al., 2011; Moliadze, Antal, & Paulus, 2010; Pirulli et al., 2013). Finally, the introduction of external noise from the electric stimulation might have altered the overall level of neural excitability and the probability of discharge of every single unit, modifying, in turn, the signal-to-noise ratio during stimulus processing (A. Fertonani et al., 2011). Miniussi and collaborators (2013) proposed a model of 'stochastic resonance' to explain the non-linear effects found in brain stimulation studies. Their model takes into account the interaction between internal activity, externally induced noise and stimulus-driven activity, predicting that in case of low target signal an adequate amount of external noise can enhance the signal (alone) above the threshold. At a neurophysiological level, the tRNS has been shown to modulate the activation and inactivation of the Na+ channels exerting the maximum excitability increase at an intermediate level of noise (Remedios et al., 2019). This short-term molecular activity due to the tRNS that increases the neuronal activation might be the neural bases for the behavioural effect observed.

Furthermore, repetitive activation and inactivation of the NA + channels could trigger the biological cascade responsible for a long-term plastic mechanism that could explain the offline after-effect and also the long-lasting effect that was found in perceptual learning studies (Chaieb, Antal, & Paulus, 2015). Given the uncertainty surrounding the neurophysiological mechanisms of tDCS, and the observed differences in terms of behavioural effects and time courses between anodal tDCS and tRNS (Antal & Herrmann, 2016; Pirulli et al., 2013), the effect of the latter might be different from those of the former and could be better suited to be coupled with perceptual learning.

The advantages offered by tRNS can be summarized as follows:

- it is easier to make predictions about its effect and to interpret the results. This reduces the probability of any unwanted effects.
- coupled with perceptual learning, it proved useful in increasing the learning rate.
- preventing sensory adaptation during the task may be helpful in increasing the transfer

One of the objectives of this thesis is to investigate the effect of single-session and repeated sessions of tRNS over the spatial integration in the occipital cortex.

In the next section, I will discuss some considerations on the safety of use of this technique.

Safety considerations

Among the tES techniques, the most commonly used is the tDCS. Over time, guidelines have accumulated in the literature that establish the limits of the safe use of this technique, as well as reviews on the possible risks encountered during experimental and clinical practice (Almousa, Alajaji, Alaboudi, Al-Sultan, & Bashir, 2018; Bikson, Datta, & Elwassif, 2009; Bikson et al., 2016; Anna Fertonani, Ferrari, & Miniussi, 2015; Liebetanz et al., 2009; Michael A. Nitsche et al., 2003; Poreisz, Boros, Antal, & Paulus, 2007; Thair, Holloway, Newport, & Smith, 2017; Woods et al., 2016). Given the similarity between the three techniques, the same safety criteria apply also for the tACS and the tRNS (Kerrie-Anne Ho, Taylor, & Loo, 2015; Inukai et al., 2016). The first safety criteria for the use of tDCS in humans were based on studies conducted by Nitsche and colleagues and where published in 2003 (Michael A. Nitsche et al., 2003). Despite some updates and clarifications, the basic rules for using this technique have not changed.

In a rat model, Liebetanz et al., (2009) found that brain lesions occurred at a current density of at least 14.3 mA/cm2 for durations greater than 10 min.

Even if a direct comparison cannot be made, the most intensive stimulation regimes used in recent human studies are two orders of magnitude lower than the limit density causing lesions in animals (K. A. Ho et al., 2016).

The following items are the most important safety considerations when designing a transcranial electrical stimulation study.

- Desired current density, defined as stimulation intensity in mA divided by the electrode size in cm2, in human studies should be 0.06 mA/cm2 or less. This corresponds to an intensity of 2 mA for a 35 cm2 electrode.
- The amount of total charge, calculated as stimulation intensity in mA multiplied by the total stimulation duration and then divided by the electrode size in cm2, should be 500 C/m2 or less. Liebetanz et al., (2009) found that the total charge that guaranteed zero lesions in the animal model was 52400 C/m2, again two order of magnitude higher than the one commonly used in human studies (Bikson et al., 2009, 2016; Anna Fertonani et al., 2015; Liebetanz et al., 2009; Michael A. Nitsche et al., 2003; Poreisz et al., 2007; Woods et al., 2016).
- The temperature increase of the stimulated tissue is to be kept under control (Bikson et al., 2009). Datta, Elwassif, & Bikson (2009) modelled the increase in temperature produced at different stimulation intensities and concluded that at intensities commonly used in humans, the increase in heat is not significant.
- Avoid metallic ion accumulation below the electrodes. Metallic ion absorption can cause a rash or other lesions to the skin, this risk increases in case of repeated sessions of stimulation, but can be prevented by using conductive gel or saline-soaked sponges as a medium (Loo et al., 2011; Woods et al., 2016).
- Check for the presence of large skull defects or skull plates that might alter the cortical current flow. The presence of defects in the skull could create dangerous local peaks in the density of the current as well as making the locus of the stimulation unreliable (Datta, Bikson, & Fregni, 2010).

Some additional considerations must then be made in the case of the clinical application of tenure techniques. For example, it has been reported that tDCS can have an effect on cortical hemodynamic responses by increasing the cerebral blood flow. This might open potential applications for the clinical treatment of ischemic strokes, but at the same time a regional alteration in the hemodynamic response could be dangerous in case of cerebral arteriovenous malformation (Hu, Zheng, Dong, Du, & Liu, 2018). Likewise, cathodal tDCS has been found helpful in the treatment of drug-resistant epilepsy (San-Juan et al., 2015; San-Juan, Sarmiento, González, & Barraza, 2018), but at the same time familiarity with epilepsy has long been considered an exclusion criterion as the stimulation can increase the risk of having seizure (Matsumoto & Ugawa, 2017).

Over time, numerous questionnaires were developed for screening participants, some of which are available online. A good starting point for the screening is the questionnaire published by Thair et al., (2017) in their review.

This questionnaire can be easily adapted to the specific needs of the individual study. In the case of clinical applications of the techniques, it is good practice that the inclusion / exclusion of the participant is evaluated together with a competent doctor.

Given the reported absence of serious adverse effects, in recent studies, the recommended limits for the amount of total charge and number of repetitions have been progressively increased. The only persistent adverse effects of tDCS are mainly skin problems, but usually side effects are limited to a tingling sensation at the skin under the electrodes (Matsumoto & Ugawa, 2017). This sensation mainly pertains to the cutaneous receptor activity of the somatosensory system and usually disappears right after the beginning of the stimulation (Michael A. Nitsche et al., 2003). The strength of this

sensation also depends on the current intensity, the conductivity of the medium, and the type of electrodes (Anna Fertonani et al., 2015; Minhas et al., 2010).

This cutaneous perception can be a limitation in the experimental protocols that require repeated sessions of the actual stimulation and the fake control stimulation, aka the "sham" stimulation. The subject could, in fact, recognize when it is actually stimulated, and this could introduce a bias in the results (Anna Fertonani et al., 2015). It is good practice to try to minimize this sensation by slowly “ramping up” and “ramping-down” the current intensity at the beginning and the end of stimulation.

An advantage of tRNS over tDCS is that of causing a lower skin sensation. In most cases, the subject cannot distinguish the difference between tRNS and sham stimulation (Anna Fertonani et al., 2015).

In general, tACS and tRNS produce fewer adverse effects than tDCS and can be considered safer. (Matsumoto & Ugawa, 2017). In conclusion, the tES in general, and the tRNS, in particular, can be considered as safe both in the basic research and in their clinical application.

Chapter V.

Contextual Influences on the Peripheral Retina of Patients with Macular Degeneration

This chapter has been published in Scientific Reports, 9(1), 9284. Contemori, G., Battaglini, L., & Casco, C. (2019). https://doi.org/10.1038/s41598-019-45648-4.

We have seen in CHAPTER II that adaptation to the absence of central input produces an enlargement of the receptive fields and loss of neural tuning. These adaptations might also influence the organisation of the lateral connections in V1 (Baseler et al., 2011b; Y. M. Chino et al., 1992). In the normal visual periphery, the range of interactions in the PRL is greater than that of the fovea (Lev & Polat, 2011; Shani & Sagi, 2005). In fact, in fovea inhibition is found is between 1 and 1.5λ while facilitation is found between 2 and 4λ. In the periphery the range varies according to the eccentricity but generally inhibition is found up to 2-3λ and facilitation up to 8-12λ (Giorgi, Soong, Woods, & Peli, 2004; Lev & Polat, 2011; Shani & Sagi, 2005). Studying the neural adaptation to the central blindness might produce better visual rehabilitation protocols by taking advantage of undergoing plastic processing. A non-invasive and convenient way of studying these neural adaptive changes is by means of psychophysical testing.

In the previous literature, there are reports of reduced collinear inhibition found in MD and this has been interpreted as a sign of neural plasticity (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). However, these studies had some important limitations. First, the sample size was very small (3-5 subjects). Second, only the PRL was tested. In the study I am going to present to you, we have tried to confirm and extend the previous results by overcoming these limitations.

Introduction

Macular degeneration (MD) causes loss of input to the region of the primary visual cortex that represents the fovea. The evidence that the adult brain is capable of plasticity (Calford et al., 2000; Gilbert & Li, 2012; Wandell & Smirnakis, 2009b) raises the question of how the cortical deafferentation in MD affects cortical functionality and, in particular, whether cortical rearrangement occurs.

The cortical reorganization hypothesis is compatible with the results of the animal studies reporting the expansion of receptive fields of neurons near the retinal lesion boundary (Calford et al., 2000; Y. M. Chino et al., 1992; C Darian-Smith & Gilbert, 1995; Corinna Darian-Smith & Gilbert, 1994; U T Eysel et al., 1999; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1991; Kaas et al., 1990). fMRI studies in humans provide instead conflicting evidence in support of the plasticity hypothesis. Some found clear activation of the foveal cortex to stimuli presented outside the central scotoma, (C. I. Baker, 2005; Chris I. Baker et al., 2008; D. D. Dilks et al., 2009; Daniel D. Dilks et al., 2014; Schumacher et al., 2008) while others did not show evidence of this functional reorganization (Baseler et al., 2011a; T. Liu et al., 2010; Masuda et al., 2008; Sunness et al., 2004). Some of the behavioural changes in MDs support, but only indirectly, the cortical reorganization hypothesis. For example, Safran and Landis (A B Safran & Landis, 1999; Avinoam B. Safran & Landis, 1996) reported that MD patients, similarly to what was found with artificial scotoma (Kapadia, Gilbert, & Westheimer1, 1994), experienced apparent displacement of images adjacent to the scotoma toward the field defect leading to perceptual completion and shape distortion. De Stefani and colleagues

(De Stefani et al., 2011) demonstrated perfect discrimination of the curvature of illusory contours across the pathological scotoma. They suggested that, following the loss of bottom-up input, the visual cortex enhances connectivity and/or low-spatial frequency response, thus mediating the formation of a neural representation of complex geometrical shapes across the scotoma. In the preferred retinal locus (PRL) of the MD patients, Chung (2013) showed a "foveal-like" distortion of the scaling of critical spacing with the eccentricity. Casco and co-workers (Casco et al., 2015) provided evidence that MD patients are better than normally sighted observers in using information allowing detection of the mirror, but not the translational symmetry of a two-dot configuration at the opposite side of the scotoma. This last result is compatible with cortical rewiring, whereby detection of the co-aligned low spatial filters crossing the scotoma becomes more efficient with MD. However, a more parsimonious explanation is that MD's peripheral vision takes its functional advantage from more efficient use of the high-level representation of the visual input. The numerous functional changes that have been observed in MD vision (Casco et al., 2003; S. T. L. Chung, 2013; Clara et al., 2015; A B Safran & Landis, 1999) are compatible with the suggestion that the visual response around the scotoma relies more on the integration fields output.

The relationship between the contextual modulation and the contour integration has been described by (Dakin & Baruch, 2009) and has been postulated to be the basis for the perceptual fill-in to occur (Golden, Field, & Hayes, n.d.) through recurrent feedback to V1 complex cells within the lesion projection zone (McManus, Ullman, & Gilbert, 2008).

To summarize, there is an important question that has no answer yet. Do the functional changes observed in the PRL result from modulation of excitatory and inhibitory contextual influences involved in contrast detection? To answer this question in this work we have looked at whether MD's peripheral vision is associated with a change in contextual influences with respect to controls and whether this change is accounted for by the same model that describes the contrast gain in normal viewer[27]. There are different ways in which the observed pattern of contextual influences in the periphery might be different in MD with respect to controls. In people with normal vision, accumulating psychophysical studies have shown contextual influences on the threshold for contrast detection coming from outside the receptive field of the channel responding to the target (Y. Adini et al., 1997; Gilbert & Li, 2012; Uri Polat & Sagi, 1993, 1994). In particular, it is well established that the visibility of low contrast Gabor patch is affected by collinear flanking Gabors of similar orientation and spatial frequencies but high contrast: Short target-to-flanker separation (1-2 times the wavelength of the target Gabor's carrier, λ) leads to suppression, whereas target-to-flanker separations of 3-4λ lead to enhancement (Y. Adini et al., 1997; Kapadia, Ito, Gilbert, & Westheimer, 1995; Lev & Polat, 2011; Uri Polat & Sagi, 1993, 1994; Shani & Sagi, 2006; Zenger & Sagi, 1996). Moreover, these contextual effects can be modulated by task repetition in a perceptual learning paradigm, in both normally sighted observers (Maniglia et al., 2011; Shani & Sagi, 2006) and patients with impaired vision (Barollo, Contemori, Battaglini, Pavan, & Casco, 2017b; Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Camilleri, Pavan, Ghin, & Campana, 2014; Casco, Barollo, Contemori, & Battaglini, 2018; Casco et al., 2014; Contemori, Maniglia, & Casco, 2014; Maniglia,

Pavan, et al., 2016; Uri Polat, 2009; D. T. H. Tan & Fong, 2008). In addition, contextual influences depend on eccentricity: in the periphery, inhibition is more prominent and contextual enhancement occurs at a target-to-flanker distance of 6λ, that is larger than in the fovea (Lev & Polat, 2011; Maniglia et al., 2011, 2015).

Since lateral connectivity has been shown to increase with practice in normal (Maniglia et al., 2011; U Polat & Sagi, 1994; Zenger & Sagi, 1996) and pathological vision (Lev et al., 2014; U. Polat, Ma-Naim, Belkin, & Sagi, 2004b; Uri Polat, 2008), use-dependent cortical reorganization might change the observed contextual influences. Partial support for the cortical reorganization hypothesis comes from recent papers showing that MD patients exhibited a modulation of contextual influences in respect of controls (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). In the present study we further address this issue attempting to specify the underlying mechanism. In addition, by comparing the effect of flankers distance on contrast detection both in the PRL and in a symmetrical retinal position (non-PRL) we also hope to address the still debated issue of whether the vision in the PRL is enhanced by the use of this region for everyday visual task (D. D. Dilks et al., 2009; Schumacher et al., 2008; Timberlake et al., 1986, 1987). A contextual modulation for target contrast detection with specific properties in the PRL would support the "Use-Dependent Reorganization" hypothesis while a strong similarity between the two tested locations would play in favour of a more conservative "Use-Independent Reorganization" hypothesis (D. D. Dilks et al., 2009). Finally, we asked whether a modulation of contextual influences in MDs affects the efficiency in performing everyday visual tasks.

Materials and Methods

Participants

Participants were 13 MD patients (mean age of 61 ± *9.16* years, range: 49-83 years) and 7 controls (mean age of 59 ± *4.12* years, range: 54-64 years). Patients were selected based on the clinical history and the Nidek MP1 microperimetry results. The dispersion of fixation was quantified during the microperimetry, and only patients with at least 80% of fixations in the range of 2° of visual angle around the focal point of the PRL were included in the sample. Patients with concomitant visual diseases other than central vision loss were not included, nor were those with a visual acuity on the ETDRS eye-chart lower than 1/20 or above 10/20. All the tests were performed monocularly, and in the case of bilateral scotoma, the chosen eye was the one with the best-spared vision based on visual acuity and microperimetry data. The eye chosen to be tested for the control group was the nondominant eye. Because the non-PRL was defined as the symmetrical retinal location of the PRL, the proximity of the optic disc or irregular shape of the scotoma could reduce the visibility of stimuli presented in this second retinal location. To check for visibility of the stimuli, during both the crowding and lateral masking tasks, patients were asked to report the number of visible elements in the non-PRL. Of the 13 MD patients, all could see the full triplet of stimuli (Gabors and letters) in the PRL, while only 8 of them could do so in the non-PRL. Because the presentation of the stimuli was randomized in the two retinal positions to reduce the frequency and the amplitude of eventual eye movements, all the patients were tested in both locations, but

only the ones who were able to see the full triplets were further considered for statistical analysis in the non-PRL position.

Details relative to age, gender, scotoma diameter, visual acuity, and PRL position are summarized in Table 1. The study was performed in accordance with the ethical standards laid down by the Declaration of Helsinki (Association, 1996). The study was approved by the Ethics Committee of the Department of General Psychology, University of Padova (Protocol 1449). We obtained written, informed consent from all participants involved in the study.

Table 1. Details of participants.

Patients	Deficit	Gender	Age	Scotoma diameter	Position of PRL	Tested eye	(VA)
MD1	CRSC	Male	50	4°	Left-up 2.0°-1.0°	LE	2/10
MD2	Macular hole	Female	49	3°	Right-up 1.5°-1.0°	RE	7/10 (LAC)
MD3	Best disease	Male	58	8°	Left-up 4°-2.7°	LE	2/10
MD4	Stargardt	Male	69	7°	Left-down 2.5° -6	LE	1/10
MD5	JMD	Female	56	4°	Right-up 2°-1°	RE	2/10
MD6	AMD	Female	62	3	Right-down 1°-1°	LE	2/10
MD7	AMD	Female	65	3°	Left 1°.5	RE	2/10
MD8	AMD	Female	63	6°	Left-down 4.5°-2°	LE	2/10
MD9	AMD	Male	61	10°	Left-down 8°-1°	LE	3/10
MD10	AMD	Male	65	6°	Left-up 4.°-2°	RE	1/10
MD11	AMD	Male	83	9°	Left-down 2°-2°	LE	3/10
C1	none	Male	58	none	none	Non-dominant	10/10
C2	none	Female	64	none	none	Non-dominant	10/10

C3	none	Male	60	none	none	Non-dominant	10/10
C4	none	Female	59	none	none	Non-dominant	10/10
C5	none	Male	64	none	none	Non-dominant	10/10
C6	none	Male	54	none	none	Non-dominant	10/10
C7	none	Female	54	none	none	Non-dominant	10/10

The MD group consisted of six patients with AMD, one patient with juvenile macular degeneration (JMD), two patients with Stargardt disease, one with Best disease, one with a macular hole, one with cone-rod dystrophy (CRD), and one with central serous chorioretinopathy. The patients underlined are those considered in the non-PRL analyzes.

Locations tested

The eccentricity of the PRL was individually estimated as a proportion of the distance from the macula and the optic disk, in degrees of visual angle. Using the image of the retinal fundus, the position of the fovea was computed based on the averages of the values determined for normally sighted observers: 15.3° temporally and 1.5° below the centre of the optic disc. The distance between the position of the fovea and the PRL position estimated by the microperimetry was then computed to derive the eccentricity of the PRL. The non-PRL position was defined as approximately correspondent to the horizontally specular area of the retina, using the macula as the centre of symmetry. One example of patients' microperimetry and the respective retinal displacement of the target Gabor in either the PRL or the non-PRL is shown in Figure 1. In the case of very small scotoma, the non-PRL position was set by default at 6° of eccentricity with respect to the PRL on the horizontal axis. This was done to allow reliable discrimination between the two gaze positions by the eye tracker. The eccentricity at which stimuli were presented to

each control subject matched that of one patient, randomly chosen. On average, the eccentricity was 4°.

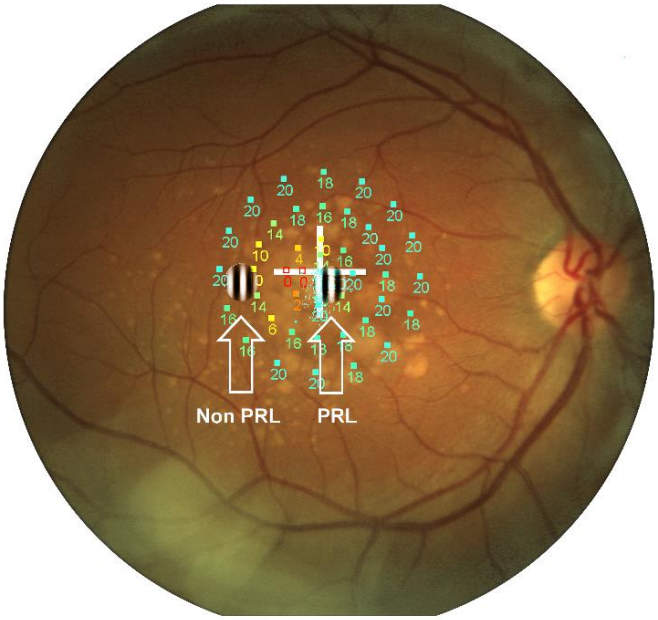

Figure 1. Illustrative example of stimuli placement.

Stimuli presented at the PRL and at the non-PRL are superimposed over the microperimetry.

Eye movement recording

Participants' fixation was controlled with an eye tracker to determine the retinal position corresponding to the patients' PRL/non-PRL and to be sure that fixation was maintained. Calibration and recording procedures were as follows. Eye movements were recorded using a Mirametrix S2 eye tracker with a sample rate of 60 Hz and an accuracy of 0.5°. The calibration of the tracker and the gaze check were integrated into the main Matlab script using the Mirametrix Matlab Toolbox and API for Windows. Thanks to a

custom calibration software, the calibration dot that normally sighted observers follow with the fovea were shifted by a constant so that, although MD patients could follow it with their PRL, the position of the eye relative to the calibration dot corresponded to that of a normally sighted observer. Due to the instability of fixation and the systematic error of the tracker, a tolerance window of ± 1.5° around the PRL fixation point was set. If the gaze of the subject before the stimulus presentation was out of this window, a warning sound was presented to allow the patient to relocate his or her gaze.

Apparatus and stimuli

Participants sat in a dark room 57 cm from the screen. Stimuli were displayed on an ASUS ML228H LCD LED 21.5-inch monitor with a refresh rate of 60 Hz and a spatial resolution of 1920 x 1080 pixels, with a pixel pitch of 0.248 mm. Stimuli were generated with Matlab Psychtoolbox (Brainard, 1997a; Pelli, 1997). Gamma correction for each color channel was applied through calibration with the Spyder 4 Elite colorimeter (DataColor). The calibration was further verified using a Minolta LS-100 photometer, which indicated that the mean luminance was 50 cd/m2. In that way, luminance was a linear function of the digital representation of the image.

In order to represent 10.7 bits of luminance (1786 gray levels) on an 8-bit display, we adopted a software solution called “Pseudo-Gray,” also known as “Bit-Stealing”(Tyler, 1997), implemented via a Psychtoolbox built-in function.

Contrast detection stimuli. Stimuli were Gabor patches consisting of a cosinusoidal carrier enveloped by a stationary Gaussian. Each Gabor patch was

characterized by its sinusoidal wavelength (λ), phase (φ), and standard deviation of the luminance Gaussian envelope (λ) in the (x,y) space of the image:

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

with λ = λ and φ = 0 (even symmetric). Gabors' spatial frequency (SF) was 2 and 3 cycles/deg (cpd) for MD patients and 3 cpd for controls. A vertical low-contrast Gabor target (Figure 2) was collinearly flanked, above and below, by two iso-oriented high-contrast Gabors (0.7 Michelson contrast). In addition, a condition with the vertical low-contrast Gabor target flanked by orthogonally oriented Gabors patches was added; with this stimulus configuration, the target detection is not modulated by lateral interactions (Uri Polat & Norcia, 1996; Uri Polat & Sagi, 1993). The contrast threshold of the target was estimated according to 1 up/3 down. Participants performed a temporal two-alternative forced-choice (2AFC). The target was presented in one of the two-time intervals, whereas the flankers were always presented in both time intervals. Observers had to report in which time interval the target was presented. Feedback was provided for incorrect trials. Each block was terminated after 120 trials or 16 reversals. Contrast thresholds were estimated by averaging the contrast values corresponding to the last 8 reversals. For the PRL/non-PRL testing, contrast levels from two separated staircases were displayed in a random order over the two different retinal positions.

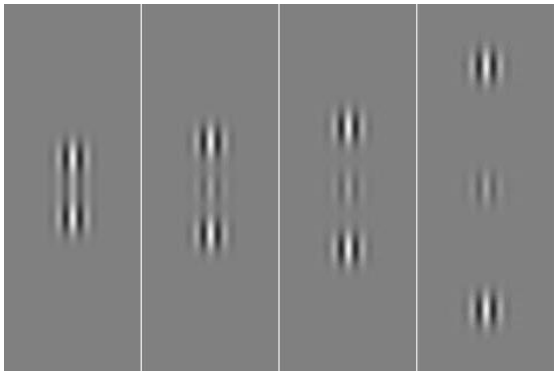

Figure 2. Stimuli used for the lateral masking paradigm.

Increasing target-to-flanker separations of2λ, 3λ, 4λ, and 8λ are shown.

The two high-contrast collinear flankers were placed at various distances from the target (i.e., 2λ, 3λ, 4λ, and 8λ). The patients were asked to maintain their gaze on the PRL, and stimuli were randomly presented over either the PRL or non-PRL position within a block. Controls had to fixate the centre of the screen, and stimuli were randomly presented either left or right of fixation.

Visual acuity and crowding stimuli. Visual acuity (eccentric VA) and crowding were measured at the same eccentricity as for the Gabor configuration. Stimuli were generated using Matlab Psychtoolbox (Brainard, 1997a; Pelli, 1997) and presented at 57 cm. The stimuli were 10 letters (D, N, S, C, K, R, Z, H, O, and V) with Sloan (Pelli, D. G., & Robson, 1988) character type, randomly presented for 133 ms. The target letter was presented randomly at the two eccentricities in the same block, either the PRL/non-PRL for MD patients or 4° left/right from fixation for controls. The size of the letters for measuring acuity threshold and the edge-to-edge spacing for measuring crowding varied according to a psychophysical adaptive procedure (Maximum Likelihood Procedure)

(Grassi & Soranzo, 2009; D M Green, 1993; David M. Green, 1990) that tracked 55% of the participants' psychometric function within a 60-trial block. The starting stroke width was 30 arcmin. Subjects had to verbally report the target letter, and the experimenter registered the answer. The threshold was the values obtained in the last trial.

The crowding stimulus had two different letters vertically flanking the target letter. The stroke width of both the target and flanking letters was set 30% higher than the VA threshold obtained at the same eccentricity and the same exposure duration. When tested in the PRL, the MD patients were able to detect all three letters at the largest spacing used (5°). This procedure is often used (Barollo et al., 2017b; Z. Hussain, Webb, Astle, & McGraw, 2012; Maniglia et al., 2011; Pelli & Tillman, 2008) to avoid an influence of VA on the measurement of critical spacing for crowding. Crowding was indexed by the critical spacing, defined as the edge-to-edge inter-letter distance at which observers could discriminate the target (the central letter) with 55% accuracy. Differently, from the centre-to-centre distance, edge-to-edge distance prevents overlay masking of the target by the flankers but has the disadvantage of co-varying with letter acuity (the bigger the target, the larger the centre-to-centre distance at zero border-to-border distance), thus ultimately underestimating crowding in people with low acuity.

Procedure

Each subject underwent a testing session of 3 hours in which VA, crowding, and the target contrast thresholds for orthogonal and several collinear configurations were measured monocularly in counterbalanced order.

Contextual influences were estimated by computing the threshold elevation (TE) as:

$$TE = \log_{10}\left(\frac{CT\_Collinear}{CT\_Orthogonal}\right) \quad \text{Eq. 2}$$

where CT_Collinear is the contrast threshold estimated in the collinear condition, and CT_Orthogonal is the contrast threshold estimated in the orthogonal condition. TE was calculated separately for each target-to-flanker distance (i.e., 2λ, 3λ, 4λ, and 8λ). We used the orthogonal threshold value obtained at 8λ as a baseline to compute TE (instead of thresholds obtained from the isolated target). The advantage is that the orthogonal configuration still maintains the facilitation induced in the task by the reduced spatial and temporal uncertainty that the presence of the flankers causes so that it is not a confounding factor for the estimation of TE (Shani & Sagi, 2005). We chose the 8λ as the orthogonal configuration because, there is little or no contextual enhancement expected at λs > 6 at the tested eccentricities, and therefore it is an ideal condition as a baseline (Lev & Polat, 2011; Maniglia et al., 2011, 2015).

Statistical analysis

Within- and between-group comparisons were carried out with ANOVAs on either contrast threshold or TE using, for pairwise comparisons, t-tests with Bonferroni correction. TE was also analysed using one-sample, one-tail t-tests based on the hypothesis of TE as either > 0 or < 0 for suppressive and facilitatory effects, respectively. Visual acuity and crowding data were also analysed with two-tailed t-tests.

Results

Contextual influence results

Contrast threshold results and TE results are shown in Figure 3. A mixed-design ANOVA conducted on the contrast threshold data on PRL, including as factors the group (patients vs. controls) and λ (2, 3, 4, and 8λ), revealed that thresholds were significantly higher for the MD patients ($F(1,18) = 13.7$, $p =. 002$, partial-$\eta 2 = 0.422$). The effect of λ was significant ($F(3,54) = 3.308$, $p = .027$, partial-$\eta 2 = 0.155$). The interaction group x λ was also significant ($F(3,54) = 4.024$, $p = .012$, partial-$\eta 2 = 0.183$). Pairwise comparisons revealed a group difference for the 3 λ ($p = .005$), 4 λ ($p < .001$), and 8 λ ($p = .002$) and higher thresholds at 2 λ compared to 3 λ ($p = .026$), 4 λ ($p = .039$). None of the differences in thresholds across λs were significant in the MD group.

A mixed-design ANOVA conducted on TE data, including as factors the group (patients vs. controls) and the λ (2, 3, 4, and 8λ) indicated that the effect of group was not significant ($F(1,18) = 2.752$, $p = .114$, partial-$\eta 2 = 0.133$), while both the effect of λ ($F(3,54) = 10.09$, $p < .001$, partial-$\eta 2 = 0.359$), and the group x λ interaction ($F(3,54) = 10.561$, $p < .001$, partial-$\eta 2 = 0.370$) were. Post hoc comparisons showed higher TE for the smallest λ compared to others (2 vs. 3λ, $p = .002$; 2 vs. 4λ, $p < .001$; 2 vs. 8λ, $p = .009$). Most importantly, there was a significant group difference at the smallest λ only ($p < .001$), and a different effect of the smallest λ in the two groups: For controls, TEs were higher at the smallest λ compared to the others (2 vs. 3λ, $p = .001$; 2 vs. 4λ, $p < .001$; 2 vs. 8λ, $p = .002$); for the MD group, there was not any difference in TE between the different λs ($p = 0.99$). Since TE > reflects inhibitory lateral interaction and TE <0

facilitatory, one-sample, one-tail t-tests were conducted to test the null hypothesis of 0 TE. As expected TE resulted generally negative for λs ≥ 3 for both MD patients (3λ: (t(12) = -3.2, p = .004; 4λ: t(12) = -1.4, p = .096; 8λ: t(12) = -2.47, p = .014) and controls (3λ: t(6) = -0.85, p = .21; 4λ: t(6) = -3.74, p = .005; 8λ: t(6) = -2.8, p = .015)), confirming that contextual enhancement occurs at larger λs in the periphery than in the fovea (Shani & Sagi, 2006; D. T. H. Tan & Fong, 2008; Zenger & Sagi, 1996). At the shortest λ, TE assumed, as expected, positive values for controls (t(9) = 4.01, p = .003); however, at the same shortest λ the values of TE for MD patients were negative (t(12) = -2.3, p = .02).

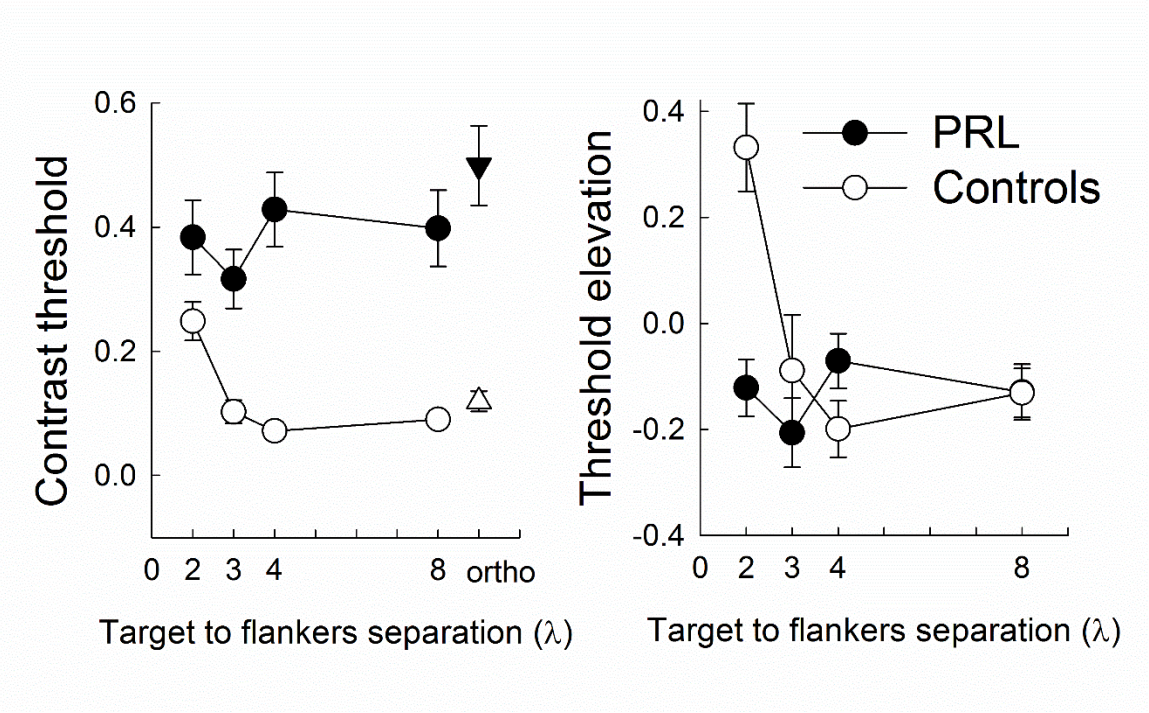

Figure 3. Contrast threshold and TE values for PRL and controls

Contrast threshold and TE values (i.e., lateral interaction curves) as a function of target-to-flanker distance. For MD patients (PRL data) and controls (data averaged across retinal positions). Contrast thresholds for the orthogonal configuration (8λ) are also shown. Bars indicate standard errors.

Comparison of contrast thresholds and TE data obtained in the PRL and non-PRL of MD patients are shown in Figure 4. Repeated-measures ANOVAs, including as factors the retinal locus (PRL and non-PRL) and the λ (2, 3, 4, and 8λ), were conducted on both the contrast thresholds and TE data of the subgroup of 8 patients that were tested with stimuli presented in both the PRL and non-PRL positions.

The ANOVA on contrast threshold revealed that neither the main factors (PRL: $F(1,19) = .077$, $p = .785$, partial-$\eta 2 = .004$; λ: $F(3,57) = .947$, $p = .424$, partial-$\eta 2 = .047$) nor the PRL x λ interaction ($F(3,57) = .463$, $p = .709$, partial-$\eta 2 = .024$) were significant. Similarly, the ANOVA on TE data did not reveal a significant effect of the retinal locus ($F(1,19) = .027$, $p = .872$, partial-$\eta 2 = .001$), of λ ($F(3,57) = .546$, $p = .653$, partial-$\eta 2 = .028$), and of the interaction between PRL and λ ($F(3,57) = .389$, $p = .762$, partial-$\eta 2 = .02$).

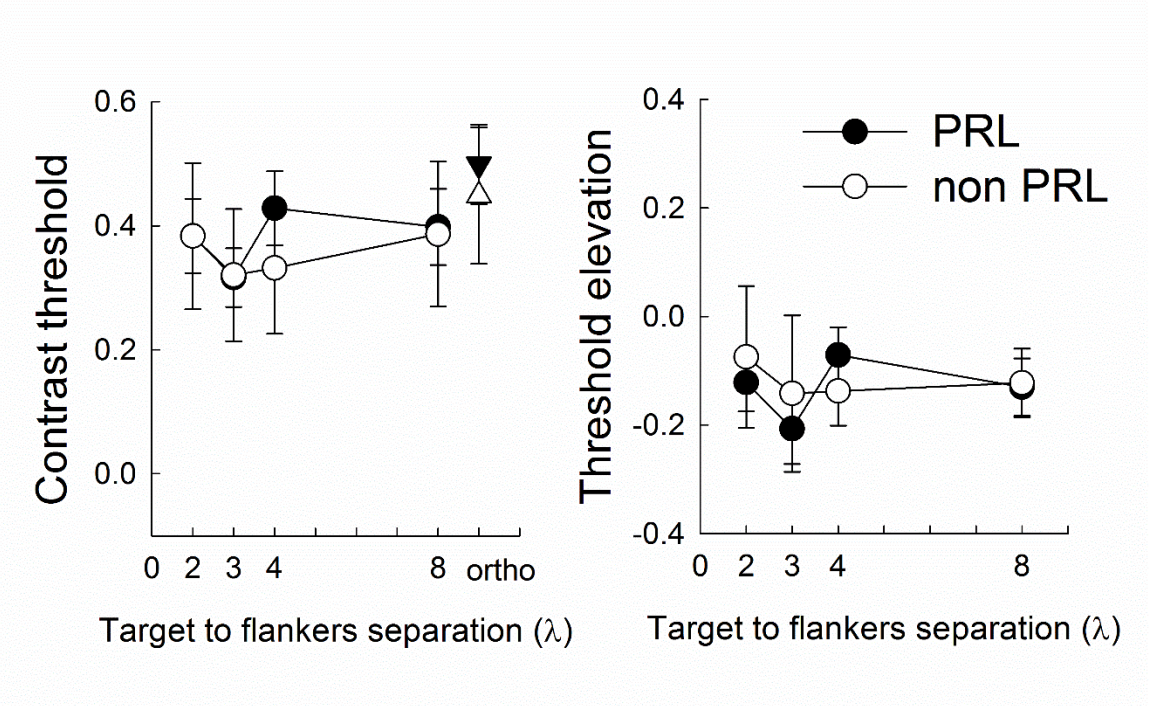

Figure 4. Contrast threshold and TE values for PRL and non-PRL

Contrast threshold and TE values (i.e., lateral interaction curves) as a function of target-to-flanker distance for 8 MD subjects in the PRL and non-PRL retinal positions. Contrast thresholds for the orthogonal configuration (8λ) are also shown. Bars indicate standard errors.

Acuity and crowding results

The visual acuity of the 8 patients who had a reliable measure in both the PRL and non-PRL are shown in Figure 5. The one-way ANOVA conducted on these data, with group as a factor (controls, PRL, non-PRL) showed a significant effect of group ($F(2,20) = 6.22$, $p = .007$, partial-$\eta 2 = .384$), indicating higher acuity for controls than MD patients both when tested at the PRL (difference = 6.917, $p = .046$) and non-PRL positions (difference = 9.167, $p = .007$). The difference between PRL and non-PRL was not significant (difference = -2.25, $p = .67$). Even considering the small sample and the high variability in VA data, this lack of difference confirms that development of a PRL is not strictly linked to an advantage in terms of visual acuity over the other retinal quadrants (Cheung & Legge, 2005; Schuchard, 2005). Moreover, the two acuity values for the 8 patients are highly correlated ($R = .78$, $p = .022$).

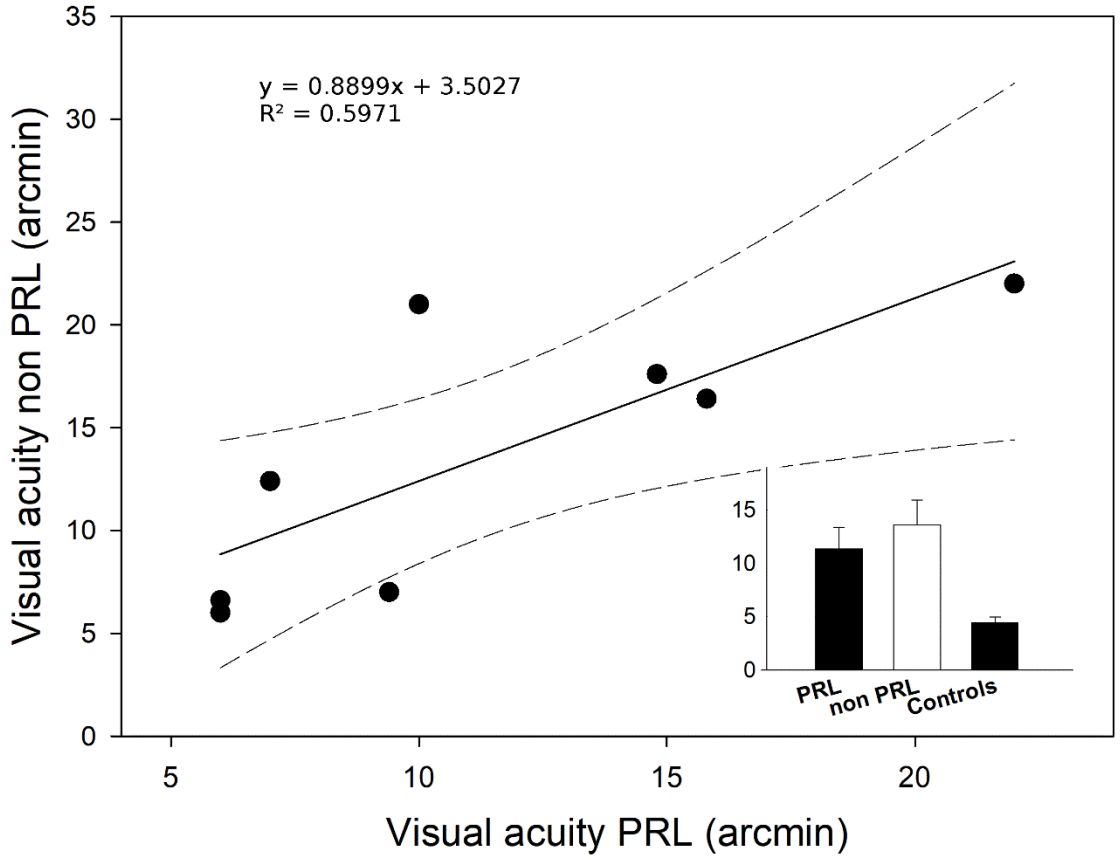

Figure 5. Visual acuity non-PRL vs. Visual acuity PRL.

Scatter plot represents visual acuity obtained with stimuli presented at the non-PRL regressed on visual acuity obtained with stimuli presented at the PRL only for the patients for which the two positions were symmetrical with respect to the fovea. Dashed lines represent 95% confidence intervals. Average visual acuity for this subgroup (n = 8), and for the control group (n = 7) is also shown in the bar chart.

Individual crowding data of the 8 patients who had a reliable measure in both the PRL and non-PRL are shown in Figure 6. The one-way ANOVA conducted on these data revealed a significant effect of group ($F(2,20) = 3.516$, $p = .049$, partial-$\eta 2 = .26$). Post hoc comparison showed a significant difference between controls and MD patients when

tested at the non-PRL (difference = 1.693, p = 0.037) but not when tested at the PRL (difference = .962, p = .3). The difference between PRL and non-PRL was not significant (difference = -0.731, p = .47). Visual acuity and crowding measures should be independent by definition. We checked this assumption by calculating the correlation between the two measures. We found that the negative correlation did not reach significance (R = -.52, p = .068) despite the fact that the operative definition of critical spacing as the edge-to-edge inter-letter distance may have inflated this estimate (see Method section).

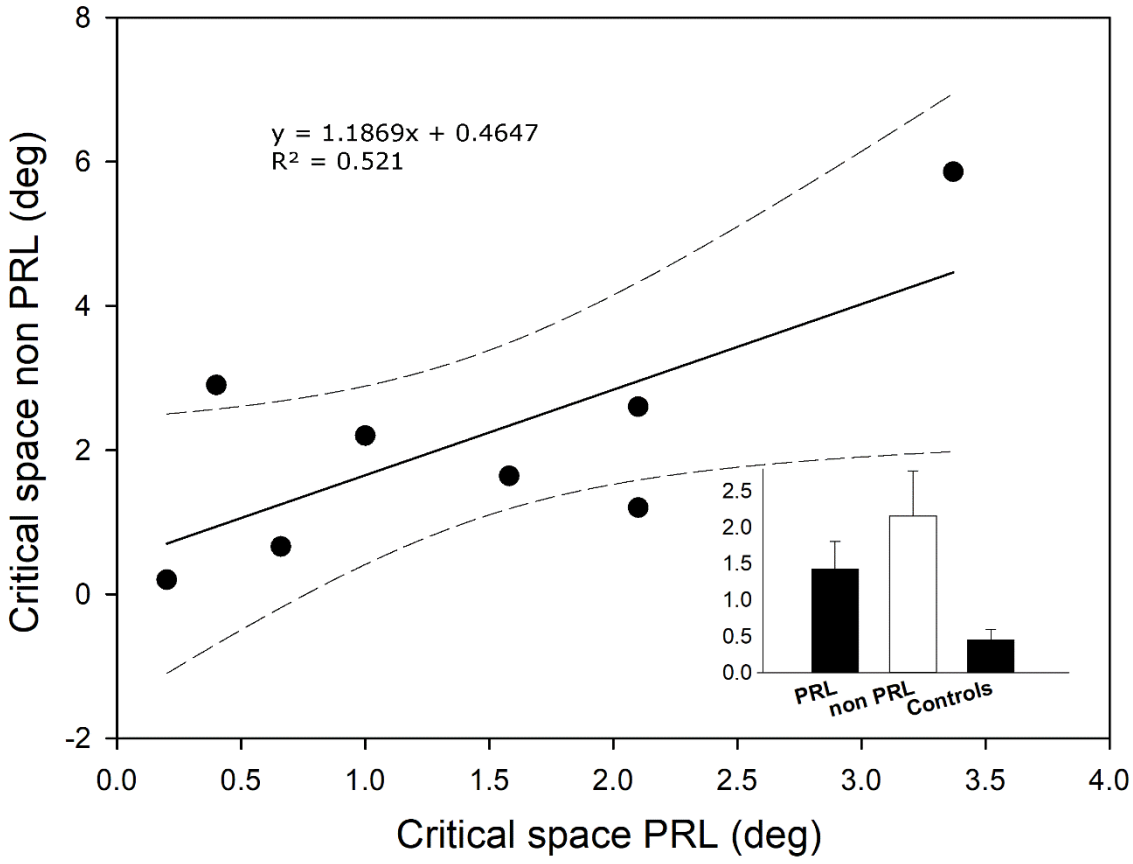

Figure 6. Critical space PRL vs. Critical space non-PRL.

Scatter plot represents critical spacing for crowding obtained with stimuli presented at the non-PRL regressed on critical spacing for crowding obtained with stimuli presented at the PRL only for the patients for which the two positions were symmetrical with respect to the fovea. Dashed lines represent 95% confidence intervals. Average critical spacing for crowding for this subgroup (n = 8), and for the control group (n = 7) is also shown in the bar chart.

Discussion

Using a two-interval forced-choice task, contrast threshold for a low-contrast target Gabor flanked by two collinear high-contrast Gabors presented at eccentricities varying between 3º and 8º was measured in a group of subjects with MD and in an age-matched control group. Target-to-flanker separation, varied in terms of the Gabor's carrier wavelength unit (λ), was 2λ, 3λ, 4λ, and 8λ. The contextual influence of the flankers was indicated by the threshold modulation (TE), indicating the change in contrast threshold obtained at each of the four λs, relative to the baseline condition with no contextual influence (orthogonal flankers, 8λ).

Results showed contextual enhancement at λs higher than in the fovea (4-8λ). At 2λ, all controls had inhibition. Only 2 of the patients had inhibition, 2 had a TE close to zero, and 9 of them had negative TE, indicating facilitatory contextual influences. This change in contextual influences at the shortest λ in MD patients was associated, both at the PRL and non-PRL, with an increase of contrast threshold for the target, as well as with reduced visual acuity and a larger crowding effect. Is the switch between inhibition and facilitation at the shortest λ an index of cortical plasticity or it could be explained by the same model used to interpret psychophysical data from normal viewers? An answer to this question comes from establishing whether TE in MDs is well described by the variation of TE as a function of flanker/target contrast ratio in normal vision (Foley, 1994; Ross, Speed, & Morgan, 1993; Snowden & Hammett, 1998; B Zenger-Landolt & Koch, 2001; Zenger & Sagi, 1996). Zenger & Sagi (1996) proposed a model for contextual influences in which:

- At a close distance, the sensitivity to a low contrast target is reduced by the presence of high contrast flankers.
- When the contrast of target increases the reduction in sensitivity progressively decreases and then turns into facilitation. The switch happens when the contrast of the target is still lower (around three times) with respect to that of the flankers.
- When the contrast of target approaches that of the flankers, there is a dip in the facilitation.
- However, when the contrast of target surpasses that of the flankers, the facilitatory effect progressively reduces and then disappear.

The model postulates a contrast dependent modulation of the contextual effect of the flankers that shift progressively from inhibition to facilitation depending on flanker/target contrast ratio. We verified this by pulling the data of the two groups together and regressing the TE at 2λ as a function of log 10(Contrastf lankers/Contrast target threshold) in the 8λ orthogonal condition. We performed a locally-weighted polynomial regression, aka lowess (Cleveland, 1979, 1981), in R (R Core Team, 2012) with a 50% smoothing span that leads to an R2 of 0.52 (correlation between raw and estimated data). Finally, we superimposed raw data and fit line over the model predictions from Zenger and Sagi (1996) at 0λ and 2λ. As the Figure 7 shows, the regression line derived from our dataset approximates very well the one predicted by the model, in particular the line that refers to the 0 λ, as expected by the fact that increasing eccentricity would shift the curve leftwards. Thus, the transition from inhibition to facilitation that most MD patients show at high contrast threshold suggests improved

efficiency in integrating/grouping elements, possibly mediated by an integration between the flanker and target within the 2nd order integrative field (Zenger & Sagi, 1996).

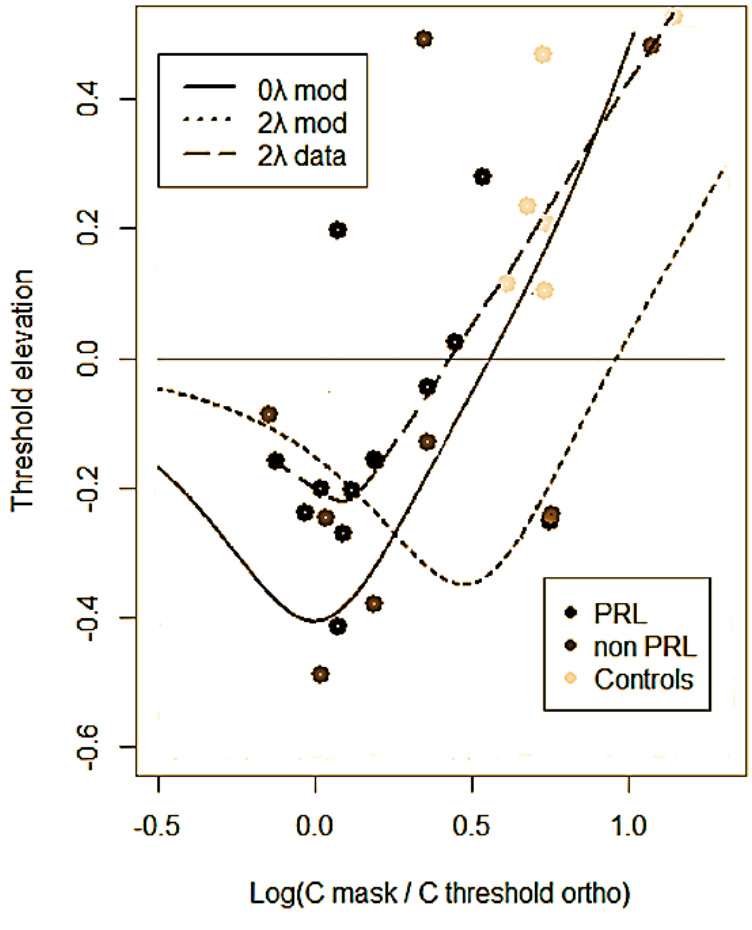

Figure 7. TEs as a function of flankers/orthogonal contrast ratio.

TEs as a function of log 10(Contrast flankers/Contrast target threshold) in the 8λ orthogonal condition are shown for the pooled data obtained by patients at the PRL (n = 13) and at the non-PRL (n = 8), and for the data of the control group (N = 7). Prediction for the 0 λ and 2λ based on the model from Zenger and Sagi (1996) are shown together with the locally weighted scatterplot smoothing (lowess) from our data.

Our results do not support the hypothesis that MD present cortical reorganization leading to a use-dependent increase of long-range connectivity. In this case, with the low contrast target, we would have obtained increased contrast enhancement at the range of target-to-flanker distances at which facilitation occurs in normal vision. In the previous literature, the reduced collinear inhibition found in MD has been interpreted as a sign of neural plasticity, linked with a change in receptive field size (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). We shed new light on this phenomenon and propose a different interpretation. If we consider together all our participants including the controls, our data show that the reduction in collinear inhibition and the switch towards facilitation are clearly linked with the baseline contrast sensitivity of the single subject in the orthogonal configuration. This switch can be well described by the same model previously proposed for the normal vision (Zenger & Sagi, 1996) and thus our results support the hypothesis that inhibitory target-flanker separations (short) become facilitatory in MD as it would do in controls if their contrast threshold were 4-5 fold higher. Taking all this information into consideration, the reduction of inhibition cannot be ascribed to neural plasticity in PRL but must be considered as a by-product of the same retinal degeneration that may deplete the patient's vision at the boundary of the scotoma.

To conclude, our result is that a reduction of contrast gain at the boundary of the scotoma is associated not only to reduced resolution (Lev & Polat, 2015), which indeed MDs show for stimuli presented at the boundary of the scotoma, but also to a change in the way neighbouring elements are integrated.

Chapter VI.

tRNS Modulates Excitatory and Inhibitory Lateral Interactions in Contrast Detection

This chapter has been accetted for publication in Scientific Reports. Battaglini L., Contemori G., Fertonani A., Miniussi C., Coccaro A., Casco C.

Delivering a weak electric current through the scalp on a cortical region at random frequencies, has shown promising results in boosting PL between blocks and reducing the number of sessions needed to observe significant improvements (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; A. Fertonani et al., 2011). A PL based on a lateral masking task can be effective in improving the visual functions in the PRL of MD patients, but a very long training is required and the amount of transfer is limited (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). Patients with MD could particularly benefit from this training since could lead to a use-dependent restructuring of the lateral connections making them potentially more similar to those of the fovea (Maniglia et al., 2011; U Polat & Sagi, 1994; Uri Polat, 2009). The possibility to train MD patients with PL + concomitant tRNS is attractive and in other clinical populations it has produced significant benefits (Campana et al., 2014). However, it is not known whether tRNS has a specific effect on lateral interactions in V1. Studying this effect could help us to better understand the mechanisms of action the tRNS and the possible specific repercussions for MD patients.

Introduction

Visual performance for a stimulus presented in a given retinal location can be modulated by the simultaneous presence of other stimuli having a different retinal position. This technique, known as lateral masking, consists in measuring contrast sensitivity for a periodic Gabor pattern (target) flanked by high-contrast Gabors collinear and iso-oriented to the target. Psychophysical studies on lateral masking showed that in central vision sensitivity reduces (threshold increases) when the distance from the flankers is ≤ 2 target wavelengths, a result suggesting lateral inhibition by the flankers. For larger target-to-flankers distances, ranging from 3 to 9 target wavelengths, the flankers facilitate target detection, as demonstrated by a threshold decrease from absolute threshold (Y. Adini et al., 1997; Yael Adini & Sagi, 2001; C. C. Chen & Tyler, 2001; Maniglia et al., 2011; Uri Polat, 1999; Uri Polat & Sagi, 1993, 1994; Barbara Zenger-Landolt & Koch, 2001). Indeed, Mizobe and colleagues (Mizobe, Polat, Pettet, & Kasamatsu, 2001) not only showed that the neurometric function to target contrast was modulated by the flankers presented outside the classical receptive field, but also that the modulation was dependent on the relative distance between target and flankers. Moreover, the separations at which facilitation occurs are larger in the periphery than in the fovea (Maniglia et al., 2011). Furthermore, psychophysical (Yael Adini & Sagi, 2001; C. C. Chen & Tyler, 2001; Uri Polat, 1999), electrophysiological (Uri Polat & Norcia, 1996), and brain imaging studies (Tajima et al., 2010) showed that the polarity of contextual modulation is also contrast dependent: inhibitory effects occur within a contrast range larger than that at which facilitation occurs.

One major question regards the neurophysiological bases of the facilitatory and inhibitory lateral interactions. Psychophysical evidence suggests that detection thresholds depend on the activation of interconnected local neural network with both excitatory (E) and inhibitory (I) neurons whose synaptic connections are activity dependent. E/I ratio depends on the contrast of the target and on the E, and I lateral input that may favour either facilitation or inhibition by the flankers depending on target-flanker separation (Y. Adini et al., 1997).

Contextual influences on contrast detection have been investigated in an accumulating mass of studies for two crucial reasons. First, they are considered to contribute to the perception of contours in natural scenes. Facilitation of detection occurs when the target-flanker configuration is collinear rather than orthogonal, that is consistent with a contour structure in which local-global orientation cohere (Bellacosa Marotti, Pavan, & Casco, 2012; Dakin & Baruch, 2009; Field, Hayes, & Hess, 1993). Many authors were refrained from drawing a too close parallel between lateral masking and supra-threshold perceptual phenomena (Robert F. Hess, Dakin, & Field, 1998). Mechanisms involved in suprathreshold perceptual tasks, such as contour integration and crowding, do not use any simple form of local contrast enhancement to perform grouping and segmentation of local elements, respectively. However, even assuming that contrast enhancement may not be the mechanism involved in either perceptual grouping or segmentation, it is quite likely that these high-level tasks and the low-level effects of contrast enhancement could be explained by common cortical circuit (Dakin & Baruch, 2009; Maniglia et al., 2011, 2015). The second reason for which contextual influences in contrast detection have caught the attention of several investigations in the last decades is

that when they are made inefficient by a visual disorder, they can be partially restored by promoting, through training, neural plasticity at the level of lateral intracortical connections in V1. Thus, modulation of intracortical connections may result in a powerful rehabilitation tool for low vision patients. Most studies have used perceptual learning to induce neural plasticity in normal and in low vision population (Barollo et al., 2017a; Casco et al., 2018, 2014; Maniglia, Pavan, et al., 2016; Uri Polat, Ma-Naim, Belkin, & Sagi, 2004; Uri Polat, Ma-Naim, & Spierer, 2009; Uri Polat et al., 2012; D. T. H. Tan & Fong, 2008).

Neural plasticity induction can be also achieved through weak currents applied transcranially. The most used of these protocols are transcranial direct current (tDCS), alternating (tACS) and random noise (tRNS) stimulation. Whereas tACS has been suggested to be suitable for interacting with endogenous brain oscillations (Asamoah, Khatoun, & Mc Laughlin, 2019; Fröhlich & McCormick, 2010; Helfrich et al., 2014; Schutter, 2016; Thut et al., 2017), tDCS, and tRNS have become increasingly popular as tools to induce neural modulation in the visual system (Battaglini, Noventa, & Casco, 2017; Behrens et al., 2017; Camilleri, Pavan, Ghin, Battaglini, et al., 2014; A. Fertonani et al., 2011). With tDCS that is a constant current, in general, the anodal electrode is associated with an increase in excitability, while an inhibitory effect is observed with the cathodal electrode(Michael A. Nitsche et al., 2008). Instead, with tRNS the direction of the current is not relevant to obtain effects (Pirulli, Fertonani, & Miniussi, 2016). In this framework tRNS similarly to anodal tDCS, has been shown to induce an increase of cortical excitability (Daniella Terney, Chaieb, Moliadze, Antal, & Paulus, 2008) but likely with a different dynamic (A. Fertonani et al., 2011) avoiding inactivation due to

adaptation of ion channels when using a constant current. In contrast to anodal tDCS, it has been hypothesized that tRNS prevents homeostasis of the system. Such stimulation consists in the application of a random electrical oscillation spectrum over the cortex; this fast oscillating field modifies the neurons' synaptic efficiency regardless of the current flow orientation (Pirulli et al., 2016; Daniella Terney et al., 2008). Mechanistically, the tRNS-induced neurophysiological effect has been suggested to originate from modulation of voltage-gated sodium channels (A. Fertonani et al., 2011; Daniella Terney et al., 2008) specifically acting on the dynamics of in/activation of the sodium channels (Remedios et al., 2019). Moreover, the behavioural improvement following tRNS has been interpreted by suggesting that the random frequency stimulation produced by tRNS sustains random neural activity in the system, i.e., noise, which serve as a pedestal to expand the sensitivity of the neurons to weak stimuli, providing in same cases inputs similar to those of the target, thereby increasing the signal-to-noise ratio (Miniussi et al., 2013). When applied over visual areas, tRNS increases perceived contrast of targets having low contrast (van der Groen & Wenderoth, 2016). In line with this approach, an intriguing possibility that better defines neurophysiological mechanisms is that, with lateral masking configurations, tRNS might induce a synaptic enhancement at the level of the lateral connections between target and flanker neurons, by inducing a temporal summation of weak depolarizing currents. Hence, specific changes in performance are related to a network-dependent stochastic resonance phenomenon (Anna Fertonani & Miniussi, 2017) i.e., the balance between excitation and inhibition is strictly related to the specific neuronal population state (E/I) and not just to generalized changes in cortical excitability. In this study, because these evidences that tRNS exceeds the beneficial

advantages of tDCS, we aimed to explore if the interaction between tRNS and visual system task dependent activity can modulate cortex excitability and therefore behaviour in a specific way. Depending on which of the two circuitries is involved, either the one accounting for increase in perceived contrast for the target or the one responsible for the modulation of target contrast by lateral interactions, a different perceptual outcome is expected. A simple contrast gain effect would be reflected in an increase in sensitivity (d') for a single target of low contrast and modulate the lateral interactions effect consequently. Based on the evidence that tRNS depolarize neurons, we expected tRNS to increase the E thalamic input only when this is weak, that is when the target contrast is low. In this case, given the evidence that E and I lateral modulation occur when the target contrast is low and high respectively (Yael Adini & Sagi, 2001; Uri Polat, 1999; Uri Polat & Norcia, 1996; Barbara Zenger-Landolt & Koch, 2001) we expected the E lateral input to be weakened with tRNS. That is, the reduced strength of lateral input, as reflected into a reduced facilitation by the flankers, would be an epiphenomenon of the change of contrast gain (Zenger & Sagi, 1996). Alternatively, tRNS effect might be dependent on target-to-flankers distance and reflect a direct modulation of the relative strength of excitatory (E) or inhibitory (I) lateral input from the flankers to a target, depending on which is weaker. In this case, we might expect an effect of tRNS even if tRNS has no effect at all on target perceived contrast.

Materials and Methods

Observers

In total, 68 young subjects participated in this study (46 females; mean age 24 ± 3 years). All participants had normal or corrected-to-normal vision and were naïve as to the purpose of the experiments. Thirty-eight participants were involved in the main Experiments 1 (N=19; 15 females; mean age 24 ± 4) and 2 (N=19; 12 females; mean age 24 ± 4) and 30 participants were involved in the Control Experiments 3 (N=15; 10 females; mean age 24 ± 2) and 4 (N=15; 9 females; mean age 24 ± 3). Participants in Experiment 1 and 3 were tested with flankers distant from the target, whereas participants in Experiment 2 and 4, were tested with the flankers close to the target. All participants took part voluntarily, and informed consent was obtained from all participants before the study initiated. The study conformed to the tenets of the Declaration of Helsinki, and the experimental methods have approval from the Ethical Committee of the University of Padova (protocol 1719).

Apparatus

Stimuli were displayed on a 22-inch. Philips 202P4 CRT monitor with a refresh rate of 85 Hz. The minimum and maximum luminance of the screen were 0.63 and 112.1 cd/m2, respectively, and the mean luminance was 56.8 cd/m2. Luminance was measured with a CRS Optical photometer (OP200-E; Cambridge Research System Ltd., Rochester, Kent, UK). A digital-to-analog converter (Bits#, Cambridge Research Systems,

Cambridge, UK) was used to increase the dynamic contrast range (12-bit luminance resolution). A 12-bit gamma-corrected lookup table (LUT) was applied so that luminance was a linear function of the digital representation of the image. The screen resolution was 1600 × 1200 pixels.

Stimuli

Stimuli were generated using Matlab Psychtoolbox (Brainard, 1997b; Pelli, 1997). They were formed by a vertical Gabor target patch and, when present, by two collinear Gabor flankers (Figure 8). Each Gabor patch consisted of a co-sinusoidal carrier enveloped by a stationary Gaussian (Eq. 3) and was characterized by its sinusoidal wavelength (λ), phase (φ), and standard deviation of the luminance Gaussian envelope (σ) in the (x, y) space of the image:

$$G(x,y)=\cos\left(\frac{2\pi}{\lambda}x+\varphi\right)e^{\left(-\frac{x^2+y^2}{\sigma^2}\right)} \qquad \text{Eq. 3}$$

with σ = λ and φ = 0 (even symmetric). Gabor patches had a spatial frequency of 1 cycle per degree (c/deg). Target-to-flankers distance was 6λ (wavelengths distance) in Experiment 1 and 3 and 2λ in Experiment 2 and 4. Since the thresholds for contrast differ between 6λ and 2λ in order to sample from the floor to the ceiling, we had to adopt two different ranges of contrasts in the two experiments. Each range has been derived from the literature(Uri Polat, 1999; Uri Polat & Sagi, 1994) and then adjusted with a pilot experiment. They varied according to eight levels: 0, 0.0020, 0.0028, 0.0039, 0.0055, 0.0077, 0.0105, 0.0150 in Experiment 1 and 3 and 0, 0.0030, 0.0058, 0.0110, 0.0250,

0.0410, 0.0800, 0.3000 in Experiment 2 and 4 (see Table 2). The contrast of the flankers was fixed at 0.6.

Table 2. Contrast range for the target at each target-to-flankers distance (λ)

Contrast											
	Very low	low						medium			
6λ	0.002	0.0028	0.0039	0.0055	0.0077	0.01005	0.015				
2λ		0.003		0.0058		0.011		0.025	0.041	0.08	0.3

To promote a suppressive effect of the flankers placed at short distances from the target (2λ), we used a relatively higher range of contrasts with respect to the 6λ distance. Note, however, that certain contrast levels in the range .003 to .011 were the same in the two λ distances. This allowed us to isolate a specific effect of the flankers, independently on target contrast.

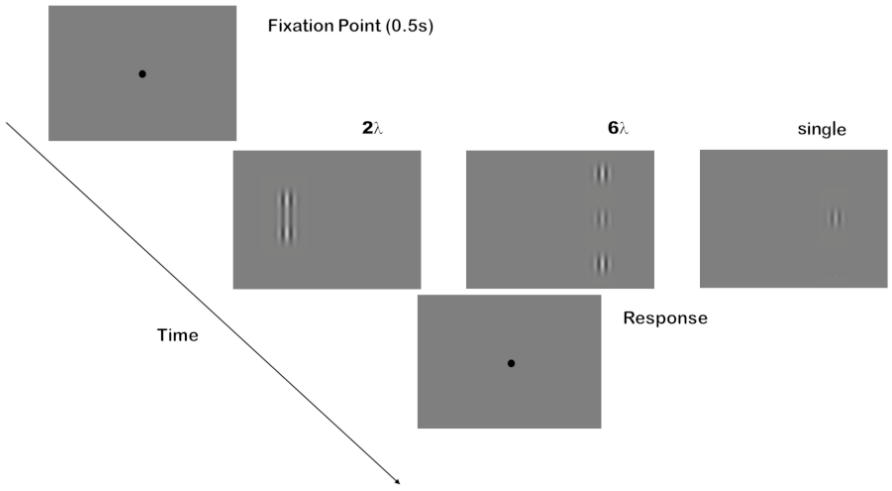

Figure 8. The stimulus configuration used in the experiments.

Left to right: target-flanker configuration at 2λ, 6λ and single Gabor target.

Procedure

Observers sat in a dark room at a distance of 57 cm from the screen. Viewing was binocular. Stimuli appeared randomly for 100ms to the left or to the right of fixation. The distance from the centre of the screen to the centre of the Gabor configuration was 4 deg. Observers were required to maintain fixation on the central fixation mark, which was always present except during stimulus presentation, to provide a transient cue for advising observers that the stimulus was present even if, at low contrast, they could not detect it. Observers performed a yes-no task in which they were asked to report whether they could perceive the central target by pressing the response key. The next trial started after 0.5s from the response keypress. Each experiment was devoted to one target-to-flankers distance (either 2λ or 6λ) and comprised a repetition of two sessions, each one consisting of 112 trials: 8 target contrast levels × 2 stimulus positions × 7 repetitions. In the first session, the target was flanked by collinear Gabor patches; in the second one, the target was presented alone. Participants performed the two sessions twice, once while they received Sham stimulation and once while they received tRNS. The order of the two configurations sessions was the same in the Sham and tRNS session, but it was counterbalanced across participants. The order of stimulation (Sham vs. tRNS) was also counterbalanced across participants in order to avoid a possible tRNS dependent after-effects.

tRNS

A battery-driven current stimulator (BrainStim, EMS, Bologna, Italy) delivered high-frequency tRNS through a pair of conductive rubber electrodes inserted in a 5 by 7-

cm physiological solution-soaked synthetic sponge. The tRNS consisted of a randomly alternating current of 1.5 mA with a 0 mA offset, whose frequency ranged from 100 to 600Hz. In the main Experiments 1 and 2, the electrode of interest was placed over V1/V2 (Oz) and the other electrode over the vertex (Cz), as in previous studies (Accornero, Li Voti, La Riccia, & Gregori, 2007; Antal et al., 2004; Battaglini et al., 2017). The experiments 3 and 4 served as a control to test the spatial specificity of stimulation in producing its effect on the contrast gain for the target and/or on E, and I lateral interactions. The only difference with the main experiments was that one electrode was placed over the forehead (between Fpz and nasion) while the reference electrode was kept over the vertex (Cz). tRNS was applied for approximately 12 minutes. It was started at the onset of the first session, and it was stopped at the end of the second session, with no pause between the two experimental sessions. The Sham stimulation consisted of 30 seconds delivered only during the first session. The duration of the fade-in/fade-out period was 15 second for both tRNS and Sham stimulation. At the end of each experimental session we asked the participant to complete a sensation questionnaire (Anna Fertonani et al., 2015). Very few participants reported mild skin sensation at the onset of the stimulation, but it disappeared after few seconds. The guessing rate of real/placebo stimulation was at chance levels.

Statistical Analysis

To ascertain that the response to the single and flanked targets depended on contrast we pooled sensitivity (d') of the person to the signal, and on the Criterion, that is the cut-off value determined by the observer trying to detect the target and regressed the

pooled data against the contrast. d' and Criterion were calculated according to the Signal Detection Theory. Two-ways repeated measures ANOVAs were then used to analyse the changes in sensitivity (SC = d'collinear - d'single) and the change in Criterion (CC = Ccollinear - Csingle) due to the contextual modulation by the flankers on the target. The main factors were: Stimulation (Sham vs. tRNS) and Contrast levels (seven levels, see Stimuli section). Post-hoc pairwise comparisons were conducted using two-tailed t-tests with Bonferroni correction. Separated ANOVAs were conducted for the data of Experiment 1-3 (6λ) and Experiment 2-4 (2λ) because the contrast levels didn't match for the two λs. One-tail t-tests based on the null hypothesis of 0 SC were also conducted to assess the polarity of contextual effects: SC > 0 indicated facilitation by the flankers were SC < 0 indicated inhibition.

Results

Main experiments results

Results of Experiment 1 are illustrated in Figure 9 (d'), and Figure 10 (sensitivity change, SC = d'collinear - d'single). Results of Experiment 2 are illustrated in Figure 11 (d') and Figure 12 (SC).

Figure 9 and 11 show the effects of tRNS on the sensitivity (d') for the single target and collinear configuration. Figure 10 and 12 show SCs (d'collinear - d'single). Figure 12 shows the Criterion results.

Pooled d's correlated positively with contrast at 6λ ($R2 = 0.64$, $p < .001$) and 2λ ($R2 = 0.46$, $p < .001$), indicating higher sensitivity as contrast increases. The ANOVA on the SC revealed a significant effect of the Contrast Levels: SC became more positive (higher d' in the collinear configuration) with increasing contrast at 6λ ($F(6,108) = 8.9$, $p < .001$, $\eta 2p = .33$) and more negative (lower d' in the collinear configuration) with increasing contrast at 2λ ($F(6,108)=25.3$, $p < .001$, $\eta 2p = .58$). Moreover, at 6λ (Experiment 1) the effect of the Stimulation is significant: tRNS reduced SC at 6λ ($F(1,18) = 5.9$, $p = .026$, $\eta 2p = .25$) independently on the Contrast Levels (Stimulation × Contrast Levels: $F(6,108) = .74$, $p = .62$, $\eta 2p = .039$). At 2λ on the other hand, an overall effect of tRNS on SC (reduction of inhibition) was not found (Stimulation: $F(1,18) = 2.48$, $p = .13$, $\eta 2p = .12$) whereas the Stimulation × Contrast Levels interaction was significant ($F(6,108) = 2.21$, $p = .047$, $\eta 2p = .11$); this indicates that tRNS reduced

inhibition, non-significantly in the first (from -.07 to .42, p = .085), and significantly in the second (from -.23 to .44, p = .015) and in the highest level of contrast (from -1.86 to -1.21, p = .01).

Pooled C data correlated negatively with contrast at 6λ (R2 = 0.36, p < .001) and 2λ (R2 = 0.33, p < .001), indicating less positive criterion as contrast increases. The ANOVA on CC (change in Criterion) didn't reveal neither an effect of Stimulation (6λ: F(1,18) = 1.57, p = .23, η2p = .08; 2λ: F(1,18) = .002, p = .96 , η2p < .001) nor of the interaction between Stimulation × Contrast Levels: (6λ: F(6,108) = .74, p = .62, η2p =.039; 2λ: F(6,108) = 2.17, p = .051, η2p = .1), indicating that the stimulation did not affect the criterion.

As Figures 9 and 11 show, not only tRNS reduced either facilitation or suppression at 6 and 2λ respectively but, for low contrast values, the effect of tRNS resulted into an inversion of SC sign, in both λ sessions. That is, positive SC, at 6λ, turned into negative whereas negative SC, at 2λ, became positive. This was confirmed by based on the null hypothesis of 0 SC (Table 3).

Table 3. Results one-tail t-tests based on the null hypothesis of 0 sensitivity change.

Configuration	Contrast	Modulation	t	*p*
6λ	.0028	-.39	-2.50	.011
	.0039	-.26	-1.65	.059
2λ	.0030	+.42	1.76	.047
	.0058	+.44	2.35	.015

One-tail t-test to compared whether SC in some contrast levels is significantly different from zero value (no modulation effect).

Control Experiments results

Pooled d's obtained in the control experiments correlated positively with contrast, both at 6λ ($R^2 = 0.46$, $p < .001$) and 2λ ($R^2 = 0.47$, $p < .001$), indicating higher sensitivity as contrast increases. The ANOVA didn't show a significant effect of Stimulation on SC, neither at 6λ ($F(1,14) = .67$, $p = .43$, $\eta_p^2 = .046$) nor at 2λ ($F(1,14) = 1.83$, $p = .20$, $\eta_p^2 = .12$). The interaction between Stimulation × Contrast Levels was also not significant, either at 6λ ($F(6,84) = 1.21$, $p = .69$, $\eta_p^2 = .044$) or at 2 λ ($F(6,84) = .50$, $p = .80$, $\eta_p^2 = .035$).

Pooled C data correlated negatively with contrast at 6λ ($R^2 = 0.25$, $p < .001$) and 2λ ($R^2 = 0.32$, $p < .001$), indicating less positive criterion as contrast increases. The ANOVA on CC reveal neither the effect of Stimulation (6λ: $F(1,14) = .44$, $p = .51$, $\eta_p^2 = .032$); 2λ: $F(1,14) = 0.1$, $p = .92$, $\eta_p^2 = .001$) nor of the interaction between Stimulation × Contrast: (6λ: $F(6,84) = .65$, $p = .69$, $\eta_p^2 = .044$; 2λ: $F(6,84) = .5$, $p = 0.8$, $\eta_p^2 = 0.035$), indicating that the stimulation did not affect the criterion.

Discussion

In the present study, we investigated the tRNS effect on either the target contrast gain or on the relative strength of excitatory (E) or inhibitory (I) lateral between the target and collinear flankers in a lateral masking configuration. As expected, the effect of the flankers in the control conditions with sham stimulation, as reflected by SC (d'collinear - d'single) (see Figures 10 and 12, black broken lines), was either facilitatory in Experiment 1, where flankers were at medium distance from the target (with SC values > 0) or inhibitory in Experiment 2, where target-to-flanker separation was short (with SC values < 0), particularly at medium-high contrast levels. tRNS modulated both these effects in a specific way.

tRNS reduces facilitation in the 6λ configuration

As Figure 9 shows, tRNS produced a contrast gain for the single target, as reflected by higher d' obtained in the session with active stimulation than in the session with Sham. Although the difference between the condition with and without electrical stimulation for the collinear stimulus is negligible, it contributes to the global effect represented in Figure 10. In fact, the SC shows a clear reduction of facilitation by the stimulation: this suggests that the two opposite effects added to produce the SC. SC is, therefore, more conspicuous than that we would expect on the basis of the effect of tRNS on the collinear configuration since most of the SC effect results from contrast enhancement by stimulation in the single target configuration. The possibility that the

effect of stimulation in the two configurations is opposite may account for the relevant result, discussed later, of a switch of SC from positive to negative at low contrasts.

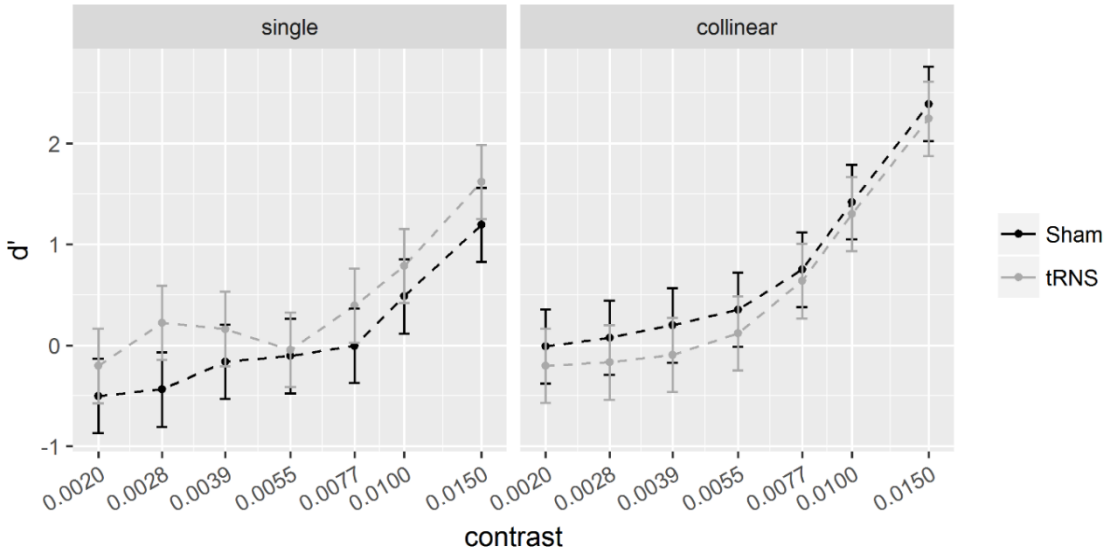

Figure 9. Sensitivity (d') for the single (left) and collinear target at 6λ.

Sensitivity (d') for the single (left) and collinear target (right) is plotted as a function of target contrast separately for the Sham and tRNS sessions. Solid bars indicate Confidence Intervals (0.95%).

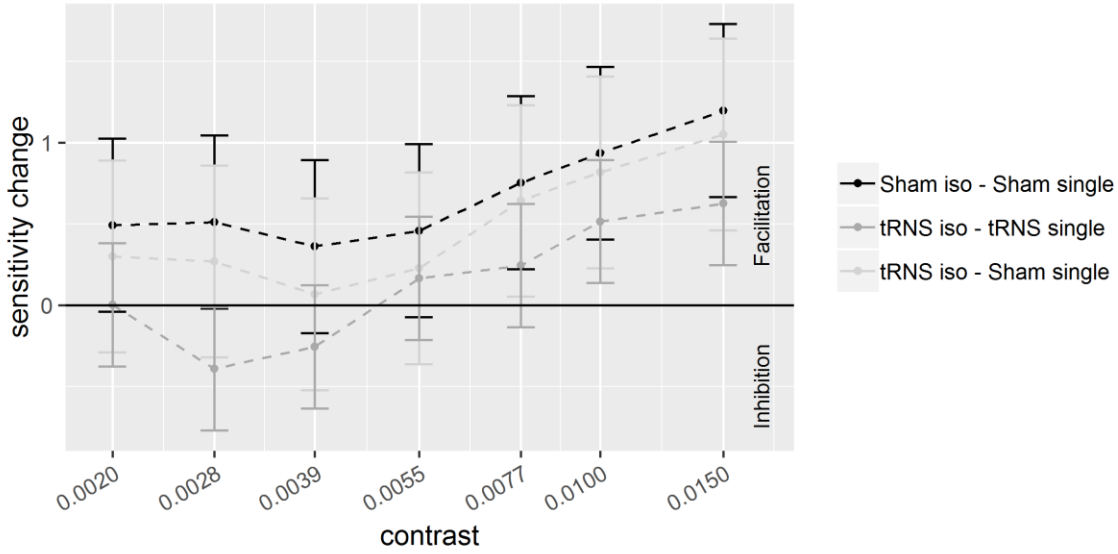

Figure 10. Sensitivity changes (SC) plotted as a function of target contrast with flankers at a distance of 6λ.

Sensitivity changes (SC), referring to the difference between d' obtained in the collinear and single target (d'collinear - d'single), are plotted as a function of target contrast with flankers at a distance of 6λ. Positive values represent facilitation by collinear flankers, whereas negative values represent inhibition. Solid bars indicate confidence interval (95%).

tRNS reduces inhibition in the 2λ configuration

The effect of tRNS at 2λ is shown in Figure 11. The stimulation does not affect d' when the target is presented isolated (single). Since it is well known that the stimulation has little effect with well visible targets, tRNS was expected to increase contrast gain at low but not high contrast. In the collinear condition, the tRNS increased sensitivity: the increased d' occurred, in particular at the levels of contrast of .0058 and .3. This selective effect of tRNS is clearly confirmed by the SC data (Figure 12), showing that tRNS reduced the negativity of SC at these low and high contrast values. Note that, as we will discuss in the next paragraph, at low contrasts SC inverts polarity.

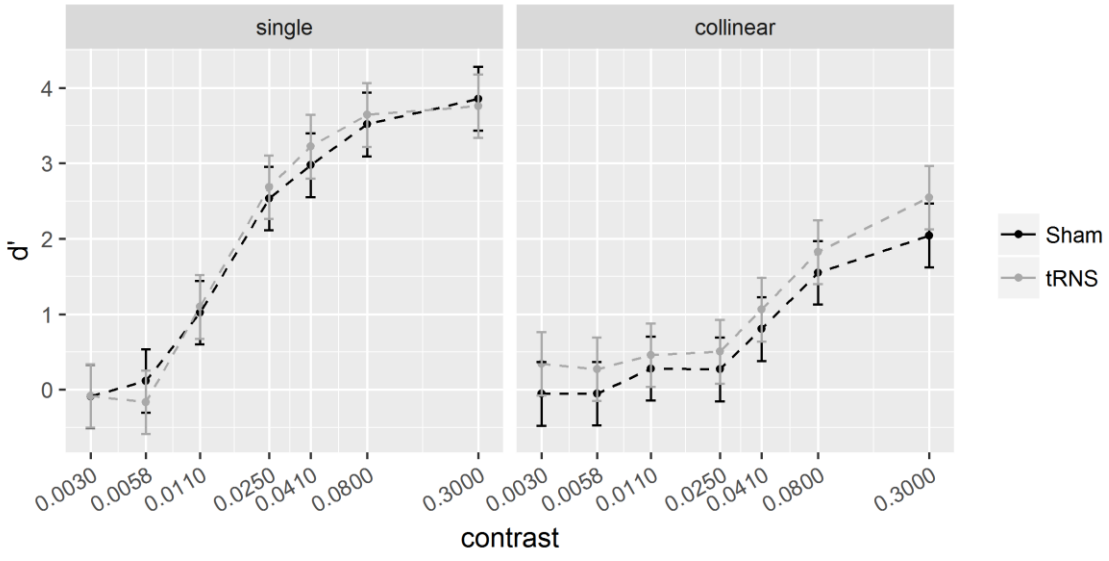

Figure 11. Sensitivity (d') for the single (left) and collinear target at 2λ.

Sensitivity (d') for the single (left) and collinear target (right) is plotted as a function of target contrast, separately for the Sham and tRNS sessions. Solid bars indicate a confidence interval (95%).

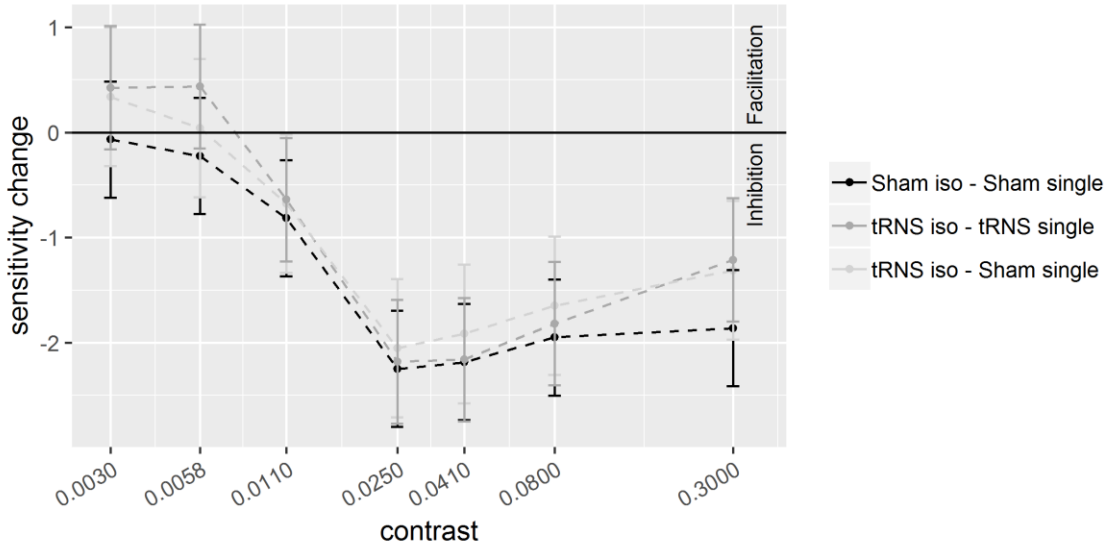

Figure 12. Sensitivity changes (SC) plotted as a function of target contrast with flankers at a distance of 2λ.

Sensitivity changes (SC), referring to the difference between d' obtained in the collinear and single target (d'collinear - d'single), are plotted as a function of target contrast with flankers at a distance of 2λ. Positive values represent facilitation by collinear flankers, whereas negative values represent inhibition. Solid bars indicate confidence interval (95%).

tRNS inverts the lateral interaction effect

It has been suggested that the facilitation/suppression of the signal by lateral interactions are the result of the balance between excitatory and inhibitory lateral interactions (Y. Adini et al., 1997; Yael Adini & Sagi, 2001; C. C. Chen & Tyler, 2001; Maniglia et al., 2011; Uri Polat, 1999; Uri Polat & Sagi, 1993, 1994; Barbara Zenger-Landolt & Koch, 2001). Our data seem to indicate that tRNS perturbs this balance. With a target-to-flanker distance of 6λ, not only tRNS reduced flankers' facilitation (Figure 10) but, at low contrast levels, it changed the sign of SC from positive to negative. Note that this effect of the tRNS on SC is mainly due to an increase of d' by tRNS in the single target configuration and also, to a lesser extent, to a decrease of d' by tRNS in the flanker configuration. With a target-to-flanker distance of 2λ (Figure 12) the tRNS modulation not only consists of a reduced suppression by the flankers but also, at lower levels of contrast, tRNS turns suppression into facilitation.

These results indicate a dissociation of the tRNS effect within the range of contrasts levels, relatively low, shared by the two target-to-flanker distances. This strongly suggests that the effect consists of modulation of contextual influences, and not simply of the local detection mechanism.

The effect of the criterion

If the tRNS effect reflects a genuine modulation of visual sensitivity, no difference in the Criterion obtained in the sham and tRNS sessions should be highlighted, regardless of whether the flankers were present or not. Figure 13 shows the criterion obtained as a function of contrast in Experiment 1 and 2 where stimulation was delivered to the occipital lobe. Clearly, the Criterion was more conservative (positive) with single

target but, as expected, this effect decreased when the target was more detectable at high contrasts. With both flanker separations, at high levels of contrast there is a small change of Criterion polarity, suggesting an increase of false alarms (Zomet, Polat, & Levi, 2016). Importantly, there was no effect of tRNS, regardless of Criterion polarity, confirming the hypothesis of a selective effect of stimulation on visual coding mechanisms and the way they are modulated by contextual influences.

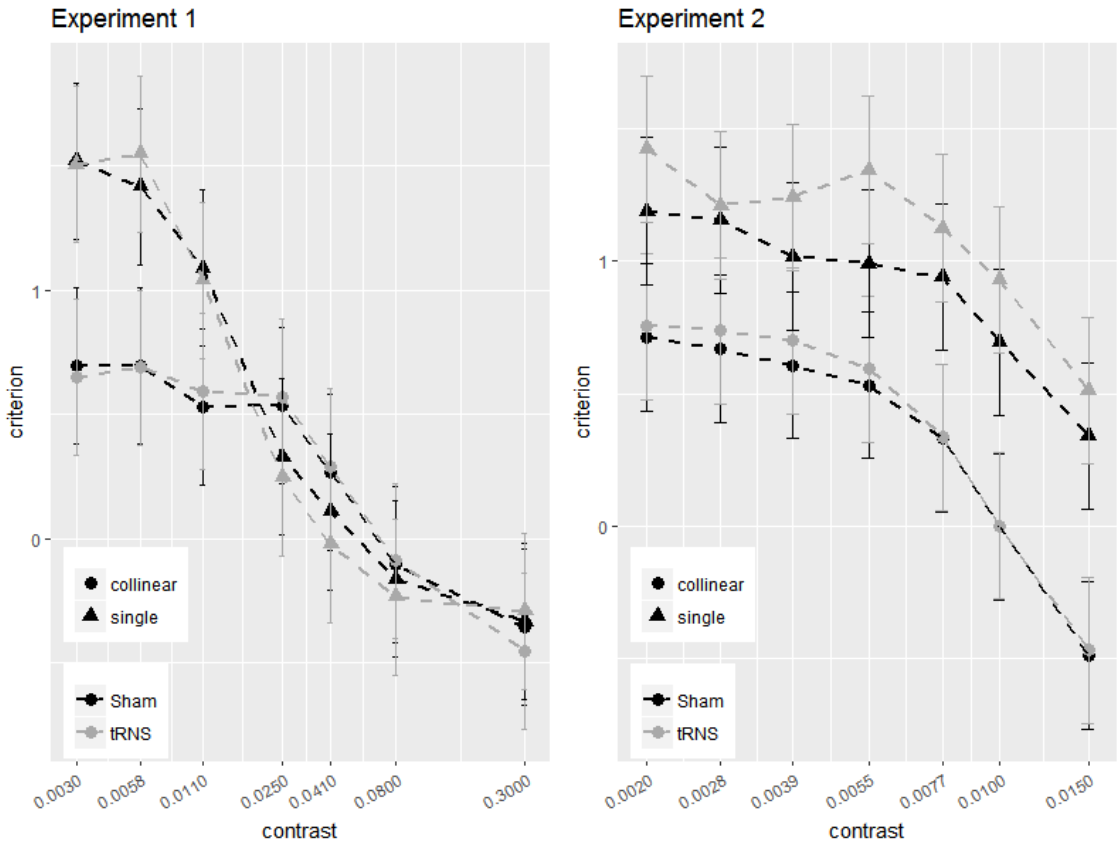

Figure 13. The figure shows the way the Criterion varies as a function of contrast in the two main experiments (Experiment 1, left panel; Experiment 2. right panel).

In each panel, Criterion C is shown for the single (triangle symbols) and collinear target (dot symbols) presented online with tRNS (grey broken lines) or with Sham (black broken lines). Solid bars indicate confidence interval (95%).

tRNS administered to a control region has no effect

When tRNS was delivered, as a control, over the forehead, with the other electrode placed over the vertex (Cz) the stimulation had no effect at all on SC and on the CC. This suggests a genuine effect of tRNS on visual coding and contextual influence mechanisms.

tRNS dependent modulation of E/I balance interpretation

To sum up, behavioural data showed an increase of d' by the flankers at 6λ and the decrease of d' at 2λ, as reflected into a positive and negative SC respectively. These results are consistent with the finding that the flankers facilitate target detection at medium λ and low contrast whereas they inhibit target detection at short λ and relatively high contrast (Y. Adini et al., 1997; Yael Adini & Sagi, 2001; C. C. Chen & Tyler, 2001; Maniglia et al., 2011; Uri Polat, 1999; Uri Polat & Sagi, 1993, 1994; Barbara Zenger-Landolt & Koch, 2001).

It has been suggested that the effect of flankers occurs because low contrast targets and large target-to-flankers separations promote activation of excitatory (E) lateral interactions between target and flankers, whereas relatively high contrast targets and short target-to-flankers separation are appropriate for activating lateral interactions or the summation of target and flankers within the target receptive field (Y. Adini et al., 1997; Yael Adini & Sagi, 2001; C. C. Chen & Tyler, 2001; Chien Chung Chen & Tyler, 2002; Maniglia et al., 2011; Uri Polat, 1999; Uri Polat & Sagi, 1993, 1994; Barbara Zenger-Landolt & Koch, 2001; Zenger & Sagi, 1996). It should be noted that the highest facilitation with the large separation is found for low contrasts (ranging from .0055 to

.015 Michelson contrast), whereas for the same contrast values the effect of flankers was negligible with a short distance. This suggests that target-to flanker distance plays the most relevant role in determining the polarity of contrast effects due to flankers in human observers.

The neurophysiological mechanism accounting for the dissociation in the effects of the contextual influence has received great attention. According to it, contrast detection tasks are mediated by the activation of E, and I subpopulations of neurons in a cortical column, with the ratio between E and I activation increasing as a consequence of two inputs: stimulus contrast (thalamic input) and the lateral input biased versus excitation (Y. Adini et al., 1997; Chien Chung Chen, Kasamatsu, Polat, & Norcia, 2001; Chien Chung Chen & Tyler, 2002; Uri Polat, 1999; Seriès, Lorenceau, & Frégnac, 2003; Stemmler, Usher, & Niebur, 1995).

We suggest that tRNS might perturb E/I balance. The way tRNS produces this effect has been associated to the way stochastic resonance mechanisms operate (A. Fertonani et al., 2011; Miniussi et al., 2013; van der Groen & Wenderoth, 2016). tRNS consists of random frequency stimulation that induces random activity into the system; this activity acts as a pedestal to boost the activation of weakly stimulated neurons. When the input signal is too weak and produces a subthreshold neural response, tRNS mediates cooperation between signal and optimal visual noise, with the result of input enhancement, selectively for subthreshold but not suprathreshold response (van der Groen & Wenderoth, 2016).

As suggested by the concept of stochastic resonance (Kitajo, Nozaki, Ward, & Yamamoto, 2003; Miniussi et al., 2013) the input at the threshold level can be better

processed within an optimum level of noise compared to without noise. In this framework, the tRNS induced noise serves as a pedestal to increase the sensitivity of the neurons to a given range of weak inputs, and the final effects are related to the functional activation induced by the state of the system. Importantly this result is corroborated by in vitro electrophysiological data (Remedios et al., 2019) endorsing the hypothesis that electrical RNS of neurons induces facilitation of sodium channels current, at an optimum level of noise for short-term application, via an excitability increase of the stimulated neural system.

We suggest that the modulation by tRNS via stochastic resonance mechanism could account for our three main results: i) tRNS affects sensitivity for the single target only at the low contrasts levels ii) the effect of tRNS on the collinear flankers occurs at both separations and consists in an overall reduction of facilitation with 6λ and a more selective reduction of inhibition with 2λ. iii) At both separations the tRNS inverts the polarity of contextual influences at the lowest levels of contrasts used with the two separations: whereas at 2λ the tRNS turns inhibitory contextual influences into facilitatory, at 6λ tRNS does the opposite.

The neural mechanism accounting for the tRNS-dependent increase of perceived contrast of the single target when it is low (at 6λ) might rely on the evidence that tRNS generally boosts weak neural input (A. Fertonani et al., 2011; Tang, Wenderoth, & Mattingley, 2017; Daniella Terney et al., 2008; Van Doren, Langguth, & Schecklmann, 2014). Given that E/I ratio due to thalamic input increases with the contrast of the isolated target, the ratio would be expected to be higher at 2 than 6λ. As a consequence, the facilitation of the isolated target resulting from the increase of neural excitability

produced by tRNS should occur where the E/I ratio is low, i.e., at 6λ. In these conditions, we would expect, as we found, an increase of contrast gain for the low contrast target. With a target of high contrast (Experiment 2) the weight of E and I is strongly biased towards E and tRNS would be ineffective in increasing contrast sensitivity for the isolated target. Our results support the hypothesis of an effect of tRNS based on the modulation E/I ratio.

Moreover, to fit the action of tRNS with that of a stochastic resonance mechanism, we have to accept that both the response to the target (by thalamic input) and to the flankers are modulated by a low/appropriate level of noise. That is, whenever the neural response is weak, it is boosted by the tRNS.

This hypothesis is compatible with the weak tRNS effect obtained when the flankers are 6λ apart from the target. At these target-to-flanker separations, as our (Figure 9) and previous data show, lateral input is biased towards excitation (Maniglia et al., 2011; Uri Polat & Sagi, 1993, 1994). Given an excess of lateral excitation, the inhibition would be comparatively weak, and therefore, we would expect tRNS to boost inhibitory connection. Indeed, we found that tRNS slightly reduced facilitation by the flankers.

At 2λ, the expected effect of the tRNS on lateral input is opposite. The stronger activation of inhibitory lateral input when close flankers are present would reduce the E/I ratio in the cortical column activated by the target. Based on this assumption, by boosting the weaker, excitatory lateral input, the tRNS would produce a reduction of inhibition.

In favour of the modulation of lateral E/I input by tRNS is our third result: the E/I balance perturbation result discussed in paragraph “tRNS inverts the lateral interaction effect”. It showed that even when the target contrast matches in the two λ distances and

therefore there is no change in thalamic input, there is still a boosting effect of lateral interactions by tRNS, but in the opposite direction at the two separations.

It should be remarked that the effects of tRNS, at large separations, may be compatible with the way the polarity of lateral interactions depends on the target contrast in normal vision. It has been shown in previous studies that for target contrast ranging from low to very low with respect to that of the flankers, the lateral input switches from facilitation to inhibition (Contemori, Battaglini, et al., 2019; Zenger & Sagi, 1996). Such a contextual modulation contrast-dependent could explain both the reduction of facilitation by tRNS and the switch from facilitation to inhibition at very low contrast (Figure 10). This model however does not explain the tRNS-dependent reduction of inhibition by the flankers at 2λ for two reasons: first this mechanism only works for a low contrast range (the contrast range used in this study at 2λ is higher than 6λ) and second tRNS should have had increased the perceived contrast of the isolated target not only at 6λ but also at 2λ, at corresponding contrast levels, but it did not. Therefore, at both separations, lateral interaction modulation by tRNS should be called into cause since the two separations produce opposite modulatory contextual effect by tRNS at corresponding contrast level. At 6λ only, the modulation of lateral interactions may also depend on perceived contrast for the isolated target.

A final comment should be made on the evidence (Figure 13) that in Experiment 2 but not 1 tRNS sets observers' criterion to a more conservative value (not significantly). However, it is unlikely that this affects the way tRNS affects lateral interactions since sensitivity does not change (Zomet et al., 2016).

To sum up, we have shown a dissociated of tRNS effect: tRNS can either reduce or increase the modulation that collinear flankers exert on contrast sensitivity of a low contrast target. Overall, tRNS increased the efficiency of whatever lateral interactions are weak: excitatory at short target-flanker separations, inhibitory at medium separations. The dissociation results from a partially complementary effect of tRNS. At large and facilitatory target-to-flanker separations tRNS increases contrast sensitivity for the low contrast target leading, as it occurs in normal vision and produces a modulation of lateral input towards reduced facilitation or to a switch from facilitation to inhibition. When the target-to-flanker separation is short and inhibitory a target contrast is high, tRNS affects directly the inhibitory lateral interactions reducing its strength.

In conclusion, the evidence that tRNS modulates intracortical lateral interactions at the low level of central visual processing in the human brain can have relevant clinical consequences. tRNS might be used to boost the effect of visual training in restoring lateral intracortical connections in V1 when these are made inefficient by visual disorders such as amblyopia and macular degeneration (Barollo et al., 2017a; Casco et al., 2018, 2014; Maniglia, Pavan, et al., 2016; Uri Polat et al., 2004, 2009, 2012; D. T. H. Tan & Fong, 2008).

Chapter VII.

tRNS Boosts Perceptual Learning in Peripheral Vision

In CHAPTER VI we have demonstrated that the tRNS allows to modulate the lateral interactions favouring the feedforward signal over the contextual influences. Under a training regimen that span over several sessions, this transient property of the tRNS could allow a more rapid and complete restructuring of the lateral interactions than the training alone. Moreover, the tRNS is known to interact with the endogenous activity of the stimulated network increasing the processing of week subthreshold stimuli under the right conditions (Anna Fertonani & Miniussi, 2017; Miniussi et al., 2013; van der Groen & Wenderoth, 2016). The cellular mechanism of this effect has recently been revealed in an article by Remedios et al. (2019) showing that tRNS is able to modulate the activation and inactivation of the Na + channels inducing a stochastic resonance phenomenon in the activity of a subpopulations of the stimulated neurons (Remedios et al., 2019). Spatial integration in early visual areas strongly influences visual crowding (N. Chen et al., 2019; Maniglia et al., 2011). By favouring the feedforward signal over the contextual influences in the early visual areas the tRNS might reduce the detrimental pooling of features among similar neighbouring elements during an identification task.

The study that I will present in this chapter has investigated the possibility of reducing visual crowding in normally sighted subjects through the combined use of PL and tRNS.

This chapter has been published in Neuropsychologia. Contemori, G., Trotter, Y., Cottereau, B. R., & Maniglia, M. (2019). https://doi.org/10.1016/j.neuropsychologia.2019.02.001.

Introduction

In peripheral vision, identification of targets among neighbouring elements is much less efficient than in foveal vision, an effect known as visual crowding (Whitney & Levi, 2011). Crowding limits peripheral reading and peripheral letter identification (S. T L Chung, 2007; Mansfield et al., 1996) and, while almost absent in healthy foveal vision (Huurneman et al., 2012), it represents a major difficulty for clinical populations suffering from amblyopia (Levi, Polat, & Hu, 1997) or central vision loss (macular degeneration (MD), Stargardt syndrome, rods-cone dystrophy, etc. (Mansfield et al., 1996). Perceptual learning (PL), the improvement in a perceptual task as a product of repeated practice (Manfred. Fahle & Poggio, 2002; Garner, 1970; Sagi, 2011a), is a promising technique that has found its way into clinical practice due to its non-invasive and inexpensive approach (Campana & Maniglia, 2015a). Several studies tested the efficacy of PL in reducing crowding, both in healthy and clinical populations (Astle, Blighe, Webb, & McGraw, 2015; Chung, 2007; Chung & Truong, 2013; Hussain, Webb, Astle, & McGraw, 2012; Maniglia et al. 2011; Maniglia, Pavan, et al., 2016; Yashar, Chen, & Carrasco, 2015). However, most of these protocols required a large number of sessions, and in some cases the improvement remained specific to the trained task. Recently, non-invasive brain stimulation has been used, alone or coupled with PL, to enhance visual abilities (Camilleri et al., 2016; Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Campana et al., 2014; A. Fertonani et al., 2011; Pirulli et al., 2013; Thompson et al., 2008). In particular, transcranial random noise stimulation (tRNS), in which a weak

electric current is delivered through the scalp on a cortical region at random frequencies, has shown promising results in boosting PL and reducing the number of sessions needed to observe significant improvements (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; A. Fertonani et al., 2011). In general, tRNS appears to boost both the early (within-session - Fertonani et al., 2011) and late (between sessions/days - Camilleri et al., 2014) components of PL. So far, PL studies used tRNS coupled with lower-level perceptual tasks, such as contrast detection or orientation discrimination, rather than training directly higher-level visual abilities, such as visual acuity (VA) or crowding. Interestingly, tRNS during contrast-detection training has been shown to induce greater transfer (the post-training improvement observed in an untrained task) to VA with respect to PL alone in both amblyopic and myopic patients (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Campana et al., 2014). The working hypothesis of our study is that stimulation on early visual cortex would promote learning of low-level features and trigger a trickle-down effect downstream of the visual processing, providing higher visual areas computing letter discrimination (e.g., the visual word form area (VWFA) in the left fusiform gyrus, Cohen et al., 2003, 2000) with a better input. Alternatively, tRNS might promote generalization of learning by reducing sensory adaptation, a phenomenon known to limit transfer of learning (Harris et al., 2012; Harris & Sagi, 2015). Consistently, Campana and colleagues (2016) showed that tRNS over V5 (a cortical area involved in the processing of visual motion, diminished the perceived duration of the motion after-effect, while tRNS over early visual areas allowed transfer of learning to an untrained visual task (visual acuity) (Moret et al., 2018). Visual crowding is known to compromise object discrimination in general and letter/word discrimination in particular. In fact, reading

under a crowded condition is slower and less accurate. The exact location at which the pooling of features among neighbouring items happens is still debated. Some authors propose that crowding occurs when elements are grouped into wholes, a process reflected in EEG by the N1 component (J. Chen et al., 2014; Chicherov, Plomp, & Herzog, 2014; Tripathy, Cavanagh, & Bedell, 2014) while others place the neural locus of crowding at an early cortical site, such as V1 or V2 (Freeman, Chakravarthi, & Pelli, 2012; Shin, Chung, & Tjan, 2017). Levi's (2008) review reconciles this in a multi-stage model where crowding occurs at both, the detection of simple features (early lateral interactions) and integration of features downstream from V1. Online tRNS is particularly effective in enhancing performance when the stimulus is sub-threshold and only if the stimulation is applied over the neural population involved in the task (A. Fertonani et al., 2011; Tang et al., 2017; van der Groen & Wenderoth, 2016). In our training, we adopted an adaptive staircase procedure that moved up and down while tracking the threshold. This way, both supra and sub-threshold trials were interleaved and non-independent from each other since the level of each trial was chosen on the basis of all previous responses. We chose an adaptive procedure in order to ensure an adequate level of difficulty throughout the training and also to better exploit the effects of tRNS given its interaction with the task difficulty. In fact, while anodal and cathodal tDCS are mostly used before the task to profit from the after-effect of the stimulation (increased or reduced cortical excitability)(Clayton et al., 2016; Anna Fertonani & Miniussi, 2017) we wanted to profit from both the ongoing modulation in the signal-to-noise ratio during the task and the general increase in the cortical excitability driven by the online tRNS, which is supposedly the best choice to induce cumulative neuroplastic changes over multiple

sessions (K.-A. Ho et al., 2013). Here, we aimed to test whether tRNS over the occipital cortex boosts PL during crowding reduction training. Moreover, in order to test whether tRNS increases generalization of learning, as observed in other cognitive (Cappelletti et al., 2013; Looi et al., 2017) and perceptual training studies (Camilleri et al., 2016, 2014, Campana et al., 2018), we tested five transfer tasks before and after the training. Generalization of learning is a highly desirable training outcome since it could inform rehabilitative interventions for clinical populations such as amblyopic patients or age-related macular degeneration (AMD) patients. Indeed, from a clinical point of view, task improvement is important but it remains of limited value if the effects are specific. We chose five transfer conditions (retinal location, orientation, task [VA] separately, and retinal location + orientation, retinal location + task [VA]) and we expected different levels of generalization based on the number of manipulated features (more transfer of learning for a single property manipulation and less transfer for combined manipulations).

Results indicate that coupling tRNS to the early visual cortex with PL of a peripheral crowding reduction task is effective in boosting between-session learning but does not increase the transfer of learning to untrained visual functions respective to PL alone (Sham condition).

Materials and Methods

Apparatus.

Stimuli were displayed on a 17” Dell M770 CRT monitor with a refresh rate of 60 Hz. All stimuli were produced using the Psychtoolbox toolbox (Pelli, 1997) in MATLAB R2012a. The monitor (1024 × 768 pixels) was placed 57 cm in front of the participants and had a spatial resolution of 1.9 arcmins per pixel. Mean luminance was 47.6 cd/m^2, as measured with a Minolta CS110 (Konica Minolta, Canada). A chin-and-head rest was used to keep the head position fixed, and the viewing was binocular. The experiment was conducted in a dark room.

Participants.

Thirty-two participants (17 females) with normal or corrected-to-normal vision took part in the study (mean age 25, range 20 – 32 years). They were randomly assigned to one of two groups (tRNS or sham). All participants gave their written informed consent prior to their inclusion in the experiment and received compensation for their participation. The study was conducted in accordance with the Declaration of Helsinki (1964). The experimental protocol was approved by the ethical committee at Centre National de la Recherche Scientifique with our institutional review board (CPP, Comité de Protection des Personnes, protocole 13018–14/04/2014).

Visual Acuity Procedure.

In order to define the size of the stimuli for the crowding task, we first measure VA individually for each participant. A central cross was displayed in the centre of the screen, and the participants were asked to fixate it and to identify a white single letter presented at 8° of eccentricity onto a black background. In order to avoid eye movements, stimulus position was randomized in a left/right manner and the presentation time was kept short (50 ms). In the absence of an eye-tracker, the use of these precautions greatly reduces (but not completely excludes) the impact of eye movements in the study. The target letter was randomly selected from a subset of 9 uppercase Sloan letters (D, S, R, Z, N, K, H, V, and C (Pelli, D. G., & Robson, 1988). The size of the letters varied according to a one-up three-down adaptive staircase procedure (Levitt, 1971), with 0.1 log unit steps, leading to an 80% of correct letter identification threshold. An experimental run ended after 12 reversals or 100 trials. Each run typically lasted 60 – 90 trials. The threshold was obtained by averaging the last 6 reversals. If the number of 12 reversals was not reached after 100 trials, the first six reversals were always discarded, and only the remaining ones were averaged. To reduce temporal uncertainty, a 50 ms sound was played prior to each target onset. At the end of each trial, participants reported verbally the letter to the experimenter who was sitting outside the experimental room in a position from where he was unable to see the monitor. The experimenter reported the answer by pressing the corresponding key on the keyboard.

Crowding Procedure.

The crowding procedure was similar to the visual acuity procedure with the difference that in each trial a trigram, rather than a single letter, was presented (see Figure

14, leftward panel). Participants were asked to identify the central letter of a peripheral trigram appearing at 8° of eccentricity (calculated from the centre of the middle letter) either on the left or right of the central fixation. The trigrams were composed of randomly selected Sloan letters among a group of nine (D, S, R, Z, N, K, H, V, and C) with no repetitions within the same trigram. Participants were then asked to report the central letter of the trigram and to ignore the two flanking letters. Stimulus position was left/right randomized, and the presentation time was 50 ms. To avoid any influence of the letter size on the task, we followed the common practice to increase the size of the letter 30 % more than the acuity threshold of the participants (Barollo et al., 2017b; Z. Hussain et al., 2012; Maniglia et al., 2011). The spacing among the three letters was varied according to a one-up three-down adaptive staircase procedure (Levitt, 1971). The experimental setup and the stopping rule for the staircase were identical to the one adopted for the VA procedure. The measured threshold defined the Critical Spacing (CS) for letter recognition. At the end of each trial, participants verbally reported the letter to the experimenter who registered the answer on the keyboard. Since crowding is particularly relevant for reading, several studies used letters as stimuli. Some of these studies calculated CS as the Letter-to-Letter distance, some others as the centre-to-centre distance between letters (Z. Hussain et al., 2012). An eventual overlap between target and flankers might reduce the validity of the measure since the task would then become a figure-ground segmentation task. On the other hand, measuring letter-to-letter spacing introduces inter-individual variability since the letter size varied according to the threshold of the participant, and the bigger the letter, the larger the centre-to-centre

distance. We chose to avoid overlapping by defining CS as the letter-to-letter distance required by the participant for an 80% discrimination accuracy.

Transfer tasks.

VA was measured to calibrate letter size in the crowding task at the same eccentricity to ensure that the size of the letter was large enough not to affect critical space measurement. VA before and after training was also used to determine whether learning transferred to an untrained but related task. In addition to VA, we measured four other transfer tasks (Figure 14): crowding at 12° (retinal position transfer), vertical crowding at 8° (orientation transfer), 12° (retinal position and orientation transfer), and VA at 12° (retinal and task transfer) (see Figure 14, upper panel). The procedure was the same as for crowding and VA. For pre-tests and post-tests, no brain stimulation (real or sham) was applied.

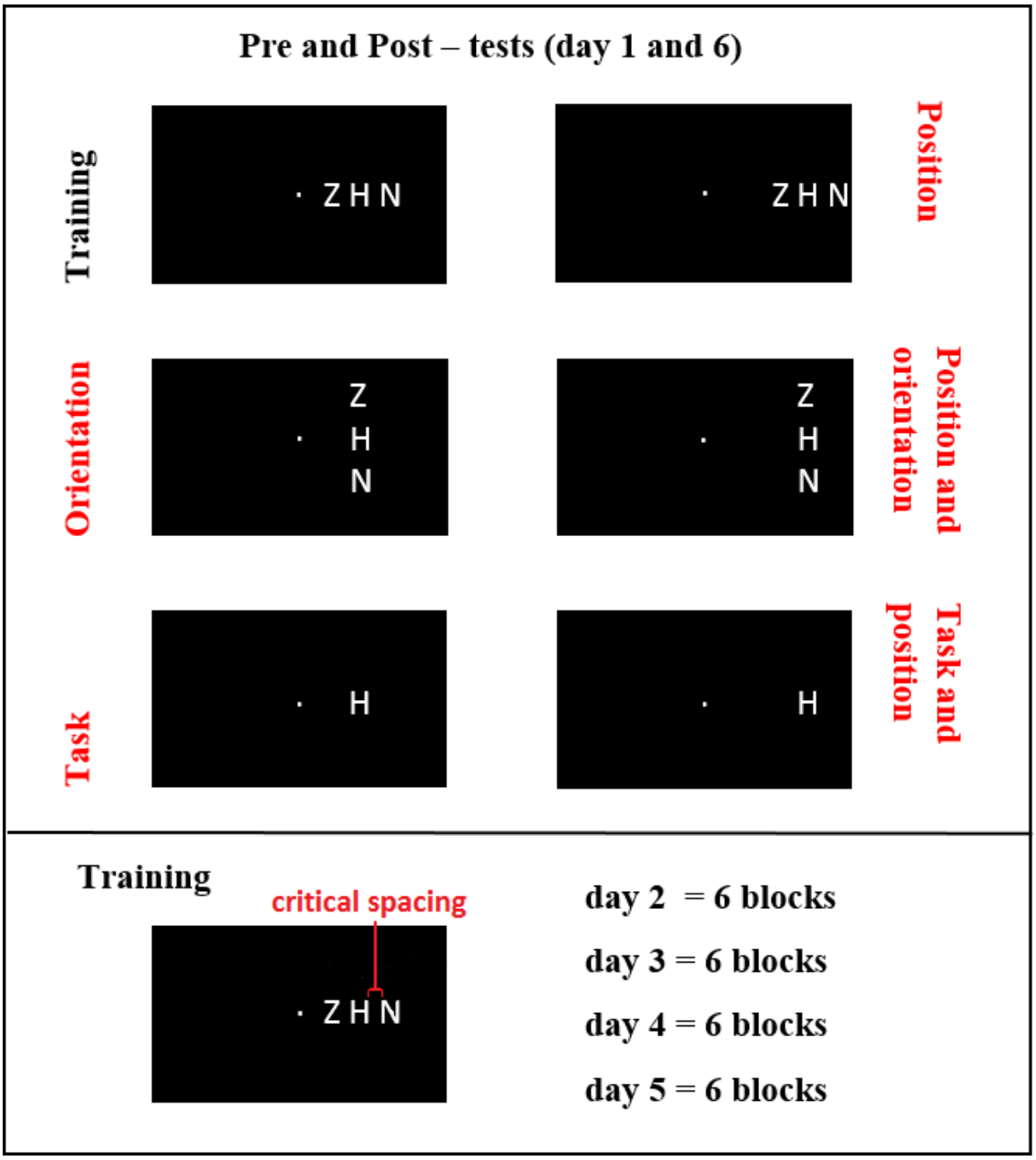

Figure 14. Configurations used in the crowding experiment.

On the upper panel, the six tasks performed on the first and sixth day (pre- and post-tests): Training configuration (horizontal crowding 8° of eccentricity), Retinal position (crowding at 12°), Orientation (horizontal crowding at 8° with vertical orientation), Task (VA at 8°), Position and Orientation (vertical crowding tested at 12°), and Position and task (VA measured at 12°). The five transfer tasks are highlighted in red. On the lower panel, the Training configuration (horizontal crowding 8° of eccentricity) tested six times

during each daily session of the training. The letters in the figure are increased in size with respect to the actual stimuli and are arbitrarily displayed on the right for clarity. In the actual experiment, the position was randomized between left and right.

Training.

The training was conducted on the horizontal crowding task (see Figure 14, lower panel). Participants were divided into two groups: Group 1 (PL plus tRNS) and Group 2 (PL alone/sham). Each participant underwent three phases: pre-tests, training, and post-tests. During pre- and post-tests, thresholds for VA at 8° and 12°, horizontal crowding at 8° and 12°, and vertical crowding at 8° and 12° were estimated. Both groups underwent four training sessions, one per day during four consecutive days. Each daily session consisted of six blocks, for a total of 24 blocks. Each session lasted approximately 30 min (~5 min per block). We did not provide direct auditory or visual feedback. However, participants were aware of the one-up three-down procedure so they could infer their performances from the trial-to-trial variation in spacing.

tRNS Stimulation.

Participants in Group 1 (PL+tRNS) were trained with concomitant electrical brain stimulation, while participants in Group 2 (PL alone) performed the training with sham stimulation. 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 and maximal current density of 0.094 mA/cm^2. This type of stimulation is characterized by an alternating current of random intensity with zero offset and values ranging from -1.5 mA

to 1.5 mA, with frequencies of fluctuation distributed across a range of 100–640 Hz with zero-mean (same as in Fertonani et al., 2011). The total duration of stimulation was 30 min to cover the entire training session. 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 27 cm^2 and was placed on the vertex. 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 non-conductive elastic bandages. For sham stimulation, we applied sponge electrodes in the same manner. At the beginning of the sham stimulation, the current was ramped up over 15 seconds and then tapered off with an equal amount of time. The same procedure was performed at the end of the stimulation. To better understand the diffusion of the current through the cortex and the size of the stimulated area according to this setup, we calculated and visualized the expected current density with the SimNibs software (Saturnino et al., 2015, Figure 15) which confirmed the current density was mostly localized in early visual areas.

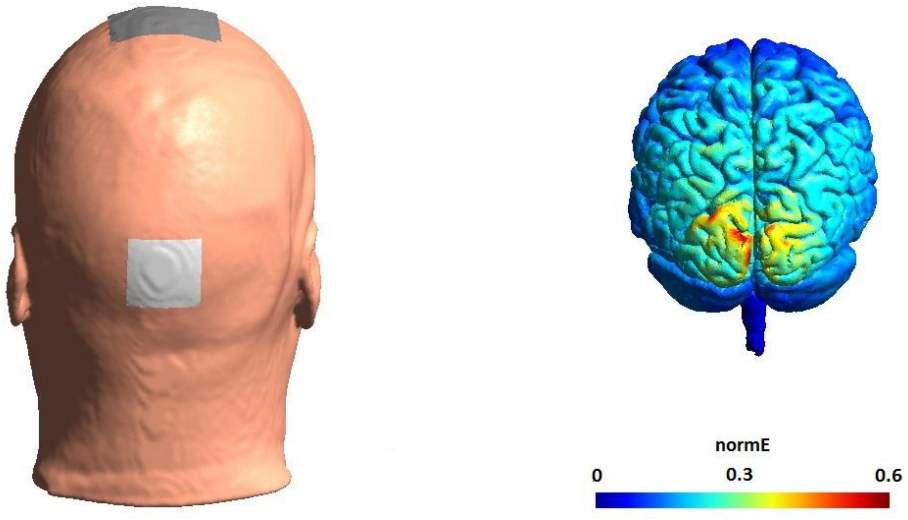

Figure 15. Electrode positioning and modeled electrical field strength (normE).

This estimate shows that the highest current density corresponded to the early visual cortices.

Data analysis.

Visual inspection of the data suggested a possible inhomogeneity in the variance of the training data between the two groups. We confirmed this by means of a Bartlett test (Bartlett's K-squared = 43.57, df = 11, p-value = 0.001), therefore we adopted non-parametric (distribution-free) inferential statistical methods. The Aligned Rank Transform for nonparametric factorial ANOVA (Wobbrock, Findlater, Gergle, & Higgins, 2011) allows a non-parametric analysis of variance to be conducted on factorial models with fixed and random effects for repeated measures. For the main effects, we performed this analysis using the "art" function of the ARTool package available at CRAN (Kay & Wobbrock, 2018). To test for interactions, we used another non-parametric ART test specifically developed to test for interactions of repeated measures design with one 'within' and one 'between' factors as described by Beasley & Zumbo (2009) and Higgins & Tashtoush (1994). This test was performed with the "npIntFactRep" function within the homonymous R package (Feys, 2015). However, because this package does not allow for testing interactions with more than one 'within' factor, we only ran interaction tests for the pre-post comparison in the trained and transfer tasks and for the between-session learning but not for the between blocks learning. All the comparisons were pre-planned, and we, therefore, reported their statistical significance without correcting for multiple comparisons. Given the number of performed comparisons (21), if all the null hypotheses were true, we should expect only 1.05 (5%)

of the comparisons to have uncorrected P values less than 0.05. This consideration is important to better evaluate the strength of the reported results (Rothman, 1990).

Results

The reduction in critical space in the trained task was evaluated between sessions. We also evaluated the transfer of learning to other untrained tasks between pre- and post-test.

PL and tRNS effect between sessions.

A two way Aligned Rank Transformation ANOVA performed on Group (tRNS vs Sham) and Sessions (pre-test, day1, day2 day3, day4, post-test) showed a main effect of Sessions ($F[5,150] = 26,24$, $p < 0.0001$) and an interaction between Group and Sessions ($F[5,150] = 2.72$, $p = 0.022$). It suggested that the tRNS group improved more than the Sham. However, since directly comparing levels of factors in a non-parametric model is not advised (Benavoli, Corani, & Mangili, 2015; Kay & Wobbrock, 2018), we did not run post-hoc analysis on this data.

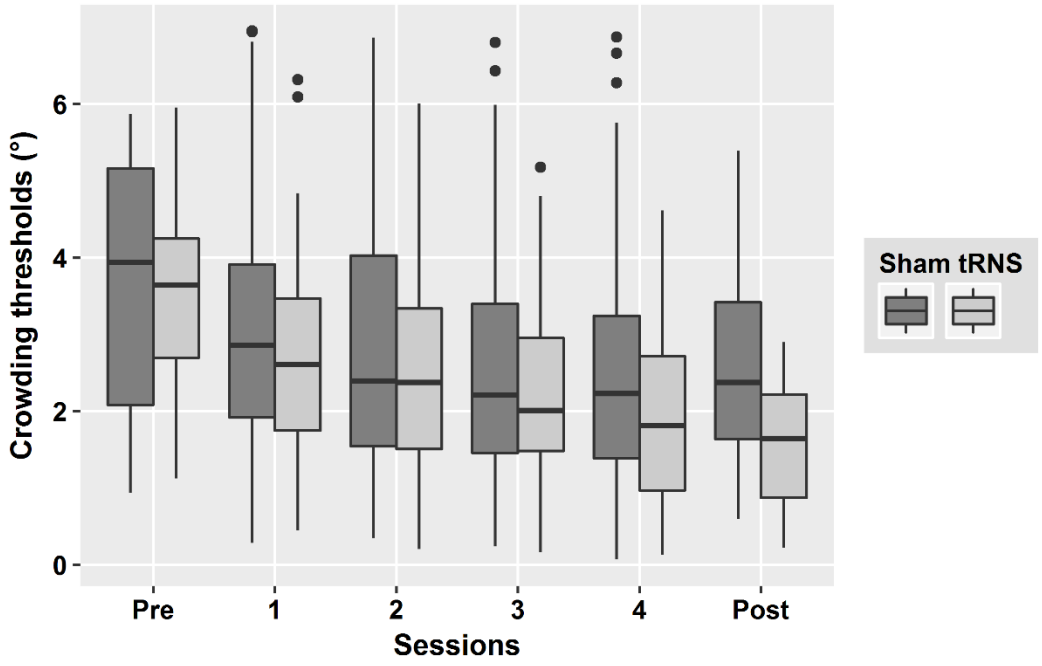

Figure 16. Between days crowding thresholds.

Crowding thresholds (in degrees of visual angle) over days in the sham (in dark grey, n = 16) and tRNS (in light grey, n = 16) groups. For each day, the figure shows separated boxes for Sham and tRNS groups. From bottom to top, boxes provide the 5th, 25th, 75th, and 95th percentiles of the distributions. The horizontal bold lines provide the median values of the distribution, and the black dots correspond to outliers.

Trained and transfer tasks.

We performed an Aligned Rank Transformation ANOVA for the trained and each of the transfer tasks. We tested Group (tRNS vs. Sham) and Training (pre-test vs. post-test) as factors plus their interaction. Results are reported below:

Table 4. Results table form statistical data analysis

a) Trained task (horizontal crowding at 8°)	• Training (F[1,30] = 51.045, p< 0.0001) * • Group (F[1, 30] = 1.432, p = 0.241) • Interaction (F [1,30] = 4.885, p = 0.0349) *
b) Retinal position transfer (horizontal crowding at 12°)	• Training (F[1, 30] = 10.216, p = 0.003) * • Group (F[1, 30] = 0.010, p = 0.920 • Interaction (F[1, 30] = 0.099, p = 0.754)
c) Orientation transfer (vertical crowding at 8°)	• Training (F[1, 30] = 2.27, p = 0.142) • Group (F[1, 30] = 3.19, p = 0.839) • Interaction (F[1, 30] = 2.089 p = 0.159)
d) Retinal position and orientation transfer (vertical crowding at 12°)	• Training (F[1, 30] = 3.968, p = 0.0585) • Group (F[1, 30] = 0.002, p = 0.961) • Interaction (F[1, 30] = 0.0756, p = 0.785)
e) Task transfer (VA at 8°)	• Training (F[1, 30] = 19.934, p = 0.0001) * • Group (F[1, 30] = 2.66, p = 0.609) • Interaction (F[1, 30] = 0.911, p = 0.347)

f) Retinal position and task transfer (VA at 12)	• Training (F[1, 30] = 6.278, p = 0.018) * • Group (F[1, 30] = 3.611, p = 0.067) • Interaction (F[1, 30] = 0.454, p = 0.505)

Results table form the Aligned Rank Transformation ANOVA for the trained and each of the transfer tasks with Group (tRNS vs. Sham) and Training (pre vs. post) as factors plus their interaction. Results are shown in Figure 17.

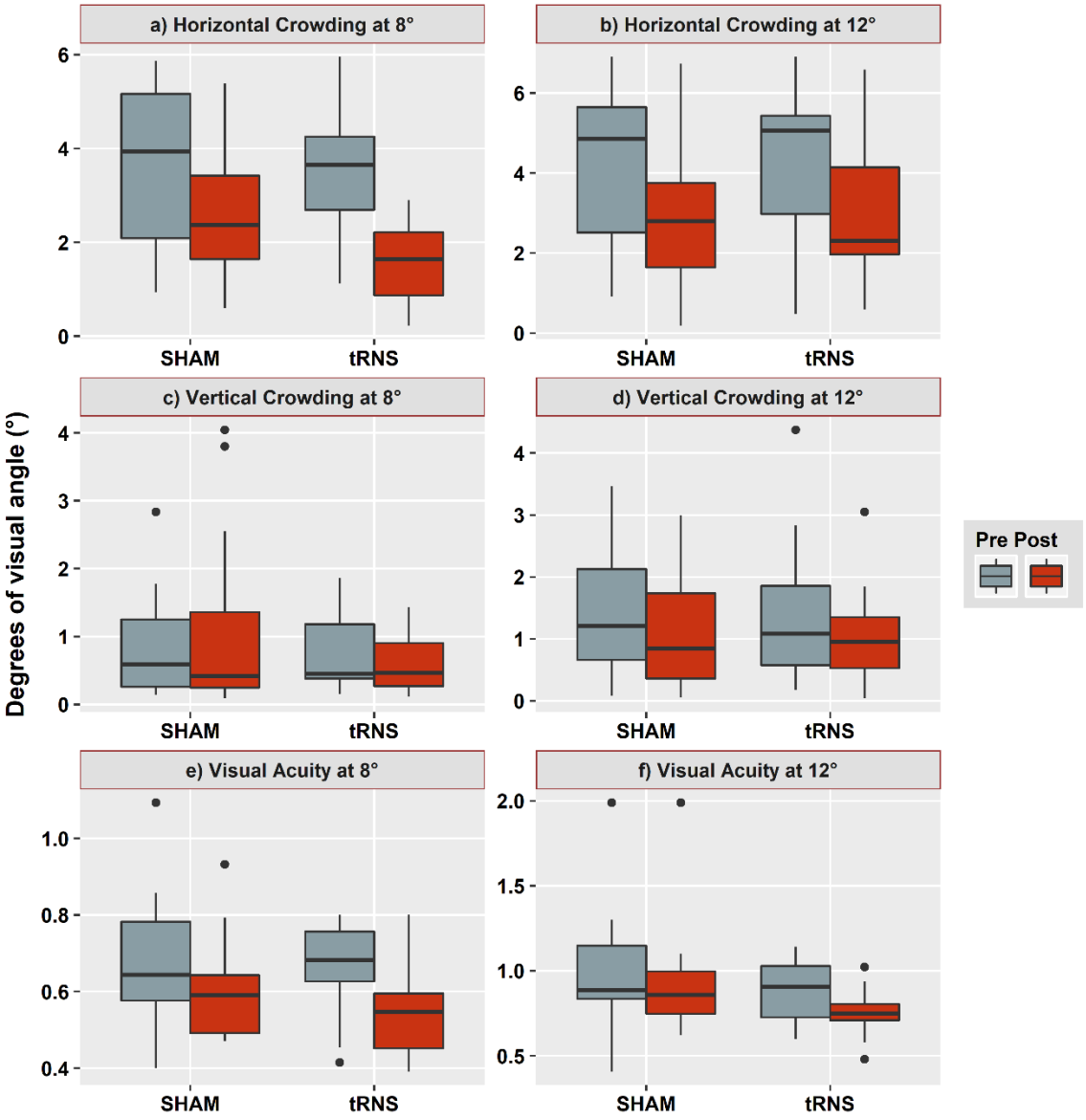

Figure 17. Training and transfer tasks results for the sham and tRNS groups.

Pre and post-training data are shown in grey and red, respectively. From bottom to top, boxes provide the 5th, 25th, 75th, and 95th percentiles of the distributions. The horizontal bold lines provide the median values of the distribution while the black dots correspond to outliers. a) Training task: crowding at 8° of eccentricity, b) Retinal transfer: horizontal crowding at 12°, c) Orientation transfer: vertical crowding at 8°, d) Position and orientation transfer: vertical crowding at 12°, e) Task transfer: VA at 8°, f) Position and task transfer: VA at 12°.

Discussion

In the present study, we compared two training protocols for reducing visual crowding, one in which participants received online electric brain stimulation (i.e., tRNS) and the other in which no electric current was delivered during the task (i.e., sham). After four days of training, both groups improved in the trained task, but the brain stimulation group reduced crowding significantly more than the sham group. Moreover, both groups showed transfer of learning to another retinal position and to visual acuity (VA). This is the first evidence of the efficacy of tRNS in boosting PL to improve performance during a peripheral vision task, a result consistent with previous studies in foveal vision (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Campana et al., 2014).

Effect of tRNS on learning

Coupling tRNS and PL resulted in greater learning than PL alone, as observed in previous studies (Campana et al., 2014; A. Fertonani et al., 2011). The mechanisms underlying tRNS are still not completely understood: co-occurrence of stimuli in close succession and the temporal summation of small depolarizing currents induced by the random sub-threshold stimulation (D. Terney et al., 2008) might facilitate the depolarization of cortical neurons, producing Hebbian LTP-like changes in the network that processes the task (Cappelletti et al., 2013; A. Fertonani et al., 2011; Miniussi et al., 2013; Snowball et al., 2013), improving in-turn performance over time (D. Terney et al., 2008). An alternative hypothesis is that the high stimulation frequency (100-640 Hz) prevents the homeostasis of stimulated neurons (A. Fertonani et al., 2011). Indeed, tRNS seems to induce greater improvements in performance than anodal tDCS, where the

current flows constantly along the same direction, despite the fact that both stimulations produce an increase in cortical excitability (A. Fertonani et al., 2011; Pirulli et al., 2013). Finally, the introduction of external noise from the electric stimulation might alter the overall level of cortical excitability and the probability of discharge of every single unit, modifying in-turn the signal-to-noise ratio during stimulus processing (A. Fertonani et al., 2011). A model of *stochastic resonance* was previously proposed to explain the non-linear effects found in brain stimulation studies (Miniussi et al., 2013). This model takes into account the interaction between internal activity, externally induced noise, and stimulus-driven activity, predicting that in the case of a low target signal, an "adequate amount" of external noise (in our case the tRNS) can enhance the signal (alone) above the threshold. Some very recent studies investigated the relationship between the intensity of the tRNS stimulation and the performance in a visual task (Tang et al., 2017; van der Groen & Wenderoth, 2016). In particular, van der Groen & Wenderoth (2016) showed that the window of maximum efficacy in terms of stochastic resonance for a subthreshold visual stimulus has a peak at current intensities around 1 mA for an electrode of 35 cm^2 placed over the occipital cortex. This intensity is indeed lower than the one we used, but also the eccentricity of the task and the contact medium used to deliver the stimulation were different, and thus the expected peak efficacy of the stimulation is shifted towards higher intensities. Moreover, in other domains like auditory perception, improvement in perception attributable to stochastic resonance was achievable with intensities higher than 1 mA (Rufener et al., 2017). Given all these considerations, we suggest that the tRNS group in the present study might have benefited from both a general increase in cortical excitability and synaptic plasticity as well as a better signal-to-noise ratio throughout the

course of the training, improving the performance between sessions, as suggested by the significant interaction.

Learning retention over time

Although our original design did not include any follow-up recording, we decided at the end of the experiment to collect additional data to further test learning retention in the trained task (horizontal crowding at 8°) over time. Ten participants (five in each group) were tested in follow-ups after three months. Because of this small sample size, the results of this follow-up experiment are tentative and are only succinctly reported here (the interested reader can, however, find all the details in the supplementary material). Interestingly, in this subsample, only the tRNS group improved significantly between pre and post-test, in agreement with the main finding of the study, which shows a larger learning effect for this group. For the sham group, despite a tendency to improve, the low statistical power due to the small sample size may have led to a “false negative" finding. The main observed effect was that, after three months, the tested subjects had substantially lost their learning benefit. This is in contrast with previous studies that showed long-term learning retention after a crowding training (Z. Hussain et al., 2012). Although this result might have been influenced by extreme values, it opens up an important reflection. It is possible that even if tRNS was able to speed up learning over a short number of trials, a larger number of blocks or a different distribution of the training sessions needed to achieve a durable improvement in the task. Indeed, the number of trials used in our training is much lower than in previous studies. Given that consolidation of learning is a central aspect for future applications of PL in healthy and

clinical populations, further research is needed to better determine the positive and negative aspects of tRNS over time.

Effect of tRNS on transfer

The tRNS group did not show a greater transfer of learning to untrained visual tasks with respect to the sham group. An argument in favour of expecting a bigger transfer of learning for the tRNS group comes from the evidence that PL specificity can be overcome by removing the sensory adaptation that emerges after prolonged exposure to the same training configuration (Harris et al., 2012). Similarly, the randomly changing electric field induced by tRNS might prevent stimulated neurons from homeostasis, increasing their activity and thereby inducing a greater generalization. Indeed, Campana et al. (2016) showed a similar effect of reduced adaptation to motion for tRNS delivered over V5, while Campana et al. (2018) reported generalization to VA for a contrast detection training coupled with tRNS on the early visual cortex. The reason why we did not observe this effect might be related to the difficulty of the training we adopted. According to the stochastic resonance model (Miniussi et al., 2013), the interaction between task difficulty and intensity of the stimulation produces an inverted U shaped curve of performance, and thus we opted for an adaptive task that could guarantee an adequate level of difficulty through the whole training regimen. Prolonged training at threshold ('difficult' training) was found to prevent learning from transferring to other retinal positions or tasks (S.-C. Hung & Seitz, 2014). Easy trials during training, on the other hand, restored transfer of learning, consistent with the reverse hierarchy theory (Merav Ahissar & Hochstein, 1997, 2000; Hochstein & Ahissar, 2002), according to

which the difficulty of the task induces a shrinking of the attentional window and an increase in learning specificity. Since the beneficial effects of the tRNS are specific for difficult training conditions, this might prevent the stimulation from altering, in a positive or negative way, the amount of generalization. However, the relationship between training and generalization of learning appears complex and might involve modifications in cortical areas beyond the ones we targeted with our stimulation (Maniglia & Seitz, 2018).

tRNS and Crowding

Similarly to previous experiments combining visual PL and brain stimulation, our tRNS targeted the occipital cortex (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Campana et al., 2014) and therefore mostly stimulated early visual areas (i.e., V1, V2/V3). The cortical substrate of crowding is a debated topic in vision science, with some studies implicating early cortical loci (Tripathy et al., 2014) and other higher-level regions (Chicherov et al., 2014; Ronconi, Bertoni, & Bellacosa Marotti, 2016). It is likely that the reduction of crowding observed in PL studies results from neural changes at different levels of the visual processing hierarchy. However, the evidence that tRNS on occipital cortex induced a greater reduction of crowding is in line with the involvement of early cortical loci. Moreover, unlike previous studies (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; A. Fertonani et al., 2011), we stimulated upstream of the visual areas where the readout module for trained task (VWFA) is supposedly located. In this way, by applying the stimulation to some cortical areas involved in the early visual processing, we can potentially trigger a trickle-down effect that affects learning and discrimination of

complex stimuli at later stages. However, given the absence of a control position for the stimulation, we cannot conclude that this result is specific for the protocol we adopted. We hope that future researchers will clarify this point.

Comparison with previous studies on crowding reduction.

Previous studies reported crowding reduction through PL (S. T L Chung, 2007; Huckauf & Nazir, 2007; Z. Hussain et al., 2012; Maniglia et al., 2011; Sun, Chung, & Tjan, 2010; Xiong, Yu, & Zhang, 2015). Chung (2007) showed a reduction of crowding of 38% (but no transfer to other tasks, i.e., reading speed). Hussain and colleagues (2012) trained adult amblyopic patients (in the fovea) and healthy participants (4° of eccentricity) on a crowding task and reported similar reduction of critical space between the two groups (~20%) but no transfer to VA. Maniglia et al. (2011) used a paradigm based on lateral masking and reported a transfer of learning to crowd reduction of about 16%. A similar paradigm used in AMD patients did produce improvements in VA, but not in crowding reduction (Maniglia, Pavan, et al., 2016). More recently, Yashar and Carrasco (2015) showed that short training (600 trials) could reduce critical space of 32%. Our training, constituted by an average of 1600 trials, showed a similar reduction for the sham group (26%), but twice that amount for the tRNS group (63%). Moreover, it is worth noting that, on average, participants in the sham group reached their plateau at the end of the third day of training, while participants in the tRNS group reduced their critical space until the last session (Figure 16).

Recently, Zhu and colleagues (2016) trained a group of healthy participants in a crowding task and reported a reduction of about 68% after 1700 trials. However,

differences in the task (orientation discrimination task in their study vs. letter identification in the present one) and paradigm (fixed flanking distance and staircase-on-orientation discrimination accuracy in their study vs staircase-on-flanking distance in the present one) make the comparison between their results and ours less straightforward. In general, crowding can be reduced either by training on critical space reduction or by improving target identification for a fixed flanker distance.

The coupling of transcranial electrical stimulation and PL has shown to increase learning when compared with PL alone, offering a fast and effective method to improve peripheral visual functions. Future studies should verify its efficacy in clinical populations that might get practical advantages from crowding reduction, such as patients with amblyopia or central vision loss (Maniglia, Cottereau, et al., 2016). At the same time, its effect on brain networks should be further examined to increase our understanding in order to improve transfer and learning retention over time. Nonetheless, the present results support the hypothesis that tRNS is a promising tool to improve visual training outcomes in general. These findings have potential implications for vision enhancement in both healthy individuals' periphery and patients suffering from central vision loss who cannot undergo the long training sessions typically needed in classic PL paradigms (Maniglia, Cottereau, et al., 2016).

Chapter VIII.

tRNS Boosts Perceptual Learning in MD Patients

In the introduction, we have seen that one of the effects of adaptation in the absence of central input is the enlargement of the receptive fields with consequent loss of neural tuning (Baseler et al., 2011a; Y. M. Chino et al., 1992). Moreover, the processing in the PRL of patients is not optimized for fine vision, and the effect of the adaptive plasticity is limited as confirmed by the study presented in CHAPTER V (Musel et al., 2011; Peyrin et al., 2017). In CHAPTER IV we have seen that the tRNS stimulation might be useful to improve PL both between and within sessions (Campana et al., 2014; A. Fertonani et al., 2011). In CHAPTER VI we have demonstrated that the tRNS might be able to help in modulating the strength of the lateral interactions in the early visual cortex. In CHAPTER VII we have seen that this modulatory effect together with the more general ability of tRNS in boosting PL, helps in the reduction of visual crowding in the periphery normal viewers. Here I present a translational study in which we applied a combined PL + tRNS approach improving residual vision in the PRL of AMD patients.

Introduction

Macular Degeneration (MD) is a visual disease characterized by central vision loss. In the case of bilateral central blindness, patients with MD start to use a peripheral retinal locus (PRL) as a replacement for the fovea. However, fixation with this locus is unstable and the processing of visual details poor (Hogg & Chakravarthy, 2006; Macedo, Crossland, & Rubin, 2011). The functional organization of the periphery is very different compared to the fovea. For example, the receptive fields are larger (V. Virsu & Rovamo, 1979), the range of the contextual influences is wider (Lev & Polat, 2011), the distribution of photoreceptor is different (Elsner et al., 2017), the parvocellular / magnocellular ratio is decreased (Azzopardi et al., 1999), the sensitivity to motion is increased, and the contrast sensitivity at low spatial frequencies is increased while at high spatial frequency is decreased (Veijo Virsu, Rovamo, Laurinen, & Näsänen, 1982; Wright & Johnston, 1983). Due to these differences, tasks that require a stable fixation and detailed spatial processing are very limited in the periphery, which renders basic everyday activities very hard to perform (Battista, Kalloniatis, & Metha, 2005). The emergence of the scotoma is a slow process that occurs in phases, sometimes with acute episodes, but generally in the course of months or years (Crossland et al., 2005; Gheorghe, Mahdi, & Musat, n.d.; Riss-Jayle et al., 2008a). In this lapse of time, spontaneous changes take place in the functional structure of the patients' visual system (Cheung & Legge, 2005). These changes are based on transient short-term plasticity mechanisms that maintain the homeostasis of the system and are already present in normal vision (Baseler et al., 2011a; Y. M. Chino et al., 1992). The exact mechanism of

action of this spontaneous adaptation, as well as its psychophysical correlates, are not clear yet and are difficult to isolate from the effects of use-dependent plasticity that takes place over time in the PRL (Contemori et al., 2019; Maniglia et al., 2018). The comparison with the periphery of subjects with normal vision has shown that MD patients have better perception of mirror symmetries outside the scotoma (Casco, De Stefani, Pinello, Sato, & Battaglini, 2015), lower critical space in visual crowding tasks (Susana T.L. Chung, 2014), and illusory contours (De Stefani et al., 2011). On the contrary, scene discrimination (Musel et al., 2011; Ramanoël et al., 2018), visual acuity and contrast sensitivity for medium and high spatial frequencies are worse (Hogg & Chakravarthy, 2006). Generally, it is difficult to say whether the spontaneous mechanisms of adaptation produce more positive or negative effects on patients' vision. In any case, the spontaneous adaptation is not sufficient to counteract the action of the degeneration (Lemos, Pereira, & Castelo-Branco, 2016b; Ogawa et al., 2014). The use-dependent cortical reorganization also has a limited impact on the visual function of the patients and is especially evident in the strengthening of connections towards the extrastriate visual areas involved in objects and scenes recognition. (Beer, Go, Plank, & Greenlee, 2015; Hernowo et al., 2014; Malania et al., 2017; Ogawa et al., 2014). Moreover, an extensive remapping of the LPZ in humans seems out of the question (Baseler et al., 2011b). Although recent research into the use of genetic therapies and retinal implants have made great strides, there are currently no therapies available to restore damaged foveal vision (Gehrs, Anderson, Johnson, & Hageman, 2006; Makin, 2019). Current treatment options focus on the use of visual aids coupled with various types of training that allow the patient to partially compensate for the loss of central

vision (Maniglia, Cottereau, et al., 2016). Recently, attention has been given to the use of training based on perceptual learning tasks that improve the residual vision in the PRL (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018; Plank et al., 2014). Among the various tasks proposed, Maniglia and colleagues (2016) tested the effectiveness of training based on a lateral masking task promoting contrast sensitivity in the PRL. This training, in its two temporal alternatives forced-choice variant, allowed not only an improvement in the trained task, but also a transfer of learning to visual acuity, visual crowding, and higher spatial frequencies compared to those trained. It should be emphasized that although the training was carried out in the monocular condition, even the untrained eye showed a significant transfer of learning at the end of the training (Maniglia, Pavan, et al., 2016). The particularity of this task is to specifically train the lateral interactions between receptive fields in the primary visual cortex, that are responsible for the early stages of integration / segmentation of the visual scene (U Polat & Sagi, 1994; Uri Polat, 2009). To do this a collinear triplet of Gabors, whose distance is manipulated between blocks, is used to train the patients. The central Gabor target varies in contrast in an adaptive manner based on the performance of the subject. The contrast of the two flanking Gabor is usually very high and is kept fixed throughout the procedure. The distance between the flanks and the target is calculated in multiples of the wavelength of the trained spatial frequency, the λ. When the separation is very small, the flankers produce an inhibitory effect which translates into an increase in the contrast threshold necessary to correctly detect the target with respect to when the latter is presented in isolation or with orthogonal flankers. With increased separations, the contrast threshold decreases and the flankers' effect becomes facilitatory (Cass & Alais,

2006; Uri Polat & Sagi, 1994). Although both are allowed, the orthogonal configuration is a preferable baseline than the single Gabor since it allows to control for the decrease in spatial and temporal uncertainty given by the presence of the flankers (Uri Polat, 1999, 2009; B Zenger-Landolt & Koch, 2001). Through the logarithm of the ratio between the collinear and the orthogonal configurations, it is possible to estimate the threshold modulation elicited by the collinear context. The neural substrate of this effect lies in the horizontal connections between columns in the early visual cortex. The repeated practice with this task at various λs allows for a restructuring of the facilitatory and inhibitory horizontal connections involved in the early stages of visuo-spatial integration. After practice, there is an increase in the signal-to-noise ratio for the trained stimuli, which in turn facilitate the readout of the higher visual areas (Z.-L. Lu & Dosher, 2004; Maniglia et al., 2011; U. Polat et al., 2004a; U Polat & Sagi, 1994; Uri Polat, 2009). Furthermore, the introduction of a feedback after the answer increase the involvement of the frontal areas during the training with a consequent strengthening of the perceptual learning through reward-associated learning (Gilbert & Sigman, 2007; Herzog & Fahle, 1997; Maniglia, Pavan, et al., 2016). The use of the lateral masking paradigm as a visual training, is indicated in all cases where the pattern of lateral interactions might be altered (Barollo et al., 2017b; Camilleri, Pavan, Ghin, & Campana, 2014; Campana & Maniglia, 2015b; U. Polat et al., 2004a).

In the normal visual periphery, the range of interactions in the PRL is greater than that of the fovea of which it should be the functional substitute (Lev & Polat, 2011; Shani & Sagi, 2005). In fact, in the fovea the typical distance at which inhibition is found is

between 1 and 2λ. On the other hand, between 3 and 4λ there is facilitation, while above 6λ there is no interaction.

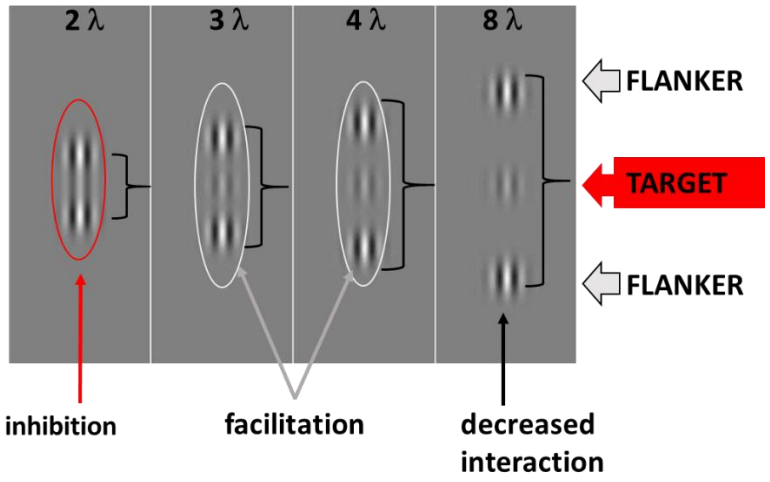

Figure 18. The range of lateral interactions in the paracentral vision.

Illustration of the range of contextual influences as expected in the paracentral vision.

In the periphery, the range varies according to the eccentricity but generally there is inhibition up to 2-3λ and facilitation up to 8-12λ (Giorgi et al., 2004; Lev & Polat, 2011; Shani & Sagi, 2005). Training the PRL with this type of task at increasing spatial frequencies as well as improving the sensitivity to contrast for the target could allow a restructuring of the lateral connections making them more performing in visual acuity tasks and potentially more similar to those of the fovea (Maniglia et al., 2011; U Polat & Sagi, 1994; Uri Polat, 2009). The study presented in CHAPTER V showed that the patients had an altered pattern of facilitation and inhibition in respect to the controls tested at the same eccentricity (Contemori et al., 2019). Maniglia (2018) had previously observed a similar result, concluding that the altered lateral interaction pattern in MD

could be due to a spontaneous neural plasticity triggered by the loss of foveal input. In our study, we challenged this hypothesis and showed that this effect is instead due to a general reduction in contrast sensitivity in patients. Through an additional analysis we have seen that the inhibition was strong for subjects who had a very good baseline contrast threshold and that was progressively reduced as the contrast threshold increased. When the ratio between target contrast and flankers' contrast was higher than 1/3 the inhibition switched to facilitation. We proposed that, not the enlargement of the receptive field, but the reduced sensitivity to contrast, is the main cause of the different pattern of contextual influences in MDs. When the baseline contrast is high, the difference in contrast between target and flankers is low, thus the three elements are more prone to be integrated together by a 2nd order integrative field (Zenger & Sagi, 1996). Prolonged training with this task at different λs could improve the contrast sensitivity in the PRL, by strengthening the lateral interactions. (Camilleri, Pavan, Ghin, & Campana, 2014; Maniglia, Pavan, et al., 2016; U Polat & Sagi, 1994). Maniglia and colleagues in 2016 found that MD patients following training of around 24 sessions have decreased inhibition and increased facilitation. In addition, the improvement in the trained task also transferred to the untrained eye, and to some untrained tasks - visual acuity and crowding (Maniglia, Pavan, et al., 2016). There two main objectives in this final thesis study: to confirm the efficacy of the lateral masking paradigm in improving vision in MD, and to see whether we can achieve an even better result by coupling the PL with the tRNS. To do so, two groups of patients have been trained with PL or with PL combined with occipital tRNS. As demonstrated in chapter VI, the tRNS allows modulating the lateral interactions favouring the feedforward signal – the genicular input – over the contextual

influences – horizontal cortical integration. This transient property of the tRNS, within a prolonged training, could allow for a more rapid and complete restructuring of lateral interactions than PL alone. Moreover, the tRNS is known to produce two more general effects in the stimulated area: a general increase in cortical excitability and a resonance phenomenon between the externally induced noise and the stimulus-related signal (Anna Fertonani & Miniussi, 2017; Miniussi et al., 2013; van der Groen & Wenderoth, 2016). Remedios et al. (2019) recently showed that at a cellular level the tRNS is able to modulate the activation and inactivation of the Na + channels. This modulation acts differently depending on the intensity of the current and the type of the stimulated neurons, but at the sweet point it could facilitate the processing of subthreshold stimuli (Remedios et al., 2019; van der Groen & Wenderoth, 2016). In CHAPTER VII we have studied the interaction between tRNS and PL in the periphery of sighted subjects (Contemori, Trotter, Cottereau, & Maniglia, 2019). Our secondary aim was to test if the tRNS was able to increase transfer to an untrained task. Transfer is thought to be limited by habituation (Harris et al., 2012; Xie & Yu, 2019) and some preliminary results suggest that tRNS could reduce it preventing the homeostasis of the stimulated population (Campana et al., 2016; A. Fertonani et al., 2011; K.-A. Ho et al., 2013; D. Terney et al., 2008). The tRNS group showed higher learning in the trained task when compared to the PL alone group, but the amount of transfer was similar in the two groups. We hypothesized that the lack of increase in transfer depended partly on the choice of the training task. In fact, V1 centred occipital stimulation may have increased plasticity and the signal-to-noise ratio in the stimulated area, consequently improving input to higher-level visual areas and thus producing a boost in perceptual learning. On the other hand,

since VWFA, the area where the triplets of letters are identified (Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005), was not directly stimulated, tRNS may not have been able to boost the transfer by preventing habituation in this region. For this reason and given the importance of increasing the contrast sensitivity in MD patients, in this fourth and final study we decided to go back to the lateral masking task as training task. To test the efficacy of the PL + tRNS in improving residual vision in MD, we trained two groups of patients for 24 sessions over 8 weeks. One group was trained with the lateral masking task alone, while the other underwent PL + tRNS. All patients were subjected to a battery of tests at the beginning, at the half, and at the end of the training to evaluate their improvement. We compared then the improvement of the two groups in the training task and in the transfer tasks at the mid-test and at the post-test.

Materials and Methods

Participants.

Study candidates were selected from the list of the ophthalmology patients of the Paul Riquet hospital in Toulouse.

The first contact was made by their ophthalmologist. If they expressed the will to participate in the study, they were invited to the hospital for a free ophthalmological assessment on the basis of which we evaluated their inclusion. All participants gave their written informed consent prior to their inclusion in the study. This study follows the ethical standards of the Declaration of Helsinki (1964) and the experimental protocol was approved by the CNRS ethical committee before the beginning of the study (Comité de Protection des Personnes, protocole 13018). Participants received reimbursement for all the travel expenses related to their participation.

Only patients with an absolute central bilateral scotoma were included in the study. Binocular visual field test was performed by means of an Octopus® 300 perimeter; Köniz, Switzerland. Only patients with visual acuity between below 3/10 and above 1/10 were considered in the study. Since the training was performed monocularly in the best eye, we only included in the study patients with a single and stable PRL in the trained eye. The presence of concomitant ocular diseases or a non-stabilized scotoma were considered grounds for exclusion. The same for the presence of diagnosed cognitive or mood disorders. Of all contacted patients, only 16 were eligible after the initial ophthalmological screening. Of these, only 12 completed the study. Of the remaining 4,

one retired after a week of training for personal reasons. One underwent chemotherapy shortly after joining the study and was therefore excluded. Two were excluded right after the pre-test as they reported that they could not perceive all of the three Gabors in the training configuration. Data were collected over three years and participants were assigned randomly to one of the two groups. To avoid the participants to bias each other, the time schedule of the testing was structured in a way to minimize possible interaction among participants.

For each MD patient, we determined the PRL position using the same procedure described by Maniglia et al. (2018). First, the fovea was localized through a high-resolution scan of the retinal fundus with a Spectral-Domain Optical Coherence Tomography (Spectralis OCT, Heildelberg Enginering, Heidelberg, Germany). Then three anatomical landmarks were selected on the retinal fundus image and their coordinates were calculated with respect to the fovea. Later, the three landmarks were used to triangulate the position of the retinal locus that corresponded to the fixation cross during the OCT acquisition. To check for the presence of multiple PRL position the procedure was repeated three times. An example image of the procedure is shown in Figure 19.

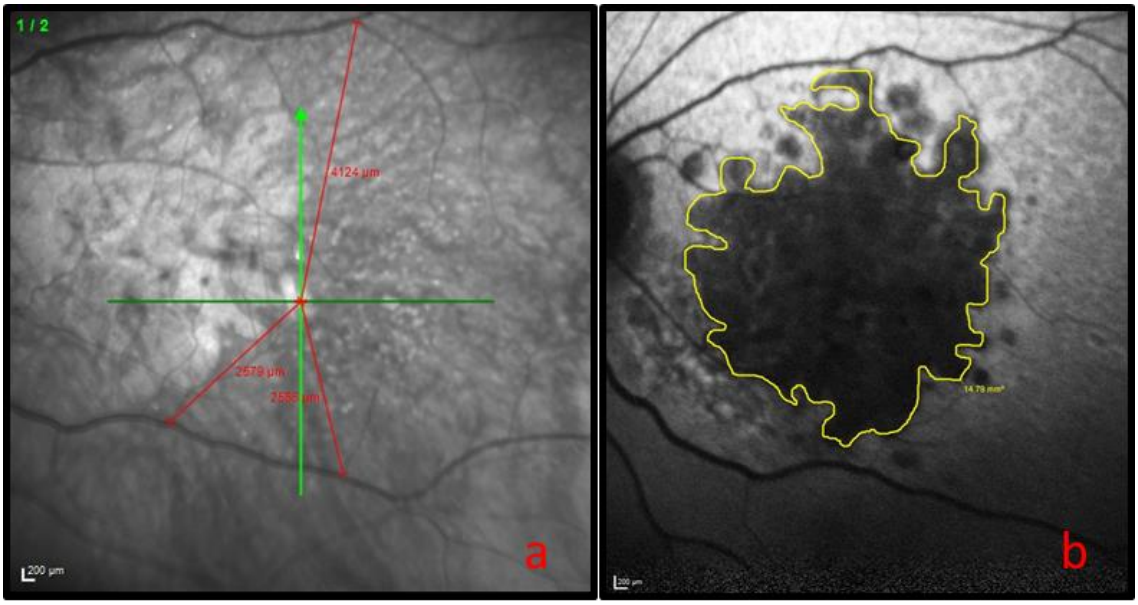

Figure 19. PRL position e scotoma size.

In the left panel (a) example of the triangulation of the PRL through the three anatomical landmarks. In the right panel (b) the patient's scotoma was highlighted before the diameter calculation.

Only patients who had a consistent PRL position across the three independent measurements where included in the study. The procedure was repeated at both the mid-test and the post-test to ensure that the PRL position was stable all over the training. Details of the sample are reported in Table 5.

Table 5. Details of the experimental sample.

Patients	Deficit	Gender	Age	Scotoma diameter	Position of PRL	Tested eye	(VA)
MD1	AMD	Female	59	17°	Left -8.0° 0.2°	LE	1/10
MD2	AMD	Female	82	22°	Left-down -5.5° 1.0°	RE	1/10

MD3	AMD	Female	53	10°	Left-down -2.6° 9.1°	LE	2/10
MD4	AMD	Female	77	12°	Left-down -8° 1.5	RE	2/10
MD5	AMD	Male	61	17°	Left-down -9° 5°	LE	1/10
MD6	AMD	Female	89	16°	Left-up -6.5° -6.5°	LE	1/10
MD7	AMD	Female	81	20°	Left-down -3° 6.4°	LE	2/10
MD8	AMD	Female	70	17°	Left-down -9.76° 5.47°	LE	1/10
MD9	AMD	Female	67	14°	Down -0.1° 4.7°	LE	2/10
MD10	AMD	Male	71	16°	Left-down -10.3° 3.8°	LE	1/10
MD11	AMD	Female	89	15°	Right-down -7.8° 1°	LE	2/10
MD12	AMD	Female	79	15.3°	Down -0.1° 6.9°	RE	1/10

Description of the experimental sample. MD patients from 1 to 5 have been trained with only PL while MD patients from 6 to 12 have been trained with PL + tRNS.

Procedure.

During pre-test, mid-test and post-test, the patients underwent the same battery of visual tasks. The battery included a contrast sensitivity measure, a visual acuity measure with Sloan letters, a tachistoscopic visual acuity measure, measure of visual crowding, a contrast threshold measure with an orthogonal and collinear lateral masking paradigm at 4 different λ (3λ, 4λ, 6λ, 8λ). The training consisted of a collinear lateral masking task with a collinear configuration. At each session of training 4 blocks were performed for a total of about 25 minutes. The target-to-flanker distance was manipulated between blocks. The 4 trained distances were 3λ, 4λ, 6λ, 8λ. During the training concomitant

tRNS stimulation was applied over the occipital cortex for the duration of the training session. Each patient was trained three sessions a week over eight weeks for a total of 24 training sessions. After 12 training session the mid-test was carried out. Post-test was collected after the end of the training.

Apparatus

Stimuli were displayed on a 17″ Dell M770 CRT monitor with a resolution of 1024×768 pixels, a refresh rate of 60Hz and mean luminance of 47.6 cd/m2. Except for the visual acuity task, stimuli were generated with Matlab Psychtoolbox (Brainard, 1997b). Each pixel subtended 2.14 arcmin. Far all the tasks that involved a contrast sensitivity measure a digital-to-analog converter (Bits#, Cambridge Research Systems, Cambridge UK) was used to increase the dynamic contrast range (13-bit luminance resolution). The monitor was linearized thanks to a 12-bit gamma-corrected lookup table (LUT). Participants set in a dark room at 57 cm from the screen (200 cm for the visual acuity test). A chin rest was used to keep the participant head at the right distance. Experiments were carried on at the Centre de la Retine, Hôpital Pierre-Paul Riquet, Purpan Hospital, Toulouse (France).

Visual acuity

To test the visual acuity we used a computerized letter recognition task known as the FrACT (Freiburg Visual Acuity and Contrast Test) software (Bach, 1996). This software is very robust, it has been used in over 100 studies and it has been validated over different clinical populations (Bach, 2006; Wesemann, 2002). This software allows to

reliably measure the visual acuity threshold for single letters by means of an adaptive staircase procedure, the Best-PEST algorithm. Stimuli are randomly selected among 10 Sloan letters: C, D, H, K, N, O, R, S, V, and Z. The patients reported the letter aloud and the experimenter that was sitting in a position from where I couldn't see the screen typed the appropriate letter on the keyboard. Two different measures where collected monocularly for each eye. Observers viewed the letters for a maximum of 30s at a viewing distance of 200 cm for a total of 30 trials. Letters were black on a white background. Acoustic feedback was automatically presented for both correct and incorrect answers. The average duration for one block was around 5 minutes.

Tachistoscopic visual acuity and crowding

To measure visual acuity and visual crowding with fast stimulus presentation, we used a procedure similar to the one presented in CHAPTER V. In this case we tested only one retinal position and thus the use of the eye tracker was not required. The participant was asked to fixate with their preferred retinal locus. In case of loss of fixation they were instructed to memorize the last answer, search for the fixation dot and then provide the verbal answer to the experimenter only once ready for the next trial. At this point the experimenter reported the answer by pressing the corresponding button on the keyboard and the next trial was initiated. Randomly selected Sloan letters (D, N, S, C, K, R, Z, H, O, V) were used as stimuli and presented in the centre of the screen for a time of 100 ms. Letters were white on a black background. The starting letter size was set to 3 deg, a size fairly above threshold for all participants. In the successive trials, the size was changed according to a psychophysical adaptive procedure from the MLP toolbox. (Grassi &

Soranzo, 2009; Green, 1993, 1990). There were 30 trials in each block, an adequate number to obtain a reliable and fast threshold (Leek, Dubno, He, & Ahlstrom, 2000). A practice dummy block was performed at the beginning to help the participant in familiarizing with the very fast presentation speed. During the dummy block the experimenter performed the task together with the patients. During the actual measurement the experimenter was sitting at a side of the desk, in a position where he could see the participant but not the monitor displaying the stimuli. The patient was forced to give a response even when could not perceive the letter. The threshold was defined as the letter size that leads to an accuracy level of 75% of correct answers. A fixation dot was displayed in the centre of the screen. The dot disappeared right before the target and then reappeared right after the target. A warning sound preceded the stimulus onset of 100ms and lasted for 50 ms. The procedure was self-paced, in a sense that the next trial was not started until the previous answer was recorded. In order to avoid lapses the participant was told that no time limit was applied to the answer and was also instructed to think carefully before answering. The total duration of the procedure was considerably variable between patients, but it never exceeded three minutes. The testing was done monocularly for both eyes.

Crowding was measured using the very same procedure as for the tachistoscopic visual acuity, except that we measured the critical space instead of the letter size. A triplet of letter was presented and the distance between the central target and the flanking distractors was varied. The threshold was defined as the critical distance that allowed for an accuracy of 75%. The size of the three letters was kept constant and corresponded to the letter size obtained in the tachistoscopic visual acuity task multiplied by 1.30. In this

way we can exclude that identification was compromised by a limit in the visual acuity (Contemori, Maniglia, & Trotter, 2016). The testing was done monocularly for both eyes. In order to allow the patient so see all the three letters, the global orientation of the triples could be horizontal or vertical, depending on the size and the shape of the scotoma. Every single letter was always vertical.

Contrast sensitivity

We measured contrast sensitivity at 4 different spatial frequency using a custom procedure similar to the lateral masking paradigm except that in this case the target was an isolated Gabor patch of 4 deg (full width at half maximum) with vertical orientation. Participants had to perform a contrast detection task with a temporal-2AFC (two-alternative forced-choice) procedure in which the target was present only in one of the two intervals. The patient had to report the interval containing the target by pressing the number “1” or “2” in the number pad of the keyboard. Each interval lasted 133 ms and the interstimulus interval was 500 ms. Target contrast varied according to a 3down/1up staircase, in which three consecutive correct responses reduced the target contrast of 0.1 log units and each wrong response increased the contrast of the same amount. The staircase terminated after 120 trials or 14 reversals. The procedure returned the Michelson contrast corresponding to 79% of correct detection estimated from the algebraic mean of the last 6 reversals. A warning sound of 50 ms indicated the beginning of each interval. Each spatial frequency was tested twice, once for each eye monocularly. The spatial frequency tested were 1, 3, 5, 7 cpd. All the eyes could be tested up to 3 cpd. The starting contrast was set to 0.3 Michelson at 1 cpd and was adapted to the patient

performance for all the other spatial frequency. The spatial frequencies were tested in ascending order and if in one of the blocks the threshold had gone beyond 0.9 Michelson the testing was interrupted. The new trial started only after the participant response was recorded correctly. Patients were instructed to think carefully before to answer, to avoid lapses. To help participant in keeping the fixation, a dot of 0.5 deg was present in the centre of the screen for the whole procedure. Participants were asked to re-centre the fixation over the dot after each trial.

Training procedure.

Patients were trained with the collinear configuration of a lateral masking task at 4 different target-to-flanker separations: 3λ, 4λ, 6λ, and 8λ. Overall the task was very similar to the one used to test the contextual influences in study 1 presented in CHAPTER V. There were two main differences: first, we trained only the PRL while in study 1 we tested also a non-PRL position; second, instead of using an eye-tracker to control for fixation stability in such a long training we adopted a strategy based on visual cues that were suggested initially by Astle et al. (2015) and then re-proposed by Maniglia et al. (2018). During the training participants were asked to keep their fixation over the central dot for the whole duration of the task. At the same time, they were trained to "not to see" a cue positioned inside the blind visual field. In case of eye movements or big drifts the cue becomes partially visible and warn the patient to reorient the fixation towards the central dot. In our training we used three red disks of 1 deg. of diameter along the internal border of the scotoma positioned in an arrow-like configuration pointing toward the PRL. The exact position of each disk varied from patient to patient

and it was initially derived from the OCT and later adjusted by trial and error until the three of them completely disappeared inside the scotoma, although remaining as close as possible to its edge. The training configuration is shown in Figure 18.

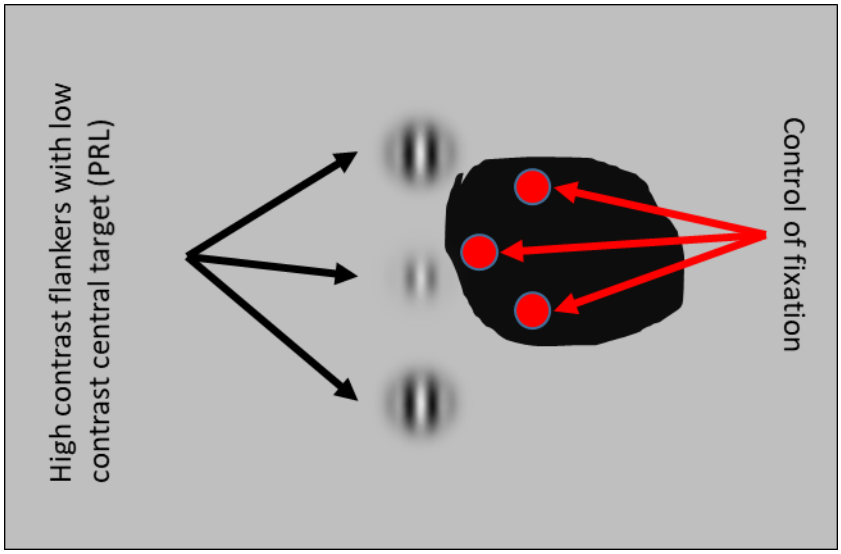

Figure 20. Training configuration with the stimuli and the control of fixation.

The control for fixation was constituted by three red disks of 1 deg of diameter. The discs were placed according to the OCT and the subjective report of the patients along the internal border of the scotoma positioned in an arrow-like configuration pointing toward the PRL. Until the patient kept the fixation over the centre of the screen (the target location in the figure), the three disks were not seen, but they become partially visible if the fixation were lost. The patient was instructed to relocate the gaze over the central fixation dot every time that one of the red disks would appear.

Except for these two modifications and for the different solution adopted for the monitor, all the other characteristics of the stimuli and task introduced in study 1 remained unchanged. We have also used the method already introduced in CHAPTER V for the calculation of the threshold elevation (TE) where the contrast threshold is estimated in the collinear condition and it is divided by the contrast threshold estimated in

the orthogonal condition. The logarithm of the ratio is then used to evaluate the TE. A positive TE means inhibition while a negative TE indicates facilitation.

tRNS stimulation

We replicated the same stimulation protocol used in study 3 in CHAPTER VII. Participants in Group 1 (PL + tRNS) were trained with concomitant electrical brain stimulation, while participants in Group 2 (PL alone) performed the training with sham stimulation. To deliver the high-frequency tRNS we used a battery-driven stimulator (BrainSTIM, EMS) with the main electrode over OZ and the return electrode over CZ. As in study 3 the stimulation consisted of an alternating current of 1.5 mA intensity with a 0 mA offset with frequencies of fluctuation distributed across a range of 100–640 Hz with zero-mean (same as in Contemori et al., 2019) and maximal current density of 0.094 mA/cm2. The duration of the stimulation covered the whole training session that was approximately 25 minutes. The stimulation was applied only during the training and was not applied during the pre-test, mid-test, and post-test and thus all the data used for the analysis have been collected in the exact same condition for both, the PL and the PL + tRNS groups.

Statistical analyses.

Given that the low numerosity of the sample and the many differences between the two groups, a direct comparison between the two would lead to misleading results. To overcome this issue and to control for individual and group differences at the pre-test, we represented data from the transfer tasks as percentage of change from the baseline and

then we performed statistical analysis to test whether there was a significant difference between the two groups. The transformation was done by dividing the score at the mid- or post-test by the score at the pre-test and then subtracting 1. In this way the performance at the mid-test and at the post-test was normalized using the baseline of the same patients prior to run the statistical tests. For the training task we calculated the thresholds elevation as the log-ratio between the collinear and the orthogonal condition. Data were pre-processed and analysed using the statistical computing environment R (R Core Team, 2012). To test for statistical significance data were fitted with a linear mixed-effects model with the subject as a random term using the "lme4" package and then p.values were calculated with a Type III Anova with Satterthwaite's approximation with the "lmerTest" package (Bates, Maechler, Bolker, & Walker, 2014; Kuznetsova, Brockhoff, & Christensen, 2017). This approach is proven to be solid in case of clustered data with repeated measures and even in case of missing or unbalanced data (Baayen, Davidson, & Bates, 2008; Barr, Levy, Scheepers, & Tily, 2013). We checked the homogeneity of variance and the linearity of the residuals through visual inspection. When necessary, Bonferroni corrected comparisons were performed using the "emmeans" function from the homonymous R package (Lenth, Love, & Herve, 2018).

Results

Training

A mixed-design ANOVA conducted on the contrast threshold data for the collinear condition, including as factors the group (PL vs. Pl + tRNS), the λ (3, 4, 6 and 8λ), and the session (pre-, mid-, post-test), revealed that the group factor was not significant ($F(1,10) = 2.192$, $p = 0.169$). The effect of λ was significant ($F(3,110) = 4.109$, $p = 0.008$). The effect of the session ($F(2,110) = 31.834$, $p = < 0.001$) and the group x session interaction ($F(2,110) = 4.286$, $p = 0.016$) were also significant, while the interaction group x λ was not ($F(3,110) = 0.560$, $p = 0.642$). Pairwise comparisons revealed that for the Pl + tRNS group, the contrast thresholds at the mid-test were lower than the thresholds at the pre-test (PL + tRNS,MID - PL + tRNS,PRE = -0.13515, se = 0.0268, t = -5.051, p = <0.001) and the thresholds at the post-test were lower than the mid-test (PL + tRNS,POST - PL + tRNS,MID = -0.087, se = 0.0268, t = -3.248, p = 0.004). For the PL group, the difference between pre and mid-test was also significant (PL,MID - PL,PRE = -0.086, se = 0.031, t = -2.730, p = 0.029), but the difference between mid and post was not (PL,POST - PL,MID = -0.01500, se = 0.0317, t = -0.474, p = 1). Results for the orthogonal condition show no difference between the groups ($F(1,10) = 1.707$, $p = 0.220$) or lambdas ($F(3,110) = 0.027$, $p = 0.994$). There was a significant effect of session ($F(2,110) = 35.123$, $p = < 0.001$) but the group x session ($F(2,110) = 1.564$, $p = 0.213$) or the group x λ interactions ($F(3,110) = 0.092$, $p = 0.964$) were not significant. Contrast thresholds for the collinear configuration are shown in Figure 21.

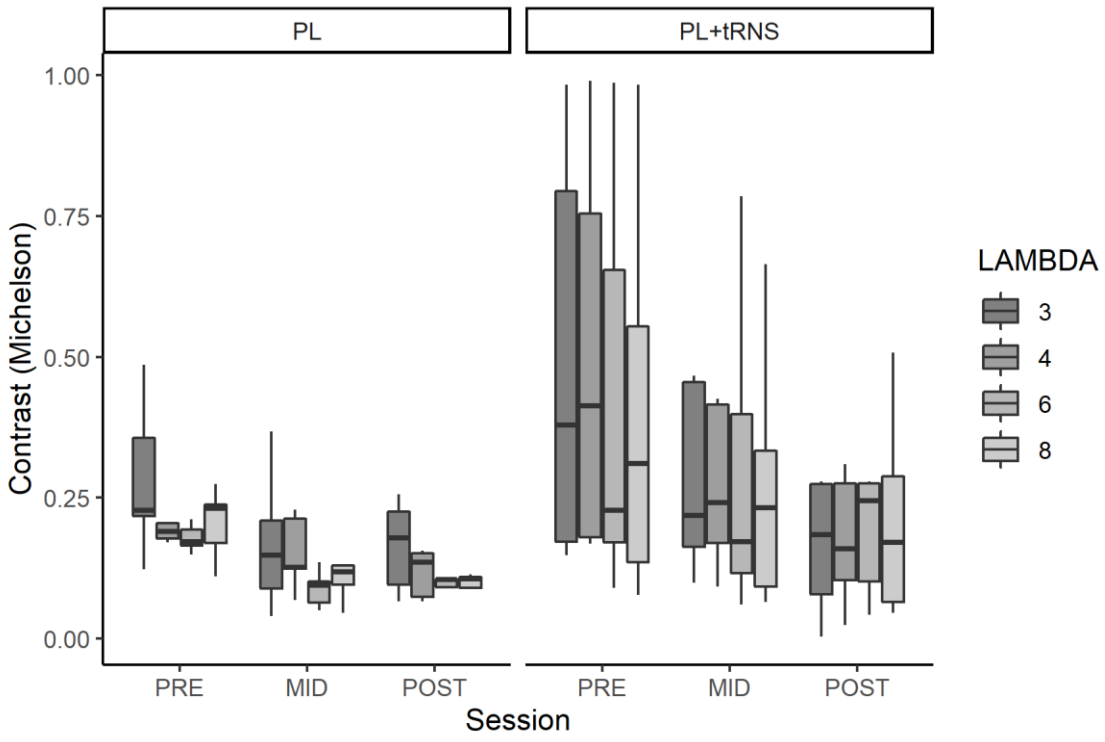

Figure 21. Contrast threshold in the trained task as a function of group, λ, and session.

Contrast threshold plotted as a function of the group (PL vs. PL + tRNS), λ (3 λ,4 λ,6 λ,8 λ) and the session (pre vs. mid vs. post). Vertical bars represent 95% percentiles.

A mixed-design ANOVA conducted on TE data, including as factors the group (PL vs. PL + tRNS) and the λ (3, 4, 6, and 8λ) indicated that the effect of group ($F(1,10) = 0.3549$, $p = 0.56$), and the effect of session were not significant ($F(2,110) = 2.889$, $p = 0.059$). We found a significant effect of λ ($F(3,110) = 4.079$, $p = 0.008$), and also a significant the group x session interaction ($F(2,110) = 3.156$, $p = 0.046$). Pairwise comparisons for the PL + tRNS group revealed that the threshold elevation at the mid-test was not different than at the pre-test (PL + tRNS,MID - PL + tRNS,PRE = 0.103, se = 0.087, $t = 1.178$, $p = 0.964$). On the contrary, the TE at the post-test was significantly

lower than at the mid-test (PL + tRNS,POST - PL + tRNS,MID = - 0.3153, se = 0.087, t = -3.590, p = 0.002). For the PL group there was no significant difference between pre and mid-test (PL,MID - PL,PRE = 0.084, se = 0.104, t = 0.817, p = 1), or between mid and post-test (PL,POST - PL,MID = 0.010, se = 0.1039, t = 0.100, p = 1). The effect plot for the TE is shown in Figure 22.

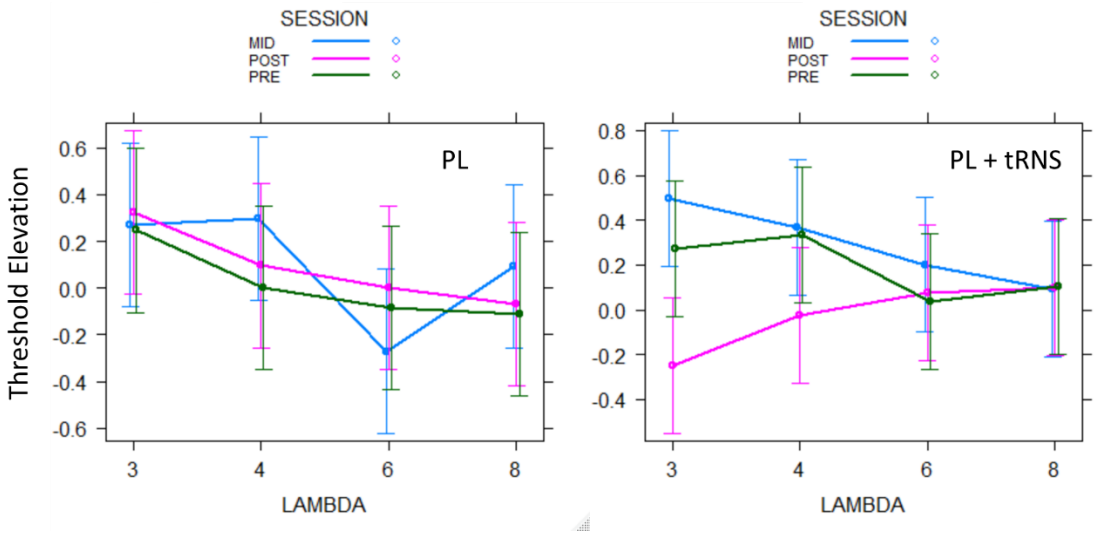

Figure 22. Threshold elevation (TE) in the trained task as a function of group, λ, and session.

Estimated variation in threshold elevation plotted as a function of the group λ (3 λ,4 λ,6 λ,8 λ) and the session (pre vs. mid vs. post). Left panel Pl + tRNS. Right panel PL. Vertical bars represent 95% confidence intervals.

Contrast sensitivity

The contrast sensitivity was calculated as LOG(1/contrast threshold). Then the ratio between the contrast sensitivity value at the mid- and post-test divided by the pre-

test minus 1 ((mid /pre)-1) was calculated as an index of improvement. In this case the higher the index the better the improvement. An index of zero means no improvement at all. For The mixed-design ANOVA conducted on index of improvement, including as factors the group (PL vs. PL + tRNS) and the eye (trained vs. untrained) and the session (mid vs. post) and the spatial frequency (1,3,5,7 cpd) indicated that, with a p.value slightly higher than the cut-off, the effect of group was not significant ($F(1,10.1) = 4.60$, $p = 0.057$). The effect of eye ($F(3,149.24) = 1.09$, $p = 0.297$), the effect of session ($F(1,149.2) = 0.805$, $p = 0.371$), and the group x session interaction ($F(1,149.2) = 0.841$, $p = 0.360$) were all not significant. We found a significant effect of the spatial frequency ($F(3,151) = 7.123$, $p = 0.0001$) and interestingly we found a significant effect of the group x spatial frequency interaction ($F(3,151) = 5.605$, $p = 0.001$). Post hoc comparisons for the group factor with the null hypothesis of zero mean showed that only PL + tRNS group differed from zero (mean PL = 0.985, se = 3.25, t = 0.303, p =1; mean PL + tRNS = 10.238, se = 2.83, t = 3.612, p = 0.008). Moreover, pairwise post hoc comparisons for the group x spatial frequency interaction revealed that the amount of improvement in the two groups was different for the two higher spatial frequencies tested (PL - PL + tRNS at 1 cpd = -0.455, se = 5.32, t = -0.085, p = 1; PL - PL + tRNS at 3 cpd = - 2.160, se = 5.32, t = -0.406, p = 1; PL - PL + tRNS at 5 cpd = -14.633, se = 5.44, t = -2.689, p = 0.050; PL - PL + tRNS at 7 cpd = -19.765, se = 5.82, t = -3.397, p = 0.008). Results are shown in Figure 23.

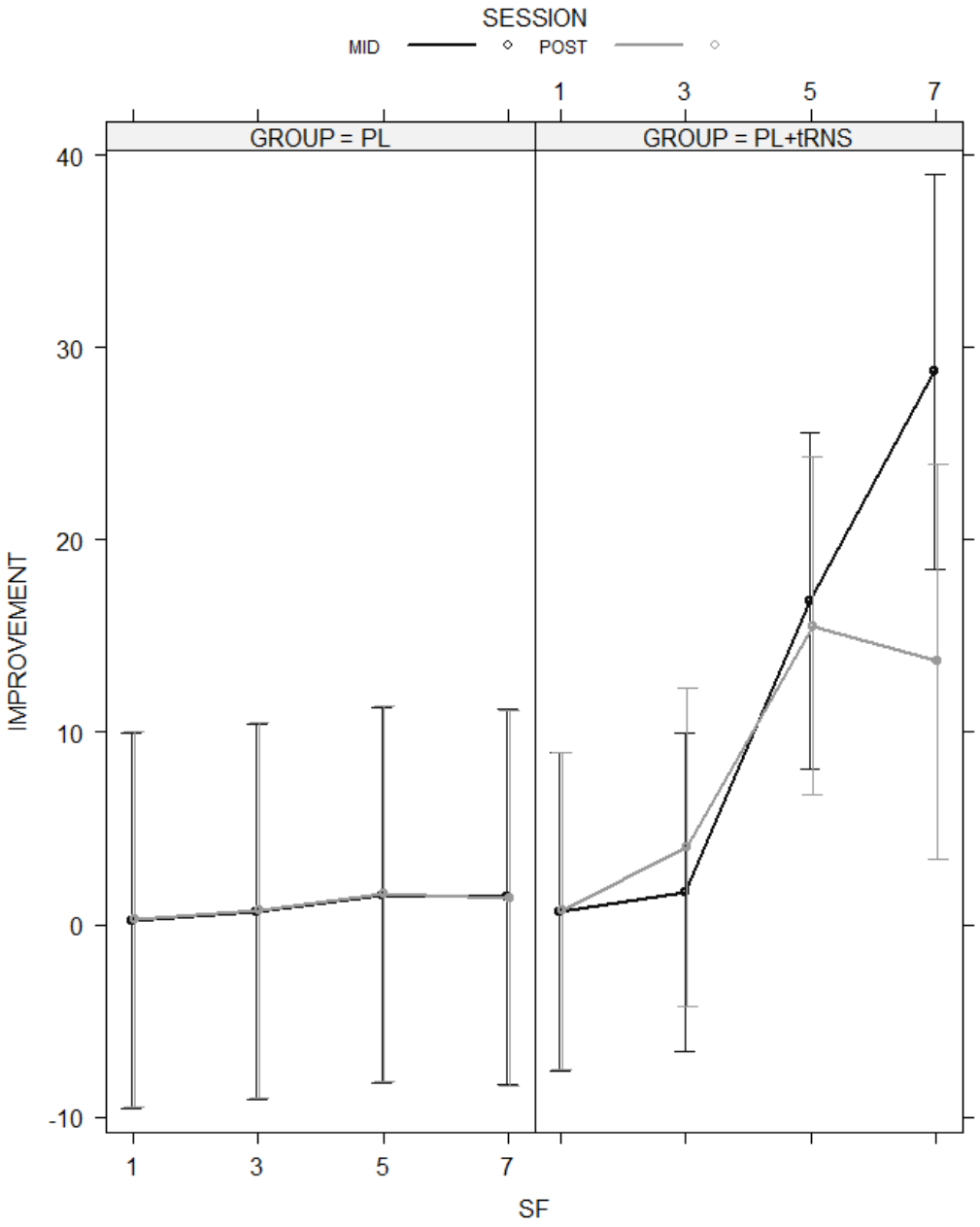

Figure 23. Improvement in contrast sensitivity.

Estimated improvement in contrast sensitivity plotted as a function of the group (PL vs. PL + tRNS), the eye (trained vs. untrained), the session (mid vs. post) and the spatial frequency (1,3,5,7 cpd). The higher the value the better the improvement. Vertical bars represent 95% confidence intervals.

Visual acuity

For the visual acuity the index of change was calculated upon the LogMar output from the FrACT Sloan test and can be interpreted as follow: a negative index means improvement, an index of zero means no change, and a positive index means a worsening in the performance after the training. The mixed-design ANOVA conducted on ratio between the letter size at the mid- and post-test divided by the baseline at the pre-test data, including as factors the group (PL vs. PL + tRNS) and the eye (trained vs. untrained) and the session (mid vs. post) indicated that the effect of group ($F(1,40) = 0.124$, $p = 0.726$), the effect of eye ($F(1,40) = 0.172$, $p = 0.726$), the effect of session ($F(1,40) = 3.152$, $p = 0.083$), the group x eye interaction ($F(1,40) = 0.0223$, $p = 0.882$) were not significant. Post hoc comparisons for the group factor with the null hypothesis of zero mean showed that the average both groups was not different from zero (mean PL = -0.049, se = 0.147, t = -0.338, p = 1; mean PL + tRNS = -0.117, se = 0.124, t = -0.946, p = 0.732). Results are shown in Figure 24.

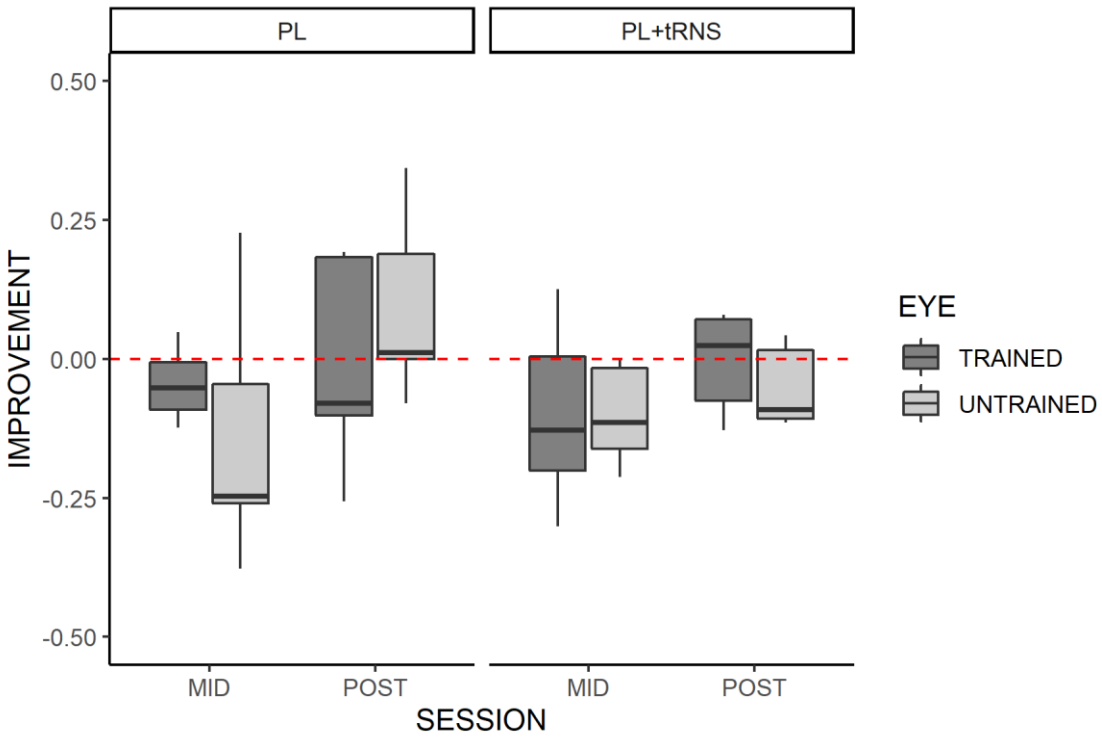

Figure 24. Results from the Sloan visual acuity test.

Sloan visual acuity thresholds plotted as a function of the group (PL vs. PL + tRNS) and the eye (trained vs. untrained) and the session (mid vs. post). The lower the value the better the improvement. Vertical bars represent 95% percentiles.

Tachistoscopic visual acuity and crowding

The index of change for the tachistoscopic visual acuity and crowding can be interpreted as follow: a negative index means improvement, an index of zero means no change, and a positive index means a worsening in the performance after the training.

For the tachistoscopic visual acuity the mixed-design ANOVA conducted on ratio between the letter size at the mid- and post-test divided by the baseline at the pre-test data, including as factors the group (PL vs. PL + tRNS) and the eye (trained vs.

untrained) and the session (mid vs. post) indicated that both, the effect of group ($F(1,40) = 7.72$, $p = 0.008$), and the effect of eye ($F(1,40) = 11.1$, $p = 0.002$) were significant, while the effect of session ($F(1,40) = 1.04$, $p = 0.314$), and the group x eye interaction ($F(1,40) = 1.02$, $p = 0.318$) were not. Post hoc comparisons for the group factor with the null hypothesis of zero mean showed that both groups differed from zero (mean PL = -0.349, se = 0.058, $t = -5.985$, $p < 0.001$; mean PL + tRNS = -0.137, se = 0.049, $t = -2.777$, $p = 0.0391$). Post hoc comparisons for the eye factor with the null hypothesis of zero mean showed that both the trained and untrained eye differed from zero (mean Trained = -0.730, se = 0.054, $t = -6.857$, $p < 0.001$; mean Untrained = -0.116, se = 0.054, $t = -2.142$, $p < 0.081$). Results are shown in Figure 25.

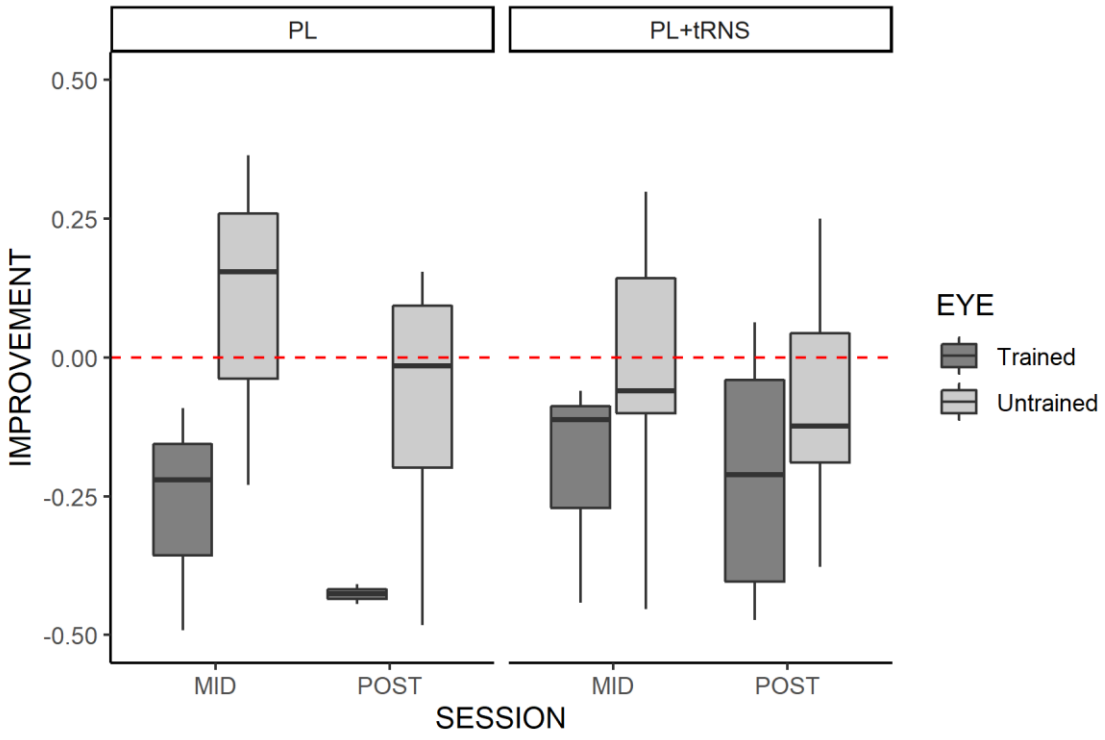

Figure 25. Results from the tachistoscopic visual acuity test.

Tachistoscopic visual acuity thresholds plotted as a function of the group (PL vs. PL + tRNS) and the eye (trained vs. untrained) and the session (mid vs. post). The lower the value the better the improvement. Vertical bars represent 95% confidence percentiles.

For the tachistoscopic crowding the mixed-design ANOVA conducted on ratio between the critical space at the mid- and post-test divided by the baseline at the pre-test data, including as factors the group (PL vs. PL + tRNS) and the eye (trained vs. untrained) and the session (mid vs. post) indicated that the effect of group was significant ($F(1,9.5) = 5.1$, $p = 0.048$), while both the effect of eye ($F(1,29.1) = 0.004$, $p = 0.95$), and session ($F(1,28.1) = 0.19$, $p = 0.664$) were not. Post hoc comparisons for the group factor with the null hypothesis of zero mean showed that the only the improvement in the PL group, differed statistically from zero (mean PL = -0.444, se = 0.165, t = -2.683, p = 0.0489; mean PL + tRNS = 0.053, se = 0.146, t = 0.366, p = 1). Results are shown in Figure 26.

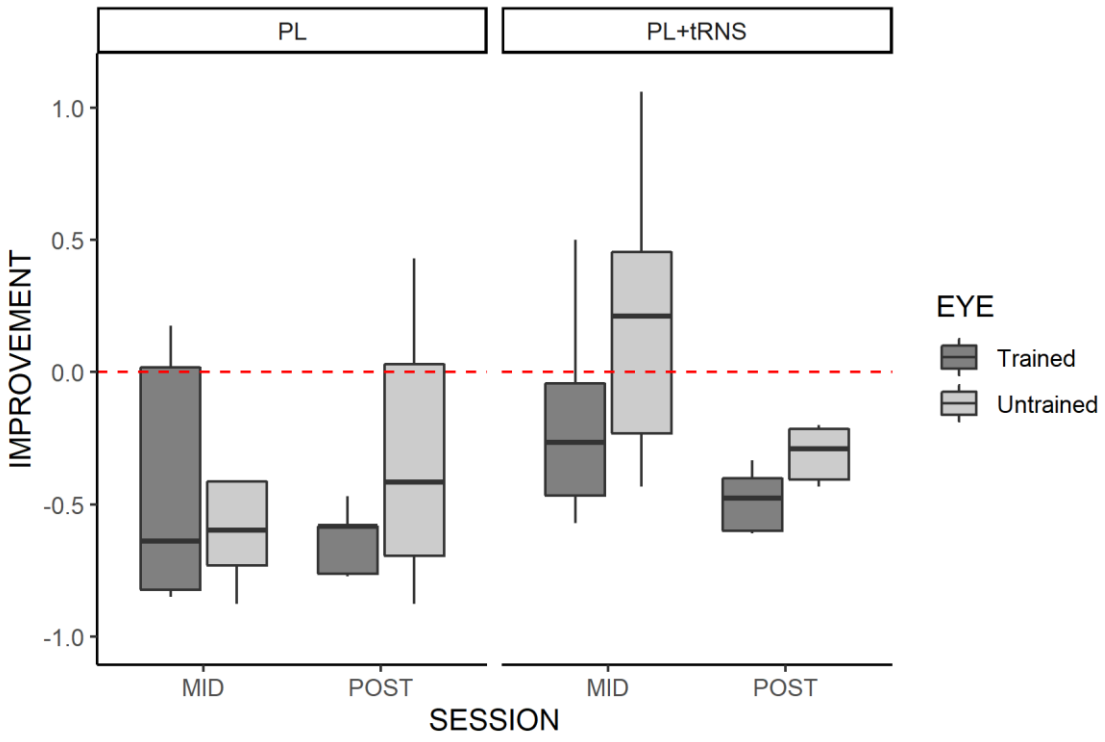

Figure 26. Results from the tachistoscopic crowding test.

Crowding thresholds plotted as a function of the group (PL vs. PL + tRNS) and the eye (trained vs. untrained) and the session (mid vs. post). The lower the value the better the improvement. Vertical bars represent 95% percentiles.

Discussion

Trained task

In the trained task we found a significant decrease in contrast thresholds after 12 training sessions for both groups. Between the 12th and the 24th training session, only the PL + tRNS group continued to improve while the PL group reached a plateau. It is essential to note that at the end of the training the contrast thresholds of the two groups were still one order of magnitude higher then what expected in controls subjects at a comparable eccentricity (see Contemori, Battaglini, et al., 2019 for the normative data). Considering the post-training contrast thresholds, the plateau was not due to a ceiling effect but more likely to some intrinsic limitation in the PL and adult plasticity (Bavelier, Levi, Li, Dan, & Hensch, 2010; Harris et al., 2012).

In this context, the tRNS was able to produce deeper learning that continued throughout the training. As we expected no effect of lateral interactions was observed in the orthogonal condition despite an overall reduction in contrast threshold for both groups.

For the TE we found a significant effect of the λ and a significant group x session interaction. Post-hoc analysis revealed that only the PL + tRNS group had a significant modulation of the lateral interaction after the training at the post-test. As can be seen in figure 22, the curve showing the TE as a function of the λs, in the pre and mid-test is above the zero line (inhibition) while after training it falls below zero (facilitation).

This result is in agreement with previous studies that found an increase in facilitation and a reduction of inhibition after training (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). In our case, however, the modulation of lateral interactions reaches significance only for the PL + tRNS group, indicating that the stimulation played a fundamental part in this process.

A further consideration concerns the duration of the training. The number of sessions was based on the previous literature that showed an improvement after the 24 sessions (Camilleri, Pavan, Ghin, & Campana, 2014; Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). A previous study showed that by combining PL with tRNS it is possible to reduce the number of sessions required to achieve improvement from 24 to 12. (Camilleri, Pavan, Ghin, Battaglini, et al., 2014) Surprisingly in our case both groups showed an improvement in the trained task already after the 12th session and therefore we could not verify that the stimulation accelerates perceptual learning by reducing the number of required sessions. On the other hand, our data are in agreement with what we have found in study 3 of this thesis and support the hypothesis that the tRNS can postpone the plateau effect during PL.

Repeating the study by increasing the number and frequency of the intermediate tests could help clarify how the tRNS alters the temporal dynamics of the PL.

Transfer tasks

The results for the transfer tasks are summarized in Table 6. In general, the results of previous studies (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018) are partly

confirmed since the PL has transferred to the untrained eye, to tachistoscopic visual acuity, and visual crowding. Furthermore, only the PL + tRNS group had transferred to higher spatial frequencies than the trained ones. But two unexpected results came out: we did not find transfer to visual acuity with Sloan letters and the PL + tRNS group did not have the expected transfer to visual crowding. Moreover, we did not find significant differences between the mid-tests and the post-tests for the two groups. This leaves us thinking that 12 sessions are enough to trigger the transfer. In the following paragraphs, I will discuss these results in detail.

Table 6. Summary of the results relative to the transfer tasks.

Group	EYE	CSC	SF 1	SF 3	SF 5	SF 7	VAS	TVA	TVC
PL	Trained	X	X	X	X	X	X	V	V
	Untrained	X	X	X	X	X	X	V	V
PL + tRNS	Trained	V	X	X	V	V	X	V	X
	Untrained	V	X	X	V	V	X	V	X

The results of the transfer tasks are summarized in the table, the green "V" symbolizes significant results, while the red "X" indicates non-significant ones. From left to right: Contrast sensitivity (CSC), spatial frequencies (SF 1, SF 3, SF 5, SF 7), visual acuity with Sloan letters (VAS), tachistoscopic visual acuity (TVA), tachistoscopic visual crowding (TVC).

Contrast sensitivity

The measurement of the contrast sensitivity curve among the various transfer tasks is certainly the closest one to the trained task. The fundamental difference is the absence of the two flankers and therefore the absence of contextual influences. In the previous literature, it has been shown that the improvement in contrast sensitivity achieved by training with lateral masking could also transfer to untrained spatial

frequencies, but at the same time, this transfer is more likely to pass from lower frequencies to higher than the opposite (for a detailed review see Sagi, 2011). In MD the processing of low spatial frequencies is much less affected by the visual deficit than that of the high ones (Musel et al., 2011; Peyrin, Ramanoël, Roux-Sibilon, Chokron, & Hera, 2017; Ramanoël et al., 2018). Training directly with medium-high spatial frequencies is not always possible since the task could be too difficult, and the patient could be frustrated by failure. The possibility of obtaining a transfer to higher spatial frequencies is, therefore, a desirable property of PL with lateral masking. The results of the contrast detection task clearly show that the PL + tRNS group improved more than the PL alone. The improvement is particularly evident at the two highest spatial frequencies tested (5 cpd, 7 cpd). Given that high spatial frequencies are necessary for the processing of details, the gain obtained could increase visual resolution in general (Uri Polat, 2009; Sagi, 2011a). This finding is in line with the result of a recent study from our lab (L. Battaglini, G. Contemori, S. Penzo, M. Maniglia, accepted in Neuroscience Letters) in which we found that tRNS enhance detection performance of an isolated Gabor only when it has a high spatial frequency (12 cpd). We hypothesized that this effect might be due to the shallow depth of tRNS. The superficial layers of the visual cortex where neurons have higher preferred spatial frequencies are more likely to be stimulated than cells in the further layers. Future research should better address this issue.

Visual acuity and tachistoscopic visual acuity.

The previous literature reports improvement in visual acuity following training with lateral masking (Camilleri, Pavan, Ghin, Battaglini, et al., 2014; Camilleri, Pavan,

Ghin, & Campana, 2014; Uri Polat, 2009). In this study, the training transferred to TVA but did not produce an improvement in visual acuity with Sloan's letters. This seemingly contrasting result can have multiple explanations. First, the colours used for background and letters in the two tasks were reversed and this could have had an impact during the testing. Patients with MD often suffer from visual glare (Hogg & Chakravarthy, 2006). In the VA test with the FrACT software, the letters presented were black on a white background, while in the homemade tachistoscopic test coded with the Psychtoolbox, the letters were white on a black background. Some of the patients reported difficulties in the first of the two tests due to the bright background colour. The glare was not constant during the measurements, but rather grew over time. This may have affected the measurement by reducing its reliability. The dispersion of the data in this task is, in fact, higher than that in the tachistoscopic task. A second reason could be related to the different duration of the stimuli. During the FrACT test, some patients reported seeing the letter in the first few moments after the onset of the stimuli, but the attempt to keep a prolonged fixation produced a later distortion of the patient's percept. This might be due to some sort of habituation effect compensated by large ocular drifts (Déruciz et al., 2004). The stimulus duration in the tachistoscopic test may have prevented this problem. The last possibility is that given the temporal structure of the task the training has especially effective over some transient visual channels and less over the sustained ones, producing a greater benefit to the tachistoscopic test (Tolhurst, 1975). This last possibility could be an interesting starting point for further research in an attempt to perfect the training.

Tachistoscopic visual crowding.

In visual crowding we found a reduction in the critical space for the PL group, but not for the PL + tRNS group. This result is surprising if we consider that in the trained task as well as in the contrast sensitivity there is an advantage of the PL + tRNS over the PL group. In addition, it is in apparent contrast with the results of studies 6 and 7 presented in this thesis. Undoubtedly a lot is still to be discovered regarding the mechanisms of transfer of the PL. A valid approach for rehabilitation could be to follow the training with lateral masking with a short training based on visual crowding. Future studies should investigate this possibility.

Conclusion

The combined use of PL with tRNS has proved effective in increasing learning in the trained task by postponing the plateau effect. It has also produced a greater modulation of contextual influences than the PL alone. tRNS also produced an increase in transfer to untrained spatial frequencies. Furthermore, in both groups there was a transfer of learning to tachistoscopic visual acuity, but only the PL group showed also transfer to visual crowding.

Although there are still grey areas, we conclude that the combined use of PL and tRNS has been effective in postponing the plateau and partially enhancing transfer. In conclusion, tRNS could be effectively used as an additional tool in the visual rehabilitation of MD patients, but further studies are needed to fine-tune the stimulation parameters and maximize the efficacy of the combined tRNS + PL treatment.

Chapter IX.

Contextual Influences on the Peripheral Retina of Patients with Macular Degeneration: further considerations.

In study 1 we proposed a different interpretation for the reduction of inhibition at the very short target-to-flanker distance that has been previously reported by Maniglia and colleagues (2018). The locally-weighted polynomial regression based on the pooled data of all participants in study 1 (MD and controls) showed that the reduction in collinear inhibition at 2λ and the switch towards facilitation are clearly linked with the baseline contrast sensitivity of the single subject in the orthogonal configuration. This relationship is well predicted by the model proposed by Zenger & Sagi (1996) that described by the variation of TE as a function of the log flanker/target contrast ratio in normal vision (Foley, 1994; Ross et al., 1993; Snowden & Hammett, 1998; B Zenger-Landolt & Koch, 2001; Zenger & Sagi, 1996). According to the model, the sensitivity to a low contrast target is reduced by the presence of the high contrast flankers – as usually observed in normal viewers – but as the target's contrast increases this inhibition progressively decreases and then turns into facilitation. However, when the target's contrast surpasses that of the flankers, the facilitatory effect progressively reduces and then disappear. It is indeed difficult to accurately test this 'dip function' with the typical lateral masking paradigm in normal viewers since there are only two ways to manipulate the contrast ratio between targets and flankers, to reduce the contrast of the flankers or to use a pedestal below the target. Both solutions are suboptimal since in the first case we would also have a reduction in the effectiveness of the flankers and in the second case, we would alter the sensitivity to the target. Here we can verify the contrast dependent

modulation of the contextual effect of the flankers by studying the inter-individual differences between participants. Due to the difference in the extent of the retinal degeneration, MDs have subjective differences in the baseline sensitivity to contrast that influence also their flanker/target contrast ratio in the baseline orthogonal condition, in which no contextual influence is expected. By pooling together the individual data of the patients we can sample the dip of the function predicted by Zenger's model. By including the control group from study 1 we can sample also the opposite extreme of the function. Overall, we have a range that goes from a log(flanker/target) contrast ratio of 0 to a ratio of 1. According to Zenger's model, the switch between inhibition and facilitation should occur at a ratio around 0.25 and 0.50 for the 2λ and 3λ respectively (Barbara Zenger-Landolt & Koch, 2001; Zenger & Sagi, 1996).

Small deviations from the model are expected given that eccentricity and lambda are not constant between subjects but nevertheless, we expect a positive linear relationship between the threshold modulation and the flanker/target contrast ratio in the baseline orthogonal condition. We wanted to verify this prediction by pooling the data collected in study 1 and those collected in study 4.

This new dataset was thus composed of the measurements carried out in study 1 and study 4 at the shortest target-to-flanker tested distance (respectively 2λ and 3λ). The data were analysed through a linear regression in which the TE of the individual participants was related to their respective contrast ratio at the baseline orthogonal condition. Also, we wanted to verify the hypothesis that training modulates lateral interactions through practice-dependent cortical reorganization. We hypothesized that training produced an improvement in the contrast sensitivity of all participants, but that

only those who show inhibition at the pre-test show modulation of lateral interaction in the post-test. After training, we expected a larger increase in facilitation in patients who started with a high inhibition and thus with a flanker/target contrast ratio in the orthogonal condition close to 1. To test this second hypothesis, we have carried out a repeated measure ANOVA by comparing TE as a function of flanker/target contrast ratio and the session for the subgroup that underwent the training. We increased the sample size and therefore the statistical power by also including 4 MD subjects from Maniglia, et al., (2016) that had been trained with the same procedure used in our study 4. Our expectation was a change of slope in the relationship between TE and flanker/target ratio between the pre- and post-test. The results are reported below.

Results

The linear regression conducted on these data revealed a significant positive relationship between the log-ratio and the TE (estimate = 0.505, t(1,38) = 5.022, p = 0.001, adjusted R-squared: 0.383) with a predicted intersection with zero (TE=0 – the switch between inhibition and facilitation) at a ratio of 0.32. Results are shown in figure 27.

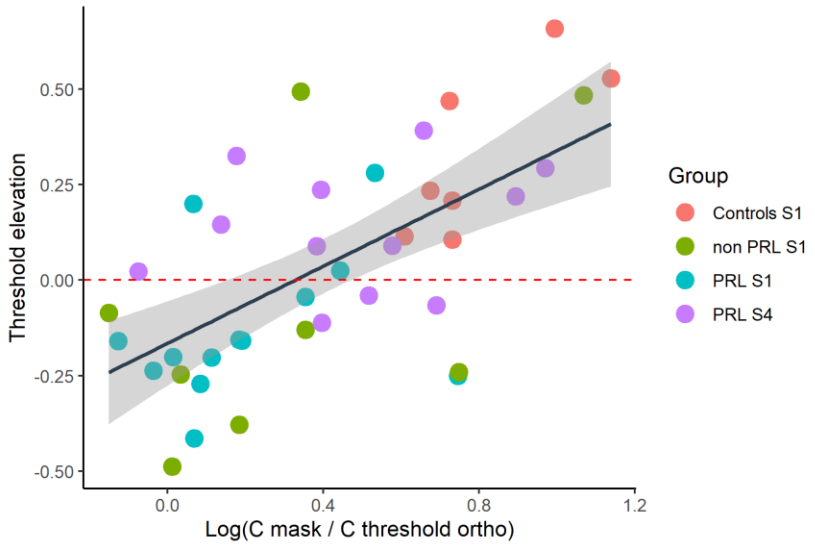

Figure 27. Threshold Elevation (TE) as a function of log(flanker/target) contrast ratio.

Threshold Elevation (TE) as a function of the log(flanker/target) contrast ratio. Pooled data from study 1 (PRL 2λ) and study 4 (PRL 3λ). The grey area represents the 95% confidence interval for the regression.

The repeated measure ANOVA performed on log(flanker/target) contrast ratio as a continuous variable and Session (pre vs post) as an ordered factor, showed no significant main effect of Session (F[1,27] = 0.166, p < 0.687) or contrast ratio (F[1,27]

= 2.053, p = 0.163). As for the effect of our interest, namely the Session x ratio interaction, the data shown in figure 27 show a trend that is in agreement with our prediction but we found that the difference in the slope was not statistically significant (F[1,27] = 3.851, p = 0.060).

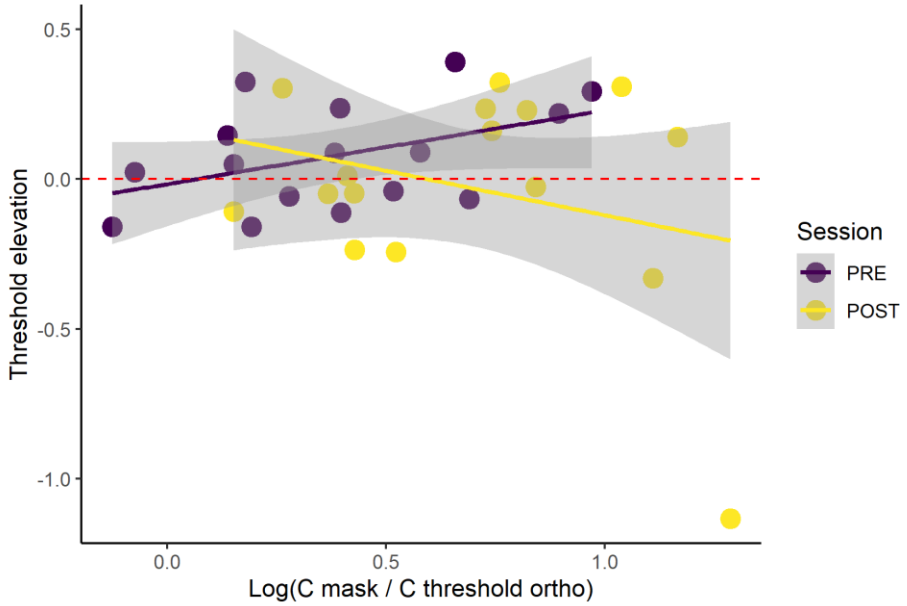

Figure 28. Threshold Elevation (TE) as a function of log(flanker/target) contrast ratio and session.

Threshold Elevation (TE) as a function of the log(flanker/target) contrast ratio and session. Pooled data from Maniglia, et al., (2016) (PRL 2λ) and study 4 (PRL 3λ). The grey area represents the 95% confidence interval for the regression.

Conclusion

The regression performed over the pooled dataset supports and confirms the previous result obtained in study 1. This result weakens the previous hypothesis of cortical reorganization proposed by Maniglia (2018) and supports instead our alternative explanation for the reduced collinear inhibition in patients based on improved efficiency in integrating/grouping elements at the stage of the 2nd order integrative field (Zenger & Sagi, 1996).

Regarding our second hypothesis of specific modulation of lateral interactions for patients with strong inhibition, the data reported are not fully conclusive. A further study could clarify the validity of our hypothesis.

Chapter X.

Overview and Future Directions

The first study was presented in CHAPTER V. This experiment aimed to evaluate the presence of spontaneous or use-dependent plasticity in the patients' PRL. In the previous literature (D. D. Dilks et al., 2009; Maniglia et al., 2018; Plank et al., 2017) there is debate whether the spared periphery undergoes a general process of adaptation triggered by the presence of the scotoma ("use-dependent reorganization" hypothesis) or whether the preferential use of the PRL for active high demanding tasks triggers a more specific use-dependent adaptation (D. D. Dilks et al., 2009; Maniglia et al., 2018; Plank et al., 2017). Knowing the type of adaptation process to which the PRL is subject is important to avoid damaging any compensatory mechanisms in place and instead to try to maximize them with the training. In this study, we tried to investigate this issue psychophysically by comparing spatial integration in the PRL, in a symmetrical retinal position (non-PRL) and a region with matched eccentricity in a control group. To do this, we probed the contextual influences by measuring the contrast gain for a vertical Gabor target, flanked by two high-contrast collinear masks compared to the orthogonal baseline condition. In line with previous literature (Maniglia et al., 2018), our prediction was to find evidence for plasticity, in the form of reduced collinear inhibition. Moreover, we expected the reduction of inhibition to be stronger in the PRL. Surprisingly, the between-groups analysis revealed that in both PRL and non-PRL, at the shortest target-to-flankers distance (2λ), the contextual influence was facilitatory, rather than inhibitory as in controls. Further analysis with data collapsed across groups showed that this effect depends on the individual contrast sensitivity at the baseline. When the target-to-flankers

contrast ratio increases the inhibition decreases and then switches to facilitation. However, when ratio surpasses 1 the facilitatory effect progressively reduces and then disappears. This relationship is well expressed by a ‘dipper' function similar to those previously reported by Zenger and Sagi (1996) for normal vision. Contrary to previous interpretations, we demonstrated that this modulation reflects neither a phenomenon of spontaneous nor use-dependent cortical plasticity. Based on this result and the previous literature it is concluded that the spontaneous reorganization process has limited effects on the PRL and that a neural based perceptual learning may be needed to improve peripheral vision in the MD.

CHAPTER VI includes the results of a study that aimed at investigating whether the contextual influences are modulated by tRNS applied to the occipital cortex of human observers during task performance. Given that the tRNS main effect is to increase cortical excitability, it could expand the sensitivity of the neurons to weak stimuli and thus lowering the contrast threshold for the target. At the same time, this increased excitability could also modulate how the target is integrated with its context by altering the relative strength of excitatory (E) or inhibitory (I) influences from the flanking elements, depending on which is weaker. In this case, we might expect an effect of tRNS even if tRNS shows no effect at all on target perceived contrast. Results show a tRNS-dependent increased sensitivity for the single Gabor signal of low but not high contrast. This is compatible with a signal-to-noise ratio improvement for stimuli that are close to the threshold. Moreover, both the inhibition at the shortest target to flanker distance (2λ) and the facilitation at the largest (6λ) are reduced by the stimulation. This result suggests a general boost by the tRNS to the feedforward signal at the expense of the strength of the

contextual influence. Based on this result it is concluded that this modulatory effect over the visual-spatial integration in the early visual cortex might help reshape the visual processing in the PRL in a more foveal fashion, also reducing the crowding effect in the periphery.

The study presented in CHAPTER VII investigated whether tRNS can effectively boost PL on a peripheral visual task over a small number of daily training sessions.

Since the tRNS proved effective in modulating contextual influences, we decided to use a training task based on visual crowding. One of the objectives was to verify the effectiveness of tRNS applied to low-level visual areas in increasing perceptual learning in visual tasks performed by higher-level areas.

Additionally, we tested whether learning transferred to untrained spatial location and task variation. We expected the tRNS to be able to increase both the learning rate and the transfer of learning. Results showed a greater learning rate within and between sessions for the PL+tRNS group respect to the sham (PL alone). Contrary to our expectations, PL+tRNS group does not show a higher amount of transfer to untrained conditions. We conclude that the combined use of PL and tRNS has a higher potential in improving peripheral visual abilities over a small number of sessions than PL alone, but that training based on a more basic visual ability such as contrast sensibility might be better suited to achieve a higher degree of transfer.

The final study presented in CHAPTER VIII brought together the findings of the experiments presented in this dissertation, investigating the combined effect of tRNS, and perceptual learning in a visual rehabilitation protocol in MD patients. Since stimulation with tRNS coupled with training in a high-level task in subjects with normal vision, did

not produce the increase in the hypothesized transfer, we decided to use the paradigm of lateral masking. Previously this paradigm proved effective in increasing contrast sensitivity in trained subjects, and more importantly, this improvement transferred to the untrained eye and higher-level tasks such as visual acuity and visual crowding (Maniglia, Pavan, et al., 2016; Maniglia et al., 2018). Furthermore, in CHAPTER II we saw how the tRNS modulates the contextual influences, our expectation, in this case, was to be able to use the modulatory activity of the tRNS to obtain a greater improvement and a transfer compared to behavioural training alone. To test this hypothesis, we used a lateral masking paradigm to train the PRL of 12 patients, and we tested them also for the crowding and the visual acuity as a transfer task. The patients were split into two groups, 7 underwent PL + tRNS while the other 5 only the behavioural training. Both groups improved after the training, but we found a modulation of the lateral interaction and transfer to some untrained spatial frequencies only for the PL + tRNS group. Conversely, only PL group improved also in the crowding task.

Although some questions remain, we concluded that the tRNS could be an efficacious way of maximizing the gain due to the perceptual learning in MD patients. Overall, this thesis provides useful insights into the functioning of the tRNS and explores a new path for visual improvement in MD with possible implications on other clinical populations.

Current perspective on Macular Degeneration Treatment

In recent years there has been a huge effort towards finding therapies and treatments for retinal degenerative diseases. Gene therapy and stem cell therapeutic strategies are currently under investigation (Fahim, 2018) as well as prostheses and retinal implants (Lewis, Ackland, Lowery, & Rosenfeld, 2015; Lohmann et al., 2019; Zrenner, 2019). Also, the tools necessary to screen for early signs of AMD, such as advanced retinal imaging with optical coherence tomography, have had a remarkable development (Jarc-Vidmar, Popovič, & Hawlina, 2006; Mohaghegh, Zadeh, & Magierowski, 2016). Despite all this now it is not possible to restore the damaged vision.

Patients with AMD who develop loss of central vision later in their life have a higher prevalence of comorbidity of depression. Low vision rehabilitation can give to the patient a sense of control over the disease mitigating the risk of depression and increasing participation in daily life activities (Cimarolli et al., 2016).

Microperimetry systems like the MP-1 are diagnostic techniques which allow to precisely map the scotoma in real-time and to measure the location and stability of fixation. They have been used also to perform biofeedback training in patients with a combination of a structured light stimulus plus acoustic feedback. This training has been proven to increase the stability of fixation, distant and near visual acuity, reading speed, and reading comprehension (Midena, Pilotto, & Convento, 2018). This training can be easily integrated with a PL + tRNS based training offering to the patients a more refined and complete training protocol.

Recently, Virtual and Augmented Reality (VR and AR) system to help patients incorrectly visualizing the relevant information in the environment have been developed. With the increasing wearability of smart devices like AR glasses, those instruments are going to rapidly change the word of visual aids (Shahshahani, Shahshahani, Grewe, Kashyap, & Chandran, 2018). Those smart devices might be used not just to highlight useful information about the visual scene, but also to increase the contrast or to train the patients with a PL paradigm in a real-life situation.

However, the cutting edge of the research on visual aids is represented by implantable devices. Despite their invasiveness, the benefits obtained are considerable. They do not only allow the patient to cope with visual impairment but allow a partial restoration of vision (Gupta et al., 2014).

To an even higher degree of invasiveness, we find retinal and cortical implants. They provide visual inputs by direct electrical stimulation of the retina. Retinal prostheses systems have also yielded promising results. However, each type of prosthesis has its advantages and disadvantages. Cortical implants, which are currently in the preclinical study phase, may provide artificial vision to patients with the complete retina and optic nerve destruction, but the technical difficulties are considerable, and the quality of the visual input is poor (Lewis et al., 2015; Lohmann et al., 2019; Roux, Gascon, Pham, Matonti, & Chavane, 2017; Roux et al., 2016; Stett & Eysel, 2016). This is due to the difficulty of providing a visual input that reflects the functional specificity of the retinal or cortical organization. After the implant, patients need long training so that they can successfully distinguish scenes or objects and often the advantage is limited to trained stimuli (Han, Qiu, Lee, Jung, & Peli, 2018). These instruments are currently

tested only in patients with very low or no residual vision, which were probably subjected to strong trans-synaptic degeneration in the years before implantation. In this case, the combination of PL and retinal implant could help the patient adapt more quickly to the new visual input, also thanks to the combined use of tRNS.

Finally, indirect help could come from recent developments in the field of neural networks and artificial intelligence. Complex computational systems can be used for increasingly accurate diagnoses (Schmidt-Erfurth, Sadeghipour, Gerendas, Waldstein, & Bogunović, 2018). Moreover, biologically plausible neural networks are able to mimic the functioning of the human visual system, from the retina to V1 and beyond (Chauhan, Masquelier, Montlibert, & Cottereau, 2018; Hopkins, Pineda-Garcia, Bogdan, & Furber, 2018; Testolin, Stoianov, & Zorzi, 2017; Testolin & Zorzi, 2016). In these systems it is possible to create a virtual lesion in the input, silencing a part of the visual field, to study how the network adapts (Andrade, Muro, & Morán, 2001; McManus et al., 2008). This could lead to understanding how and where the PRL develops, the phases and timing of spontaneous adaptation, even which is the best rehabilitation strategy.

Can tRNS be used in visual rehabilitation?

The idea of using a lateral masking paradigm in the visual rehabilitation of bilateral central blindness comes from the attempt to remodel the lateral interactions in the PRL to make them similar to those in the fovea. Being trained on contrast sensitivity in the first instance, we expected an improvement in contrast sensitivity for the trained stimulus, but the ultimate goal was to achieve an increase in visual acuity and a reduction in visual crowding so as to bring benefit to the patient in the daily life activities. In CHAPTER VI we demonstrated how tRNS modulates lateral interactions by promoting feedforward processing. In CHAPTER VII we have shown how this contributes to a greater reduction in visual crowding following perceptual learning. These two results obtained in groups of subjects with normal vision testify to the general effect of tRNS. In CHAPTER VIII we saw how tRNS increases perceptual learning and transfer following training based on lateral masking in a clinical population. In CHAPTER IX, combining different datasets we confirmed and extended the result presented in study 4.

Training with lateral masking has been already adopted to treat a series of visual diseases (Uri Polat, 2009) such as amblyopia (U. Polat et al., 2004b), presbyopia (Uri Polat, 2009), myopia (D. T. H. Tan & Fong, 2008). With due consideration, our results can be easily generalized to all those clinical populations that have been shown to benefit from training with the lateral masking task. Moreover, by deepening our basic knowledge of the neuromodulatory action of the tRNS over the visual system, it will be possible to extend the use of this technique in conjunction with different perceptual training. This

will open the doors for the application of PL + tRNS protocols for many more clinical populations.

Limitation of the thesis

Even a meticulously prepared study is not without limitations, even more so when dealing with a clinical population. The major limits are related to the difficulty in finding participants. Undoubtedly the recruitment of patients was slow and complicated, and it took three years to arrive at the current sample size. Because of this, in the two studies that included patients, the research was conducted using relatively small samples; 12 MD patients and 7 control participants with normal vision in study 1 (CHAPTER V), 12 patients subdivided in one group of 7 and one group of 5 in study 4 (CHAPTER VIII).

Although for study 1 (CHAPTER V) these numbers should be considered as an improvement over the previous literature, replicating study 4 (CHAPTER VIII) over an even larger sample will be necessary in order to strengthen the conclusions. Second, in study 3 (CHAPTER VII) and 4 (CHAPTER VIII) despite having a sham condition, a second control group with a stimulated location different from the occipital pole as we have done in experiment 3 (CHAPTER VI) was not tested. Lastly, different procedures and different accuracy thresholds have been used in study 1 (CHAPTER V), study 3 (CHAPTER VII) and 4 (CHAPTER VIII). In fact in study 3, for the training, we had to adjust the procedure (accuracy threshold was increased), so as to present a greater number of stimuli in each block to increase the training effect and prevent the participant from feeling frustrated due to excessive difficulty. Because of this, the size of the critical space between the three experiments is not directly comparable. The studies presented in this dissertation are, however, the first to investigate the effects of tRNS on the contextual

influences in the visual cortex of MD patients and healthy controls. We used well established and replicable measures that lead to novel results.

Future direction and general conclusion

The studies presented in this thesis are a necessary brick in the development of an efficient and effective rehabilitation paradigm for the potential vision in the PRL of patients with MD. Despite this, some questions remained unresolved, and new ones emerged. Despite the effectiveness of the tRNS in increasing the effects of perceptual learning, much remains to be done in optimizing the parameters of the stimulation as well as the training task. Moreover, the advantage in terms of transfer although present was lower than expected and new studies could reveal the key to obtain a greater transfer. Another key point to develop is the integration of training based on lateral masking with other types of training, for example, based on moving stimuli. The literature regarding the perception of movement following the loss of central vision is limited, but as we have seen, the results so far in our possession suggest that instead of being invalidated by trans-synaptic anterograde degeneration, the perception of movement is strengthened following the adaptation to the central scotoma. This compensatory plasticity could be the target for future training based on perceptual learning coupled with tRNS.

The duration of the improvements obtained must also be clarified. Carrying out follow-ups in the near future will allow us to understand whether the virtuous circle triggered by the training is stable overtime or not.

Another potential of the training to be explored is to allow a faster and faster adaptation of the patients' vision to the retinal implants. The technology for the plants is making great strides, but it is clear that in order to be able to correctly use a degraded visual input like that offered by the current plants, a long training is needed, which

requires a high restructuring of the visual information processing network. In this thesis, we have seen how it is possible to modulate lateral interactions at early stages of processing, favouring the processing of feedforward and allowing restructuring of visual-spatial integration. This property of tRNS will surely be useful in the future to accelerate the adaptation to retinal implants by patients.

Another way is to combine the tRNS + PL with drug administration. Numerous studies are showing that some substances allow for extra plasticity in the visual cortex (Baker, D.H., Smith, A.K. & Wade, 2015; Fuchs & Flügge, 2014; Greuel, Luhmann, & Singer, 1988; Kang & Vaucher, 2009; Rokem & Silver, 2013). Particularly promising is the use of acetylcholine reuptake inhibitors that act selectively on muscarinic or nicotinic receptors present in the primary visual cortex. The effect of increasing the bioavailability of acetylcholine on the visual system seems comparable to the effect we found with tRNS (Kang et al., 2014). Cholinergic projections from nucleus basalis activate excitatory nicotinic receptors in layer IV of V1 and thus potentiate pyramidal cells that carry retinal activation. They also activate inhibitory muscarinic receptors in layers 1-11 reducing cortico-cortical conduction (Bhattacharyya, Veit, Kretz, Bondar, & Rainer, 2013; Pinto et al., 2013; A. J. Yu & Dayan, 2005). This way, activation of Nucleus Basalis enhances the processing of task-relevant stimuli at the detriment of the overall spatial integration. Simply put, it modulates the strength of horizontal connections downwards and favours the feedforward in a way similar to what we saw in study 2 of this thesis (Kang et al., 2014). It is suggestive of imagining a PL + tRNS paradigm with concomitant Ach treatment. The combined effect of the drug and the stimulation could be additive with the results of bringing the effectiveness of the PL to an even higher level.

In conclusion, although some unresolved questions remain, the results presented in this thesis support the potential of PL + tRNS in the improvement of the residual visual abilities in adults with bilateral central blindness. Before an extensive clinical application, further studies are needed to maximize the effectiveness of the treatment. Moreover, this thesis has brought new results that contribute to the understanding of the plasticity of the human brain in general, with possible repercussions for other clinical populations.

Supplementary material

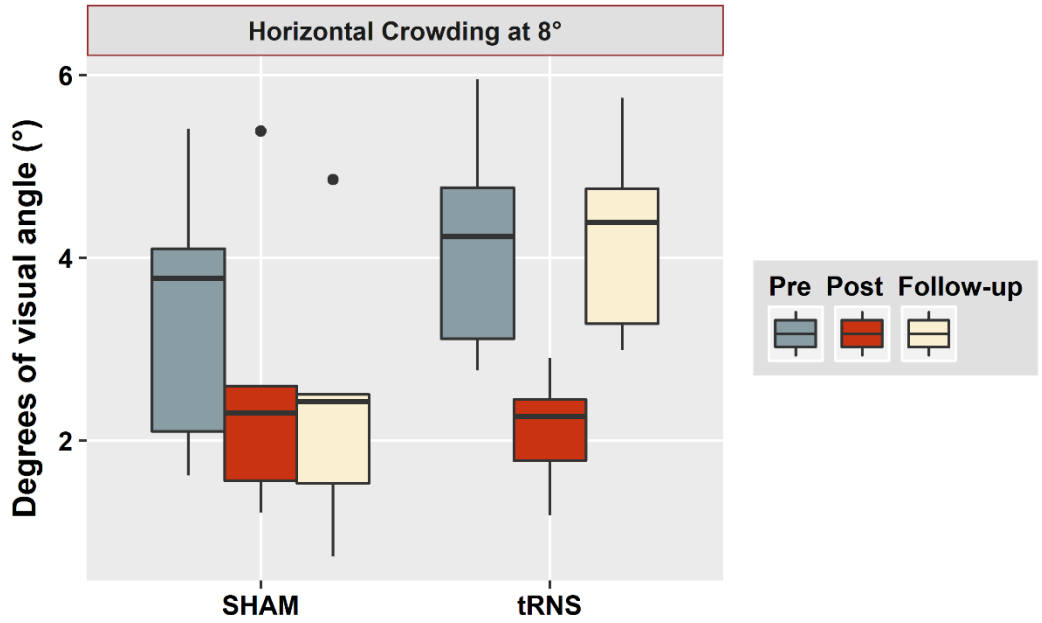

Figure 29. Training and follow-up results for the Sham (n = 5) and tRNS (n = 5) subgroup.

Pre, post-training, and follow-up data are shown in grey, red and cream colors, respectively. From bottom to top, boxes provide the 5th, 25th, 75th, and 95th percentiles of the distributions. The horizontal bold lines provide the median values of the distribution. The black dots correspond to outliers.

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