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Dominance wave propagation during binocular rivalry in mild glaucoma

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ABSTRACT

Glaucoma is both a progressive optic neuropathy and a neurodegenerative disease affecting structures in the primary visual pathway. Other vision-associated areas may also be affected, including the corpus callosum which is involved in inter-hemispheric transfer. This study evaluated dominance wave propagation during binocular rivalry to probe the efficacy of the inter-hemispheric transfer in 20 patients with mild open angle glaucoma and 25 age-matched controls. The two groups were matched for functional measures such as stereo-acuity, binocular visual acuity, and visual field mean deviation. Monocular functional and structural measures were equivalent for the left and right eye of each participant. Using Wilson et al.'s travelling wave paradigm [Nature, 412 (2001) 907–910], intra- and inter-hemispheric failure rates of traveling wave transmission and the travelling wave propagation times were recorded for the two groups. For the control group, the wave propagation failure rate was significantly greater for the inter- than for the intra-hemispheric condition, but for the glaucoma group, the failure rates were equally high for the two conditions. The wave propagation time was significantly longer for the inter- than for the intra-hemispheric condition for the control group, while the opposite was true for the glaucoma group. These results reveal changes in the wave dynamics of rivalry dominance in patients with mild glaucoma who otherwise have normal performance on standard functional measures.

1. Introduction

Glaucoma is a progressive, degenerative eye disease and the leading cause of irreversible vision loss in people over 40 years of age (Quigley & Broman, 2006; Varma, Lee, Goldberg, & Kotak, 2011). Despite preserved good central vision until later stages, patients with glaucoma show impairments in many aspects of visual processing, in ocular motor control, and in functional vision. For example, for lower levels of visual processing these patients exhibit higher motion detection thresholds (Bullimore, Wood, & Swenson, 1993; McKendrick, Badcock, & Morgan, 2005; Silverman, Trick, & Hart, 1990; Trick, Steinman, & Amyot, 1995; Westcott, Fitzke, & Hitchings, 1998), longer latency for vection responses (Brin, Tarita-Nistor, González, Trope, & Steinbach, 2019; Tarita-Nistor, Hadavi, Steinbach, Markowitz, & González, 2014), reduced contrast sensitivity (Hawkins, Szlyk, Ardickas, Alexander, & Wilsensky, 2003; McKendrick, Sampson, Walland, & Badcock, 2007), and decreased stereopsis (Essock, Fechtner, Zimmerman, Krebs, & Nussdorf, 1996). Changes in the ocular motor system are reflected by abnormal saccadic eye-movement control (Kanjee, Yucel, Steinbach, Gonzalez, & Gupta, 2012; Lamirel, Milea, Cochereau, Duong, & Lorenceau, 2014), while functional changes are shown in atypical eye-hand coordination (Kotecha, O'Leary, Melmoth, Gant, & Crabb, 2009), reduced reading abilities (Ramulu, Swenor, Jefferys, Friedman, & Rubin, 2013; Ramulu, West, Munoz, Jampel, & Friedman, 2009), difficulties navigating the environment (Friedman, Feeman, Munoz, Jampel, & West, 2007; Ramulu, 2009; Turano, Rubin, & Quigley, 1999), and increased risk of falls (Black, Wood, & Lovie-Kitchin, 2011) and motor vehicle collisions (Haymes, Leblanc, Nicolela, Chiasson, & Chauhan, 2007).

Physiologically, glaucoma is characterized by progressive loss of retinal ganglion cells (RGCs), but the exact mechanism of the disease remains to be elucidated (Quigley, 1999). The RGCs damage is propagated — through the mechanism of Wallerian degeneration — in all the neural structures of the primary visual system, including the retina, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus, optic radiation, and the visual cortex (Boucard et al., 2016; Chen et al., 2013; Garaci et al., 2009; Gupta, Ang, Noel De Tilly, Bidaisee, & Yucel, 2006; Hernowo, Boucard, Jansonius, Hooymans, & Cornelissen, 2011; Zhang et al., 2012). Recent findings suggest the neurodegeneration is not limited to the primary visual system, but that there are widespread structural changes in the brain, including in the corpus callosum — the largest white matter bundle connecting the two brain hemispheres

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(Boucard et al., 2016; Williams et al., 2013). In some brain structures neurodegeneration associated with glaucoma depends on disease severity in an unusual way: for example, when compared to controls, the volume of the corpus callosum is significantly larger in early glaucoma but significantly smaller in moderate and advanced stages of the disease. It has been suggested that the increase in the volume of the brain structures in the initial stages of the disease may be indicative of either an inflammatory response to neuronal injury, or — although unlikely — of neuroplasticity (Williams et al., 2013). Nevertheless, these results point to a degenerative mechanism in glaucoma independent from that due to the propagation of RGC damage.

The corpus callosum is the most important structure involved in inter-hemispheric transfer and its efficacy can be probed using the phenomenon of binocular rivalry. When two dissimilar stimuli are presented in retinal correspondence and viewed dichoptically so that each eye sees exclusively one stimulus, the brain cannot combine the two images into a unified percept. Instead, the two stimuli rival for perceptual dominance with only one being perceived briefly and then the dominance switches to the previously suppressed stimulus, in a continuous cycle (Alais & Blake, 1999; Blake & Wilson, 2011; Lee & Blake, 1999; Lee, Blake, & Heeger, 2007; Miller et al., 2000; Tong, Meng, & Blake, 2006). When the two stimuli are projected to only one hemifield, rivalry is processed in the contralateral hemisphere, but when the stimuli are projected to both hemifields binocular rivalry processes in the two hemispheres need to be synchronized by the corpus callosum (O'Shea & Corballis, 2003). Changes in perceptual dominance happens gradually particularly for larger stimuli (Blake, O'Shea, & Mueller, 1992); these transition waves of perceptual dominance can be examined using the Wilson, Blake, and Lee (2001) travelling wave paradigm (see Methods section for a detailed description of this paradigm). Depending on the experimental setup, binocular rivalry can be used as a tool for investigating the intra- and inter-hemispheric processing of visual information.

In healthy observers, inter-hemispheric travelling wave propagation takes on average 173 ms longer than intra-hemispheric wave propagation, and this perhaps represents the time penalty required to cross the long-range callosal fibers (Wilson et al., 2001). The inter-hemispheric travelling wave is propagated through the callosal fibers of the splenium that connect the left and right V1 (Genç et al., 2011), suggesting that anomalies of the wave dynamics would be indicative of callosal damage. Indeed, patients with mild traumatic brain injury — who are especially susceptible to long axonal damage —show high failure rate of travelling wave transmission but, counterintuitively, the propagation time is shorter inter- than intra-hemispherically (Spiegel, Laguë-Beauvais, Sharma, & Farivar, 2015).

The purpose of this study was to probe the efficacy of the inter-hemispheric transfer in patients with mild glaucoma who otherwise have no functional deficits using Wilson et al. (2001) travelling wave paradigm. We hypothesized that the travelling wave dynamics are affected in these patients particularly in the inter-hemispheric condition.

2. Materials and methods

2.1. Participants

Participants were 20 patients with bilateral mild open angle glaucoma (mean age 65 years ± 12 SD) recruited from the Eye Clinic at the Toronto Western Hospital, Toronto, Canada, and 25 age-matched controls with healthy vision (mean age 63 years ± 10 SD) recruited from ads posted around the same hospital, volunteers or staff members. All patients had a confirmed diagnosis given by a glaucoma specialist, were under pharmaceutical treatment to normalize intraocular pressure, and seen on a regular basis to monitor disease progression. Based on their visual field test, the patients' glaucoma severity was classified as stage 0 to 1 on the Hodapp-Parrish Anderson Glaucoma Grading Scale, which corresponds to no or mild visual field loss. All participants had no other ocular pathologies with the exception of symmetric mild cataract, no significant monocular or binocular functional deficits, and no significant functional or structural asymmetries in the two eyes. All participants with a history of neurological diseases or cognitive impairment were excluded. Fourteen patients had a diagnosis of primary open angle glaucoma (POAG) and 6 had normal tension glaucoma (NTG). The research was approved by the institutional ethics board and conducted in accordance with the tenets of the declaration of Helsinki. Written informed consent was obtained from all participants. Clinical and demographic characteristics of the two groups are shown in Table 1 and a detailed analysis of the structural and functional measures are presented in the Results section.

Table 1
Demographic and clinical characteristics (mean ± SD) of the glaucoma and control group.

	Glaucoma	Control	p value
N [M/F]	20 [12/8]	25 [16/9]	–
Age (years)	65 ± 12	63 ± 10	0.50
Stereo acuity (s)	40 ± 34	29 ± 30	0.24
Visual acuity 96% contrast (logMAR)			
Binocular	−0.07 ± 0.08	−0.13 ± 0.12	0.05
Right eye	−0.03 ± 0.07	−0.10 ± 0.12	***0.02***
Left eye	−0.04 ± 0.08	−0.10 ± 0.09	***0.02***
Visual acuity 25% contrast (logMAR)			
Binocular	0.03 ± 0.11	−0.03 ± 0.11	0.09
Right eye	0.08 ± 0.11	0.00 ± 0.11	***0.02***
Left eye	0.09 ± 0.13	0.02 ± 0.11	0.08
Visual field mean deviation (dB)			
Right eye	−0.01 ± 1.96	0.85 ± 1.76	0.14
Left eye	−0.15 ± 1.94	0.49 ± 1.68	0.25
Retinal nerve fiber layer (μm)			
Right eye	81.6 ± 12.2	87.7 ± 8.8	0.06
Left eye	79.8 ± 8.9	86.3 ± 10.4	***0.03***
Average cup-to-disc ratio			
Right eye	0.67 ± 0.07	0.49 ± 0.11	***0.000***
Left eye	0.66 ± 0.10	0.49 ± 0.09	***0.000***
Vertical cup-to-disc ratio			
Right eye	0.67 ± 0.07	0.47 ± 0.10	***0.000***
Left eye	0.66 ± 0.11	0.49 ± 0.11	***0.000***
MoCA cognitive test	28.2 ± 1.4	28.1 ± 1.9	0.88

2.2. Apparatus and stimuli

2.2.1. Functional and structural measures

The following functional measures were obtained: 1) monocular and binocular visual acuity at high (95%) and low contrast (25%) at a distance of 6 m with a computerized version of the ETDRS (Early Treatment Diabetic Retinopathy Study) chart (single line) using the Accommodata Stimuli System, Version 3.5 (Haag–Streit, Mason, OH) and a letter-by-letter scoring system; 2) stereo acuity with the Random Dot Stereoacuity Test (Good-Lite Company, Elgin, IL); and 3) monocular visual field sensitivity (mean deviation or MD) for each eye with the Humphrey Field Analyzer (Humphrey Field Analyzer; model HFA-II 750; Carl Zeiss Meditec, Dublin, CA) using the 24–2 Swedish Interactive Threshold Algorithm-Standard. Cognitive function evaluation was performed with the Montreal Cognitive Assessment test (MoCA, www.mocatest.org). Structural measures were obtained for each eye with the spectral domain optical coherence tomography (OCT, model Cirrus; Carl Zeiss Meditec, Dublin, CA) using a 200 × 200 optic disc cube protocol scan, and included average cup-to-disc ratio, vertical cup-to-disc ratio, and peripapillary retinal nerve fiber layer (RNFL) thickness.

2.2.2. Psychophysical measures

We used Wilson et al. (2001)'s travelling wave paradigm and our version of the stimuli — shown in Fig. 1 – was similar to that used by Genç et al. (2011) and Spiegel et al. (2015). In short, one low contrast

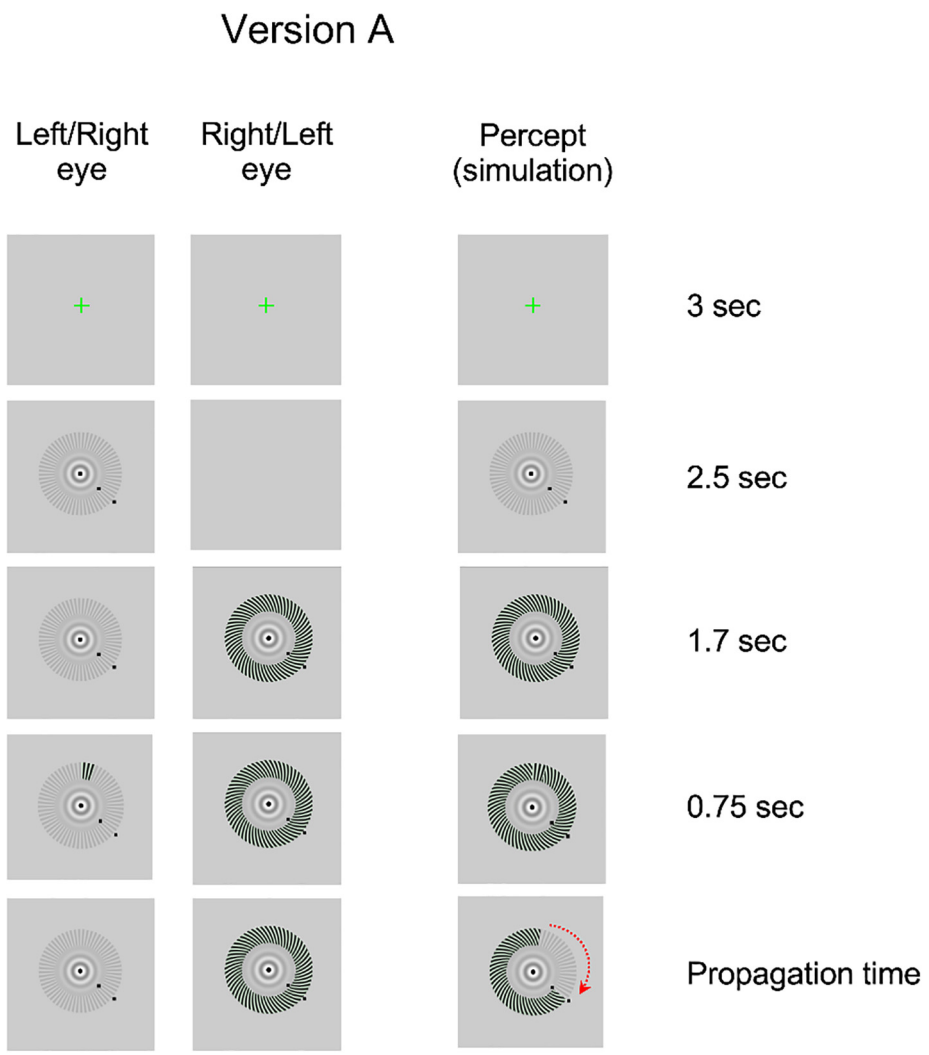

Fig. 1. Stimuli for travelling wave initiation, shown dichoptically. This figure shows version A of the experiment. Time sequence of stimulus presentation is shown on the right column.

ring-shaped stimulus and one high contrast stimulus were presented dichoptically using a double mirror stereoscope. The low contrast stimulus was the "target" and presented first. Shortly after, the high contrast stimulus was presented to the other eye. Typically, this suppresses the target stimulus completely. Next, a local increment in contrast (a "trigger") of the target stimulus was presented to facilitate the propagation of dominance of this stimulus. The trigger had 4 angular locations relative to the arriving point (the two black dots in Fig. 1), but the distance between the trigger and the arriving point was always 120 deg in polar coordinates. The trigger and arriving point were either in the same or in different hemifields. While keeping a steady fixation on the bullseye pattern, participants pressed the spacebar when the travelling wave reached the arriving point by the shortest angular distance. If no travelling wave was initiated, participants were instructed to wait for the next trial. The computer program registered the time of travelling wave propagation on the short arc and the travelling wave transmission failure rate. Two versions of the test were created: version A with the arriving point situated at 130 deg (lower visual field) and version B with the arriving point situated at 310 deg (upper visual field). Within each version, there were 4 conditions (2 locations of the trigger × 2 kinds of dichoptic presentations) with 10 replications per condition. This produced a total of 40 trials that were randomly presented. The trigger's location was chosen to be either in the same hemifield as the arriving point (i.e., intra-hemispheric processing) or in different hemifields (i.e., inter-hemispheric processing). For version A, the trigger was shown either at 10 deg or at 250 deg and for version B the trigger was located either at 190 deg or at 70 deg. The vertical meridian is represented in both hemispheres (Hubel & Wiesel, 1967) and consequently the trigger and arriving point in the inter-hemispheric condition must be positioned far from the vertical midline to ensure that the wave is propagated from one hemisphere to the other. It has been shown that the maximum independence of cortical representation is obtained when the stimuli are farther than 40 deg (polar angle) from the vertical meridian (Tootell, Mendola, Hadjikhani, Liu, & Dale, 1998); defining 0 deg as the vertical meridian and counting clockwise, the zones of maximum independence are when the stimulus from the right hemifield is situated between 40 deg and 140 deg and that from the left hemifield between 220 deg and 320 deg. In the inter-hemispheric condition of both versions of the test, the trigger and the arriving point were within these zones. One version of the test (i.e., A or B) was chosen randomly for each participant.

Fig. 1 shows the stimuli. The strokes of the green fixation cross were 1 deg in height and 0.1 deg in width. The central bullseye section was a Gabor patch consisting of an 0.8 cpd concentric sinusoidal grating with a Gaussian envelope with a standard deviation of 1.5 deg. The fixation circle was a black disc 0.7 deg in diameter. The target (i.e., low contrast stimulus) and high contrast stimulus that produced the rivalry had an inner diameter of 4 deg and an outer diameter of 6.5 deg. They both included radial spiral bars with a sinusoidal profile and a spatial

frequency of 60 cpd. The high contrast stimulus was green and had an additional spiral component. The trigger had an angular length of 19 deg, was high contrast, green, and had no spiral component. VPixx, a graphics and psychophysics software (http://www.vpixx.com), was used for stimulus design, controlling the experiment, and recording the data.

2.2.3. Procedure

All participants were tested during a single 2-hour session as follows. First, the study was explained in detail and informed consent obtained. Second, functional (i.e., monocular and binocular visual acuity at high and low contrast, stereo acuity thresholds, and monocular visual field sensitivity for each eye), structural (i.e., RNFL layer, average cup-to-disc ratio, vertical cup-to-disc ratio for each eye), and cognitive (i.e., MoCA test) measures were obtained. Finally, the psychophysical test was conducted in a darkened room with the computer screen as the only light source. For this, participants had their head stabilized with a chin rest and the apparatus positioned such that the centre of the screen was at eye level using an adjustable table. It was verified that the participants were able to fuse two fixation crosses presented dichoptically. The experiment was explained using a step-by-step visual demonstration of the stimuli and the possible visual percepts. This demonstration was presented as many times as the participants needed to understand the task. Then, the 40 trial experiment – version A or B, randomly selected – began.

Each trial began with a 3 s fixation period, after which the low contrast stimulus was presented to one eye and then the high contrast stimulus to the other eye after a 2.5 s delay. After 1.7 s from the high contrast stimulus presentation, the trigger appeared on the target (i.e., the low contrast stimulus) for 0.75 s. Once the trigger disappeared, the participants were instructed to press the spacebar of a keyboard if and only if they saw the travelling wave reaching the arriving point on the short arc; if the travelling wave was initiated but did not reach the arriving point, or the wave went on the long arc, or there was no travelling wave initiated, they were instructed not to press the spacebar and to wait for the next trial. Each trial was 20 s long in total, with a time to failure of 12.04 s. The experiment proceeded with no breaks, but was restarted any time a participant felt he or she did not understand the task. Fig. 2 shows a schematic of the trials.

2.2.4. Data analysis

The main outcome measures were 1) travelling wave transmission failure rate and 2) time of travelling wave propagation, for both intra- and inter-hemispheric conditions. An Intra/Inter Ratio – defined as the ratio of the intra-/inter-hemispheric performance – was also computed. Data were analyzed primarily with parametric tests such as independent samples t-tests, paired samples t-tests, and mixed factorial analyses of variance (ANOVAs). When the sphericity assumption was violated, the ANOVA effects were adjusted with a Greenhouse-Geisser correction. The familywise error rate was controlled with the Bonferroni approach when multiple comparisons were performed. In isolated instances of high variability in the data, the Mann-Whitney U non-parametric test was used. An alpha level of 0.05 was used for all tests.

3. Results

3.1. Participants: functional and structural differences

Because the rivalry results could be affected by asymmetries between the right and the left eye, we assessed the functional and structural measures within each group with paired-samples t-tests. Functional measures of each eye included visual fields mean deviation, and visual acuity at high and low contrast. Structural measures included RNFL measurements, average cup-to-disc ratio, and vertical cup-to-disc ratio. The left eye was not significantly different from the right eye on any of the functional and structural measures, for the glaucoma group (smallest $p = 0.08$) and for the control group (smallest $p = 0.06$).

We further examined the binocular functional differences between the two groups with independent samples t-tests. There were no significant differences in stereo-acuity ($p = 0.50$) or binocular acuity at high ($p = 0.051$) and low ($p = 0.09$) contrast. Monocular functional differences between the two groups were also examined. The visual

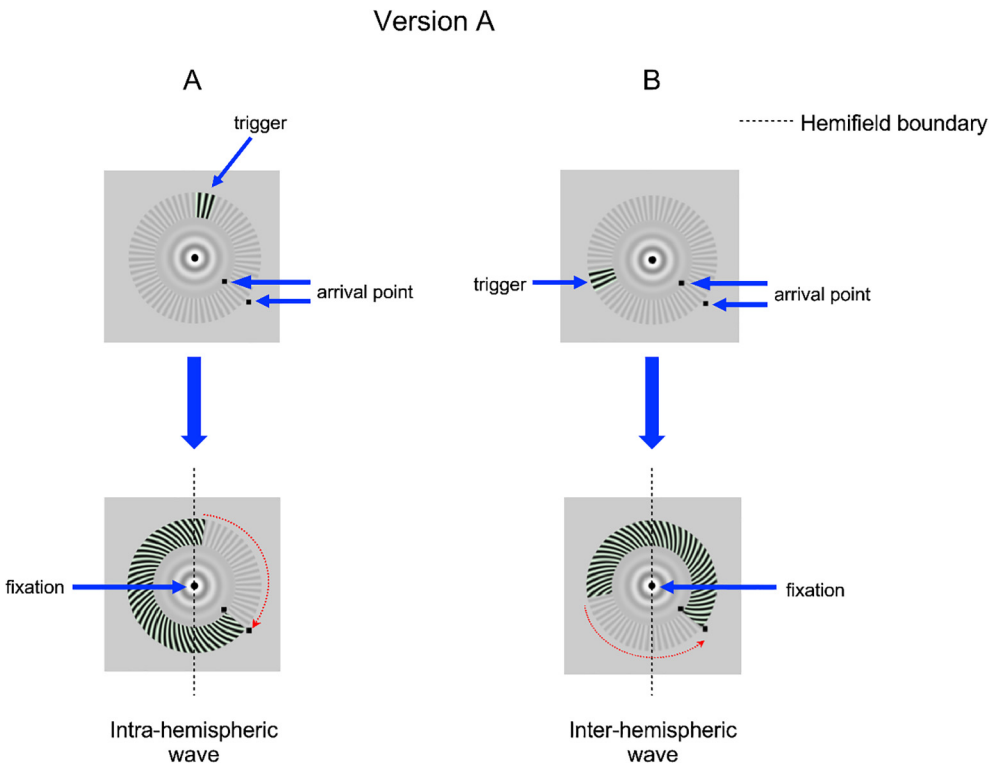

Fig. 2. Schematics of the travelling wave propagation for intra-hemispheric (left panel) and inter-hemispheric (right panel) condition, shown on version A of the experiment. The top figures show the trigger presented on the target stimulus. The bottom figures show the successful wave propagation along the short arc to the arriving point.

field's mean deviation of the left eye as well as that of the right eye were not significantly different between the two groups (smallest p = 0.14). Monocular visual acuities were normal in both groups, with averages slightly better than 0.0 logMAR (Snellen 20/20) at high contrast. The differences between groups in monocular acuity were in general statistically (p value range 0.02 to 0.08) – but never clinically – significant: the largest difference was of 0.08 logMAR (or 4 letters) for the right eye's visual acuity at low contrast. The functional and structural measures of the two groups are shown in Table 1.

3.2. Failure rates of travelling wave transmission

In order to evaluate the failure rates of traveling wave transmission, we calculated the Intra/Inter Ratio: a value greater than 1 means that the failure rate for the intra-hemispheric condition is greater than that of the inter-hemispheric condition, a value equal to 1 means the failure rates for the two conditions are the same, and a value smaller than 1 means that the failure rate for the intra-hemispheric condition is lower than that of the inter-hemispheric condition. The Intra/Inter Ratio of the glaucoma group (mean = 1.0 ± 0.3 SD) was significantly higher than that of the control group (mean = 0.8 ± 0.4 SD), independent-samples *t*-test t(43) = 2.9, p = 0.006.

We further analyzed the failure rates with a 2 (Conditions: intra-, inter-) × 2 (Group: control, glaucoma) mixed factorial ANOVA. Although the failure rates were reported as percentages (i.e., percentage of trials that did not elicit a response), we treated these values as parametric data. There were a significant Condition main effect F(1, 43) = 7.9, p = 0.007, partial $\eta^2 = 0.16$ and a significant Condition × Group interaction effect F(1, 43) = 6.9, p = 0.01, partial $\eta^2 = 0.14$. Overall, the inter- failure rate was significantly higher than the intra- failure rate, but pairwise comparisons showed that these rates were not different from each other for glaucoma group, p = 0.9; however, the inter- was significantly larger than the intra- failure rate for the control group, p < 0.001. In addition, the intra-hemispheric failure rate was significantly higher for the glaucoma group than for the control group, p = 0.014, but the inter-hemispheric failure rate was similar for the two groups, p = 0.42. Averages for the intra- and inter-hemispheric traveling wave transmission failure rates and the Intra/Inter Ratio for the two groups are shown in Table 2 and in Fig. 3.

3.3. Travelling wave propagation time

The Intra/Inter Ratio for travelling wave propagation time had a median of 1.3 (mean = 1.6 ± 1.2 SD) for the glaucoma group and a median of 0.93 (mean = 0.87 ± 0.2 SD) for the control group. Because of high variability in the data, the difference between groups was assessed with a non-parametric test. The Mann-Whitney *U* test showed that the two groups differed significantly U = 55, p < 0.001. These results indicate not only a significant difference between the two groups, but also that the time of the travelling wave propagation was shorter for the inter- than for the intra-hemispheric condition for the glaucoma group (Intra/Inter Ratio greater than 1), while the opposite was true for the control group (Intra/Inter Ratio smaller than 1). The results are shown in Fig. 4 panel A. These results were confirmed with an independent-samples *t*-test on the log transformed data, t (36) = 3.77, p = 0.001.

Table 2
Averages (± SD) for intra- and inter-hemispheric traveling wave transmission failure rates and the Intra/Inter Ratio for the control and glaucoma group.

Group	Intra-hemispheric failure rate (%)	Inter-hemispheric failure rate (%)	Intra/Inter Ratio
Control	49 ± 3	64 ± 3	0.8 ± 0.4
Glaucoma	70 ± 2	70 ± 2	1.0 ± 0.3

We also computed the time difference of the travelling wave propagation for the two conditions (inter – intra). For the control group, there was a time penalty for wave propagation in the inter-hemispheric condition of a median of 0.26 s (mean = 0.49 s ± 0.70 SD). For the glaucoma group, the median difference was −0.52 s (mean = −0.59 s ± 1.1 SD), which also indicates that the propagation was faster in the inter- than in the intra- hemispheric condition. The Mann-Whitney *U* test showed that the two groups differed significantly U = 60, p = 0.001 on this measure as well. This result is shown in Fig. 4 panel B.

Travelling wave propagation time was further analyzed with a 2 (Conditions: intra-, inter) × 2 (Group: control, glaucoma) mixed factorial ANOVA. This analysis revealed only a significant Condition × Group interaction effect, F(1,36) = 13.7, p = 0.001, partial $\eta^2 = 0.28$. Follow-up analysis showed that the propagation time was significantly longer for the inter- than for the intra-hemispheric condition for the control group p = 0.014, while the opposite was true for the glaucoma group, p = 0.012. The results are shown in Fig. 4 panel C.

3.4. Travelling wave: POAG vs NTG

In the glaucoma group, 14 patients (mean age: 66 years ± 11 SD) had a diagnosis of POAG and 6 patients (mean age: 63 years ± 14 SD) had NTG. The 2 subgroups were matched in age (p = 0.59). These 2 subgroups did not differ significantly in any psychophysical measures: intra- and inter-hemispheric failure rates of travelling wave transmission, the Intra/Inter Ratio of the failure rates, intra- and inter-hemispheric travelling wave propagation time, the Intra/Inter Ratio of the propagation time, and the time difference in travelling wave propagation between intra- and inter-hemispheric conditions (smallest p = 0.16).

4. Discussion

In this study we examined the travelling wave dynamics of binocular rivalry in patients with mild glaucoma who otherwise had no significant functional deficits. Wave transmission failure rates were equally high for the inter- and intra- hemispheric conditions in the glaucoma group, but the control participants had a significantly lower failure rate for the intra- than for the inter-hemispheric condition. Interestingly, in the glaucoma group wave propagation was faster for the inter- than for the intra- hemispheric condition, while the opposite was true for the control group. Although counterintuitive, the latter result is consistent with findings from patients with mild TBI. Taken together, these findings show changes in the dynamics of the dominance wave during binocular rivalry that could be detected before any other functional deficits produced by glaucoma.

During binocular rivalry with traditional stimuli two different images viewed dichoptically compete for perceptual dominance, resulting in a bistable percept whose rate of change and time of single stimulus dominance can be quantified (Blake & Wilson, 2011; Lee et al., 2007). These measures provide information about excitatory-inhibitory neural activity both within and between hemispheres and reveal functional aspects of the inter-hemispheric transfer facilitated by the corpus callosum — the main structure involved in inter-hemispheric transfer (Berlucchi, 2014). Wilson et al. (2001)'s travelling wave paradigm is a special case of binocular rivalry that is suitable for studying the gradual change of perceptual dominance, providing further insights into the neural dynamics of binocular rivalry and the integrity of inter-hemispheric transfer.

The travelling wave paradigm involves presenting a low contrast stimulus to one eye and a high contrast stimulus to the other eye that typically dominates continuously. This is in accordance to the Levelt's first law of binocular rivalry which states that increasing the strength of the stimulus in one eye will result in a prolonged dominance of this

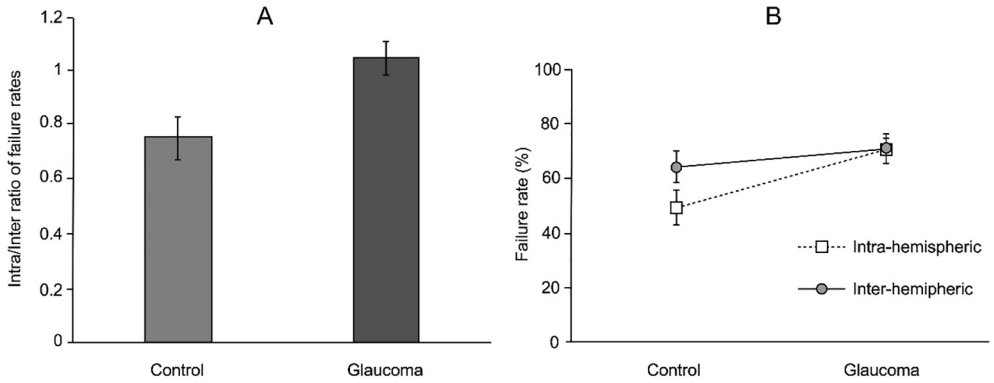

Fig. 3. Travelling wave transmission failure rates of in the intra- and inter- hemispheric conditions, for the control and glaucoma group. Panels show: A) intra-/inter-hemispheric failure rate ratio (Intra/Inter Ratio); and B) average failure rates. Error bars are ± 1SE.

stimulus (Levelt, 1966). Nevertheless, when a local increment of high contrast (i.e., the trigger) is presented briefly on the low contrast stimulus, this can release the strong inhibition allowing the suppressed stimulus to begin a wave of dominance with its origin at the trigger's location. The waves' dynamics are typically examined up to the arriving point marked on the high contrast stimulus. It appears that in healthy controls the release of inhibition is facilitated when the trigger and the arriving point are presented within the same hemifield (Fig. 2A) rather than in separate hemifields (Fig. 2B) because we found lower wave transmission failure rate in the intra- than in the inter-hemispheric condition. No such facilitation was observed in glaucoma group: the wave transmission failure rate was equally high irrespective of the trigger's location (i.e., same or different hemifields). However, a distinction must be made between failure of wave *initiation* and failure of wave *transmission*. Wave initiation —which requires the release of inhibition— is a necessary but not a sufficient condition for successful wave transmission. In the current study, the participants were instructed to press a button if and only if the travelling wave reached the arriving point on the shortest arc. There were instances when the trigger initiated the travelling wave but the wave failed to propagate over the established angular distance. This was counted as a failed transmission but not as a successful wave initiation. Our results point both to an inability to initiate the travelling wave and to problematic propagation of rivalry dominance in the intra-hemispheric condition in glaucoma. Since we did not count the occasional reports of wave initiation that failed to travel to the arriving point, we are unable to untangle this issue completely. Moreover, no particularly strong intra-hemispheric inhibitory processes were detected with traditional rivalry paradigm using stimuli that were equal in strength and presented to only one hemifield in patients with mild glaucoma because their rivalry rates (i.e., number of perceptual switches per minute) did not differ from controls (Samet, González, Trope, & Tarita-Nistor, 2019).

Wilson et al. (2001) showed that the travelling wave of dominance propagates across V1 at a cortical speed predicted by the cortical magnification factor and, in conditions where inter-hemispheric transfer of visual information is involved, there is a time penalty of about 173 ms likely due to the neural transmission going through the long callosal fibers. This delay of transfer between hemispheres was initially measured in 4 experienced observers (Wilson et al., 2001), and the finding was later replicated although with high variability in the data (Genç et al., 2011; Spiegel et al., 2015). The longer inter- than intra-hemispheric travelling wave propagation was also predicted by studies examining grouping of rivalry targets spatially separated that were presented dichoptically to the same or different hemifields and to

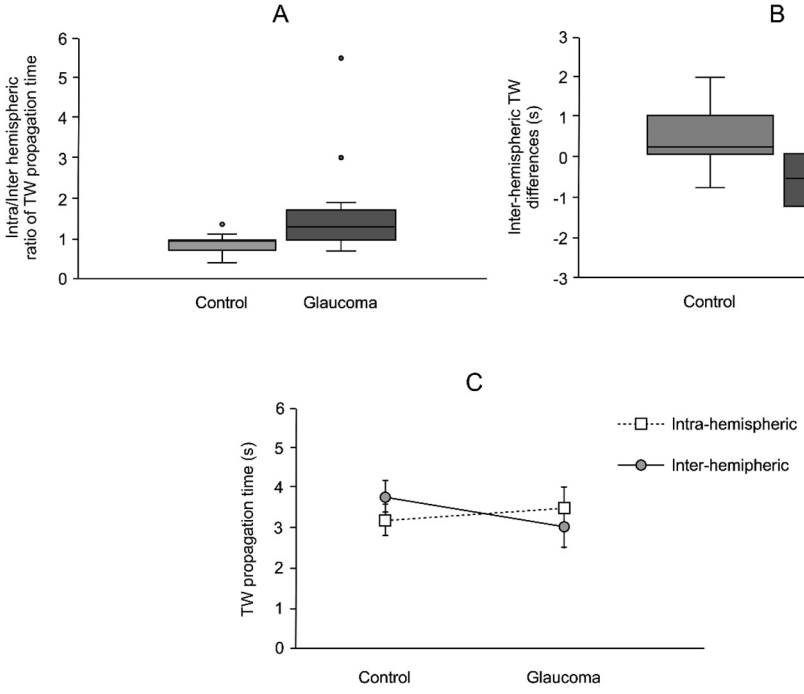

Fig. 4. Travelling wave propagation time in the inter- and intra- hemispheric conditions for the two groups. Panels show: A) the Intra/Inter Ratios where a value smaller than 1 indicates faster propagation time in the intra- than in the inter-hemispheric conditions; B) Time difference between the two conditions, and C) the average time for travelling wave propagation. Error bars are ± 1SE.

the same or different eyes (Stuit, Paffen, van der Smagt, & Verstraten, 2011, 2014). In conditions involving eye-based dominance of an image (i.e., one eye sees two identical images, spatially separated, that are presented in the same or in both hemifileds, while the other eye sees other two identical images presented in similar arrangements as the other eye) there is a stronger grouping for targets presented in the same hemifield than in both hemifields. These findings imply stronger connectivity between adjacent rivalry zones within hemifields, predicting faster intra- than inter- hemispheric wave propagation in healthy participants (Stuit, Paffen, van der Smagt, & Verstraten, 2011). The control group in our study showed a median delay of 260 ms in inter-hemispheric wave propagation and, despite highly variable data, most of the participants (19 out of 25) showed longer inter- than intra-hemispheric propagation time. Interestingly, the glaucoma group produced the opposite effect: there was an overall faster inter-hemispheric propagation, with only 5 out of 20 patients showing the delay observed in controls. These results are consistent with data from patients with mild traumatic brain injury who are susceptible to long axonal injury (Spiegel et al., 2015).

These findings are counterintuitive and currently we do not have a solid explanation for them, but our attempt to elucidate these results is as follows. In healthy controls the delay in inter-hemispheric wave propagation is strongly but negatively correlated only with radial diffusivity of callosal fibers connecting the V1 segments as revealed by a diffusion tensor imaging technique (Genç et al., 2011). That is, the shorter the delay in inter-hemispheric travelling wave propagation, the larger the diffusion of the white-matter microstructure of the fibers connecting the V1 of the two hemispheres. It is plausible that the large axonal diameter of the fibers in the V1callosal segment may facilitate faster axonal conductivity or that differences in fiber density and myelination explain this negative relationship in healthy participants (Genç et al., 2011). In patients with mild glaucoma — as were those included in this study — there is an indication of neuro inflammation in brain structures including in the corpus callosum (Streit, 2012; Williams et al., 2013). The inflammatory responses can produce an increase in neuronal conductivity (Galic, Riazi, & Pittman, 2012; Goldstein, Church, Hesp, Popovich, & Mctigue, 2016) in the long callosal axonal fibers resulting in faster inter-hemispheric transfer. It is conceivable that this explanation will gain support from further imaging studies examining the corpus callosum microstructure in conjunction with the behavioural travelling wave data similar to that conducted in healthy controls (Genç et al., 2011); however, to date our explanation remains a supposition. Given the widespread structural changes in the glaucomatous brain (Boucard et al., 2016; Chen et al., 2013; Garaci et al., 2009; Gupta et al., 2006; Hernowo et al., 2011; Williams et al., 2013; Zhang et al., 2012) a multitude of other factors could have contributed to the observed findings. Nevertheless, the important issue remains that faster inter- than intra-hemispheric wave propagation has been reported in two neuro-injured clinical populations, both in mild stages, one chronic (glaucoma) and one acute (traumatic brain injury) (Spiegel et al., 2015). More research involving advanced imaging techniques is needed to elucidate these findings.

In conclusion, the travelling wave dynamics of binocular rivalry dominance are abnormal in patients with mild glaucoma and these changes in rivalry dominance can be detected behaviorally before any significant functional deficits.

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