

Spatial relationship perception is not affected by short-term cortical reorganization

ABSTRACT

Aims: Long-term cortical reorganization after cortical damage can induce abnormal spatial relationship perception (spatial anisotropy) but there is also evidence of short-term, reversible cortical re-modulation even in the absence of cerebral damage: simulated hemianopic deprivation, in fact, is found to affect the positional judgment. This study investigates if the same occurs for spatial relationship perception.

Study design: Case series.

Place and duration of study: Service of Neuro-Ophthalmology, University of Turin, Italy, from January 2020 to July 2020.

Methodology: Spatial relationship perception (SRP) of three subjects was measured in the presence of simulated homonymous hemianopia with a psychophysical procedure that estimates the discrimination threshold between elliptical and circular stimuli centered to the fixation point. The extent of the deprivation was graded as the distance of the proximal border of the nonresponsive area from the fixation point.

Results: Overall, spatial relationship perception is not affected by the hemifield deprivation in terms of distance of the scotoma from the fixation point ($P= 0.26$), laterality ($P= 0.07$), and distance X laterality ($P= 0.15$). However, a significant effect of distance and laterality ($P= 0.01$ and $P= 0.02$, respectively) was found in the sole observer who showed an anisotropic perception in normal (no-simulated) condition.

Conclusion: SRP appears to be robust toward the reversible spatial remapping induced by simulated hemianopia along the deprived area. However, the response of the visual system to artificial visual deprivation seems conditioned by pre-existing anisotropy.

Keywords: Hemianopia, Simulation, Artificial Scotoma, Cortical Reorganization, Anisotropy.

1. INTRODUCTION

Spatial relationship perception is an ecologically important function, as it is a size-invariant cue to identify objects [1,2]. Spatial relationship perception (SRP) allows estimating the relative extent of the visual space along the x-, y-cardinal axis [3], and can be derived by measuring the sensitivity to the aspect ratio of geometrical shapes, like squares vs. rectangles or circles vs. ellipses [1-4].

Preferential processing along the x-, y-direction can be referred to as *spatial relationship anisotropy* (SRA): in this case, horizontal or vertical spatial distortion of visual objects is expected.

In a previous study [3] we assumed that the difference in discrimination threshold between vertical/horizontal ellipses and circles (i.e. their aspect ratio) reflects the amount of spatial anisotropy of the visual system. In that investigation, we found that SRP was not perfectly isotropic in more than half (55%) of the recruited sample, with the majority of the subjects who showed lower sensibility along the horizontal axis, i.e. an aspect ratio biased along the vertical [3]. Even if this mild SRA seems irrelevant in the normal population, abnormal

anisotropy is argued to affect reading performance in dyslexic children [5,6] and is found in neuro-ophthalmological conditions like neglect [7-11] and especially hemianopia [12-14].

In these cases, underestimation of the spatial extent along the horizontal coordinate is observed in the ipsilesional field when brain-lesioned observers are asked to compare the relative size of rectangles or lines presented close to the hemianopic region. In a patient with left upper quadrantanopia, for example, Dilks and colleagues reported perceptual anisotropic spatial distortion in the inferior region facing the scotoma, where rectangles and circles were perceived as vertically “stretched”. Supported by fMRI evidence, they argued the phenomenon depended on the long-term cortical reorganization of the non-responsive receptive fields in V1 following post-stroke visual deprivation [12]. In a subsequent study with ellipses and circles as stimuli, we found similar results in a patient with left inferior quadrantanopia [15].

A similar spatial distortion was reported by Kapadia [16] in terms of relative spatial mislocalization also in normal observers at the boundary of a small artificial scotoma: when the central bar of a triad of lines straddled the edge of the deprived region, it was perceived as being pulled toward its center. Upon this basis, in addition to the permanent long-term cortical reorganization postulated by Dilks and colleagues in patients with occipital lesions, short-term and reversible cortical re-modulation following an artificial perceptual deprivation has been posited in healthy subjects.

However, the misperception of spatial localization reported by the group of Kapadia occurred only when part of the triad was *within* the artificial scotoma, whereas it was not observed when it was localized *outside* the deprived region. In line with this finding, a simulated perimetric deprivation (quadrantanopia) did not induce an anisotropic spatial distortion of circles and ellipses outside the deprived region [15].

Based on these pieces of evidence, it is reasonable to assume that, contrary to long-term cortical reorganization, short-term receptive field remodulation determines spatial mislocalization across a very short extent of space that straddles the borders of the artificial scotoma: if the area under examination does not trespass on the deprived region, it is not affected.

If spatial relationship perception is involved in the same mechanisms of short-term cortical reorganization as spatial localization, it should turn anisotropic (or more anisotropic) if part of the stimuli used for its estimation localizes within the boundaries of the simulated visual amputation, in line with the finding of Kapadia and associates.

To address this issue, in this study spatial relationship perception of three normal subjects has been investigated in different conditions of simulated hemianopia by measuring the aspect ratio of elliptical targets whose boundaries were partially localized within the blind hemifield. To anticipate our results, spatial relationship perception is not affected by the cortical remodulation in the presence of simulated hemianopia, not even when part of the tested visual space localizes within its boundaries.

2. METHODS

Spatial relationship perception of three normal subjects in simulated conditions of homonymous hemianopia (left or right bilateral hemifield deprivation) has been examined in the central visual field with elliptical and circular stimuli centered to the fixation point. The extent of the artificial defect was graded as the distance of the proximal border of the nonresponsive area from the fixation point: 3 degrees, 1 degree (macular sparing), and macular splitting (the border of the scotoma bisects the fixation point).

SRA in each condition of visual deprivation has been compared with the non-simulated condition.

2.1. Measurement of spatial relationship perception

In previous investigations, we defined spatial relationship perception (SRP) as the visual function able to recognize the difference in the extent of a shape along the vertical and horizontal coordinates [3,5]. The minimum difference required to discriminate between a vertical or a horizontal ellipse and a circle is assumed to reflect the sensitivity to spatial relationships along the y- and x-coordinate, respectively [3]. Spatial relationship anisotropy (SRA) is defined as the differential sensibility to the spatial extent along the two cardinal references and is computed as x-,y-differential threshold.

The procedure was described in detail in a previous paper [3]. A staircase psychophysical algorithm (accelerated stochastic approximation [17]) is used to estimate the discrimination threshold between circles and ellipses horizontally- or vertically-oriented displayed on an LCD color monitor (1280 x 800 pixels, 10.1 inches, refresh rate 60 Hz). Each stimulus, presented on a grey background (luminance: 40 cd m⁻²), had an average size of 300 arcmin, with the contour (luminance 160 cd m⁻²) 1.8 arcmin wide at the viewing distance. At each trial and the observer was required to identify the stimulus, either as a circle or as a horizontal or vertical ellipse, according to a three alternative forced-choice response procedure (3AFC, figure 1).

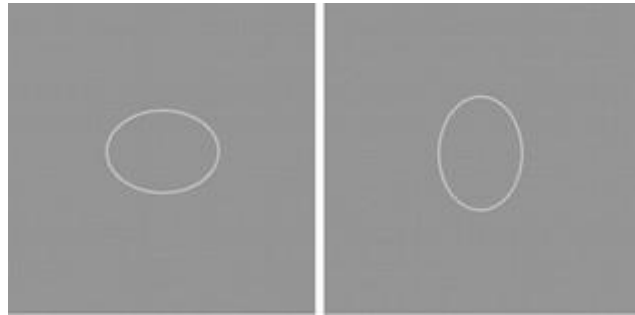


Fig. 1. Example of the elliptical targets as displayed to the subject. IR: $\pm 26\%$.

Presentation time was 200 msec which is short enough to prevent initiation and completion of saccades [18]. The x-, y-aspect ratio of the ellipses ranged from 1% to 34% with one percent point corresponding to a difference between the cardinal axes of 3.3 arcmin at the viewing distance. The examiner recorded the verbal response of the observer (“circle”, “horizontal ellipse”, “vertical ellipse”) by pressing the left or right button on a remote control. Thresholds are expressed as Interaxis Ratio (IR) that is the percent difference between the focal axis fa and the perpendicular axis pa of the elliptical stimuli, according to the formula:

$$IR (\%) = 100 [fa(x,y) - pa(y,x)] / fa(x,y)$$

It is evident from the equation that the smallest $fa(x,y) - pa(y,x)$ that makes an ellipse barely recognizable reflects the spatial relationship sensitivity of the subject under examination. The visual system is isotropic if the spatial relationship sensitivity is the same along the horizontal and vertical axis (i.e. if SRP is independent of the stimulus orientation: $fa(x) - pa(x) = fa(y) - pa(y)$). Otherwise, spatial relationship anisotropy (SRA) is computed as the difference between the discrimination threshold along the x-, y- cardinal axis (Horizontal Threshold, HT and Vertical Threshold, VT, respectively) assessed independently by using two interleaved tracks. Normative data in adult subjects have been previously reported [3].

2.2. Simulation of the hemianopic conditions

The left or right half of two neutral trial lenses were covered with a semicircular opaque filter. The occlusion was fitted to spare 3 or 1 central degree(s) of the visual field (*macular sparing*: 3 deg or 1 deg) or to bisect the fixation point (*macular splitting*). Proper calibration was achieved by using a sheet placed in front of the subject at the same viewing distance as the testing distance. A vertical line was presented at the center of the sheet with two couples of parallel lines (green and blue) on each side of the fixation point so that their linear distance from the midline in metric units was made correspondent to the angular extent of the central field sparing (green: 1 deg; blue: 3 deg). The subject, with one eye covered, trimmed the position of the opaque film by moving it toward the center of the lens until the line corresponding to the extent of sparing to be tested disappeared. The procedure was repeated three times to verify the correct positioning of the filters (figure 2).

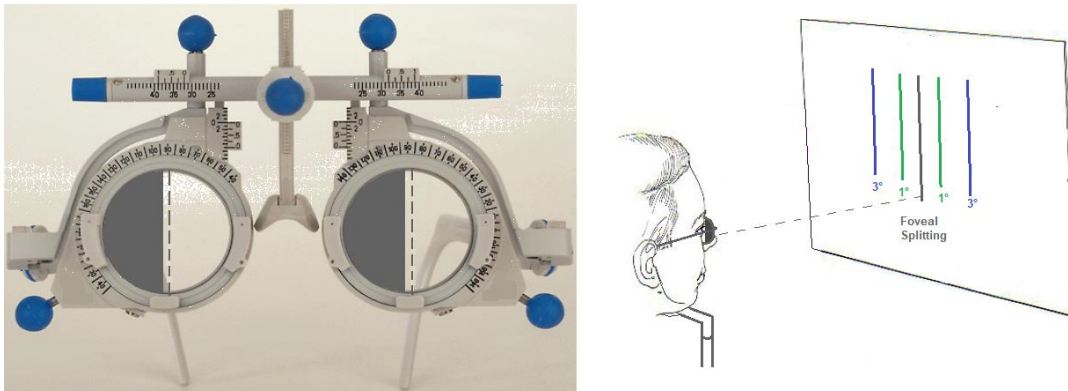


Fig. 2. The appearance of the semicircular sectors fitted on the left /right side of both lenses to reproduce a homonymous right (in this case) or left hemianopia and the calibration system.

Standard Automated Perimetry (30 central degrees, Octopus 301, Haag Streit, Bern,) was then performed to make sure the calibration was correct (figure 3).

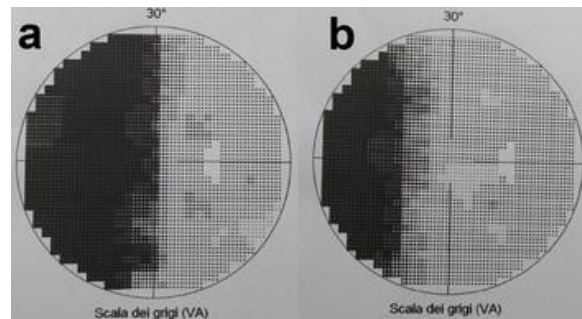


Fig. 3. Standard Automated Perimetry (30 central degrees, grayscale map), left simulated homonymous hemianopia in the right eye; a: foveal splitting, b: 3 degrees macular sparing.

2.3. Observers

Three subjects (all females) participated in the study after giving their informed consent: AM, coauthor, FG, and CC, (age: 21,22, and 22 respectively). AM and FG wore contact lenses for a bilateral myopic defect of -3.50 and -2 spherical diopters, respectively. CC had normal visual acuity. AM was left-handed, FG and CC were right-handed. The ophthalmological examination (comprehensive of biomicroscopy of the anterior segment, funduscopy, tonometry, visual acuity estimation, prismatic cover test, and refraction assessment) of the three volunteers was unremarkable, with best-corrected visual acuity 60/60. Participants were all naïve to psychophysical testing, so each subject underwent a short practice session to become acquainted with the experimental procedure before running the examination.

Viewing was binocular. Immediately after placing the semicircular sectors on the left /right side of both lenses to reproduce the hemianopia, the session started with the onset of a white flickering point (34.2 min arc wide, 6.6 Hz, total duration: 1000 msec) at the center of the screen, aimed to stimulate fixation. Immediately after the last winking, targets were displayed for 200 msec.

The examination took place in a dim room (illuminance 0.15 lux) during the late morning. The observer sat comfortably on a chair with the head placed on a chinrest 70 cm in front of the screen. Each trial was randomized. After each trial, a resting period of about 10 minutes was allowed.

Subjects were administered the test three times per experimental condition (that were: no occlusion, 3° of macular sparing, 1° of macular sparing, and foveal splitting) for the left and right simulation, to obtain 12 estimates for right simulated hemianopia (RH_{sim}) and 12 estimates for left simulated hemianopia (Rh_{sim}) in each participant. The experimental conditions were administered in randomized order.

2.4. Statistical analysis

The Kruskal-Wallis test was performed to assess if spatial relationship perception differed significantly between the three subjects in natural conditions (without visual deprivation). Subsequently, Friedman Test was used to analyze the trend of SRP as a function of the macular sparing for each subject.

To assess the interaction between sparing vs, laterality (left/right deprivation) vs. sparing x laterality, nonparametric two-way analysis of variance was performed for each subject and then for the whole sample.

3. RESULTS

The median VT, HT, and SRA referred to each participant in non-simulated conditions are reported in table 1.

Table 1. Median RI% (IQR). Non-simulated condition.

	HT	VT	SRA
Subject 1 (AM)	3 (2.25÷3.75)	2 (1.25÷2)	1 0.25(÷2.50)
Subject 2 (FG)	1 (1÷2.50)	3 (2.25÷4.50)	-2 (-2÷ -1.25)*
Subject 3 (CC)	2 (1.25÷2.75)	2 (2÷3.50)	-1 (-1÷ -0.25)
<i>P</i>	KW(2.33): <i>P</i> = .31	KW(3.30): <i>P</i> = .19	KW(6.38): <i>P</i> = .04

Kruskal-Wallis test revealed no differences in the horizontal and vertical threshold of the three subjects. It should be noted that spatial relationship perception was more anisotropic in subject FG.

A two-way analysis of variance performed on the cumulative data showed no interaction of spatial relationship perception with macular sparing, laterality, and sparing x laterality (table 2 and figure 4).

Table 2. Two-way ANOVA in the whole sample. SRP in homonymous hemianopia as a function of macular sparing, laterality, and sparing x laterality.

Whole sample	HT	VT	SRA
Sparing	F(0.36): P= .69	F(2.18): P= .12	F(1.38): P= .26
Left /right	F(1.00): P= .32	F(2.39): P= .12	F(3.22): P= .07
Sparing x left/right	F(1.09): P= .34	F(1.03): P= .36	F(1.92): P= .15

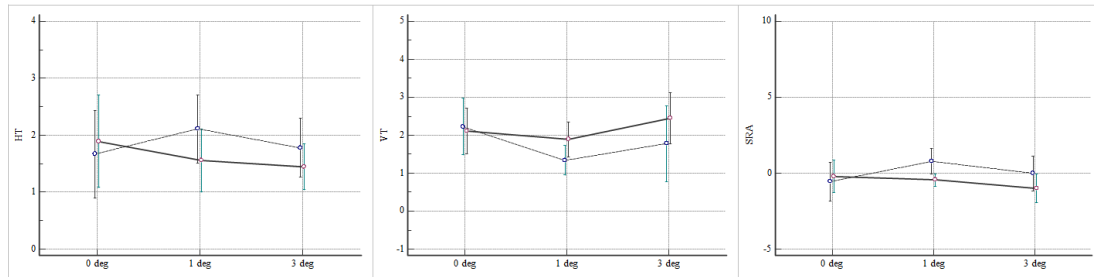


Fig. 4. Spatial relationship perception as a function of sparing in the whole sample. Bars: IQR. Continuous lines: simulated right hemifield (RH_{sim}); dashed lines: simulated left hemifield (Lh_{sim}).

Table 3 shows the three variables that characterize SRP as a function of central sparing in each participant. Friedman test did not reveal significant effects of right and left simulated hemianopia at the three levels of macular involvement, except for the anisotropic subject FG, who showed reduced anisotropy as the macular sparing was made smaller. In this case, SRA was higher in the sparing 1 deg and splitting condition compared to the sparing 3 deg in RH_{sim}, and in the sparing 1 deg compared to the sparing 3 deg and natural condition in LH_{sim}.

Table 3. SRP in right and left simulated homonymous hemianopia as a function of the macular sparing in the three subjects, Median (IQR). The natural condition (no simulated hemianopia) is added as a reference.

Subj. 1 (AM)	SIMULATED RIGHT HEMIANOPIA			SIMULATED LEFT HEMIANOPIA		
	HT	VT	SRA	HT	VT	SRA
(Natural cond.)	3(2.25÷3.75)	2(1.25÷2)	1(0.25÷2.50)	3(2.25÷3.75)	2(1.25÷2)	1(0.25÷2.50)

Sparing 3 deg	2(2÷2)	2(1.25÷2)	0(0÷0.75)	2(2÷2.75)	1(1÷1)	1(1÷1.75)
Sparing 1 deg	2(1.25÷2)	1(1÷1.75)	0(0÷0)	2(1.25÷2)	1(1÷1.75)	1(-0.50÷1)
Splitting	1(1÷1.75)	2(2÷2.75)	-1(-1.75÷-0.25)	1(1÷3.25)	2(1.25÷2.75)	-1(-1.75÷2)
<i>P</i>	F(5): <i>P</i> = .05	F(1.63): <i>P</i> = .27	F(3.33): <i>P</i> = .09	F(0.76): <i>P</i> = .55	F(1): <i>P</i> = .45	F(0.34): <i>P</i> = .79

Subj. 2 (FG)	SIMULATED RIGHT HEMIANOPIA			SIMULATED LEFT HEMIANOPIA		
	HT	VT	SRA	HT	VT	SRA
(Natural cond.)	1(1÷2.50)	3(2.25÷4.50)	-2(-2÷ -1.25)	1(1÷2.50)	3(2.25÷4.50)	-2(-2÷ -0.25)
Sparing 3 deg	1(1÷1)	3(3÷3.75)	-2(-2.75÷ -2)	1(1÷1.75)	2(2÷2)	-1(-1÷ -0.25)
Sparing 1 deg	1(1÷1.75)	2(2÷2)	-1(-1÷ -0.25)	2(2÷3.50)	1(1÷1.75)	1(0.25÷2.50)
Splitting	2(1.25÷2)	2(2÷2.75)	-1(-1÷ -0.25)	1(1÷1.75)	2(2÷2.75)	-1(-1.75÷)
<i>P</i>	F(0.73): <i>P</i> = .56	F(1.94): <i>P</i> = .22	F(7.37): <i>P</i>= .01*	F(3.14): <i>P</i> = .10	F(3.33): <i>P</i> = .09	F(6.70): <i>P</i>= .02*

Subj. 3 (CC)	SIMULATED RIGHT HEMIANOPIA			SIMULATED LEFT HEMIANOPIA		
	HT	VT	SRA	HT	VT	SRA
(Natural cond.)	2(1.25÷2.75)	2(2÷3.50)	-1(-1÷ -0.25)	2(1.25÷2.75)	2(2÷3.50)	-1(-1÷ -0.25)
Sparing 3 deg	1(1÷1.75)	2(2÷2.75)	-1(-1÷ -1)	2(1.25÷2)	1(1÷4)	0(-2.25÷0.75)
Sparing 1 deg	1(1÷2.50)	2(2÷2.75)	-1(-1÷ -0.25)	2(2÷2)	1(1÷1.75)	1(0.25÷1)
Splitting	3(1.50÷3.75)	1(1÷2.50)	0(0÷2.25)	2(1.25÷2)	2(1.25÷3.50)	-1(-1.75÷0.50)
<i>P</i>	F(1.37): <i>P</i> = .33	F(4.75): <i>P</i> = .05	F(2.71): <i>P</i> = .13	F(0.57): <i>P</i> = .65	F(1.63): <i>P</i> = .27	F(1.75): <i>P</i> = .25

To further analyze the interactions between spatial relationship perception, homonymous macular sparing, and laterality, a two-way analysis of variance has been performed with HT, VT, and SRA as the dependent variable, and sparing, laterality, and sparing x laterality as independent variables. Significance levels are reported in table 4 for AM, FG, and CC.

Table 4. Two-way ANOVA in individual subjects. SRP in right and left homonymous hemianopia as a function of macular sparing and laterality.

Subj. 1(AM)	HT	VT	SRA
Sparing	F(0.69): <i>P</i> = .51	F(3.57): <i>P</i> = .06	F(1.60): <i>P</i> = .24
Left /right	F(0.69): <i>P</i> = .42	F(1.28): <i>P</i> = .27	F(1.63): <i>P</i> = .22
Sparing x left/right	F(0.23): <i>P</i> = .79	F(0.42): <i>P</i> = .66	F(0.13): <i>P</i> = .87

Subj. 2(FG)	HT	VT	SRA
Sparing	F(2.37): $P= .13$	F(7): $P= .01^*$	F(6.64): $P= .01^*$
Left /right	F(2): $P= .18$	F(9): $P= .01^*$	F(7.14): $P= .02^*$
Sparing x left/right	F(2.37): $P= .13$	F(3.): $P= .08$	F(3.07): $P= .08$

Subj. 3(CC)	HT	VT	SRA
Sparing	F(0.83): $P= .44$	F(0.23): $P= .79$	F(1): $P= .39$
Left /right	F(0.07): $P= .79$	F(0.03): $P= .85$	F(0): $P= 1.00$
Sparing x left/right	F(.14): $P= .35$	F(0.63): $P= .54$	F(2.03): $P= .17$

As shown, no interaction was found between spatial relationship perception and macular sparing, laterality, and macular sparing x laterality in AM and CC. Again, in FG a significant effect of the extent of macular sparing and laterality on VT and SRA is observed: vertical threshold and spatial anisotropy were lower at 0 and 1 deg of sparing than at 3 deg (VT: $P= .009$; SRA: $P= .01$) and in LH_{sim} vs RH_{sim} ($P= .01$ and $P= .02$, respectively: figure 5).

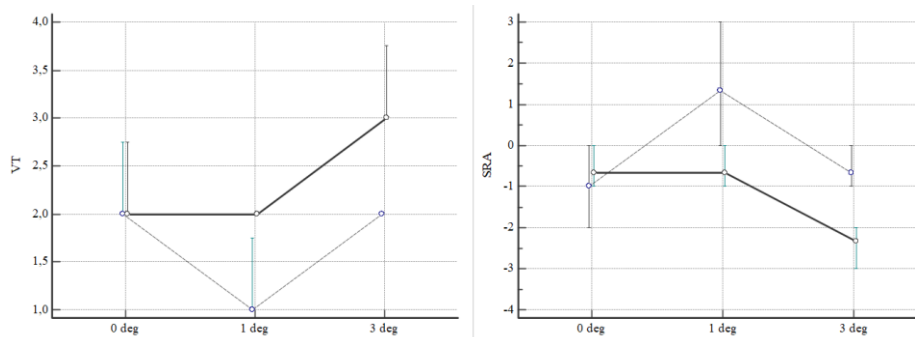


Fig. 5. Change of spatial relationship perception as a function of sparing in subject 2 (FG). Bars: IQR. Continuous lines: RH_{sim} ; dashed lines: Lh_{sim} .

4. DISCUSSION

According to a strand of research, patients with visual field loss after brain injury exhibit long-term cortical reorganization: the receptive fields within the deafferented cortex expand and respond to stimuli that normally activate an adjacent region of the visual space [12]. The perceptive result of this remapping is positional misjudgment (line bisection error [19,20]), perceptual bidimensional distortions [21-23], and a misestimate of the aspect ratio of shapes like rectangles and circles [12,14,15].

In a patient suffering from post-stroke left inferior quadrantanopia, spatial anisotropy was found to be abnormal near the boundary of the deprived region, decreased as a function of the distance from the blind area, and turned isotropic at about 6 degrees from the scotoma

[15]. This trend supports the long-term cortical reorganization of the nonresponsive receptive fields subserving the scotomatous region, as stated by Dilks and colleagues.

Cortical reorganization is posited to take place even in the presence of an artificial scotoma [16]. Like in the case of brain-injured patients, (reversible) short-term remapping in the normal primary visual cortex is shown to produce biased positional judgment, as shown by Kapadia and colleagues who studied the effect of an artificial scotoma on the spatial localization of triads of lines.

The psychophysical estimate of the distance of the middle one of three stacked horizontal bars to the top or bottom one at different extents from the center of the scotoma revealed a positional bias toward the scotoma when part of the triad was inside the deprived region. And yet, the effect disappeared if the three bars were outside the scotoma, even if as close as to overlap its lower limit.

Contrary to spatial localization, our finding shows that spatial relationship perception is insensitive to the cortical remodulation induced by simulated hemianopia, not even when part of the visual space under investigation is within the deprived region.

The cumulative analysis of the observations, in fact, reveals that SRP is not affected by the extent of the macular sparing irrespective of the left or right side of the visual loss.

In sum, if the enlargement of the deafferented cortical receptive fields reduces the ability to estimate the relative position of close stimuli, it does not generate an asymmetry in the visual processing along the cardinal axes (assuming this enlargement is spatially uniform).

The discrepancy between our results and the finding of Kapadia and colleagues is in line with a previous study by van Ee and Erkelens [24]. The authors demonstrated that the functional (and, arguably, anatomical) mechanism that determines spatial relationship perception is dissociated from the mechanism responsible for perceived direction, so that their susceptibility to simulated visual deprivation may be different. Further consideration of this issue is tangential to this paper, but it is worth considering that the visual space recruited by our stimuli was consistently wider compared to the stimuli used by Kapadia (300 arcmin vs. 42 x 102 arcmin). Arguably, the positional judgment studied by Kapadia and colleagues operates on a local scale, whereas spatial relationship perception depends on global visual processing. Consequently, the two tasks may involve different visual channels with different neuronal responses to short-term cortical reorganization. Indeed, it is known that the parvocellular (*sustained*) channel is more sensitive to high spatial frequencies, that is to say, more sensitive to detailed local analysis whereas the magnocellular (*transient*) pathway is preferentially involved in the processing of global configurations [25,26]. The possibility that short-term cortical remodulation involves selectively the parvocellular system requires further investigation.

It remains that the perceptual response to the hemianopic deprivation seems conditioned by the way spatial relationships are processed in normal (no deprived) conditions, as suggested by the data from subject FG. Contrary to the other two participants, FG showed a slight anisotropic perception of the visual space and, in fact, this was the only case affected by the hemianopic deprivation. In FG, anisotropy and the spatial distortion along the horizontal axis tended to normalize as the distance of the boundary of the hemianopic scotoma from the fixation point decreased. Starting from the considerations of Regan and Hamstra [4], it cannot be ruled out that the pools of detectors selective for horizontal and vertical axes, when unbalanced, are more susceptible to short-term cortical remapping. To shed light on this issue, this trend should be investigated by recruiting samples that in normal conditions exhibit different anisotropic behaviors.

Whether the robustness of SRP to the cortical remapping induced by the artificial hemianopia depends on a biasing effect stemming from the procedure (type of stimuli) adopted, is an issue to be considered. As a matter of fact, curvilinear stimuli are robust toward occlusion, because the response of V4-neurons tuned to curvatures in the presence of partial occlusion is stronger compared to other shape-selective neurons [27,28]. For this reason, circles and ellipses risk making the measurement not sensitive enough and could

have been replaced by squares and rectangles; yet, curvilinear stimuli seemed to us more suitable since they have no edges, so the judgment based on the angle of intersection between diagonals is avoided [4].

5. CONCLUSION

In conclusion, unlike localization judgment, spatial relationship perception appears to be insensitive to short-term cortical reorganization induced by a simulated visual deprivation: it is, in fact, substantially unaffected by simulated homonymous hemianopic defects, irrespective of the macular sparing and laterality. However, the response of the visual system to an artificially induced hemianopia is conditioned by the amount of spatial relationship isotropy in normal (non-simulated) conditions. Further investigation is needed to better clarify the effect hemianopic visual deprivation has on spatial relationship perception.

CONSENT

All authors declare that a written informed consent for publication was obtained from the three participants in the study.

ETHICAL APPROVAL

This study was approved as a Bachelor's dissertation by the Ethics Committee of the University of Turin (Date:12/11/2021/No. 89329) and was performed under the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTEREST

The authors have declared no competing interests.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration with all authors. Author AM performed the bibliographic research and tested the patients. Author CA designed the study, performed the statistical analysis, and revised the manuscript. Author CR wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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