



Visuo-spatial attention to the blind hemifield of hemianopic patients: Can it survive the impairment of visual awareness?

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ARTICLE INFO

Keywords:

Visuo-spatial attention
Perceptual awareness
Hemianopia
fMRI
Functional connectivity

ABSTRACT

The general aim of this study was to assess the effect produced by visuo-spatial attention on both behavioural performance and brain activation in hemianopic patients following visual stimulus presentation to the blind hemifield. To do that, we tested five hemianopic patients and six age-matched healthy controls in an MRI scanner during the execution of a Posner-like paradigm using a predictive central cue. Participants were instructed to covertly orient attention toward the blind or sighted hemifield in different blocks while discriminating the orientation of a visual grating.

In patients, we found significantly faster reaction times (RT) in valid and neutral than invalid trials not only in the sighted but also in the blind hemifield, despite the impairment of consciousness and performance at chance. As to the fMRI signal, in valid trials we observed the activation of ipsilesional visual areas (mainly lingual gyrus – area 19) during the orientation of attention toward the blind hemifield. Importantly, this activation was similar in patients and controls. In order to assess the related functional network, we performed a psychophysiological interactions (PPI) analysis that revealed an increased functional connectivity (FC) in patients with respect to controls between the ipsilesional lingual gyrus and ipsilateral fronto-parietal as well as contralesional parietal regions. Moreover, the shift of attention from the blind to the sighted hemifield revealed stronger FC between the contralesional visual areas V3/V4 and ipsilateral parietal regions in patients than controls. These results indicate a higher cognitive effort in patients when paying attention to the blind hemifield or when shifting attention from the blind to the sighted hemifield, possibly as an attempt to compensate for the visual loss.

Taken together, these results show that hemianopic patients can covertly orient attention toward the blind hemifield with a top-down mechanism by activating a functional network mainly including fronto-parietal regions belonging to the dorsal attentional network.

1. Introduction

In everyday life attention plays an important role in guiding behaviour by selecting relevant information among the enormous amount of stimuli in the environment.

The assessment of the orienting component of attention has been a topic of interest for a long time, with the main aim of casting light on its neural basis. The dichotomy model (Corbetta and Shulman, 2002, 2008) postulated the existence of a bilateral dorsal network activated by

endogenous and exogenous attention-directing spatial cues (top-down and bottom-up voluntary allocation of attention) and a right ventral network that responds to unexpected task-related stimuli appearing outside the attentional focus. The former responds to symbolic cues indicating to shift attention to a spatial location and involves cortical areas such as bilateral frontal eye fields (FEF), intraparietal sulcus/superior parietal lobe (IPS/SPL), the middle frontal gyrus (MFG) (Hopfinger et al., 2000) and exerts top-down influence on visual areas. The latter involves the right temporo-parietal junction (TPJ), the ventral

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<https://doi.org/10.1016/j.neuropsychologia.2020.107673>

Received 31 January 2020; Received in revised form 13 October 2020; Accepted 4 November 2020

Available online 10 November 2020

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frontal cortex (VFC), insula, IFG, MFG. Several studies have provided further knowledge on the segregated and integrated nature of these two networks during the execution of attentional tasks (Vossel et al., 2012, Diquattro et al., 2014) or during resting state (Fox et al., 2006). In 2013, Macaluso and Doricchi proposed a more complex model of attention, linking together the concepts of attention and prediction. They found that in a complex, naturalistic environment, the posterior parietal cortex (PPC) is activated by salient visual stimuli triggering orientation of spatial attention. This indicates that also saliency maps (bottom-up signals) representing the priority of visual stimuli are located in the dorsal attentional network. At the same time, they suggested that the activation of the ventral attentional network is mediated by internal goals and expectations (Natale et al., 2010) as the mere bottom-up signal is not sufficient (Indovina and Macaluso, 2007). Therefore, according to their model, the ventral attentional system performs a dynamic trial-by-trial evaluation of the cue-target contingency considering expectations and predictions and sending this match-mismatch information to the dorsal system to update higher order salience and priority maps that modulate the activity of the occipital cortex.

Orienting moves the focus of attention toward a specific location in space, but can this shift of attention modulate the activation of visual cortex? In 2007, Sylvester et al. (Sylvester et al., 2007) observed a peak of activity in visual areas for the attended location and a suppression of nearby cortex when asking participants to shift attention to a peripheral position, confirming the possibility that attention modulates the activation of visual areas. Further support comes from studies combining functional magnetic resonance (fMRI) and transcranial magnetic stimulation (TMS) over regions belonging to the attentional networks. Ruff et al. (2006; 2008) found an increase in the activation of visual cortex as a consequence of TMS applied over FEF and IPS, with a bigger effect produced by TMS over right FEF. In 2010, Blankenburg et al. (Blankenburg et al., 2010) confirmed the indirect modulation produced on visual cortex activity by TMS applied over PPC, thus highlighting the importance of the current attentional state for modulating the influence of right PPC on occipital visual areas. Similar results have been obtained by simultaneously applying TMS and recording EEG. As an example, Capotosto et al. (Capotosto et al., 2009) found that FEF and IPS may exert top-down influence on visual processing via disruption of alpha desynchronization of brain oscillations (for a review see Driver et al., 2010). Finally, new findings have been obtained by assessing effective, directed connectivity among regions of interest during the execution of an attentional task. Granger causality (Roebroek et al., 2005) and Dynamic Causal Modelling (DCM Friston et al., 2003; Vossel et al., 2012) confirmed that IPS and FEF exert a top-down influence on visual areas during the spatial orienting of attention.

Visual awareness represents the subjective sensation of seeing something (Block, 1995) and is strictly related to visuo-spatial attention as visual stimuli can more easily be detected or identified when attention is oriented toward a given location (Posner, 1980). However, the relationship between visual awareness and attention is still under debate. Indeed, while it is quite clear that attention and awareness are distinct processes, the relationship among them is still an open topic: is attention necessary and sufficient for consciousness to arise?

A positive response would lead to the conclusion that no consciousness can exist with a complete lack of attention. Instead, a negative response would support a dissociation between attention and awareness (Lamme, 2004; for a review, see Koch and Tsuchiya, 2006).

Different studies go in the direction of this interpretation by showing that attention can influence neural activity despite stimuli remaining unconscious (Wyart and Tallon-Baudry 2008; Bahrami et al., 2007). Further pieces of evidence in favour of this hypothesis is represented by results by Chica et al. (Chica et al., 2013) who reported the existence of two different brain networks that mediate awareness and visuo-spatial attention: a spatial attention-independent network involving bilateral temporo-occipital areas, SPL, right Angular Gyrus and left IPS associated with conscious report and a spatial attention-dependent network

involving left FEF and right IPL, encoding attended stimuli. Moreover, they observed that conscious perception depends on the level of bottom-up activation of sensory cortices, the level of vigilance and the top-down amplification produced by brain activity in higher association regions (Chica et al., 2016). Studies of structural connectivity located the neural basis of the interaction between attention and consciousness in the third branch of the superior longitudinal fasciculus (SLF III), a pathway that mediates attentional modulation and conscious perception (Chica et al., 2018). For understanding the relationship between attention and consciousness an additional problem is represented by the wide variety of forms that attention and consciousness can assume, leading to the idea that different kinds of attention can be produced by different kinds of consciousness (for a review, see Marchetti, 2012).

A clinical population that can shed light on the relationship between visual attention and consciousness is represented by hemianopic or quadrantanopic patients, characterized by visual impairment in a half or in a quadrant of the visual field as a consequence of a brain lesion in the contralateral occipital lobe or central visual pathways. Some of these patients might show “blindsight”, that is, the unconscious ability to detect or discriminate some features of stimuli presented to the blind hemifield (see a recent discussion by Danckert et al., 2019). Kentridge et al. (1999a, 1999b; 2004), studying a hemianopic patient with blindsight, GY, found faster reaction time (RT) and higher accuracy for valid than invalid trials in an endogenous attentional paradigm even when the stimuli were presented in the blind hemifield. This confirmed that attention is not sufficient for awareness but can still lead to a behavioural advantage in processing visual stimuli in the blind hemifield. Some years later Kentridge et al. (2008) found the same results in healthy participants using meta-contrast masking, thus confirming the idea that attention and awareness are different both as cognitive processes and in terms of their neural substrates. Studies on deficits of spatial attention and possible rehabilitation techniques in hemianopics are infrequent and most neuropsychological (Lädavas et al., 1990, 1994) and neuroimaging studies have been performed on hemineglect patients (see for example Robineau et al., 2019; Umarova et al., 2011). Hemineglect is a visuo-spatial impairment characterized by the failure in orienting attention toward the contralesional hemifield, a bias toward the ipsilesional space and general disorders of awareness while visual skills are preserved.

Few studies have been carried out to assess whether hemianopic patients without hemineglect could orient attention toward the blind hemifield and how the underlying neural mechanism works in terms of whole brain activation and functional connectivity. They could shed light on the neural basis of visuo-spatial attention toward blind areas of the visual field as a result of post-chiasmatic pathways or cortical areas damage. Besides the interest of understanding the cerebral and cognitive substrate of unconscious attention, positive neural evidence would represent a starting point in the development of rehabilitation techniques based on the use of covert attention toward the blind hemifield (Zihl, 2010). To achieve that, we tested behavioural performance and recorded the fMRI signal during the execution of an endogenous visuo-spatial attentional task in a group of six hemianopic patients and six healthy control participants. The inclusion of a control group performing the same task with the same stimulus features as patients was not accidental. Indeed it allows to assess behavioural and neural differences among cognitive processes of paying attention to visible stimuli either in both hemifields of controls or in the sighted hemifield of patients, and to unseen stimuli in the blind hemifield of patients.

In the current study, we asked participants to discriminate stimulus orientation in order to assess the effect of visuo-spatial attention on a feature usually related to the activation of V1 (Hubel and Wiesel, 1974; Boynton, 2005). We used an endogenous rather than exogenous cue because this kind of attention has demonstrated to be dissociable from consciousness (Wyart et al., 2012) and to exert weak influence on conscious perception of near-threshold stimuli (for a review see Chica and Bartolomeo, 2012). Moreover we decided to use a highly predictive

symbolic cue (75%), as it has a stronger effect in modulating RT and increasing the activation of visual areas (Vossel et al., 2012). Finally, we assessed the modulation produced by unconscious orienting or reorienting of attention on functional connectivity (FC) between ipsilesional or contralesional primary visual cortex and the whole brain by performing a Psychophysiological Interactions (PPI) analysis (O'Reilly et al., 2012).

2. Method

2.1. Participants

We recruited six male quadrantanopic and hemianopic patients (mean age = 59.3 years, SD = 8.29, see Table 1), right-handed, with long-standing post-chiasmatic lesions causing visual field loss as assessed with Humphrey campimetry (see Table 1 and Fig. 1) and six age-matched healthy participants (3 females; mean age = 60 years, SD = 10.16) with no history of neurological disorders. To be included in the study, patients had to present Homonymous Hemianopia or Quadrantanopia as a consequence of brain damage that had occurred more than three months before the first testing session, no other neurological or psychiatric disorder, a visual campimetry showing the width and location of the blind field and a T1-weighted MRI image showing the brain damage. Moreover, they were examined to exclude general cognitive impairment and Hemineglect, by means of a battery of tests including Mini-Mental State Examination (Folstein et al., 1975), Line Bisection (Schenkenberg et al., 1980), Diller letter H cancellation (Diller et al., 1974) and Bells cancellation (Gauthier, 1989). All participants had normal or corrected-to-normal visual acuity. Informed consent was obtained after they had been fully informed about the experimental procedures and their right of quitting at any time. The study was approved by the Ethics Committee of the European Research Council and of the Azienda Ospedaliera Universitaria Integrata of Verona.

Using the 1 mm³ isotropic T1-weighted image acquired for each patient, we created a mask of each lesion to better visualize its location and extent. We used the bias-field corrected T1-weighted image in native space to create a mask of each lesion by drawing it using the software ITK-SNAP (Yushkevich et al., 2006). The lesion mask was then normalized to the standard MNI space with a spatial resolution of 1 mm, using linear transformation (FLIRT). Finally, we used the software MRICron (Rorden and Brett, 2000) to create two images representing the overlap between left (Fig. 2, upper panel) or right (Fig. 2, lower panel) brain lesions on the ch2. nii template brain (Holmes et al., 1998).

2.1.1. Experimental procedure

We used a Posner-like endogenous visuo-spatial attentional task (Posner, 1980) to assess whether hemianopic patients could covertly orient or reorient attention toward the blind or the sighted hemifield. Patients and healthy volunteers were asked to discriminate the orientation of a grating (vertical or horizontal) by pressing as quickly as possible one of two buttons, counterbalanced across participants. At the beginning of the trial (see Fig. 3) a central cue (arrow) was shown for 200 ms to indicate the hemifield where the stimulus was most likely to appear. After the cue disappeared there was an interval between 300 and 600 ms before presentation of a target with a duration of 1500 ms. During this time, participants were to respond even when the stimulus was not consciously perceived in the blind hemifield. In valid trials, the grating appeared in the attended position (75% probability), while in invalid trials it appeared in the unattended position corresponding to the symmetrical position in the opposite hemifield (25% probability) (see Fig. 3). Finally, in neutral trials, a central double arrow (cue) was presented, followed by a lateralized grating either in the sighted or the blind hemifield.

The stimulus was generated using E-Prime 2.0 software and consisted of a single black-and-white 4° × 4° grating oriented horizontally (0°) or vertically (90°) on a grey background of 17.72 cd/m² luminance,

with a spatial frequency of 0.875 c/° and flickering at the fundamental frequency of 30 Hz. Contrast modulation and retinal eccentricity were adjusted for each patient in order to ensure that the visual stimulus could not be consciously perceived (see Table 2 for details). To identify the borders of the blind area and to be able to position visual stimuli accordingly, we performed a binocular visual campimetry in a separate behavioural session prior to the fMRI experiment (for a further description of the procedure, see Sanchez-Lopez et al., 2017). Based on the results of the campimetry, we chose a specific stimulus position at the beginning of this fMRI session. Concerning contrast modulation, we started the training by applying the same value used in previous EEG and behavioural experiments, asking patients to verbally confirm whether they could not see the grating. Otherwise, the contrast was gradually reduced until the patient confirmed he/she could not see it. In each healthy participant, stimulus eccentricity and contrast modulation was chosen by matching him/her with one specific patient. The association between response button and stimulus orientation was counterbalanced across participants. Two out of six patients performed the task with the right hand because of motor problems (thumb and finger). Also in this case, the response buttons were chosen by matching a healthy participant with a specific patient.

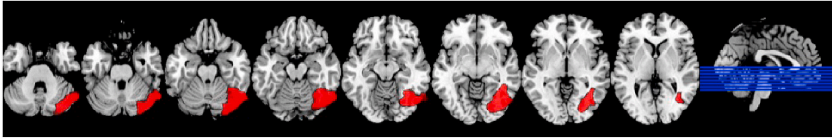
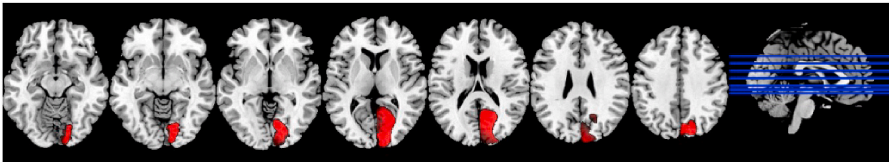
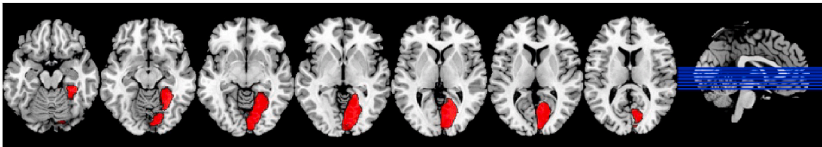
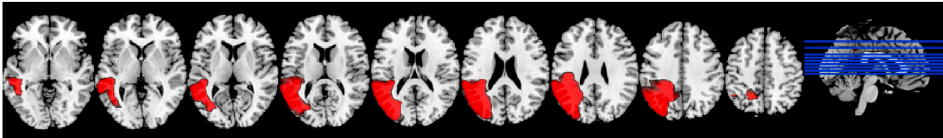
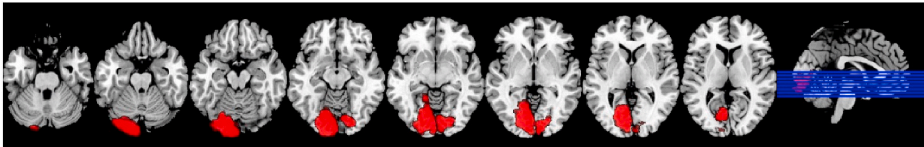
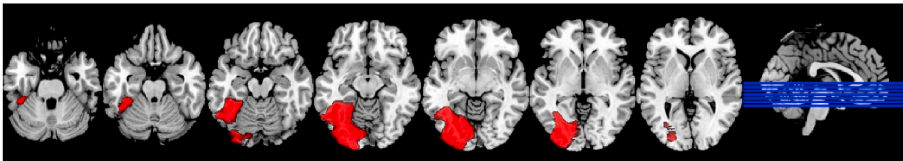
Patients were trained on the attentional task outside the scanner using the same stimulus position as that previously chosen with the visual mapping procedure. Controls performed the same kind of training with the stimulus in the same position of age-matched single patients. Following this training, all participants were tested inside the MRI scanner. The visual stimulus was presented on a monitor (resolution: 1920 × 1080 pixel) with a refresh rate of 60 Hz, positioned at the back of the MRI scanner bore, using the same parameters (luminance, duration, position) as in the training. Participants viewed the monitor via a double mirror mounted on the head coil. The screen subtended a visual angle of 20 × 11°. The experimental paradigm consisted of a mixed-design with sustained covert attention oriented toward the same visual quadrant during a whole block, while cue validity and visual hemifield stimulation changed in a random order within the same block. We used a blocked rather than a randomized visual cueing paradigm to make the task easier for patients and to assess the effect produced by sustained visuo-spatial attention.

The fMRI session consisted of 4 runs, each lasting 260 s. Each run included five experimental blocks of sustained attention counterbalanced among runs and interleaved by six 14 s rest periods. Within each block, valid and invalid condition were alternated in a pseudo-random order. Each experimental block was composed by 12 trials and gratings' orientation was alternated in a pseudo-random order, for a total amount of 60 trials per run. Within each block, 75% of trials were valid (attention directed towards the same location as the stimulus) while the remaining 25% were invalid (stimulus and attention at different locations) trials. In each run, one entire block was dedicated to a neutral condition characterized by a bilateral allocation of attention and the presentation of a lateralized stimulus. During the whole session, an MRI compatible camera was used to check for the occurrence of ocular movements. Verbal feedback was given to participants concerning their ability to maintain fixation.

2.1.2. MRI acquisition and preprocessing

Scanning took place in a 1.5 T Philips MRI scanner at the Borgo Roma Hospital in Verona, using a 15-channel head coil. Functional images were acquired covering almost the whole brain by recording from slices running parallel to the calcarine fissure. 130 vol were acquired (T2*-weighted echo-planar imaging, with 32 slices acquired in an ascending order, repetition time = 2000 ms, echo time = 35 ms, field of view = 230 × 230, FA = 30°) in each run and 4 dummy scans were added at the beginning of each run in order to avoid T1 saturation. Preprocessing and statistical analyses were performed using FSL v6.0 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL>) (Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012). During preprocessing, non-brain tissue was

Table 1
Patient's clinical description.

Patient (age)	Lesion/Visual Deficit
AP (49)	<p>Lesion involving the inferior anterolateral portion of the right occipital lobe with extension to the posterior part of the temporal lobe and the upper part of the right cerebellar hemisphere. Partial sparing of the Calcarine fissure.</p> <p><i>Visual Defect:</i> Upper left homonymous quadrantanopia caused by Meningioma removal in May 2016.</p> <p><i>T1-weighted image:</i> March 2017 <i>fMRI session:</i> 07/2017</p> 
BC (70)	<p>Lesion involving the medial portion of the right occipital lobe, with an extension over the parieto-occipital fissure. There is an important involvement of the lingual and fusiform gyri involving the occipital pole, with alterations of the Calcarine fissure.</p> <p><i>Visual Defect:</i> Lower left homonymous quadrantanopia caused by an ischemic stroke in August 2016.</p> <p><i>T1-weighted image:</i> May 2017 <i>fMRI session:</i> 09/2017</p> 
GB (66)	<p>Lesion involving the vascular territory of the right posterior cerebral artery, including the calcarine fissure as well as the lingual and fusiform gyrus.</p> <p><i>Visual Defect:</i> Left lateral homonymous hemianopia caused by an ischemic stroke in October 2017.</p> <p><i>T1-weighted image:</i> May 2018 <i>fMRI session:</i> 05/2018</p> 
AN (57)	<p>Left temporo-parietal lesion as consequence of a craniotomy to remove the consequences of brain hemorrhage. The lesion involves the left temporo-parietal lobe, the middle occipital gyrus, the occipital lobe and the upper portion of the left optic radiations.</p> <p><i>Visual Defect:</i> Right lateral homonymous hemianopia caused by a cerebral hemorrhage in November 2013.</p> <p><i>T1-weighted image:</i> April 2017 <i>fMRI session:</i> 08/2017</p> 
ML (57)	<p>Lesion of both inferior portions of the occipital lobes, more evident on the left side that involves the occipital pole, lingual and fusiform gyrus.</p> <p><i>Visual Defect:</i> Right lateral homonymous hemianopia caused by an ischemic stroke in June 2016.</p> <p><i>T1-weighted image:</i> November 2018 <i>fMRI session:</i> 11/2018</p> 
DD (57)	<p>Lesion involving the left inferior-lateral part of the occipital lobe with extension to the lingual and fusiform gyri. Laterally, the lesion is below the lateral occipital sulcus.</p> <p><i>Visual Defect:</i> Upper right quadrantanopia caused by a cerebral thrombosis with cortical and cerebellae occipital stroke in June 2016.</p> <p><i>T1-weighted image:</i> October 2017 <i>fMRI session:</i> 11/2017</p> 

Neuroradiological description of the lesion, type, onset of the injury, date of the acquisition of the T1-weighted image and of the recording of the fMRI session and multi-slice representation of the T1-weighted images with the overlapped mask of the lesion. Left column: Patient's names and age. Middle column: Neuroradiological description of the lesion and representation of the mask of the lesion.

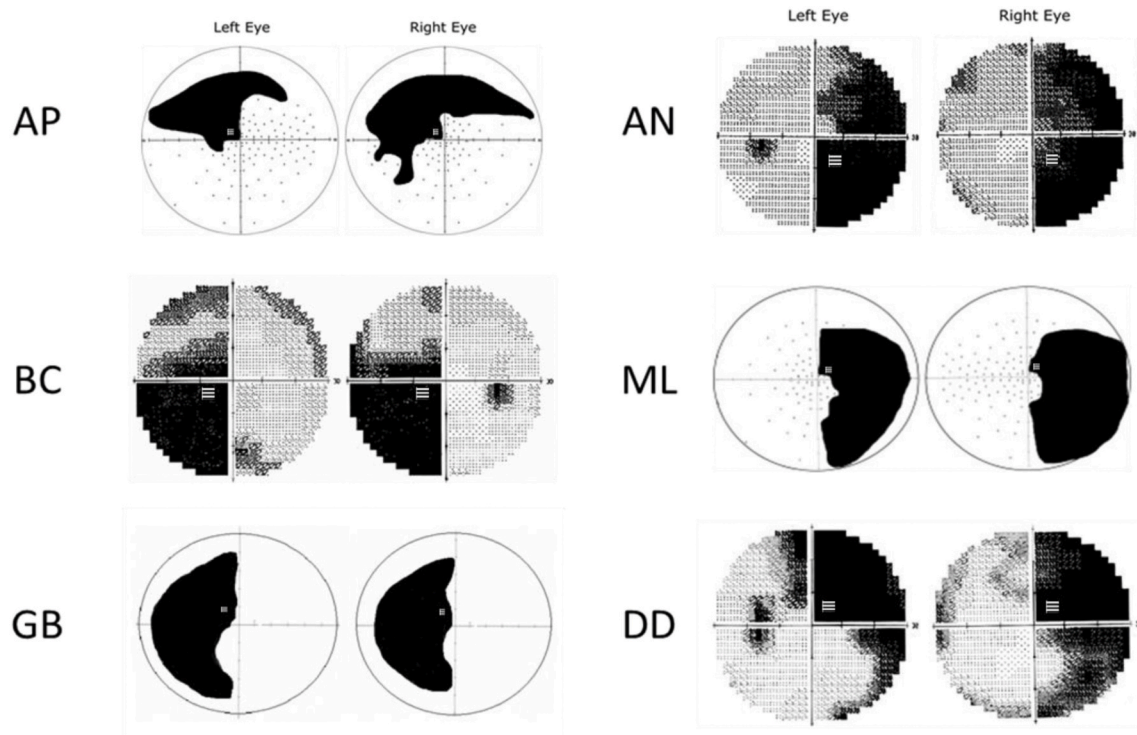


Fig. 1. Humphrey monocular campimetry of each patient and visualization of the central position of the stimulus during the attentional task (black and white grating). Campimetry of patients AP, GB and ML represent 120° of visual angles (60° left, 60° right); Campimetry of patients BC, AN and DD represent 60° of visual angles (30° left, 30° right). Campimetries of patients AP, BC, AN and ML are adapted from [Sanchez-Lopez et al. \(2017; .2020\)](#).

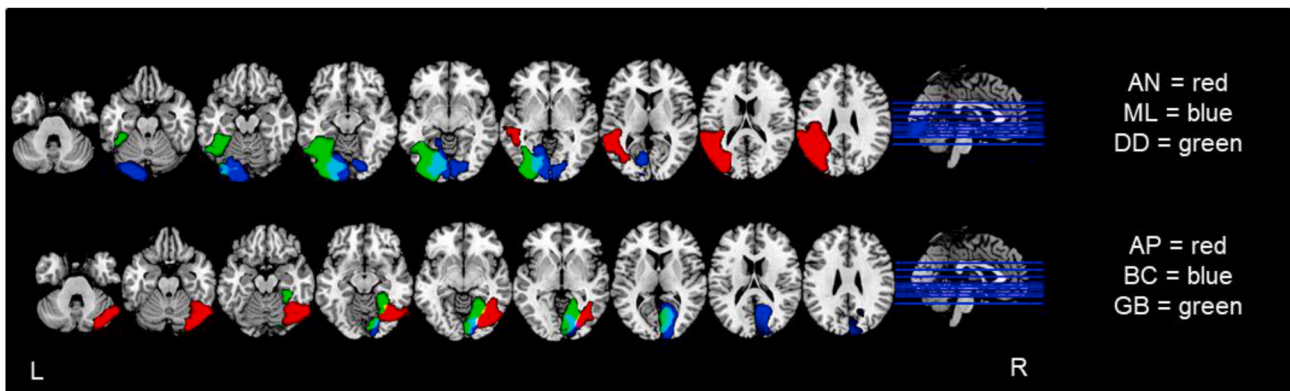


Fig. 2. Representation of patients' lesions.

Overlapped lesions of left (upper) and right (lower) damaged patients on the ch2bet.nii template of MRICron, represented on multiple slices. Each color represents one patient. Upper panel: patient AN = red; patient ML = blue, patient DD = green. Lower panel: AP = red; patient BC = blue; patient GB = green. Light blue or yellow regions represent the overlap between different sets of patients.

extracted using BET (Brain Extraction Tool). Motion correction was performed using MCFLIRT (FMRIB Linear Image Restoration Tool with Motion Correction). Functional data were spatially smoothed using a Gaussian kernel of FWHM of 5 mm and a high-pass temporal filtering. After motion correction, MELODIC-ICA was applied to extract Independent Components from the signal and ICA-AROMA was performed on them to remove motion-induced signal variations in fMRI data ([Pruim et al., 2015](#)). Before performing the analysis described in the following section, functional images were registered to both

high-resolution structural images using FLIRT after applying BET and to a standard MNI brain template using both FLIRT and FNIRT (FMRIB Nonlinear Image Registration Tool).

3. Data analysis

3.1. Behavioural data

Behavioural analysis was conducted on accuracy and RT for either

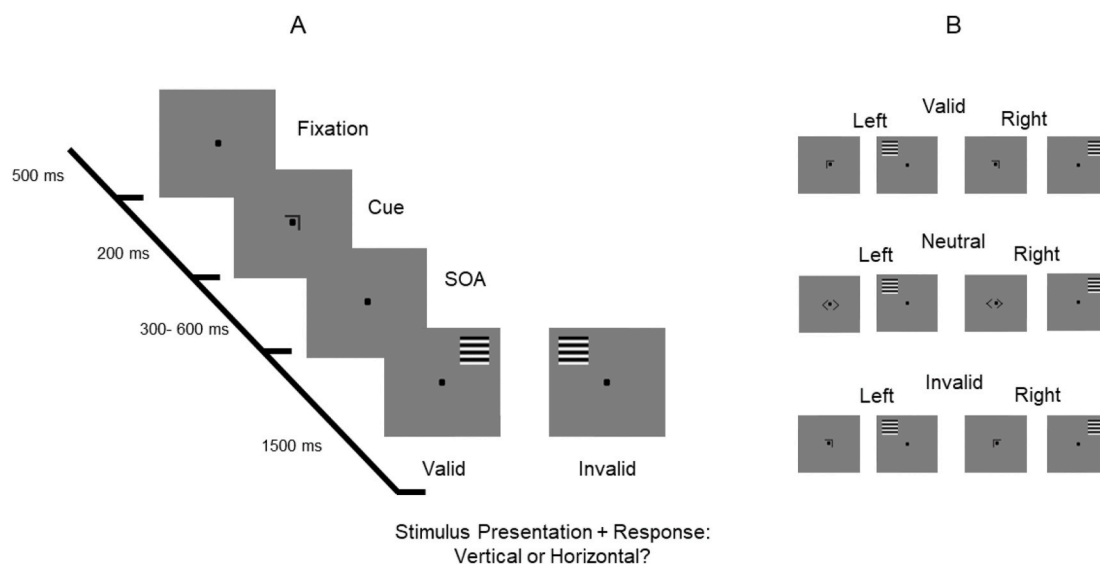


Fig. 3. Experimental procedure. A: Example of trial sequence in valid or invalid trials. B: All possible combinations of valid, neutral and invalid conditions for stimuli presented in the upper visual hemifield. Sustained attention was oriented blockwise towards the left or right side of the screen.

Table 2
Stimulus Position and Contrast for each patient.

Patient	Stimulus Position	Michelson Contrast
AP	x = 5°, y = 5° - Upper hemifield	0.93
BC	x = 6°, y = 1° - Lower hemifield	0.85
GB	x = 8°, y = 6° - Upper hemifield	0.86
AN	x = 6°, y = 6° - Lower hemifield	0.86
ML	x = 6°, y = 3° - Upper hemifield	1
DD	x = 5.5°, y = 5° - Upper hemifield	1

Left column: Patient's ID. Central column: stimulus position for each patient (see also Fig. 1). Right column: Michelson contrast for each patient.

hemifield.

In both groups, percentage of correct responses was used for statistical analysis. According to the high percentage and variability of missed responses and anticipations in the blind hemifield of patients, we decided to calculate the percentage of correct responses in two ways: (1) on the basis of those trials in which a response was given, and (2) on the basis of the total amount of trials. We performed statistical analysis on both results.

Patient AN was excluded from the statistical analysis for two reasons. First, because of a low percentage of responded trials (around 8% in the invalid blind condition) as that patient used to miss or to anticipate numerous responses (see Fig. 4 and Table S1 for details). Second, as AN was the only patient who showed a performance at chance in the invalid and neutral condition when considering the accuracy based on the total amount of trials, even when stimulating the sighted hemifield.

To assess whether accuracy was significantly different from chance level, we carried out an exact binomial test for each patient and condition. To assess how accuracy differs between patients and controls depending on the validity of the cue and the hemifield, we performed a three-way mixed ANOVA with Group (patients/controls) as between-subject factor, and Cue Validity (valid/invalid/neutral) and Visual Field Stimulation (left/right or blind/sighted) as within-subject factors.

According to the similarity in the distribution of RT observed when considering mean RT of either all or correct responses (see Fig. 7), we decided to perform statistical analyses on RT of correct responses. RT was analyzed with a three-way mixed ANOVA with Group (patients/controls) as between-subject factor and Cue Validity (valid/invalid/neutral) and Visual Field Stimulation (left/right or blind/sighted) as within-subject factors, following the same logic as for accuracy. RT

faster than 150 ms from stimulus onset were considered as anticipations and discarded (see table S1 for detailed information). Statistical analyses were implemented in R (R Core Team, 2014).

3.2. Functional data analysis

Functional data analysis was performed excluding patient AN, whose lesion was extended beyond the occipital lobe, including the left parietal cortex. This widespread lesion made it difficult to compare AN's data with those of the remaining patients.

For group analysis, we aligned patients' anatomical and functional scans to a uniform pathological template following the procedure described by Ajina et al. (2015) and applied in numerous other studies (Nelles et al., 2002, 2007, 2009), to artificially create a group of left hemianopes and be able to extract a mean group activation. Therefore, for patients with a lesion in the left occipital lobe (n = 2), we flipped structural and functional data on the horizontal plane as if all patients had sustained damage to the right hemisphere resulting in left hemianopia. For this reason, we will refer to the ipsilesional and contralesional instead of right and left hemisphere in the remainder of this paper.

The first aim of the study was represented by the assessment of whole brain activity during orienting and reorienting of attention. For this purpose, BOLD time course data were analyzed using a GLM approach. Specifically, four regressors were defined at the single-subject level (valid and invalid, separately for left/blind and right/sighted hemifield) reflecting the 2 × 2 factorial nature of our design. Age and gender were entered as nuisance regressors. Moreover, a confound matrix of time-points corrupted by large motion was extracted by applying the fsl_motion_outliers tool and included in the design matrix to remove the effects of large motions on the analysis.

Following the logic used by Vossel et al. (2012), events were time-locked to the onset of the cue (for the analysis of valid trials) and to the target (for the analysis of invalid trials) and the whole duration of the trial was included in the analysis. For each subject, eight contrast images were created and entered into a second-level within-subject ANOVA. Fixed-effect third-level analysis with a cluster defining threshold $z = 3.1$ ($p < 0.001$) and a cluster probability threshold of $p = 0.05$ were applied, entering age and gender as nuisance regressors, to create within- and between-group Z-statistic maps focusing mainly on four contrasts of interest: 1) Valid trials versus baseline, separately for each hemifield, to assess the orienting attentional network and 2)

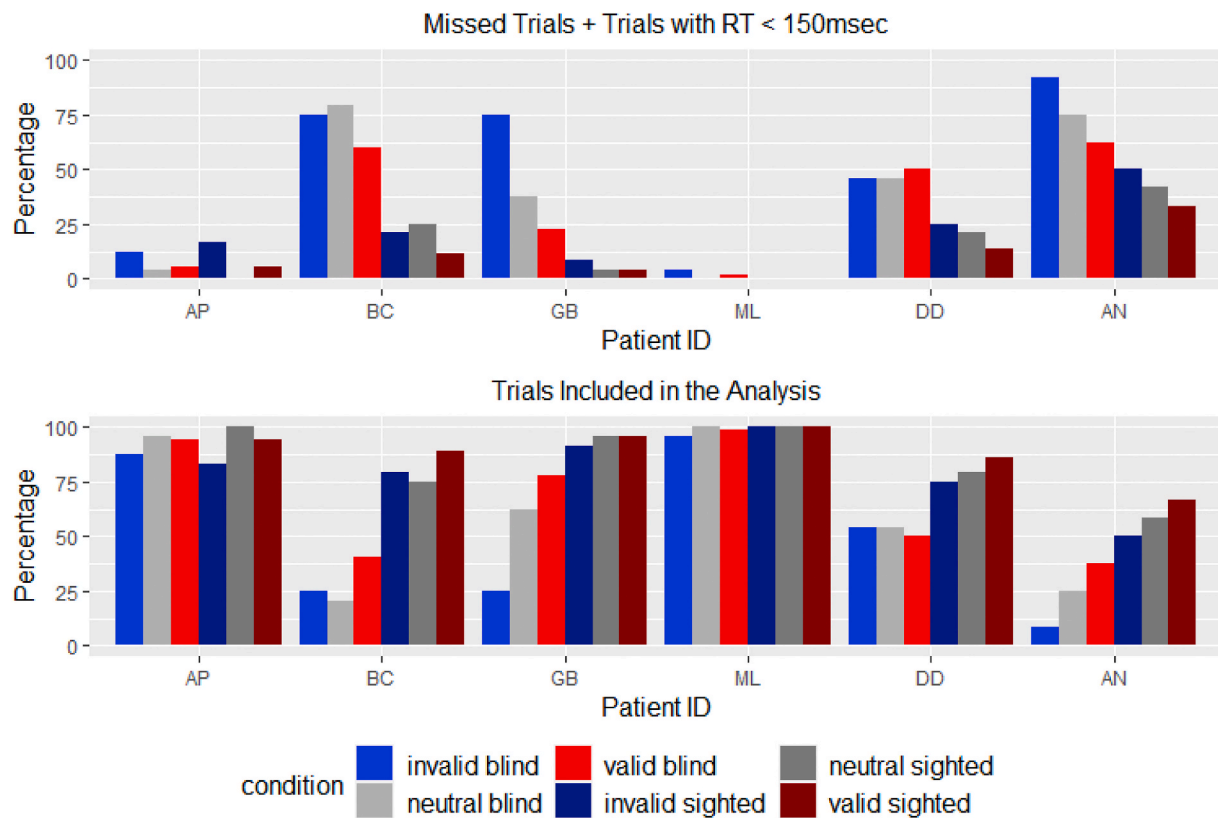


Fig. 4. Upper panel: Percentage of missed trials and anticipations, separately for each patient (x-axis) and condition. Lower panel: Percentage of trials included in the analysis, separately for each patient and condition.

Invalid versus valid trials, separately for each hemifield, to assess the reorienting attentional network. We reasoned that the former would reveal brain activity during the endogenous orientation of attention followed by stimulus presentation in the cued position, while the latter would reveal brain activity during the automatic shift of attention toward an un-cued location, as consequence of a task-relevant stimulus presentation (reorienting of attention after the onset of the stimulus), without considering the activation related to the stimulus presentation. In this case, the effect produced by stimulus presentation would be deleted by the specific contrast of interest as the stimulus would appear at the same location in both valid and invalid trials. Note that since we used a fixed-effect analysis (given our small sample size), our results reflect the data of our specific population and do not allow to make claims regarding the wider population of hemianopic patients.

The second aim of the study was represented by the assessment of the FC underlying the activation of visual areas extracted from the GLM univariate analysis. To do so, we applied a PPI analysis to evaluate the modulation produced by orienting and reorienting attention on the FC between contralateral primary visual cortex and the whole brain. PPI enables to assess which voxels across the brain modulate the correlation with a seed ROI under a specific experimental condition.

The standard pipeline of the PPI analysis is composed by three main steps: selection of the seed, extraction of the time-course of activity from that seed and assessment of the interaction between the time-course of the seed and the task regressor by performing a GLM analysis (O'Reilly et al., 2012). Our seed of interest was represented by the portion of contralateral visual areas that showed a high activation during the orienting of attention in valid trials (contrast valid > baseline). To identify such a seed, we used the anatomical bilateral ROI of the primary visual cortex without any threshold (Juelich Atlas) as a mask in which we carried out a GLM analysis ($z = 3.1$) with two regressors defined according to the position of the stimulus (left/blind or right/sighted). Once we performed this analysis for both groups, we extracted the resulting

activation map and applied it as a mask to the GLM group-analysis based on the contrast of interest valid > baseline previously described, to locate the portion of contralateral V1 whose activation was modulated by the orienting of attention. Then, we performed a conjunction analysis between the activation extracted from controls and patients to locate the area modulated by attention in both groups. This pipeline allowed to locate the main peak of activation extracted from both patients and controls when paying attention to the contralateral visual field, by applying a mask composed by sub-regions of V1 activated following contralateral visual stimulation, independently from orientation of attention. Thus, after extracting the main peak of activation for left and right V1, we created a sphere of 6 mm around them, and used it as a seed region for the PPI analysis. The time-course was extracted from the seeds at single-case level, coregistering the mask with the functional space of each subject. Thus, to assess the FC, we performed a high-level fixed-effects GLM analysis with age and sex as nuisance regressors, and with the interaction between the contrast of interest and the time course extracted from the corresponding seed as explanatory variable. The resulting statistical maps were thresholded applying two cluster thresholds ($z = 1.96$ and $z = 2.3$) and a cluster probability threshold of $p = 0.05$, extracted and visualized on the brain surface (Vossel et al., 2012).

All statistical maps were superimposed on a 3D volume MNI template in fsleyes to locate the brain activation observed using the probabilistic Juelich (Eickhoff et al., 2005) and the Harvard-Oxford cortical structural Atlas (Desikan et al., 2006). To visualize the statistical maps on the cortical surface or on layers of T1-weighted image template, we used BrainNet Viewer (Xia et al., 2013) and MRICron. Statistical tests were implemented in FSL.

3.3. Behavioural performance: Accuracy

Fig. 5 shows the accuracy across different conditions, separately for

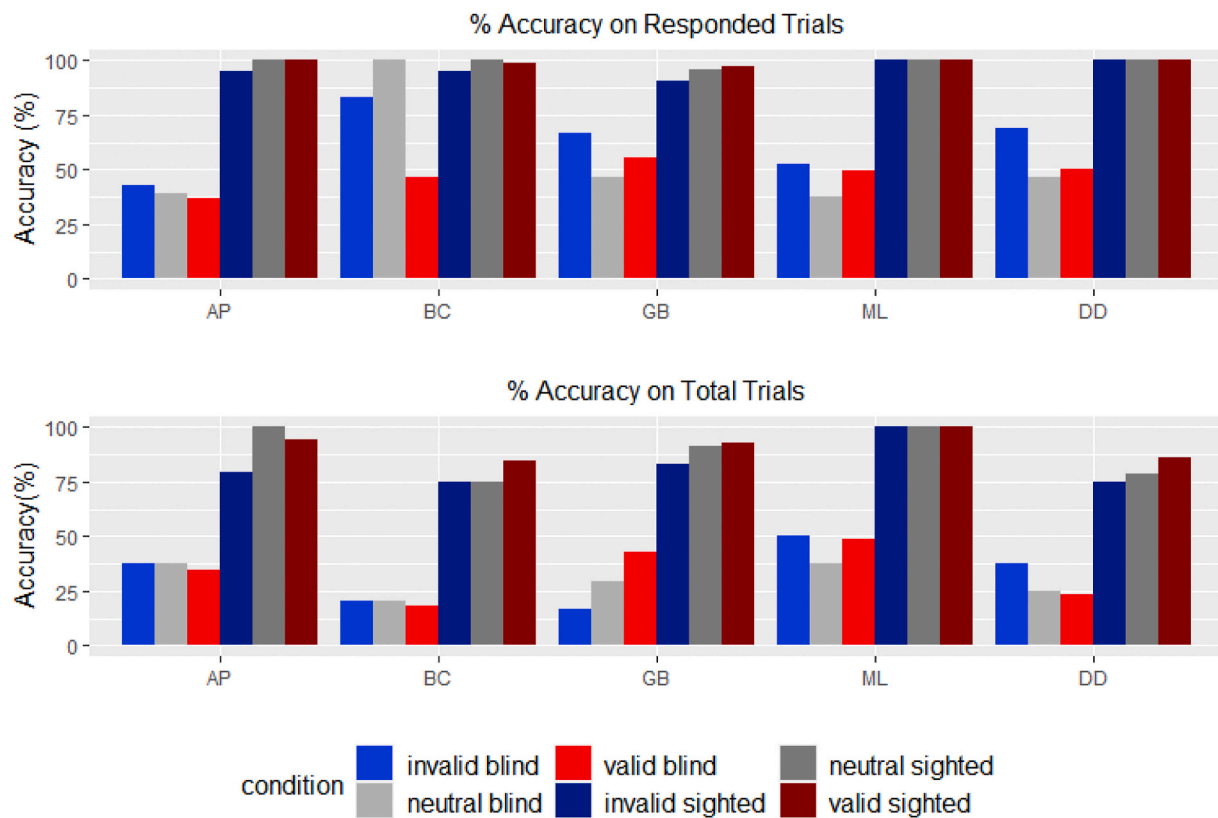


Fig. 5. Upper panel: Percentage of accuracy based on given responses, separately for each patient (x-axis) and condition. Lower panel: Percentage of accuracy based on the total amount of trials, separately for each patient and condition.

each patient, calculated based on the given responses (upper panel) and on the total amount of trials (lower panel). As can be seen, we obtained a difference between the two trends of accuracy, mainly when considering the blind hemifield of those patients who showed a high percentage of missed responses (patients GB and BC, see Fig. 4). In the former, the accuracy was higher than chance in almost all conditions, even if not significantly, due to the low number of trials included. Instead, in the latter, the performance was significantly below chance in the invalid condition in patients BC ($p = 0.006$) and GB ($p = 0.0015$), in the valid condition in patients AP ($p = 0.013$), BC ($p < 0.001$) and DD ($p < 0.001$), and in the neutral condition in patients BC ($p = 0.006$) and DD ($p = 0.0226$). Only in patient ML the performance in the blind hemifield was always at chance level. Due to this great difference, we decided to perform statistical analysis on the accuracy calculated in both ways.

When calculating the percentage of correct responses based on the number of trials in which a response was given (Fig. 4, upper panel), the mixed ANOVA indicated a significant effect of Group [$F(1,9) = 63.282$, $p < 0.001$, $\eta^2G = 0.661$] with patients less accurate (76.4%) than controls (98.7%) and of Visual Field Stimulation [$F(1,9) = 49.675$, $p < 0.001$, $\eta^2G = 0.636$] with higher performance in the sighted/right (98.1%) than blind/left (79.1%) hemifield. No significant effect of Cue Validity was observed. Moreover, we found a significant interaction between Group and Visual Field Stimulation [$F(1,9) = 55.725$, $p < 0.001$, $\eta^2G = 0.663$]. For the post-hoc analysis we assessed the simple main effect of Visual Field Stimulation on accuracy in both groups by applying a Bonferroni adjustment leading to statistical significance being accepted at the $p < 0.025$ level. The simple main effect of Visual Field Stimulation on accuracy was statistically significant only for patients ($F(1,14) = 80.4$, $p < 0.0001$, $\eta^2G = 0.754$), indicating higher performance in the sighted (98.1%) than blind (54.8%) visual hemifield.

When calculating the percentage of accuracy based on the total amount of trials, as previously described, (Fig. 4, lower panel), the mixed ANOVA revealed a significant main effect of Group [$F(1,9) =$

98.521, $p < 0.0001$, $\eta^2G = 0.882$], with patients being less accurate (59.9%) than controls (97.6%) and Visual Field Stimulation [$F(1,9) = 925.779$, $p < 0.0001$, $\eta^2G = 0.79$] with the sighted/right hemifield more accurate (92.5%) than the blind/left hemifield (68.4% ms). No significant effect of Cue Validity was observed. Moreover, we found a significant interaction between Group and Visual Field Stimulation [$F(1,9) = 1093.151$, $p < 0.001$, $\eta^2G = 0.816$]. In the post-hoc analysis we observed that the effect of Visual Field Stimulation on accuracy was statistically significant for both patients ($F(1,14) = 616$, $p < 0.001$, $\eta^2G = 0.886$) and controls ($F(1,17) = 6.34$, $p = 0.022$, $\eta^2G = 0.117$), indicating higher performance in the sighted (87.8%) and left (98.8%) visual hemifield (see Fig. 6).

Taken together, these results indicate the same trend of significance when calculating the percentage of accuracy based on either the given responses or the total number of trials, with general higher accuracy in controls than in patients and a significant effect of Visual Field Stimulation.

It is important to notice that the mean percentage of correct responses in the group of patients was surprisingly above chance when calculated on the basis of the amount of given responses, while it turned out to be at chance when including the numerous missed trials and anticipations (see Fig. 6), thus representing a more realistic measure of their ability to discriminate the orientation in comparison to their level of confidence. These results reflect the fact that the shift of attention was not sufficient to improve behavioural performance. Interestingly, in the verbal report at the end of each session, patients usually reported a visual feeling associated with the onset of the flickering stimulus that was independent from deployment of attention and that did not facilitate the orientation discrimination.

3.4. Behavioural performance: Reaction Times

In all patients we observed a similar trend of RT when considering all

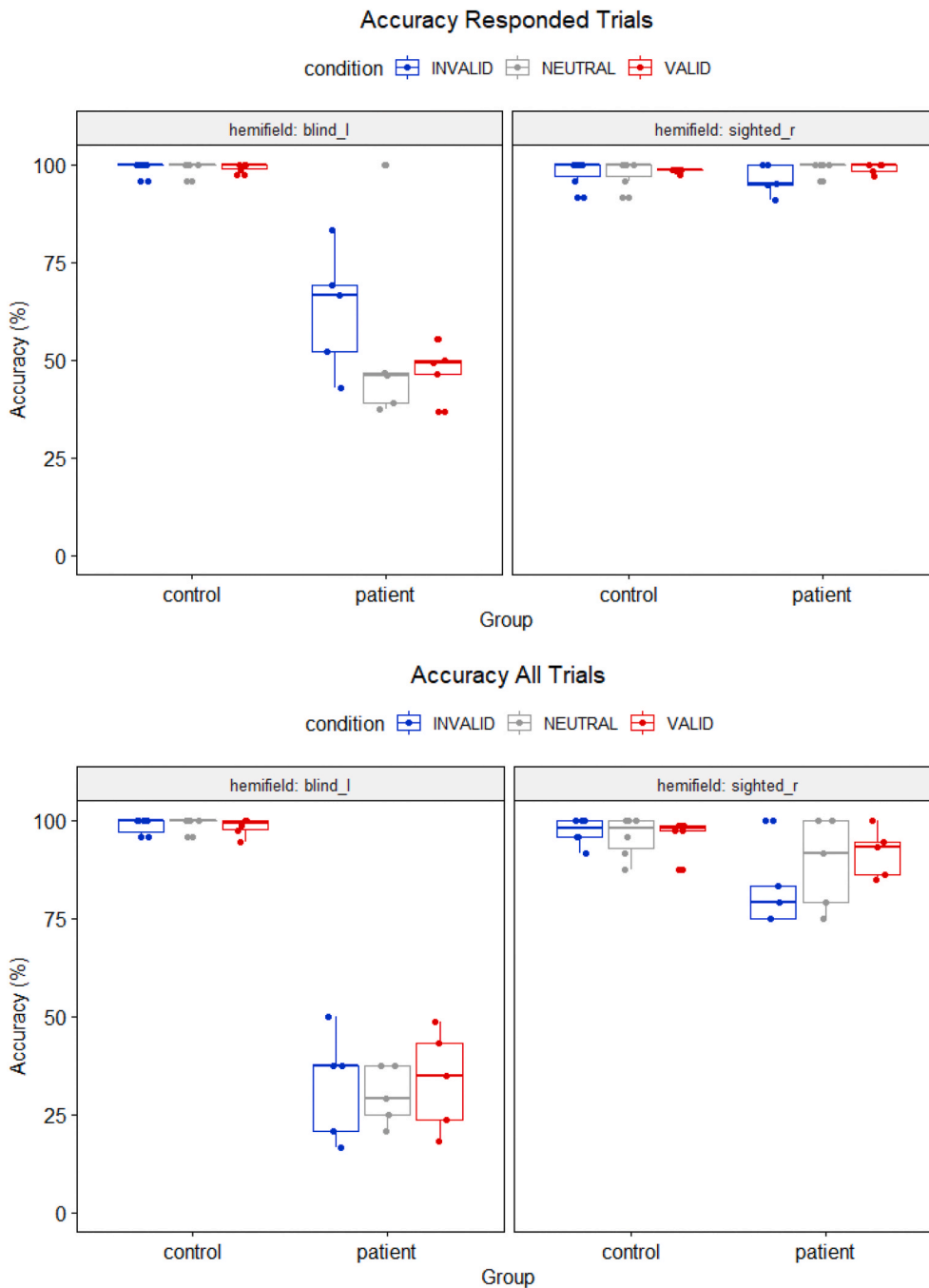


Fig. 6. Boxplot showing the percentage of accuracy in discriminating stimulus orientation in the valid (red), neutral (grey) and invalid (blue) condition, in both the blind/left and the sighted/right hemifield. The boxplot spans the interquartile range (IQR) between the first and the third quartile; the horizontal line shows the median of the data; the whiskers are the two lines outside the box that extend to the highest and lowest observations [the “minimum” (Q1-1.5*IQR) and the “maximum” (Q3+1.5*IQR)]. Each dot represents one subject. Upper panel: percentage of accuracy calculated on the amount of responses given; Lower panel: percentage of accuracy calculated on the total amount of trials, including missed trials and anticipations. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

trials and correct responses (Fig. 7). For this reason, we decided to perform the statistical analysis on the RT of correct trials.

The mixed ANOVA revealed a significant main effect of Group [$F(1,9) = 5.64$, $p = 0.042$, $\eta^2 G = 0.359$], Cue Validity [$F(2,18) = 14.556$, $p = 0.0002$, $\eta^2 G = 0.066$] and Visual Field Stimulation [$F(1,9) = 15.848$, $p = 0.003$, $\eta^2 G = 0.048$]. Indeed RT were slower in patients (1029 ms) than controls (809 ms), in Invalid (960 ms) than Neutral (888 ms) and Valid (878 ms) trials, and in the Sighted/Right (878 ms) than in the Blind/Left (939 ms) hemifield. There was a significant interaction between Group and Cue Validity [$F(2,18) = 9.29$, $p = 0.002$, $\eta^2 G = 0.043$] and between Group and Visual Field Stimulation [$F(1,9) = 9.39$, $p = 0.013$, $\eta^2 G = 0.029$]. For the post-hoc analysis we assessed the simple main effect of Cue Validity and Visual Field Stimulation on RT in both groups by applying a Bonferroni adjustment leading to statistical significance being accepted at the $p < 0.0125$ level. The simple main

effect of Cue Validity on RT was statistically significant only for patients [$F(2,18) = 11.4$, $p = 0.0006$, $\eta^2 G = 0.137$]. This surprising result can be related to the easiness of the task for normal sighted participants, as a consequence of the duration (1500 ms) and the high visibility (high-contrast) of the stimulus shown. These characteristics may have reduced the attentional effect in normally sighted participants. All pairwise comparisons were run between different levels of Cue Validity in patients, and a Bonferroni adjustment was applied. RT was significantly different between the valid and invalid condition ($p = 0.019$) and between the invalid and neutral condition ($p = 0.015$), with longer RT in the invalid (1127 ms) than both neutral (998 ms) and valid (970 ms) condition. The simple main effect of Visual Field Stimulation on RT was statistically significant only for patients [$F(1,14) = 15.2$, $p = 0.002$, $\eta^2 G = 0.094$], with slower RT in the blind (1087 ms) than in the sighted (970 ms) hemifield (see Fig. 8).

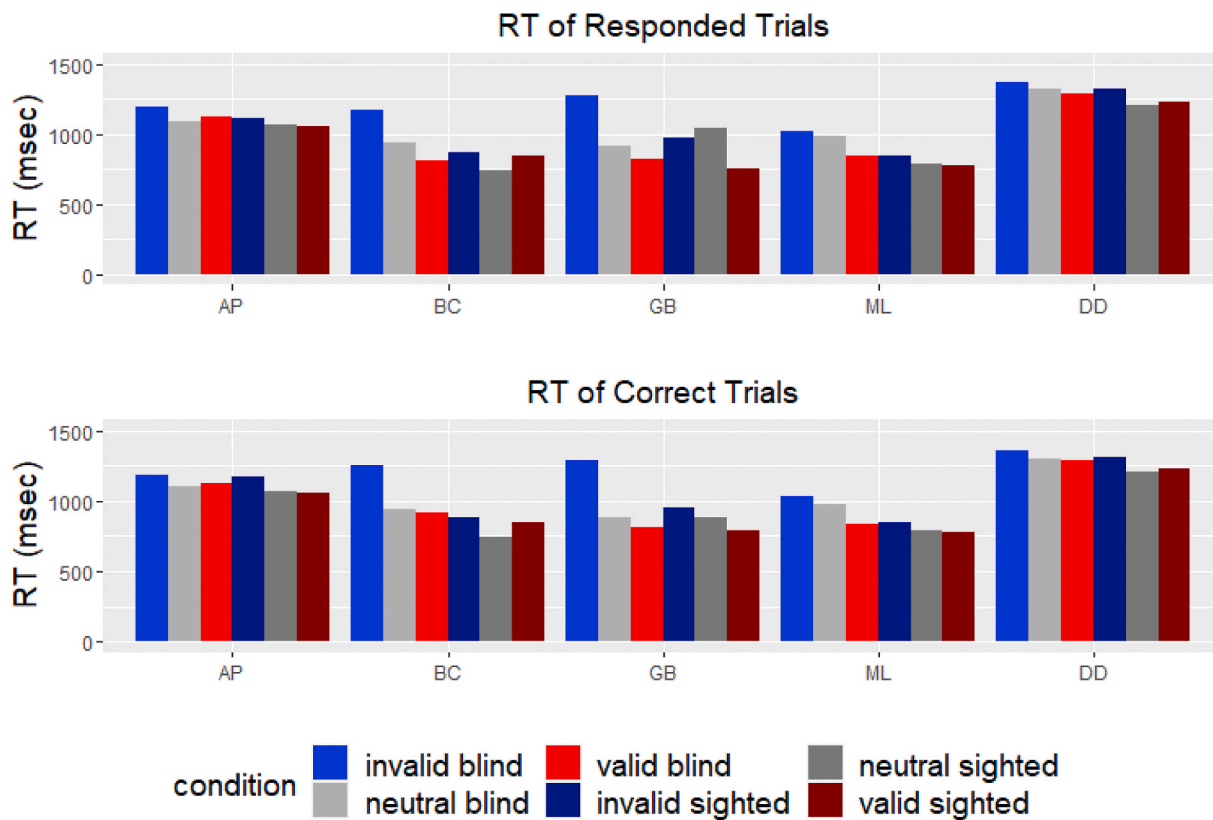


Fig. 7. Upper panel: Mean RT of all responded trials, separately for each patient (x-axis) and condition. Lower panel: Mean RT of correct trials, separately for each patient (x-axis) and condition.

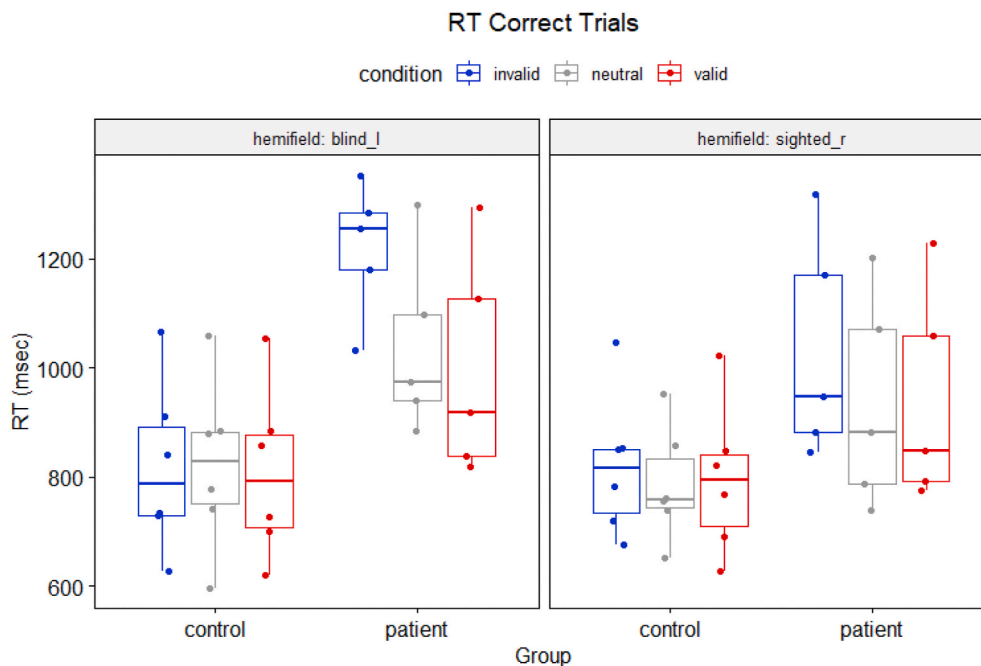


Fig. 8. Boxplot showing RT for correct responses in discriminating stimulus orientation in the valid (red), neutral (grey) and invalid (blue) condition, in both the blind/left and the sighted/right hemifield. Each dot represents one subject. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

These results indicate a modulation of RT in patients, characterized by faster RT in the valid and neutral compared to the invalid condition, as well as in the sighted than in the blind hemifield. Moreover, they revealed a non significant difference in RT between valid and neutral

condition, with slightly faster RT during the process of allocating attention toward one specific hemifield (valid). Finally, we observed significantly faster RT in controls than in patients in both hemifields. This result can be explained by a general slowdown of RT affecting

mainly but not only the blind hemifield, as a consequence of the lesion. This phenomenon has been described mainly in simple detection tasks and defined as “sightblindness” by Bola et al. (2013) and Cavezian et al. (2015).

In sum, despite the impairment of awareness, we observed a modulation of RT produced by attention in patients, with a progressive increase of RT from valid to neutral to invalid condition.

4. Results: univariate GLM analysis

4.1. Orienting of attention

To study the neural bases of orienting attention toward the blind or the sighted hemifield, we performed a GLM univariate analysis focusing on the contrast valid > baseline, as previously described. In the valid condition, the quadrant indicated by the cue (arrow) and the actual position of the grating coincide.

In patients, orienting attention toward the **blind hemifield** yielded significant activation in a bilateral network involving fronto-parieto-occipital regions such as hMT+, Inferior Parietal Lobule (IPL), aIPS, SPL, MFG, left FEF, ipsilesional Supramarginal and Angular Gyrus and, interestingly, LOC, occipital fusiform and lingual gyrus and a portion of area V1 and V2 (MNI coordinates 11, -66, -9; $z = 4.25$). These results indicate the activation of a widespread network involving ipsilesional visual areas in addition to bilateral fronto-parietal regions, despite damage to the central visual pathways and impairment of conscious perception (see Fig. 9, left upper panel). Orienting attention toward the **sighted hemifield** yielded significant activation mainly of

contralateral visual areas (primary visual cortex, V2, V3 and V4) involving a portion of the lingual gyrus symmetrical to the activation observed in the ipsilesional hemisphere when orienting attention to the blind hemifield (MNI coordinates -11, -70, -9; $z = 3.76$), bilateral LOC, hMT+ and precentral and postcentral gyrus (see Fig. 9, right panel). The activation of contralateral hMT+ when stimulating either the blind or the sighted hemifield, was expected as a consequence of the stimulus flickering. The multislice representation (Fig. 9, lower panel) clearly shows that the stimulation of the blind hemifield (red color) elicits a more widespread activation than the sighted hemifield, involving not only the contralateral hemisphere. An important result is represented by the activation of the ipsilesional lingual gyrus while orienting attention toward the blind hemifield, with the main peak in MNI coordinates 18, -90, -18 ($z = 5.64$) corresponding to a portion of visual areas V1 and V2. Instead, the orientation of attention toward the sighted hemifield mainly involved regions in the contralateral occipital lobe.

When directly contrasting the orientation of attention towards the two hemifields, we observed a higher activation of ipsilesional fronto-parietal regions when orienting attention to the blind hemifield, and of contralesional occipital regions when orienting attention to the sighted hemifield (see Figure S1).

In controls, orienting attention toward the **left hemifield** yielded significant activation in contralateral V1 and V2, ipsilateral extrastriate visual areas and bilateral fronto-parietal regions, hMT+ and LOC. In this case, we observed a bilateral involvement of visual areas with a stronger recruitment of contralateral visual areas (see Fig. 10, left). Orienting attention toward the **right hemifield** activated bilateral occipital

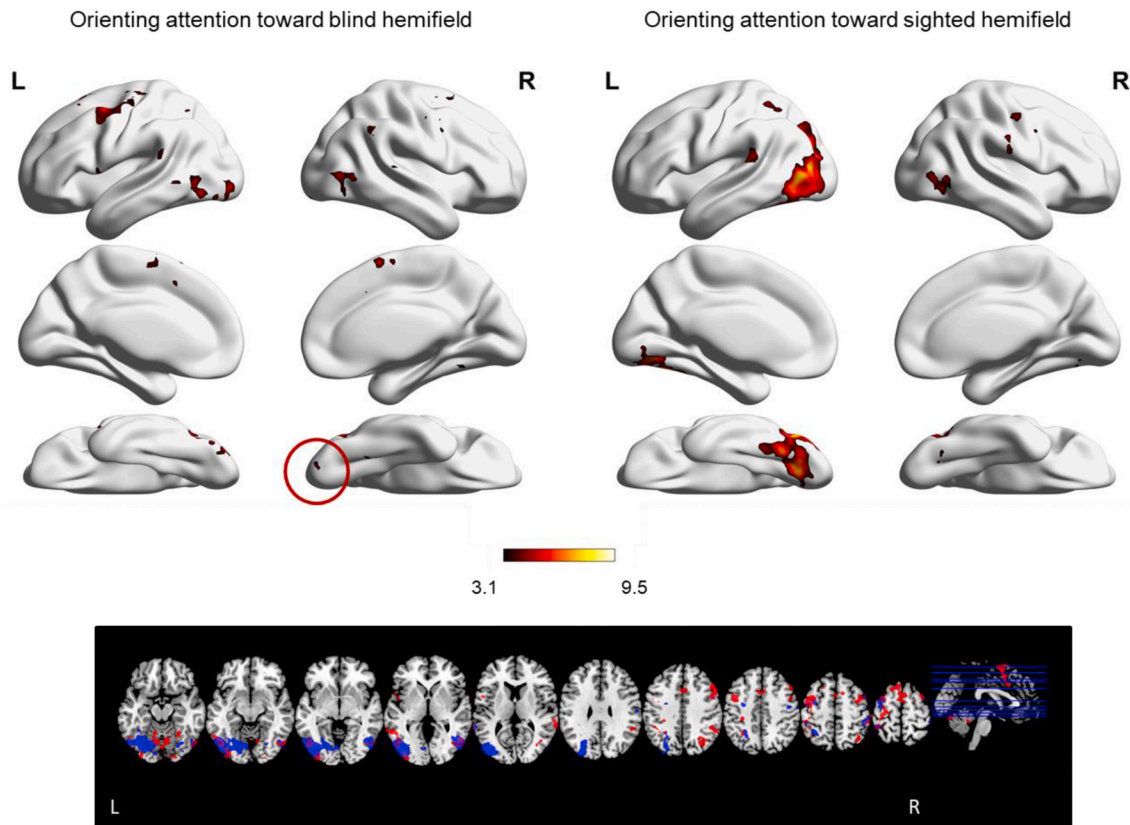


Fig. 9. Patients. Whole brain activation during the orientation of attention (GLM contrast valid > baseline) to the blind or sighted hemifield in valid trials. Left upper panel: Effects of orientation toward the blind hemifield. The red circle indicates the activation in the ipsilesional lingual gyrus. Right upper panel: Effects of orientation toward the sighted hemifield. Whole-brain statistical maps resulting from the GLM contrast valid > baseline (fixed-effect analysis) are shown on the cortical surface and have been thresholded using Random Field Cluster-based correction ($z = 3.1$, cluster probability threshold = 0.05). The color scale indicates the level of activation. Lower panel: statistical map depicting brain activation following stimulation of the blind (red) and sighted (blue) hemifield on multislice T1-weighted image. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

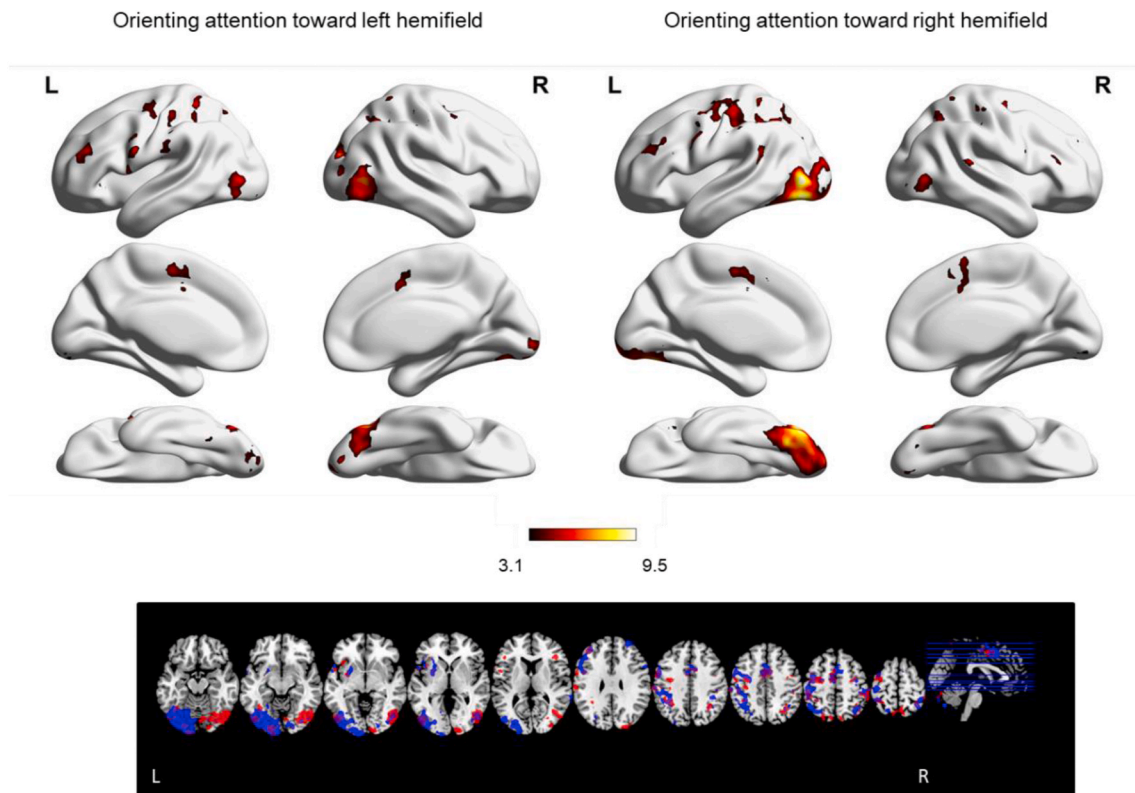


Fig. 10. Control participants. Whole brain activation during the orientation of attention (GLM contrast valid > baseline) to the left or right hemifield in valid trials. Left upper panel: Effects of orientation toward the left hemifield. Right upper panel: effects of orientation toward the right hemifield. Whole brain statistical maps resulting from the GLM contrast valid > baseline (fixed-effect analysis) are shown on the cortical surface and have been thresholded using Random Field Cluster-based correction ($z = 3.1$, probability threshold = 0.05). Color scale indicates the level of activation. Lower panel: statistical map depicting brain activation following stimulation of the left (red) and right (blue) hemifield on multislice T1-weighted image. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

regions, hMT+ and fronto-parietal regions (IFG, aIPS, SPL, SMG and Angular Gyrus). Also in this casethere was an involvement of contralateral visual areas, with a higher recruitment of the contralateral primary visual cortex (see Fig. 10, right panel).

Taken together, these results indicate a clear involvement of fronto-parietal regions in addition to contralateral primary visual cortex and area hMT+ during the orienting of attention toward either the left or the right hemifield. The general higher activation of left than right premotor cortex might reflect the motor response bias toward the left hemisphere as four (two patients and two controls) out of 12 participants responded using only the right hand (contralateral activation) while the others responded using both hands (bilateral activation).

The between-group comparison in orienting attention toward the blind/left hemifield revealed a stronger activation in controls than patients of the left frontal pole and premotor cortex. In contrast, we observed higher activation in patients than controls in bilateral frontal regions, namely ipsilesional MFG and contralesional MFG and SFG (Figure S2). The non-parametric Fligner-Killeen test (Conover et al., 1981) revealed a significantly higher variability in patients than controls in the mean activation extracted from these significant clusters ($\chi^2 = 5.0568$, $df = 1$, p -value = 0.025) (see Figure S3). Interestingly, no difference was observed in the portion of the ipsilesional lingual gyrus that was activated in both groups. These results show that the orientation of attention toward the blind hemifield elicited an activation of contralateral lingual gyrus that was similar in both groups, despite the lesion in patients. When considering the orienting of attention toward the sighted/right hemifield, we observed a significantly higher activation in controls than patients mainly of contralateral visual areas (V1, V2) and bilateral frontal regions (Figure S2).

These results highlight a group-difference in the mechanism of

orienting attention to the sighted/right hemifield, possibly due to a lower cognitive effort in patients when paying attention to a visual hemifield where visible stimuli are shown, to compensate for the higher cognitive effort when paying attention to unseen stimuli in the blind hemifield.

4.2. Reorienting of attention

For what concerns brain activation during the reorienting of attention, we carried out the contrast invalid > valid in order to be able to control for activation related to stimulus presentation focusing only on the shift of attention from the sighted to the blind hemifield and vice versa. In both conditions the stimulus was shown at the same location, while attention was oriented toward different hemifields (see Fig. 11).

In patients, reorienting of attention toward the blind/left hemifield did not yield any significant activation, while in the group of controls we extracted significant activation of the left primary visual cortex, ipsilateral to the stimulation, and right LOC, contralateral to the visual stimulus. Interestingly, in this case we did not find any activation of either the ipsilesional or the contralesional visual areas in patients. In contrast, reorienting attention toward the sighted hemifield elicited significant activation of bilateral frontal regions, medial precuneus and contralesional parietal regions, without any significant activation of the contralesional primary visual cortex. Instead, in controls we observed the involvement of contralateral visual areas with a significant activation of LOC, V2 and cuneal cortex. The direct contrast between the reorienting of attention toward the blind and sighted hemifield in patients did not reveal any significant difference between the two hemispheres, despite the visual impairment.

In contrast, the between-group comparison revealed a higher

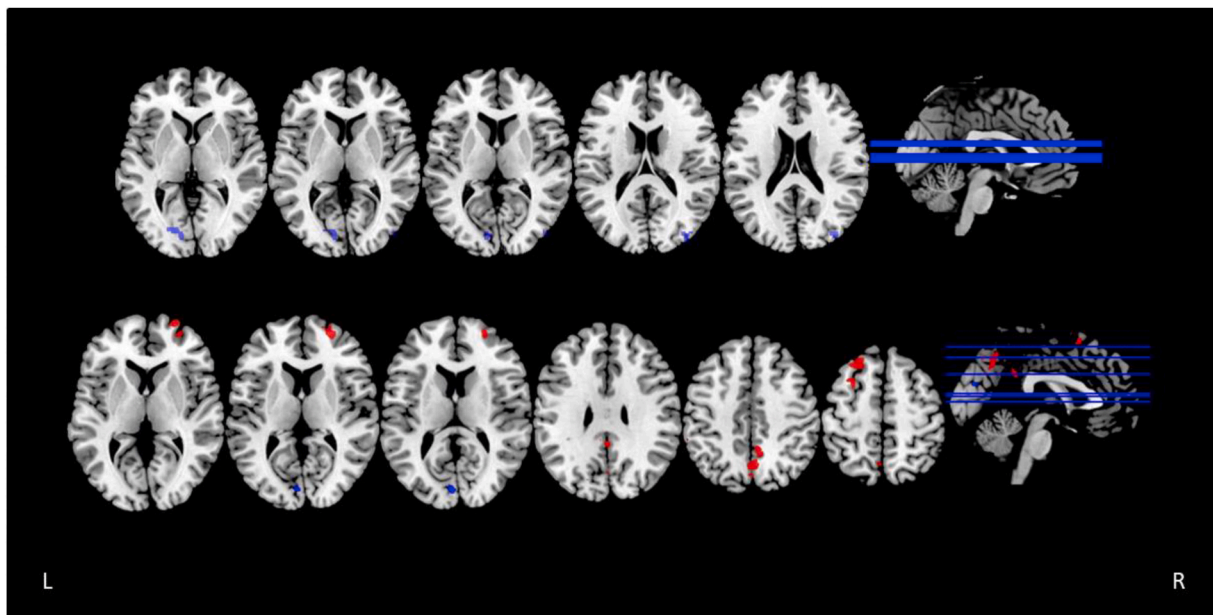


Fig. 11. Multislice representation of brain activation during reorienting of attention toward the blind/left (upper) or the sighted/right (lower) hemifield in patients (red) and controls (blue). Whole brain statistical maps resulting from the GLM contrast invalid > valid (fixed-effect analysis) and thresholded using Random Field Cluster-based correction ($z = 3.1$, probability threshold = 0.05). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

activation of the right primary visual cortex and area LOC in controls than in patients during the reorienting of attention to the blind hemifield. To better understand the direction of this difference, we extracted the mean activation from each cluster, separately for the invalid and valid condition. In this way, we could easily observe that the difference between patients and controls was mainly driven by the invalid

condition, where right V1 and LOC were clearly more activated in controls than patients, while the activation in the valid condition was similar for both groups, or even slightly higher for patients (ipsilesional-right V1) (Fig. 12, upper panel). These results show that ipsilesional visual areas are not activated during the reorienting of attention to the blind hemifield, unlike what happens during the cognitive mechanism of

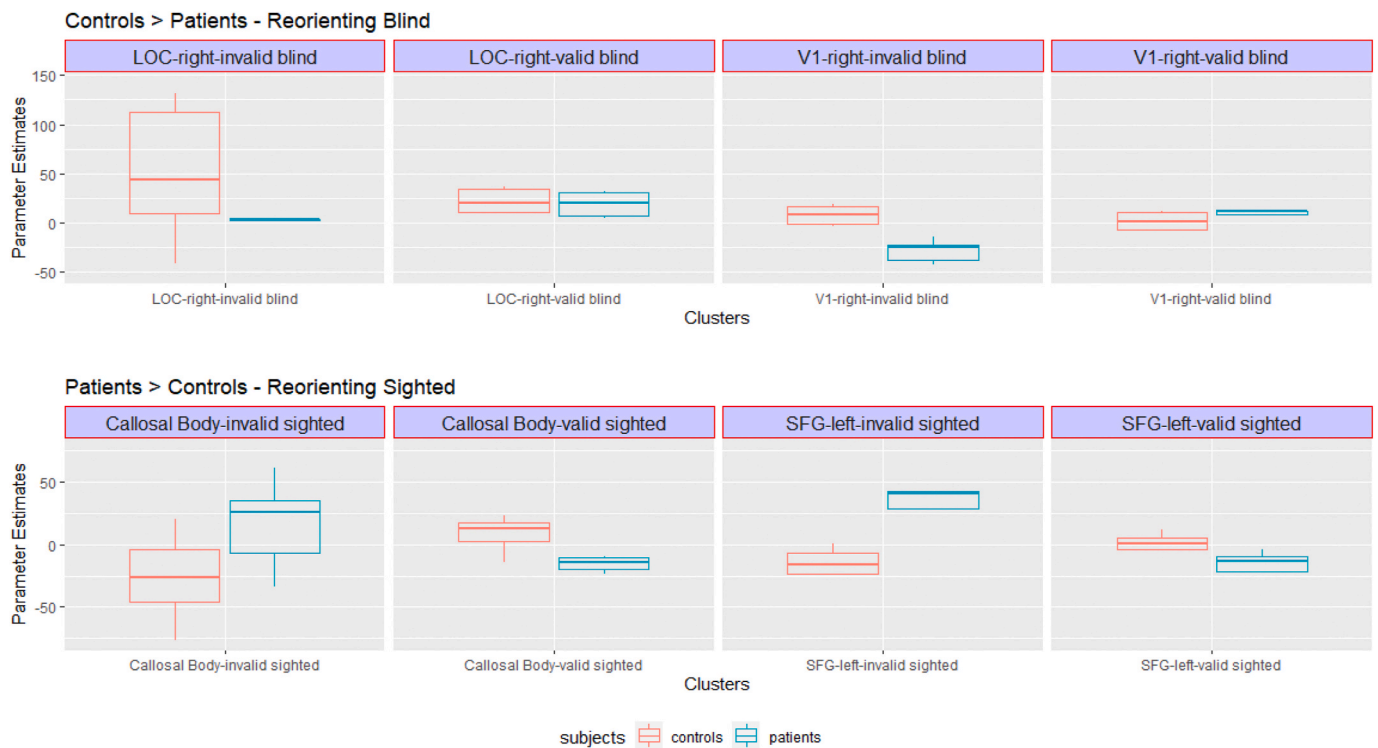


Fig. 12. Parameter estimates extracted from different clusters significantly activated in Controls > Patients during the reorienting of attention to the blind/left hemifield (upper panel) and in Patients > Controls during the reorienting of attention to the sighted/right hemifield (lower panel). Blue boxplots represent patients; red boxplots represent controls. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

orienting attention to the same hemifield.

The between-group comparison during the reorienting of attention to the sighted hemifield revealed a higher activation in patients than controls mainly of the contralesional SFG, driven by the higher activation in the invalid condition in patients (see Fig. 12, lower panel), while in the valid condition the activation was slightly higher in controls.

These results indicate that the observed between-group differences are mainly driven by the invalid condition that modulates the activation of either ipsilesional occipital regions (higher in controls) during the reorienting of attention to the blind hemifield or contralesional SFG (higher in patients) during the reorienting of attention to the sighted hemifield. No significant differences were found between the variances of the two groups.

4.3. Results: functional connectivity

We performed a PPI analysis to assess the functional mechanism underlying the modulation produced by attention on the activation of ipsilesional visual areas when paying attention to the blind hemifield. The regions of interest used as seeds were the same for both groups as they were extracted from the conjunction analysis, previously described. Both were located in the occipital pole and fell into the mask of the primary visual cortex extracted from the Juelich Atlas (MNI coordinates right seed: 16, -90, -16; left seed: 16, -78, -14). In Figs. 13 and 14 we

showed only significant results applying the following colorcode: light red nodes survive the threshold $z = 1.96$ ($p < 0.05$), light blue nodes survive both thresholds $z = 1.96$ and 2.3, dark blue nodes represent FC that only survives the threshold $z = 2.3$ ($p < 0.01$).

At first glance, it is important to notice that in patients, during the orienting of attention toward the blind hemifield (Fig. 13, upper red panel), there was a general increase of the FC mainly within the ipsilesional hemisphere, despite the presence of the lesion. The results show an increase of intra-hemispheric FC between the ipsilesional seed and fronto-occipito-parietal regions as the frontal operculum cortex, the insular cortex, the lingual gyrus, SPL and the medial precuneus. Moreover, we found an increase of the inter-hemispheric FC with parietal regions, such as SPL, aIPS, SMG and IPL. We observed similar results when contrasting patients vs controls for the same cognitive process (Fig. 13, lower red panel). In this case, we found an increase of FC involving both hemispheres and mainly ipsilesional MFG, contralesional postcentral gyrus and bilateral precuneus, LOC and SPL. These results highlight the involvement of ipsilesional fronto-parietal regions in the functional network centred in the ipsilesional seed, modulated by the mechanism of orientation of attention toward the blind hemifield in valid trials. No significant results were found in either controls or controls > patients.

When considering the orientation of attention toward the right hemifield in controls (Fig. 13, upper blue panel), we found an increase of

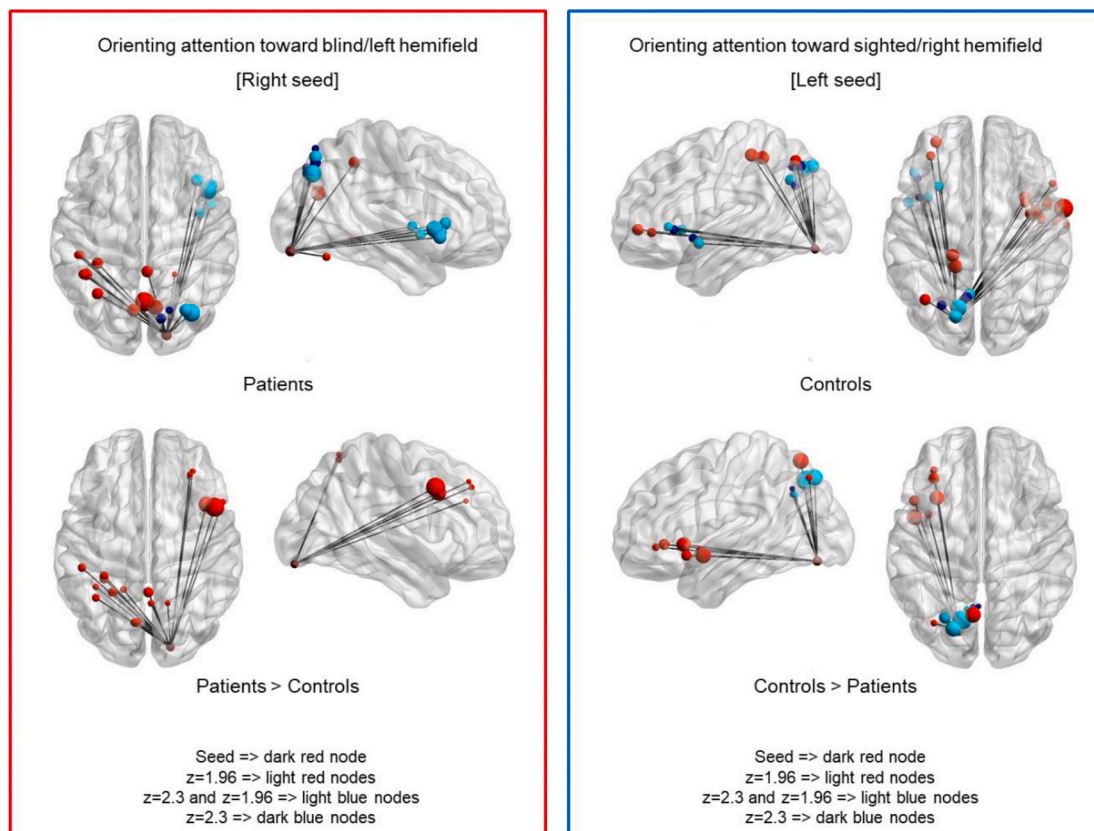


Fig. 13. Results of PPI analysis of orienting attention toward the blind/left and sighted/right hemifield represented on an axial and sagittal cortical surface. Red panel. Upper: Orienting attention to the blind hemifield (patients). Functional connectivity between the right seed and the whole brain, modulated by the contrast of interest valid blind > baseline. Lower: Patients > Controls. Functional connectivity significantly higher in patients than controls, between the right seed and the whole brain, modulated by the contrast of interest valid blind/left > baseline. Blue panel. Upper: Orienting attention to the right hemifield (healthy controls). Functional connectivity between the left seed and the whole brain, modulated by the contrast of interest valid sighted/right > baseline, in the group of controls. Lower: Controls > Patients. Functional connectivity significantly higher in controls than patients, between the left seed and the whole brain, modulated by the contrast of interest valid sighted/right > baseline. Node size represents z-values extracted from the PPI analysis. Dark red node indicate the location of the seed; light red nodes survived the threshold of $z = 1.96$; light blue nodes survived thresholds $z = 1.96$ and 2.3; dark blue nodes represent results that survive the threshold of $z = 2.3$. Edges represent correlation coefficients extracted from a binary matrix. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

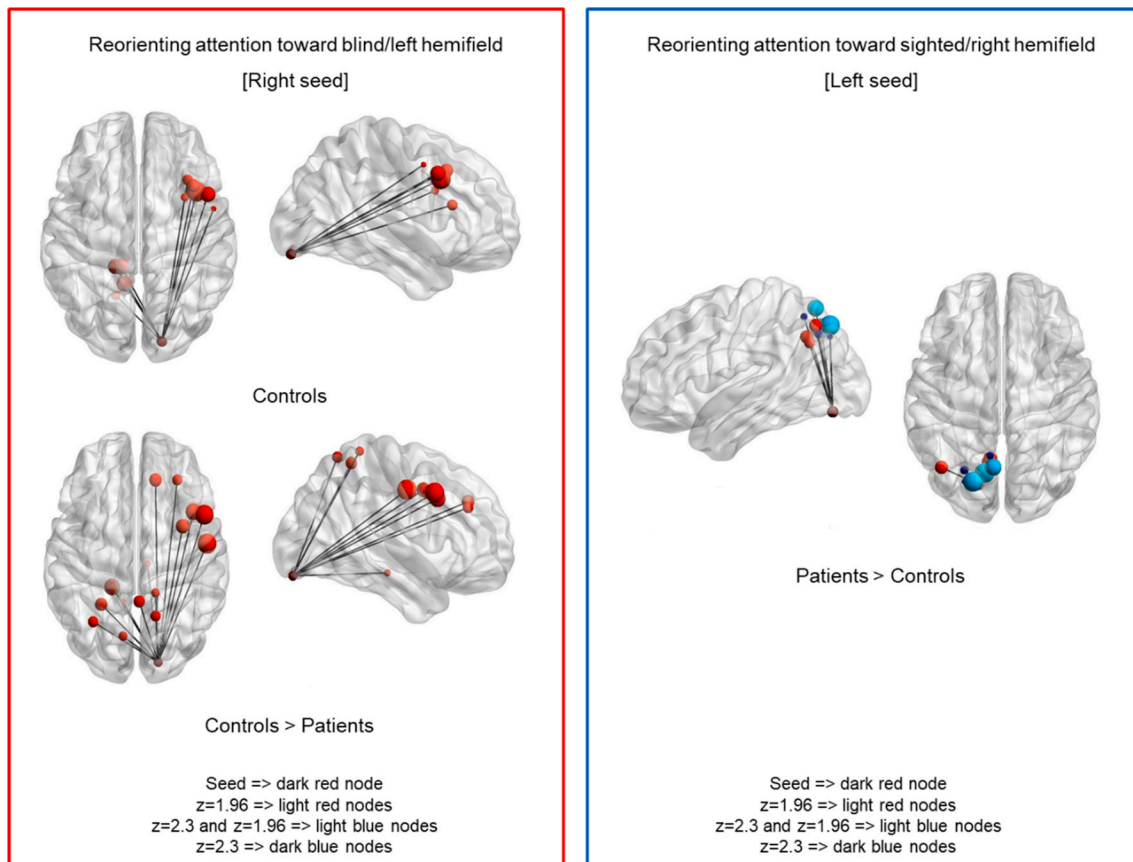


Fig. 14. Results of PPI analysis of reorienting attention toward the blind/left and sighted/right hemifield represented on an axial and sagittal cortical surface. Red panel. Upper: Reorienting attention to the left hemifield (healthy controls). Functional connectivity between the right seed and the whole brain, modulated by the contrast of interest invalid > valid. Lower: Controls > Patients. Functional connectivity significantly higher in controls than patients, between the right seed and the whole brain, modulated by the contrast of interest invalid > valid. Blue panel. Reorienting attention to the right hemifield: Patients > Controls. Functional connectivity between the left seed and the whole brain, modulated by the contrast of interest invalid > valid. Node size represents the z-values extracted from the PPI analysis. Dark red node indicates the location of the seed; light red nodes survived the threshold of $z = 1.96$; light blue nodes survived thresholds $z = 1.96$ and $z = 2.3$; dark blue nodes represents results that survived the threshold of $z = 2.3$. Edges represent correlation coefficients extracted from a binary matrix. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

intra-hemispheric FC between the left seed and ipsilateral fronto-parietal regions, namely Frontal Pole, Precuneus, SPL, IPL and aIPS, bilateral insular cortex and STG. A similar ipsilateral mechanism results from the contrast controls > patients, indicating an increase of intra-hemispheric FC with left fronto-parietal regions and insular cortex (Fig. 13, lower blue panel). No significant results were found in either the group of patients or in the contrast patients > controls. These results indicate the absence of significant positive FC in patients between left visual areas and the whole brain during the orientation of attention toward the sighted hemifield.

When considering the shift of attention from the right to the left hemifield in controls (Fig. 14, upper red panel), we found an increase of FC between the right seed and ipsilateral MFG as well as contralateral parahippocampal and lingual gyrus. A similar pattern of FC was found when contrasting controls vs patients, in addition to the left precuneus and bilateral parietal regions, such as SPL and IPL (Fig. 14, lower red panel). In the process of shifting attention from the blind to the sighted hemifield (Fig. 14, blue panel), we observed a significant increase in FC between the contralesional seed and ipsilateral parietal regions (precuneus and SPL) only in the contrast Patients > Controls.

5. Discussion

5.1. Behavioural results

The first important result of this study is the attentional effect found on RT in patients in the orientation discrimination of stimuli presented to the blind hemifield, in terms of faster RT in the valid and neutral than in the invalid condition. A similar effect was observed for the blind hemifield of patient GY (Kentridge et al., 1999a, 1999b, 2004) or in both hemifields of healthy participants when using meta-contrast masking (Kentridge et al., 2008). Interestingly, we did observe only a non-significant difference in RT between orienting attention toward one hemifield (valid condition) and toward both hemifields (neutral condition), in terms of slightly faster RT in the valid condition.

It is important to note that our patients used to miss numerous responses in the blind hemifield reflecting their low level of confidence in providing a response, even when the blind hemifield was the attended location. For this reason, we considered it more realistic to calculate the performance based on the total amount of trials. In this case, the accuracy was below or at chance in all participants, indicating a high difficulty in discriminating stimulus orientation. This result is not unexpected as orientation is a feature related to V1 (Hubel and Wiesel, 1974; Boynton, 2005), an area that was at least partially damaged in all our patients. Moreover, in this case we did not find a significant effect of Cue Validity, indicating that attention was not significantly modulating

the performance in either patients and controls.

Taken together, these results confirm that attention is not a sufficient condition for performance and awareness to improve (the occasional visual feeling reported was not associated with the allocation of attention), even if it can yield an advantage in terms of RT in discriminating stimuli shown in the blind hemifield. Different results have been published by [Hsu et al. \(2011\)](#) in normal participants. They assessed behavioural performance with both aware and unaware stimuli under different attentional conditions and observed a benefit on RT during voluntary orientation of attention (65% valid trials) only when participants were aware of the stimuli. Differences in both experimental design and analysis can explain the difference with our results. However, these findings go in the same general direction, supporting the view that attention and consciousness can operate independently from each other ([Schurger et al., 2008](#); [Wyart and Tallon-Baudry, 2008](#)).

5.2. Brain imaging: orienting of attention

5.2.1. Patients

An important contribution of this study is represented by the assessment of both whole brain activation and FC during orienting or reorienting of attention to unseen stimuli shown in the blind hemifield following a predictive cue.

A main result we obtained during the orientation of attention to the blind hemifield was the activation of ipsilesional occipital regions, mainly the lingual gyrus and a portion of areas V1 and V2. The lingual gyrus has been demonstrated to be involved in early visual processing and has been associated with visual attention ([Mangun et al., 1998](#)), internally directed cognition ([Benedek et al., 2016](#)) and visual imagery ([Kosslyn et al., 2001](#)). This finding is of particular interest as it not only confirms the modulation produced by attention on the activation of visual areas that correspond to the position of visual stimulation ([Posner and Gilbert, 1999](#); [Martínez et al., 1999](#); [Gandhi et al., 1999](#); [Tootell et al., 1998](#)), but it extends this result also to the ipsilesional hemisphere of hemianopic patients. Importantly, the activation of this region was similar in both groups. This is in line with our behavioural results demonstrating that attention can influence the neural activity of visual areas even when stimuli remain unconscious. In this regard, it is important to mention two limitations of our study. The first is represented by the absence of an experimental condition without allocation of visual attention. In order to cope with this problem, we analyzed the BOLD signal related to the neutral condition, when we asked patients to pay attention to the whole visual field (bilateral central arrow) during the orientation discrimination of stimuli shown in the blind hemifield (contrast of interest neutral > baseline). Importantly, in this case we did not observe a significant activation of the ipsilesional lingual gyrus, while we did observe the activation of contralateral visual areas V2 and V3 and of bilateral IPL (see [Figure S4](#), upper panel), likely due to the mechanism of bilateral allocation of attention. These results confirm that the activation of the ipsilesional lingual gyrus previously described was not related either to the mere presentation of contralateral visual stimulation or to a generalized cognitive process of paying attention, but to the orientation of visuo-spatial attention specifically to the blind quadrant. The second limitation is represented by the absence of a direct evaluation of the level of awareness during the fMRI experiment. The lack of such an assessment, due to temporal constraints inside the scanner, does not allow us to rule out the possibility of degraded vision in the blind hemifield of our patients. Despite that, the careful assessment of stimulus features (stimulus contrast and position) and the accuracy in forced-choice orientation discrimination tasks previously performed ([Sanchez-Lopez et al., 2019](#)), strongly suggest that our results are unlikely related to degraded visual processing. That said, it is important to highlight that we can not rule out completely this possibility. Finally, when looking beyond the occipital lobe, during the orienting of attention to the blind hemifield, we observed a significant recruitment of fronto-parietal regions, namely bilateral aIPS, SPL, MFG

and left FEF that belong to the dorsal attentional network.

In order to assess the functional network underlying the activation of this ipsilesional occipital region, we analyzed changes in FC associated with the orientation of attention by means of psychophysiological interaction analysis (PPI). Interestingly, we observed a significant increase of FC between the right lingual gyrus and both hemispheres, involving fronto-occipito-parietal regions, such as the frontal operculum, SPL, IPL, aIPS, SMG and precuneus, when patients were engaged in orienting attention to the blind hemifield. When contrasting patients with controls, we found the additional involvement of the ipsilesional MFG and bilateral LOC. This functional mechanism appears stronger in patients than controls, possibly indicating either a compensatory mechanism activated as a consequence of the lesion, or a general higher cognitive effort due to the visual impairment. These results confirm the activation of a functional network connecting the ipsilesional lingual gyrus with bilateral parietal (IPL, aIPS, SMG) in addition to occipital regions, usually activated during the orientation of attention (occipito-parietal circuit) (for a review, see [Trés and Brucki, 2014](#)). Thus, despite the absence of directionality, on the basis of our results we can assume that the activation of ipsilateral lingual gyrus observed during the orientation of attention to the blind hemifield can be modulated by a top-down attentional mechanism ([Bressler et al., 2008](#); [Vossel et al., 2012](#)).

Instead, when looking at the same cognitive process in the sighted hemifield, we found a less widespread activation focused mainly in contralateral occipital regions and hMT+, possibly due to the flickering of the stimulus, and no significant modulation of FC.

Taken together, these results suggest the idea that both the widespread activation and the modulation of FC can be a consequence of the higher cognitive effort when paying attention to the blind than to the sighted hemifield. These results seem to contradict behavioural data presented by [Tant and colleagues in 2002](#), who reported an attentional bias toward the sighted hemifield in hemianopics during a low-level perceptual task (grey scales task), as a consequence of the unilateral sensory loss. The behavioural performance of patients in our experiment does not suggest that the easiness of the task could explain this difference (accuracy around 80% in the invalid condition in the sighted hemifield), but instead that patients were biased in paying attention to the blind hemifield, possibly trying to compensate for the visual loss. Finally, our results support an attentional effect already observed following multisensory training. Indeed, [Dundon and colleagues in 2015](#), collected electrophysiological evidence of behavioural improvement and reduction of attentional bias to the sighted hemifield in hemianopic patients trained for 2 weeks with an audio-visual training (for a review see [Bertini et al., 2016](#)).

5.2.2. Controls

In controls, during the orientation of attention toward either the left or the right hemifield, we confirmed the activation of the typical brain regions belonging to the dorsal attentional network: aIPS, FEF and SPL, in addition to a strong involvement of contralateral visual areas and bilateral hMT+. Using PPI, we observed a functional coupling between left visual areas and ipsilateral fronto-parietal regions when participants were engaged in orienting attention to the right hemifield. This functional network was similar and symmetrical to the pattern found in patients when orienting attention to the blind hemifield and confirms the action of a top-down mechanism of attention on visual areas.

5.3. Brain imaging: reorienting of attention

5.3.1. Patients

In this study, we were interested also in assessing the whole brain activation during the shift of attention following the presentation of a peripheral stimulus in the unattended location. In this case we were expecting to observe the activation of a right ventral attentional network as a consequence of the presentation of an unexpected task-relevant

target (Corbetta and Shulman, 2002, 2008). In patients, when considering the shift of attention from the sighted to the blind hemifield, we did not observe any significant activation. Moreover, even when looking at the modulation of FC in the same condition, we did not find any significant result. This absence of results suggests the difficulty for unseen stimuli to activate the right ventral network usually involved in detecting unattended, salient and behaviourally relevant stimuli, when the latter are shown in the blind hemifield.

In contrast, when considering the shift of attention to the sighted hemifield, we observed the activation of a bilateral network involving fronto-parietal regions, namely ipsilesional frontal pole, contralesional MFG, SFG and central precuneus. An interesting result is represented by the involvement of the MFG. In 2015, Japee and colleagues, (Japee et al., 2015) demonstrated that activity in left and right MFG was highly coupled during the assessment of resting state functional connectivity. Moreover, right MFG is considered a *hub* connecting the two attentional networks (Fox et al., 2006). Thus, this activity observed in the intact hemisphere might hint at its functional reorganization, as a consequence of the lateralized lesion. Finally, in the same condition, we observed a positive FC between left visual areas and ipsilateral occipito-parietal regions (SPL and precuneus), indicating a positive correlation between contralateral visual areas and ipsilateral dorsal regions during the shift of attention from the blind to the sighted hemifield. Also in this case, the increase of FC remains in the intact hemisphere, highlighting the functional deficit affecting the ipsilesional hemisphere.

These results indirectly confirm the higher cognitive effort of patients when paying attention to the blind hemifield, as they highlight a higher effort in the process of disengaging and shifting attention from the blind to the sighted hemifield than vice versa. Interestingly, during this cognitive process we observed higher activation as well as higher FC in patients than in controls.

5.3.2. Controls

In controls, the activation extracted from the contrast invalid vs valid in either the left or right hemifield yielded a focused activation involving regions belonging to the occipital lobe, mainly contralateral to the visual stimulation. When considering the shift of attention to the left hemifield, the PPI analysis revealed an increase of FC between the right seed and regions belonging to the ventral attentional network, mainly the Middle Frontal Gyrus. In addition, when contrasting Controls > Patients, we obtained significant differences also in bilateral parietal regions, such as the IPL, an area considered to be part of the ventral attentional network and usually responsible of the attentional impairment in neglect patients (Mort et al., 2003) and SPL, a region belonging to the dorsal attentional network. The involvement of these two regions confirms the flexible and dynamic interaction between dorsal and ventral areas during the shifting of attention to unexpected, salient stimuli (for a review, see Vossel et al., 2014) shown in the contralateral hemifield.

Taken together, these results indicate the presence of a positive correlation between the activation of right visual areas and both the ventral and dorsal attentional networks, modulated by the cognitive process of reorienting attention to the contralateral visual hemifield. These findings are in line with other studies, based on the assessment of effective connectivity in healthy participants (DCM - Vossel et al., 2012).

5.3.3. Limitations

An important limitation of this study is the small sample size. As a consequence, we had to perform a fixed-effect analysis, so that our results reflect the data of our specific population and are not generalizable to a wider population of hemianopic patients. Moreover, it was impossible to assess differences in terms of brain activation between patients with left and right lesions, despite the wide knowledge about laterality effects in the attentional process. Finally, the time elapsed between the pathological event and the fMRI scanning session was different in patients although they were always at the chronic stage. Unluckily, the difficulty in finding hemianopic patients fit enough to perform this kind

of task inside an MRI scanner made it impossible to overcome the problem of sample size. Another limitation was the impossibility to have access to an MR-compatible eye tracker so that we could only perform visual inspection of eye movements by using an MRI compatible camera during the scanning session.

6. Conclusions

In conclusion, this study provides evidence of an attentional effect on both behavioural performance and brain activation during the orientation of attention to the blind hemifield. Our findings confirm the dissociation between attention and awareness and shed light on the modulation produced by attention on the activation of ipsilesional visual areas, in a group of hemianopic patients. The activation of these areas seems to be due to a top-down attentional mechanism that involves regions belonging to the right dorsal attentional network, despite the presence of a lesion. Moreover, all results go in the direction of a higher cognitive effort in patients when paying attention to the blind in comparison to the sighted hemifield, and when shifting attention from the blind to the sighted hemifield, possibly as an attempt to compensate for the visual loss. Finally, these results support the possibility of using covert attention to the blind hemifield as a rehabilitation technique (see Zihl, 2010).

Author contributions

Pedersini C.A.: Conceptualization, Methodology, Software, Formal Analysis, Data Curation, Writing – Reviewing and Editing. Lingnau A.: Conceptualization, Formal Analysis, Writing - Reviewing and Editing. Sanchez-Lopez J.: Conceptualization, Methodology. Cardobi, N.: Data Curation. Savazzi, S.: Conceptualization, Methodology, Software. Marzi, C.A.: Conceptualization, Methodology, Supervision, Funding Acquisition, Writing - Reviewing and Editing.

All authors contributed to manuscript discussion, revision, and finally approved the submitted version.

Acknowledgement

This study was supported by European Research Council (ERC) [Grant number 339939 “Perceptual Awareness”]. Authors would like to thank Valentina Varalta, Cristina Fonte, Nicola Smania and Massimo Prior for their contribution to patients’ recruitment and initial clinical examination, Giorgia Parisi for help in testing participants and Gina Joue in designing the experiment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuropsychologia.2020.107673>.

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