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Research report

Blindsight in children with congenital and acquired cerebral lesions

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ABSTRACT

It has been shown that unconscious visual function can survive lesions to optical radiations and/or primary visual cortex (V1), a phenomenon termed "blindsight". Studies on animal models (cat and monkey) show that the age when the lesion occurs determines the extent of residual visual capacities. Much less is known about the functional and underlying neuronal repercussions of early cortical damage in humans. We measured sensitivity to several visual tasks in four children with congenital unilateral brain lesions that severely affected optic radiations, and in another group of three children with similar lesions, acquired in childhood. In two of the congenital patients, we measured blood oxygenation level dependent (BOLD) activity in response to stimulation of each visual field quadrants. Results show clear evidence of residual unconscious processing of position, orientation and motion of visual stimuli displayed in the scotoma of congenitally lesioned children, but not in the children with acquired lesions. The calcarine cortical BOLD responses were abnormally elicited by stimulation of the ipsilateral visual field and in the scotoma region, demonstrating a profound neuronal reorganization. In conclusion, our data suggest that congenital lesions can trigger massive reorganization of the visual system to alleviate functional effects of early brain insults.

1. Introduction

Although the primary visual cortex (V1) is a fundamental stage for visual information processing, subjects with lesions of V1 often have substantially spared visual function (Poppel et al., 1973; Weiskrantz et al., 1974; Barbur et al., 1980; Stoerig and Cowey, 1997; Radoeva et al., 2008). Consistent with a key role of V1 in visual awareness, residual vision for these patients is associated with a lack of consciousness, a condition termed *blindsight* (Weiskrantz et al., 1974). Subjects with blindsight are able to direct their eyes toward visual stimuli presented within the scotoma (Poppel et al., 1973;

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Weiskrantz et al., 1974), to point toward it (Danckert et al., 2003) and in many cases to discriminate the orientation (Morland et al., 1996), the direction of motion (Barbur et al., 1980), the spatial distribution (Sanders et al., 1974) and the wavelength (for a review see: Stoerig and Cowey, 1997) of the stimuli. In the literature a distinction has been drawn between blindsight without visual awareness (Type I) and blindsight associated with awareness of the presence of the stimulus, without perceiving it (Type II) (Weiskrantz, 1997; Sahraie et al., 2010). However, the behavioral discriminations with forced-choice testing are similar for the two types of blindsight (Sahraie et al., 2010). Although many functional aspects of blindsight have been extensively studied, the neural correlates underlying this phenomenon are as yet poorly understood (Cowey, 2010). Some evidence points to major anatomical and functional reorganization of neuronal circuitry. In a recent study on subject GY, an hemianopic subject whose right V1 is lesioned, Bridge et al. (2008) show abnormal contralateral connections between the right lateral geniculate nucleus (LGN) and the left MT+/V5, as well as cortical connections between the two MT+/V5 areas that are absent on controls. Both these aberrant connections bypass calcarine cortex. Abnormal contralateral projections from superior colliculus (SC) to associative, parietal and primary visual areas have also been observed (Leh et al., 2006). Taken together, these data indicate that SC and LGN may have a key role in the reorganization of neuronal structures subserving blindsight (Tomaiuolo et al., 1997; Leh et al., 2010; Tamietto et al., 2010) supporting earlier evidence from monkey and cat lesion studies (Payne et al., 1996; Sorenson and Rodman, 1999; Lyon et al., 2010; Das et al., 2012). However, a contribution associated with a plastic reorganization of primary visual cortical circuitries cannot be excluded. A recent study showed that the spared V1 can respond to ipsilateral stimuli in the hemianopic visual field, but only after prolonged visual training (Henriksson et al., 2007) that also restores perceptual awareness.

Both in cat and monkey, early cortical lesions yield more extensive residual capabilities than those occurring in adulthood, including near-normal shape discrimination (Cornwell et al., 1989; Cornwell and Payne, 1989), motion discrimination (Moore et al., 2001) and visual orienting oculomotor behaviors (Moore et al., 1996). Interestingly, one of the factors that makes blindsight more likely is the age at lesion (Ptito and Leh, 2007) and blindsight subjects who acquired the damage during childhood (e.g., the extensively studied subject GY by the age of 8) are those that show a more profound neural reorganization (Leh et al., 2006; Bridge et al., 2008). A study on a large group of subjects with occipital lesions acquired between late teens and around 30 years reported a solid correlation between age at lesion and the probability that the scotoma shrinks during the years following brain injury (Teuber, 1975). Similarly, recovery of visual capabilities was greater in patients who underwent hemispherectomy at the age of 7, compared with cases where the surgery occurred later in life (Perenin, 1978; Perenin and Jeannerod, 1978). Of particular interest are the clinical cases in which brain lesions occur very early, around birth, when the visual system is highly plastic and susceptible to massive neurophysiological reorganization and capable of compensating for functions normally attributed to the damaged structures (Kiper et al., 2002; Knyazeva et al., 2002). Werth (2006) reported the case of a child who underwent hemispherectomy at 4 months of age, but later developed a normal visual field comparable to age-matched controls. Recently, Muckli et al. (2009) reported V1 blood oxygenation level dependent (BOLD) activation with a retinotopic map to ipsilateral stimuli in a patient born with only one hemisphere.

In this study we measured residual perceptual capacities in children with homonymous hemianopia caused by unilateral lesions involving the posterior cortico-subcortical visual pathways caused by medial cerebral artery stroke occurring around the time of birth, which usually affects the optic tract or optic radiations (Jacobson et al., 2010). We compared hemianopic patients with congenital optic radiation lesions with those who acquired similar lesions during childhood to reveal the functional and anatomical reorganization potential of the human visual system in response to an early (perinatal) brain lesion.

2. Subjects and methods

2.1. *Clinical description*

This study was conducted under ethical approval from the Stella Maris Scientific Institute Ethics Committee. Subjects and parents gave informed consent in accordance with the Declaration of Helsinki. Subjects belonged to two different groups: “congenital” and “acquired” brain lesions children. All subjects in the first group had experienced neonatal arterial infarction around term whilst children of the second group suffered similar arterial damages from vascular insult occurring later in childhood (see Table 1). Brain lesions of all subjects were documented by MRI-scans. For all subjects vascular trauma resulted in complete or severe unilateral damage of optic radiation (see Figs. 1 and 6 for anatomical MRI of S2) that in turn causes a scotoma in the hemifield contralateral to the lesion. The visual field of each patient was assessed by means of an automated perimetry system (KOWA AP 340: similar to the Humphrey perimeter). Each eye was tested at full strength and full field (237 points), monitoring fixation. No subject showed peripheral or refractive errors, except for a mild (.5 diopter) astigmatism in S4. All have a normal intelligence quotient as measured by Wechsler scales. They all have a motor disability classified as hemiplegia (Hagberg et al., 1975) due to the brain lesion. Age at testing ranged from 11 to 17 years. Table 1 reports a detailed clinical history of each subject.

Subjects with congenital lesions all have very extensive unilateral damage to the left or the right temporal–parietal cortex, extending to occipital and frontal cortex. Importantly, all had damage to the optic radiations, but only S2 (see also Fig. 6) had a lesion of the calcarine cortex in the affected hemisphere. All subjects have major visual field defects contralateral to the side of the brain lesion, and S2 showed a complete hemianopia in the right hemifield with no central sparing.

The acquired lesion group comprised two children who had experienced a rupture of a cerebral artery between

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Table 1 – Clinical data.

Group	Sex	Age	Lesion					Outcome		
			Timing	Side	Site	Optical radiation	Description	Motor	Epilepsy (drugs)	Visual field
Congenital										
S1	f	16 y	Perinatal	R	F, T, P, O, sc	R partially	MCA infarct: main branch	L hemi	No	LLQ
S2	m	15 y	Perinatal	R	T, P, O, sc	R completely	MCA infarct: main branch	L hemi	Yes (CBZ, TPM)	LHH
S3	m	13 y	Perinatal	Bil > L	T, P, O, sc	L partially	MCA infarct: main branch	R hemi	Yes (VPA)	RLQ + part of RUQ
S4	m	17 y	Perinatal	L	T, P, O, sc	L partially	MCA infarct: main branch	R hemi	Yes (CBZ)	RLQ + part of RUQ
Acquired										
S5	f	11 y	6 y	Bil > R	F, T, P, O, sc	R completely	MCA infarct: main branch (Moya Moya Syndrome)	L hemi	Yes (VPA)	LHH
S6	f	16 y	13 y	R	sc	R completely	Rupture of AVM at the level of IC, Th and CR	L hemi	No	LHH
S7	f	17 y	15 y 9 m	L	sc	L completely	Rupture of AVM at the level of IC, Th and CR	R hemi	No	RHH

f = female; m = male; y = year; m = month; R = right; L = left; Bil = bilateral; F = frontal; P = parietal; T = temporal; O = occipital; sc = subcortical; MCA = middle cerebral artery; AVM = arterio-venous malformation; IC = internal capsule; Th = thalamus; CR = corona radiata; hemi- = hemiplegia; CBZ = carbamazepina; TPM = Topiramate; VPA = valproic acid; LLQ = Left lower quadrant; LHH = left homonymous hemianopia; RLQ = Right lower quadrant; RUQ = Right upper quadrant; RHH = right homonymous hemianopia.

13 and 16 years, and one child with Moyamoya disease (a progressive occlusive disease of the cerebral vasculature with particular involvement of the circle of Willis and the related arteries). In all cases, the lesions were extensive, although slightly smaller than for the congenital subjects, and involved right or left subcortical structures extending to the optic radiations but leaving calcarine cortex intact. All 3 subjects had a complete hemianopia and no central sparing for S5 and S6 and a partial sparing in S7.

Four age-matched subjects with normal vision were recruited to obtain normative data.

2.2. *Psychophysical tests*

Visual stimuli were generated by a Cambridge VSG 2/5 framestore and presented with a refresh rate of 100 Hz on a Pioneer color plasma monitor subtending 40° × 30° from the viewing distance of 114 cm (with a spatial resolution of 13 pixels/°) and 80° × 60° at a distance of 57 cm. All stimuli were presented on a gray background [Commission Internationale de l'Eclairage (CIE) coordinates xyY: .35, .35, 200 cd/m^2]. Subjects were instructed to keep fixation on the central red disk (CIE coordinates xyY: .63, .35, 90 cd/m^2) subtending .2° and the fixation was monitored visually by an experimenter. In addition, for subject S4 eye movements were recorded with an infrared sensor eye tracker (ASL model 504, sampling frequency of 60 Hz) and data analyzed offline. All trials in which subjects' eyes moved from fixation during stimulus presentation were excluded from data analysis.

2.2.1. *Cross-hemispheric alignment task*

Two gratings windowed in a circular aperture of 2° radius were presented simultaneously for 200 msec in the left and right hemifield with a horizontal eccentricity ranging from 10° to 18° and variable vertical eccentricities with one stimulus falling within the scotoma. One subject (S4) was also tested with 4° radius stimuli at horizontal eccentricities of 20° and 35°, at the viewing distance of 57 cm. In three subjects with lower visual field defects (S1, S3 and S4), the fixation point was shifted upward toward the edge of the monitor to increase the area of possible stimulation and the data were collected at an average vertical eccentricity of 12°, well within the scotoma. For all trials, the stimulus in the spared visual field was presented with vertical eccentricities of ±5° relative to screen center. The stimulus in the blind field was displaced with an elevation of ±5° relative to the stimulus in the normal visual field. This procedure ensured that the absolute position of the stimulus in the spared field could not provide any useful cue for the localization task. The stimuli were sinusoidal gratings of 20% contrast, .5 cpd spatial frequency and oriented horizontally.

The elevation difference (Δ) between the stimulus in the scotoma and the stimulus in the spared field was varied from trial to trial by an adaptive staircase QUEST (Watson and Pelli, 1983) and the subjects were required to indicate the side where the stimulus had the higher elevation [Two Alternative Force Choice (2AFC)]. We calculated the proportion of trials in which subjects reported that the stimulus in the scotoma was higher, as a function of the elevation difference (Δ). The data (about 120 trials collected over 2 or 4 sessions) were fitted with cumulative Gaussian curves and thresholds were calculated as half of the elevation difference yielding 25% and 75% performance.

2.2.2. *Contrast sensitivity for motion and orientation*

A single grating (.5 cpd) windowed within a square or diamond aperture with 2° side was presented at random on either side of fixation, 15° from the vertical midline, 10° below the horizontal meridian so that the stimuli in the blind hemifield fell well within the scotoma. For motion-direction discrimination

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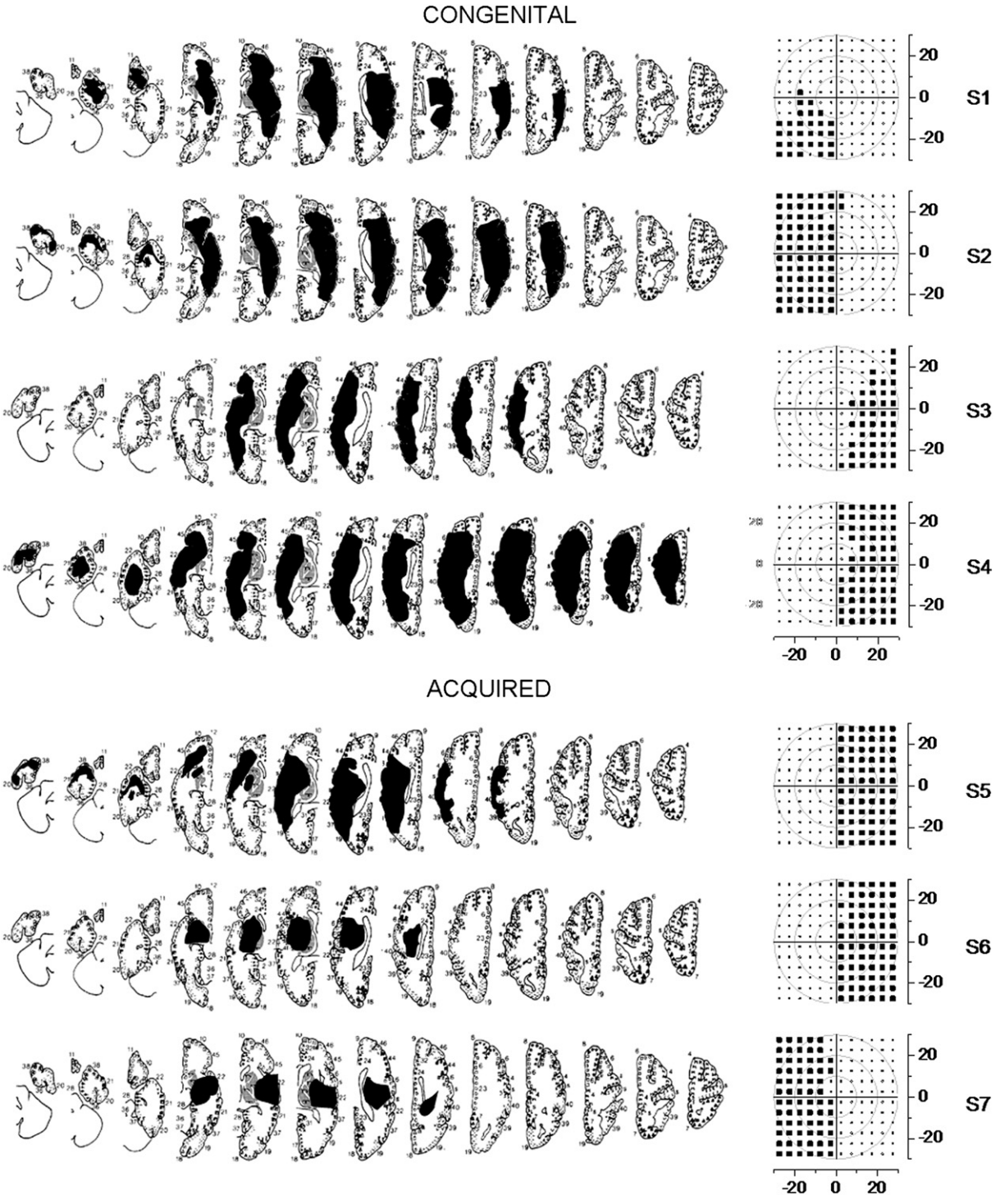

Fig. 1 – Lesion reconstruction and visual field perimetry. Graphical reconstruction of the lesion and of visual field perimetry. Top panel: data of the four congenital subjects. Bottom panel: data of the three subjects with lesions acquired during childhood. Lesions are illustrated in black on the Damasio and Damasio (1989) atlas. Visual field perimetry obtained with the KOWA are re-sampled at 5° resolution. Black squares indicate the visual field where subjects could not detect a 100% contrast stimulus.

the grating was vertical, drifting leftward or rightward at 4 Hz within a square aperture, for orientation discrimination the grating was stationary at ±45° orientation within a diamond aperture. The stimulus presentation duration was 200 msec to minimize the possibility of saccadic movements toward the stimulus location. Stimuli contrast was varied according to an adaptive staircase QUEST (Watson and Pelli, 1983) that homed in on threshold (contrast level yielding 75% of correct

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responses). Subjects indicated the direction of motion or the orientation, guessing when unsure. Usually 80 trials were collected, and in 2 subjects the measurements were repeated at least twice over a period of one–two years (during the medical check-up).

2.2.3. *Procedure*

Before each session of psychophysical data collection, the task was explained to the subject, using long exposure stimuli and allowing eye movements. Subjects were briefed at the beginning of the session that in each trial the stimuli were always presented and that the procedure required a forced choice between two alternatives in all cases (2AFC), even when some of the stimuli were not visible. We explained that in these cases, that could be also very frequent, he/she should decide at random or on "vague feelings". To check that the task was clear, we recorded 10–15 training trials where the stimuli were always positioned outside the scotoma. During the data acquisition, while controlling fixation, subjects' responses were reported verbally and recorded by an experimenter. To exclude improvement due to perceptual learning we gave no feedback and tried to collect the data in limited number of trials, using adaptive staircases. If the test required more trials, it was repeated in subsequent sessions separated by months to avoid perceptual learning. In the initial trials of data collection, many subjects complained that they did not see the stimuli, but they were encouraged to take a guess. We also asked to report if they had a feeling of the presence of a stimulus in the hemianopic field. In addition, every 5–10 trials, we asked if they consciously perceived some stimuli in the blind field. No subject reported being aware of stimuli in the hemianopic field.

2.3. *Imaging methods*

Two subjects (S2 and S4) with congenital brain lesions were scanned twice, on separate days (with gaps of 2 years for S4) for motion selectivity and retinotopy. The ability of subjects to maintain fixation was assessed outside the scanner and for subject S4 was measured during the scanning session (with Resonance Technology infrared camera and Arlington Research software). No breaks of fixation were ever observed, either inside or outside the scanner, other than small saccades less than 1°. For all functional magnetic resonance imaging (fMRI) stimuli the resolution of the display was 600×800 pixels with a refresh rate of 60 Hz.

2.3.1. *Functional imaging (fMRI)*

Imaging data for the new data set were acquired on a GE 1.5 T HD Neuro-optimized System (General Electric Medical Systems) fitted with 40 mT/m high-speed gradients. Functional data were acquired with a single-shot gradient-echo, echo planar (EPI) sequence. Acquisition parameters were as follows: 21 axial slices of 5 mm thickness, 64×64 matrix, 3×3 mm in-plane resolution, 50 msec echo time (TE), 3000 msec repetition time (TR), 90° flip angle. Each scan of the main experiment comprised 124 or 164 functional volumes (the first four volumes were discarded to allow stabilization of the BOLD signal) for retinotopy and was repeated twice in each session. Coverage included supra-tentorial structures and most of the cerebellum. Moreover a whole-brain fast spoiled gradient recalled acquisition in the steady-state T1-weighted series (FSPGR) was collected in the axial plane with TR 12.4 msec, TE 2.4 msec, inversion time (TI) 700 msec, flip angle = 10°, yielding 124 contiguous 1.1 mm axial slices with an in-plane resolution of $1.1 \times 1.1\,mm^2$. We also measured Diffusion Tensor Imaging (DTI) to confirm the presence of a lesion of optic radiations in the lesioned hemisphere (results not shown). BOLD responses were analyzed using Brain Voyager QX (version 1.9, Brain Innovation). Functional data were temporally interpolated and re-sampled to compensate for systematic slice-dependent time differences. Odd–even slice intensity differences resulting from the interleaved acquisition were eliminated. The overall image intensity was normalized within scans to a standard value to compensate for inter-scan intensity differences. The data were realigned to the first volume of each scan, using a six-degree-of-freedom rigid-body affine transformation to compensate for head motion during the scanning procedure. The functional data were transformed into a standard coordinate system, derived from the intact hemisphere. Finally, the data were spatially re-sampled to a cubic voxel with a linear size of 1.0 mm and analyzed using a General Linear Models in which the BOLD time course was modeled by convolving the duration of the stimulus with an assumed hemodynamic response function.

For retinotopic mapping, the cortical representation of vertical and horizontal meridians was identified by presenting one hundred moving dots (.33° diameter, expanding or contracting every 2.0 sec, limited lifetime of 300 msec) in two opposing sectors (±10°) along the two principal meridians on the Resonance Technology goggles that stimulate about $30 \times 20°$ of the binocular visual field. The contrast of the dot was about .8, half white and half black, the mean luminance of the display about 30 cd/m^2.

Each sector (±18° of visual angle) extended from the screen center (corresponding to the fixation point) to the extreme border of the monitor and was presented for 15 sec, twelve times in each scan. To identify the upper, lower, right and left visual quadrants, 22 moving dots were presented within four circular sectors of ±42° angle centered along the ±45° orientation. The quadrants (10° radius) were presented one at the time in clockwise order with four repetitions of each quadrant. For motion selectivity, dots moved along a spiral flow field that changed gradually in 2 sec from pure expansion, to inward spiral, clockwise rotation, spiral, contraction and so on and contrasted against stationary dots with the same limited lifetime within a circular window of 11° radius.

3. Results

3.1. *Behavioral results*

All congenital hemianopic subjects showed evidence of unconscious visual perception in all three behavioral tasks [Blindsight Type I (Weiskrantz, 1998)], while the subjects with similar brain lesions acquired during adolescence showed no signs of residual vision in the blind field. Interestingly, despite the locomotion deficit associated with the hemiplegia, the

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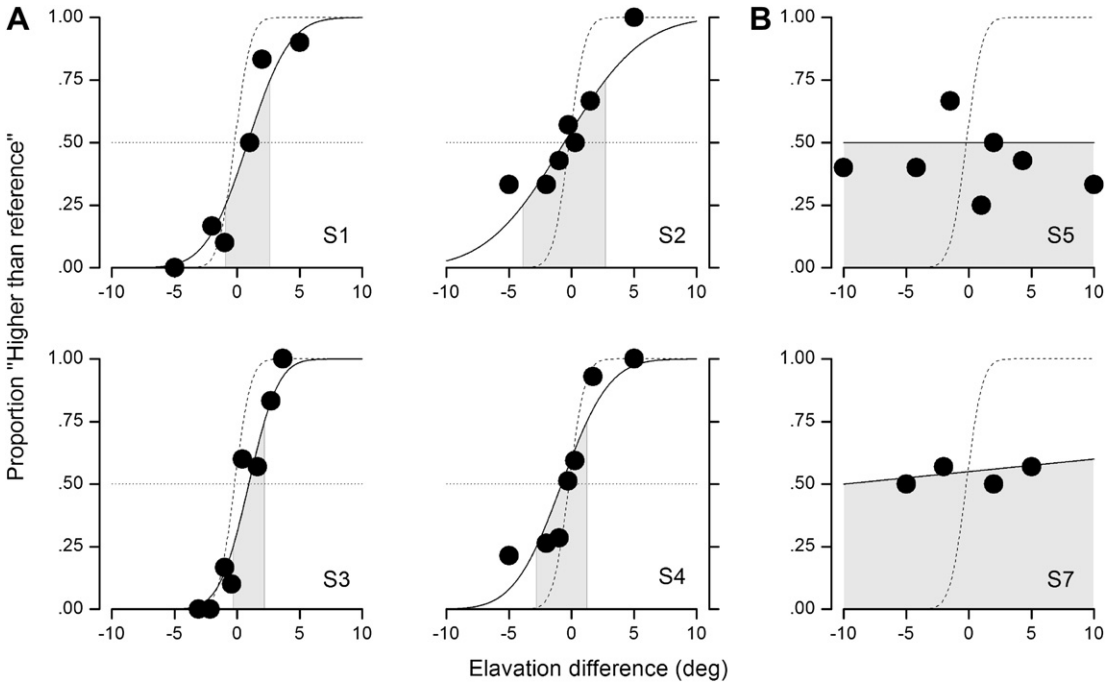

Fig. 2 – Psychometric curves for the cross-hemispheric alignment task. Percent of trials in which subjects responded that the stimulus in the scotoma was higher than the reference, as a function of the elevation difference between the two stimuli. Single data points represent binned responses at a given elevation difference; continuous lines are best fitting psychometric curves. The shaded area highlights the region between 25% and 75% "higher" responses, corresponding to twice the Just Noticeable Difference (JND). Dashed curves show average normative data of healthy subjects. A: psychometric curves for the four congenital subjects; B: psychometric curves for two acquired subjects.

congenital patients were always able to avoid obstacles while walking, as has been documented in other blindsight patients, including a patient with both primary visual cortices lesioned (de Gelder et al., 2008). Fig. 2A shows psychometric curves for the congenital hemianopic subjects and Fig. 2B for two of the early-acquired hemianopic subjects for the intra-hemispheric alignment task, the dashed curves reporting average performance for normal subjects. The graphs show spatial judgment accuracy as a function of elevation difference between two stimuli, one displayed in the spared hemifield and the other in the scotoma. Particular care was taken to avoid presenting stimuli outside the scotoma. All congenital subjects performed well above chance for elevation differences greater than 1°, with maximum accuracy of more than 90% correct responses for the greatest elevation tested (5°), despite the brief presentation time of the stimuli (200 msec). The average threshold (defined as half the elevation difference yielding 25–75% performance) was 2°, higher than that measured in typical subjects (.8° ± .3°: the average psychometric function indicated by dashed curves), but quite adequate in many real life tasks such as object avoidance. On the contrary, the two subjects with brain lesions acquired in adolescence were unable to perform the task, with performance close to chance even for elevation differences of 10°, indicating they could not retrieve any spatial information about stimuli presented within the scotoma. Importantly, both the congenital and the acquired lesion subjects, when questioned if they "saw" the stimulus in the scotoma, replied negatively.

In subject S4 we increased task difficulty by testing at larger eccentricities. The performance at 35° eccentricity is about 3.5°, close to normal (around 1°) in the same condition (Fig. 3). The alignment thresholds of S4 for central stimuli were also good, less than twice those of typical subjects, indicating that

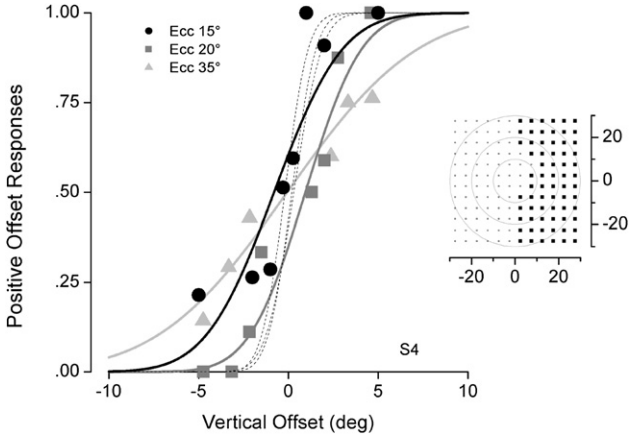

Fig. 3 – Psychometric curves for the elevation task at 3 different horizontal eccentricities for subject S4. The three eccentricities (15°, 20° ad 35°) are color-coded from dark to light colors respectively. Normative data for the three eccentricities are shown as dashed curves. Inset shows the perimetry of subject S4, re-sampled at 5° resolution.

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the mechanisms mediating this ability may be relatively unimpaired.

Evidence of unconscious perception in the blind hemifield of congenital subjects is also provided by their sensitivity to motion and orientation. Fig. 4 shows the psychometric functions for orientation discrimination. Contrast thresholds for discriminating grating orientations in the spared hemifield were between .6% and 1% for all hemianopic subjects, similar on average to those of fully healthy adult controls ($1 \pm .2\%$). All hemianopic subjects with acquired brain lesions performed at chance, even at the maximum luminance contrast tested (50%). However, all congenital subjects were able to unconsciously discriminate orientation of stimuli presented within the scotoma with only a small impairment of contrast thresholds, of about a factor of 4.

A similar pattern of results held for motion-direction discrimination. For both clinical groups, contrast thresholds for stimuli presented in the spared hemifield ranged between .5% and 2%, similar to normative values ($1.1 \pm .3\%$ as shown by the dashed curves in Fig. 5). Congenital hemianopic subjects (with the exception of S2) were also able to discriminate motion direction for stimuli presented within the scotoma. Contrast thresholds ranged between 3% for subject S1 up to 10% for subject S3 indicating unconscious visual motion processing in the blind hemifield was impaired (more than 1 log-unit) but not completely abolished. Interestingly for S1 and S4 the thresholds of the normal and the hemianopic visual fields were very similar, although both were slightly impaired compared with typical subjects. On the other hand, hemianopic subjects with acquired brain lesions showed a complete lack of sensitivity to visual motion of stimuli presented within the scotoma, performing at chance even for contrast of 90% (results not shown for brevity).

3.2. *Cortical BOLD responses*

In two subjects (S2 and S4) with congenital lesions (those with more extensive visual field defects) and 3 normal subjects, we were able to measure BOLD responses to random-dot stimuli distributed over $\pm 10^{\circ}$ along the horizontal and vertical meridians and the four separate quadrants of the visual fields. Fig. 6 shows the reliable ($p < .0008$) BOLD responses for upper and lower quadrants of the left visual field in a normal subject and in the congenital subject S2. The stimuli in the normal subject stimulate the right visual cortex, contralateral to the stimulated visual field. The right hemisphere of subject S2 has a large lesion with a small sparing of the occipital pole. However, no activity of the right occipital pole was elicited by the visual stimulus, consistent with the lesion of the optic tract and optic radiation revealed by neuro-anatomical scan. The left hemisphere appears on first inspection anatomically normal, but surprising results were obtained by stimulation of the hemianopic visual field. These stimuli elicited strong responses in a large territory of the ipsilateral visual cortex,

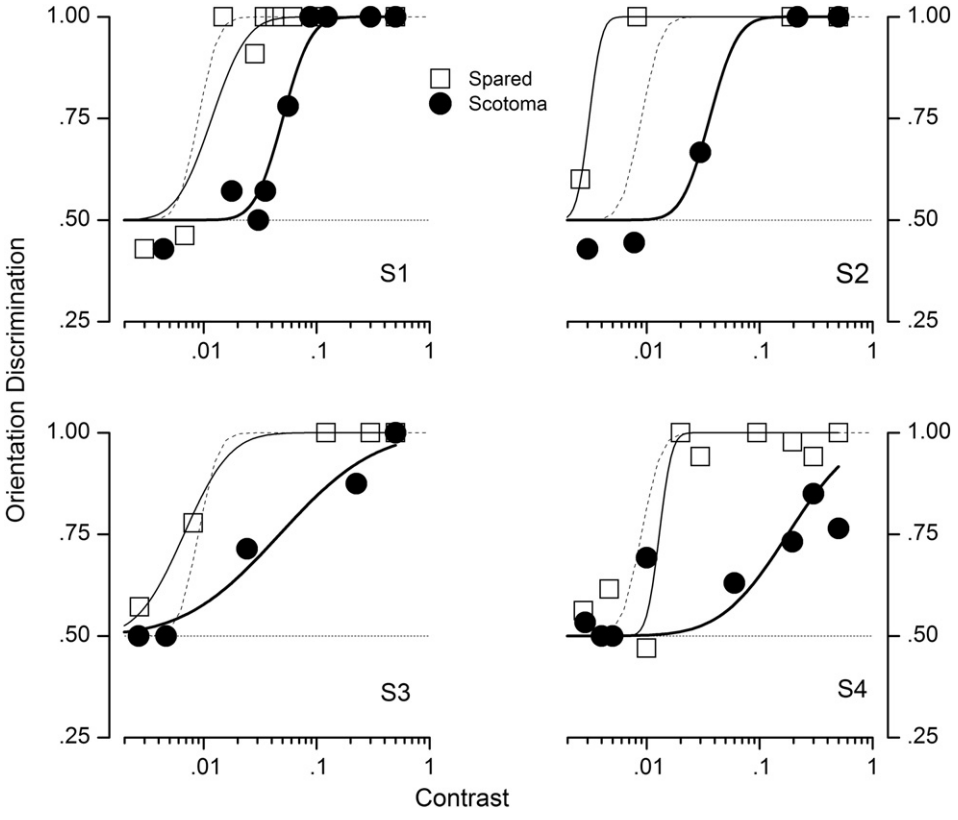

Fig. 4 – Contrast sensitivity for orientation discrimination. Psychometric curves for orientation discrimination of sinusoidal grating stimuli presented either in the scotoma (black circles) or in the spared hemifield (hollow squares), at horizontal eccentricity of 15°, spatial frequency .5 cpd, presentation time 200 msec. Continuous lines are the best cumulative Gaussian fit. At high contrasts all subjects attain near perfect performance even in the blind hemifield.

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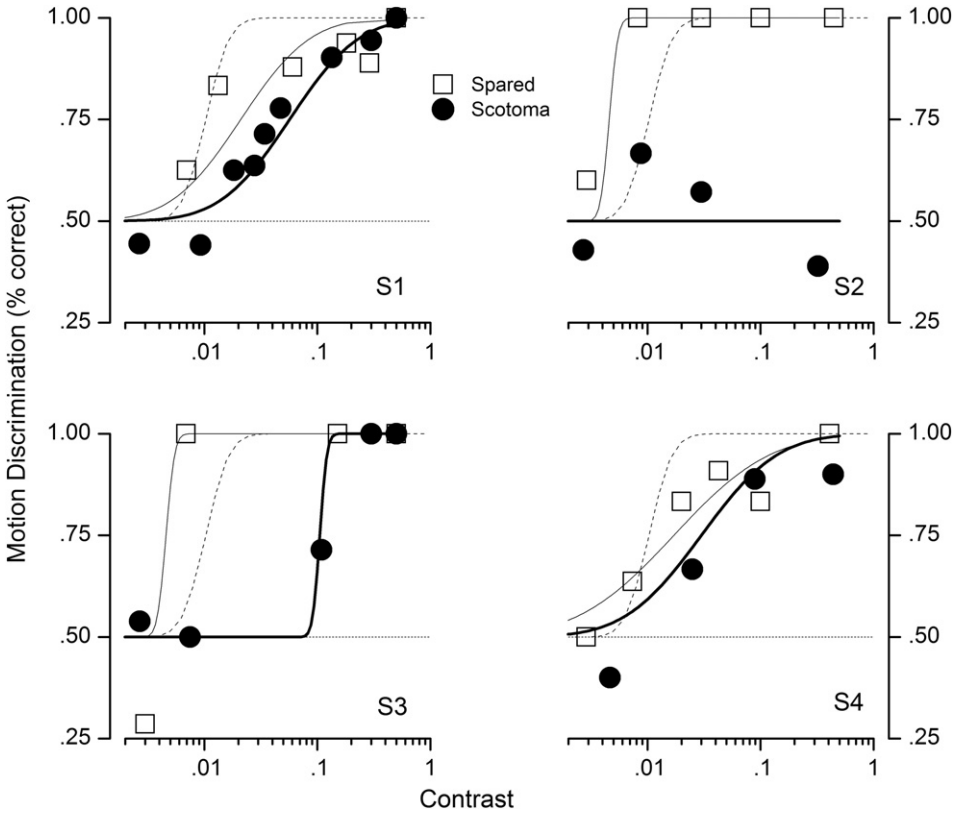

Fig. 5 – Contrast sensitivity for motion-direction discrimination. The stimuli were sinusoidal gratings of frequency .5 cpd, presented inside a square window of 4° at horizontal eccentricities equal to 15°. All other conventions as for Fig. 4.

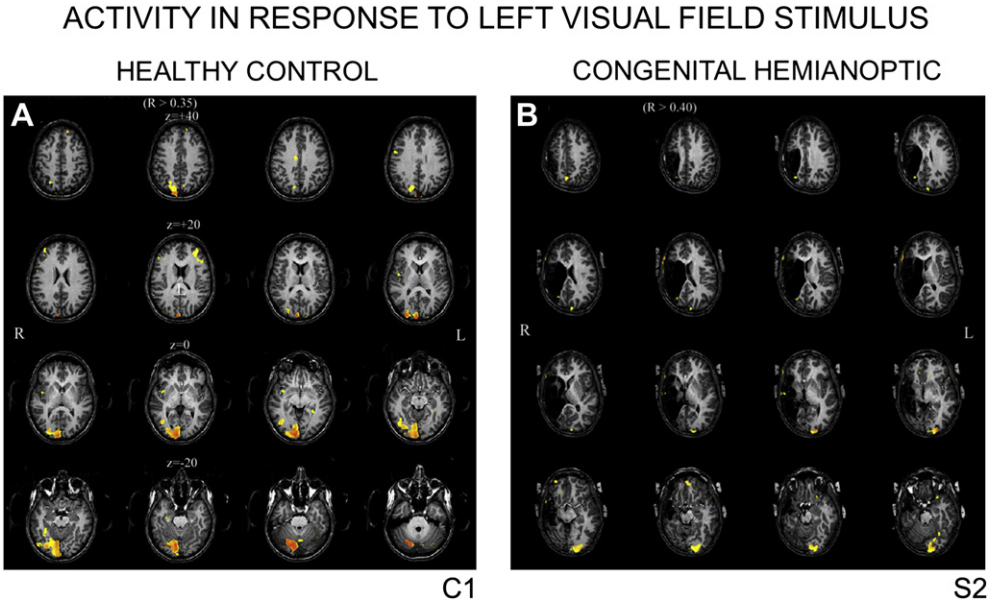

Fig. 6 – MRI brain scan and BOLD activity in response of the left visual field stimulation in a normal subject (A) and in congenital lesion subject S2 (B). The lesion is very extensive over most of the temporal, parietal and occipital lobe and with clear involvement of subcortical optical radiation. Superimposed to the anatomical slice is illustrated the BOLD activity in response to the stimulation of the upper and lower quadrants of the hemianopic visual field against homogenous background with p (no-corrected) < .0008. Note that the stimulation produced strong activity in the ipsilateral occipital cortex in S2, but it is limited to the contralateral occipital cortex in C1.

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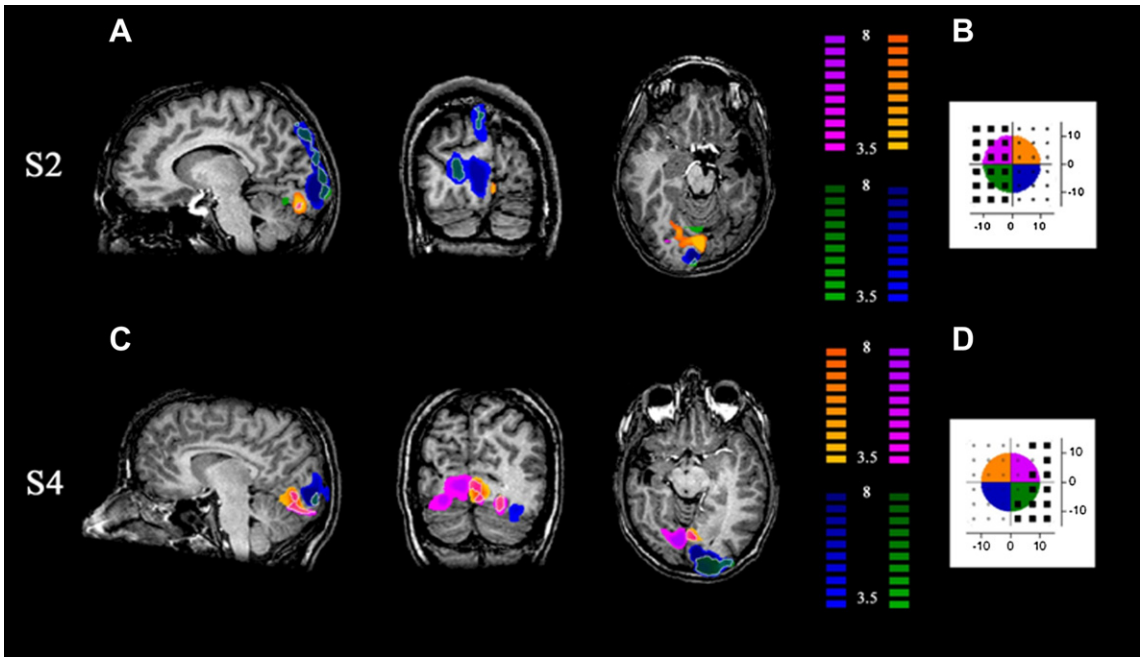

Fig. 7 – Statistical t-map of BOLD response to expanding–contracting visual motion presented in 12° quadrants of visual field in patient S2 (A) and S4 (C) in neurological convention (t-scale on color code on the left). B and D show the perimetry and the color-code of the visual quadrant for the BOLD responses. The activity to intact visual stimulation (contralateral visual field) is always Orange for the upper and Blue for the lower visual field; for the hemianopic visual field it is in Purple for the upper and Green for the lower visual field. The white borders highlight the regions that show co-activation to two visual stimuli. Note that both in S2 and S4 intact hemisphere is representing ipsilateral visual stimuli.

never observed to date in normal subjects (compare BOLD activity of S2 and of C1 of Fig. 6). Fig. 7A illustrates in color the representation of the upper (Blue) and lower (Orange) quadrants of the normal visual field and in the upper (Purple) and lower (Green) quadrant of the hemianopic visual field. S2 showed a strong response along the calcarine sulcus to stimuli presented along the horizontal meridian (not shown), with the ventral activity elicited by contralateral superior visual field and dorsal activity elicited by the contralateral inferior visual field (Blue and Orange of Fig. 7A). Interestingly, the responses partially overlap with the cortical territory that usually represents stimuli at similar eccentricity in the normal visual field (highlighted in the Fig. 7A with white boundaries).

Similar results were also obtained in the second subject studied by fMRI (Fig. 7C and D). This subject has a scotoma (with macular sparing) in the right lower visual field, which extends to the more peripheral part of the upper visual field. Consistently, the anatomical scan and the DTI indicated the presence of a small spared white matter bundle reaching the occipital lobe.

The stimuli positioned outside the scotoma, covering the 10° quadrant of the visual field (Orange upper-left; Blue lower-left normal visual fields; and Purple upper-right visual field) all elicited strong activity in the contralateral hemisphere, both along or close to calcarine sulcus, and in the lateral-occipital cortex. However, stimulation of the central 10° in the lower-right visual field (Green) also elicited a strong response in the ipsilateral cortex both along the calcarine and the lateral cortex. Interestingly, the upper-field stimulation is represented ventrally respect to the calcarine sulcus (in the contralateral cortex) and the lower-field dorsally (in the ipsilateral cortex), indicating some retinotopic organization in these aberrant representations.

4. Discussion

Our results suggest that children with congenital (but not with acquired) postnatal brain lesions show spared visual perception (although unconscious) in the affected hemifield, clear evidence for blindsight. The imaging results suggest that residual vision in children with congenital hemianopia may be mediated by massive reorganization of their visual system, as the V1 of the intact hemisphere also responds to stimuli in the ipsilateral 'blind' hemifield. Our data suggest a different type of reorganization and visual plasticity in subjects with congenital unilateral extensive brain lesions compared with subjects with similar lesions acquired during childhood, reinforcing previous evidence in patients with bilateral calcarine lesions (Kiper et al., 2002; Knyazeva et al., 2002). Although the proportion of subjects with acquired V1 lesions during adulthood who show blindsight is controversial (Weiskrantz, 2004) and is estimated to be from 1/20 to 8/10 (Sahraie et al., 2003), no study has yet demonstrated it in all tested subjects for three different tasks, as in the present study. This indicates that the level of brain plasticity and reorganization potentials at the time of lesion is an important property for the instauration of blindsight, consistent with the animal brain-lesion literature. Cats with cortical lesions

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performed in infancy discriminate shapes as well as intact cats, even for complex patterns, such as targets embedded in a noise background, while animals lesioned in adulthood show poor performance (Cornwell et al., 1989; Cornwell and Payne, 1989). Moore et al. (1996) compared performance on an oculomotor detection and localization task in monkeys with striate cortex ablation performed in adulthood against those performed during the visual critical period. While the first group was not able to perform the motor task, nor recover performance by learning, animals with early brain lesions did show residual capacities soon after the lesion and were able to recover to normal performance by the end of the testing session. Similarly, the ability to localize and discriminate visual motion depends on the time the brain lesions are performed. Monkeys with early striate cortical lesions can move the eyes toward moving dots, as well as provide an eye movement congruent with the stimulus motion direction, indicating normal summation of motion signals within the scotoma (Moore et al., 2001). The extraordinary level of residual vision found in early lesioned animals is associated with a massive rewiring of the visual system, including selective visual pathway reinforcement, neuronal degeneration and adjustment of neural activity (for a review see: Payne et al., 1996).

In adult animals visual information can reach visual associative cortex (V2-MT) through many routes, and SC is one key station relaying information both through pulvinar and by back-projection to LGN (Berman and Wurtz, 2008, 2010, 2011). In addition, there is clear evidence for direct K-pathway projections from LGN to associative cortex (Schmid et al., 2010). Supposing that monkeys and humans share similar pathways, our data suggest that these extra-striate pathways may not be necessary to mediate blindsight. No evidence was found for lesions involving SC and LGN in both groups of patients, and similar lesions of the optical radiations were observed both in congenital and early-acquired patients, although the latter did not show blindsight. On the contrary, our data seem to suggest that blindsight requires some degree of brain rewiring and cortical reorganization. In GY, one of the most-studied blindsight subject with V1 lesions, DTI tractography showed an aberrant anatomical projection of contralateral LGN to MT+ (Bridge et al., 2008) supporting rewiring of subcortical pathways. DTI tractography of the visual pathways of hemispherectomy subjects with blindsight, revealed also that SC is connected to many ipsi- and contralateral cortices, including V1, while only ipsilateral projections were observed in hemispherectomized subjects without blindsight, or in controls (Leh et al., 2006). Functional imaging studies have also provided evidence for a pivotal role of SC for unconscious vision. Sahraie et al. (1997) found that in subject GY, while conscious visual motion discrimination relies on activity of visual neocortex, unconscious discrimination requires activation of SC together with medial and orbital prefrontal cortex. Leh et al. (2006) investigated behaviorally the role of SC in a group of blindsight hemispherectomy subjects by applying a spatial summation paradigm between stimuli concurrently presented in the blind and spared hemifield. The results indicate that while achromatic stimuli facilitate reaction times, S-cone-isolating stimuli did not. As SC does not receive retinal signals from S-cones (Marrocco and Li, 1977; Schiller and Malpeli, 1977), a lack of facilitation for S-cone-isolating stimuli suggest that SC is involved in blindsight. Similar effects have also been demonstrated by fMRI (Leh et al., 2010), where facilitation was observed for achromatic stimuli in MT, but not V1. Unlike the study of Leh et al. (2006), our congenitally lesioned subjects have strong BOLD representation of the ipsilateral visual field in the calcarine cortex, indicating a rewiring involving early visual processes and not limited to extra-striate cortices. Interestingly the two patients whom we studied by fMRI have lesions that clearly affected associative visual cortices including MT complex. This may be the critical difference that promotes reorganization of spared V1. One possibility for explaining ipsilateral activity in the spared V1 is that some of the retinal ipsilateral projections to LGN and SC, observed during early development in young animals and possibly also in human infants (Chapman, 2003), did not degenerate given the massive lesions to one hemisphere at birth. A recent study showed that there are cases in humans where the spurious ipsilateral projections are functional in adulthood. For example, a patient born with only one LGN and cortex, and one eye, has a representation of both the ipsi- and contralateral visual field in the spared LGN and V1 (Muckli et al., 2009). Similar LGN representation of the ipsilateral visual field could be present in our congenitally lesioned subjects, explaining both the psychophysical abilities and the BOLD responses. However, this alternative would not be consistent with a dense scotoma. The aberrant information carried by direct retinal-LGN-V1 projections should be treated as normal and should give rise to conscious perception, as is the case for the patient by Muckli et al. (2009). Our subjects were nearly always unaware of the presence of the stimulus in the scotoma. This leaves the possibility that the rewiring, or the aberrant projections, do not involve LGN, but rather SC that should send visual information to the contralateral visual cortex bypassing ipsilateral cortex and callosal connection. This would be consistent with previous evidence discussed above.

A crucial point in the interpretation of our data may be the presence of macular sparing in subjects with congenital, but not acquired lesions. However, it is unlikely that macular sparing can explain the results for two reasons. Firstly, we tested subjects at different eccentricities to be sure that the stimuli did not encroach on the macula. Secondly, one subject with congenital lesions had no macular sparing, but showed visual performance similar to that of all other subjects with congenital brain lesions.

Unconscious performance of our subjects with congenital lesions was not only above chance, but in almost all tasks reached optimal performance (100% of correct response) for supra-threshold signals (high contrast or large elevation difference) with a presentation time as short as 200 msec. This is unlikely to be due to overtraining, given that the tasks were performed only three or at most four times, too little to establish learning. However, these data are in agreement with previous studies in adult subjects showing behavioral performance equal or better for the hemianopic field (Weiskrantz et al., 1995; Henriksson et al., 2007; Trevethan et al., 2007). They are also consistent with a previous developmental study from our group (Tinelli et al., 2011), where we found that subjects with congenital lesions and visual field defects were able to perform visual search task at normal levels, with no differences between the contralateral and

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ipsilateral visual fields. Interestingly, this was a characteristic of all the congenital patients, suggesting a type of blindsight with higher residual capacities, probably subserved by a plastic reorganization of visual circuitry. This would be in agreement with the general assumption of a more efficient reorganization following early brain damage, known as the Kennard principle, which has been extensively demonstrated for the visual system in animal models, but less in humans (Kennard and Fulton, 1942; Moore et al., 1996).

The more profound neural reorganization in our subjects would also explain why V1 BOLD responses to ipsilateral stimuli are not usually observed in blindsight (Morland et al., 2004; Radoeva et al., 2008). Only one other report showed that the spared V1 can respond to the ipsilateral hemianopic visual field, but this occurred after an intensive training that lasted 4 years (Henriksson et al., 2007). This opens the way for a rehabilitation program for acquired lesions in young patients, where plasticity is stronger.

Our congenital patients show robust but aberrant V1 activation to ipsilateral stimulation in the scotoma, but they have no conscious perception of it. This suggests that V1 is not sufficient for awareness, nicely complementing the argument from ffytche and Zeki (2011) that V1 is not necessary for awareness, implicating a variety of circuitries mediating consciousness. In conclusion, our data show the great potential for plasticity of the visual brain following congenital lesions, able to fulfill many unconscious visual functions through abnormal reorganization involving V1.

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