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CORTEX 103 (2018) 179–198

Available online at www.sciencedirect.com

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Research Report

Supramodal agnosia for oblique mirror orientation in patients with periventricular leukomalacia

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ARTICLE INFO

Article history:
Received 6 August 2017
Reviewed 22 January 2018
Revised 9 March 2018
Accepted 12 March 2018
Action editor H. Branch Coslett
Published online 22 March 2018

Keywords:
Agnosia
Orientation perception
Oblique orientation agnosia
Supramodal orientation perception
Mirror orientation perception
Periventricular leukomalacia

ABSTRACT

Periventricular leukomalacia (PVL) is characterized by focal necrosis at the level of the periventricular white matter, often observed in preterm infants. PVL is frequently associated with motor impairment and with visual deficits affecting primary stages of visual processes as well as higher visual cognitive abilities. Here we describe six PVL subjects, with normal verbal IQ, showing orientation perception deficits in both the haptic and visual domains. Subjects were asked to compare the orientation of two stimuli presented simultaneously or sequentially, using both a two alternative forced choice (2AFC) orientation-discrimination and a matching procedure. Visual stimuli were oriented gratings or bars or collinear short lines embedded within a random pattern. Haptic stimuli comprised two rotatable wooden sticks. PVL patients performed at chance in discriminating the oblique orientation, both for visual and haptic stimuli. Moreover when asked to reproduce the oblique orientation, they often oriented the stimulus along the symmetric mirror orientation. The deficit generalized to stimuli varying in many low level features, was invariant for spatiotopic object orientation, and also occurred for sequential presentations. The deficit was specific to oblique orientations, and not for horizontal or vertical stimuli. These findings show that PVL can affect a specific network involved with the supramodal perception of mirror symmetry orientation.

1. Introduction

It is well established that the visual processes mediating object recognition can be dissociated from those implicated in object orientation perception. According to the dual visual pathway theory, the ventral cortical areas are involved in object recognition independently from orientation, while the perception of object position in the space and in relation to the observer's viewpoint are mediated by the dorsal stream to support action guidance (Goodale 2011, 2014; Goodale & Milner, 1992; Milner and Goodale 1993, 2008; Mishkin & Ungerleider, 1982; Mishkin et al., 1983; Ungerleider &

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https://doi.org/10.1016/j.cortex.2018.03.010

Mishkin, 1982, pp. 549–586; Whitwell, Milner, & Goodale, 2014).

The description of orientation agnosia, the inability to perceive object orientation in space despite preserved object recognition supports this theory (Turnbull, Beschin & Della Sala, 1995; Turnbull, Beschin & Della Sala, 1997, Cooper & Humphreys, 2000, Karnath, Ferber, & Bulthoff, 2000, Harris et al., 2001, McCloskey, 2004, Riddoch et al., 2004, Fujinaga, Muramatsu, Ogano, & Kato, 2005, Robinson, Cohen, & Goebel, 2011). Some rare patients with lesions along the dorsal pathway selectively incurred in symmetry confusion, exhibiting mirror writing and reading or orientation agnosia for symmetric stimuli (Buxbaum, Coslett, Schall, McNally, & Goldberg, 1993; Davidoff & Warrington, 1999; Davidoff & Warrington, 2001; Harris et al., 2001; Lambon-ralph, Jarvis, & Ellis, 1997; Martinaud et al., 2014; Priftis, Rusconi, Umilta, & Zorzi, 2003; Riddoch & Humphrey, 1988; Rodriguez, Aguilar, & Gonzalez, 1989; Schott, 2007; Turnbull and McCarthy 1996; Valtonen, Dilks, & McCloskey, 2008; Vinckier et al., 2006).

The deficit selectivity of these rare patients suggests that mirror orientations are analyzed by at least partially independent networks with respect to the other orientations. Indeed a recent voxel-based lesion-symptom mapping on a cohort of patients suffering from stroke reported only partial overlap of the lesioned sites along the dorsal pathway in patients with orientation agnosia or agnosia for mirror stimuli (Martinaud et al., 2016).

Imaging studies on healthy volunteer have identified an extensive cortical network underlying symmetry and orientation perception. Interestingly this system is activated also by multisensory visuo-tactile signals (Bauer et al., 2015; Bona, Herbert, Toneatto, Silvanto, & Cattaneo, 2014; Kohler, Clarke, Yakovleva, Liu, & Norcia, 2016; Sasaki, Vanduffel, Knutsen, Tyler, & Tootell, 2005; Sathian & Zangaladze, 2002; Sathian, Zangaladze, Hoffman, & Grafton, 1997; Tyler et al., 2005). Similar bilateral occipito-parietal activation during visual and tactile orientation judgments as well as during symmetry perception suggests the existence of amodal neural substrates for these tasks.

That mirror images are somewhat special with respect to the other orientations is also suggested by developmental studies. Habituation paradigms showed that four-month old infants confuse mirror symmetric stimuli, despite can discriminate oblique orientations (Bornstein, Gross, & Wolf, 1978). Symmetric oblique orientations in particular seem to pose the biggest challenge. Gregory, Landau & McCloskey (2011) analyzed the frequency of errors made during forced choice tasks in 4–5 years old children. Children were able to choose the correct orientation in 63% of the trials for the oblique orientation and 74% for the cardinals, when there was no memory load. The error-distribution analysis showed that children often confused mirror stimuli around the object principal axis of elongation (OPA, i.e., with respect to the object) and around the extrinsic vertical axis (EVA, i.e., with respect to the vertical external axis), performing left-right reflection. Correct categorization of left-right oblique orientations mature by the age of 6 years in normal children, while 90° errors are rare for cardinal orientations since very early in life (Palomares, Landau, & Egeth, 2009). These results suggest that an important difference should be made between perception of diagonal and cardinal orientations, the former being much more difficult to categorize than the latter for healthy children. At adult age almost no left-right errors are made, although decisions can still take longer for mirror symmetry (Gregory & McCloskey, 2010; Sekuler & Houlihan, 1968). This late development is probably linked to the written language and reading acquisition, known to refine human ability to distinguish between left-right mirror images (Kolinsky et al., 2011; Pegado and Comerlato, 2014; Pegado, Comerlato, Ventura, Jobert, Nakamura & Buiatti, M, 2014; Pegado, Nakamura & Hannagan, 2014).

Mirror visual symmetry deficit is rarely observed in developmental disorders, with the exception of Williams syndrome. These children fail to report correctly mirror symmetry images particularly for the left-right reversal, suggesting that mirror symmetry visual perception is mediated by dorsal pathways that is strongly affected in this pathology (Atkinson & Braddick, 2011; Atkinson et al., 2003).

In the present experiment we describe a group of six subjects with periventricular leukomalacia (PVL) with supramodal agnosia for oblique mirror orientations, providing evidence that perception of oblique object orientations is dissociated from cardinal orientation and that the underlying network is shared between different modalities.

PVL refers to lesions to the cerebral white matter, usually occurring between the 24th and 36th week of gestational age (Volpe, 2009). Depending on the size and location of the PVL necrosis, a wide spectrum of clinical symptoms can be observed, from severe visual impairment, combined with cerebral palsy and mental retardation to mild visuo-motor impairments and normal intelligence (for a review see: Jacobson & Dutton, 2000). Previous studies have described visual-perceptual impairment in these subjects, such as restriction of visual field, deficit in crowding, visual integration (identification of whole figures from incomplete visual information), object recognition and motion perception (Cioni et al., 1997; Fazzi et al., 2004; Guzzetta et al., 2009; Jacobson, Ek, Fernell, Flodmark, & Broberger, 1996; Morrone et al., 2008; Stiers, De Cock, & Vandenbussche, 1998). Here we show that few of these children can also have mirror orientation agnosia that can greatly impact on their everyday life. The deficit can create difficulties in a wide range of contexts: from simple games with dolls (that were often dressed the other way around) to more complex learning activities at school, such as drawing and understanding the properties of geometrical shapes.

2. Methods

2.1. *Subjects*

Sixty patients with a neuroradiological diagnosis of PVL that referred to the Stella Maris Scientific Institute in Pisa were evaluated with a symmetry test assessing pictures orientation discrimination (see below). Six patients (four females and two males, aged between 12 and 23 years old) demonstrated a specific difficulty in discriminating between mirror images and were included in the present study. Three younger or age matched subjects with no neurological disorder were also tested as controls (10, 12 and 14 years old respectively). This

study was conducted with ethical approval of the local ethics committees (Stella Maris Scientific Institute Ethics Committee and Comitato Etico Pediatrico Regionale—Azienda Ospedaliero-Universitaria Meyer—Florence, Italy), that are in line with the declaration of Helsinki. Parental informed written consent was obtained for each participant.

2.2. Clinical assessment

All subjects underwent an extensive visual assessment evaluating visual acuity by optotypes, visual field perimetry, optic atrophy, refractive errors, characterization of the oculomotor pattern including evaluation of fixation and the description of abnormal eye movements such as nystagmus, presence of strabismus and stereopsis with the Lang test, color perception with the Ishihara test, contrast vision with LEA symbols, translational motion and symmetry perception in pictures with in-house tests.

In the picture-symmetry test patients were presented with two line drawings of the same object (for example a bike or a cup, see Fig. 1A–B). The images could be horizontally or vertically aligned, or misallied and they could appear either in the canonical view or rotated of ±90°. Trials where objects had the same orientation were intermingled with trials containing two mirror images of the same drawing (Fig. 1A–B). Patients were asked to say whether the two drawing of the same object were identical. We took particular care in explaining that the judgment should not be based on the object that the drawing represented, as those were always identical in the individual trial. Within each trial, objects could differ in their orientation around the y-axis (left-right reflection) or the around both y- and x-axes (left-right and up-down reflection). Object recognition under unusual views was tested with the Visual Object and Space Perception (VOSP) battery.

All subjects underwent a neuropsychological assessment, evaluating IQ with WISC-III. Three subjects underwent also the VMI visuo-perceptual test and other five subjects the reading ability test. All subjects underwent anatomical MRI scanning, allowing the identification of structural abnormalities, such as thinning or atrophy of the white and gray matter and PVL lesions. Table 1 summarize the test results.

2.3. Psychophysical evaluation

In randomized order, subjects performed an orientation categorization task, an orientation reproduction task and a posting task, administered in several variants in older children (see results). Visual stimuli were presented in a dimly lit room on either a calibrated CRT screen (Sony 21", resolution 1280z1024) or on a calibrated LCD screen 17" (LG L1730SF, resolution 1024 × 768) at refresh rate of 60 Hz. Stimuli were generated and presented under Matlab 9.0 using PsychToolbox routines (Brainard, 1997).

2.3.1. Orientation categorization task

Two black bars (1 × 6 degrees) on a gray background were displayed at ±7 degrees of eccentricity from a central fixation point on the horizontal plane. Stimuli were shown for 1 sec, and subjects were required to judge whether the orientations of the bars was identical or not, in a two alternative forced choice paradigm. Bars could appear either with cardinal (for convention we labeled horizontal and vertical orientation as 0 and 90° respectively) or diagonal (+or−45°) orientations.

We tested the generality of the deficit with several other visual stimuli in a subsample of subjects. In particular, we repeated the task substituting the line with Gabor patches (7.5° diameter, spatial frequency: .7 cycle/degrees, contrast: 20%), or two second-order stimuli comprising clouds of small white bars (7.5° diameters, each bar subtending 4 × 20 arcmin drawn on a virtual array spaced 30 arcmin) half of which were coherently oriented to form a thick bar embedded in a randomly oriented pattern (see Fig. 1C).

To test for simultagnosia, we presented the stimuli sequentially (1s ISI) in the center of the screen. We also used two Gabor patches with different spatial frequency (respectively .7 and 1.4 cycle/degrees) presented simultaneously.

We further tested if the orientation agnosia was specific to spatiotopic or egocentric or retinotopic coordinates system by presenting the stimuli with a 45 deg head tilt, or by screen tilting or in the supine body position.

To investigate whether the observed orientation deficit was affecting also other modalities, we collected haptic orientation categorization trials in open loop condition with a screen occluding the vision of the hands and stimuli to the subject. Subjects sat in front of a table and touched two wooden sticks (dimension 1 × 6 cm) spaced about 20 cm center to center with respect to the subject's mid-line. Participants were invited to touch the right bar with the right hand and the left bar with the left hand and to report whether the bars had the same or different orientation. Subjects were presented with either cardinal, oblique or mixed (one cardinal and one oblique) orientations.

To evaluate if subject responses were above chance we used a one-sample Wilcoxon signed rank test against chance. A related-sample Wilcoxon signed rank test was used to test directly the difference in performance between orientations (cardinal *vs* oblique). Independent sample Mann–Whitney *U* Test was used to compare performance across groups (PVL *vs* controls). Error bars reported in the bar graphs are 5%–95% confidence intervals assuming a binomial distribution, calculated via custom Matlab script.

2.3.2. Orientation reproduction task

The same stimuli used for the orientation categorization task were used for the reproduction task: participants were asked to rotate one of the two bars until their orientations were matched perceptually. Subjects rotate the bars clockwise or counterclockwise by pressing the right or the left arrow respectively. We allowed unlimited time to perform the match.

The same task was also performed in the haptic modality in open loop, with subjects required to estimate the bar orientations with separate hands. After exploring the orientation of the reference bar with one hand, subjects rotated the other bar with the other hand until the two orientations matched. The final degree of rotation was recorded by measuring the angle indicated by the rotated bar with a protractor.

In two subjects we tested a cross modal version of the reproduction task. Subjects viewed a black bar on one side of

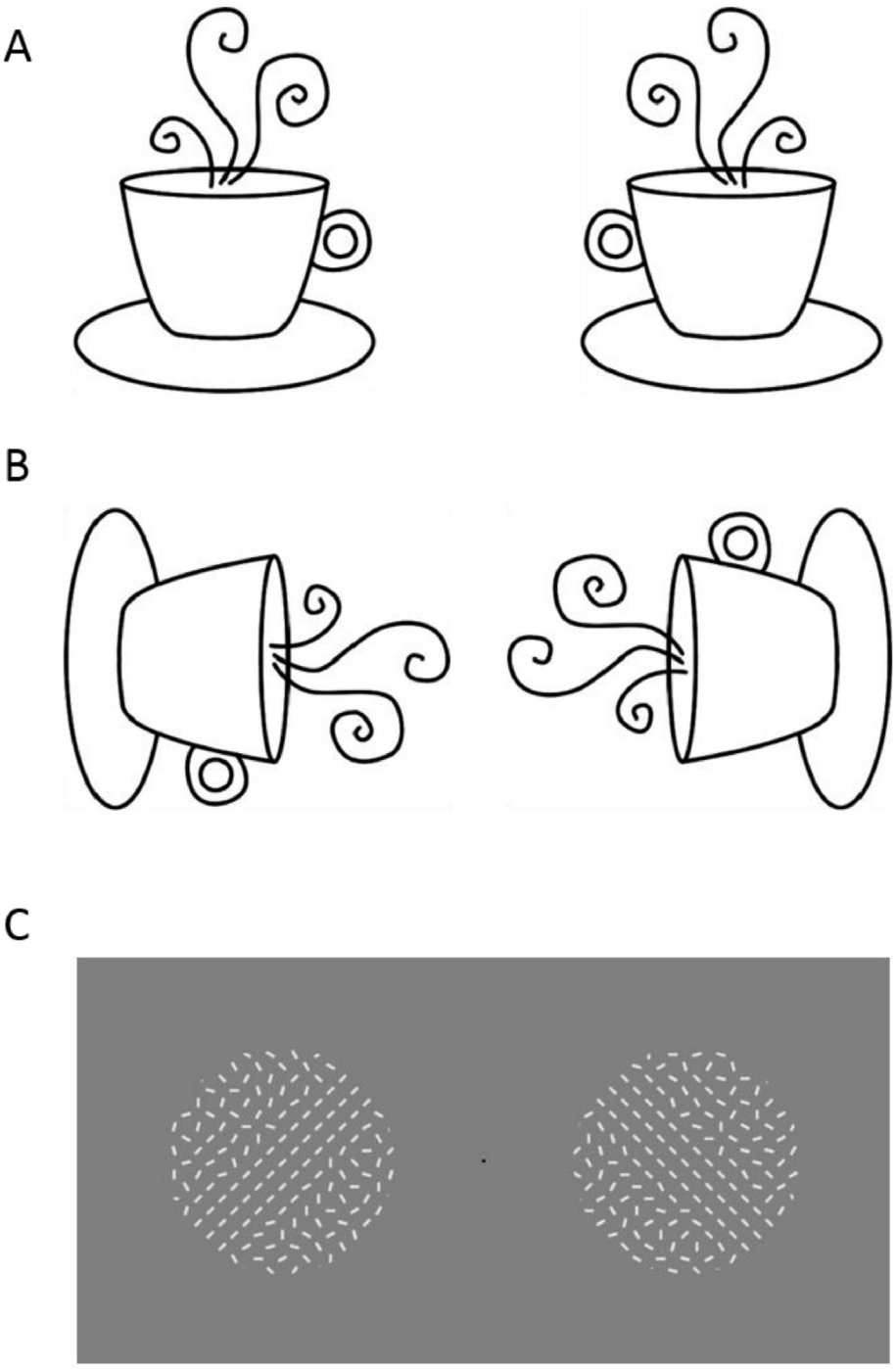

Fig. 1 – Example of the stimuli included in the symmetry test (A and B) and of the second order pattern used in one control experiment (C).

the screen while reproducing its orientation by manually rotating the wooden bar, which was hidden from their vision and presented in the other hemispace.

In order to evaluate if the participants were able to match local visual cues to solve the task, we visually presented a black bar superimposed on a full screen black and white grating (spatial frequency = .7°), and participants were asked to rotate the black bar until it matched the orientation of the full screen grid.

For each of the four orientation tested, the percentage of trials was plotted as a function of the errors from veridical. Mean absolute errors for cardinal and diagonal orientations and across groups were compared by bootstrap sign-test.

Table 1 – Results of the patients' clinical assessments.

Patient	S1	S2	S3	S4	S5	S6
Demographic Data						
Gender, M/F	F	F	M	F	F	M
Age at test, y	23	12	13	15	14	15
Right-handed	yes	yes	yes	yes	no	no
Neonatal Data						
Gestational age, wk	27	31	26	31	33	30
Birth weight, g	1350	1570	1200	1280	1700	1500
Delivery	cesarian	cesarian	spontaneus	cesarian	cesarian	cesarian
Neurological co-morbidities	epilepsia	–	–	epilepsia	epilepsia	–
Medication	–	–	–	–	Topiramate	–
Neuromotor outcome						
Spastic diplegia	+ > left side	+ > left side	+	+	+ > right side	+ > left side
Type	IV	III	IV	IV	IV	II
GMFM levels	3	2	1	1	3	5
MACS levels	1	2	1	1	1	2
Ophthalmic Data						
Optic nerve	Normal	Atrophy in LE	Atrophy	Normal	Mild Atrophy	Mild Atrophy
Strabismus	Convergent squint>LE	Surgery for convergent squint in LE	Convergent squint	Convergent squint > RE	Divergent squint in RE	Convergent squint > RE
Refractive errors	Myopia RE1,25 LE -1	Myopia and Astigmatismus; SK RE -2,5–2 (160) SK LE -2.00 -2 (20)	Myopia and Astigmatismus RE -6.00; –2.75; –5 LE -7.50; –4.00; 5	Myopia SK RE -1,25 SK LE 1,00	Hypermetropia SK RE +1,5 SK LE +2.00	Astigmatismus RE -.75 (180)
Visual acuity (Optotypes)	RE 10/10 LE 9/10	RE 9/10 LE 9/10	RE 2/10 LE 1/10	RE 7/10 LE 10/10	RE 8/10 LE 9/10	RE 6/10 LE 7/10
Nystagmus	–	–	+	+	–	–
Stereopsis (Lang test)	–	–	–	–		
Campimetry (manual)	Low left quadrant VFR > 50°	low right quadrant VFR > 20°	Nan	Nan	Nan	Nan
Contrast vision (LEA symbols)	100% contrast LogMAR 0,1; 10% contrast LogMAR 0,1; 2,5% contrast LogMAR 0,3	100% contrast LogMAR 0,1; 10% contrast LogMAR 0,4; 2,5% contrast LogMAR 0,5	100% contrast LogMAR 0,7; 10% contrast No response; 2,5% contrast No repsonse	100% contrast LogMAR 0,1; 10% contrast LogMAR 0,1; 2,5% contrast LogMAR 0,3	100% contrast LogMAR 0,1; 10% contrast LogMAR 0,1; 2,5% contrast LogMAR 0,3	100% contrast LogMAR 0,1; 10% contrast LogMAR 0,4; 2,5% contrast LogMAR 0,5
Color vision (Ishihara test)	+	+	Deuteranopia	+	+	+
Translational motion	+	+	+	+	+	+

(*continued on next page*)

Table 1 – (*continued*)

Patient	S1	S2	S3	S4	S5	S6
Neuropsychological assessment						
WISC-III						
QIV	115	109	118	115	70	70
QIP	72	69	65	80	40	58
Visuo-Perceptual Test						
DTVP-A - GVPI	Nan	<1° Pc	Nan	4° Pc	Nan	<1° Pc
DTVP-A - MRPI	Nan	<1° Pc	Nan	5° Pc	Nan	<1° Pc
VMI	Nan	<1° Pc	Nan	4° Pc	Nan	<1° Pc
VOSP (standard score)						
Incomplete letters	+ (20)	+ (18)	+ (19)	+ (19)	+ (18)	+ (17)
Silhouettes	+ (24)	+ (26)	+ (23)	+ (20)	+ (21)	+ (18)
Object decision	+ (18)	+ (19)	+ (18)	+ (17)	+ (16)	+ (17)
Progressive silhouettes	+ (13)	+ (12)	+ (11)	+ (12)	+ (13)	+ (13)
Symmetry test - average (% errors)	33	48	41	46	41	48
Symmetry test – left-right reflections (% errors)	44	52	56	64	44	60
Symmetry test – left-right and up-down reflections (% errors)	16	44	22	22	38	33
Reading test	+	+	+	+	some problems	
MRI findings						
Type	PVL	PVL	PVL	PVL	PVL	PVL
Location	SOCa and SOCp; thinning of CC	SOCa and SOCp; thinning of CC	SOCa and SOCp; thinning of CC	SOCa and SOCp; subcortical structures (putamen); thinning of CC	SOCa and SOCp; thinning of CC	SOCa and SOCp; subcortical structures (putamen); thinning of CC

Abbreviations: GMFM: Gross Motor Function Measure, MACS: Manual Ability Classification System, SK, VRF, LE, RE: Skiascopy, Visual Field Reduction, Left Eye, Right Eye, WISC: Wechsler Intelligence Scales for Children, QIV QIP: Verbal IQ; Performance IQ, DTVP-A, GVPI, MRPI: Developmental Test of Visual Perception-Adolescent and Adult, General Visuo-Perceptual Index, Motor Reduced Visual Perception, VMI, VOSP: Developmental Test for Visual-Motor Integration, Visual object and Space perception test, PVL: Periventricular Leukomalacia, SOCa and SOCp: Semioval center anterior and posterior, CC: Corpus callosum.

2.3.3. *Posting task*

Subjects were asked to match the orientation of the same bar used for the orientation categorization task with a piece of cardboard held in their hand, mimicking a posting action into the letter box, i.e., the black bar (Goodale, Milner, Jakobson, & Carey, 1991). For each of the four orientations tested, the percentage of trials were plotted as function of the errors from veridical and mean absolute errors were evaluated by bootstrap sign-test.

2.3.4. *Spatial frequency and orientation discrimination thresholds*

To evaluate low-level visual sensitivity we tested spatial frequency and orientation discrimination thresholds with a 2AFC. To measure spatial frequency threshold we simultaneously presented two grating patches of different spatial frequencies (7.5° diameter, spatial frequency: .7 cycle/degrees, contrast: 20%) at ±10 deg eccentricities for 1s. Within each trial the two gratings always had the same orientation that could be either vertical, horizontal or ±45°. Subjects were required to judge whether the two gratings had the same or different spatial frequency (bar thickness).

In two highly collaborative subjects, we measured the orientation discrimination threshold for ±45° in separate sessions. A luminance-modulated Gabor grating (7.5° diameter, spatial frequency .7 cycle/degrees, contrast 20%) was briefly presented (1 sec) in the center of the screen at ±2.5, ±5, ±7.5, ±10, ±15, ±22.5, ±30° from oblique orientation, and the subjects had to report whether the orientation appeared more vertical or more horizontal. The proportion of 'more horizontal' responses was fit as a function of the grating orientation with a cumulative Gaussian function. The 50% point estimated the point of subjective equality (PSE), and the difference in degrees between the 50% and the 75% points gave the just notable difference (JND).

3. Results

Table 1 summarizes the results of the patients' clinical assessments. All patients were born preterm and with PVL lesions identified by MRI in the anterior and posterior regions of the semioval center. S4 and S6 presented additional lesions in the subcortical structure, namely in the putamen. Representative MRI FLAIR images from S4 show the mentioned lesions in the proximity of the ventricles (areas of hyperintensity marked by red arrows in Fig. 2). Fig. 3 shows other representative slices of T1-weighted images from S1, S4 and S5. Sagittal views show lesions (hypointense in T1 images) appearing in proximity of the parietal region. In addition, all patients showed thinning of the corpus callosum, as highlighted by the transveral views in Fig. 3.

Due to PVL lesions, all subjects presented spastic diplegia. At the neurological evaluation, none of subjects presented ataxia. Three subjects suffered from epilepsy and S5 was under treatment when tested. The ophtalmologic evaluation showed that the visual field was spared in most of the subjects, with the exception of S1 and S2 who presented a reduction of the peripheral field at eccentricities greater than 30° (Fig. 4). All patients suffered from strabismus, which prevented stereoscopic vision. Color and motion perception were normal in all subjects, central contrast vision was normal in all except one subject (S3). None of the patients suffered from visual object agnosia, as demonstrated by the normal scores obtained in the test evaluating object recognition under unusual views. Cognitive profiles were in line with the typical PVL pattern (Fazzi et al., 2004; Jacobson & Dutton, 2000): verbal IQ was well within the normal range in most of the subjects, and never below the borderline values of 70, while the performance IQ was close or under threshold for all patients, reflecting the deficits in the visuo-spatial component. The visuo-perceptual impairments were confirmed also from the VMI test. All patients failed the drawing symmetry test where they had to judge whether the two drawings of the same object were identical, with an average error rate of 43 ± 6% (single subject's performance averaged across the two types of mirror reflections are reported in the neuropsychological assessment in Table 1; "Symmetry test—average"). Patients misjudged on average 53 ± 7% of trials when presented with the left-right mirror symmetric images (Fig. 1A for an example) and 29 ± 9% of trials when presented with the left-right plus up-down reflection images (Fig. 1B), suggesting that up-down reflection provided an additional cue to the drawing categorization with respect to just the left-right reflection. Table 1 lists detailed patients results for the two type of reflections ("Symmetry test—left-right reflections" and "Symmetry test—left-right and up-down reflections"; percentage of errors is calculated within each reflections' type). We had the chance to test only one control subject with this test: the youngest. The youngest control participant (10 years old) committed in total only 2 errors over 160 trials and in both cases he classified two identical images as 'different', while accurately judging all mirror images.

Consistently with the drawing symmetry test, we also observed severe deficits in the orientation categorization task. Fig. 5 shows single subject performance both for the visual (A) and the haptic (B) tests. When judging cardinal orientations in visual and haptic domains, all PVL patients made almost no errors, reaching accuracies of 96 ± 4% (one-sample Wilcoxon signed rank test against chance: $p = .02$) and 91 ± 9% (one-sample Wilcoxon signed rank test against chance: $p = .02$) respectively. Their performance did not differ from the one scored by control participants (control group accuracy: 97 ± 2% and 99 ± 1%; not significant difference across groups, independent sample Mann–Whitney *U* Test: $p = 1$ and $p = .57$ for the visual and haptic domain respectively). However, when tested at diagonal orientations, PVL patients' performance was close to chance level (one-sample Wilcoxon singed rank test against chance: $p = .68$ and $p = .10$ for the visual and haptic tests), and clearly worse with respect to the cardinal orientations in both modalities (related-samples Wilcoxon signed rank test for visual modality: $p = .02$; for haptic modality: $p = .04$). In comparison, control subjects' accuracy in judging diagonal orientation was high and equal to the performance for the cardinal orientation (98 ± 1% and 97 ± 2%, related-samples Wilcoxon signed rank test for visual modality: $p = .65$; for haptic modality: $p = .31$). Judgments of diagonal orientation were therefore significantly impaired in PVL patients with respect to the control subject (independent sample

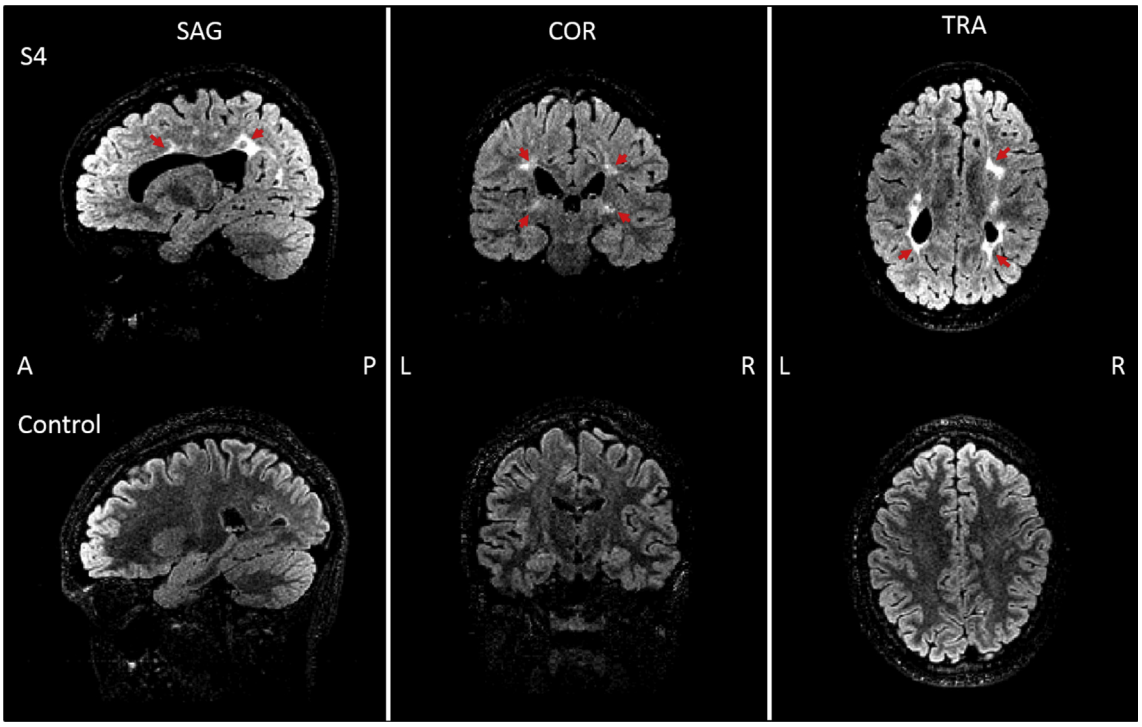

Fig. 2 – MRI FLAIR images from S4 (top row) and a healthy control subject (bottom row). In S4 areas of hyperintensity highlighted by red arrows identify PVL lesions. A: anterior; P: posterior; L: left; R: right; SAG: sagittal; COR; coronal; TRA: transversal view.

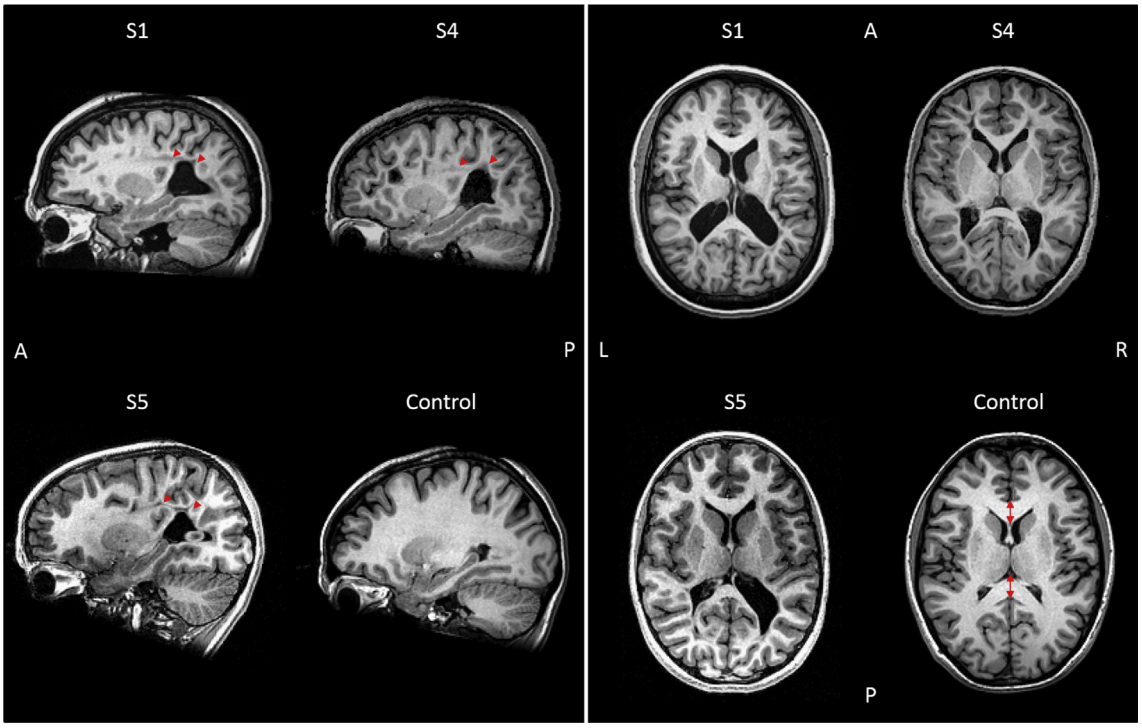

Fig. 3 – T1-weighted MRI images from S1, S4, S5 and a control subject. Arrows in the sagittal slices (left) highlight the PVL lesions and mislocalized growth of gray matter next to the parietal regions. Transversal slices (right) show the thinning of the corpus callosum with respect to the control subject, whose normal thickness is marked by the red double headed arrows. A: anterior; P: posterior; L: left; R: right.

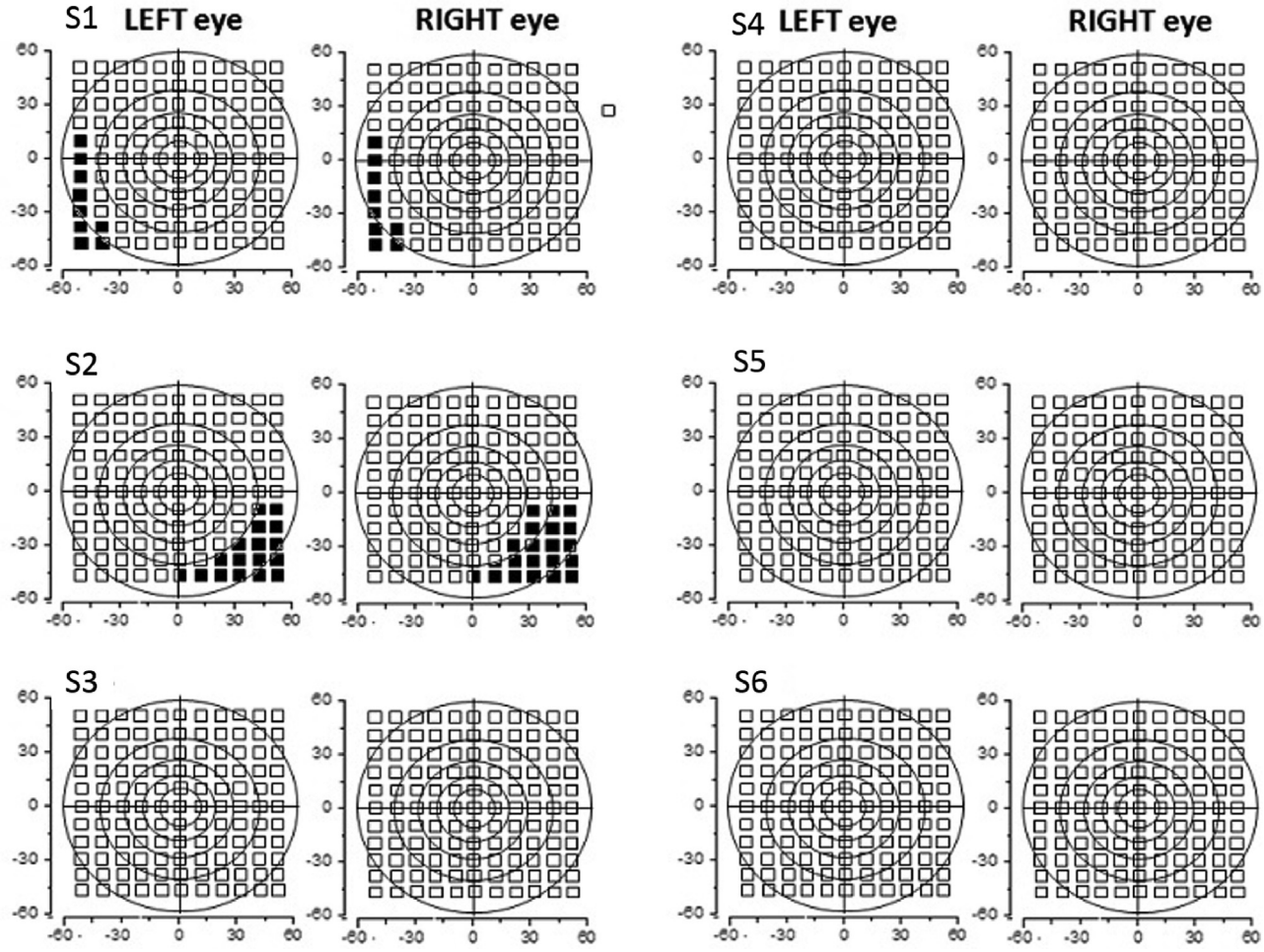

Fig. 4 – Campimetry of the six patients included in the study. Only S1 and S2 had a visual reduction, which nevertheless spared at least the central 20°–30° where the visual stimuli were projected.

Mann–Whitney *U* Test: $p = .024$ and $p = .036$ for the visual and haptic domain respectively).

In some cases (mainly for S5), we observed 'below chance' accuracies. This may reflect either a systematic incorrect categorization of orientation or that only one of the oblique orientations was more strongly altered, increasing the percentage of response "different". However a close look at S5's performance separately for different orientations did not reveal any specific deficit. Moreover S5's performance was not always below chance, as in the case of 2nd order stimuli or with gratings with different spatial frequency. Overall we cannot interpret S5's performance as suggestive of any specific deficit within diagonal orientations, but rather it seems to be simply erratic. Importantly, children were correctly classifying cardinal orientations, demonstrating that the concept of 'same/different' and that the task itself were well understood.

We additionally asked participants to compare haptically wood sticks with mixed orientations, i.e., one being oblique and the other cardinal. PVL subjects made almost no errors when comparing oblique with cardinal orientations (reaching accuracies of 94 ± 3%, one-sample Wilcoxon signed rank test against chance: $p = .04$), suggesting that only mirror symmetric orientations are confused with each other and that the difficulty does not affect all orientations indiscriminately.

To verify that the orientation deficit is general and not related to low level characteristics of the stimuli, S4, S5 and S6 were further tested with Gabor patches and second order oriented patterns (see Fig. 4C). Judgments of diagonal orientations were equally impaired for both type of stimuli in PVL patients, with no subjects performing significantly better than chance (signed test: $p > .05$ for each subject and condition, Fig. 6). On the contrary, control subjects classified both cardinal and diagonal orientations well above chance both when judging Gabor patches and second order oriented patterns (accuracy for cardinal orientations: 100% with both type of stimuli; accuracy for diagonal orientations: 87 ± 5% and 98 ± 2% when judging Gabor and second order patterns respectively; all signed tests against chance: $p < .05$).

The deficit observed in PVL patients is not a form of simultaneoagnosia (Fig. 6B), given that the accuracy for sequentially presented bars was always at chance (signed test: $p > .05$ for each subjects and conditions). Interestingly, orientation judgments of two different objects, such as two gratings of different spatial frequency (Fig. 6B), did not improve performance, reinforcing the finding that the deficit

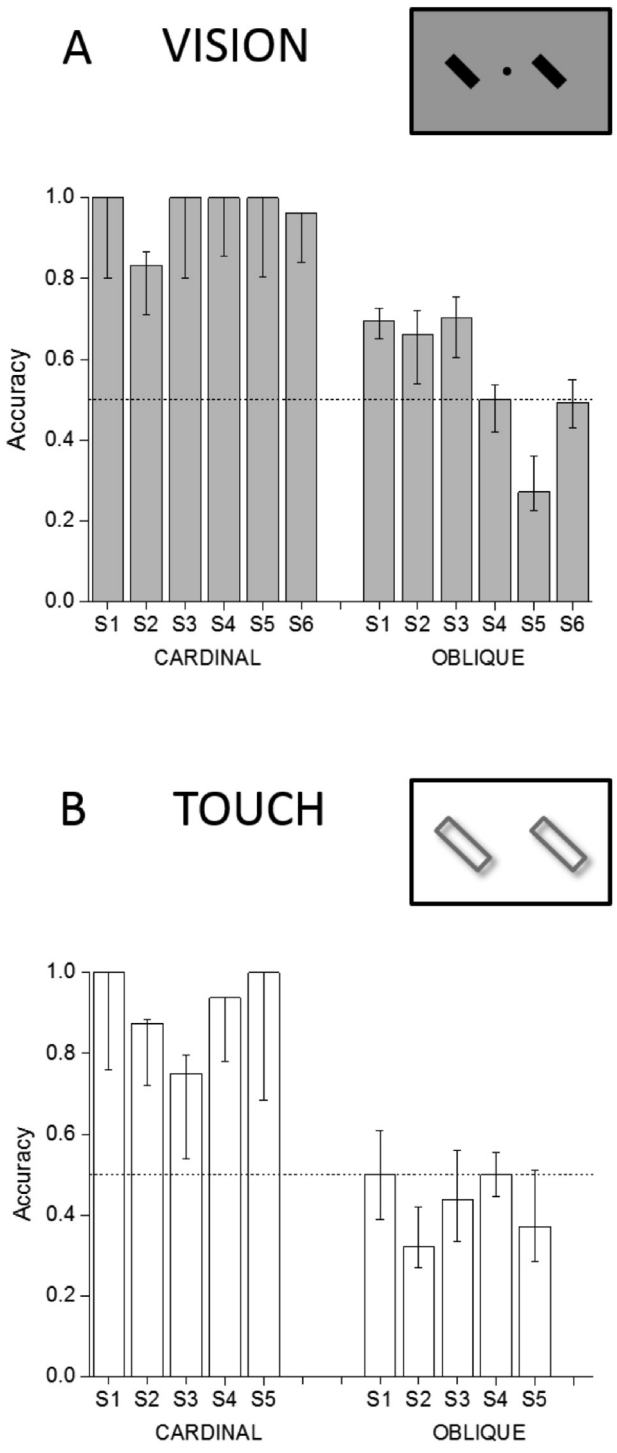

Fig. 5 – Single subjects (S1–S6) percent accuracy scored during the orientation discrimination task when the visual (A) or the haptic (B) modalities were tested. Performance during the cardinal and diagonal orientation judgments are grouped separately. In both modalities, while cardinal orientations are well discriminated, judgments of diagonal orientations are at chance. Error bars are confidence intervals at 95%.

is specific to oblique directions and not to the simultaneous presentation of the same object.

Having assessed that the deficit is related to object orientation in space, we performed additional tests to identify the coordinate system that define oblique orientations (Fig. 7). The coordinate system could be anchored to the monitor frame, the subject's head or to gravitational vertical. S1 and S5 were tested with their head's tilted 45° counterclockwise (Fig. 7A). In none of these subjects did the head tilt improve response accuracy for diagonal orientation judgments, compared with the upright position (sign test: $p > .05$ in both subjects), suggesting that the deficit was linked to the object or to the frame axis, and not to the orientation on the retina. This suggests that the deficit is craniotopic and not retinotopic.

The subjects could have exploited the alignment between the bars and the monitor border to correctly perform the task with cardinal orientations. In S4 rotating the monitor frame by 45 deg (Fig. 7B) improved categorization of the oblique spatiotopic orientation, but this did not impair performance during judgments of cardinal spatiotopic orientations. In S5 the pattern of results was invariant with monitor rotation (sign test: $p > .05$), indicating that the effect is not due to the frame visual cues, but that it is linked to spatiotopic coordinates. S4 might have exploited the frame cues when judging diagonal orientations with the monitor tilted (sign test: $p = .0001$), given the perfect performance. Overall these results suggest that the perception of the cardinal orientation was genuinely preserved in both subjects and was independent from the retinal and head system of reference.

Finally to test the role of the external frame of reference during orientation judgments, S4 and S5 were tested while lying supine on a bed with the screen either upright or at 45° in front–parallel plane (repeating the tilt monitor rotation, Fig. 7C). Change of external-world frame of reference did not play any role in this deficit (sign test: $p > .05$), with S4 and S5 performance similar to those obtain in upright position. S4 confirmed the use of the monitor frame of reference while judging diagonal orientation (sign test: $p = .003$).

To quantify how the subjects categorized the diagonal orientations, we measured their performance in a reproduction task. Fig. 8 shows the results for the visual (A) and the haptic (B) modalities, pooling together trials from all PVL subjects. In both modalities the mean absolute errors for oblique stimuli were markedly higher than those in the cardinal conditions (for vision: 39 ± 2 *vs* 7 ± 1.2, bootstrap sign-test $p < .0001$; for haptic: 40 ± 5 *vs* 8.5 ± 1.6, bootstrap sign-test $p < .0001$). The subjects were highly imprecise for oblique, but not for cardinal orientations. In half of the trials they reproduced oblique orientations with its mirror symmetric orientation, and correctly in the remaining half of the trial, resulting in a mean error of about 40°. Control subjects reproduced both cardinal and diagonal orientation in both modalities with higher accuracy with respect to the PVL patients, although reproducing diagonal orientations was slightly more difficult than reproducing cardinals (for vision modality: 6.7 ± 2.54 *vs* .77 ± .21 for diagonal and cardinal

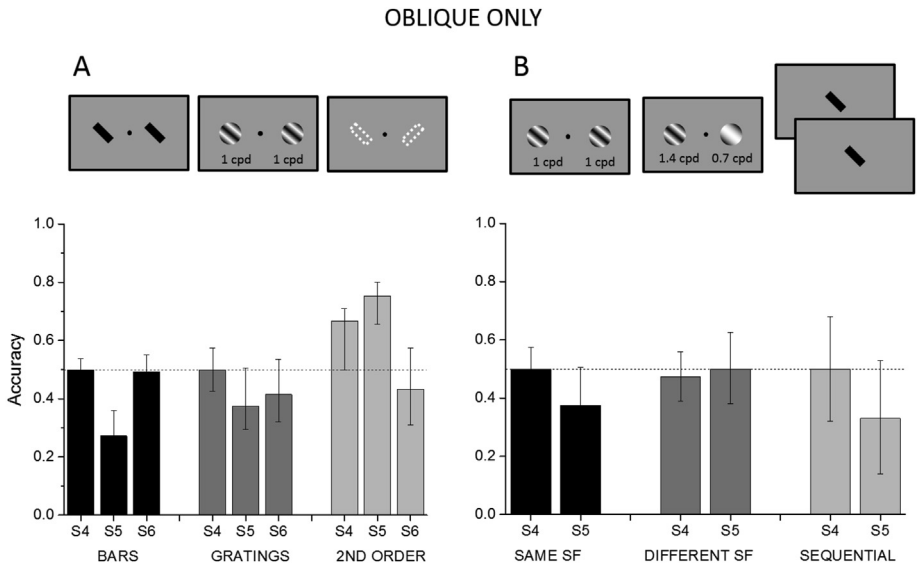

Fig. 6 – Additional control experiments. Single subject performance for diagonal orientation discrimination presented with various visual stimuli (A): black bars (black), Gabor patches (dark gray) and second-order patterns (light gray). Testing for simultagnosia (B): comparison of accuracy discrimination for gratings with same or different spatial frequency and for sequentially presented bars. The deficit for diagonal orientations persists across different kinds of stimuli and presentation modalities.

respectively, bootstrap sign-test $p < .0001$; for haptic modality: 9.1 ± 2.6 *vs* 2.7 ± .4 for diagonal and cardinal respectively, bootstrap sign-test $p < .0001$). The two groups differed both for the precision in reproducing diagonal (PVL *vs* controls in vision: 39 ± 2 *vs* 6.7 ± 2.54, and in haptic: 40 ± 5 *vs* 8.5 ± 1.6, bootstrap sign-test $p < .0001$ in both cases) and cardinal orientations (PVL *vs* controls in vision: 7 ± 1.2 *vs* .77 ± .21, and in haptic: 8.5 ± 1.6 *vs* 2.7 ± .4, bootstrap sign-test $p < .0001$ in both cases). While the small difference between the two groups in the cardinal orientations can be ascribed to the lower fine-motor abilities of the PVL patients, this factor can hardly explain the larger difference between the two groups when reproducing diagonal orientations.

Given the similarity between the visual and the haptic orientation deficit, we tested whether it also occurred cross-modally. PVL patients had to reproduce the orientation of a visually presented bar by rotating the bar used in the haptic condition in open-loop. Also in this case (Fig. 9) mean absolute errors for oblique stimuli were higher than those in the cardinal conditions (30 ± 6 *vs* 6.3 ± 1.3, bootstrap sign-test $p < .0001$). S4 and S5 showed similar errors with the reproduction task in the visual (Fig. 9A), haptic (Fig. 9B) and cross-modal conditions (Fig. 9C), reproducing nearly 50% of the trials of oblique orientation with the mirror symmetric.

The deficit in the reproduction task was so strong that most of the PVL subjects were not able to use local visual cues generated by the superimposition of the bar (test) on a grating background (Fig. 10A). While participants could accurately reproduce the cardinal orientations, diagonal bars were often represented as mirror oriented (mean absolute errors for obliques *vs* cardinals: 22.5 ± 3 *vs* 4.4 ± 1.7, bootstrap sign-test $p < .0001$). An exception was subject S4 who perfectly performed the task, most likely exploiting the local visual cues matching between the bar and the grating, consistent with the behavior observed for the tilted monitor (Fig. 7B).

Finally, we tested the patients with a posting task (Fig. 10B) in closed loop, given that this task has been used successfully to dissociate between vision for perception and vision for action (Goodale et al., 1991). Subjects were shown a black bar that represented the letter box hole and were asked to post a piece of paper into it, with open view of their hand. Interestingly, there was no orientation deficit under these conditions: performance was extremely accurate in all cases, the mean absolute errors for oblique and cardinal stimuli were not significantly different (.7 ± .12 *vs* .45 ± .11, bootstrap sign-test $p > .05$).

All our PVL patients also had some early visual deficit and reduced visual acuity. To assess that early vision was not the limiting factor in the categorization task, we measured spatial frequency and orientation discrimination thresholds (Fig. 9). Spatial frequency discrimination (Fig. 11A) was not impaired in S4, while it was slightly impaired in S1 and S6 when tested with gratings with both cardinal and oblique orientations, given that typical performance is 98 ± 2% for cardinal and 93 ± 4% for diagonal (measured in the same setup). During this task patients where shown with two patches of the same orientation but different spatial frequencies, and were asked to judge whether the stimuli were the same or different. In order to provide a correct 'different' response, the patients had to inhibit the aberrant orientation information and focus their attention only on the spatial frequency difference, explaining the small deficit with respect to the typical performance. Indeed it is reassuring that the performance is equal for the cardinal and the oblique orientations.

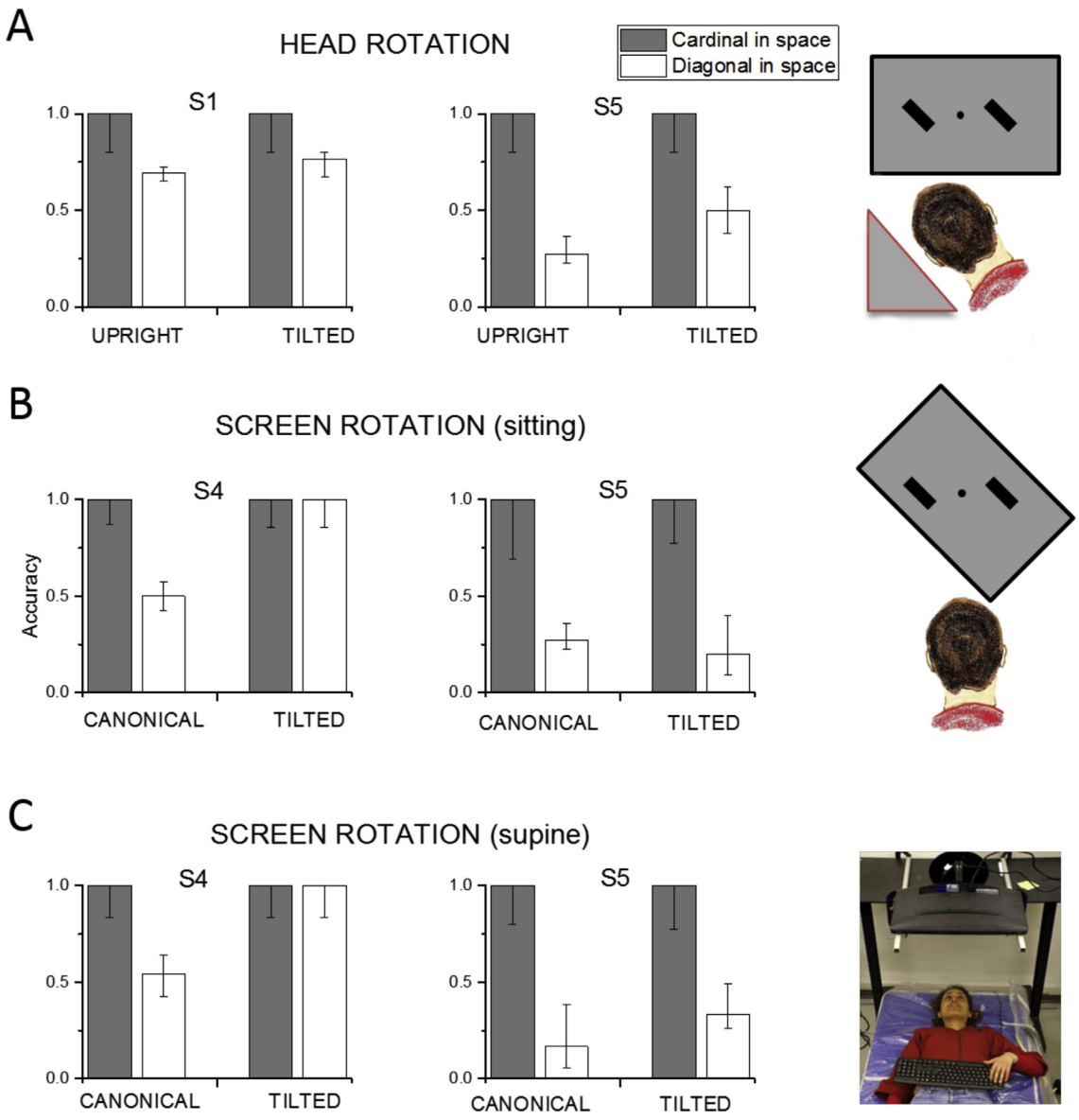

Fig. 7 – Additional control experiments. Single subject orientation discrimination accuracy for cardinal (gray bars) or diagonal (white bars) orientations during head rotation (A) or screen rotation (B) while sitting on a chair and during screen rotation while lying supine on a bed (C). Although strategies related to the frame of reference may sometimes be used, the impairment during diagonal orientations discrimination is affecting a spatiotopic coordinate system and is independent from gravity.

In S4 and S5, the most collaborative patients, we also measured the orientation discrimination thresholds around the diagonal orientations. S4 showed a very good threshold for ±45° (Fig. 11B, JND = 2.9 and JND = 2.0 respectively), comparable with typical thresholds (JND = 4.4 ± .7). S5 had worse sensitivity (Fig. 11C, JND = 11.6 and JND = 17.1 respectively). The small increase in orientation thresholds is consistent with the reduced acuity of S5 and with the presence of epilepsy in this patient (Edden, Muthukumaraswamy, Freeman, & Singh, 2009; Li et al., 2008; Sillito, 1979; Treiman, 2001). However, we cannot rule out that the orientation categorization performances of Figs. 5–7 were affected also by the degraded precision around the critical orientations.

4. Discussion

We have described a small group of PVL patients showing a supramodal deficit in orientation perception of oblique symmetric stimuli. Diagonal orientations, both when presented in the visual and in the haptic modality, were poorly represented and consistently confused with their mirror counterpart. By contrast, cardinal orientations were accurately perceived in both modalities. The deficit for oblique orientations was consistently observed across different types of visual stimuli, pointing to a general impairment of the "concept of orientation", not linked to the specific low-level attributes of the image.

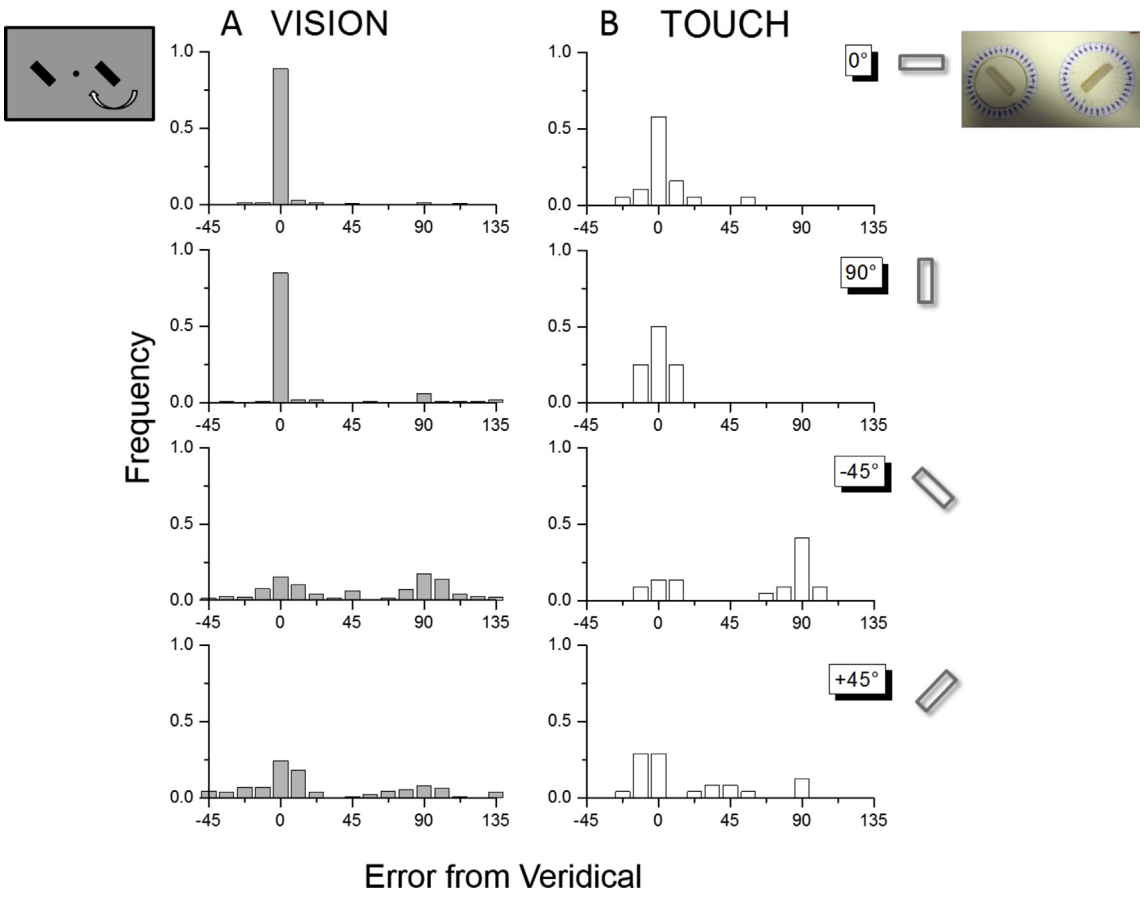

Fig. 8 – Frequency of the reproduced orientations plotted as degrees of error from the veridical in the visual (A) and haptic (B) modalities. Histograms centered around 0° and 90° indicate correct and mirror reproduction respectively. Subplots are separated for the orientation to be reproduced, as specified in the legends and icons. For convention we refer to horizontal orientations with 0°, to vertical with 90° and to the two diagonals with ±45° respectively. In both modalities, while cardinal orientations are mostly correctly reproduced, diagonal orientations are often reproduced with their mirror image.

The orientation deficit could not be explained in terms of simultaneous agnosia. Indeed it persisted even when comparing two different visual images (gratings with different frequencies), and when showing sequentially presented stimuli in the center of the screen. Visuospatial attentional deficits and visuospatial neglect, known to be associated with disruption of white matter tracts that might have been affected in our PVL patient too (Thiebaut de Schotten et al. 2011, 2014), are also unlikely to explain our results, given the orientation selectivity of the reported deficit.

Cortical visual-perceptual impairments are known to occur in preterm children with brain damage. PVL patients usually suffer from motor problems that affect eye mobility and coordination, and these could in principle be the cause of the visual deficits. It could be argued that strabismus which prevents the development of stereoscopic vision might have impeded the normal development of space perception in our patients. Depth perception is often inferred by converging diagonal lines falling on our retina and misperceiving oblique lines with their mirror counterpart could potentially have a very confusing effect on perspective perception. However our patients were sensitive to the classical visual illusions (involving linear perspective, size constancy, relative height and so on) demonstrating that they could represent the relations between objects in space and infer depth in complex visual images from monocular cues.

Moreover, it is very difficult to relate oculo-motor deficits, and strabismus in particular, with the agnosia for oblique symmetric stimuli observed here, also in the haptic domain. The mild upper limb motor impairment present in our subjects cannot explain the haptic results either, as the motor control necessary to rotate the wooden bars during the reproduction task is very similar for both cardinal and oblique orientations. Additionally, performance purely related to the visuo-motor control deficit would have resulted in an imprecise reproduction around the correct orientations, not in systematic mirror flip of the oblique stimuli.

Overall, the described deficit is consistent with a pattern of agnosia for oblique mirror orientation, not referred to the object itself but rather to an external vertical symmetry axis.

The agnosia for oblique mirror orientation described here should not be confused with the previously described 'mirror agnosia', also occurring after parietal damage (Binkofski, Buccino, Dohle, Seitz, & Freund, 1999; Ramachandran, Altschuler, & Hillyer, 1997). Patients with mirror agnosia failed to reach objects when seen throughout a mirror. The

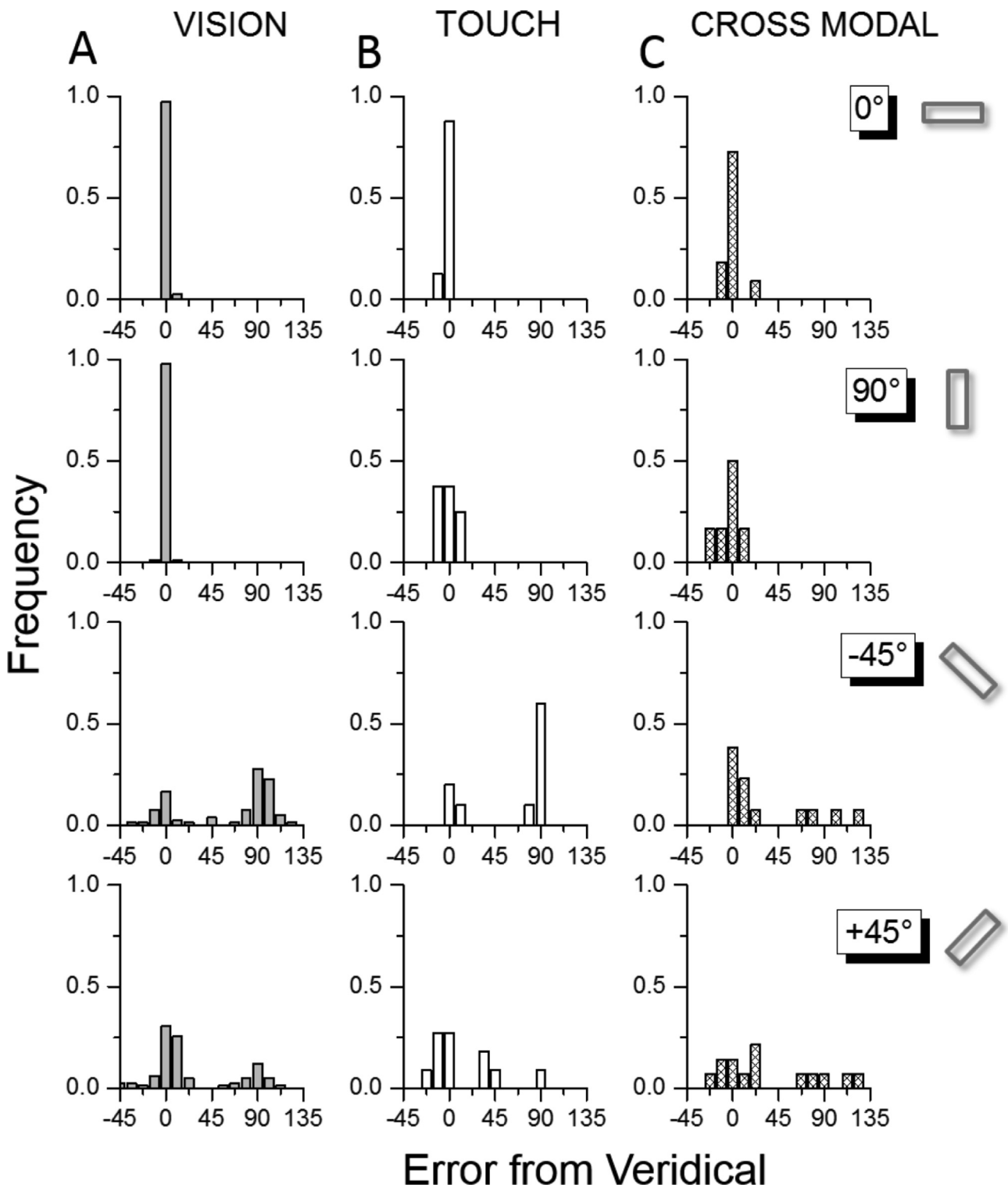

Fig. 9 – Testing for cross-modal orientation agnosia. Performance in the orientation reproduction task tested in the visual (A), haptic (B) and visuo-haptic open loop (C) modality. The mirror confusion of diagonal bars holds both within and across modalities.

difficulty with mirror-guided reaching was present also in patients with mirror ataxia however they could learn, if instructed, to correctly point toward the real object. None of the patients included in the current study presented signs of ataxia at the neurological evaluation. However, we cannot completely exclude the presence of mirror ataxia (nor mirror agnosia), given that we did not test the subjects with a mirror, It would certainly be interesting to test the patients described

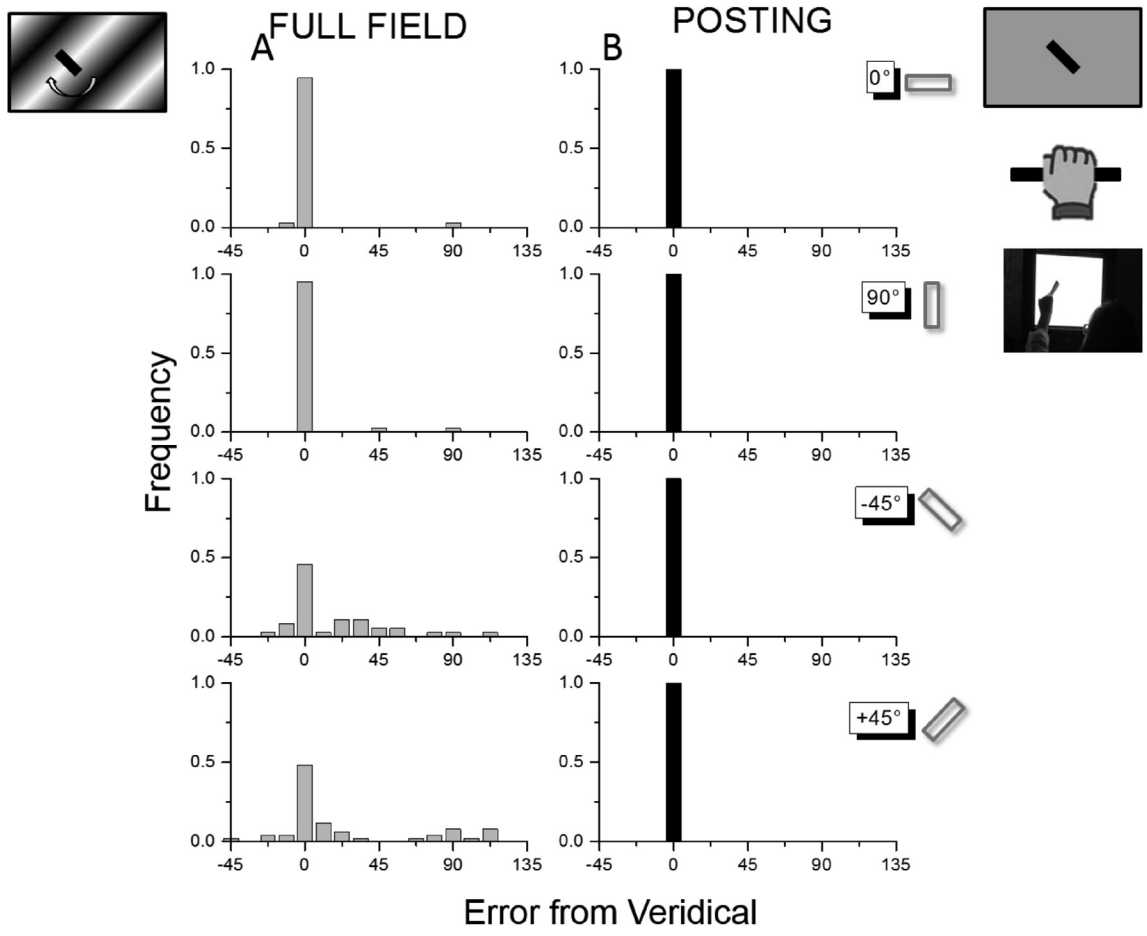

Fig. 10 – Distribution of reproduced orientations when aligning a black bar with a full-field grating (A) and when performing a closed-loop posting task (B). The possibility to perform local cue matching was not enough to cancel the diagonal orientation difficulty, while the visuo-motor integration can fully relieve the impairment.

in the current study with a mirror to evaluate whether they also present mirror agnosia with or without mirror ataxia.

Only one patient has previously been described with similar orientation deficits in both visual and in haptic modalities (Valtonen et al., 2008). However, the reproduction errors in this patient affected all orientations, while our patients were extremely good with cardinal orientations, but selectively impaired with oblique stimuli, both visual and haptic.

Developmental researches have shown that left-right symmetry reflection errors also occur in healthy children (Gregory, Landau, & McCloskey, 2011). However, these errors are thought to disappear after 6 years of age (Palomares et al., 2009), while our youngest patient was 12 years old. None of our control subjects consistently committed left-right reflection errors, extending the data reported in literature to our tasks. Therefore, PVL lesions might have prevented the normal development of mirror symmetry and of diagonal orientation processing, and no plastic recruitment of different network allowed reaching normal perception. Given that our patient age spanned up to 23 years, it is also unlikely that the deficit reflects a late development or that it could be compensated in adulthood.

In some cases, the orientation impairment was so strong that it persisted even with a 45° tilt of the frame of reference. This tilt could have potentially helped the patients to correctly solve the task, as the bar could be referred to the monitor border. However only one subject benefited from the frame of reference to solve the task in the oblique orientation, reinforcing the suggestion that S4 could use local visual cues to correctly align a bar superimposed to an oriented background (Fig. 10A). Importantly, even in this subject, the frame of reference could not explain the good performance observed during judgments of cardinal orientations during monitor rotation, as the accuracy for those did not drop to chance level.

Previous studies on healthy adult subjects showed that gravitational vestibular signals can modulate orientation threshold suggesting that some orientation mechanisms are linked to vestibular coordinates (Harris et al., 2015; Lacquaniti et al., 2015, Mikellidou, Cicchini, Thompson, & Burr, 2015). Altering gravitational and vestibular cues, by asking the subjects to perform the task while lying on a bed or with their head tilted, did not change the results. The deficit for oblique, but not for cardinal orientations, was still observed. The fact that the deficit was independent of head tilt and of gravity cues suggests that it is most likely linked to the external spatial coordinates and independent of gravity. By tilting the subject's head by 45° the cardinal orientations were projected

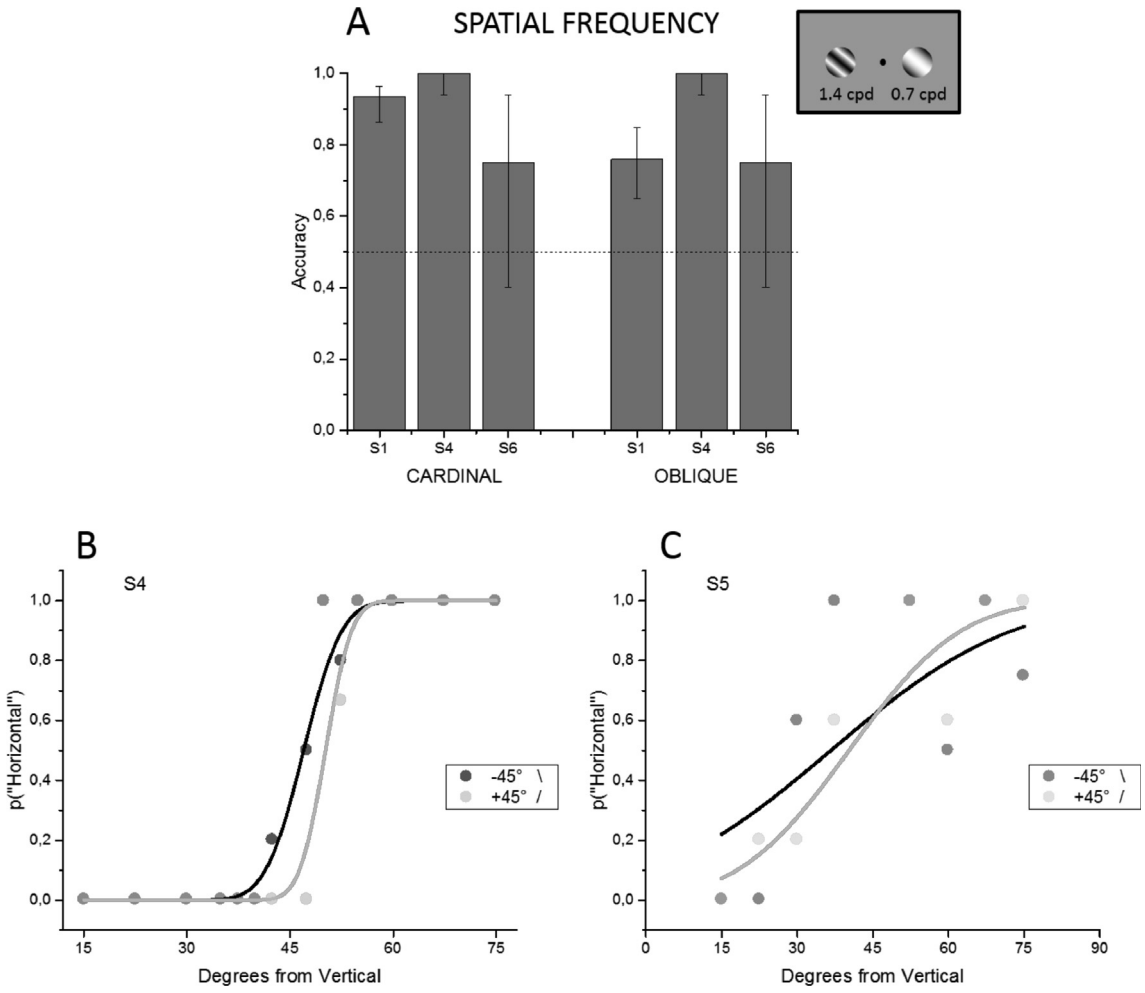

Fig. 11 – (A) Discrimination accuracy of spatial frequency across cardinal or diagonal orientations. Spatial frequency sensitivity was in the normal range in S4, but impaired in S1 and S6 (however see main text). (B) Psychometric functions (proportion of 'more horizontal' as a function of degrees difference from vertical) for S4 and S5 around +45 (gray) and −45 (black) orientation. Orientation discrimination thresholds around the critical orientations were normal in S4 and very high in S5. Nevertheless this cannot explain an abstract and supramodal orientation deficit (see text for discussion).

obliquely on the retina, yet the deficit remained linked to diagonal orientations, to the external coordinates. All these data indicate that the deficit may originate from the processes that mediate the spatial coordinate transformation from retinotopic to spatiotopic representations of visual signals, and from spatiotopic to hand-reference representations (affordance) for haptic signals, and vice-versa. Many distinct regions of the parietal sulcus subserve the ultimate goal of representing the object in the appropriate frame of reference and orientation to interact with the object. The categorization of visual features that constitute the important landmarks delimiting objects, like segmented edges and lines, take place in the most posterior part of the intraparietal sulcus in areas such as the CIP and the TOS (Castaldi, Frijia, Montanaro, Tosetti, & Morrone, 2013; Perna, Tosetti, Montanaro, & Morrone, 2008). Presumably from this feature information surface orientation is computed in higher lever intraparietal cortex (Dilks, Julian, Kubilius, Spelke, & Kanwisher, 2011; Shikata et al., 2003), and only at later stages finger position information is fused with visual information to guide grasping movements (Shikata et al., 2003). Interconnections between the dorsal pathway and the frontal lobe elaborate the visual information needed to guide grasping movements (Culham & Valyear, 2006; Davare, Kraskov, Rothwell, & Lemon, 2011; Grafton, 2010) and hand posture during reach. Importantly, many of these areas along the dorsal pathway encode object orientation independently of the modality, visual or tactile, suggesting the existence of a multisensory orientation network (Kitada et al., 2006), as also suggested by a recent study on rats (Nikbakht, Tafreshiha, Zoccolan, & Diamond, 2018). In humans, these more general and abstract transformations might finally culminate in representation of skilled object-related action, i.e., abstract representation of movements and action appropriate for a familiar object independently from a specific location or orientation of the object and of the body posture (Buxbaum, Kyle, Grossman, & Coslett, 2007).

Given that much evidence shows that parietal cortex may be particularly affected in PVL subjects (Fiori et al., 2015; Guzzetta et al., 2009), it is likely that the deficit observed

here for the oblique orientation is linked to posterior parietal lesions. This is also consistent with the fact that the deficit is invariant in spatiotopic coordinates. The affordance of an oblique object is not equal for the two hands, one hand preferring to grasp the line that requires no wrist rotation. This simple function requires quite complex remapping of spatial coordination between object orientations in external space and hand orientation and trajectory. If during development this transformation never functions properly because of the parietal lesion of posterior IPS, it would be reasonable to expect an alteration also of the visual categorization of orientation. If so, this would be consistent with other evidence showing that deficit of the action system can impair vision (Arrighi, Cartocci, & Burr, 2011). Our subjects did not have a problem with object rotation per se, performing much better in distinguishing between double reflections with respect to a mirror vertical reflection, as shown by the drawing symmetry test. The fact that the patients had more pronounced categorization difficulties with left-right symmetric images with respect to images with double reflections suggest that the up-down rotation might help to solve the task. In everyday life the axis around which reflections are most likely to occur is certainly the vertical one. A bike for example can be often oriented leftward or rightward and only in rare cases it can be seen upside down. Therefore vertical symmetries might be elaborated with priority with respect to other type of reflections, constituting a special case of view invariant object representation.

With an impaired dorsal pathways, our patients may lack the neuronal hardware that remaps the object orientation in external space, and therefore confuse the oblique orientations of our stimuli in the same way that neurons in the ventral area selective for vertical reflection would.

At first sight the fact that our subjects do not show the deficit in the posting-task may appear to conflict with a parietal lesion. However, among the areas usually affected by PVL lesions the intraparietal area AIP, which is particular important for grasping, is the less involved (Fiori et al., 2015). As for the case of the patient DF (Goodale, 2011) this area may receive direct visual information, bypassing the lesioned intraparietal cortex, which is highly likely to be damaged in PVL patients. The patients described here differ in a few important aspects from DF. Firstly, their orientation agnosia is specific for oblique and they perceive ±45° as equal, while DF confused all orientations. Secondly, our patients have a haptic agnosia, while in DF the reported orientation deficit is only visual. So although both DF and our subjects could partially compensate for the deficit when using the vision for action system, they may be very different in the type of lesion. Contrary to DF, our patients may not have a ventral pathway lesion, as they do not suffer from object agnosia. At the same time our subjects may have a partial damage to the dorsal stream. Finally one important difference between our patients and DF is that here we are describing a developmental deficit, not a lesion acquired in adult age. It is possible that our PVL patients had ventral stream lesions, but they compensate the deficit during the post-natal critical period. Because these lesions occurred very early in life massive plastic changes may have taken place, leading to an abnormal reorganization of ventral stream. The ventral stream might be still functioning, but abnormally rewired, leading to orientation errors in spatiotopic coordinates.

Neuroimaging results on healthy subjects have highlighted the role of extrastriate areas along both the dorsal and ventral pathway in symmetry perception (Bauer et al., 2015; Bona et al., 2014; Kohler et al., 2016; Sasaki et al., 2005; Tyler et al., 2005). It is possible that PVL lesions compromised the functioning of this network along both streams.

In the symmetry perception literature, one of the most influential hypotheses was the classical 'callosal' hypothesis. It proposes that symmetry perception is achieved by exploiting the symmetrical nature of the human visual system (Mach, 1886/1959; Julesz, 1971; Milner and Jeeves 1979) through a point-by-point matching of the left and right visual fields, which are projected to the opposite hemisphere. The symmetrical matching would be achieved by the callosal fibers that connect corresponding points of the two hemispheres. All our PVL patients presented thinning of the corpus callosum which might have contributed to the symmetry perception deficit. However, symmetry perception in healthy subjects is still possible, although with lower precision, when the images are shown in periphery or around different axis, challenging the callosal theory (Barlow & Reeves, 1979; Saarinen, 1988). Likewise cases of acallosal patients showed that they were still able to detect symmetry (Herbert & Humphrey, 1996). Finally a recent electrophysiological study demonstrated that symmetry can be detected by independent networks within each hemisphere (Wright, Makin, & Bertamini, 2017). In our group of patients, PVL lesions were present in many other anterior and posterior periventricular regions, and the anatomical anomalies were not limited to the callosal thinning. Therefore it is possible that both mechanisms potentially involved in symmetry detection, both that operating the across-hemisphere matching, as well as the hemispheric-independent networks, were affected in our patients, at least for oblique orientations. However, as detection for cardinal stimuli was not majorly affected in our patients and the horizontal symmetry reflection improved performance in the symmetry task, we suggest that within the symmetry detection mechanisms (whatever they are) there should be a sub-specialization for different orientations.

5. Conclusion

In conclusion these findings suggest the existence of a supramodal visuo-haptic network for perception of mirror images that works in spatiotopic coordinates. This network may have an additional sub-specialization for different orientations, cardinal or diagonal, which can be selectively disrupted by PVL lesions. PVL lesions may have occurred along the dorsal pathway at a very early stage of life and hampered the orientation network that elaborates affordance when processing diagonal orientations, yet allows cardinal orientation detection, with important repercussion on daily life, for example geometrical learning.

Acknowledgements

The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FPT/2007-2013) under Grant agreement no.338866 ESCPLAIN and from Progetti di ricerca di interesse nazionale "PRIN Miur" (2016-2019) titled "Adult visual cortex plasticity: from animal models to humans".

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