UNIVERSITÀ DEGLI STUDI DI PISA

Dottorato in Neuroscienze di Base e dello Sviluppo

Neuroplasticity of the visual system after early brain lesion

thesis by

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Solo adesso, arrivata alla fine di questa bella esperienza, trovo il coraggio di voltarmi indietro e di ripercorrere il cammino che mi ha portato fino a qui. E' iniziato tutto con una telefonata dalla quale ho appreso che avevo superato l'esame per entrare alla facoltà di Medicina (l'incubo del numero chiuso!). Ogni volta che ripenso a quel momento sento ancora i battiti del mio cuore che iniziano ad accelerare e rivivo quei pochi istanti, in cui la segretaria si è allontanata dal ricevitore per andare a scorrere rapidamente la lista di coloro che rientravano nel numero prestabilito, con ansia. Ancora mi salgono le lacrime agli occhi quando odo risuonare le parole che mi dicono che sono entrata…e solo allora mi sono resa conto che il sogno iniziava a diventare realtà.

Non posso però fare a meno di ripercorrere questo viaggio senza pensare a tutte quelle persone che hanno segnato questo cammino….e mi rendo conto che sono davvero tantissime. Devo un ringraziamento speciale al Prof. Pietro Pfanner, che con le sue parole, profonde e incisive allo stesso tempo, durante una lezione all'interno del corso di Pediatria, mi ha fatto capire ciò che volevo fare "da grande": la Neuropsichiatra Infantile. I suoi insegnamenti, sul senso più profondo di questa disciplina spero, rimangano per me, sempre, le fondamenta del mio lavoro. Altrettanto importante è stato l'incontro con la Prof.ssa Mara Marcheschi che, accogliendomi alla Stella Maris con grande calore, mi ha permesso di conoscere una persona alla quale sarò sempre grata, la Dott.ssa Stefania Bargagna. Questa, non solo ha seguito i miei esordi con estrema sensibilità e dolcezza, ma grazie al suo esempio, ho capito che la "semplicità" e l'"umiltà" sono due elementi fondamentali per poter far bene questo mestiere. A lei, un ringraziamento speciale va, anche, per avermi lasciata libera di fare scelte "diverse" dalle sue.

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percorso di crescita scientifica nel contesto di un ambiente formativo e culturale di livello eccezionale. La sua guida è stata fondamentale in tutti questi anni e soprattutto credo che le sue parole e la sua fiducia mi abbiano sempre spronato a credere in quello che stavo facendo e a dare il meglio.

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Chapter 1

Introduction

1.1   General mechanisms of visual plasticity

The ability of the brain to reorganize itself in the process of learning a task is certainly one of the most interesting phenomena that distinguish the nervous system from all other tissues. This ability has been called "plasticity", and it appears to be greatest during infancy, at a time when many of the neural pathways are still in phase of maturation. Children have, for instance, an enhanced capacity for learning and memory compared to adults as reflected in their ability to learn a second language, play musical instruments or become proficient in technical sports.

The neural changes associated with learning in the human brain generally involve neural networks that are designed for a given function, and that are generally located in the same part of the brain across different individuals: the visual cortex for all that concern the vision. These regions may develop to differing degrees through our interactions with the environment, but their locations in the brain have also a strong genetic component.

This phenomenon has been well studied in the visual system development. In 1977, Hubel and Wiesel [1] have shown that if one eye, during a period called "critical", is deprived of vision, there is an irreversible visual impairment and a corresponding lack of development of the ocular dominance columns. Plasticity declines with age and visual experience is required just after birth and for a critical time period. After that period, altered visual inputs have very little effect on the structural organization and before the critical period, visual input does induce some structural changes in the visual cortex, but can not yet incite an ocular dominance [2, 3]. The anatomy of

the brain is, thus, modified by environmental factors. Experience determines the development and preservation of visual cortical circuitry in accordance with Hebb's principle: "when an axon of cell A... excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased" [4].

At the moment, we know that in the macaque the critical period is within the first 6 months after birth. Depriving the macaque of the patterned vision in one eye during the critical period, even for only a week, produces a permanent visual impairment [1].

On the other side, even if the molecular and genetic mechanisms that regulate visual plasticity are largely unknown, the role of neurotransmitters and neurotrophins in visual plasticity [5-7] has been demonstrated by experiments in mammals. Injection of neurotrophins (NT4, 5) modifies the formation of ocular dominance columns in cats and cortical infusion of BDNF (brain derived neurotrophic factor) lead to a loss of ocular dominance columns [7]. Synaptic efficiency (both increases and decreases) can be triggered by N-methyl-D-aspartate (NMDA) glutamate receptors' stimulation [8] and the final geometry of the ocular dominance columns is also regulated by GABA inhibitory circuits [9].

In apparent contrast with the modular organization of brain functions, it is now well known that the brain can also transfer functions outside the traditional areas, in particular when the brain is forced to compensate for neuronal damage. This phenomenon has been called "adaptive plasticity", and is thought to be greater in children compared to adults with similar lesions. This assumption is supported by several observations, the most striking concerning language development. Children with early left hemisphere damage can develop normal language abilities, while lesions of similar site and extent in the adult brain would produce obvious patterns of aphasia [10]. Even if an entire hemisphere is removed at an early stage of development (for instance in the treatment of severe epilepsy), children can, most of the time, develop normal language and cognitive function [11].

Similar mechanisms have been hypothesized as to visual development. Tests of visual performance of humans that have incurred lesions of the primary visual cortex in infancy or

childhood are limited and reports are largely confined to case studies. Even so, they do reveal visual capacities that are superior in the cases with early brain damage respect to those individuals that sustained damage of the primary visual cortex when mature. Girl MS was studied by Innocenti and others [12]. She was born prematurely at 30 weeks gestational age and suffered bilateral ischemic damage of the primary visual cortex as a result of bacterial meningitis at 6 weeks of age. Longitudinal testing showed that subject MS has grown out of initial deficits and she matched performance of children of her own age on a variety of tasks including spatial and contrast sensitivity measures, figure-ground segmentation based on textures and vernier visual acuity. Performance was very high on the figure-ground tasks when figure and background differ in luminance, colour, or motion, and different brain pathways were used to make the discriminations. However, she maintained a severe impairment on "Poppelreuter" [13] figures that require extraction of forms from multiple overlain outlines. These results reveal selective sparing on some visual cognitive tasks, but permanent deficits on others. Lesions acquired somewhat later in childhood produce a different picture. For example, subject GY incurred unilateral destruction of the primary visual cortex when he was 8 years old as a result of head injury sustained in a traffic accident [14]. He was able to make saccadic eye movements into the blind hemifield, he was able to follow the path of a moving spot with arm movements, and he could discriminate between opposite directions of movement and between targets moving at different speeds, although he was not conscious of the presence of the stimulus [15-17]. These features are shared with other subjects with lesions of the primary visual cortex, but sustained later in life. What distinguishes GY from the other subjects is that he can switch to an aware mode where he is conscious of the presence of stimuli and can verbally report on stimulus position, aspects of spectral content, and the direction and velocity of stimulus movement providing that the size, contrast, displacement, and velocity are high enough [18-21].

Plasticity may be greater in early childhood, leading to abnormal cortical organization and greater sparing of function. By late adolescence and adulthood, as patterns of adult deficits reveal, such plasticity becomes increasingly less evident. These hypotheses have not been fully investigated in the human brain and general consensus has not been reached but animal models confirmed the complexity to find a plain relation between age and damage. For instance, after an animal experiment on rats based on the performance after frontal lesions at different

developmental ages, Kolb and Gibb [22] concluded that the effects of damage vary qualitatively with the developmental events occurring at the time of injury. In their experiment rats showed a poor recovery if the cortex was damaged immediately following the completion of neurogenesis, and good recovery when injury occurred during the time of maximum synapse formation.

In a very interesting review, Payne and collegues compared the behavioural, physiological and anatomical repercussions of lesions of primary visual cortex, incurred by developing and mature humans, monkey and cats [23]. Comparison of the data on the effects of lesions incurred earlier or later in life suggests that earlier, but not later, damage unmasks a latent flexibility of the brain to compensate, partially, for functions normally attributed to the damaged cortex. The compensations are best documented in the cat and they can be linked to system-wide repercussions that include selected pathway expansions and neuron degenerations, and functional adjustments in neuronal activity. Even though evidence from humans and monkeys is extremely limited, it is argued on the basis of known repercussions and similarity of visual system organization and developmental sequence, that broadly equivalent phenomena most likely occur in humans and monkeys following early lesions of primary visual cortex.

1.2 Purposes of the thesis

As expressed above, the possible mechanisms of functional reorganisation after brain damage are very complex and strongly influenced by a high number of factors. Among them, the time of the lesion and its localisation and severity seem to play a major role in the determination of the final outcome.

So far, most of the studies concerning the anatomo-functional correlations of brain lesions have been done in animal models or in adults, while for children with congenital lesion there are only few studies and often with discordant results.

In the recent past, high-definition neuroimaging techniques have been fully developed allowing the achievement of much more precise information on the type and extent of the lesion and on the involvement of the various cortical and subcortical areas involved in visual function, providing a better understanding of the correlation between structure and function. These studies have provided evidence that the normal development of visual system depends on the integrity

of a network which includes optic radiations and primary visual cortex but also other cortical and subcortical areas, such as the frontal or the temporal lobes or the basal ganglia.

The possibility to test various aspects of visual function related to these areas has also further improved our understanding of the correlation between visual function and neonatal brain lesions and the effect of a neonatal lesion on the developing brain.

The collaboration with the Institute of Neuroscience-CNR (Pisa) in the present study has allowed to design specific tests for the assessment of various aspects of visual function, such as the perception of different types of motion, and to apply them to a large population of infants with different types of brain lesions.

The main models used in our study are the term and the preterm child. In particular, we have been interested to separately investigate the two principal patterns of damage found in these infants, the diffuse (bilateral lesions) and the focal (unilateral lesions) damage. The main goals of our study concerned the study of visual development in these infants, and the correlation of their functions to the type, localisation and severity of the lesions.

Our analysis can be broadly subdivided into two main aspects:

1) <u>The analysis of visual abilities in children with congenital bilateral brain lesions</u>. Visual function will be assessed using standardised behavioural and electrophysiological tests, but also new psychophysical techniques. The results will be compared with the pattern of brain damage shown on early serial MRI.

2) <u>The analysis of the different patterns of visual abilities in children with unilateral brain lesions both congenital and acquired</u>. This will be accomplished by using structured and standardised visual tests and comparing the results to the pattern of brain damage analysed with early serial magnetic resonance imaging (MRI). Some preliminary and more specialised studies based on functional MRI (fMRI) for the assessment of visual reorganisation after brain damage will also be presented.

More specifically the following aspects will be treated in the thesis:

Chapter 1

• **Chapter 2:** An overview of the main patterns of lesion occurring in the animal model will be presented. In particular, the aspects covered will be the neuropathological and neurophysiological basis of damage, the main clinical pictures and finally a general outline of the anatomo-functional correlations.

• **Chapter 3:** Bilateral brain lesions with particular regard to periventricular leukomalacia will be the main subject of the chapter. In particular, studies by the author in this domain will be presented, covering the topic of the correlation between patterns of bilateral lesions and visual function by means of a structured analysis of i) visual acuity and ii) perception of flow motion. Furthermore, the inversion of perceived direction of motion caused by spatial under-sampling in two children with periventricular leukomalacia will be described.

• **Chapter 4:** The preliminary data of the ongoing doctoral studies on the evaluation of the perception of "Biological Motion" in children with periventricular leukomalacia by means of psychophysical tests will be reported. The aim of the study is to clarify whether the impairment in the perception of "Biological Motion" is isolated or associated to other types of visual perception deficits.

• **Chapter 5:** Congenital or acquired unilateral brain damage will be the main subject of the chapter. In particular, preliminary data of the ongoing doctoral studies on the reorganisation of the visual system will be presented, covering i) the topic of the correlation between patterns of congenital or acquired unilateral brain damage and visual function aspects with particular regards to visual search abilities; ii) the different response to a multisensory stimulation in children with congenital and acquired lesion and hemianopia.

• **Chapter 6:** The preliminary data of the ongoing doctoral studies on the reorganization of visual cortex by means of functional MRI in a child with hemianopia and congenital unilateral brain lesion, will be presented.

• **Chapter 7**: Summary, conclusions and future perspectives.

Chapter 2

Visual function deficit after early lesion of retro-chiasmatic visual structures: animal models

2.1 Introduction

What are the repercussions of early lesions on neurons, brain pathways, neuronal properties, and activity levels? What types of neural processes and behaviours are spared, and what functions are permanently impaired? Are cerebral functions redistributed to accommodate the functional compensations? Is there a functional price to pay for the sparing of neural functions? Do the repercussions produce a different brain? Finally, what is it about the young cerebral cortex that makes it different from the mature cerebral cortex in the way that it responds to focal damage?

Here, we'll report the principle results resumed in an interesting review by Payne ad collegues [23] on data gathered from cats. These data are highly relevant to understanding the repercussions of early focal lesions in humans because, in broad terms, there are many aspects of brain connections, layout, and function that are similar to those of monkeys, and by extension humans [24-26]. Moreover, there are also great similarities in the developmental program of cats, monkeys, and humans [27-29], yet the developmental tempo of the cat brain is considerably faster than that of both monkeys and humans.

One enormously important aspect of the work on cats is its relevance to the clinical arena and the understanding of the repercussions of focal cerebral lesions sustained by the premature or neonatal brain. This view obtains because the maturational status of the newborn cat approximates that of the early third trimester human fetus and is of particular significance

because of its relevance to comprehending the repercussions of focal lesions in the growing numbers of fragile, premature infants born each year with a birth weight of ≤ 1.5 kg.

They are the youngest of the group of viable infants born, and some estimate that between 40% and 60% of them suffer from some form of cerebral damage (e.g., [30, 31]). So far, what has emerged from the data on cats is the new perspective that the repercussions of early damage of the primary visual cortex, designated areas 17 and 18 [32], spread throughout the entire visual system [25, 33]. They shape pathways and circuits into new and useful forms that underlie functions that are retained into adult life, and optimize the individual's interactions with the environment under the new conditions, and they are considered "adaptive". Such positive features are a distinguishing characteristic of the plastic capacities of the brain, and they should be distinguished from the non-specific and disordered alterations in pathways and function that may also be induced by lesions, but that have no useful function. However, there may also be some permanent deficits that can be linked to degeneration of specific subsystems within the visual system.

These sequelae spread to all other major components of the highly interconnected visual system from the retina, through the nuclei in the thalamus (lateral geniculate, lateral posterior, and pulvinar), to regions of parietal and temporal cortices (Fig. 2.1). These repercussions have a substantial impact on neural function and behavior. Lesion-induced alterations include regressive sequelae such as the death of distant neurons normally highly connected with the damaged region, and consequent reduction or elimination of brain pathways, as well as permanent degradations in neural and behavioural performance.

The non-regressive sequelae form the platform for progressive changes such as the expansion of pathways that bypass damaged and degenerated regions, and they form the substrate for neural compensations that result in sparing of neural performance and behaviour.

2.2 Impact of Lesions of the Primary Visual Cortex

2.2.1 Lesions Incurred in Adulthood

Lesions of the primary visual cortex sustained in adulthood have a broad and substantial detrimental impact on a host of visually guided behaviours (Table 2.1, column 4).
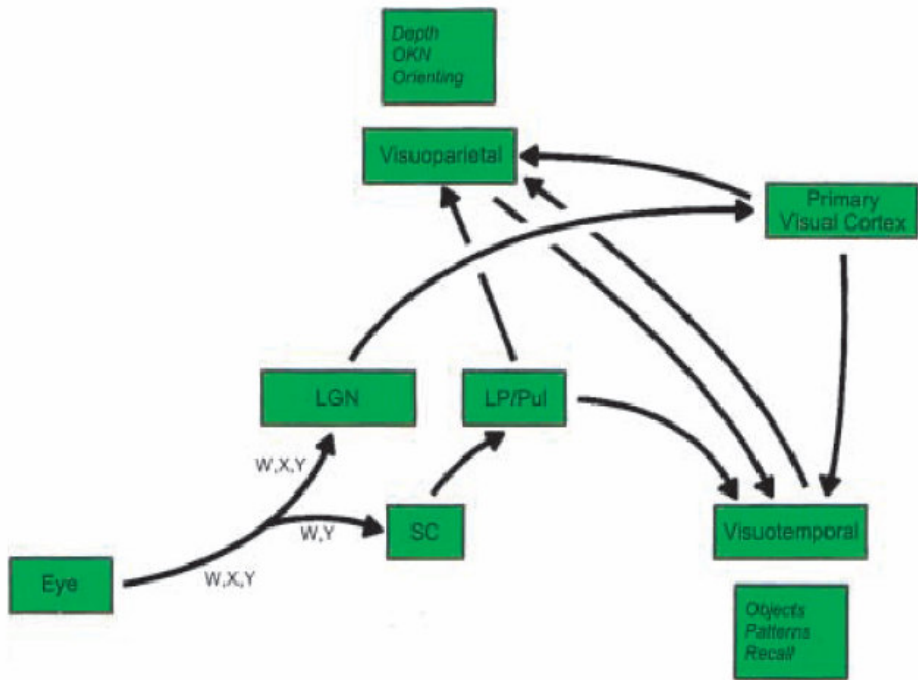
Fig. 2.1 Summary diagram of major visual pathways. LGN = lateral geniculate nucleus; LP/Pul = lateral posterior/pulvinar complex; SC = superior colliculus. Major destinations of retinal signals are identified by type, as are the contribution that visuoparietal and visuotemporal cortices make to visually guided behaviors (*italics*). Green symbolizes normal structures and functional performance of neurons and the individual. OKN = Optokinetic nystagmus.

The impacts extend from basic visual functions such as visual acuity, through largely reflexive, action-based, and spatial functions, which are normally associated with the visual regions of the parietal cortex, through two-dimensional form, learning and memory operations, which are normally associated with the visual regions of the temporal cortex (yellow cells). However, simpler visual operations such as learning and recognizing simple three-dimensional forms (row 7) and neural operations underlying orienting to an auditory stimulus (row 6) are largely or completely unaffected by the lesions (green). The broad spectrum of the behavioural deficits reflects principally the removal of the primary visual cortex and its signal processing functions,

and the disconnection of the extrastriate cortical regions from large numbers of visual signals that enter the cortical network via the lateral geniculate nucleus and primary visual cortex (Fig. 2.2 A). The most prominent disconnection is from the numerically dominant β retinal ganglion cells that survive and continue to transmit X signals, but they are not connected in any significant way to cerebral structures.

The absence of these signals from cerebral circuits severely reduces acuity among other visual measures (Table 2.1, row 1, column 4). Consequently, the signals derived from them are not processed and they do not contribute to behaviour. Moreover, there is a severe degradation of sophisticated receptive field properties and neural activities in the visuoparietal cortex (Fig. 2.2 A, yellow shading), whereas activities assayed in the retina with electrophysiological methods or in the visuotemporal cortex with metabolic markers appear to be unaffected (green). The lesion has no detectable impact on the composition of pathways from the retina to LGN or those pathways that bypass the primary visual cortex, such as those from the thalamus or visuotemporal cortex to the visuoparietal cortex.

2.2.2 Impact of Lesions of the Primary Visual Cortex: Postnatal Week 1

Lesions of the primary visual cortex sustained during the first postnatal week result in both sparing and permanent impairments in visually guided behaviours. The impairments parallel the severity of impairments induced by equivalent lesions sustained in adulthood.

For example, visual performance based on acuity and form-learning and -memory tasks that require discrimination of patterns with surround masking distractors is no better in the cats with early lesions than in cats that sustained the same lesion in adulthood (Table 2.1, column 5, rows 1 and 10, yellow cells). This latter, cognitive deficit reveals permanently impaired cerebral functions.

However, the same cats have high proficiencies discriminating simpler forms or figures obscured by an overlain masking grid, and they are superior to the diminished performances of cats that sustained primary visual cortex lesions as adults (column 4, rows 9 and 11, red).
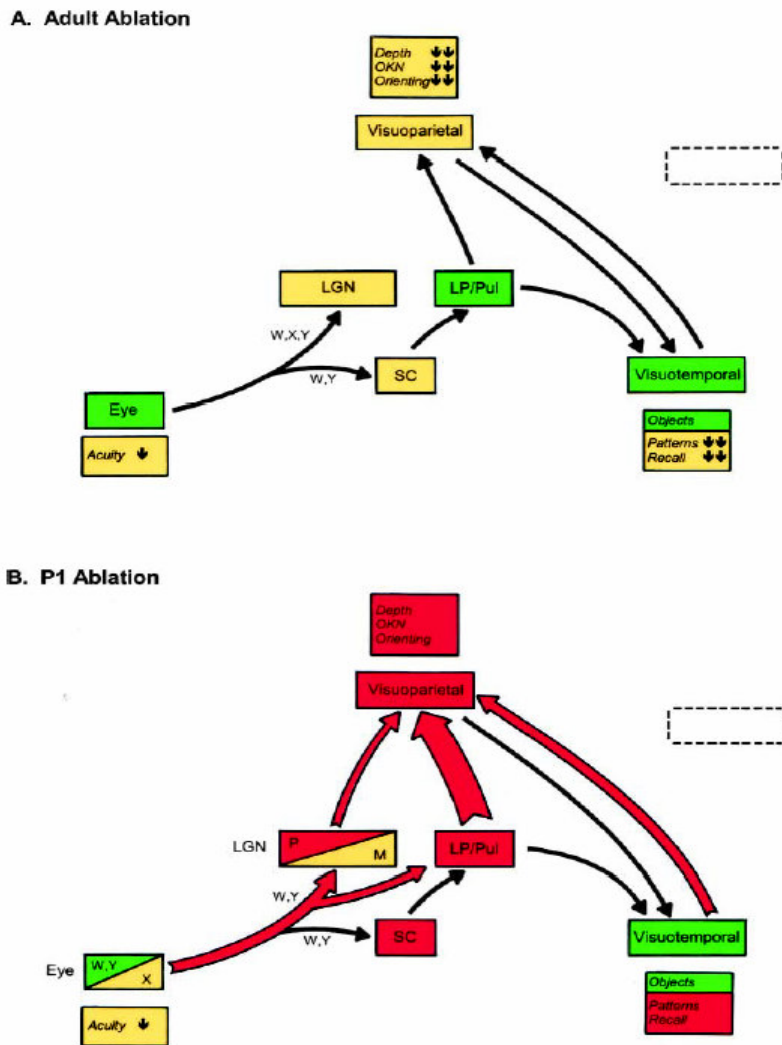
Fig. 2.2 Restructuring of visual pathways and impact of lesions of the primary visual cortex sustained in adulthood (A) or on the day of birth (P1). Yellow identifies neuron degenerations, degraded neuronal properties, lowered activity levels, and impaired visually guided behaviors. Red identifies spared neurons, expanded pathways, neural compensations (receptive field properties or activity levels), and sparing of visually guided behaviors. For clarity, cortical projections to superior colliculus are not shown. OKN = Optokinetic nystagmus; LGN = lateral seniculate nucleus; LP/Pul = lateral posterior/pulvinar complex; SC = superior colliculus (Data are drawn by Payne and collegues [23])

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Sparing on this set of pattern discriminations with overlain grids is also complete, or almost complete, if the lesions incurred in infancy are made in two stages with 3 days between operations (row 11 *). These tasks are normally associated with the visuotemporal cortex (column 1). There is also overall superior performance on tasks normally associated with the visuoparietal cortex such as judging depth, optokinetic nystagmus, and reorienting of visual attention (rows 2–5). On some tasks, such as orienting, the same cats benefit from additional training [34]. The superior performance by cats on the visuotemporal and visuoparietal tasks, compared to cats with lesions sustained in adulthood, is strong evidence for sparing of a constellation of visually guided behaviors and underlying neural operations, and they must be accompanied by significant adjustments in brain connections. Like cats with lesions sustained in adulthood, there is little detectable impact of earlier lesions on the ability to discriminate between highly dissimilar objects or on auditory orienting (rows 6 and 7). Many neurons in structures distant from the lesion die, whereas others survive. For example, 90% or more of the X-cells in both retina and LGN die (Fig. 2.2 B, yellow shading), whereas W and Y cells survive and they form the platform for pathway expansions and neural compensations (Fig. 2.2 B, green and red shading). The surviving W and Y ganglion cells increase the density of their projections to the parvocellular (P) layers of LGN and establish a new projection to the lateral posterior nucleus (LP; Fig. 2.2 B). In addition, the spared neurons in the magno-(M) and parvo-cellular layers of LGN contribute to increased projections to the visuoparietal cortex. Their numbers, though, are surpassed by the expansion of an already significant projection from the medial component of the lateral posterior/pulvinar complex (LP/Pul) that receives substantial visual signals fed forward from the superior colliculus. In toto, they provide a massive expansion of visual projections into the visuoparietal cortex. This expansion has a parallel in the increased numbers of neurons in the visuotemporal cortex that also project to the visuoparietal cortex, and probably in the reciprocal pathway. All of these expansions are accompanied by at least maintenance, if not an increase in overall level of neural activity in brain pathways (green and red shading, respectively), and sparing of receptive field properties of binocularity and direction selectivity in the cortex. Together, they provide additional measures of neural compensations induced by early lesions of the primary visual cortex.

Tab. 2.1 Summary of spared and impaired visual performance following lesions of the primary visual cortex sustained in adulthood or during the first postnatal week. Tasks are grouped according to neural structure that contributes most fully to the neural operations. ++++ = high level of performance; ↓↓↓ = great reduction in performance (severe deficit): ↓↓ = lesser reduction in performance (moderate deficit): ↓ = slight reduction in performance (minor deficit). Green shading represents normal high levels of proficiency on tasks. Yellow shading represents impaired performance. Red shading represents partial or complete sparing

	1 Visual Region	2 Visual Property	3 Intact	4 Adult Lesion	5 P1 Lesion
1	Retina	Basic Property Acuity[1]	++++	↓↓↓	↓↓↓
2		Reflex, Action, Space Depth[2,3]	++++	↓↓↓	↓
3	Parietal	OKN[3]	++++	↓↓↓	↓
4	Cortex	Orienting			
5		Visual[3-5]	++++	↓↓↓	↓
6		Auditory[4,5]	++++	++++	++++
7		Form, Learning, Memory Objects	++++	↓	++++
8	Temporal	Patterns			
9	Cortex	Simple[6,7]	++++	↓↓	++++
10		Masked – Surround[6,7]	++++	↓↓↓	↓↓↓
11		Overlain[6,7]	++++	↓↓↓	↓*

* = no or lesser deficit following two stage lesions. OKN = Optokinetic nystagmus.

Studies cited are limited to those that employed comparable stimuli and testing procedures in assays of performance of the different groups of cats. 1) Mitchell (2002); 2) Cornwell and others (1978); 3) Shupert and others (1993); 4) Payne an others (2000); 5) Payne and Lomber (2001); 6) Cornwell and others (1989); 7) Cornwell and Payne (1989).

2.3 Linkages—Behavior, Neuronal Properties and Anatomy

The data summarized above become more fully comprehensible in the context of experimental results showing that there is no evidence for sparing of visually guided behaviors when the early

lesion includes visuoparietal and visuotemporal regions in addition to the primary visual cortex, because performance in the early lesion group is inferior to that of cats with lesions limited to the primary visual cortex, and it is as poor as performance in the adult-lesion group [35, 36]. The poor performance is understandable because these larger lesions eliminate all, or virtually all, of the cerebral cortical machinery for the processing of visual signals. From these data the authors conclude 1. that an appropriate system-substrate needs to remain for neural compensations to emerge and 2. that the substantial expansion of pathways into and out of the visuoparietal cortex, and possibly the visuotemporal cortex, are obligatory components of the neural compensations that overcome numerous otherwise profound deficits in neural performance and behavior. Howewer, the compensantions are not complete because the magnitude of the sparing does not equate with the highly proficient performances by intact cats   because neurons in the visuoparietal cortex do not adopt properties of neurons eliminated by the ablation of the primary visual cortex [37]. Thus, it appears that the visuoparietal cortex is able to compensate and establish a normal set of properties, but it cannot adopt attributes of eliminated cortices. Evidence for neuronal compensations in the retina and lateral geniculate nucleus are currently lacking. Although it is straightforward to comprehend how pathway expansions are adaptive and contribute to the neural compensations, the contribution of neuron death and elimination of neural circuits to the compensations is less comprehensible. We interpret the deaths as purging the brain of poorly connected and largely superfluous neurons that may otherwise interfere or dilute signal processing. The net outcome, then, of the degenerations is a more efficient and accurate processing of signals in the remaining circuits, which we speculate are prerequisites for more normal levels of neuronal processing and accurate performance on a number of perceptual and cognitive functions by cats with early lesions.

2.4   A different brain?

In the intact brain, each region of the cerebral cortex is unique in terms of its architecture, connectional signature, functional maps, inventory of receptive field properties, and its contributions to neural processing and behavior. But the multiple repercussions of the early lesions of the primary visual cortex modify all of these attributes, and we conclude that the early

lesion triggers the development of a different brain, and we are prompted to ask: Is there a redistribution of functions across the modified expanse of the cerebral cortex? For example, functions normally localized to one region may become dispersed across a broader region of the cerebral cortex as signals are redistributed. Anatomical evidence to support this view is provided by the expanded projection from the visuotemporal cortex to the visuoparietal cortex and in the reciprocal direction (Fig. 2.2 B), as well as by the expanded projection from the visuoparietal cortex that reaches the visuotemporal cortex via the superior colliculus and LP/Pul (not shown). Thus, it may be that the processing of signals in the visuoparietal cortex is altered in significant ways by the signals arriving from the visuotemporal cortex and vice versa. The first experiments to test this proposition have been carried out. The tests have used localized cooling, via subdurally implanted cooling loops, to reversibly deactivate the visuoparietal and visuotemporal cortices in behaving cats in conjunction with four tasks: 1) visual orienting, 2) pattern recognition, 3) object recognition, and 4) auditory orienting (Fig. 2.3). In intact cats, visual orienting is completely abolished by cooling deactivation of the visuoparietal cortex (Fig. 2.3 A, column 1, light blue cell) but is completely unaffected by cooling deactivation of the visuotemporal cortex. In contrast, pattern- and object-recognition processes are completely disabled by cooling deactivation of the visuotemporal (Fig. 2.3 A, columns 2 and 3, light blue cells), but not the visuoparietal, cortex, and deactivation of neither region has an impact on orienting to a sound stimulus (Fig. 2.3 A, column 4, open cell). Following visual cortex lesion in adulthood, performance on both the visual orienting and pattern recognition tasks is severely impaired (Fig. 2.3 B, yellow cells), but without significant impact on object recognition or auditory orienting (Fig. 2.3 B, green cell). As indicated earlier, the early lesion of the primary visual cortex largely spares visual orienting and complex-pattern recognition and has only minor impact on object recognition and no impact on auditory orienting (Fig. 2.3 C, red cells). Cooling deactivations reveal that visual orienting remains strongly dependent upon the visuoparietal cortex. However, the dependence is not complete, because full deactivations, as revealed by modified 2DG uptake, do not completely abolish orienting, as it does in intact cats (Fig. 2.3 C, column 1, intermediate blue cell). In the same cats, independent cooling deactivation reveals a new essential contribution of the visuotemporal cortex to high proficiency on the task (column 1, dark blue cell). Moreover, the impact of combined visuoparietal and visuotemporal deactivations does not exceed the impact of the sum of the independent deactivations (column 1, light blue

cell). This result suggests that no other region than the visuotemporal cortex acquires a role in guiding visual orienting movements. In the opposite direction, visuotemporal-unique representations spread to the visuoparietal cortex. For example, cooling deactivation of the visuotemporal cortex in cats that sustained early lesions of the primary visual cortex impairs performance on pattern discriminations as it does in intact cats. However, in the cats with early lesions, the reduction is less profound and does not reach chance levels exhibited during visuotemporal cooling in intact cats (cf. blue cells in columns 2 and 3, Fig. 2.3 A and C). However, in the very same cats, there is also a reduction in proficiency of performance on the pattern recognition task when the visuoparietal cortex is deactivated (dark blue cell). Moreover, during the visuoparietal deactivation, the cats can relearn the task, whereas there is no evidence that performance can improve during visuotemporal deactivation. The visuoparietal cortex does not contribute to visual discrimination of three dimensional objects, which remain critically dependent upon the visuotemporal cortex alone, as it does in intact cats (column 3). Thus, following the early lesion of the primary visual cortex, the visuoparietal cortex also contributes to the recognition and discrimination of complex, masked patterns that require processing of signals across extensive regions of the cortex. Presumably, in intact cats, a significant fraction of this essential processing is carried out in the primary visual cortex. These observations demonstrate a functional reorganization of neural substrates contributing to visually guided behaviours; there is a muted role of the visuoparietal cortex and a heightened role of the visuotemporal cortex in guiding orienting behaviour with the converse pertaining to the neural bases of complex pattern discriminations. Nevertheless, the visuotemporal cortex remains critical for the relearning of over-learned and simpler pattern discriminations. These data show that at least two highly localizable functions of the normal cerebral cortex are remapped across the cortical surface as a result of an early lesion of the primary visual cortex. Moreover, the redistributions have spread the essential neural operations underlying orienting behavior from the visual parietal cortex to a normally functionally distinct type of cortex in the visual temporal system, and in the opposite direction for complex-pattern recognition. However, it is not known if there is a "price" to pay for the redistribution, or if functions normally associated with respective regions are reduced, displaced, or "crowded out" as proposed by Teuber [38], as the regions make contributions to new aspects of visually guided behaviour not normally represented. This change in function is a possibility because it is known that visuospatial

abilities are reduced when sparing of language functions can be demonstrated in humans [38, 39].

A) Intact

Primary Visual Cortex

	Visual Orienting	Pattern Recognition	Object Recognition	Auditory Orienting
Performance	++++	++++	++++	++++
Parietal Deactivation	↓↓↓↓	0	0	0
Temporal Deactivation	0	↓↓↓↓	↓↓↓↓	0

B) Adult Ablation

	Visual Orienting	Pattern Recognition	Object Recognition	Auditory Orienting
Performance	+	+	+++	++++

C) Infant Ablation

	Visual Orienting	Pattern Recognition	Object Recognition	Auditory Orienting
Performance	+++	+++	+++	++++
Parietal Deactivation	↓↓	↓	0	0
Temporal Deactivation	↓	↓↓	↓↓↓	0
Parietal & Temporal Deactivation	↓↓↓	↓↓↓	↓↓↓	0

Fig. 2.3 Performance of Intact (*A*), Adult lesioned (*B*), and infant (*P1*)-lesioned (*C*) cats on 1) visual orienting, 2) complex-pattern recognition, 3) object recognition, and 4) auditory orienting tasks, and the impact of cooling deactivation of visual parietal and visual temporal cortices. Color conventions are summarized for Table 1. In addition, for impact of cooling deactivation: light blue = maximum deficit; intermediate blue = substantial deficit; dark blue = lesser deficit. Behavioral performance: ++++ = highly proficient performance; +++ = competent performance; ++ = modest performance; + = poor performance. Impact of cooling: ↓↓↓↓ = Proficiency on task is abolished or reduced to chance levels; ↓↓↓ = severe reduction in performance; ↓↓ = modest reduction; ↓ = minor reduction.

In *C*, note should be made of initial proficiency prior to cooling. For example, on the orienting task there is considerable sparing of function, but performance is not at normal levels, and it is designated "+++". During combined cooling of visuoparietal and visuotemporal regions, the cat is unable to reorient its attention, and the reduction in performance is designated "↓↓↓" and impact of the cooling is maximal.

Chapter 3

Organisation of the visual system in children with bilateral brain lesions: the model of periventricular leukomalacia

3.1 Introduction

Even if the degree of functional sparing can vary with the age at which the cortical damage was incurred, it depends also on the extension of the lesion. On animal models bilateral lesions seem to cause a much more damaging to the behavioural output of the developing brain than equivalently large unilateral lesions [40] with more difficult activation of compensation mechanisms.

One of the most frequent bilateral lesion in children with congenital brain damage is the so-called "periventricular leukomalacia (PVL)" that consists of hypoxic-ischemic damage of periventricular white matter typical of preterm infants, usually occurring at the beginning of the third trimester of gestation [30]. This lesion generally involves the cortico-spinal tract, and is therefore associated to a motor impairment primarily affecting the lower limbs [41]. In most cases however, it also involves the optic radiations due to their particular distribution around the posterior horns of the lateral ventricles, giving rise to different types of visual disorders [42-45] and, at present, PVL is considered the major cause of visual impairment in prematurely born children [46].

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The aim of the series of studies reported in this chapter has been to evaluate the development of visual functions in children with bilateral brain lesions and in particular with PVL. We aimed at analysing the possible correlations between the site and extent of the lesions, characterised by MRI, and visual development, with particular regard to visual acuity and to perception of different types of motion. All the studies presented have been specifically performed in the context of the doctoral project.

3.2 The assessment of visual acuity in children with periventricular damage: a comparison of behavioural and electrophysiological techniques

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Different techniques have been used for the early assessment of visual acuity in infants with brain lesions, including PVL. In several studies behavioural methods have been applied, based on the spontaneous preference of the infant for a complex pattern, as in the acuity card (AC) paradigm [22, 47, 48]. Other authors have instead used electrophysiological techniques, such as different types of visual evoked potentials (VEP) [49-51]. Abnormal results are usually found with both approaches in a significant proportion of subjects with congenital brain damage [42, 52, 53]. However, when the two methods are used in the same population, the results are often conflicting probably due to the heterogeneity of the populations assessed or to the specific characteristics of the techniques used [54-56].

Behavioural and VEP measures of visual acuity are in fact feasible and deemed reliable and valid in infants and children with PVL, and both measures may be used in clinical practice. However, different results from the two techniques can be found as VEP acuity mainly depends on the integrity of the pathway from the eye to the visual cortex, while behavioural responses integrate higher processing and rely on additional factors such as attention and ocular motor abilities which may be affected in children with neurological disorders [50]. In the present study we assessed the concordance between grating acuity tested with sweep VEPs and ACs in a group of children with PVL, also exploring the possible bases of discordant results.

3.2.1 Subjects and Methods

Twenty-nine children (age range 9 months-13 years) with a neuroradiological diagnosis of PVL, referred to the Stella Maris Scientific Institute in Pisa between years 2004 and 2006, were selected for this study. A parental informed written consent for the study was obtained in all cases. The research was approved by the Ethical Committee of the Stella Maris Foundation.

The type of cerebral palsy was defined according to the criteria of Hagberg et al [57]. Subjects with severe ophthalmologic abnormalities (such as retinopathy of prematurity stage III or upwards, major refraction problems, optic nerve atrophy) were not included in the study. In all subjects, the following assessments were performed: i) a behavioural and electrophysiological measure of visual acuity and ii) a detailed evaluation of other aspects of visual function. In those subjects in which good quality MRI scans were available a quantitative/qualitative assessment of the characteristics of the lesion was also performed. Cognitive development was assessed by the Griffiths scales [58] in children below three years of age and by the Wechsler scales in the others [59, 60].

Assessment of visual acuity

Visual acuity was assessed by means of the Teller Acuity Cards (TAC) [61] and the sweep VEP [62-65]. The assessments were performed within the same session in random order.

Teller Acuity Cards: this test is based on a preferential looking paradigm, i.e. the spontaneous behavioural reaction of newborns and infants consisting on gazing or turning of the head toward the most salient of two or more alternative visual stimuli [61]. The stimulus consists of a series of stripes (grating) displayed on cards, and the acuity value is defined by the smallest stripe width that consistently elicits a preferential looking response. The spatial frequency of the cards ranges from 0.32 to 38 cycles/cm with a difference of ½ an octave between one card and the next one. Acuity values are expressed in minutes of arc (or cycles per degree) and can be compared to normative data reported in the literature [42, 61, 66-69].

Sweep Visual Evoked Potentials: Stimulus generation and signal analysis were performed using the Power Diva system (Digital Instrumentation for Visual Assessment, Smith- Kettlewell Eye Research Institute, San Francisco, California) on separate computers (PowerMacintosh G3 Apple) [49, 63, 64]. Stimuli were displayed on a CRT monitor (Mitsubishi Diamond-Pro 17").

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The grating acuity stimulus consisted on a sine-wave vertical grating that alternated with a matched space-averaged luminance field displayed at 80% contrast (average luminance, 43 cd/m2) at a rate of 3.76 Hz on-off modulation. The spatial frequency range was varied from 2 to 16\20 cyc/deg according to the age and the visual disability of the subject. The grating was swept from high to low spatial frequency during a 10-second trial. The viewing distance was 80 cm. We recorded 4 to 10 trials for each subject. Raw scalp potential recordings for each 10 second trial were digitalized to 16-bits precision and partitioned into 10 sequential epochs of 1 second duration (bins). For each bin, a recursive, least square algorithm was used to generate a series of complex-valued spectral coefficients representing the amplitude and phase of response components tuned to various harmonics of the stimulus frequency. These spectral coefficients for each bin were averaged together across trials for each subject, channel, harmonic and stimulus condition. Statistical significance was assessed based on a T^2_{circ} statistic, a phase sensitive, variance-normalized measure of mean amplitude. Response thresholds were calculated separately for each condition by regression of amplitudes from the bins where the response decreased linearly to the point of stimulus invisibility. The range of bins eligible for regression depended on the statistical significance and phase consistency of the response. Once the range was determined, the threshold value was established by extrapolating the regression line to 0 response amplitude. Brain electrical activity was recorded with Grass gold-cup electrodes placed on the scalp with a conductive gel. Three active electrodes in a row were placed over the occipital pole at O1, Oz, and O2, each of them three cm apart from the other, with reference and ground electrodes placed on Cz and Pz, respectively, based on the International 10-20 system. Electrode impedance was between 3 and 10 Kilo-ohms and the EEG was amplified at a gain of 20,000 or 50,000 depending on the age of the subject (Grass Model 12 amplifiers with analogue filter setting of 0.3 to 100 Hz. Measured at -6dB points). During a recording session, subjects sat alone or on a parent's lap in front of the monitor and an operator attracted their attention with a small toy on the center of the monitor. When the subjects were not attending to the stimuli recordings and sweeps (but not the stimulus appearance) were interrupted. When the stimulus resumed, its values were set as they were 0.5 seconds before the interruption. We did not use the first and last bin for analysis.

Assessment of other aspects of visual function

A full ophthalmological assessment was performed in all subjects exploring in particular the presence of ocular abnormalities, optic atrophy and refractive errors.

Oculomotor behaviour was assessed by means of the observation of fixation, following, and presence of abnormal eye movements, such as spontaneous nystagmus. Strabismus was tested by examining symmetry of the corneal light reflex and by the cover test.

Visual-field size was assessed using kinetic perimetry [66]. During central fixation of a centrally positioned white ball, an identical target is moved from the periphery towards the fixation point along one arc of the perimeter. Eye and head movements towards the peripheral ball are used to estimate the outline of the visual field. Normative data for fullterm and preterm infants are available [42].

On the basis of the results of the individual aspects explored a global vision score was obtained according to the classification system of Randò et al. [70].

Assessment of brain damage

MRI were scored according to the following criteria:

1)   Global lesion score: the characteristics of the lesion were scored by means of the classification system of Cioni et al. [71] based on the following items: size of lateral ventricles, evidence and extension of white matter damage and of white matter loss, thinning of corpus callosum, evidence and size of cystic areas, size of the subarachonoid space and abnormalities of cortical grey matter. Each item was scored on a three grade scale, with score 3 indicating the most severe MRI abnormalities. The scores of the seven items were summed to obtain a total score for each infant. The total scores were also classified on a three grade scale (Table 3.1).

2)   Global atrophy index: an indirect index of global white matter damage was obtained as the ratio of the sum of ventricular body and extracerebral space to the whole brain surface (Fig. 3.1 a) (Ito's criteria, modified [72]). The measure was performed on MRI axial scans at a level just above the foramen of Monro.

3)   Corpus callosum index: an indirect index of posterior white matter damage was obtained as the ratio between the thickness of the genu and the thickness of the body (index

1) or the splenium (index 2) (Fig. 3.1 b) (Iai's criteria modified; [73]). The measure was performed at midsagittal MRI scanned level.

Tab. 3.1 Global lesion score [71]

#	Ventricle size	WM abn. SI	WM reduction	Cysts	Subarach. space	Corpus callosum	Cortical GM	Total score	Global grade
1	3	2	2	2	3	2	1	15	**2**
2	3	3	3	3	3	3	3	21	**3**
3	2	2	2	2	2	2	1	13	**2**
4	2	3	3	1	2	2	1	14	**2**
5	na	na	na	na	na	na	na	na	**na**
6	1	2	2	1	1	1	1	9	**1**
7	2	2	2	1	2	2	1	12	**2**
8	1	2	2	1	1	2	1	10	**1**
9	2	2	2	2	2	1	1	12	**2**
10	3	2	3	2	3	2	1	16	**2**
11	2	2	2	2	1	1	1	11	**1**
12	3	2	2	1	1	1	1	11	**1**
13	2	2	2	1	2	2	1	12	**2**
14	na	na	na	na	na	na	na	na	**na**
15	1	2	2	1	1	1	1	9	**1**
16	2	2	2	1	1	1	1	10	**1**
17	2	2	2	3	2	2	1	14	**2**
18	2	2	2	1	1	1	1	10	**1**
19	2	2	2	1	2	2	1	12	**2**
20	2	2	2	1	1	1	1	10	**1**
21	3	3	3	2	3	3	1	18	**3**
22	2	2	2	3	2	1	1	13	**2**
23	2	2	2	1	2	2	1	12	**2**
24	3	2	2	1	3	1	1	13	**2**
25	2	1	1	1	1	1	3	10	**1**
26	na	na	na	na	na	na	na	na	**na**
27	na	na	na	na	na	na	na	na	**na**
28	1	2	2	1	1	1	1	9	**1**
29	2	3	2	1	2	1	3	14	**2**

WM=white matter; **abn**=abnormal; **SI**=signal intensity; **subarach**=subarachnoidal;
GM=gray matter
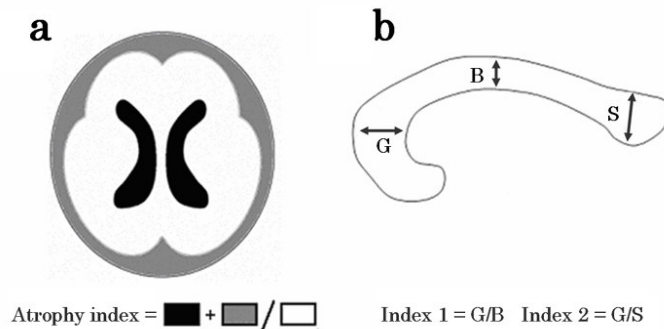
Fig. 3.1 Representation of global atrophy index (a) and corpus callosum posterior thinning indexes (b) Black=ventricular body; Gray= extracerebral space; White= whole brain surface. b) 1=genu; 2= splenium

The assessment of global brain damage was performed in 25/29 subjects who disposed of good quality MRI scans. Quantitative measures were only possible in 21/25 due to the availability of the required sections.

Statistical analysis

The correlation between TAC and sVEP was calculated by means of the Pearson's parametric test for bivariate correlation while the comparison between the mean values at TAC and sVEP was done by means of the Student's t-test. In order to investigate the possible influence of different factors on TAC and VEP development, we correlated these values and the index between the VEP/Teller ratio (which reflects the concordance of the two measures) to the anatomical indexes, gestational age and age at test, the global vision score and subscores. These correlations were calculated by means of the Pearson's parametric test when possible and by the Spearman's non parametric test in the other cases. A p value below .05 was taken as significant.

3.2.2 Results

The clinical description of our cohort is reported in Table 3.2. Mean gestational age was 32 weeks (range 25-40).

At least one of the aspects of visual function assessed was abnormal in all subjects but one. Strabismus was present in 24 children (21 esotropia and 3 exotropia), oculomotor disorders in 21

Tab. 3.2 Clinical data

	Assess. Age (ms)	Gestational Age	Weight	Neurological Diagnosis	I.Q.	Strabismus	Ocular Motricity	Visual Field	TAC	Sweep VEP	TAC cy/deg	Sweep VEP
1	9	29	1315	T	Mild	EI	Ab	R	●	●	6,5	6,64
2	11	26	750	T	Severe	EI	Ab	N	●	●	6,5	6,81
3	15	40	2550	T	Mild	EI	Ab	N	○	○	11,4	11,2
4	16	28	1210	D	Normal	E	Ab	N	○	○	13	12,58
5	19	28	1070	D	Normal	E	N	N	◐	◐	10,3	19,89
6	20	29	1380	D	Normal	EI	N	N	◐	◐	13	12,3
7	20	28	1020	T	Mild	EI	Ab	R	○	◐	12	7,59
8	24	31	1500	T	Severe	EI	Ab	R	◐	○	9,8	0
9	27	37	2500	T	Normal	EI	Ab	R	◐	◐	11,4	10,31
10	32	32	1080	T	Severe	XI	Ab	R	○	○	18,2	15,63
11	33	28	750	D	Mild	EI	Ab	N	●	●	9,1	9,47
12	35	36	1250	D	Mild	EI	N	R	◐	●	13	11,33
13	36	32	1300	D	Mild	EI	Ab	R	◐	●	19	10,83
14	37	40	3070	T	Severe	XI	Ab	R	●	●	0,8	0
15	40	33	1700	D	Normal	EI	Ab	R	○	○	16	16,29
16	44	40	1050	D	Normal	\	N	N	○	○	26	20
17	45	32	1650	T	Mild	EI	Ab	R	◐	◐	11,4	10,98
18	48	37	1120	T	Normal	EI	Ab	N	◐	◐	13	16,43
19	49	33	2480	D	Mild	EI	Ab	R	○	-	20	na
20	58	30	1050	D	Normal	EI	N	R	○	◐	26	11,06
21	61	25	630	T	Severe	EI	Ab	R	◐	◐	0	0
22	67	32	1250	D	Normal	\	N	N	◐	◐	16	9,23
23	78	27	1200	T	Severe	EI	Ab	R	●	◐	4,2	7,64
24	90	30	950	T	Mild	EI	Ab	R	◐	●	13	8,57
25	139	26	1390	D	Mild	\	Ab	N	●	●	9,1	9,03
26	147	32	1230	D	Mild	\	Ab	N	◐	●	15,8	9,53
27	155	40	2100	H	Normal	\	N	N	○	●	26	14,64
28	156	39	3010	D	Severe	EI	N	N	○	●	24	9,63
29	156	33	1400	D	Mild	XI	Ab	N	○	○	19	17,07

E= esotropia ; **T**=Tetraplegia; **D**=Diplegia; **H**=Hemiplegia; **E(I)** = Intermittent Esotropia ; **X** = exotropia ;

X(I) = intermittent exotropia ; **N**=normal; **Ab**= abnormal; **R**= reduction ●= abnormal; ◐= visual acuity

between 1 and 2 SD; ○= normal; **na**= not available

and visual field reduction in 15. Ten subjects had an intelligence quotient (IQ) in the normal range, 12 presented a mild retardation and the remaining 7 a severe retardation. All subjects showed a cerebral palsy, which was a hemiplegia in one child, a diplegia in 15 and a tetraplegia in the remaining 13.

Visual acuity

When visual acuity was assessed with the TAC, six subjects showed abnormal values (<2SD), 12 showed borderline values (between 1 and 2 SD) while the remaining 11 were normal. With sweep VEPs worse results were generally obtained: 11 subjects showed abnormal visual acuity, 10 borderline and only 7 showed normal values. In the remaining subject sweep VEPs were recorded twice but no reliable results were obtained due to the presence of excessive artefacts.

A highly significant correlation was found between TAC and sweep VEP, with a p value < 0.001 at Pearson Test (Fig. 3.2). However, the difference between the mean acuity values obtained with TAC and sweep VEPs was statistically significant (Student T test; p value=0.011). In 8/29 subjects the value of acuity measured by TAC was more than 50% higher than the measure obtained by sweep VEPs, and in two of the eight it was more than double. Conversely, only 2/29 subjects showed an acuity on sweep VEPs between 50 and 100% higher than the value obtained on the TAC.
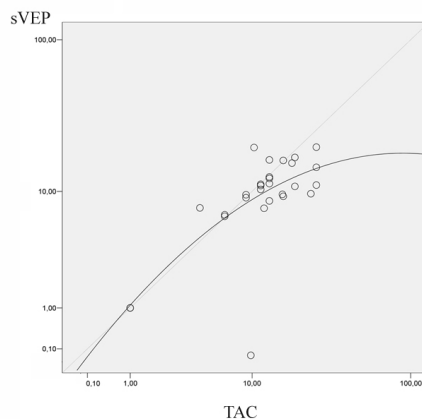
Fig. 3.2 Correlation between TAC and sweep VEP values

Chapter 3

Correlation between visual acuity and clinical features

TACs were significantly correlated with all the visual subscores, except for strabismus and visual fields, with gestational age (p= .021) and with chronological age (p= .037). A significant correlation was also observed with several aspects of brain damage such as the thinning of corpus callosum (p= .022), the subscore of global lesion classification assessing the size of cystic area (p= .029), and the atrophy index (p= .025).

Sweep VEPs were significantly correlated with all the visual subscores, except for strabismus and visual fields, with thinning of corpus callosum (p= .025) and size of lateral ventricles (p= .019).

Correlation between VEP/TAC ratio and clinical features

No correlation was found between VEP/TAC ratio and visual score and subscores, gestational age or chronological age. A significant correlation existed with global atrophy index (p= .041) and with the corpus callosum posterior thinning (index 2) (p= .05) as shown in Fig. 3.3. No statistical correlation was found between the VEP/TAC index and the global lesion score.
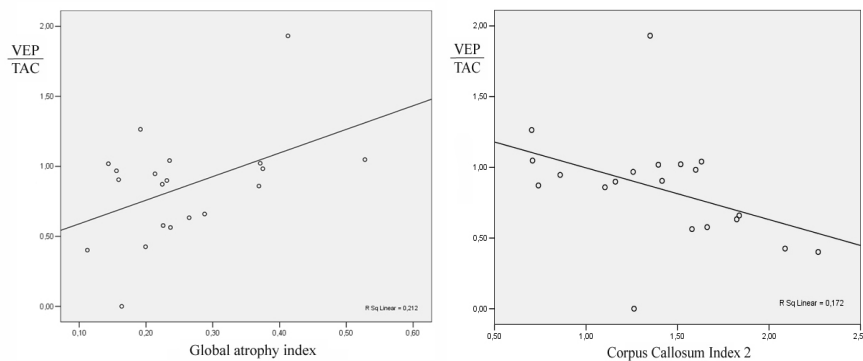
Fig. 3.3 Correlations between VEP/TAC ratio and brain damage

3.2.3 Discussion

The main purpose of the study was to explore the degree of concordance between electrophysiological and behavioural measures of visual acuity in children with PVL. These two

methodologies are commonly used in young infants or non collaborative patients as they are based on passive responses or spontaneous reactions. In the present study we used the sweep VEP technique, an electrophysiological method particularly indicated in paediatric populations for the short time of execution, and the Teller ACs, one of the most diffuse behavioural techniques in children with brain damage and cerebral visual impairment.

In accordance with previous reports comparing electrophysiological and behavioural measures of visual acuity in healthy infants and clinical populations [54-56, 74-76], we found in PVL children significant correlation coefficients between the two methods. However, when analysing the difference of the means for the two groups of measures, Teller acuities resulted significantly higher than VEP acuities, in contrast with most previous studies in children with other types of congenital brain damage. In several cohorts of children with CVI, often secondary to hypoxic-ischaemic encephalopathy at term, visual acuities were reported to be higher when assessed with VEPs, than with behavioural tests [49, 50]. A similar pattern was also observed in children with multiple neurological deficits by Orel-Bixler and co-workers, who found a better VEP acuity in 12/41 assessed patients as opposed to a better preferential looking (PL) acuity in only 2/41 [56]. This pattern has been interpreted as a result of the interrelation between the type of damage and the specific mechanisms underlying visual responses explored by the two techniques that are thought to involve the central nervous system at different levels. VEPs are time-locked responses to visual stimuli assessing pathway conduction and cortical activity of the primary visual cortex, and are thus mainly dependent from the integrity of the central visual structures [77, 78]. Preferential looking techniques are based on behavioural responses with gaze/attention shift and target exploration, and thus also require processing of high visual associative areas or attentional networks. Concordant with this hypothesis is the finding of a relative prevalence of VEP over PL acuity in normal developing infants, as a result of the higher complexity of the behavioural task, with PL acuity reaching VEP values only around 14 months post-term [79]. The different rate of maturation of the two responses has been interpreted as related to the process of myelination, which is faster in the optic radiations compared to extrastriatal visual pathways [80].

In term-born children with hypoxic-ischemic encephalopathy or in those with multiple neurological handicap and CVI, a diffuse bilateral involvement of cortical brain structures is generally present. This is often associated to a global developmental delay and important

attentional deficits, which are likely to affect to a greater extent the performance on behavioural than electrophysiological testing. This would explain the relative deficit of PL acuity, particularly in those children with greater developmental delay [56]. Our finding of an inverse pattern of distribution of acuity, i.e. PL acuity significantly better than VEP acuity, in children with PVL may be interpreted in the light of these reports. In fact, the typical site of brain damage in PVL children is the white matter around the posterior horns of the lateral ventricles, i.e. the region where the optic radiations are located. This may result in a direct damage of the geniculo-striate pathway, but with a relative sparing of cortical visual structures. As a consequence, it may be hypothesised that the plastic mechanisms of adaptive reorganization based on the reinforcement of the extra-striatal visual pathways are virtually unconstrained and thus potentially able to produce a good recovery of function. In these conditions, the effects of brain reorganization might be better appreciated with behavioural procedures that are likely to benefit more from the process of plasticity, as opposed to electrophysiological techniques, that are highly dependent on direct anatomical integrity of primary visual pathways. This interpretation is also consistent with animal studies showing a substantial sparing of visual orientation and pattern recognition in adult cat who underwent complete resection of the primary visual cortex at birth, as opposed to those operated later in life. Following early lesions, spared visual functions are remapped across the cortical surface and redistributed to a more spread network of functionally distinct areas of the visual system, which are able to compensate to a great extent for the primary visual brain damage (see [23] for a review).

The high correlation we found between the VEP/Teller ratio, which reflects the concordance of the two measures, and the anatomical indexes of brain damage, may support the hypothesis of a differential sensitivity of the two techniques to periventricular brain damage. In fact, the relative prevalence of Teller acuity was found to be significantly correlated both to the degree of posterior thinning of the corpus callosum and to the degree of global brain atrophy (negative correlation). We propose that in our cohort the relative hypotrophy of the splenium of the corpus callosum may represent an indirect measure of the integrity of the occipital cortex itself, and so of the geniculo-calcarine pathway, as it contains fibers connecting the two homologous striate regions [6, 81-83] and is, as shown in the animal model, very prone to plastic changes following visual impairment [84]. On the other hand, the degree of global atrophy might be related to the level of extra-striatal visual pathway expansion, as suggested by numerous animal

studies exploring plastic modifications and fiber restructuring in the visual system following a perinatal damage (see [23] for a review). In this view, the relative prevalence of Teller acuity values in our patients might be interpreted as the effect of an involvement of the primary visual structures together with a sparing of extra-striatal plastic potentials.

In conclusion, we showed a high correlation between electrophysiological and behavioural techniques in children with PVL, similarly to what was reported in other groups of children at high risk for CVI. However our results also suggest that behavioural measures can be, at least in PVL children, a better expression of visual functionality, as they reflect to a certain extent the efficacy of the compensatory mechanisms following brain damage (neural plasticity). This is consistent with animal studies showing how neural networks alternative to the primary visual pathways may be significantly enlarged and give rise to a high degree of functional compensation. This proposal needs to be confirmed by the use in prospective studies of different imaging methodologies able to provide better and more direct measures of structural injury or pathway reorganisation, such as diffusion tensor imaging or voxel based morphometry.

3.3   Perception of flow motion in children with early periventricular brain damage

In humans, motion is analysed at various cortical levels, including primary and secondary visual cortex. The main area specialised for motion analysis is the human middle temporal (MT) area or V5, the homologue of MT monkey cortex [85, 86]. Neural activity in this region (in humans) shows strong motion opponency [87], increases linearly with motion coherence [88] and has been shown (in monkey and humans) to correlate closely with motion perception [88, 89]. In addition, area MT responds well to coherent versus random motion, suggesting that it is implicated in the perception of global rather than local motion [90-92].

In humans, acquired bilateral damage of the lateral temporo-occipital cortex and the underlying white matter (bilaterally involving MT) was found to be strongly associated with abnormalities of motion perception [93-95]. Impairment of motion perception in these conditions appears to be hardly reversible [95], possibly as a consequence of the limited potential of functional

reorganization associated to late acquired bilateral damage. Conversely, very little is known on the possible effects of lesions occurring prenatally or around birth, when the nervous system is still largely immature and different pathways of functional reorganization might be expected to be activated.

Abnormalities of global motion perception were recently described in children with bilateral periventricular leukomalacia (PVL) [96, 97], a typical prenatal or perinatal lesion bilaterally affecting the white matter surrounding the ventricles, often involving the optic radiations [98] and potentially disrupting the posterior cortico-cortical connections [99]. In these studies, visual abnormality consisted of a loss of sensitivity to point-light biological motion, a specific type of stimulus to which the visual system is particularly sensitive, that was found significantly impaired in subjects with PVL as opposed to age-matched preterm controls [100]. The question whether the deficit observed is specific to biological motion or more generally related to basic coherent global motion was however not specifically addressed.

The presence of more basic deficits of motion processing was never systematically explored in children with PVL. Some of us recently reported visual motion abnormalities in a group of children with congenital hemiplegia, a small part of whom showed a PVL on magnetic resonance imaging (MRI) [101]. In those cases however, periventricular damage was either unilateral or strongly asymmetrical, as also shown by the corresponding unilateral motor disorder. More recently, similar deficits were found in a small number of subjects with a mild periventricular brain damage in a study exploring visual perception in very low-birth weight children [102]. In that study however, subjects with retinal disorders (retinopathy of prematurity) or even without any apparent neuro-ophthalmologic abnormality were also included, making hard to identify the specific contribution of periventricular damage itself to the motion processing deficit.

The aim of the present study was to assess the ability of children with PVL to perceive motion stimuli using psychophysical testing based on various components of the optic flow. In order to evaluate the contribution of various risk factors, we correlated the results of PVL children to the extension of brain damage, the quality of motor function and to other aspects of visual function. As most of our PVL subjects were born preterm, we also studied a group of low-risk preterm children with no evidence of brain damage and normal outcome.

3.3.1   Subjects and Methods

Participants were selected from children referred to the Division of Child Neurology and Psychiatry according to the following criteria: (a) clear signs of PVL on MRI, according to the criteria indicated in the literature [71]; (b) a verbal IQ within normal limits, (c) the absence of main ocular anomalies including cataract, optic atrophy and retinopathy of prematurity, and (d) a full neurological and gross motor function assessment. Thirteen subjects were selected, but two of them were completely unable to perform one of the psychophysical tests and were therefore excluded from the study. The mean age of the remaining 11 was 10.6 years (range: 8.2 – 12.9; 7 males); mean gestational age was 31.9 weeks (range 26-36) and mean birth weight was 1638 gr (range 1020-2500). All patients had at least one MRI examination. The MR images were assessed retrospectively by two of the authors (GC, AG) unaware of clinical data, with high concordance of the two scores (correlation coefficient >0.90). To grade the severity of the lesions, a classification system specific for PVL was used (Table 3.3 [42]). Motor outcome was assessed by means of the Gross Motor Function Measure (GMFM-88), a test specifically designed to evaluate gross motor function in children with CP [103]. A level of function ranging from 1 (high function) to 5 (low function) was obtained for each child.

The control group consisted of fifteen age-matched term-born children, recruited from the local primary school (mean age: 10.1 years, range: 8.5 – 12.4; 6 males). As most of our PVL children were born preterm, we also assessed a group of ten preterm-born children (mean age: 10.7 years, range: 10 – 13; mean gestational age 29.2 weeks, range 26-32; mean birth weight 1466 gr, range 970-1950; 4 males), recruited from the follow-up program of the Neonatal Unit of Pisa University, according to conditions b and c of the patient group selection criteria. All children of this group had received ultrasound scanning at birth showing no abnormalities or transient periventricular flares (lasting less than 10 days).

The study was approved by the Ethical Committee of the Stella Maris Scientific Institute. Informed consent for participation was obtained from parents of all children.

Chapter 3

<u>Basic visual assessment</u>

Ophthalmologic examination was performed in all patients in order to exclude major ocular disorders, including optic nerve atrophy, retinopathy of prematurity, cataract and refractive errors.

Table 3.3 Grading of MRI findings [42]

a)	Size of lateral ventricles	Grade 1	*Normal size of both ventricles*
		Grade 2	*Bilateral mild enlargement*
		Grade 3	*Bilateral enlargement, of severe grade in at least one ventricle*
b)	WM abnormal signal intensity	Grade 1	*Normal WM or bilateral involvement of only PT WM*
		Grade 2	*Diffuse bilateral involvement of PV WM*
		Grade 3	*Bilateral involvement of SC WM*
c)	WM reduction	Grade 1	*Not reduced*
		Grade 2	*Reduction of PV WM in both hemispheres or of SC WM diffusely in one hemisphere*
		Grade 3	*Reduction of SC WM diffusely in both hemispheres*
d)	Cysts	Grade 1	*No cysts*
		Grade 2	*Few cysts (n<3) uni- or bilateral involving PV regions or only one large cyst involving SC WM*
		Grade 3	*Bilateral multiple cysts (n>3) involving PV regions and/or SC WM*
e)	Size of subarachnoid space	Grade 1	*No enlargement or limited to one lobe*
		Grade 2	*Diffuse but mild enlargement*
		Grade 3	*Diffuse and severe enlargement*
f)	Corpus callosum	Grade 1	*Normal or thinning involving the posterior body*
		Grade 2	*Thinning involving the entire body*
		Grade 3	*Diffuse thinning*
g)	Cortical grey matter *(ulegyria and cortical dysplasia)*	Grade 1	*No cortical abnormalities*
		Grade 2	*Unilateral cortical abnormalities*
		Grade 3	*Bilateral cortical abnormalities*
Tot	Total score	Grade 1	*Sum of previous scores 7-11*
		Grade 2	*Sum of previous scores 12-16*
		Grade 3	*Sum of previous scores 17-21*

PT= paratrigonal; **PV**= periventricular; **SC**= subcortical; **WM** =white matter

Grating acuity was tested using the Teller acuity cards [61], with acuity defined as the finest stripe width of the grating for which the subject consistently responded. Visual-field size was assessed using kinetic perimetry. During central fixation of a centrally positioned white ball, an identical target was moved from the periphery towards the fixation point along one arc of the perimeter. Eye and head movements towards the peripheral ball were used to estimate the outline of the visual field. Oculomotor behaviour was assessed by means of observation and video-recording of fixation and following motion, and searching for the presence of abnormal eye movements, such as spontaneous nystagmus. Strabismus was tested by examining symmetry of the corneal light reflex and by the cover test. Visual attention was scored according to a global qualitative evaluation of visual behaviour during the entire duration of the assessment, in particular of the oculomotor tasks.

Stimuli and experimental procedure

Sensitivity for motion coherence was assessed by measuring coherence thresholds for perceiving circular and translational motion. The stimuli comprised 100 small dots (each subtending 35' arc), half black and half white, generated by a C program running in DOS. Stimuli were presented to subjects on a Sony CRT (17'') monitor (50 cd/m^2), subtending 22 X 22 deg when viewed from a distance of 60 cm in a dimly lit room. A proportion of the dots were caused to drift coherently at a local speed of 10 deg/sec (limited lifetime of 5 frames, framerate 75 Hz), while the remainder of dots (noise dots) were displayed at random positions each frame. The coherent motion was either rightwards or leftwards (chosen at random) for the translation condition, or clockwise or counter-clockwise (all dots constant linear speed) for the circular condition. Coherence was varied from trial to trial to home in on the detection threshold, using the QUEST algorithm [104]. Sensitivity was defined as the maximum proportion of noise that produced 75% correct direction discrimination, calculated offline by fitting all data of a particular condition (from 27 to 90 trials) with cumulative Gaussian functions.

3.3.2 Results

Clinical and MRI data

Details of the clinical features of PVL subjects are reported in Table 3.4.

Gestational age and birth weight were not available in one patient who had been adopted at 12 months of age. All subjects developed a bilateral spastic cerebral palsy. Gross motor function level ranged from I to III. Normal results in all aspects of visual functions assessed were only found in two out of 11 patients. The most frequent visual abnormalities were strabismus and abnormal oculomotor behaviour present in 6/11 subjects, followed by acuity reduction in 4/11 and refraction errors in 3/11 subjects. Abnormalities of visual field were only found in one subject who showed a bilateral reduction.

Table 3.4 Clinical data of PVL children

| N. | GA | Birth weight | Verbal IQ | Visual functions | | | | | Flow motion | | GM FM |
				Ophthalm. exam.	Acuity (Snellen)	Visual fields	Oculomotor Behaviour	Strab.	Rot.	Trans.	
1	34	1650	N	N	20/40	N	N	No	7,8	5,31	I
2	30	1500	N	N	20/20	N	N	AC	1,9	2,59	I
3	34	1970	N	Hyperm.	20/15	N	Hypom. saccades	AC	7,31	8,7	I
4	28	1020	N	Myopia	20/80	N	Dysm. saccades	AD	-	5,2	I
5	31	1800	N	N	20/30	N	Hypom. saccades	AC	1,12	2,54	I
6	na	na	N	N	20/20	N	N	No	26,85	29,35	III
7	28	1250	N	N	20/20	N	Hypom. saccades	No	12,46	5,1	III
8	39	2500	N	Myopia	20/80	N	N	AC	1,59	3,25	I
9	32	1640	N	N	20/20	N	Hypom. saccades	No	2,75	2,37	I
10	26	1050	N	N	20/60	Bil. Red.	Dysm. saccades	CA	7,38	5,62	III
11	37	2000	N	N	20/20	N	N	No	11,18	-	I

GA=gestational age; **na**=not available; **IQ**=intelligence quotient; **N**=normal; **MiR**=mild retardation; **Bil.Red**.=bilateral reduction; **A**=alternating; **C**=convergent; **D**=divergent; **L**=left; **R**=right; **GMFM**=Gross Motor Function Measure [103]

The neuro-radiological data of our group are shown in Table 3.5. MRI abnormalities were mild in 7/11 subjects and moderate in the remaining 4/11. No visual abnormalities were found in the two control groups with the exception of a mild myopia in two preterm-born children.

Table 3.5 Neuroradiological scores (see table 3.3)

N.	a	b	c	d	E	f	G	tot
1	1	3	2	1	1	1	1	1
2	1	2	2	1	1	1	1	1
3	1	2	2	1	1	1	1	1
4	2	2	3	1	1	2	1	2
5	3	3	3	1	1	1	1	2
6	3	3	3	1	2	2	1	2
7	1	2	2	1	1	2	1	1
8	2	3	2	1	1	2	1	2
9	2	2	2	1	1	1	1	1
10	2	2	2	1	1	1	1	1
11	1	1	1	1	1	1	1	1

<u>Sensitivity to global motion</u>

We first measured coherence sensitivity for global motion along a translational or circular trajectory. As described in the methods section, subjects were required to discriminate the direction of motion, either rightwards from leftwards (translational motion) or clockwise from counter-clockwise (circular motion). The motion coherence of the stimuli was varied by diluting the stimuli with random noise to produce psychometric functions like those of Fig. 3.4.
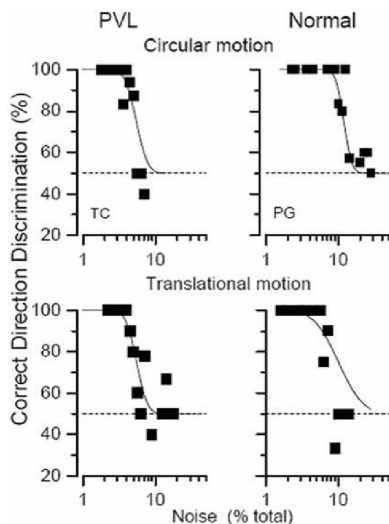
Fig. 3.4 Psychometric functions (percent correct discriminations as a function of percent noise) for a PVL patient (left) and an age-matched control (right) for circular motion (upper) and translational motion (lower). As the percentage of noise in the stimuli increases, performance begins to drop from perfect (100%) to chance (50%). The data are fitted by a cumulative gaussian function, and threshold taken as the point where it passes 75%. Note that the shape and steepness of the curves for the PVL and control subject are similar, suggesting that there was no difficulty in measuring performance in PVL patients

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The functions of both the PVL patients and the controls were all orderly, varying monotonically from perfect performance at high coherence levels to chance (50%) at low coherence levels. That the functions are orderly and as steep as the control shows that PVL patients were able to do the task reliably. The sensitivity index was taken to correspond to 75% performance, calculated from the fitted cumulative gaussian.

The average motion coherence sensitivities for our PVL group, compared with the two control groups, are reported in Fig. 3.5.

Fig. 3.5 Average sensitivity of the three groups for two types of coherent motion, translation (upper graphs) and rotation (lower graphs). Error bars indicate the standard error of the mean

A one way ANOVA was performed on the data, showing that a significant difference was present between the three groups both for the translational motion (p=0.013) and for the rotational motion (p=0.000) (Table 3.6).

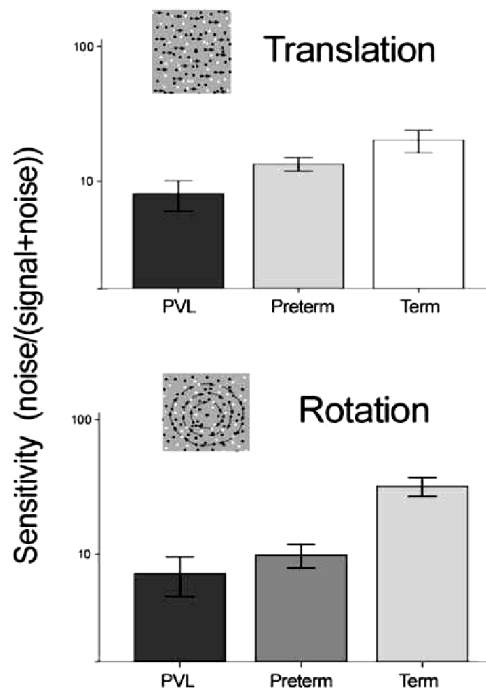**Table 3.6** Statistical analysis by means of ANOVA between average motion coherence sensitivities for PVL compared with the two control groups

Test	Groups	N	Mean (SD)	F	P value
Translation	Term controls	14	24,9 (19,9)	4,975	,013
	Pre-term controls	10	13,8 (8,1)		
	PVL	11	7,4 (7,7)		
Rotation	Term controls	15	32,7 (19,7)	12,658	,000
	Pre-term controls	10	9,9 (6,6)		
	PVL	10	7 (8)		

 Post-hoc Bonferroni test revealed that PVL subjects showed significantly lower sensitivities than term-born children for both the translational (p=0.012) and the rotational (p=0.000) motion, while no differences were present with preterm controls. In addition, preterm infants showed lower sensitivities than term controls, which were significant for the rotational motion (p=0.001), and not significant for the translational motion (p=0.2).

Individual data for the three groups of subjects are shown in Fig. 3.6. All tended to cluster around the reference line (y-intercept=0; slope=1) with sensitivities generally below 10 for the PVL subjects, above 20 for the term controls and somehow intermediate for the preterm controls.

Correlation of global motion sensitivity with MRI and clinical data

A Spearman non-parametric test was performed on the data. No correlation was observed between the sensitivity for either circular or translational motion and i) the result of any specific visual test or the total number of visual abnormalities, ii) the gestational age, iii) the mental level, iv) the GMFM level and v) the MRI subscores or total score.
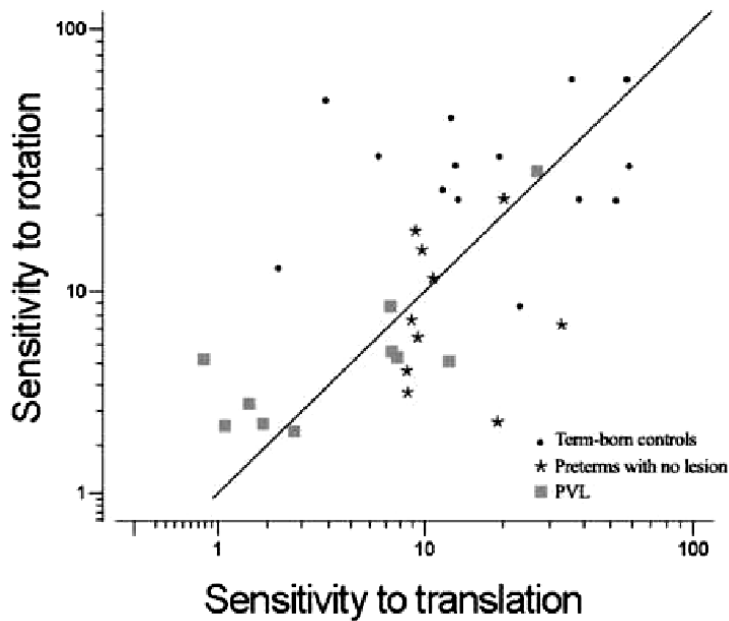
Fig. 3.6 Coherence sensitivity for rotation plotted against that for translation. The large squares refer to PVL patients, the stars to the low-risk preterm children and the black circles to term-born controls. The diagonal line reflects equal sensitivity to the two types of motion

3.3.3 Discussion

The main result of the study indicates that, in children with PVL sensitivity both to translational and rotational motion is on average significantly reduced compared to age-matched controls. Deficits of motion processing were not related to the number of other visual abnormalities or the results on any single visual test, thus suggesting a different mechanism in the origin of these disorders. To our knowledge, the only disorder of visual function found to correlate with abnormal motion sensitivity in PVL children is retinopathy of prematurity (ROP) [102], possibly due to an abnormal visual input to the subcortical magnocellular pathway [105, 106] and to the MT complex [86]. In our sample however, visual peripheral disorders including ROP, were specifically excluded thus making unlikely such a pathogenetic mechanism. The possible

influence on our results of other factors such as degree of prematurity, mental level or motor function was also explored by looking for significant correlations with motion perception, but none of these factors appeared to vary with sensitivity to translational nor to rotational motion.

We did not find a significant correlation between motion sensitivity and various MRI indexes of severity of brain damage. This is consistent with our previous findings in children with congenital brain injury and hemiplegia, who presented in some cases with bilateral periventricular lesions similar in aetiology to those of the present study [101]. In that study visual motion impairment was not related to the specific involvement of one or more cortical lobes, nor to the presence of a unilateral or bilateral damage, thus undermining the hypothesis of a strict correlation between site of damage and functional impairment, in case of congenital lesions.

Sensitivity to translational and rotational motion showed lower mean values in PVL children compared to low-risk preterm children, but interestingly the difference did not reach statistical significance. This is in line with the findings of MacKay and co-workers who recently explored different levels of local and global motion processing in a group of very low-birth weight children [102]. In that study, preterm children showed a significantly worse performance in all tasks assessed, as opposed to term controls. However, no differences were detected within the sample between children with periventricular damage, retinopathy or without brain damage. The same group also reported a significant impairment in detection and recognition of motion-defined forms, a function involving a number of motion-sensitive areas [107-109], in preterm children irrespective of the presence of brain damage or retinal abnormalities [102, 110]. These findings suggest that premature birth can be associated to selective damage of multiple brain motion processing subsystems, not only in patients with neuro-ophthalmological damage (ROP, PVL), but also in the absence of any apparent lesion.

Taken together, our results point to a more basic vulnerability in the motion processing stream, which would be reflected in a general and not specific impairment of motion perception [111]. This is also suggested by the observation of a similar vulnerability in a series of neurodevelopmental disorders including Williams syndrome [112, 113], autism [114], developmental dyslexia [115-117] or fragile X syndrome [118]. In all these conditions, visual motion impairment could be secondary to the differential vulnerability of the motion processing

stream during development, which may be disrupted by a wide range of neurodevelopmental disorders. The general results of the present study support this proposal.

A more specific correlation with the site and extent of periventricular brain damage in children with PVL was reported for the impairment of visual processing of biological motion [96, 97]. In these studies, the authors were able to demonstrate how the severity of visual impairment was not related to the degree of prematurity or to the motor ability but rather to the extent of PVL over the parieto-occipital complex, suggesting a specific lesion-related restriction of brain's spontaneous compensatory plasticity in the development of this type of visuo-perceptual competence. Our results are not necessarily in contrast with this hypothesis. They might be interpreted in the light of previous fMRI findings in humans supporting the hypothesis of separated neural networks involved in processing biological motion as opposed to other types of motion [119, 120]. Some clinical studies in patients with brain lesions point to the same direction indicating how biological motion might be selectively impaired with preserved ability to process other types of motion stimuli [121, 122], or viceversa [94]. Similar evidence can be also found comparing studies on neurodevelopmental disabilities. For example, children with Williams syndrome can reliably judge facing of a slightly camouflaged point-light walker [123], but may show poor performance in discriminating coherent motion from noise compared to coherent form [124].

An alternative interpretation of our and previous data is that, despite being at least partially segregated, the visual streams underlying biological and flow motion can be more globally impaired in children with PVL or other developmental disorders, with mechanisms that are to some extent overlapping. The finding in separate studies and cohorts of an impairment of biological motion and flow motion in children with PVL may support this hypothesis, while the different measures used to assess periventricular brain damage in these studies may account for the lack of accordance. This is however not sufficient to exclude different underlying mechanisms for the two disorders. In order to properly address this question, studies exploring with comparable tasks the different typologies of motion stimuli in the same population are needed. This would also be of help in the evaluation of structure-function relationship, as in the various studies this aspect is analysed with different approaches. In this respect, children with PVL appear to be particularly appropriate as they show similar and easily comparable brain

lesions, frequently affecting the central visual structures, with an often preserved global intelligence quotient.

On the whole the data presented here extend previous findings by other groups on the impairment of motion sensitivity in children with PVL, showing how these patients might be vulnerable to a more basic impairment of the motion processing stream. Preterm birth appears to play a role in the origin of the disorder, although it probably does not account for the whole extent of the visual deficit observed in children with associated periventricular damage. Very little is however known on the neurophysiological bases of these disorders and on their functional consequences in every-day life. It is conceivable that the impairment of motion sensitivity may play a role in the functional abilities of these children including locomotion and goal directed motor function [125]. The investigation of this hypothesis will unquestionably be a central issue for future research in the field of child disability.

3.4   Inversion of perceived direction of motion cause by spatial under-sampling in two children with periventricular leukomalacia

In humans, motion is analysed at various cortical levels, including primary and secondary visual cortex (V1/V2). The major area specialised for motion analysis is the human MT complex, the homologue of monkey middle temporal cortex MT or V5 [85, 126]. Neural activity in this region (in humans) shows strong motion opponency [87], increases linearly with motion coherence [88] and has been shown (in monkey and human) to correlate closely with motion perception [89]. Other areas include a portion of V3 [127] and portions of area IP. Area MT responds well to coherent versus random motion, suggesting that it is implicated in the perception of global motion [90-92]. Interestingly, MT also shows spatiotopicity in its response to motion, meaning it is selective in real-world rather than retinal coordinates[128]. Area V3A also differentiates coherent from random motion [111, 124, 129, 130]. Periventricular white matter damage is a common cause of early brain injury in preterm infants with low gestational age and low birth weight, accounting for most of the neurological morbidity in preterm infants. The most severe form of this condition, cystic periventricular leukomalacia (PVL), consists of a

focal necrosis of variable severity at the level of deep white matter, surrounded by a more diffuse and milder injury of the tissue mainly affecting oligodendrocytes precursors [131]. This lesion typically involves the corticospinal tract at the level of the posterior part of the corona radiata, resulting in a motor impairment primarily affecting the lower limbs, diplegic cerebral palsy. In most cases, however, the damage also involves the geniculo calcarine tracts that are in close proximity to the posterior horns of the lateral ventricles, giving rise to variable degrees of cerebral visual impairment. The most common visual disorders in children with PVL are reduced acuity, visual field restriction and oculomotor difficulties, particularly with saccades [42, 132] that may or may not be a consequence of damage to the optical radiation or to other cortico-cortical fiber connections. An association between PVL and impairment of object recognition has also been reported [45, 133-135], which is significantly correlated to specific anatomical features, such as decreased volume of the peritrigonal white matter and thinning of the parieto occipital white matter [73] [136]. Recently we have shown that the perception of flow motion in diplegic children with cystic periventricular leukomalacia is impaired, both for translational and rotational flow motion [137]. However the impairment is small, less than a factor of two. During this study we observed two cases of PVL children, with similar anatomical lesions to the others in the sample, where motion perception was affected in a most bizarre way, with translation being consistently seen in the wrong direction. We report in detail one of these cases.

3.4.1   Subjects and Methods

<u>Subjects</u>

During our previous study [137] of 16 PVL patients, two (GB and SL) were observed with completely abnormal motion perception (described in the results section). However, their clinical characteristics were very similar to the rest of the sample reported in Guzzetta et al. [137]. Of the two GB was a particularly cooperative patient, and was tested exhaustively, Patient SL, unfortunately, was not very cooperative, was easily distracted and soon lost interest in the task. As the testing was clearly causing stress, we felt ethically bound to stop testing. For SL we were able to demonstrate only the basic effect of inverted motion. Table 3.7 summarizes the clinical details of the two patients.

Table 3.7 Clinical details of the two patients who perceives SL and GB

		Patient SL	Patient GB
Age at test		10	16
Gestational age		32 weeks	29 weeks
Verbal IQ		normal	normal
Visual assessment			
	Refractive errors	mild myopia	mild myopia
	Acuity (Snellen)	20/100	20/20
	Visual fields	normal	normal
	Oculomotor function	dysmetric saccades	normal
	Strabismus	convergent	absent
MRI findings			
	Ventricular size	normal	bilateral mild enlargement
	Periventricular gliosis	diffuse bilateral	diffuse bilateral
	Periventricular WM	bilateral reduction	bilateral reduction
	Cysts	no	no
	Subarachnoid space	normal	normal
	Corpus callosum	mild posterior thinning	mild posterior thinning
	Cortical gray matter	normal	normal
Neurological diagnosis		spastic diplegia	spastic diplegia

Psychophysics

Sensitivity for motion coherency was assessed by measuring coherence thresholds for perceiving circular, radial and translational (up-down, left-right and diagonal) motion. The stimuli comprised 100 small dots (each 35 arc mins), half black and half white, presented to subjects in a dimly lit room on a 17" Sony CRT monitor (50 cd/m2), subtending 22 X 22 deg when viewed from viewing distance 60 cm. A proportion of dots drifted coherently at a local speed of 10 deg/sec (limited lifetime of 10 frames, framerate 75 Hz), while the remainder of dots (noise dots) were displayed at random positions each frame (see icons in Fig. 3.7).

For the majority of the testing, the coherent motion was either upwards or downwards (chosen at random) for the translation condition, clockwise or counter-clockwise for the circular condition, and expansion or contraction for the radial motion (all dots had constant local speed in all conditions), viewed binocularly with a presentation time of 250 ms (some controls for monocular viewing were also collected). Motion coherency of the stimuli was varied from trial-to-trial using the QUEST algorithm (Watson & Pelli, 1983) by substituting a proportion of the points with random noise, and measuring percent correct over a range of noise levels to produce the psychometric functions like those of Fig. 3.7. Sensitivity was defined as the maximum proportion of noise that produced 75% correct direction discrimination, calculated offline by

fitting all data of a particular condition (from 27 to 90 trials) with cumulative Gaussian functions. No feedback was given to the children. GB's parents were informed of the specific deficit of their son after the first 6 months, by which time most of the tests had been completed. GB was probably aware of his perceptual deficit during the eye movement testing and the driving simulation test (performed primarily to test his ability as a potential driver of a special vehicle for disabled people).
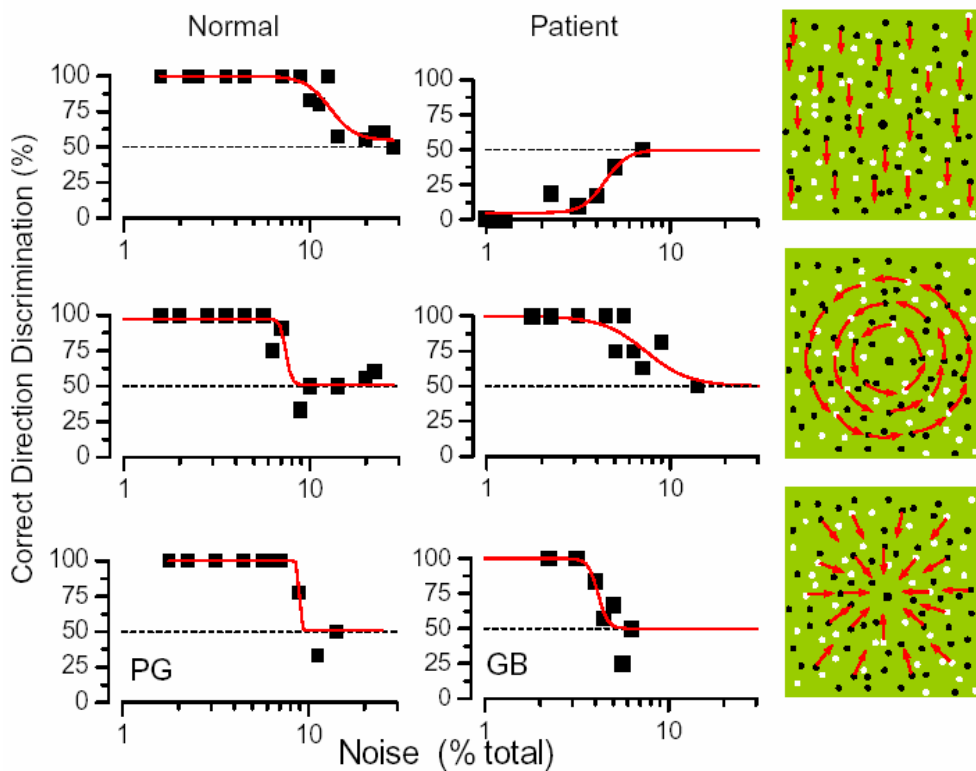
Fig. 3.7 Psychometric functions (percent correct discriminations as a function of percent noise) for patient GB and an age-matched control PG for translational, radial and circular motion. While the psychometric functions for circular and radial motion are normal psychometric functions, going from perfect performance for low levels of noise to chance behaviour at high levels, those for translational motion are quite different, running in the other direction, from 0% performance to chance. GB consistently saw the motion in the wrong direction, with about the same noise threshold as that for seeing circular and radial motion in the right direction (about 5%). The icons at left illustrate the type of motion

For the contrast sensitivity measurements, stimuli were generated by VSG framestore (Cambridge Research Systems) and displayed on the face of a Barco monitor at 512 X 512 pixels resolution at 126 Hz framerate, with mean luminance 10 cd/m2, viewing distance 100 cm (the low luminance was chosen to allow measurements of contrast sensitivity for equiluminant gratings). Stimuli were sinusoidal gratings of various spatial frequencies and orientations, caused to drift upwards or downwards (horizontal gratings), or rightwards or leftwards (vertical gratings), behind a diamond mask (that minimised edge effects that can create spurious cues of drift direction). Subjects had to identify the direction of drifting in two-alterative forced choice (in a given session direction was always horizontal or vertical). Stimuli were presented within a Gaussian temporal window, usually of time constant of 100 ms. Some testing was performed with a 300 ms Gaussian presentation, yielding no major differences. In one condition we also determined detection thresholds by requiring subjects to discriminate the orientation (not the drift direction) of the drifting grating, 45º clockwise or counter-clockwise from the vertical (behind a square mask). As with the coherence measurements, grating contrast was varied after each response of the observers, following the adaptive QUEST [104]. Final thresholds were determined by fitting a cumulative Gaussian to the resultant probability of seeing curves (on logarithmic abscissa). Grating acuity was tested using the Teller acuity cards [61], with acuity defined as the finest stripe width of the grating for which the subject consistently responds. Visual-field size was assessed using kinetic perimetry. During central fixation of a centrally positioned white ball, an identical target is moved from the periphery towards the fixation point along one arc of the perimeter. Eye and head movements towards the peripheral ball are used to estimate the outline of the visual field. Eye movements were measured with an infrared sensor (ASL model 504) at a sampling frequency of 60 Hz. For the OKN measurements, the subject observed a high contrast drifting grating or a uniform field of white random dots drifting across a black background on a large television screen (50x70deg, 60 Hz interlaced), with the head restrained with a comfortable head rest. The eye positions were calibrated on 9 positions before the recording, and the calibration was repeated at the end of the recording session. The horizontal and vertical eye position signal was analyzed using the software provided by the ASL. Strabismus was tested by examining symmetry of the corneal light reflex and by the cover test. Visual attention was scored according to a global qualitative evaluation of visual behaviour during the entire duration of the assessment, in particular of the oculomotor tasks.

Chapter 3

fMRI Methods

BOLD responses were acquired by 1.5 T General Electric LX Signa Horizon System (GE, Milwaukee, USA), equipped with Echo-speed gradient coil and amplifier hardware, using a standard quadrature head-coil. Activation images were acquired using echoplanar imaging (EPI) gradient-recalled echo sequence (TR/TE/flip angle=3s/50ms/90°, FOV=280x210 mm, matrix=128 x 128, acquisition time: 3'12''). Volumes consisted in 18 contiguous 4 mm thick axial slices, covering from the inferior temporal-occipital edge to the middle-parietal region (from about z -28 to 45 mm), acquired every 3 sec. Time-course series of 64 images for each volume were collected in the 6 epochs. The first epoch lasted 12 sec more to allow the signal to stabilize and this initial period was eliminated from any successive analysis. An additional set of anatomical high resolution 3D FastSPGR data set (TR/TE/flip angle = 150 ms/2.3ms/120°; RBW=12.8 kHz; FOV=280x280 mm, matrix = 256x256; isotropic dimension: 1.1 mm, NEX:2; Acq.Time:12'26''min), was acquired in order to generate a 3-dimensional whole brain recontruction and a bi-commensural axial projection to estimate the anatomical Talairach coordinates [138]. For generating a statistical map of the BOLD response, Brain Voyager 2000 4.6 software package (Max-Planck Society, Germany and Brain Innovation, Maastricht, the Netherlands) was used. All volumes from each subject were adjusted with the application of rigid body transforms for residual motion-related signal changes. Functional data were smoothed spatially (Gaussian kernel with a 4-mm full width at half maximum) but not temporally. Statistical activation maps were obtained using cross-correlation or General Linear Model analysis, with thresholding at $p<0.0022$ with cluster size limit of two voxels. EPI images were co-registered with the 3D anatomical data in order to define the Talairach-Tournoux coordinates. The stimuli were random dot kinematograms, similar to those used to measure coherence sensitivity (50 dots, 300 ms life-time, 1 deg diameter dot size). Three types of coherent motion were used, translation, rotation (both inverting direction every 2s) or flow fields that changed gradually in 2 seconds from pure expansion, to inward spiral, clockwise rotation, spiral, contraction and so on. The dots moved along trajectories with a constant local speed of 7 deg/s both for the coherent and the noise stimuli (Morrone et al. 2000). Stimuli were presented on LCD goggles (Resonance Technology) with a visual field of 22 X 30° and a luminance of about 30 cd/m2. The resolution of the display was 600 X 800 pixels with refresh rate of 60 Hz.

The research project was approved by the Ethical Committee of the Stella Maris Scientific Institute. Informed consent was obtained from all parents and from the children.

3.4.2   Results

<u>Seeing reversed motion</u>

Figure 3.7 reports psychometric functions for discriminating the direction of global motion along a translational, circular or radial trajectory for subject GB and an age-matched control (PG). In all cases the measurements were forced-choice, with subjects discriminating upward from downward motion, clockwise from counter-clockwise motion or expansion from contraction (radial motion). The functions of the age-matched control were all orderly, varying monotonically from perfect performance at high coherence levels to chance (50%) at low levels. For radial and circular motion GB's psychometric functions are very similar to those of the control, going from perfect performance for low levels of noise to chance behaviour at high levels. However, the results for translational motion are spectacularly different: at high noise levels performance was at chance, but at low noise levels performance falls *below* chance to 0% correct, *perfectly incorrect discrimination*. In other words, GB consistently saw the motion in the wrong direction. Interestingly, the noise threshold for seeing translational motion in the wrong direction (the 25% correct point, corresponding to 5% noise) was very similar to that for seeing circular and radial motion in the right direction, and the form of the psychometric function was similar to the other two. This value was also very similar to average sensitivity for discriminating translational motion observed with the same techniques in a sample of age-matched PVL children (7%: [137]), and not much worse than that for age-matched controls (~10%). Patient SL was less collaborative and soon lost interest in the task. However, we did measure percent correct for 100% coherence and 250 ms presentation time for translation (shown in Fig. 3.8 by the triangle), and to obtain a threshold for circular motion (Fig 3.8, similar to the average PVL performance). GB was possible to study extensively. Fig. 3.8 reports percent correct judgements for 100% coherence as a function of stimulus duration. For presentation times of 250 ms (the duration used for Fig. 3.7), discrimination was almost perfectly incorrect for both subjects. At longer presentation times, however, performance for GB became less consistently incorrect. At 4 second exposure durations, the tendency inverted and performance

reached 82% correct. However, careful observation of the patient and subsequent debriefing revealed that this improvement at very long durations was not so much due to improved perception, as to clever deduction. GB observed the top and bottom of the screen to see where the dots were disappearing. This was an effective strategy only when the presentations were long enough to see enough disappearances to deduce direction, and even then it was not perfect. Using left-right or diagonal translation, or presenting the stimuli monocularly did not change significantly the effect. Also changing the size of the stimulus by changing viewing distance (from 40 cm to 4 m), or halving or doubling the velocity, did not change the inversion effect. The effect was robust over a wide range of stimuli.
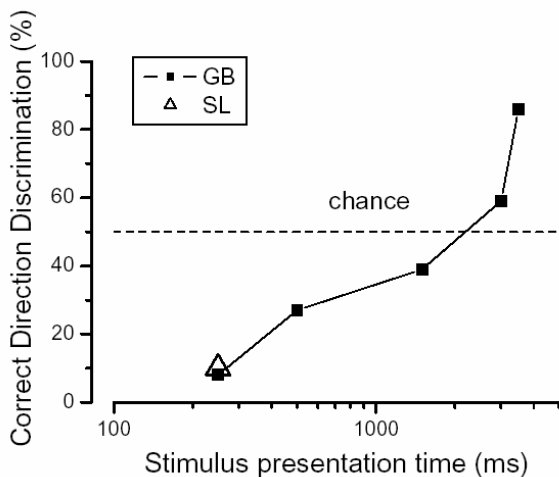
Fig. 3.8 Discrimination performance as a function of stimulus duration. Discrimination "improved" systematically with stimulus duration, from almost perfectly incorrect at 250 ms, to 82% correct at 4 sec presentations. The squares report data from GB, the triangle SL

Sinusoidal gratings

We next measured motion discrimination for sinusoidal gratings of various spatial frequencies to see if the motion inversion generalized to narrow-band stimuli with no added noise. Interestingly, GB reported no inversion of direction for sinusoidal gratings, under any conditions. Fig. 3.9 shows contrast sensitivity for motion discrimination of gratings drifting at 3 Hz, as a function of spatial frequency for GB (filled diamonds) and an aged-matched control (open circles).
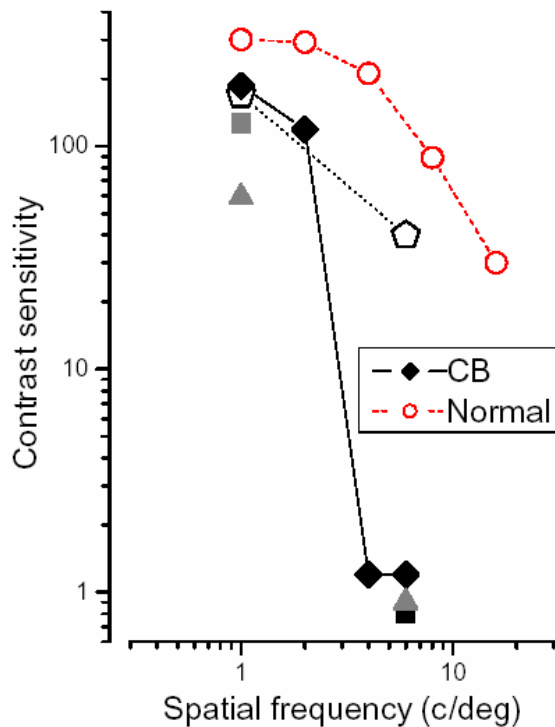
Fig 3.9 Contrast sensitivity for seeing the direction of gratings as a function of spatial frequency. The filled diamonds refer to GB and the open circles to an age-matched control. The grey square and triangle show results for GB at 6 and 15 Hz respectively. The open pentagons show the sensitivity to discriminate orientation of the grating, not direction of motion. The temporal frequency for all other data points was 3 Hz. Sensitivity of less than unity means that performance did not reach criterion at maximum contrast

At relatively low spatial frequencies (1 c/deg) GB's performance was similar to the normal, correctly perceiving motion direction with contrast sensitivity of 200 (0.5% contrast). However, performance declined rapidly with spatial frequency, falling to 1 at 4 c/deg (while the sensitivity of the control remained around 200). The square and triangular symbols show results for gratings drifting at 6 and 15 Hz (respectively). The pattern is similar as for 3 Hz: good sensitivity at 1 c/deg, but none at 6 c/deg. However, under none of these conditions did GB see

drift in the wrong direction, as with the random-dot kinematograms. Interestingly the deficit at high spatial frequencies was specific to judging motion direction: GB had good contrast sensitivity if he had to report the orientation of a drifting grating instead of the direction of motion (open pentagon symbols with dashed line).

Eye-movements

The poor performance in motion perception predicts that eye tacking movements will also be compromised. Fig. 3.10 shows example tracking records for a jump-ramp target [139] for an aged-matched control (left) and for GB (right). The typical performance, illustrated by the traces at left, is for subjects to saccade in the direction of the jump, followed by smooth tracking movement matched to the speed of the drifting dot. Latencies for commencing the pursuit movement, often taken as an index of the time necessary to process motion information ranged from 200 to 300 ms. Sometimes a small corrective saccade was necessary to refoveate the target, but the tracking generally kept the target within about a degree of the fovea, and nearly stationary on the retina (see blue trace).
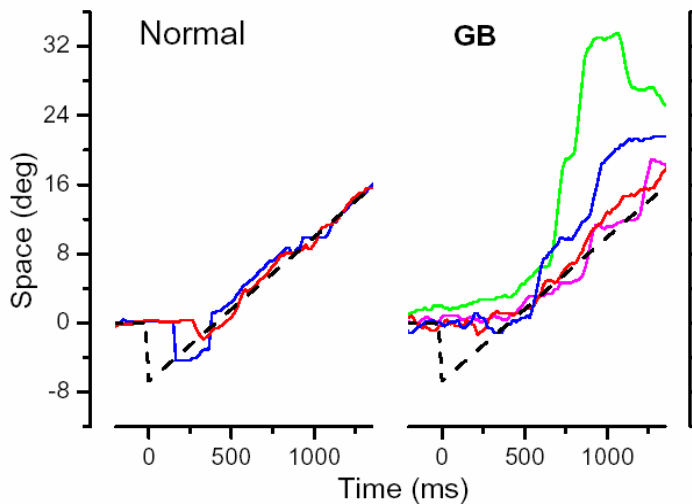
Fig. 3.10 Examples of tracking records for a jump-ramp target (dot size 1 deg) for GB (right) and an agedmatched control (left). The traces of the control are typical, showing a saccade in the direction of the jump, followed by smooth tracking movement matched to the drift speed. The traces for GB are completely different, with no initial saccade in the direction of the jump, and very long latencies for initiation of pursuit tracking. Tracking was extremely inaccurate for GB, more a series of rapid, saccadic-like movements keeping up roughly with the target.

GB's behavior was completely different. There was no initial saccade in the direction of the jump, and the latency for initiation of pursuit tracking was excessively long, around 500 ms. Once the tracking had started, it was extremely inaccurate, more a series of rapid, saccadic-like movements roughly keeping step with the target.

Although smooth pursuit movements were severely impaired for GB, optokinetic nystagmus (OKN) was perfectly normal. Fig. 3.11 shows responses to observing a 50x70deg grating drifting at 10 deg/sec.

The following responses to the drifting wide-field stimuli were reasonably normal, both in the slow phase (lasting up to a second) and the rapid phase. The only difference was that his latency to commence OKN was often slower than that for the controls. Clearly the impediment for tracking is selective to small target, reflecting a perceptual rather than a motor problem.

Fig. 3.11 Optic-kinetic nystagmus (OKN) eye-movements of GB (lower) and control (upper) while observing a 50X70° grating drifting rightwards at 10 deg/sec. The traces for GB are similar to those of the control, showing clear periods of tracking near the drift speed, followed by corrective controls.

Chapter 3

Driving simulation

In order to assess GB's perceptual abilities in a semi-natural situation (and to advise his parents on his capacity to drive a motorized vehicle), we tested him with a driving simulation video game based on a straight t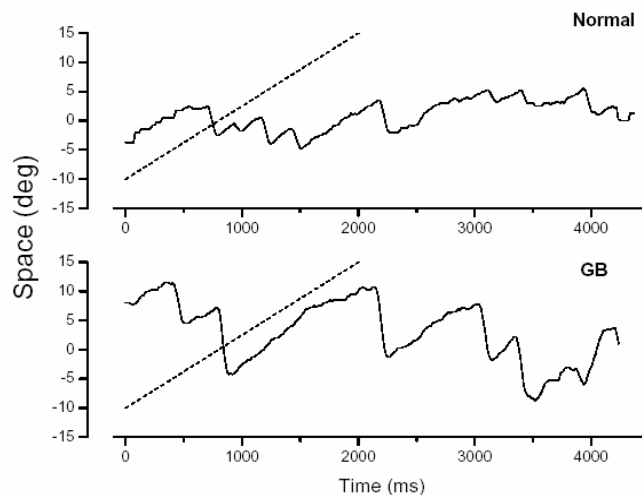rack with perpendicular interesting streets, projected on a wide screen (100 x 70deg). The requirements of the game were navigation of the vehicle, stopping for different visual stimuli, both moving (car and pedestrian) and stationary (such as traffic light). The motion in the scenes was mainly peripheral, with the focus of the flow in the centre of the track. Although no age-normalized data exist on this specific video-game, GB showed a peculiar behavioral pattern. He was good at driving the car through the street path at various simulated speeds, but showed problems in stopping the car without swerving when a moving obstacle crossed the street, suggesting that he apprehended the impending collision with the moving object too late. The same reaction difficulty was apparent with changing street lights. However, this difficulty was not related to a mere delay of reaction times, as demonstrated by the fast arresting response he showed in relation to non-moving stimuli.

fMRI responses

To gain further insight into the cortical areas compromised we measured the BOLD activity of GB, and an age-matched control, in response to translating and rotating stimuli (compared with blank controls). Fig. 3.12 shows responses in primary and secondary visual cortex, and two putative motion areas V3 and MT complex (indicated by green arrow). For both translational and circular motion there was a strong response in V1/V2 in both GB and the control. The response in V3 and V3A was also prominent for GB and control, although a clear differentiation of retinotopic areas is difficult without topographic mapping, particularly in a pathological brain where Talairach localization is reduced. A clear difference in activity between the control and GB was evident along the inferior temporal sulcus. For GB, however, MT+ was activated only by circular motion, while both types of motion activated a similar located area for the control. As previously observed, radial flow activated a more anterior region with respect to the inferior temporal sulcus [90, 91] in the normal control. This result is surprising given that the motion is contrasted with a blank stimulus, and that the response of primary areas is quite normal. To study more closely the motion-specific response of GB, we measured BOLD activity when circular or translational motion was alternated with locally matched random motion (Fig. 3.13).
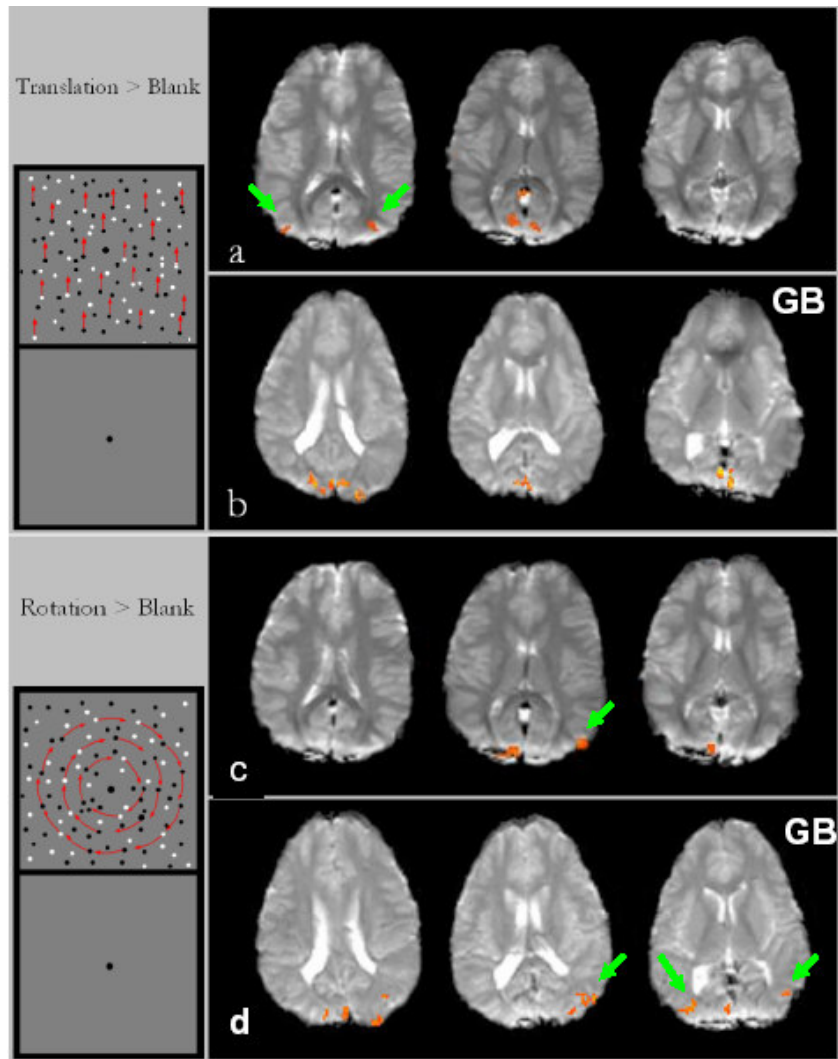
Fig. 3.12 BOLD responses in primary and secondary visual cortex, and two putative motion areas V3 and MT complex (indicated by green arrow). For both translational and circular motion there was a strong response in V1/V2 in both GB and the control. The response in V3 (**-38, -85 +8**) for GB is also prominent. However, MT+ was activated only by circular motion for GB (**-48, -62, 1** and **55, -65, 14**), while both forms of motion activated the area for the control.
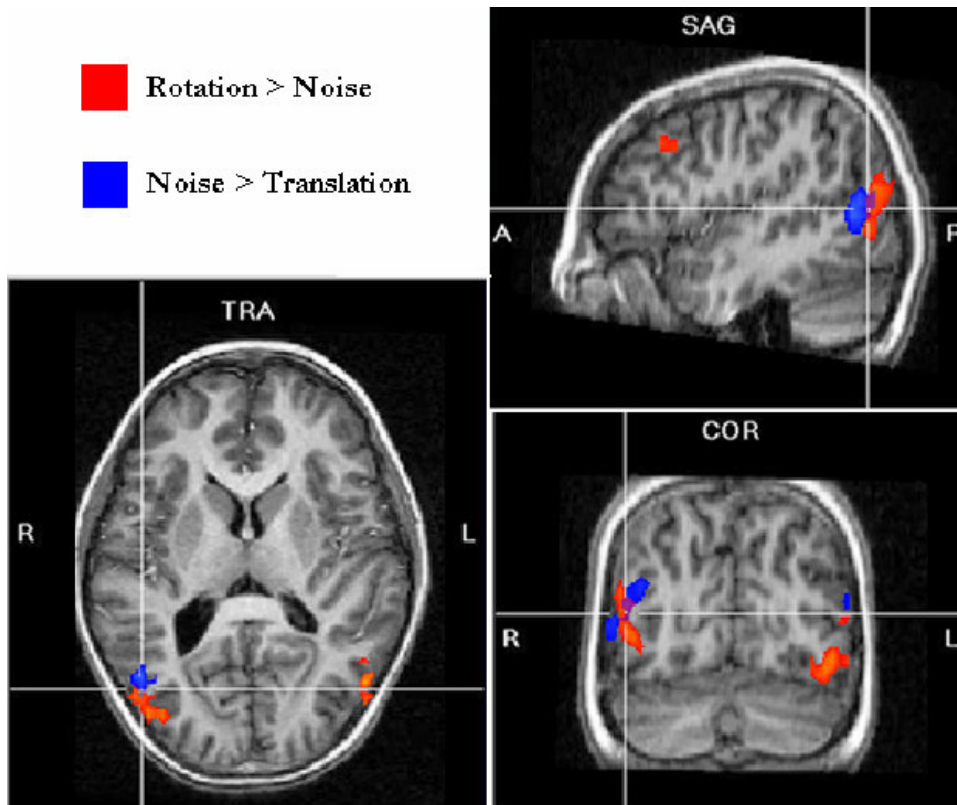
Fig 3.13 BOLD activity of GB in response to circular (inverting direction every 2 s) and translational motion, alternated with locally-matched random motion. Circular motion produced strong BOLD in the low MT+ area (areas labeled in red for positive correlation z=3.1), but translational motion produced a smaller response than random noise with matched speed (area labeled in blue and corresponding to z= – 3.1). The focus of the positive activity in response to the circular motion versus noise extended from (55, – 65, 14) to (48, –60, 8) and from (–48, –60, 8) to (–48, –62, 1), while the focus of the negative response to translation versus noise was slightly shifted.

Circular motion, that alternated direction every 2 s, elicited strong BOLD activity in the MT+ area (red labelled activation) that is located along all the inferior temporal sulcus (from z=1 to

about z=14) both in the left and right hemisphere. Translational motion produced a smaller response than noise in these areas. Interestingly, the major area activated is located in a slightly different position along the sulcus that crosses the response to rotation. There was also a weak negative signal (correlated with noise rather than with coherent translation) in areas V3 and V1/V2 (not shown) suggesting that the locus of the deficit might precede MT. The rotation versus noise produced a reliable and positive response in V3 and V3A, but not primary areas (consistent with previous reports: [130]). A preference for incoherent motion in V1/V2 has been previously observed in normals, but was related to a noise comprising several velocities, due to the random refresh at each frame [124] and to a low density stimuli [140]. The response of normal subjects to the same translation versus noise stimuli used for GB never produced a negative response in V1,V2, V3 and V3A areas.

Modeling the effect

The systematic inversion of perceived motion direction suggests that the system is aliasing the motion signal. A familiar example of aliasing is the so called "wagon wheel effect", where the spoked wheels in a Western movie seem to move backwards when they reach a certain speed. This results from the periodic nature of the spokes of the rotating wheels, so if one spoke moves more than halfway towards the position of the next spoke in the time of one frame, it will be paired with the successive spoke, causing the direction of motion to invert [141]. Technically the inversion is known as *aliasing*, resulting from the fact that the rate of sampling by the filming technique is less than twice that of the repetition rate of the spokes, which is the minimum frequency necessary for vertical sampling (the *Nyquist* frequency). What could cause the aliasing in this case? The under-sampling could result from damage to the optic radiation, damaging the inputs to the motion-selective neurons. In this section we attempt to simulate the effects of sparsely distributed the input to the motion detectors. The flow of the model is illustrated by the centre panels of fig. 3.14. There are four separate stages, an initial lowpass filter, spatial sampling, second low-pass filter and a final evaluation of motion direction. The initial filter essentially results from the optics and the finite size of the receptive fields of retinal neurons and the centre-peripheral antagonism of the receptive field. The sampling stage assumes that the receptive fields that constitute the inputs to the motion-selective cells form an irregular lattice, each separated from its neighbor by an average distance that will be the inverse of the

sampling rate (the minimum sampling distance was 0.11 deg that for a 500 ms lifetime and a 1deg/s velocity correspond to a maximum of 4 samples per dot trajectory). The second filter stage relates to the spatial and temporal tuning of the ensemble of cortical motion detectors (or other neurons downstream of them) that receive the sampled information. Fig. 8 illustrates the effect of each stage of the model on the stimulus (upper panels) and its Fourier transform (lower panels). We consider only the vertical spatial direction (represented on the ordinate) and time (on the abscissa). With this representation the translating stimuli follow short downward trajectories equal to their limited lifetime, shown by the runs of dots at 45º in Fig. 3.14 A. The few isolated dots are the noise dots, repositioned to a new random position each frame. The real component of the Fourier transform of the stimulus is shown underneath. Most energy falls in the upper quadrant, indicating that the motion was predominantly downward. Fig. 3.14 B shows the image after spatio-temporal filtering by the retina (details in caption), that has the effect of smoothing the image in space- time.

Fig. 3.14 C and its Fourier transform shows the result of multiplying this image multiplied by the sampling matrix, which would correspond to the sparsely positioned cortical motion detectors. There is now considerable energy in the lower quadrant (upward motion), nearly balanced with the downward motion. After further spatio-temporal filtering (Fig. 3.14 D: probably imposed at cortical level), the much of the energy in the upper quadrant is removed so that in the lower quadrant becomes dominant, implying that upward motion would be seen.

This second stage filtering simulates the action of the spatio-temporal selectivity of the ensemble of motion detectors. The shape of this secondary filter is crucial in simulating the data: a second-stage spatial filter that is band-pass rather than low-pass, or a low-pass with a larger bandwidth, would eliminate the bias towards upward motion (see discussion). Indeed the inversion effect is replicated because the peak of the aliasing spectra comes close to the low spatial frequency for the downward motion, while the peak for the upward motion is filtered out by the low spatial frequency selectivity of the motion detector. In this implementation the motion was sampled regularly. However, similar results were obtained with random sampling, provided that there was a minimum distance between sampling and that it was in the range of aliasing (maximum allowed for this motion parameter is 0.08deg). To predict the perceived direction of motion, we assume a subtractive stage, typical of many motion models [142, 143], that judge the direction from the difference of the overall energy in the two quadrants.
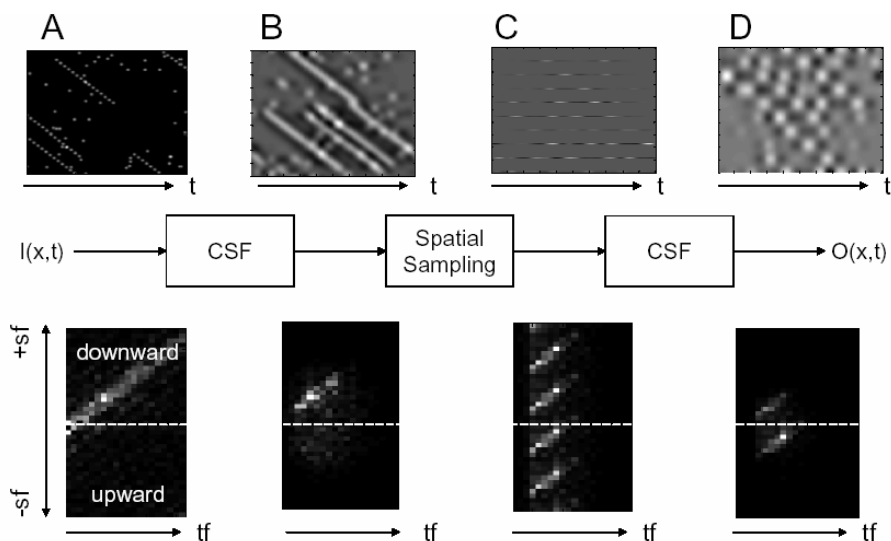
Fig. 3.14 The centre panels illustrate the four separate stages to the model: initial low-pass filter, spatial sampling, second low-pass filter and a final evaluation of motion direction. The upper panels show the stimulus and the lower panels its Fourier transform. Fig. A illustrates the vertically translating stimulus (ignoring the horizontal dimension). The real component of the Fourier transform of the stimulus is shown underneath, with most energy falling in the upper quadrant, indicating that the motion was predominantly downward. Fig. B shows the image after spatio-temporal filtering by the retina, and its Fourier transform. Fig. 8C and its corresponding Fourier transform show the result of multiplying this image by the sampling matrix, that would correspond to the sparsely positioned neurons that constitute the input to the cortical motion detectors. There is now considerable energy in the lower quadrant, implying upward motion. After further spatio-temporal filtering (Fig D), the energy is dominant in the lower quadrants, implying that upward motion would be seen. The filters are given by:

$$f(y,t) = \left(e^{\left(\frac{-y^2}{2\sigma_{SH}^2}\right)} - 0.5 e^{\left(\frac{-y^2}{2\sigma_{SL}^2}\right)} \right) \left(e^{\left(\frac{-t^2}{2\sigma_{TH}^2}\right)} - e^{\left(\frac{-t^2}{2\sigma_{TL}^2}\right)} \right)$$

where for the initial filter $\sigma SH = 5.4$ c/deg, $\sigma SL = 2.25$ c/deg, $\sigma TH = 6.75$ c/deg, $\sigma TL = 3.5$ c/deg. For the second-stage filter, only the low pass spatial function was present, with $\sigma SH = 4.5$ c/deg, and the other parameters of the temporal functions remained the same. Sampling was at 0.11°, lifetime 500 ms and velocity 1 deg/sec (similar results were obtained over a factor of two range of velocities)

The model was implemented in the Fourier domain, measuring all the energy (square root of the integral of the power) that belongs to the first (upward motion) and second (downward motion) quadrant. For simplicity, no normalization stage (eg [144]) was introduced, as we observed that this operation did not alter the simulation very much, given that total energy changes only slightly with sampling frequency when normalized for number of samples. Fig. 3.15 shows the result of the model as a function of motion coherence level, for sparse and dense (near continuous) sampling. For a wide range of coherence levels, the sparse sampling predicts motion in the reversed direction.
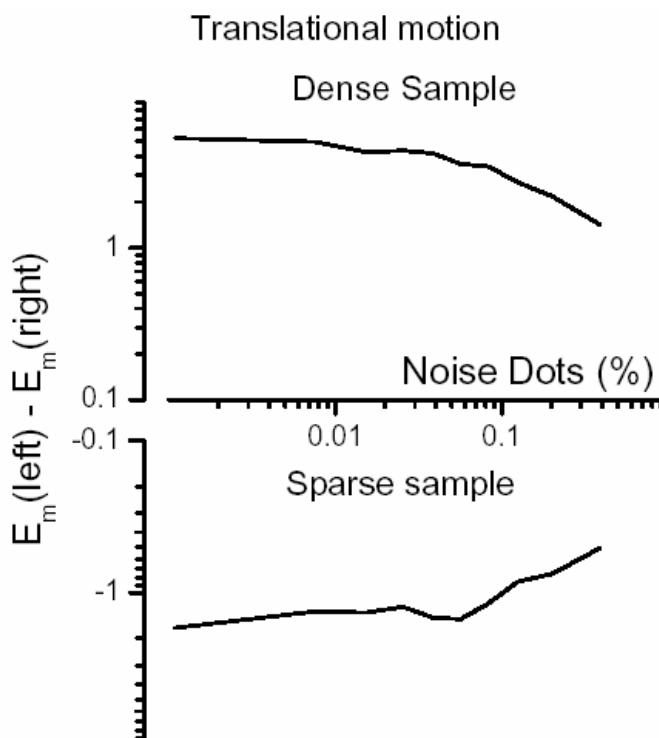
Fig. 3.15 Output of the motion model with sparse and dense sampling, as a function of motion coherence level. The sparse sampling always produces a prevalence of inverted energy. In both cases, the energy differences fall off with coherence at a similar rate, indicating that thresholds should be similar. Each point at each coherence is an average of 80 different new stimuli. The sparse sampling of the image was 0.11 deg, the dense 0.005 deg; stimulus velocity 1deg/c, lifetime 500 ms, average density of 0.1 dots/deg^2.

At very low coherence levels, the difference of energy in the reversed direction decreases, but never inverts. Interestingly, the amount of motion energy for the sparse sampling falls at about the same rate as that for the dense sampling, predicting that the inverted thresholds for sparse sampling should similar to the veridical thresholds for dense sampling (as is observed with GB). Similar results were obtained decreasing velocity by a factor of 3 or increasing it by a factor of 2. The critical parameters to achieve this simulation are minimum spatial sampling (a less severe sampling would not produce the inversion), and second stage filtering that boasts selectively the spurious low spatial frequencies and high temporal frequencies in the wrong direction. We also ran the prediction for sinusoidal gratings, as a function of spatial frequency, for sparse and continuous sampling (Fig. 3.16).
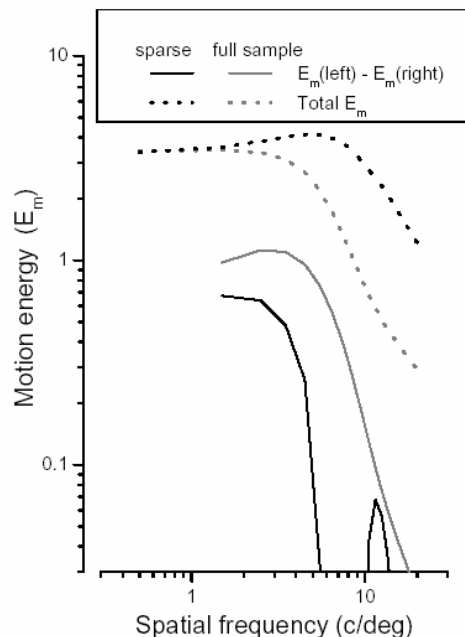
Fig. 3.16 Directed motion energy for drifting sinusoidal gratings as a function of spatial frequency, for sparse (0.11deg, grey lines) and near-continuous (0.005 deg, dashed lines) sampling. The sparse sampling predicts veridical motion for spatial frequencies below about 5 c/deg, with a rebound of inverted motion around 10-12 c/deg. However, this rebound is of low amplitude, probably below threshold. Velocity was kept constant at 1 deg/sec.

The sparse sampling predicts veridical motion for spatial frequencies below about 5 c/deg, with a rebound of inverted motion around 10-12 c/deg. However, this rebound is of low amplitude, probably below threshold.

3.4.3 Discussion

We have described two PVL patients that not only had severely impaired motion perception, but consistently and reliably saw motion in the opposite direction. This occurred only for translational motion, not circular or radial motion, and only for random dot kinematograms, not sinusoidal 14 gratings. Interestingly, the sensitivity threshold for seeing reversed translational motion in one patient was similar to that for seeing correct rotational and radial motion, and similar to that for seeing correct translation in other PVL patients and typically developed children [137]. With sinusoidal gratings, contrast sensitivity for direction discrimination plummeted rapidly to zero at three cycles per degree (a relatively low spatial frequency), but the direction was never perceived inverted. Orientation sensitivity for gratings drifting at the same temporal frequency was well within the normal range, showing that even for sinusoidal gratings, the deficit was specific for motion discrimination.

Selective impairment of contrast sensitivity for direction discrimination has been observed in adult patients with middle-temporal lesions [95]. The same patients also show a clear deficit for coherence thresholds, in good agreement with electrophysiological and fMRI studies that implicate MT-MST complex in the elaboration of motion signals to mediate the perceptual thresholds[88, 89]. However, no case of perceptual inversion of motion direction has ever been reported, either in monkeys with experimental lesions [145] or in lesioned patients [146, 147]. In our patient GB, translational motion never activated MT complex, even when contrasted with blank stimuli. When contrasted with random noise there was a clear response in the controlateral hemisphere along the region that is usually called MT (see [91]), but the response was negative (stronger for random noise than coherent motion). A similar preference for noise was observed in occipital areas within BA 17, 18 and 19. While a preference for random noise has been observed previously in the literature [124] [140] it is usually occurs with a noise that comprises several velocities, due to random refreshment of each frame or to a low density of the random dots. The noise used here to contrast the coherent translation has the same local speed and the same limited life-time of the coherent motion dot. In our laboratory, contrasting these motions

produces a null or week response in calcarine cortex and a positive response in V3 and V3A (see also [130]). The preference for noise over coherent translation is consistent with a perceptual deficit for translation, and also with the existence of the specificity within the MT complex for this type of motion. This result would indicate that the signal elicited by coherent motion does not reach MT, or that it is heavily reduced. On the other hand, the activation generated by rotation or radial flow seems to be normal both for the occipital cortex [130] and MT complex. The segregation of the two regions along the inferior temporal sulcus also seems normal, with the translation selective area more dorsal and posterior, crossing at a certain point along the sulcus as observed in detail by Smith et al. [91]. Radial and rotational flow motions are analyzed by different neuronal mechanisms from those for translational motion, with very large neuronal receptive fields that summate local-motion signals over an extensive area [148-150]. That GB's perception and BOLD activation are compromised for translational but not for flow-motion reinforces the evidence for separate cortical sub-areas in MT, with independent function and different vulnerability to damage. The eye movement results are also consistent with a central site of the damage. The subject had great difficulty in pursuing an isolated target, presumably because he cannot see the motion. However, large-field stimulation with low-spatial frequency gratings elicits near normal OKN. Given that the cortical circuitry controlling pursuit and OKN are thought to overlap to a great extent (but not completely), it is reasonable to believe that the deficit is in the perceptual analysis and not in the motor control of the eye movement. Lesions in MT in monkey induce a strong but transient deficit of pursuit eye movement, and also erratic and delayed "catch-up" saccades to refoveate during pursuit [139]. The inability to perceive correctly direction of motion seems not to be related to the view of field, with the same impairment observed with a single dot and the 20 deg random dot display used for the direction discrimination task. The anatomical lesions and the other neuropsychological and neurological tests for the two patients reported here were very similar to those of other PVL patients reported by our laboratory [137]. Their lesions were absolutely typical for PVL patients, and even careful neuro-radiological examination did not reveal additional sub-cortical or cortical lesions. One possibility is that the optic radiations of the two patients were more impaired than the others, and that this was not anatomically resolvable. Perhaps the impairment is predominantly to the magnocellular afference, thought to be more vulnerable to compression damage [151]. The magnocellular pathway is clearly implicated in motion perception, while the parvo-cellular

pathway is thought to be more important for visual acuity and form. This would be consistent with the fact that spatial acuity and contrast sensitivity were normal for GB, and the fact that previous research has shown that PVL patients tend to show a motion rather than form perception deficit [101]. The bizarre inversion of motion direction suggests that the system is somehow *aliasing* the motion signal, in a form of "wagon wheel effect", where the spoked wheels in a Western movie seem to move backwards when they reach a certain speed. This effect results from motion being sampled discretely rather than continuously, by a sampling technique like cinematography or television. There has been some suggestion that a similar effect can occur without discrete sampling, implicating a sampling process in the brain [152], but this idea has been effectively dismissed by controlled experiments [153, 154]. It therefore seems more likely that the effect results from spatial rather than temporal under-sampling, possibly a result of damage to the optic radiation. Figs. 8-10 show results of simulations predicting an inversion of motion direction by severe under-sampling, in a way that could occur if many inputs to motion selective neurons had been destroyed. The simulations predict the inversion of motion direction, and that the coherence thresholds for the inverted motion should be similar for those of veridical motion (with appropriate sampling). Sinusoidal gratings of low spatial frequency should be seen as veridical. However, the spatial sampling predicted that motion direction should not be discernable for frequencies higher than about 4 c/deg, as observed with GM. In theory, inverted motion may be seen in a very narrow band of spatial frequencies around 10 c/deg, but this would be very difficult to measure in practice, as the thresholds would be very high and the spatial frequency quite critical. Why the reversed motion should occur only for translational motion and not for circular or radial motion is far from obvious. One point to note is that translational motion seems to be processed, at least in part, in different neural centers from radial motion [90]; these areas could have different properties that make them more vulnerable to under-sampling. A crucial part of the model is the second-stage spatio-temporal filter, that filters out much of the energy, leaving a surplus in the reverse direction. Changing the characteristics of this filter can have a large effect on the output: for example, broadening the spatial low-pass filter, or making it bandpass causes the output to be veridical rather than biased. If, for example, the areas that detect circular and radial motion had less severe low-pass filtering, then the aliasing would be less. At present there is no data to confirm this suggestion, but it seems reasonable, given that very low spatial frequencies provide

useful information for translation, but not for radial or rotational motion. Indeed this could be a useful line to pursue in future research (in normal adults).

In conclusion, our results reinforce previous evidence that translational motion is processed by structures that are functionally, and probably anatomically distinct from those that process circular and radial motion. That PVL lesions can lead to under-sampling of motion, and the paradoxical perception of inverted motion provides important clues about the neural mechanisms that analyze motion in human.

Chapter 4

Ongoing studies on the perception of "Biological Motion" in children with periventricular leukomalacia: is a specific deficit?

4.1 Introduction

Biological motion (BM) is the term used to describe motion patterns characteristic of living beings. Detection of such motion patterns is a fundamental property of the human visual system. Humans can efficiently detect another living being in the visual environment, and are able to retrieve many features from its kinematics. An experimental approach to uncouple information from BM from other non-dynamic sources of information is to represent the main joints of a person's body by bright dots against a dark background [100]. Employing this point-light display technique, observers can easily recognize a human walker, determine his or her gender [155-160], recognize various action patterns [161], identify individual persons [156] and even recognize themselves [162].

Neurons sensitive to BM have been reported in the superior temporal polysensory area (STP) in the superior temporal sulcus (STS) [163]. This area (STP) is well known because receives projections from the anterior parts of the dorsal and ventral visual streams, and Vaina [164] suggests that it is the site of their synthesis [165]. In particular, the dorsal substream specialized for the analysis of complex motions, including MT, MST, and FST, and the inferior temporal

cortex [166], an area crucial for object recognition [167-172], terminate in STP in the superior temporal sulcus (STS). Furthermore, neurons in STS show remarkable selectivity for faces.

Perception of biological movement is however linked to the implicit knowledge of the brain about the execution of movement [173, 174]. It was shown that perception of hand movements is altered in patients in which execution of hand movements is associated with chronic arm pain [175, 176]. Yet, it is unclear whether and, if so, how the perception of biological motion is limited by an observer's experience with his or her own restrictions in production of body movement. This is especially true when motor development has been impaired from the very beginning or extremely early in life.

Recently Pavlova et al. [96, 97], tested visual processing of biological motion in adolescents who were born premature with and without brain injury, and in healthy term-born peers. Brain injury consisted of PVL, a damage that is often associated with motor impairment of lower limbs. They found that patients with PVL had lower sensitivity to perception of biological motion respect to both control groups but no correlation between perception of biological motion and motor abilities was reported. A good correlation with the extension of the lesion was instead suggested.

The authors didn't investigate if this is a specific deficit in the abilities of perception of biological motion or if there is a more "basic" deficit on motion processing and form processing. Aim of this study is to analyse in subjects with PVL abilities in different types of tasks such as perception of translation, detection and direction discrimination of a walker made of black points. To exclude the presence of more "basic" deficits, we administered to all subjects a form coherence task to investigate the integrity of the ventral stream and a motion coherence task to investigate the integrity of the dorsal stream.

4.2 Subjects and Methods

Participants were selected from children referred to the Division of Child Neurology and Psychiatry according to the following criteria: (a) clear signs of PVL on MRI, according to the criteria indicated in the literature [71]; (b) a verbal IQ within normal limits, (c) the absence of

main ocular anomalies including cataract, optic atrophy and retinopathy of prematurity, and (d) a full neurological assessment. Twelve subjects were selected: the mean age was 11,3 years (range: 9 – 15; 5 males); mean gestational age was 31.9 weeks (range 26-36). All patients had at least one MRI examination (see Table 4.1).

The control group consisted of nine age-matched term-born children, recruited from the local primary and secondary school (mean age: 9.1 years, range: 7 – 11; 5 males). As most of our PVL children were born preterm, we also assessed a group of twelve preterm-born children (mean age: 10.4 years, range: 9 – 13; mean gestational age 30 weeks, range 26-32; 7 males), recruited from the follow-up program of the Neonatal Unit of Pisa University, according to conditions b and c of the patient group selection criteria. All children of this group had received ultrasound scanning at birth showing no abnormalities or transient periventricular flares (lasting less than 10 days) (see Table 4.1).

The study was approved by the Ethical Committee of the Stella Maris Scientific Institute. Informed consent for participation was obtained from parents of all children.

4.2.1 Psychophysical stimuli and procedures

All visual stimuli were presented on a Sony Trinitron LCD monitor with a screen resolution of 1024*768 pixels, 32 bit color depth, refresh rate of 60 Hz and a mean luminance of 25 cd/m^2. Visual stimuli consist of point like walkers sampled by mean of 11 black dots (each 4.6 arcmin diameter) attached to the head and the main joints (ankles, knee, and shoulder) of an invisible human body. The entire walker silhouette subtended a visual angle of 4.5° in height and 3.1° in width considering the pattern obtained at half gait cycle (when walker arms were stretched at maximum). The subject's view distance was 114 cm. Each dot of the walker figure remained visible for the entire 3 sec presentation and moved on average at the speed of 2.1 deg/sec.

"Translation" condition

In the "Translation" experimental condition, the motion investigated was not biological but consisted of simple horizontal translation. In this case on each presentation a static silhouette of a walker (corresponding to ¼ of the gait cycle) translated horizontally either from 3° on the left of the screen center up to 3° on the right or the other way around. The task of the subjects was to

Table 4.1 Clinical data

	GA	Sex	Age test	Lesion	Motor Outc.	Trans.	Detect.	Direc. Discr.	Form z-score	Motion z-score
PVL										
CD	34	m	15 aa	PVL	D	185,617	11,73	52,7	-3,26	-1,37
CA	34	m	15 aa	PVL	D	44,9	21,02	72,83	-5,2	-1,37
RC	36	f	10 aa	PVL	D	112,22	57,72	20,55	-	-
TG	30	f	16 aa	PVL	D	21,75	8,8	13,71	-	-
BB	29	f	10 aa	PVL	D	43,19	58,82	39,34	-0,07	-
CB	32	f	12 aa	PVL	D	241,84	39,11	53,42	-	-
GI	31	m	10 aa	PVL	D	34,152	21,905	22,57	-2,175	-5,59
OF	34	m	12 aa	PVL	D	103,88	43,237	22,91	-5,66	-1,87
EA	31	f	9 aa	PVL	D	68,87	-	28,21	-	-
BF	32	f	7 aa	PVL	D	64,125	44,71	16,66	-2,94	-1,06
CA	32	m	10 aa	PVL	D	54,136	12,736	25,84	-3,86	-5,34
CV	32	f	10 aa	PVL	D	70,384	14,736	30,032	-3,5	-2,95
Preterms										
CI	26	f	9 aa	-	N	100,102	121,27	68,551	-0,70536	-2,51613
CC	27	f	13 aa	-	N	144,13	46,87	61,102		-
GA	31	m	10 aa	-	N	174,271	67,176	65,988	-1,62857	-5,05323
ON	29	m	11 aa	-	N	186,093	147,96	55,056	-1,62857	-
PF	32	m	11 aa	-	N	229,62	75,496	62,644	-2,78929	-0,03548
RG	32	f	11 aa	-	N	298,96		45,352	-0,70536	-1,70645
RC	32	f	10 aa	-	N	104,173	67,81	85,681	0,026786	-0,79839
RG	32	m	10 aa	-	N	102,92	79,96	143,42	-0,50714	0,608065
TE	29	m	9 aa	-	N	185,68		19,002	-2,47321	0,191935
DPL	32	m	10 aa	-	N	177,379	69,544	112,132	0,853571	0,404839
BI	28	m	10 aa	-	N	151,17	14,124	69,125	-3,125	-1,08387
FR	30	m	11 aa	-	N	115,226	48,799	51,853	-1,89464	0,40
Controls										
DA	Term	f	10 aa	-	N	166,11	66,075	69,341	-	-
MV	Term	f	10 aa	-	N	100,06	127,764	80,576	-	-
BM	Term	f	11 aa	-	N	97,096	47,512	55,5	-	-
DVC	Term	f	9 aa	-	N	103,36	100,54	61,075	-	-
CL	Term	m	9 aa	-	N	258,4	187,432	95,668	-	-
NN	Term	m	9 aa	-	N	222,76	86,446	69,4	-	-
SL	Term	m	9 aa	-	N	145,89	127,368	52,264	-	-
DS	Term	m	8 aa	-	N	114,62	162,155	34,464	-	-
SA	Term	m	7 aa	-	N	143,10	168,754	52,319	-	-

G.A.= Gestational Age; **Trans. =** Translantion; **Detect.=** Detection; **Direc. Discr.** =Direction Discrimination; **m**=male ; **f**=female ; **D**=Diplegia ; **N**=Normal

verbally indicate the translation direction of the walker to the experimenter that recorded the answer by pressing one out of two key on the PC keyboard.

"Detection" condition

In the "Detection" experimental condition a dot like walker stimulus was displaced randomly 3° on the left or on the right of the screen center. Symmetrically on the opposite position it was displayed an upside down scrambled walker (walking in the same direction as the original walker) as a control for dots density distribution. Subjects had to indicate where, right or left-hand side, was the upright positioned walker displayed.

"Walking direction discrimination"

In the "Walking direction discrimination" a dot like walker stimulus was displayed around the screen middle line with a displacement jitter of +/- 1 degree. The subject's task consisted in discriminating the direction of ambulation that could randomly be to the left or to the right. In all conditions subjects were required to provide the right answer out of 2 different possibilities and were invited to guess whenever they were not sure of the answer to provide to (2AFC). On each presentation the stimulus patter may be masked by visual noise comprising dots of the same size and color as those constituting the dot like walker. Noise dots moved randomly across the screen (in an area of about 7 degrees from the screen center) with a constant speed of 2.1 deg/sec. The amount of visual noise on each presentation was defined trial by trial by the adaptative staircase QUEST [104] that homed in on the 75% of correct response.

Form coherence and Motion coherence test

Coherence stimuli were displayed on an Acorn A5000 computer monitor viewed at a distance of 40cm (visual angle 38 _ 281). The form stimulus was a static array of randomly orientated short line segments (white lines on a black background, density 1.3 segments/deg2) containing a target area on one side of the display where segments were oriented tangentially to form concentric circles. The proportion of tangentially oriented (coherent) line segments amongst the randomly oriented noise segments in the target area defined the coherence value for each trial. The motion stimulus comprised two random dot kinematograms (white dots on a black background, density 4 dots/deg2), one of which was segregated into three horizontal strips, such

that the direction of the coherent motion of the middle target strip was opposite to that of the two outer strips. The dot array on the opposite side of the screen displayed a uniform direction of coherent motion consistent with the direction of the two outer strips. During trials a variable proportion of the dots oscillated horizontally across each array forming coherent motion (velocity 6 deg/s), while the remaining dots moved in random directions (incoherent motion; updates occurred every 20 ms). The direction of coherent motion reversed every 240 ms. To limit subjects' use of tracking strategies, the trajectory of each signal dot had a limited lifetime of six video frames (120 ms). The additional 'noise' created by the disappearance of signal dots at the end of their lifetime was taken into account when calculating coherence levels on this task. Figure 4.1 illustrates both the form and motion displays.
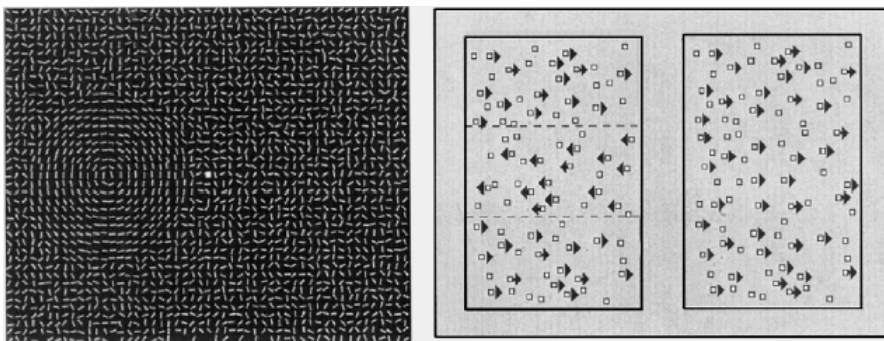
Fig. 4.1 Schematic diagram of the stimuli used to test form coherence (left) and motion coherence (right)

Perceptual thresholds were obtained using two-alternative forced-choice paradigms whereby participants were required to locate the target regions, which were presented either in the left or the right half of the display. Stimuli were presented on the screen for a maximum of 10 s and between trials subjects' attention was drawn to the midline with a flashing or oscillating spot. In either task, the initial coherence level on each task was set to 100% and 2–6 practice trials were conducted. In the test phase the coherence level of the target regions was varied according to a modified version of the two-up/onedown staircase procedure [177, 178]. Starting at 100%, coherence was decreased stepwise between each trial, and the level at which the first incorrect response occurred formed the starting point for four reversals. Threshold was defined as the

mean coherence level during the last four reversals. Each subject performed the staircase procedure once for each task. The motion and form coherence tasks were run successively for each subject, with the order of presentation of the two tasks counterbalanced across subjects

4.3 Results

4.3.1 Psychophysical testing

The average translation, detection and direction discrimination sensitivities for our PVL group, compared with the two control groups, are reported in Fig. 4.2.

Fig. 4.2 Average sensitivity to translation task, detection task and direction discrimination task reported by controls (green), preterms without brain lesions (blue) and PVL subjects (red)
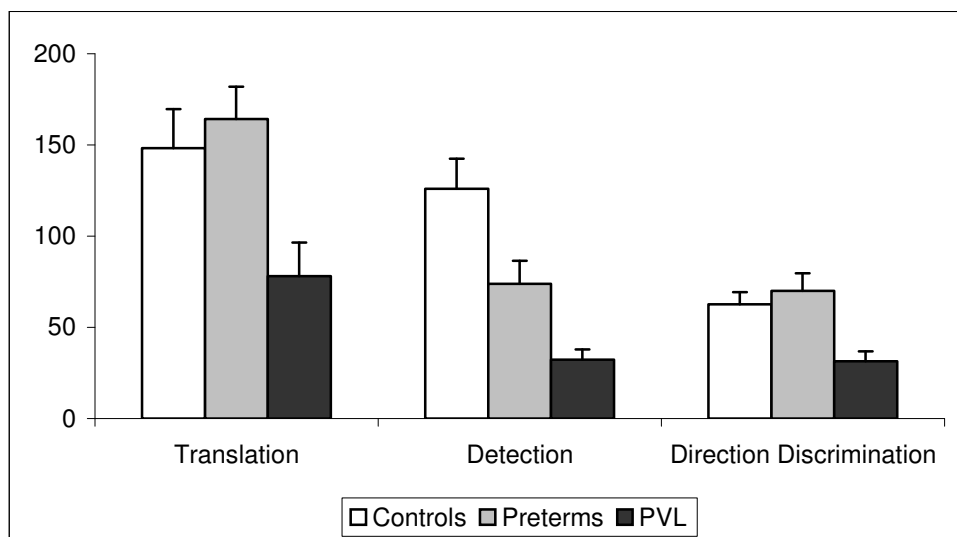
A one way ANOVA was performed on the data, showing that a significant difference was present between the three groups for the translation task (p=0.011), the detection task (p= 0.000) and the direction discrimination task (p=0.002) (Table 4.2).

Table 4.2 Statistical analysis by means of ANOVA between average motion coherence sensitivities for PVL compared with the two control groups

Test	Groups	N	Mean (SD)	F	P value
Translation	Term controls	9	148,16 (21,5)	5,311	,011
	Pre-term controls	12	164,14 (17,7)		
	PVL	12	78,13 (18,3)		
Detection	Term controls	9	125,9 (16,5)	15,211	,000
	Pre-term controls	10	73,9 (12,6)		
	PVL	11	32,27 (5,6)		
Direction Discrimination	Term controls	9	62,6 (6,7)	7,773	,002
	Pre-term controls	12	69,9 (9,7)		
	PVL	12	31,46 (5,3)		

Post-hoc Bonferroni test revealed that PVL subjects showed significantly lower sensitivities than term-born children for all three tests, the translation (p<0.05), the detection (p<0.001) and the direction discrimination (p<0.05). Post-hoc Bonferroni test revealed also that PVL subjects showed significantly lower sensitivities than preterm controls for all three tests, the translation (p<0.05) and the detection (p<0.05) and the direction discrimination task (p<0.005). No differences was present between preterm without cerebral lesions and controls except for the detection task (p<0.05).

Form coherence test

All PVL children except one have results below the 2 SD respect to normative data [101] showing an important deficit about ventral stream pathway. Preterm children without brain lesions have all values in the normal range except in three cases (Table 4.1 and Fig. 4.3)

Correlation between Form coherence values and psychophysical testing

A statistical significant correlation (evaluated by means of Pearson t-test) was found both between form coherence z-score and detection sensitivity (p= 0.022), and between form coherence z-score and direction discrimination sensitivity (p= 0.026). (Fig. 4.3).
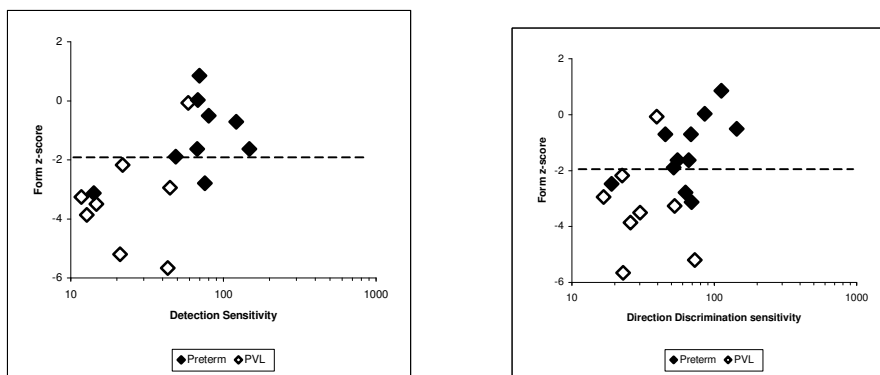
Fig. 4.3 Correlation between form coherence z-scores and a)detection sensitivity b) direction discrimination sensitivity. In red we reported PVL subjects and in blue subjects born preterm without brain lesions

Motion coherence test

About PVL children three (3/7) have results below the 2 SD and all the others more than 1 SD respect to normative data[101]. Preterm children without brain lesions have all values in the normal range except in two cases (2/10) (see Table 4.1)

Correlation between Motion coherence values and psychophysical testing

No statistical significant correlation (evaluated by means of Pearson t-test) was found between motion coherence z-scores and the three types of psychophysical stimuli.

4.4 Conclusions

In our study we found that children with PVL had a lower sensitivity to the perception of biological motion (the task called direction discrimination) as Pavlova and co-authors [96, 97] reported in their works, but we can't consider it a specific disorder. In fact, in a previous study (see par.3.3) we reported that, in children with PVL, sensitivity both to translational and rotational motion is on average significantly reduced compared to age-matched controls and we asked to ourselves if the visual streams underlying biological and flow motion, can be more

globally impaired in children with PVL or other developmental disorders, with mechanisms that are to some extent overlapping. In that study we found also that preterm children without brain lesion had lower sensitivity to translational and rotational motion respect to controls, even if not in a statistically significant way, but Pavlova, in her studies didn't report a specific deficit of BM perception in children born preterm.

In the literature is reported that patients with normal sensitivity to motion speed, direction, and pattern, may fail to perceive BM [125]. Unexpectedly, patients with bilateral lesions along the dorsal pathway involving the human homologue of MT, such as patients LM and AF [94], who were impaired on many aspects of visual motion perception to the extent that they are referred to as almost or completely ''motion-blind,'' can reliably recognize human actions in point-light displays. Similarly surprising, patient EW, with bilateral ventral lesions involving the posterior temporal lobes [179], suffered from prosopagnosia and object agnosia, but could easily and correctly recognize BM. Vaina et al [164] hypothesized that whereas motion stimuli activate primarily the dorsal system and form and face stimuli primarily the ventral system, recognition of BM stimuli may activate both systems as well as their confluence in STP. So a deficit in tasks of motion perception linked to a deficit in tasks of form recognition may explain a deficit in perception of BM.

For this reason we administered to our subjects not only the task "direction discrimination" but also two "controlled" stimuli. The first in which it was necessary to recognize only the direction of motion ("translation") and the second in which it was necessary to recognize the walker by means of the form ("detection"). In this way we were able to investigate, on one side, the integrity of the dorsal stream and, on the other side, the integrity of the ventral stream. To exclude every doubt we had two groups of controls, one born at term and one of children born preterm without brain lesions.

Our results show that, PVL subjects, have a global deficit in all the three tasks administered and differed in a significant statistical way both from controls born at term and from children born preterm. Preterms, instead, didn't report statistically significant differences from controls born at term, except for the task "detection"(lower sensitivity). Our results show, in subjects with PVL,

a global impairment both for motion tasks and for recognition tasks and not only a specific deficit for BM. This seems to confirm Vaina's suggestion that if one of the two ways (dorsal or ventral) is not compromised, one subject has a good perception of BM, while if both are compromised there is also a deficit in the perception of BM.

Less clear is what happens in subjects born preterm, since that they reported, respect to controls, lower mean values to translational and rotational motion [137] but also lower values to the task called "detection". MacKay and co-workers [102], recently, explored different levels of local and global motion processing in a group of very low-birth weight children born preterm and showed a significantly worse performance in all tasks assessed, as opposed to term controls. The same group also reported a significant impairment in detection and recognition of motion-defined forms, a function involving a number of motion-sensitive areas [107-109], in preterm children irrespective of the presence of brain damage or retinal abnormalities [102, 110].

For this reason we decided to investigate better dorsal and ventral stream by means of motion coherence test and form coherence test in subjects with PVL and in preterms without brain injury comparing their results to normative data collected on more than one hundred of subjects [101].

We found that PVL children reported pathological scores (lower than 2 SD) both in the form coherence task (all the subjects except one), and in the motion coherence task (more than half of the subjects), confirming the hypothesis of a damage both of the dorsal and the ventral stream. In children born preterm without brain injury we found scores within 2 SD both at the form coherence test and at the motion coherence test .

These data have clearly confirmed the compromission of both pathways, dorsal and ventral stream, in subjects with PVL, while in preterm infants without brain lesion there is no compromission, explaining why we didn't find a deficit in the direction discrimination task.

Detection values lower than controls in preterm subjects can be linked to a deficit in the perception of motion defined forms as sustained by McKay and coauthors [102].

Finally it is of great interest the statistical correlation between form coherence task z score and direction discrimination task: it is a clear message that in case of form coherence task it is very important to investigate also direction discrimination skills.

Chapter 5

Spontaneous and induced reorganisation of the visual system in children after congenital or acquired unilateral brain lesions: the model of multisensory integration

5.1 Introduction

The final formation and function of the neocortex and associated systems of humans and many other mammals can be shaped early in life by lesions that interfere with the innate development of architecture, patterns of connections, and mapped functions. The lesions trigger modifications in structure, rewirings, and representations and, in some instances, the modifications are adaptive and result in sparing of functions that would otherwise be lost, or severely handicapped, by equivalent lesions incurred later in life [39, 180-186]. Moreover, the degree of functional sparing can vary with the age at which the cortical damage was incurred, and it is accompanied by anatomically demonstrable changes in brain wiring on animal models [25, 33, 36, 187-189].

The aim of the series of studies reported in this chapter has been to evaluate the development of visual functions in children with congenital unilateral brain damage or acquired early in life (but always in paediatric age). In particular we aimed at analysing the different behaviour in the same task -a visual search one- and at describing possible correlations between the type of damage and the timing of lesion (congenital or acquired). We finally reported our experience of a

multisensorial treatment in subjects with hemianopia and we aimed at analysing the different behaviour in patients of the same age with brain damage incurred at different ages.

5.2 Greater sparing of visual search abilities after early rather than acquired unilateral brain damage

Visual search refers to the capacity of a subject to find a target among simultaneously presented distractors [190] and it is based on visual abilities such as a fast visual processing and an accurate control of ballistic eye movements (saccades) that guide the fovea to the target location [191-193]. Many brain areas are involved in this type of task: in particular there exist two major intracortical streams, the so-called ventral and dorsal pathway, that transmit information from posterior sites (the visual areas V1 and V2) to anterior cortical areas. The first is important because is involved in the "pattern recognition" and the second because is interested in the " spatial localization" which is required to plan visually guided movements.

Adult studies have shown that also unilateral damage to the post-chiasmal visual pathway is often associated to visual search disorders [194]. This type of cerebral damage is, in fact, associated to homonymous hemianopia (HH), that is the loss, in part or completely, of vision in the visual field contralateral to the side of lesion. These subjects, cannot process images in the same way as normal controls and usually have difficulties with reading and detecting stimuli and finding objects in the visual space which corresponds to the affected field region. Their search pattern is characterized by frequent exploratory saccades into the blind part of the visual field [77, 115, 195] with repeated saccades and fixations to the same objects, resulting in longer search times and longer unsystematic scanpaths [195-197]. In addition their fixations dwell in their intact hemifield and their saccades are less regular and accurate and too small to allow rapid, organised scanning.

In children, little is known on the possible effects of brain damage on visual search abilities. Netelenbos et al. [198], studied a small group of seven school-aged children with

heterogeneously acquired unilateral brain lesions but without visual field defect and sensory or motor deficits. They reported abnormal values on visual search tasks only in children with right-hemisphere lesions. Different results are described by Schatz et al. [199], who studied thirty-three children with acquired stroke secondary to sickle cell disease. The authors found a greater degree of slowing in responses for the visual field contralateral to the individual's injury and, in particular, subjects with unilateral left injury showed a steeper increase in response time for the right visual field compared to the left visual field.

Very little is known, however, on the possible effects of lesions occurring prenatally or around birth, when the nervous system is still largely immature and different pathways of functional reorganization might be expected to be activated. Animal studies on cats [40, 200, 201] are strongly suggestive of a dramatically different effect of early brain damage on visual orienting, as opposed to later damage, suggesting an important role of the superior colliculus in the sparing of visual function.

For this reason we decided to study the different patterns of visual searching in a group of children with congenital and acquired unilateral brain lesions (with a clinical diagnosis of hemiplegia), with and without hemianopia.

5.2.1 Subjects and Methods

Twenty-five children with a diagnosis of hemiplegia, aged 6-14 years, were enrolled in this study. Fourteen children had an acquired cerebral lesion (6 left and 8 right) and the remaining eleven had a congenital one (6 left and 5 right). Time elapsed since brain damage was at least 1 year, in subjects with acquired cerebral lesion; the clinical diagnosis of hemiplegia was done according to Ferrari-Cioni classification [202]. The main clinical data of the subjects are summarized in Table 5.1.

All the subjects had at least a Magnetic Resonance Imaging. In order to minimize the effect of associated neuropsychological disorders, patients with additional impairments such as mental retardation were excluded. In addition, patients with severe ophthalmologic abnormalities (such as major refraction problems, optic nerve atrophy) were not included in the study. Visual acuity

lower than 8/10 for near and far vision, or with "blurred vision" or defective light or dark adaptation were not accepted for this study.

All patients underwent the assessment of: i) a computerized visual field and/or behavioural kinematic visual field and ii) a visual search tests battery.

Computerized Visual Field: automated perimetric visual field was tested by means of KOWA AP 340 system. Each eye was tested with a full threshold and full field, 237-point, with incorporating fixation monitoring

Kinematic Visual Field: A small white ball (a Stycar ball of 40 mm in diameter) gradually moves from 90°laterally towards the child's midline. The child was asked to indicate when they first saw the ball. Eye movements of the child were also observed to estimate the angle of the visual fields and their symmetry.

Visual search battery

This battery consisted of four tests, all modified from Zihl, 2000 [203] : the Apple test, the Frog test, the Smile test and the E–F test. Patients were shown the stimulus arrays (52° x 45°, horizontally and vertically respectively) projected on slides at a distance of 120 cm and they were required to actively explore the visual field by using eye, but not head, movements to search for visual targets. They had to report the presence of the target, by pressing a 'yes' key response if the target was present and a 'no' key response if it was absent. Correct responses and reaction times (RTs) for each hemifield were recorded. Normative data for ages between 6 to 13 years were collected on 200 healthy students (25 for each class of age).

*Apple test (Fig. 5.1 a)***:** Each stimulus array contained 10 stimuli, distributed at random over the array. The stimuli consisted of red apples, projected on a black background. Ten trials were presented: eight trials in which the target was present (4 in the right hemifield and 4 in the left one) and 2 in which the target was absent. Patients were instructed to fixate the red cross located in the centre of the slide (i.e. fixation point) and to search, after the disappearance of the cross, for a single target (i.e. the "yellow apple") embedded among distracters (the "red apples").

*Frog test (Fig. 5.1 b)***:** Each stimulus array contained 13 stimuli, distributed at random over the array. The stimuli consisted of green trees, projected on a black background. Eleven trials were

presented: eight trials in which the target was present (4 in the right hemifield and 4 in the left one) and 3 in which the target was absent. Patients were instructed to fixate the red cross located in the centre of the slide (i.e. fixation point) and to search, after the disappearance of the cross, for a single target (i.e. the "frog") embedded among distracters (the "trees").

Smile test (Fig. 5.1 c): Each stimulus array contained 9 stimuli, distributed at random over the array. The stimuli consisted of little white faces, projected on a black background. Ten trials were presented: eight trials in which the target was present (4 in the right hemifield and 4 in the left one) and 2 in which the target was absent. Patients were instructed to fixate the red cross located in the centre of the slide (i.e. fixation point) and to search, after the disappearance of the cross, for a single target (i.e. the "sad" face) embedded among distracters (the green letters "smile faces").

E–F test (Fig. 5.1 d): Each stimulus array contained 22 stimuli, distributed at random over the array. The stimuli consisted of green letters, projected on a black background. Twenty trials were presented: 16 trials in which the target was present (8 in the right hemifield and 8 in the left one) and 4 in which the target was absent. Patients were instructed to fixate the red cross located in the centre of the slide (i.e. fixation point) and to search, after the disappearance of the cross, for a single target (i.e. the green letter 'F') embedded among distracters (the green letters 'E').
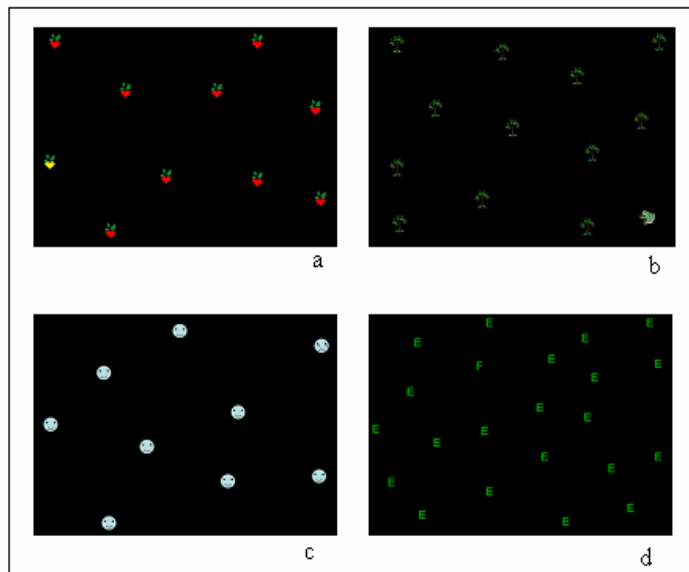

Fig. 5.1 Visual search test battery: a) Apple test; b) Frog test; c) Smile test; d) EF test

Chapter 5

Statistical analysis

RTs reported by each subjects were compared with normative data and converted to a z-score using data from normal control children of comparable age. Abnormal results were considered with z-score above 2, corresponding to 2 standard deviations (SD). The correlation between z-scores in the different groups was analysed by means of Student's t test, with critical significance at .05

5.2.2 Results

General characteristics of the population are shown in Table 5.1.

Visual Field assessment

In all the cases in which it was possible to assess visual field defect both by means of automated technique both by means of behavioural technique we found a good concordance.

Among children with acquired hemiplegia seven reported no visual defects, 5 a homonymous hemianopia (2 left; 3 right) and 2 a quadrantanopia (1 with a reduction in the upper left visual field and 1 with a reduction in the upper right visual field).

Among children with congenital hemiplegia 7 reported no visual field defect and 4 a homonymous hemianopia (2 left; 2 right).

Based on the results of the visual field, we divided our cohort in four groups : 1) children with acquired hemiplegia with no visual field reduction; 2) children with congenital hemiplegia and no visual field reduction; 3) children with acquired hemiplegia and visual field reduction and 4) children with congenital hemiplegia and visual field reduction.

Visual search tests

We considered the RTs according to the target was in the ipsi-lateral (IL) or in the contra-lateral (CL) hemifield to the side of the lesion. In fig. 5.2 we reported our results in all the four single tests and a total score obtained by the mean values of RTs reported in all the four tests.

Table 5.1 Clinical data

Subjects	Gender	Assessment age (years)	Type lesion	Lesion	Localization lesion	Hemiplegia	Visual Field Defect
1	m	6	A	R	F,P, sc	L	-
2	f	8	A	R	sc	L	-
3	m	10	A	R	sc	L	-
4	m	9	A	L	sc	R	-
5	f	11	A	L	F, T, sc	R	-
6	m	11	A	L	sc	R	-
7	f	12	A	L	sc	R	-
8	f	10	A	R	sc	L	LHH
9	f	13	A	R	P, sc	L	ULQ
10	m	13	A	Bil > R	F, T, P, O, sc	L	LHH
11	m	10	A	L	sc	R	RHH
12	f	13	A	L	sc	R	RHH
13	m	14	A	L	F, T, P, sc	R	RHH
14	f	10	A	L	T, O, sc	R	URQ
15	f	6	C	R	sc	L	-
16	f	10	C	R	sc	L	-
17	f	10	C	R	T, sc	L	-
18	f	9	C; II	Bil >L	T, P, sc	R	-
19	m	10	C	L	F, T, P, sc	R	-
20	m	10	C	L	sc	R	-
21	f	10	C	L	sc	R	-
22	f	8	C	R	F, T, P, O, sc	L	LHH
23	m	11	C	R	T, P, O, sc	L	LHH
24	m	9	C	Bil >L	T, P, O, sc	R	RHH
25	m	15	C	L	T, P, O, sc	R	RHH

m=male; **f=** female; **A=** acquired; **C=** congenital; **F=**Frontal; **P=** Parietal; **T=** Temporal; **O=**Occipital; **R=** right; **L=** left; **LHH=**left homonymous hemianopia; **ULQ=** upper left quadrantopsia; **URQ=** upper right quadrantopsia; **RHH=**right homonymous hemianopia

Chapter 5

Side of brain lesion

No statistical differences were found between the side of brain lesion (left or right) and visual search scores, neither in children with acquired lesions nor in children with congenital lesions.

Visual search in patients without hemianopia

Children without hemianopia of both groups generally showed RTs within the 2 SDs for their age. Children with acquired lesions tended to have higher RTs than those with congenital lesions, although the differences did not reach significance
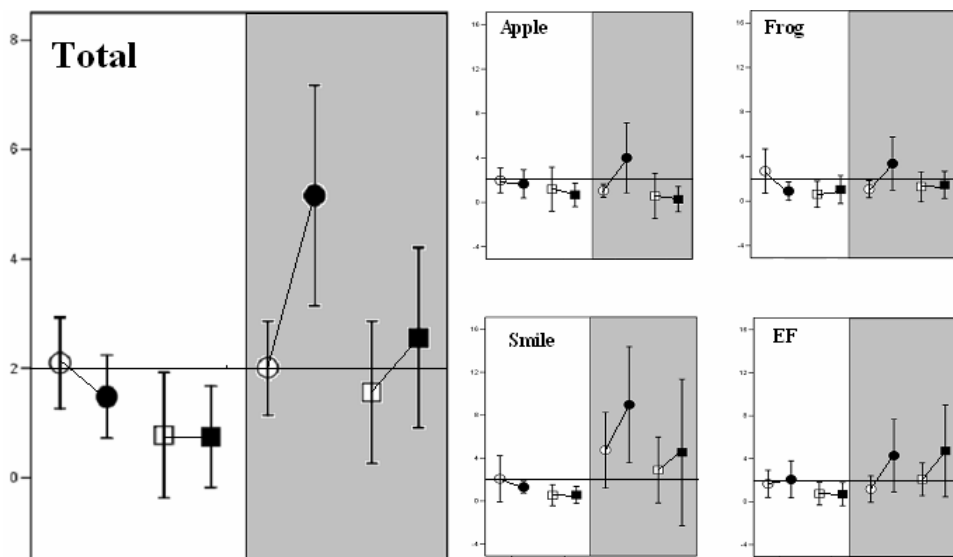

Fig. 5.2 Reaction times (RT) z-scores reported by children with acquired (circle) or congenital (square) children in the ipsi-lateral hemifield (empty symbol) or contro-lateral hemifield (full symbol). The white part indicates subjects without hemianopia and the grey part indicates subjects with hemianopia

values; they also reported higher RTs when exploring the ipsilesional hemifield, as opposed to the contralateral one, with differences that reached significant values for the Frog test.

Visual search in patients with hemianopia

Children with hemianopia of both groups generally showed RTs within the 2 SDs for the exploration of the ipsilesional hemifield and RTs above the 2 SD for the exploration of the

contralateral one. Children with acquired lesions showed higher RTs when exploring the hemianoptic field, contralateral to the damaged hemisphere, respect to the non hemianoptic field. This difference was observed in all tests and was statistically significant for the total assessment ($p<0.01$) and for the Smile test ($p<0.05$). Children with congenital lesions showed similar RTs when exploring the ipsilesional and the contralesional (hemianoptic) field, with the exception of the E/F test, where they showed significantly higher RTs for the hemianoptic field ($p<0.05$).

Number of correct responses

No statistical difference was reported among the four groups about the number of correct responses both for target both for catch trial.

5.2.3 Discussion

Our results suggest that children with unilateral acquired and congenital brain lesions and hemiplegia have a different strategy of visual search if they have HH or not. In particular for simplicity we will first analyse the subjects with brain lesions without HH and then, those with brain lesions and HH.

Children with acquired brain lesions but without hemianopia showed RTs at the upper end of the normal range. It is surprising that a difference was present between values at the ipsilesional visual field (longer reaction times) compared to the contralesional one (shorter reaction times). This was present in all the tests with the exception of the E/F, and was statistically significant when pooling the results of all the tasks together. This pattern of response was not observed in children with acquired brain lesions and no hemianopia by Netelenbos et al. [198] and Shatz et al. [199] who reported no deficits or more general abnormalities of visual search, particularly in children with right hemisphere damage. Conversely, our data are in accordance with Gainotti's studies [204, 205]. The author was able to show, in adult patients with unilateral brain damage, also ipsilateral disorders of the attention due to a widespread lowering of general attention. It may be thus suggested that the observed behaviour is the expression of a compensating strategy based on a more "top-down" cognitive approach on visual search, consisting in a preference in starting the exploration from the contralesional hemifield. At variance with Netelenbos and

Shatz's studies, all our patients presented with hemiplegia, contralateral to the damaged hemisphere and it can be hypothesised that the presence of motor impairment might explain the observed differences. Our children, being conscious of which one is the impaired motor side, can recall the attention quite in that direction, being sure that the other side is the "healthy"one. This mechanism remembers what has been suggested by Gainotti and co-authors for subjects with neglect [204]. In such cases the author hypothesised that as soon as the patient becomes conscious of the tendency to orient automatically his attention toward one half of the space he, intentionally, directs his attention to the contra-lateral half of the space, inverting the direction of scanning. This would also explain why in our cohort, the faster exploration of the contralesional field was present irrespective of the side of brain damage.

Children with congenital brain lesions without hemianopia have a visual search pattern similar to controls of the same age, with values within the two SD. No differences are present between the ipsilesional and the contralesional visual field in any of the four tests. They also show RTs which are generally shorter than those of children with acquired lesions and no hemianopia. Taken together these findings suggest a great deal of functional compensation following congenital damage, which results in better performance and lack of asymmetries.

Children with acquired brain lesions and hemianopia have "pathological" results in particular to the contralesional visual field. We found a statistical difference between values at the visual field ipsilateral to the lesion (shorter reaction times) respect to those at the contralateral visual field (longer reaction times). This pattern is similar in all the four tests and is in accordance with that reported in adults by Zhil who suggested a "slowness of vision" in the contralateral hemifield to the side of the lesion [195]. This "slowness" has been hypothesised to be linked to the use of hypometric saccades in the affected hemifield. Groner et al. [206], developed the concept of "local" and "global" saccades to indicate respectively saccades smaller than 1° and larger than 1.6° and Pambakian has shown that adult patients with HH have a lower ratio of global to local saccades toward their blind side. Probably this is the strategy utilized to explore all the hemianoptic visual field because children with visual field reduction have a general difficulty to have a spatial representation and so they need to explore all the parts of the screen, also when not necessary.

Children with congenital brain lesions and hemianopia have "pathological" RTs only in the contralesional visual field but less than children with acquired lesion. In fact the mean values -

ipsi and contra- are very similar, respect to children with acquired lesions. The only significant difference was found in the E/F test, the task with the highest density of distractors. It may be suggested that they are able to utilize successfully, despite their hemianopia, the low level visual information for "bottom-up" processing. This implies that the visual information can reach at some level the visual system and that this would be possible only in presence of a congenital lesion and a higher degree of reorganization capabilities. Since that in all our children with congenital hemiplegia and hemianopia the damage involves occipital cortex and optic radiations we can hypothesise that, this type of reorganization is possible only by means of the superior colliculus (SC). The SC is in fact an important oculomotor structure involved in the execution and initiation of saccades and in target selection [207] and is part of the colliculo-geniculo-pulvinar- extrastriate pathways that mediates some residual visual functions in hemianopia [208].

This is in accordance with a previous theory of Zihl [203] who found that, among adult subjects with hemianopia, a small part can show a spontaneous oculomotor compensantion mechanism. In these cases brain damage was limited to the optic radiations and/or the primary visual cortex, while in all patients with persistent impairment of visual exploration, the damage additionally involved either the posterior portion of the ipilateral thalamus (pulvinar nuclei) or the ipsilateral parieto-occipital cortex.

Futhermore, this is highly consistent with the animal model, and in particular with the studies by Payne and colleagues [40] who explored visually guided orienting behaviour in cats with congenital unilateral and bilateral occipital lesions. In cats with bilateral occipital lesions the authors demonstrated that trigger excitatory cortical pathways expanded beyond the intermediate layers and into the superficial layers of the superior colliculus. In cats with unilateral lesions they found also that the expansions of the capacity to orient might be augmented by additional direct excitatory crossed cortico-collicular projections from the intact hemisphere that add to the excitatory boosts provided by ipsilateral cortico-collicular expansions.

The investigation of this hypothesis will unquestionably be a central issue for future research in the field of child disability.

5.3 Visual search improvement in hemianopic children after audio-visual stimulation: differences between children with congenital and acquired lesions

It is well recognized that the possession of multiple ways of sensing the world offers many potential benefits [209, 210]. In the last years, a vast body of evidence has been provided about the ability of our brain to take advantage from the integration of information derived from different sensory modalities [209-211].

Neurophysiological studies in animals [209] have shown, in superior colliculus (SC) and regions of the cortex, the existence of neurons responding to stimuli from different sensory modalities. In particular, multisensory neurons form a major component of the output circuitry of SC, since nearly three-quarters of the SC's neurons with descending efferent projections to brain stem motor areas are multisensory. Thus, multisensory integration might play a significant role in behaviours mediated by the SC, such as the attentive and orientation behaviours as well as saccadic eye movements [212].

Recent behavioural studies in humans have documented that audio-visual interaction can improve visual detection [213-216], and visual localization [217] and reduce saccadic reaction times (RTs) [218-222]. In particular, it has been found that a sound, spatially and temporally coincident to a visual stimulus, can improve visual perception in the blind hemifield of hemianopic patients [223].

In 2005, Bolognini et al. [224], developed a new rehabilitation approach based on the audio-visual stimulation of the visual field and they applied this method to eight subjects with a visual field reduction due to an acquired lesion in adult life. The results showed a progressive improvement of visual detection during the training and an improvement of visual oculomotor exploration that allowed patients to efficiently compensate for the loss of vision. They found also, a transfer of treatment gains to functional measures assessing visual field exploration and daily-life activities, which was found stable at 1 month follow up control session.

Based on these findings, we investigated the possibility to induce a long lasting amelioration of visual field defects also in children with the same deficit. We were interested i) to explore if

this type of treatment was efficient also in children with visual field defect and ii) to evaluate if there were different responses in children with acquired lesions respect to children with congenital lesions. If our hypothesis about plasticity mechanisms based on superior colliculus .is right, for subjects with congenital hemiplegia and hemianopia (see par. 5.2.3), we expect that children with congenital lesion have no improvement after this type of treatment.

5.3.1 Subjects and Methods

Subjects

Selection of patients was based on complete availability of visual perimetry. Four children with chronic visual field defect participated in the study: 3 with acquired brain lesions (G1) and 1 with congenital lesion (G2). Details concerning sex, age, lesion sites and the presence of visual field defect are reported in Table 5.2. The patients had suffered unilateral lesion in the right or left posterior hemisphere, as confirmed by MRI scanning (see Fig. 5.3).

Patients showed a normal hearing, as measured by audiometry in each ear, with no sign of asymmetry between ears, and a normal or corrected binocular visual acuity for near and far space. Patients with neglect were excluded from the study. All patients underwent a computerized visual field test and a neuropsychological examination of visual field disorders that consisted in the assessment of i) correct number of visual detections; ii) visual search abilities and iii) reading speed.

Table 5.2 Summary of the clinical data

Lesion	Sbj(s)	Age at test (gender)	Age of lesion	Side of lesion	Type of lesion	Visual Field defect
Acquired (G1)	C.T.	15 ys (m)	14 ys	Left	C, sc	Right Hemianopia
	I.A.	10 ys (f)	9 ys	Left	C, sc	Right Henianopia
	M.L.	17 ys (f)	16 ys	Right	C, sc	Left Heminaopia
Congenital (G2)	F.A.	12 ys (m)	0 ms	Right	C, sc	Left Hemianopia

Sbj(s) = subjects; **G1**= Children with acquired brain lesions; **G2**= child with congenital brain lesion; **ys**= years; **m**= male; **f**=female; **C**= cortical; **sc**=subcortical
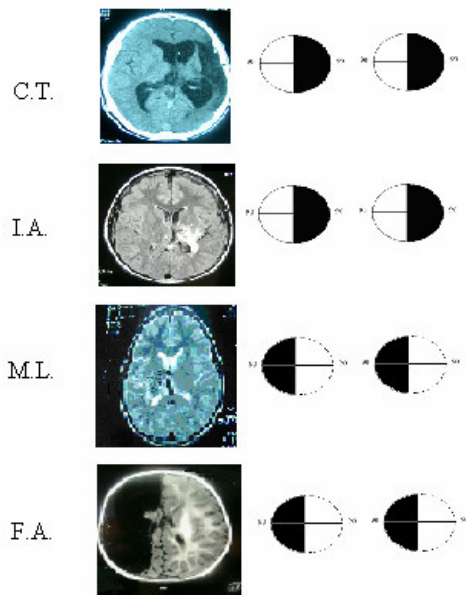
Fig. 5.3 MRI and visual field of each subjects

<u>Visual detections</u>

Unimodal visual test

Visual detections were assessed by using the apparatus employed for the presentation of the training procedure (see Fig. 5.5). A visual target was presented for 100 ms in different spatial positions, at 8, 24, 40 and 56 degrees from either side of the central fixation point. One hundred eighty trials were presented: 8 trials for each of the 8 visual positions and 16 trials in which no visual stimulus was presented, i.e. catch trials. The total number of trials was equally distributed in three blocks. Patients were instructed to press a response button after the detection of the targets and visual detections for each spatial position were recorded.

In order to investigate whether patients were able to compensate for the visual field loss by using eye movements, patients underwent each test under two conditions. In the Eye-Movements Condition, patients were free to use eye movements to detect the visual target. Otherwise, in the

Fixed-Eyes Condition, eye movements were not allowed and the fixation was monitored by the experimenter.

Visual search

Visual search test consists of six subtests (all modified by Zihl, 2000 [203]): the Apple test, the Frog test, the Smile test, the E–F test, the Triangles test and the Number test.

For details about the first four subtests see par. 5.2.1.

Triangles test (Fig. 5.4): patients were shown stimulus arrays, each containing 21 stimuli, distributed at random over the array and presented on a black background. Different shapes of the same size were used as stimuli: yellow squares as distracters and yellow triangles as targets. The number of targets presented in each trial varied from 0 to 6. As the number of targets increased, the number of distracters decreased, thus in each stimulus array there were always 11 stimuli. The total number of trials was 11. Patients were instructed to fixate a red cross presented in the centre of the slide (i.e. fixation point) and, after the disappearance of the cross, to search and report the total number of targets. Moreover, after having found a target, patients had to indicate it by using a light pointer. Correct responses and time for searching performance were recorded.

Numbers test (Fig. 5.4) : Eight stimulus arrays, each containing 10 numbers (from number 1 to 10) distributed at random over a black background, were presented. The task was to point to the individual numbers in an ascending order using a light pointer. Time for error-free searching performance was recorded.
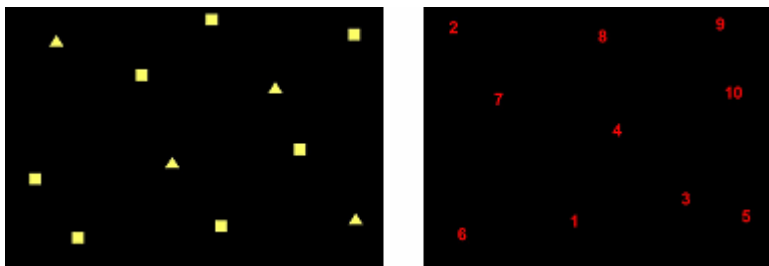

Fig. 5.4 Visual search: Triangle test and Number test

Patients were shown the stimulus arrays (52° · 45°, horizontally and vertically respectively) projected on slides at a distance of 120 cm and they were required to actively explore the visual field by using eye, but not head, movements to search for visual targets.

Reading speed

Lecture of a simple text was made for a time of 120 seconds. The number of errors and the syllables read for second was then calculated. We asked the child to read with fixed head but free of moving his/her eyes.

3.3.2 Audio-visual training

Apparatus and stimuli

The apparatus consisted of a semicircular structure in which the visual and the acoustical stimuli were positioned. The apparatus was a plastic horizontal arc (height 30 cm, length 200 cm) fixed on the table surface. The acoustical stimuli were eight piezoelectric loudspeakers (0.4 W, 8 V), located horizontally at the subject's ear level, at an eccentricity of 8, 24, 40, 56 degrees in the hemianopic hemifield and in the intact hemifield. The loudspeakers were covered by a strip of black fabric, attached to a plastic arc, preventing any visual cues about their position. The sounds were created by a white-noise generator (80 dB). Six visual stimuli were located directly in front of the loudspeakers: the light displays, poking out of the black fabric, were placed at an eccentricity of 24, 40 and 56 degrees to either side of the fixation point. Note that we refer to the auditory positions by labels A1–A8 moving from left to right, and similarly we described the corresponding visual stimuli positions by labels V1–V6 (see Fig. 5.5).

The visual stimulus consisted of the illumination of the red LED (luminance 90 cd m^{-2} each). The visual stimulus and the acoustical target had the same duration of 100 ms. Timing of stimuli was controlled by a computer, using a custom program (XGen-Experimental Software, http://www.psychology.nottingham.ac.uk/staff/cr1/) and a custom hardware interface.
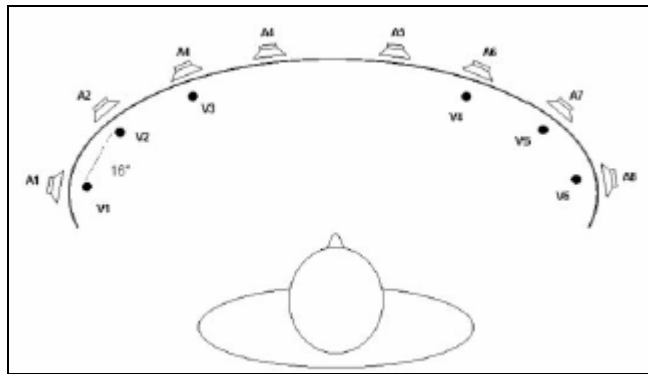
Fig. 5.5 Bird's eye schematic view of the position of loud speakers and light displays.

Training procedure

Patients sat on a chair in at 70 cm in front of the apparatus, facing straight ahead, with their body midline aligned with the centre of the apparatus. To present visual targets in the blind region of the visual hemifield, the central fixation point was moved along the central vertical axis of the apparatus. The fixation point was on the median plane for patients with homonymous hemianopia. Patients were required to look at the fixation point, a white star, and to explore the blind hemifield by shifting their gaze towards the visual stimulus, without head movements. They were instructed to detect the presence of the visual target by pressing a button and to ignore the auditory stimuli, since they were not predictive of the presence of the visual target. Before each trial, fixation was monitored visually by the experimenter standing behind the apparatus, facing the subject. The experimenter starts each trial only after the correct posture was achieved. The treatment was carried out under binocular conditions.

Three different kinds of sensory stimulation were presented: (i) unimodal visual condition, in which only the visual target was present; (ii) unimodal auditory condition, in which only the auditory stimulus was present, i.e. catch trial; (iii) crossmodal visual-auditory condition: a sound presented together with the visual target. In the crossmodal conditions, the sound could be presented either in the same position of the visual stimulus, i.e. spatially coincident crossmodal condition (SP), or in a different position, i.e. spatially disparate crossmodal condition, at 16 and

32° of nasal (16n, 32n respectively) or temporal (16t, 32t respectively) disparity from the visual target.

During the training, the hemianopic hemifield was more intensively stimulated than the intact hemifield. For each block, 48 trials were presented: 9 unimodal visual trials (6 trials for the hemianopic hemifield and 3 for the intact hemifield); 8 unimodal auditory trials (6 for the hemianopic hemifield and 2 for the intact hemifield); 8 crossmodal spatially coincident trials (6 for the hemianopic hemi- field and 2 for the intact hemifield); 23 crossmodal spatially disparate trials (20 for the hemianopic hemifield and 3 for the intact hemifield). The number of blocks varied for each patient, depending on individual progress in each stimulus onset asynchrony (SOA) session (see below).

Since visual exploration in hemianopic patients is usually difficult and time-consuming, the training was rendered less difficult by having different temporal intervals between the two stimuli. Thus, the training was divided in six sessions with different temporal intervals (SOA) between the acoustic and the visual stimulus. The treatment started with 500 ms of SOA, i.e. the auditory stimulus preceded the visual target 500 ms, and the SOA was reduced in steps of 100 ms (i.e. 400, 300, 200 and 100 ms) up to the last session of the training, in which the stimuli were simultaneous (i.e. 0 ms of SOA). Each SOA session terminated when a hit ratio of at least 50% in unimodal visual condition was obtained. Once the patient reached this criterion, the next SOA session began.

The treatment finished when patients detected >50% of unimodal visual stimuli for three consecutive blocks of trials in the simultaneous presentation of audio-visual stimuli (last SOA session). This percentage, although it represents a low level of performance, was positively correlated with visual search amelioration in an adult pilot experiment [126, 224] aimed to establish the criterion for the end of the treatment.

It is worthwhile to remember that due to the target exposition time (100 ms), the task was very difficult for the patients.

Each daily session lasted about an hour and a half, separated by some breaks according to the patients' performance and tiredness. The duration of the training was between 3 and 4 weeks.

In accordance with Bolognini et al. [224] the training was done in a low illuminated and sound attenuated room for children with acquired lesions.

In the child with congenital lesion it was necessary to do the same training, instead, in more difficult condition - an illuminated room- otherwise he was able to perceive the red light giving a lot of correct answers.

<u>Testing procedure</u>
Treatment efficacy was evaluated by using a multiple-baseline design. Each patient was tested before the treatment, after treatment and after a resting period of 1 month. In one case (C.T.) we were able to do a follow up till 12 months.

5.3.3 Results

All the analyses were carried out using different ANOVAs. Whenever necessary, pairwise comparisons were conducted using Newman–Keuls test.

<u>Assessment of visual detections</u>
For each group of patients (G1 and G2), the improvement of visual detections was assessed by using a two-way ANOVA on the percentages of visual detections to stimuli presented in the hemianopic hemifield in two tests (Unimodal Visual Field test). Since all patients had an almost correct performance in the intact hemifield (near 100% of visual detections), the analyses were conducted only for the impaired hemifield. The main factors were Condition (Eye Movements and Fixed-Eyes) and Session with the following conditions: baseline, post-training, 1 month post-training conditions both for children with acquired lesions (G1) both for the child with congenital lesion (G2).
 In the Unimodal Visual test, the interaction Condition · Session was significant in G1 [F =22.775, P < 0.000] while it was not significant in G2 [F = 0.989, P= 0.409] (see Fig. 5.6 a and b).

<u>Visual Search</u>
For each subtest of the Visual Search test, percentages of correct responses was always cery high (near 100%), so we didn't do any statistical analysis. RTs were instead analysed separately for

the two groups of patients (i.e. G1 and G2) by using different one-way ANOVAs with Session as main factor (baseline, post-training, 1 month post-training conditions).
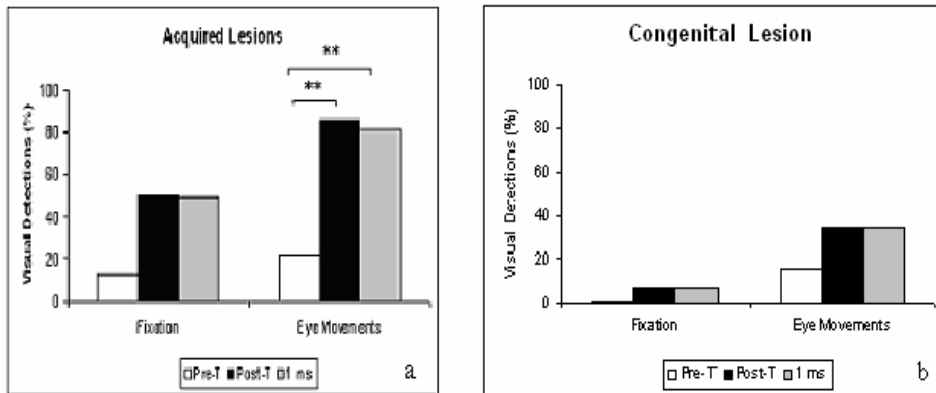

Fig. 5.6 Unimodal visual test. (a) Mean percentages of visual detections in the different evaluations for the group G1. White bars = baseline; black bars = post-training; grey bars = 1 month post-training. On the left, patients' performance in Fixed-Eyes Condition; on the right, patients' performance in Eye Movement Condition. The asterisk indicates a significant difference between conditions: **$P < 0.005$ (b) Mean percentages of visual detections in the different evaluations for G2.

For Apple test, Frog test, Triangles test and Numbes test, the main factor Session was significant in G1 (children with acquired lesions) when RTs were considered and the significant post-hoc comparisons are reported in Fig. 5.7 A-B). Also in the two tests Smile an EF, RTs are decreased in the post-training and in 1 month post-training condition but not in a significant way.

In the case C.T., in which we have a follow up at 12 months from the baseline, the results reported in the post-training and 1 month post-training conditions are confirmed.

In G2 (child with congenital lesion) the effect of Session was significant only when RTs were considered in the Triangle test; in all the other tests non effect of session was found (Fig. 5.7 C–D).

Reading speed

A little improvement has been identified in reading speed in children wit acquired lesion (G1), with values of 2,06 sillables/sec at the baseline evaluation to 2,6 sillables/sec after treatment and 1 months after training (see Fig. 5.8).

No improvement has been identified in the child with congenital lesion (G2) with values of 3,37 at the baseline to 3,45 sillables/sec after treatment.
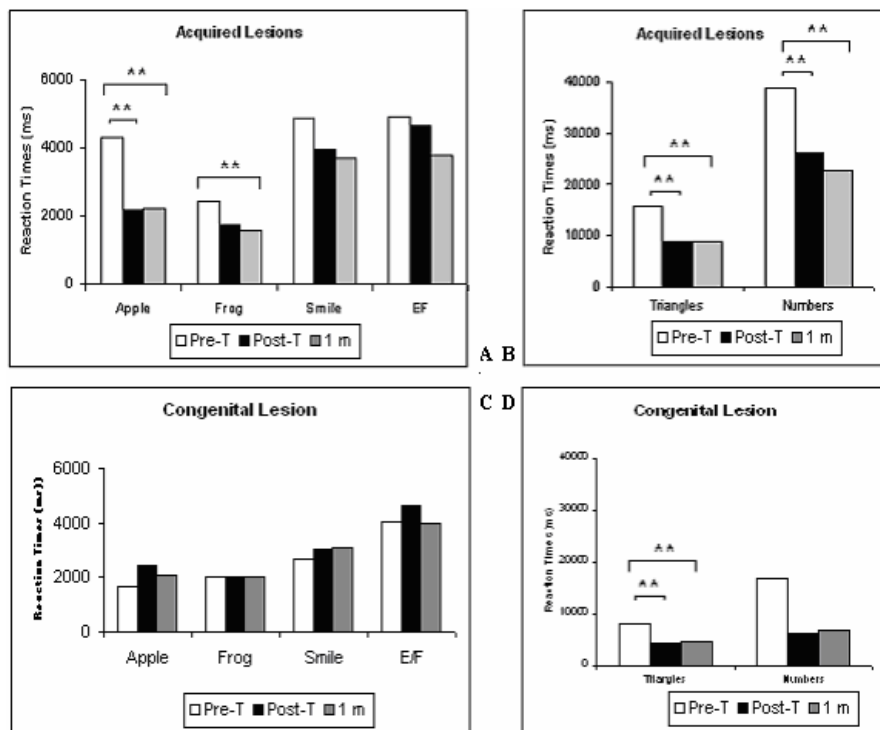
Fig. 5.7 Visual search tests: A) Mean RTs in the Apple, Frog, Smile and EF test for group G1 (children with acquired lesions); B) Mean RTs in the Triangles and Numbers test for group G1; C) Mean RTs in the Apple, Frog, Smile and EF test for group G2 (child with congenital lesion); D) Mean RTs in the Triangles and Numbers test for group G2. White bars = baseline; black bars = post-training; grey bars = 1 month post-training. The asterisk indicates a significant difference between conditions: **$P < 0.005$.
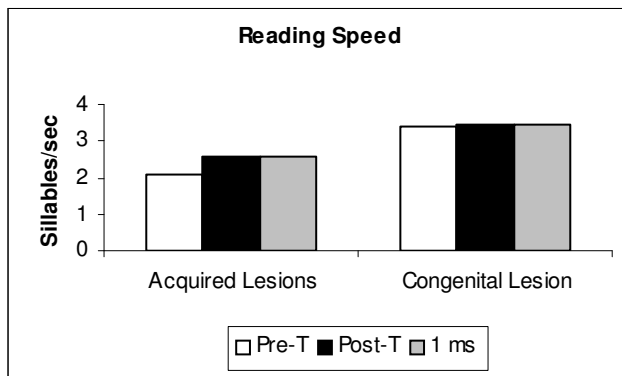
Fig. 5.8 Reading speed in children with acquired and congenital lesions

5.3.3 Discussion

The mechanism of multisensory integration might become particularly important when a sensory modality is damaged; the possibility to integrate sensory inputs from different sensory modalities, related to the same external event, can enhance the impaired unimodal processing, improving the perception of sensory events difficult to be perceived unimodally due to the unimodal sensory defect. So, in this study we have evaluated the possibility to utilize multisensory integration to compensate visual field deficit such as hemianopia in children both with acquired lesions (as adults) and congenital lesion (only one child).

Our results are in accordance with those on adults by Bolognini et al. [224] but only in children with acquired brain lesions. We found instead a different behaviour in the child with congenital lesion.

Children with acquired lesions, as adults [224], improved in the test assessing the number of visual detections (i.e. Unimodal Visual test), when they were let free to use eye movements to perform the tasks (Eye-Movements Condition). Only a little improvement, but not in a statystical way was present when we asked to the children to keep their eyes fixed on the central point. These results are in line also with a previous study on patients with hemianopia [225], in which saccades were trained with compensatory visual field training on a large training board: after the training, the authors found a marked improvement of detections and RTs only when patients use explorative eye movements, but not with eyes fixating. In the present study, the

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improvement obtained after the treatment did not only involve visual detections, but also the visual search behaviour. The improvement of children's performance was highly consistent across about all the tests assessing visual exploration (Visual Search tests), as documented by the reduction of visual scanning times obtained after the treatment. Children's visual search behaviour became more efficient and faster after the treatment, probably implying an enlargement of the search field, defined as the size of the visual field that a patient can actively scan via eye movements [226].

The amelioration of children's performance can be explained, as in adults, with the implementation of the oculomotor system: multisensory integration might have enhanced the responsiveness of the oculomotor system, reinforcing orientation towards the blind hemifield and oculomotor visual exploration mediated by multisensory structures, such as the SC [227]. Thus, the multisensory implementation of the oculomotor system allows patients to detect the presence of visual events in the affected areas both with a bimodal and unimodal stimulation. The important role of the oculomotor system in mediating the amelioration induced by the audio-visual training is suggested by the results obtained by patients in tests assessing visual disorders. In contrast, a weak or no amelioration at all was found in the same tests under the condition with fixed-eyes. The discrepancy between the two conditions suggests that the amelioration in visual perception induced by the training is not due to an enlargement of the visual field, but it is mostly mediated by the oculomotor system.

The amelioration of visual exploration had also positive consequences on reading speed: after the training, we observed an improvement of single word reading performance in all the three children. Finally, we were able to demonstrate that the treatment effects are stable, at least till 12 months after the beginning of the training.

We have already said that the child with visual field defect due to congenital lesion has a different response to audio-visual training. In the test assessing the number of visual detections (i.e. Unimodal Visual test), there was only a little improvement in the condition in which he was let free to utilize eye movements, but not in a statistical way. No improvement was found with fixed eyes. Also in all the tests assessing visual exploration (Visual search tests) was found no improvement in RTs except for Triangles test.

An interesting thing, is, otherwise, that if we look at the RTs recorded in all the visual search tests by this child at the baseline session (i.e before the training), we see that they are very similar to those recorded by children with acquired lesions after training session. We also must remember that in condition of dark light this child was able to respond in a correct way also to the Unimodal Visual test, so we have been obliged to do the training with the lights on. This suggests that the child with congenital lesion probably has already activated, in a spontaneous way, an efficient compensantion mechanism. This is in accordance with what has been so far studied only in animal models and, nobody, till now, had investigated on human children. Payne [40], has demonstrated that cats with occipital unilateral lesions sustained during the first postnatal week (P1–4), or at the end of the first postnatal month (P27–30), orient to stimuli presented in the contralesional field as proficiently as to stimuli introduced into the ipsilesional field. The author postulated that the greater sparing is based on modifications in both excitatory and inhibitory circuitry linked to the intact hemisphere, with particular regard to additional direct excitatory crossed cortico-collicular projections from the intact hemisphere that add to boosts provided by ipsilateral cortico-collicular expansions.

In conclusion our results suggest that audio-visual training can induce a long-lasting (at least 12 months) activation of visual responsiveness of the oculomotor system only in children with acquired lesions and no spontaneous recovery and that this mechanism is probably mediated by the intact SC, while no efficacy has on children with congenital lesions were, probably, adaptive plasticity mechanisms has been already activated at birth.
Obviously, other studies are necessary to confirm this hypothesis and more patients must be studied.

Chapter 6

Ongoing studies on the reorganization of visual cortex in children with hemianopia due to congenital cerebral lesions: the role of fMRI

6.1 Introduction

When a brain lesion involving the visual system occurs at either a cortical or subcortical level, the target of restorative central nervous system (CNS) plasticity would be to ensure the recovery of visual function: this target can be achieved either by functional compensation coming from spared structures or by a restoration or a rebuilding of the damaged ones, or both.

Functional compensation by intact structures may be obtained when alternative and spared cortical areas take over the functions formerly assumed by the damaged structures, resulting either in the restoration of the impaired function or in the development of alternative behavioural strategies.

Structural reorganisation mainly consisting on the reconstruction of a neuronal network or disrupted connections by synaptogenesis and axonal or dendritic sprouting, may also be involved in the restoration of visual function. All this is now clear for motor function since that local axonal sprouting, long-distance axonal elongation and synaptogenesis have in fact been clearly demonstrated in adjacent cortex and undamaged hemisphere of adult rats subjected to stroke, suggesting that structural plasticity may take place even when the injury occurs after the end of the developmental period [228]. Less clear is what happens to the visual system.

Plasticity in the visual cortex has been described in several primate studies but little has been published and studied about the capacity of the human primary visual cortex to undergo long-term functional reorganization.

The aim of this chapter is to explore what happens at cortical level in hemianopic children. Recently, neuroimaging studies [229] have indicated residual responsiveness to blind hemifield stimulation in the extrastriate cortex of the unaffected hemisphere in adult patients with vascular or surgical lesions (acquired lesions) [230, 231], so we first describe the study of Nells and co-authors and then we'll report our experience in a child with hemianopia due to neonatal arterial infarction (congenital lesion).

6.2 Cortical activation in hemianopia after stroke in adult patients

Nells et al. [231], enrolled thirteen stroke patients (median age 60 ys), and investigated patterns of brain activation in those patients with post-stroke visual field defects after a single occipital cortex stroke. He found interesting results that we'll briefly resume first in controls then in stroke patients.

As expected, during stimulation of either hemifield in control subjects maximum increase of rCBF was seen in the contralateral primary visual cortex. This area of maximum rCBF changes also extended to the peristriate and extrastriate cortex covering Brodmann areas 18 and 19. Weaker and much smaller activation was also found in the extrastriate cortex ipsilateral to the side of stimulation (Fig. 6.1).
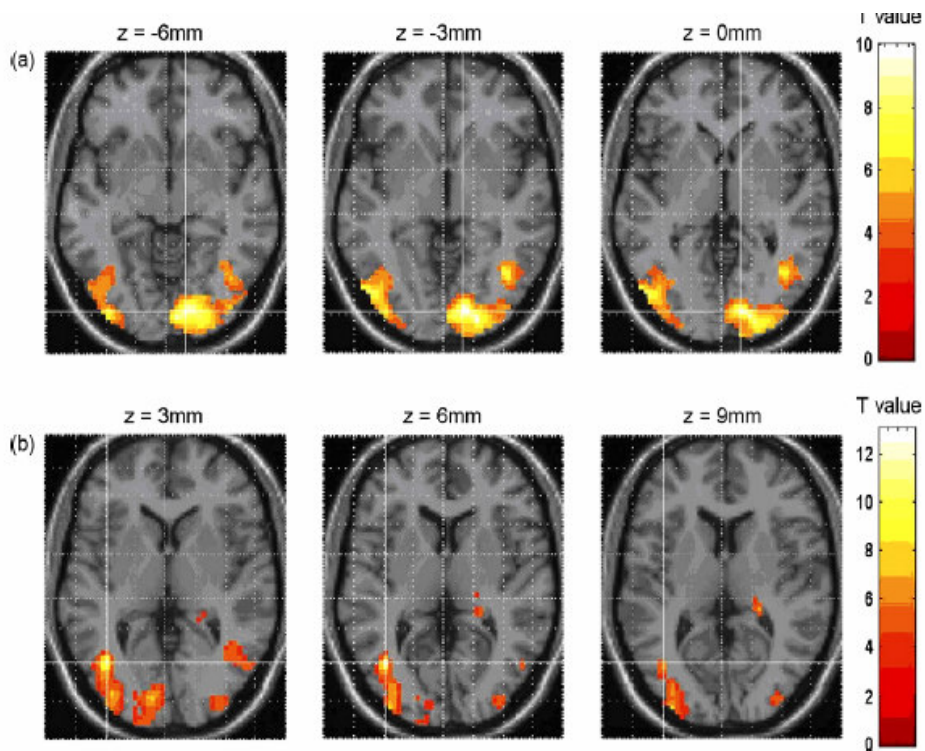
Fig. 6.1 Activation during hemifield stimulation in control subjects (hemifield stimulation vs. rest): (a) stimulation of left hemifield, (b) stimulation of right hemifield.

During stimulation of the unaffected (left) hemifield in patients, an area of maximum activation was again observed in the contralateral primary visual cortex (Fig. 6.2 a). As in normal subjects, activation also involved the peristriate and extrastriate cortex. During stimulation of the hemianopic (right) hemifield bilateral activation of the extrastriate cortex in areas 18 and 19 was found. The extrastriate activation of the ipsilateral hemisphere extended medially towards area 17, but the ipsilateral primary visual cortex did not show significant increases in blood flow. The contralateral primary visual cortex was not activated (Fig. 6.2 b).
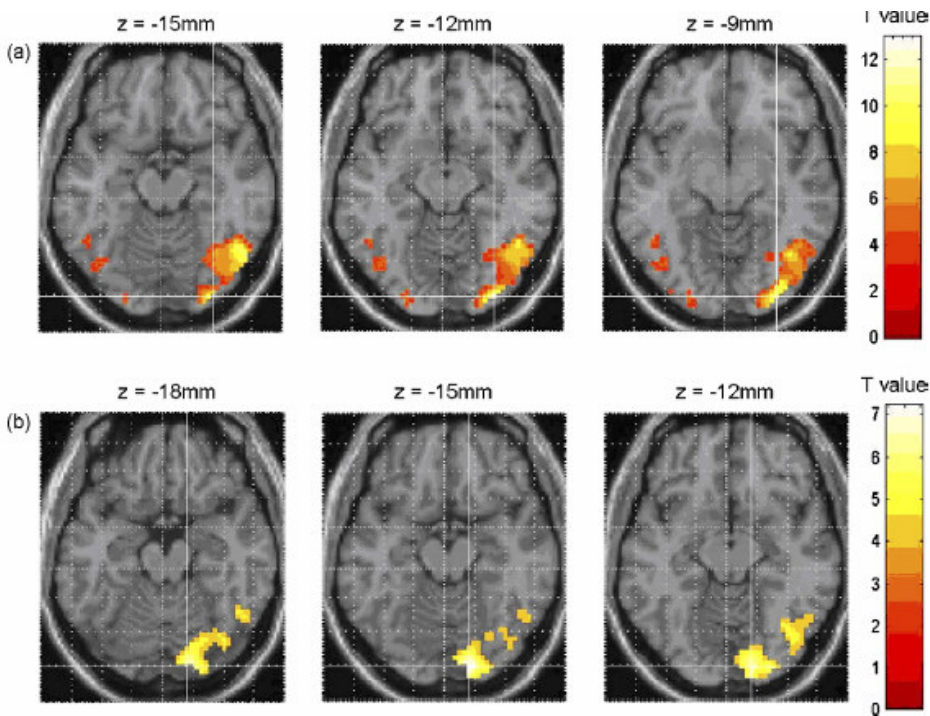
Fig. 6.2 Activation during hemifield stimulation in stroke patients with right-sided hemianopia (hemifield stimulation vs. rest). (a) Stimulation of the unaffected (left) hemifield and (b) stimulation of the hemianopic (right) hemifield.

Areas that were significantly more activated in stroke patients compared to normal subjects during stimulation of the hemianopic (right) field were identified by subtracting increases of rCBF during right hemifield stimulation in normal subjects from those in patients. In this analysis, significant increases of rCBF were found in BA 18 of the ipsilateral extrastriate cortex (Fig. 6.3 a). Conversely, areas that were significantly more activated in normal subjects compared to stroke patients during stimulation of the right hemifield were identified by subtracting increases of rCBF of patients from those of normal subjects. In this analysis, significant increases of rCBF were found in the contralateral primary visual cortex, area 17 (Fig. 6.3 b).
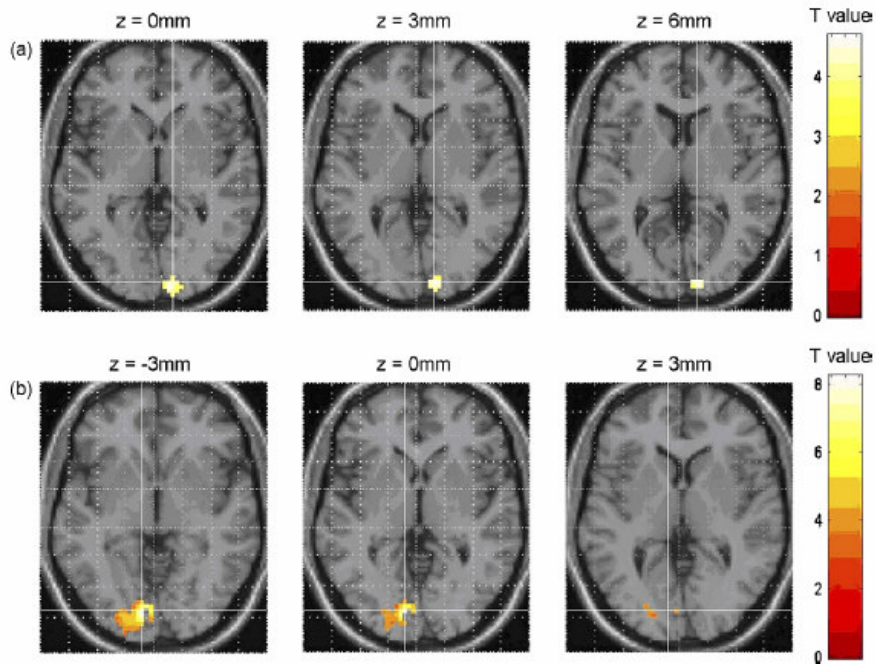
Fig. 6.3 Differences in cortical activation during hemifield stimulation of affected (right) side in patients vs. right side in control subjects, multi-group study, $P < 0.001$. (a) relative activation of patients in the ipsilateral extrastriate cortex and (b) relative activation of control subjects in the contralateral primary visual cortex

Stimulation of the hemianopic side in patients with occipital strokes induced ipsilateral (contralesional) activation of the extrastriate visual cortex. This pattern of activation was different to that seen in normal subjects where contralateral activation of striate and extrastriate regions was the main finding, but these data are in accordance with previous studies in patients with other cerebral lesions such as hemispherectomy [230] and a developmental anomaly of the visual cortex [232] where ipsilateral activation of the visual cortex has been reported .

Chapter 6

6.3 Cortical activation in a child with hemianopia due to congenital cerebral lesion

To our knowledge nobody has till now investigated what happens in children with hemianopia and if there are differences between subjects with congenital lesions and subjects with acquired lesions (as adults) even if early in life. As described above (par 3.2 and 3.3) they develop different compensation mechanisms, more efficient in those with congenital lesions who have a "normal life" and less efficient in children with acquired lesions with problems in daily life activities (more similar to adult behaviour). So we decided to study, with a similar paradigm to that describe above, one child (twelve years old) with right congenital lesion (neonatal arterial infarction) and left hemianopia.

6.3.1 Methods

BOLD responses were acquired by 1.5 T General Electric LX Signa Horizon System (GE, Milwaukee, USA), equipped with Echo-speed gradient coil and amplifier hardware, using a standard quadrature head-coil. Activation images were acquired using echoplanar imaging (EPI) gradient-recalled echo sequence (TR/TE/flip angle=3s/50ms/90°, FOV=280x210 mm, matrix=128 x 128, acquisition time: 3'12''). Volumes consisted in 18 contiguous 4 mm thick axial slices, covering from the inferior temporal-occipital edge to the middle-parietal region (from about z -28 to 45 mm), acquired every 3 sec. Time-course series of 64 images for each volume were collected in the 6 epochs. The first epoch lasted 12 sec more to allow the signal to stabilize and this initial period was eliminated from any successive analysis. An additional set of anatomical high resolution 3D FastSPGR data set (TR/TE/flip angle = 150 ms/2.3ms/120°; RBW=12.8 kHz; FOV=280x280 mm, matrix = 256x256; isotropic dimension: 1.1 mm, NEX:2; Acq.Time:12'26''min), was acquired in order to generate a 3-dimensional whole brain recontruction and a bi-commensural axial projection to estimate the anatomical Talairach coordinates [138]. For generating a statistical map of the BOLD response, Brain Voyager 2000 4.6 software package (Max-Planck Society, Germany and Brain Innovation, Maastricht, the

Netherlands) was used. All volumes from each subject were adjusted with the application of rigid body transforms for residual motion-related signal changes. Functional data were smoothed spatially (Gaussian kernel with a 4-mm full width at half maximum) but not temporally. Statistical activation maps were obtained using cross-correlation or General Linear Model analysis, with thresholding at $p<0.0022$ with cluster size limit of two voxels. EPI images were co-registered with the 3D anatomical data in order to define the Talairach-Tournoux coordinates. The stimuli were random dot kinematograms, similar to those used to measure coherence sensitivity (50 dots, 300 ms life-time, 1 deg diameter dot size) randomly stimulating each one of the four quadrants. Stimuli were presented on LCD goggles (Resonance Technology) with a visual field of 22 X 30° and a luminance of about 30 cd/m2. The resolution of the display was 600 X 800 pixels with refresh rate of 60 Hz.

The research project was approved by the Ethical Committee of the Stella Maris Scientific Institute. Informed consent was obtained from all parents and from the children.

6.3.2 Results

During stimulation of the hemianopic (left) hemifield bilateral activation of the extrastriate cortex in areas 18 and 19 was not found. The extrastriate activation of the ipsilateral hemisphere extended medially towards area 17, and also the primary visual cortex showed significant increases in blood flow but the contralateral primary visual cortex was not activated (Fig. 6.4)
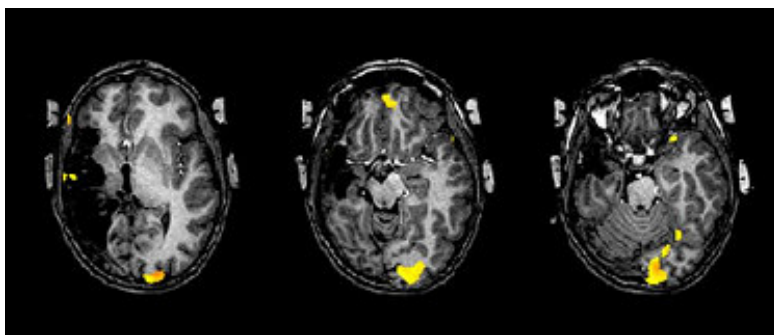

Fig. 6.4 Activation during hemianoptic hemifield stimulation in child with right congenital lesion and with left-sided hemianopia (hemifield stimulation vs. rest).

During stimulation of the unaffected (right) hemifield an area of maximum activation was again observed in the contralateral primary visual cortex. As in normal subjects, activation also involved the peristriate and extrastriate cortex.

6.4 Conclusions

The bilateral extrastriate activation in healthy individuals can be attributed to transcallosal transfer in response to unilateral presentation of visual information [233]. It is a remarkable fact of the human brain that the widely distributed occipital fibers converge to cross the callosum as a compact fiber bundle confined to the splenium as demonstrated by Dougherty 2005 a and b [81, 82] by means of DTI techniques and that the organization and information carried by these fibers is of great interest for visual recognition and identification [234, 235].

The ipsilateral extrastriate activation of the intact hemisphere, in the absence of contralateral striate activation, is a distinct finding during stimulation of the hemianopic field of patients with both congenital and acquired lesions. Several mechanisms may explain the ipsilateral activation of the visual cortex. As in control subjects, the activation could result from pre-existing transcallosal pathways. The extent of ipsilateral processing, however, differed between stroke patients and control subjects. Whereas stimulation of either side in controls and of the unaffected side in patients showed predominant contralateral activation, stimulation of the hemianopic side in patients induced relatively stronger ipsilateral activation.

An alternative interhemispheric connection in processing visual information may occur via the superior colliculi. Postmortem studies in man suggest that visual information may cross at the collicular level and bypass the striate cortex [236]. There is also evidence from studies of event-related potentials and event-related magnetic fields for a direct thalamic functional pathway to extrastriate visual areas [108].

Chapter 7

Summary and conclusions

During the past two decades, it has been learned a great deal about the plastic capacities of the connections in the animals, shown that the wiring is adaptive and that it results in functional neuronal compensations and the sparing of visually guided behavior. These advances have been possible because of the great suitability of the cat, its visual system, and its developmental program to intervention by experimentalists. Although these studies have intrinsic merit, they also have a broader context and applicability for increasing our understanding of the repercussions of early lesions, in other parts of the cerebral cortex, and on their associated systems.

Even with the progress that has been made in recent years, a lot is always unknown in particular for the human brain. Studies on animals, have shown that normally highly localizable functions of the cerebral cortex can become remapped across the cortical surface as a result of the early lesion. In so doing, the remappings produce a different brain. However, it is not known if there is a price to pay, or if functions are crowded out, when one lobe contributes to neural processing normally localizable solely within another lobe.

These mechanisms of response to injury appear to be, to some extent, more effective in the young brain, and this has been demonstrated also in the human brain, for example, by the development of normal language skills following an early damage to the dominant hemisphere. However, the mechanisms of functional reorganisation after early lesions have shown to be far more complex and multifaceted than originally thought, and many questions are still standing. What is it about the young cerebral cortex that makes it different from the mature cerebral cortex in the way that it responds to damage? What are the types of neural processes and behaviours that are normally spared, and what are those permanently impaired? What are the repercussions

of early lesions on neurons, brain pathways, neuronal properties, and activity levels? What are the other factors beside timing that can influence the quality of plasticity? May the treatment induce funcitonal reorganization? These and other questions are being addressed in the present time.

In consideration of the actual knowledge concerning the mechanisms of response to brain damage, the aim of our work has been to study the correlation between the characteristics of early brain lesions in children born at term or preterm and the functional outcome with particular regard to visual functions. We tried to cover 2 main topics: i) the effect of the extension of the lesion - bilateral versus unilateral congenital brain lesions- and ii) the effect of the timing of lesion -congenital unilateral brain lesions versus acquired unilateral brain lesions-. Obviously also in the case of acquired lesions the damage was within the paediatric age and for this reason we can consider it an early damage.

The first step of our analysis has been the selection of patients and the characterisation of their brain lesions. Thus we had the possibility to study a population of infants and children with a full definition of their initial lesion and their early clinical evolution.

The effects of the early (congenital) bilateral brain damage

The pattern of brain damage has been classified according to specific criteria which include the involvement of the white matter, of the grey matter and the integrity of corpus callosum. In the context of this framework, it has been possible to investigate the correlations between these patterns of lesion following periventricular leukomlacia and the visual evolution, with particular regard to visual acuity and different types of "higher level" visual function involving the dorsal and the ventral stream.

As a general result, our studies confirmed the low potential of functional reorganisation after bilateral brain damage, as only children with normal MRI or very mild changes developed normally. However, the different pattern of extension of the lesion showed highly specific features. About visual acuity for example, we investigated the interrelation between the type of

damage and the specific mechanisms underlying visual responses explored by two techniques – electrophysiological (VEP) and behavioural (PL)- that are thought to involve the central nervous system at different levels. The first tecnique is able to assess the pathway conduction and the cortical activity of the primary visual cortex, being so mainly dependent from the integrity of the central visual structures [77, 78], while the second is based on behavioural responses with gaze/attention shift and target exploration, and thus also requires processing of high visual associative areas or attentional networks. Our findings of a PL acuity significantly better than VEP acuity, in children with PVL may be interpreted as an indirect sign of plastic mechanisms of adaptive reorganization based on the reinforcement of the extra-striatal visual pathways in case of direct damage to the geniculo-striate pathway with a relative sparing of cortical visual structures.

About "high level" visual functions our studies have clearly demonstrated the low potential of functional reorganisation after bilateral brain damage. For this reason, in fact, we presented, to our children, different types of motion stimuli (coherent, flow, biological motion) to investigate the functioning of the dorsal pathway: howeuer, our results confirm the extreme vulnerability of this stream to early damage as reported also in other neurodevelopmental disorders [112, 113], [118]. This can be considered a general and not a specific impairment of motion perception [111]. Only in two cases we described a specific deficit, different to all other subjects, consisting in the inversion of perceived direction of motion and we hypthotised that it was caused by spatial under-sampling. Furthermore, no functional reorganization seems possible also for the ventral stream. Subjects with PVL failed to give right answers also in recognition tasks mediated by means of the ventral pathway.

The compromission both of the dorsal and of the ventral stream can explain also the impairment in the perception of the biological motion that is possible by means of neurons localized in the superior temporal polysensory area (STP) in the superior temporal sulcus (STS) [163]. This area (STP) is well known because receives projections from the anterior parts of the dorsal and ventral visual streams, and some authors [164] suggest that it is the site of their synthesis [165]. An interruption of these connections may preclude the possibility of a correct functioning of the neurons utilize for biological motion perception.

The effects of the congenital and the acquired unilateral brain damage

Chapter 7

In the series of studies we have performed during this doctoral project we have been able to deepen our knowledge of the anatomo-functional correlation after unilateral brain lesion, therefore achieving indirect information about general mechanisms of functional reorganisation. This has been possible because we have studied subjects with the same type of lesion (unilateral) acquired at different ages, using similar methodologies and obtaining comparable results.

The comparison between children with congenital and acquired unilateral brain lesion has demonstrated a different pattern of functional reorganization and adaptation mechanisms in a simple task such as that of visual search. This is particular true when an important visual field defect (homonymus hemianopia) is present. As reported on animal models our studies suggested that to have a damage at birth is better than to have a damage later. Children with congenital lesion give answers very similar to controls without brain damage while children with acquired lesion give answers very similar to subjects with unilateral lesions acquired in adulthood. It may be suggested that children with congenital lesion are able to utilize successfully, despite their hemianopia, the low level visual information for "bottom-up" processing. This implies that the visual information can reach at some level the visual system and that this would be possible only in presence of a congenital lesion and a higher degree of reorganization capabilities. Since that all our children with congenital hemiplegia and hemianopia have a damage to occipital cortex and optic radiations we can hypothize that this type of reorganization is possible only by means of the superior colliculus (SC) that is an important oculomotor structure involved in the execution and initiation of saccades and in target selection [207]. SC is part of the colliculo-geniculo-pulvinar- extrastriate pathways that mediates some residual visual functions in hemianopia [208]. In superior collliculus there are neurons that are able to respond to stimuli from different sensory modalities and what we have hypthozed is that children with congenital lesion immediatly use this "alternative" way, while children with acquired lesions begins to utilize this compensantion mechanism only after an intensive training of multisensorial stimulation.

An indirect way that gives reason to this idea is the fact that trying to do the same type of multisensorial treatment to a child with congenital lesion and to children with acquired lesions, we obtained different results. The child with congenital lesion doesn't improve (because his

values in visual search tasks were already similar to controls), while children with acquired lesion had excellent results with a good reduction of the RTs to visual search tasks.

Finally, by means of fMRI, we were able to demonstrate, even if in a single child with congenital lesion, the ipsilateral extrastriate activation of the intact hemisphere, in the absence of contralateral striate activation, during stimulation of the hemianopic field.

Final remarks

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In these years we have performed a series of studies in a cohort of children with early brain lesions (congential and acquired) that were highly characterised by neuroimaging in terms of site, extent and severity. We believe that our work has provided a contribution to the evaluation of the functional consequences of these early lesions, and therefore also of the different mechanisms of visual reorganisation in relation to the type of brain damage. We confirmed a higher plastic potential of unilateral lesions as opposed to bilateral ones finding some key structures of the newborn brain that seem more effective in the adaptive reorganisation such as the superior colliculus. We confirmed also a higher plastic potential of congenital unilateral lesions as opposed to acquired ones but we were able to demonstrate that also training strategies may be usefully employed to potentiate the natural capacity of the brain to overcome the challenges and contribute to considerable neural compensations, sparing of neural functions, that result in relatively normal organized behaviors.

In conclusion, we believe that our studies confirmed how the mechanisms of response to damage of the immature brain are different from those of the adult nervous system, but are certainly not less complex. The influence of the environment, the timing, the developmental drive and many other factors play a fundamental role that is still far from being fully understood. We are also conscious to have provided only a very little contribution and that further, endless studies involving different approaches and backgrounds are essential to continue this challenging and infinite mission that is the understanding of the human brain.

APPENDIX

In the present appendix details concerning publications (in-extenso papers in international indexed-journals or book chapters) of the author on the topics covered by this thesis will be provided. All the studies stemming from the doctoral work will be indicated by an asterisk. All publications will be subdivided according to the chapters in which related arguments were treated in this thesis. For all data that are part of the project and that are still in press or have not been yet published, a specific indication will be made.

Chapter 3

*Tinelli F, Pei F, Guzzetta A, Bancale A, Mazzotti S, Baldassi S, Cioni G. The assessment of visual acuity in children with periventricular damage: a comparison of behavioural and electrophysiological techniques. Vision Research *in press*

*Guzzetta A, **Tinelli F**, Del Viva M, Bancale A, Pascale RR, Cioni G. Perception of flow motion in children with early periventricular brain damage. *Submitted*

*Morrone MC, Guzzetta A, **Tinelli F**, Tosetti M, Del Viva M, Montanaro D, Burr D, Cioni G. Inversion of perceived direction of motion in two children with periventricular leukomalacia caused by spatial under-sampling. Journal of Cognitive Neuroscience *in press*

Chapter 4

Data and analysis reported in the present chapter are personal unpublished data that are part of the doctoral project

Chapter 5

*Guzzetta A, **Tinelli F**, Bancale A, Cioni G. Disturbi visivi e oculomotori. In: Le forme spastiche della paralisi cerebrale infantile. Springer-Verlag Italia 2005.

*Mercuri E, Guzzetta A, **Tinelli F**, Ricci D, Cioni G. Visual function in children with neonatal brain lesions. In: Neurological assessment in the first two years of life. Mac Keith Press 2007

Data and analysis reported in the present chapter are personal unpublished data that are part of the doctoral project

Chapter 6
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