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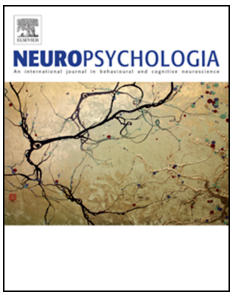

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PII: S0028-3932(20)30389-4

DOI: https://doi.org/10.1016/j.neuropsychologia.2020.107717

Reference: NSY 107717

To appear in: *Neuropsychologia*

Received Date: 27 April 2020

Revised Date: 27 November 2020

Accepted Date: 4 December 2020

Please cite this article as: Bhat, A., Biagi, L., Cioni, G., Tinelli, F., Morrone, M.C., Cortical thickness of primary visual cortex correlates with motion deficits in periventricular leukomalacia, *Neuropsychologia*, https://doi.org/10.1016/j.neuropsychologia.2020.107717.

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Cortical thickness of primary visual cortex correlates with motion deficits in periventricular leukomalacia

Akshatha Bhat [1,5], Laura Biagi[4], Giovanni Cioni[1,3], Francesca Tinelli[1], M Concetta Morrone[1,2]

1-Department of Developmental Neuroscience, Laboratory of Vision, IRCCS Fondazione Stella Maris, Pisa, Italy

2-Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, Italy

3-Department of Clinical and Experimental Medicine, University of Pisa, Italy

4-Laboratory of Medical Physics and Magnetic Resonance, IRCCS Fondazione Stella Maris, Pisa, Italy

5- Department of Neuroscience, University of Florence, Italy

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ABSTRACT

Impairments of visual motion perception and, in particular, of flow motion have been consistently observed in premature and very low birth weight subjects during infancy. Flow motion information is analyzed at various cortical levels along the dorsal pathways, with information mainly provided by primary and early visual cortex (V1, V2 and V3). We investigated the cortical stage of the visual processing that underlies these motion impairments, measuring Grey Matter Volume and Cortical Thickness in 13 children with Periventricular Leukomalacia (PVL). The cortical thickness, but not the grey matter volume of area V1, correlates negatively with motion coherence sensitivity, indicating that the thinner the cortex, the better the performance among the patients. However, we did not find any such association with either the thickness or volume of area MT, MST and areas of the IPS, suggesting damage at the level of primary visual cortex or along the optic radiation.

Key words: cortical thickness, voxel-based morphometry, individual differences, MT, motion perception, PVL

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INTRODUCTION

Several cortical areas are identified as being involved in various levels of visual motion processing in humans. The specialized areas for motion analysis are part of the visual dorsal pathways (Galletti & Fattori, 2018) and among those areas MT, MST and V6/V6a play a major role in the analysis and perception of flow motion in humans (O. J. Braddick, O'Brien, Wattam-Bell, Atkinson, & Turner, 2000; Cardin V, 2010; Gaglianese, et al., 2017; Mikellidou, et al., 2018; Morrone, et al., 2000; Pitzalis, Sereno, et al., 2013; Tootell, Reppas, Dale, et al., 1995; Tootell, Reppas, Kwong, et al., 1995; Zeki, et al., 1991). Activity of neurons in the MT and MST area varies linearly with motion coherence (Rees, Friston, & Koch, 2000) and correlates with motion perception (Britten, Newsome, Shadlen, Celebrini, & Movshon, 1996) . The major visual input to the MT complex is provided by direct feedforward from early cortical areas, like V1, V2 and V3. However many of the dorsal stream areas also receive direct thalamic input (Bourne & Morrone, 2017; Bridge, Leopold, & Bourne, 2015) in primates and in humans, which becomes important in mediating some form of perception in conditions of V1 lesion, like in blindsight (Ajina, Pestilli, Rokem, Kennard, & Bridge, 2015; Weiskrantz, Warrington, Sanders, & Marshall, 1974). In typical children there is large variability of flow motion sensitivity, only partially explained by a developmental trajectory, with structural cortical areas contributing towards the large variability. In a large sample study, Braddick et al. (2016) examined correlations of children's individual motion sensitivity with structural variations in different brain areas. The authors found a strong correlation with Intraparietal areas, but not with MT, suggesting that, in children, the limiting factor may be posed by the allocation of attention to motion signals. In addition, they observed a reduced occipital lobe cortex, implying a front-end analysis of motion signals. We believe that the Braddick et al. (2016) result calls for a new interpretation of the deficit of flow motion perception observed in many neurodevelopmental disorders, from dyslexia to cerebral palsy, and that the origin of the deficit may arise from disfunction of occipital cortical area and not necessarily of MT.

Deficits in visual motion perception (Birtles, Braddick, Wattam-Bell, Wilkinson, & Atkinson, 2007; Oliver Braddick, Atkinson, & Wattam-Bell, 2003) have been consistently reported in the literature among premature and very low birth weight subjects during infancy (for review see Atkinson, 2017; O. Braddick & Atkinson, 2011). Motion perception deficits are widespread in premature groups, even where there is no direct evidence of brain lesions,

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suggesting a high vulnerability of the dorsal pathway in prematurity. MacKay and colleagues (2005) have also shown that sensitivity to global motion perception (flow motion) was lower for preterm-born children both with and without periventricular damage, relative to term age-matched control (Atkinson & Braddick, 2007; Gunn, et al., 2002; Taylor NM, 2009). In particular, children with spastic diplegia and cystic PVL have, on average, impaired perception both for translational and rotational flow motion (Guzzetta, et al., 2009). However, there is great individual variability, with some patients having paradoxical and very specific abnormal perception. For example, we (Morrone, et al., 2008) observed PVL children with normal rotational or expansional motion perception of random dot kinematogram (RDK), who consistently reported the opposite direction of translating motion even at high coherence of the RDK, suggesting a malfunctioning of some basic mechanism of motion detectors. The inversion of perceived direction of motion was attributed to under-sampling of motion signals, which possibly may result from damage of the optic radiation itself, that provide the input to V1 direction selective neurons.

These peculiar deficits and the large variability observed suggest that the deficit in PVL may vary depending which particular pathway is affected by lesions along the optic radiation (Merabet, Mayer, Bauer, Wright, & Kran, 2017). In other words, in some subjects lesions of optic radiation may induce a generalized loss of peripheral magno-cellular pathways, in others the parvo-cellular pathway may be damaged resulting in agnosia, which is observed in some PVL children (Castaldi, Tinelli, Cicchini, & Morrone, 2018; Perez-Roche, et al., 2017) and, in others, optic radiation projecting to V1 may be totally spared but the lesions could affect the parallel bundles running more medially that project to MT and other dorsal motion areas. These different lesions would produce different perceptual deficits in the domain of motion.

While high resolution studies of optic tracts which could reveal small diffuse anatomical deficits, like in PVL, are difficult with present technologies, assessment of structural differences in the visual cortex are more feasible. Behavioral performance in visual functions have been often correlated with variation of surface, volume and thickness (Frank, Reavis, Greenlee, & Tse, 2016; Kanai & Rees, 2011) of the visual cortex. Here we investigated whether the poor sensitivity to global motion found in PVL children is associated with extrastriate areas such as MT+ and IPS or the primary cortical areas. Specifically, we investigated whether the grey matter volume or the

thickness of striate or extra striate areas predict the flow motion performance among patients with Periventricular Leukomalacia.

METHODS

We selected 13 patients (mean ± SD, aged 11.2 ± 4.5 years, five males) from those referred to the Laboratory of Vision of the Fondazione Stella Maris. The inclusion criteria were 1) clear signs of periventricular leukomalacia (PVL) on perinatal brain ultrasounds and on MRI performed at later age, according to the criteria indicated in the literature (Cioni, Bartalena, Biagioni, Boldrini, & Canapicchi, 1992) , 2) at least one brain MRI after 3 years of age, 3) good/normal or corrected-to-normal visual acuity, 4) absence of oculomotor dysfunctions and 5) good fixation and no spontaneous nystagmus. The last inclusion criterion is essential to avoid artefactual impairment on visual motion discrimination performance. Given the stringent selection criteria, we were able to select only 13 patients from more than 130 in the follow up screening of the Laboratory of Vision. All selected patients were preterm with gestational age less than 34 weeks, all had cerebral palsy (spastic diplegia); all had normal verbal IQ. A lesion severity score was obtained for all subjects using a visual semi-quantitative scale for the classification of brain MRI, specifically designed for individuals with cerebral palsy (Fiori, et al., 2014).

We also recruited 12 typical children between 7 and 11 years old, all with normal or corrected to normal vision to compare with motion sensitivity of PVL patients.

			Global score of Lesion										
				Right Hemisphere				Left Hemisphere					
	age (y)	gender	Total	R PV	R M	R CSC	R BG and BS	L PV	L M	L CSC	L BG and BS	CC	Cereb
1	9	M	15.5	3.5	2.5	0	1	3.5	3	0	1	1	0
2	15	F	14.5	3.5	2	0	1	3.5	2.5	0	1	1	0
3	8	F	10.5	3.5	1.5	0	0	3.5	1	0	0	1	0
4	8	F	5.5	2	1.5	0	0	1	1	0	0	0	0
5	7	M	8.5	2.5	2	0	0	2.5	1.5	0	0	0	0
6	10	M	10	2.5	2	0	0	2.5	2	0	0	1	0
7	7	F	10	2.5	1	0	1	2.5	1	0	1	1	0
8	12	F	16.5	3.5	2.5	0	2	4	2.5	0	1	1	0
9	21	F	14	3.5	2.5	0	0	3.5	2.5	0	0	2	0
10	19	M	4.5	0.5	0.5	0	0	1.5	1	0	0	1	0
11	14	F	14.5	4	3	0	0	3.5	3	0	0	1	0
12	10	F	10.5	0	0	0	0	3.5	3	0	1	2	1
13	7	F	14.5	4	1.5	0	1	4	2	0	1	1	0

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Table 1. Demographical data and lesion severity scores for all patients. The total score corresponds to the sum of raw scores of each hemisphere, subcortical structures (basal ganglia, BG, and brainstem, BS), corpus callosum (CC) and cerebellum (Cereb). For each hemisphere, the score is evaluated by considering a subdivision in three layers, a periventricular layer (PV), a middle white matter layer (M) and a cortico/subcortical layer (CSC).

The study was approved by the Ethics Committee of the Fondazione Stella Maris. Written informed consent for participation was obtained from all adult subjects and from the care providers of the children, in addition to verbal assent from the children.

Stimuli were presented to participants in a dimly lit room on a Sony CRT (17 inch) monitor with a mean luminance of 50 cd/m2, subtending 22x22 degrees when viewed from a distance of 57 cm. The tasks were run successively for each participant, with the order of presentation counterbalanced across participants. There were four to six training trials consisting of 100% coherent stimuli administered before the test trials to explain the task.

Stimuli comprised 100 small dots (each subtending 35 arc min), half black and half white. A proportion of the dots were caused to drift coherently at a local speed of 10 degrees/s (limited lifetime of five frames, frame rate 75 Hz), while the remaining dots (noise dots) were stationary (for five frames). At each frame 20% of dots were randomly assigned new positions, producing the appearance of dynamic flicker. The coherent motion was either clockwise or counter- clockwise (all dots had constant linear speed) for each trial. Participants were required to indicate the direction of the perceived motion pattern. 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. Sensitivity, defined as the inverse of the proportion of coherent dots producing 75% correct direction discrimination (Total Dots/ Coherent Dots), was calculated by fitting all data of a particular condition (at least 40 trials) with cumulative Gaussian functions.

Some of the PVL patients also participated in a previous experiment where motion and form sensitivity were assessed using the paradigm by Gunn et al. (2002). The noise dots in these tasks have the same speed of the coherent motion whilst, in our stimuli, noise dots are stationary. Table 2 reports the threshold of the 3 tasks

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performance in z-score in order to compare the relative deficits. The normative data for the motion/form is taken from Gunn et al. (2002).

Imaging Methods

Imaging data were acquired on a GE 1.5 T HDx (General Electric Medical Systems) fitted with 40 mT/m high-speed gradients. The MRI session consisted of one structural session. A whole-brain fast spoiled gradient recalled acquisition T1-weighted series (3D BRAVO) was collected in the axial plane with Time of Repetition (TR)= 12.5 ms, Time of Echo (TE)=2.4 ms, Time of Inversion (TI)=450 ms, Flip Angle (FA)=13°, 1 mm slice thickness, in-plane resolution of 1mm.

Pre-processing of anatomy: All anatomies underwent a standard segmentation procedure using Freesurfers's *recon-all* command (Dale, Fischl, & Sereno, 1999), which produces white/grey matter segmentation and created meshes representing left and right hemisphere. Subject hemispheres were registered to the common template 'fsaverage' to allow the registration of the regions-of-interest (ROIs) from the cortical template (Glasser, et al., 2016). We used HCP's multi-modal cortical parcellation atlas (Glasser, et al., 2016) which has detailed visual areas and has also been validated with retinotopy studies (Benson, et al., 2018)

Definition of ROIs and Computing thickness: Cortical ROIs were firstly projected onto the average anatomy 'fsaverage' using the cortical template (Glasser, et al., 2016) and mapped back from 'fsaverage' space to the native cortical space using the mri_surf2surf function. Cortical thickness was calculated as the distance between the white/ grey matter boundary and the pial surface (Dale, et al., 1999; Dickerson, et al., 2008). Reported cortical thicknesses for each ROI were the average across cerebral hemispheres within two bilateral ROIs.

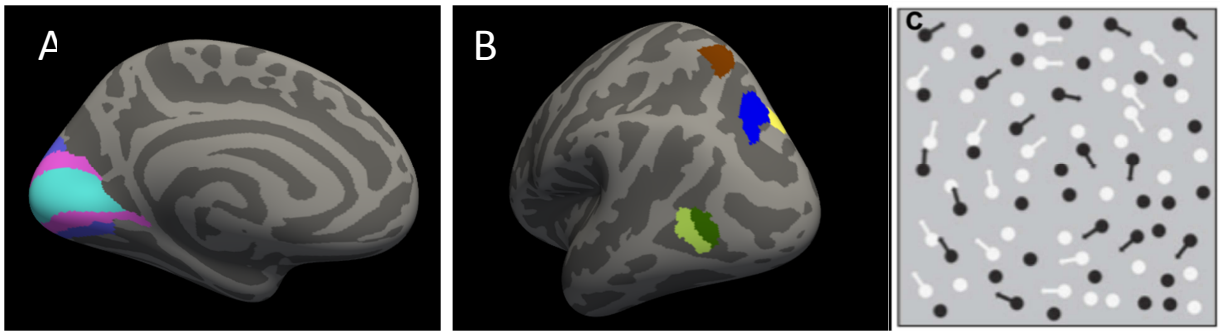

Figure 1. A, B: Locations of regions of interest (ROIs) on the inflated left hemisphere of an average brain. *The medial view is depicted on the left side of the figure and the lateral view of the hemisphere is shown on the right side. In Panel A, V1, V2 and V3 ROIs are illustrated in light-blue, magenta and blue respectively. In panel B Mt, MST, V6A, IPS1 and VIP are illustrated in dark green, light green, yellow, blue and brown. All ROIs are obtained from the* HCP *Glasses atlas* (Glasser, et al., 2016). ***C: Schematic diagram to illustrate the stimuli used to test circular motion sensitivity.*** *The moving dots are illustrated by the vector and their proportion define motion coherence of the stimulus.*

Voxel Based Morphometry Analysis:

The Voxel-based morphometry analysis was used to investigate the volume of the grey matter within the defined ROIs, using the SPM12 package (Welcome Trust Center for Neuroimaging, London, UK, http://www.filion.ucl.ac.uk/spm/software/spm8/) implemented in Matlab (Math Works, Natick, MA, USA). The T1-weighted volumetric images were analyzed using the standard SPM pipeline with DARTEL algorithm to achieve an accurate inter-subject registration with an improved realignment of small inner structures (Ashburner, 2007). Standard steps were followed: (a) checking for scanner artifacts and gross anatomical abnormalities for each subject; (b) setting the image origin to the anterior commissure; (c) segmenting the images into the GM and WM images; (d) importing the parameter files produced by the tissue segmentation in the DARTEL procedure; (e) affine transform of segmented brain maps into the MNI space (Ashburner, 2007); (f) modulation of segmented images with the Jacobian determinants derived from the spatial normalization and (g) checking for homogeneity across the sample and using standard smoothing by an 8-mm-full width-half maximum Gaussian kernel (Ashburner, 2007; Good, et al., 2001). This preprocessing yielded the smoothed modulated normalized data in the MNI space, further used for the volume count. Using the same ROIs defined for cortical thickness, total grey matter volume is

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calculated, as estimated by the MATLAB *get_totals.m* script implemented for SPM (http://www.sc.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m). The grey matter volume of the individual subject is scaled by the ratio between the overall brain volume of the subject and the overall average brain volume across all subjects.

RESULTS

All 13 subjects were able to complete the psychophysical task with an average coherence sensitivity equal to 3.5 (0.54 ± 0.07 l.u.), corresponding to a mean threshold across subjects of 28% dots moving coherently. The average sensitivity of typical children with age matched to the younger age group of PVL subjects is equal to 12 (1.1 ± 0.08 l.u.). These values are in line with previous reported data from the literature on PVL subjects and typical children using the same stimuli (Guzzetta, et al., 2009). Table 2 reports the individual values and z-score for flow motion measured in the present experiment and the z-score deficit for two other performances obtained from the form and motion tasks used by Gunn et al. (2002). On average the deficit for our motion stimuli is similar to the motion deficit by Gunn et al. (2002).

SUBJECT	Flow Sensitivity (L.u.)	Flow (z-score)	Form (z-score)	Motion (z-score)
S1	0.25	-2.9	-9.1	-7.3
S2	0.94	-0.4		
S3	0.28	-2.9	-3.2	-3.2
S4	0.88	-0.6	-3.2	0.0
S5	0.13	-3.4	-1.0	-1.8
S6	0.50	-2.0		
S7	0.49	-2.0		
S8	0.67	-1.4	-1.5	-1.0
S9	0.65	-1.5		
S10	0.78	-1.0	-0.5	0.0
S11	0.61	-1.6	-2.6	-0.4
S12	0.68	-1.4	-6.1	-2.8
S13	0.21	-3.1		
Mean	0.54	-1.9	-3.4	-2.1

Table 2. Comparisons of the z-score deficits between the flow motion task and form/motion tasks using the Gunn et al. (2002) stimuli. The first column show the flow coherence sensitivity in logarithmic units

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Subjects had a small impairment of visual acuity, on average 0.08± 0.03 LogMAR. We found no significant correlation between Motion Sensitivity and Visual Acuity (p=0.091, r= -0.49, BF=0.87) or with neuronal damage and only a marginally significant correlation of motion sensitivity with age (p=0.043 r=0.56 BF=1.6), consistent with the previously reported maturation trajectory of motion discrimination (Atkinson, 2017; Hadad, Maurer, & Lewis, 2011; Narasimhan S, 2012). In a preliminary analysis we performed a full brain grey matter correlation (Voxel-based morphometry analysis) with motion sensitivity, but we found no reliable correlation FDR for clusters greater than 170 mm^3. This was expected given that we were only able to recruit 13 subjects for the study, although we screened more than 130 potential patients with PVL. Given the small sample, we opted for a Region of Interest Analysis on major visual areas. We selected areas V1, V2, V3, MT, MST, V6a, IPS1 and VIP given that all these could be accurately located using the atlas currently available in visual science (Glasser, et al., 2016). We selected VIP because this area is close to the focus of the area correlation with motion sensitivity revealed by Braddick (2016) and corresponds to the focus of the non-symbolic number perception (Castaldi, Vignaud, & Eger, 2020); we selected V6a as an important area with direct input to MT/MST in the monkey (Pitzalis, Bozzacchi, et al., 2013; Pitzalis, Sereno, et al., 2013) and IPS1 as an intraparietal area related to attention (Szczepanski, Konen, & Kastner, 2010). We tested whether the variability in perception of circular flow motion and visual acuity was associated with variability in brain structure by using two measures: cortical thickness and grey matter (GM) volume averaged across the ROIs. We also took into account age in the regression model.

Cortical Thickness: Figure 2 shows the correlation of motion sensitivity with cortical thickness in areas V1, V2, V3 and MT. The used ROIs are shown in figure 1 mapped onto the average brain. We found a significant negative correlation between cortical thickness and sensitivity for motion coherence in PVL patients in the bilateral visual area V1 ($r = -0.75$, $p = 0.001$, BF=15) and bilateral V2 ($r = -0.70$, $p = 0.005$ BA=4.9) (Figure 2A,2B). The negative correlation with motion coherence sensitivity indicated that the thinner the cortex in these regions, the better the sensitivity of an individual. Interestingly, a non-significant trend for negative correlation is still present for area V3 (Fig 2C, p=0.11 BF=0.7), but is completely lost for areas MT (fig 2D) and MST (not shown) which both show a Bayes factor less than 0.3, indicating substantial evidence for the null hypothesis (random association between MT and MST and cortical thickness and sensitivity). A similar lack of significant correlation was evident for VIP and V6A,

two other important areas for cortical motion analysis, and for IPS1. All these areas showed a Bayes Factor below 1.3 suggesting, if any, only marginal correlation. The lack of association of sensitivity with thickness of MT and the other motion sensitive areas is surprising.

The age range of our PVL subjects was quite large, and cortical thickness in some associative areas continues to mature with age (Tamnes, et al., 2010). We did not find significant correlation of thickness parameters with the age of the patients for most areas, with the exception of a small trend of negative correlation for V1 ($p=0.05$ and BF=1.5) and a robust and strong negative correlation for V2 ($r=-0.72$, $p=0.005$ and BF=12) and IPS1 ($r=-0.73$, $p=0.004$ and BF=12). To determine whether the correlation with sensitivity was affected by age, we opted to compute partial correlation considering age as an additional regressor. Even the partial correlation results fail to provide an association of sensitivity with area MT, resulting in a $r=0.2$ ($p=0.6$; BF= 0.2), or with IPS1 ($p=0.5$, BT 0.3) or V2 ($p=0.15$, BF=0.6). The same partial correlation procedure applied to V1 data, resulting in a Bayes factor of 3 ($r=-0.63$, $p=0.028$), which confirmed a robust association between sensitivity and V1 thickness.

Thickness of areas V1 and V2 are highly positively correlated, ($r = 0.87$, $p = 0.0001$), less so with V3 ($r=0.60$, $p=0.03$) and not at all with MT ($r=0.02$, $p=0.97$). Interestingly IPS1 thickness, which decreases strongly with age, is strongly correlated with V2 (BF=12), weakly with V1, V3 and V6 (BF < 3) and not at all with MT and MST. MT and MST thickness are highly correlated ($r=0.74$, $p=0.0037$, BF=13).

We also considered whether visual acuity may be a good indicator of cortical thickness. Figure 3 shows the scatter plot of acuity (in LogMar) and thickness for V1 and MT. For both areas, the Bayes factor was around 0.2- 0.3, strongly suggesting the lack of association between the two parameters.

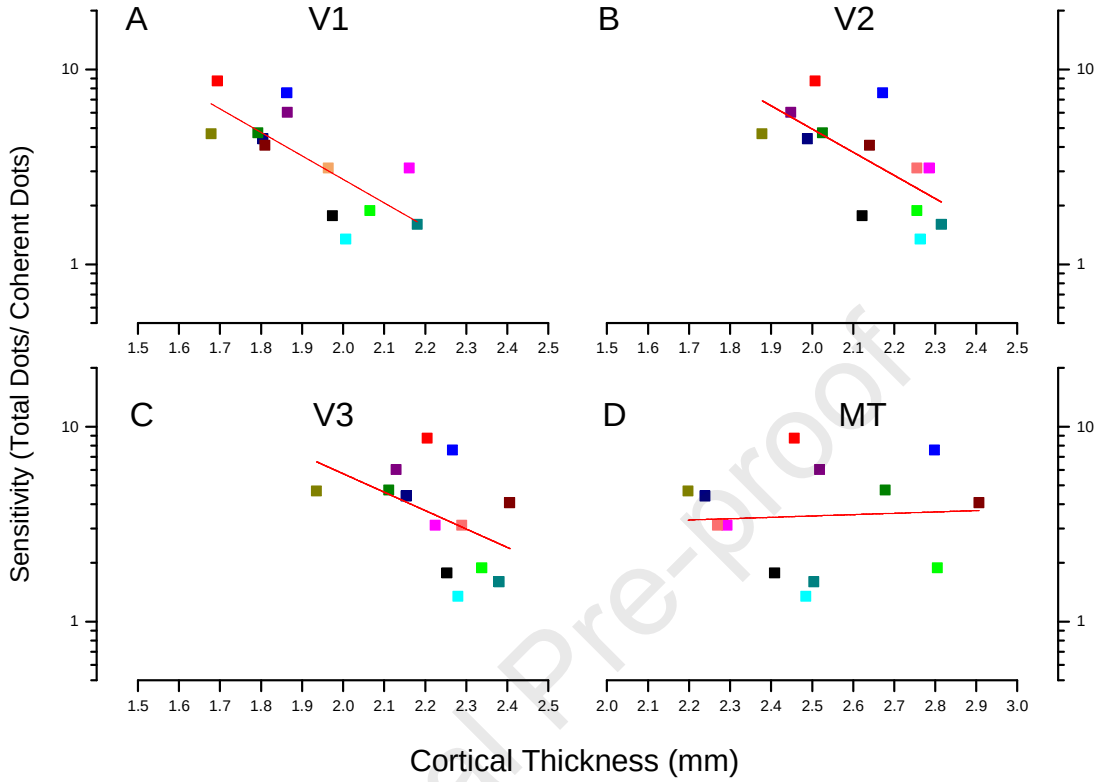

Figure2. *Correlation of cortical thickness of A: area V1, B: area V2, C: area V3 and D: area MT with patient's sensitivity for motion coherence perception. Thickness values are the average values of the ROIs of the two hemispheres. Different symbols correspond to the different subjects.*

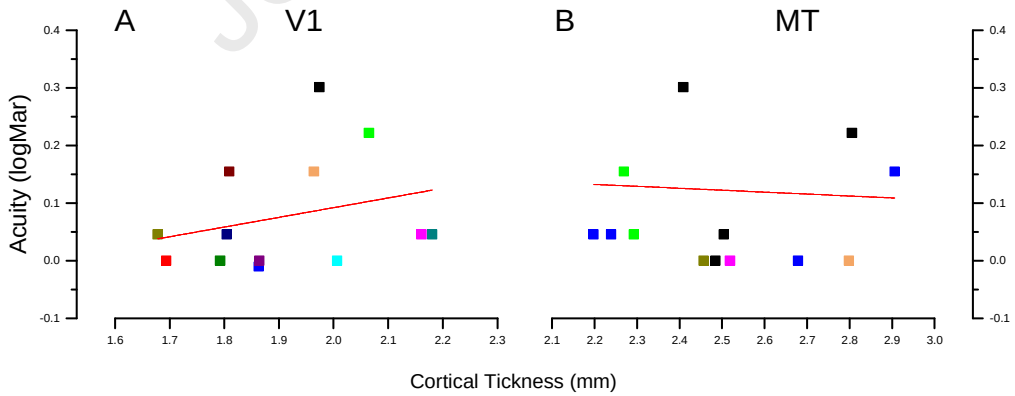

Figure3.

Correlation of cortical thickness of area V1 and MT with patient's visual acuity. All details as in figure 2

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Voxel-Based Morphometry:

To cross-validate our findings, we conducted a voxel-based morphometry (VBM) analysis of GM density (Ashburner, 2007) on the same data set and the same ROIs used in the thickness analysis. In this case, we did not find significant correlations between GM volume and patients' motion coherence performance in early visual area V1 ($r = 0.29$, $p = 0.31$), and in motion sensitive area MT+ ($r = 0.39$, $p = 0.16$). (Figure 4).

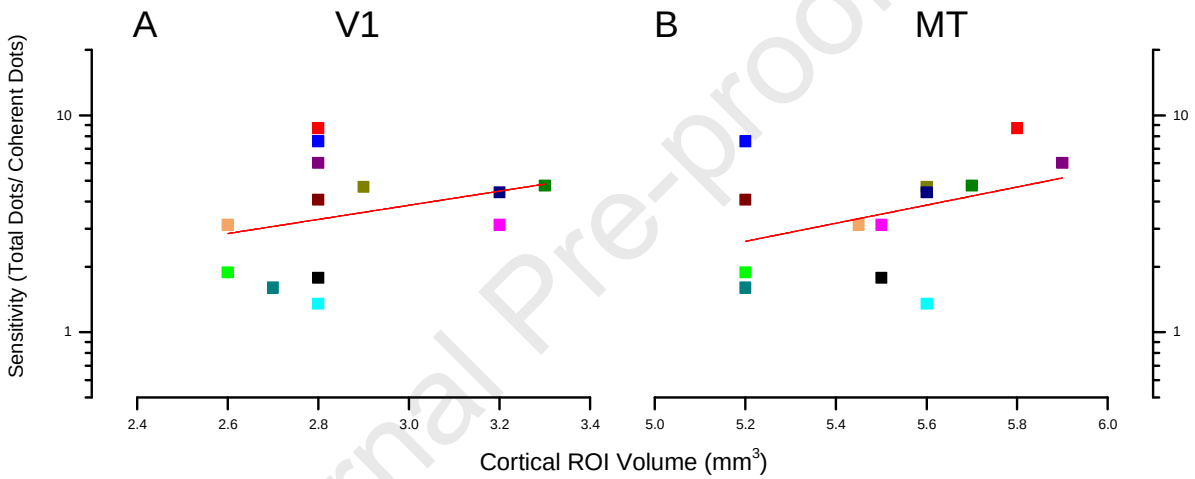

Figure 4. *Correlation of Grey matter (GM) volume of A: area V1 and B: area MT+ with motion coherence sensitivity. All details as in figure 2*

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DISCUSSION

These findings add to the scant literature of cortical thickness in cerebral palsy patients (Kelly, et al., 2015 ; Liu, et al., 2019; Pagnozzi, et al., 2020; Reid, et al., 2017). To the best of our knowledge, this is the first study exploring the association between anatomical differences and behavioral performance in visual functions among PVL populations. Our results demonstrate a strong negative correlation between sensitivity for motion coherence and primary visual cortex. Patients with thinner V1 were better at perceiving coherent motion at higher noise levels, while no such correlation was observed for the motion area MT, MST or other areas of the dorsal pathway. This result is surprising and suggests that the locus of the deficit is in V1 or earlier.

The lack of correlation in areas associated with dorsal pathways may contrast with the well-known selectivity of MT/MST, VIP and V6a motion (O. J. Braddick, et al., 2000; Cardin V, 2010; Gaglianese, et al., 2017; Mikellidou, et al., 2018; Morrone, et al., 2000; Pitzalis, Sereno, et al., 2013; Tootell, Reppas, Dale, et al., 1995; Tootell, Reppas, Kwong, et al., 1995; Zeki, et al., 1991) to coherent motion. It may also be considered not consistent with the correlation results between motion form detection and grey matter volume in IPS, demonstrated by Braddick et al. (2016), given that VIP ROI is anatomically included in the focus of the correlation. However, there are differences in the task and stimuli that may explain the different result. In our task the subject had to report the direction of the coherent motion integrated through all visual stimulus areas, while in Braddick et al. (2016) all subjects had to segment the form of a coherent flow from random direction noise of the same speed. This task is more complex and may require the analysis by higher motion area. In addition, in our stimuli noise dots were stationary and dynamically allocated at new positions every 70ms, generating a sense of dynamic flicker. In Braddick et al. (2016) the dots had the same speed as the coherent dots. V1 processing would not be able to detect the form by segmenting the motion signal, as we and others have demonstrated in BOLD experiments (O. J. Braddick, et al., 2000; Morrone, et al., 2000). The stimulus differences between experiments may shift the limiting factor for sensitivity from high to lower cortical area. The other major difference is the subject population. The limiting factor for sensitivity in typical children may be different from that in PVL. PVL is congenital, encompasses a non-focal white matter degeneration, and optic radiation is affected by the pathology (Groppo, et al., 2014). This anatomical evidence are consistent with early damage at the level of V1 innervation. In this light our result showing increased

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V1 cortical thickness in PVL could provide an indirect but reliable measure of optic radiation damage that would be clinically more feasible to measure.

It is well known that the MT+ complex is functionally subdivided into the MT/TO1 area, which responds to contralateral visual motion stimulation, and the MST/TO2 area that responds to both ispilateral and contralateral visual fields (Amano, Wandell, & Dumoulin, 2009; Huk, Dougherty, & Heeger, 2002; Morrone, et al., 2000). The two areas show the same BOLD selectivity to fast and slow motion (Mikellidou, et al., 2018), but a clear difference in selectivity for optic flow processing along complex trajectories such as spiral, expansion and rotational motion (Morrone, et al., 2000). Given that BOLD fMRI measures for MT+ can accurately estimate the underlying neuronal electrophysiological selectivity to motion, we might have expected a difference in the correlation with motion selectivity, if the limiting factor were located in this area. The fact that we observe no difference in correlation reinforces the idea of an earlier limiting factor. The thickness of MT and MST are highly correlated in PVL subjects, which poses difficulties in interpreting the lack of correlation of cortical thickness with perceptual motion discrimination. A direct BOLD motion response or direct ECoG registration would be more appropriate (Gaglianese, et al., 2017; Morrone, et al., 2008) to disentangle the different involvements of these area in PVL patients.

The result that the MT cortical thickness parameter did not correlate with motion sensitivity may be seen at odds with the current knowledge that MT processing limits our flow motion perception. However recent literature is converging with the idea that during development many of the properties of MT neurons are also determined by a direct subcortical thalamic input. In marmosets we know that this direct input, which normally would be pruned during typical development, becomes stabilized in presence of neonatal V1 lesion (Bourne & Morrone, 2017; Bridge, et al., 2015; Fox, Goodale, & Bourne, 2020; Warner CE, 2012). The shifting in the limiting factor in motion perception from MT to V1 in PVL patients might be consistent with a periventricular lesion that also affects this developing tract that connects LGN with MT. Tracts that connect dorsal visual area with LGN run more centrally and closer to the ventriculi than optic radiation projecting to V1 (Kurzawski, Mikellidou, Morrone, & Pestilli, 2020), reinforcing this idea. In future, it would be interesting to be able to address this question using high resolution DTI in human connectome in PVL patients.

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The behavioral performance increases with age in our sample group ($r = 0.53$, $p = 0.03$). So thin visual areas correlating with the better performance could reflect (but also predict) the severity of damage of these congenital patients. However, the partial correlation analysis with age of the subjects as an additional regressor dismisses this criticism, given that the obtained Bayes Factor strongly supported the validity of a negative correlation of sensitivity with V1 thickness.

We did not observe any correlation with any performance parameters and volume analyzed with VBM. The differences between cortical thickness and VBM results could be due to a number of factors such as measurement of different aspects of GM structure. Interestingly, the literature suggests that these two parameters do not necessarily go hand in hand. A possible reason for the difference between the grey matter volume and the cortical thickness results is that, although cortical thickness changes can be detected in the volume measure, because volume is also dependent on surface area and therefore possibly cortical folding, it is less sensitive to specific changes in thickness compared with thickness measures (Hutton, Draganski, Ashburner, & Weiskopf, 2009). Hence, cortical thickness might be a more sensitive measurement to detect regional grey matter micro-changes that are missed by conventional voxel-based techniques at the earlier stages of the neurodegeneration due to partial volume effects (Hutton, et al., 2009; Seo, et al., 2012).

Anatomical developmental studies document monotonic thinning of cerebral cortex starting from the age of 4 years (Brown, 2017; Fjell, et al., 2015; Parker, et al., 2020; Raznahan, et al., 2011; Sowell, et al., 2004; Thambisetty, et al., 2010; Vandekar, et al., 2015). Synaptic pruning, white matter encroachment on grey matter due to increasing axonal myelination, and changes in the extracellular matrix are assumed to underlie developmental changes and differences seen in grey matter volume between childhood and adulthood (Gogtay, et al., 2004; Gogtay & Thompson, 2010; Sowell, et al., 2004). Specifically, these structural changes may be related to more efficient and faster processing of information, which affects not only general intelligence, but also specific cognitive domains (Squeglia, Jacobus, Sorg, Jernigan, & Tapert, 2013). Elimination of unnecessary synaptic connections and increases in myelination could be contributing to the observed results in the above-mentioned studies. All these maturation processes are impaired during the development of preterm children (Volpe, 2009a, 2009b). PVL is characterized by lesions to the cerebral white matter, usually occurring between the 24th and 36th

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week of gestational age. There is often observed deficiency of fully differentiated oligodendrocytes and hypo-myelination with dilated ventricles (Cheong, et al., 2009; Volpe, 2009a). As it is with the healthy developing population (Song, Schwarzkopf, Kanai, & Rees, 2015), we show that in PVL thinner cortex is also associated with better visual performance. The alternative explanation of the negative correlation of V1 thickness and motion sensitivity may be formulated by considering cross-modal plasticity. Congenitally blind subjects have thicker V1, probably reflecting the reorganization of V1 circuitry to process other sensory inputs (Jiang, et al., 2009; Park, et al., 2009). A partially deafferented V1, as a consequence of optic radiation lesion in PVL newborns, should plastically rearrange to process other sensory inputs and hence become thicker than in normal controls. A comparison between two blind children with and without PVL shows decreased white matter connections, particularly in the occipital pole (Merabet, et al., 2017), supporting an altered input to V1 in PVL.

It is interesting that visual acuity (VA) deficits do not correlate with any anatomical measures. It is well known in the clinical practice that VA is not a good predictor of PVL disabilities. Indeed, many PVL patients, despite having good oculomotor control and normal VA, can have profound alteration of vision. Many have agnosia, for faces (Perez-Roche, et al., 2017), and objects but also for simple features like orientation or symmetry (Castaldi, et al., 2018) . Others have alteration more specific for the dorsal pathways, like the motion perceptual deficit observed here. However, even within the population with only altered motion perception, there are a wide variety of deficits, some very peculiar like the reliable perception of the inverse direction of motion (Morrone, et al., 2008). As suggested in the study of these patients, the deficit may be traced to specific pathways of the optic radiation. Magnocellular pathways of the optic radiation are more sensitive to compression damage than parvocellular pathways, having a larger diameter of the axons. It is possible that, in many patients, the compression reduced the density of the magnocellular input to V1, inducing a reduction of the flow motion sensitivity and, in extreme cases, the reduction is so pronounced to induce under-sampling of motion and, hence, the perception of inverse direction in special circumstances. This is consistent with the finding of unimpaired visual acuity of the patients that it is mediated mainly by the parvocellular pathway, especially for foveal targets.

Given the importance of understanding the reorganization of the motion pathway in the PVL children, it is suggested that more patients should be tested in flow motion in future. Unfortunately, we were only able to

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recruit 13 patients given the stringent criteria and in particular the need to have an MRI after 5 years of age, despite having screened more than 130 PVL patient records. Although the sample is small, it was crucial to avoid artefactual data collection due to abnormal eye movements that can greatly impact on motion perception. However, having demonstrated in this clean sample that the correlation of sensitivity with V1 is very strong, as suggested by a Bayes Factor of 15, we hope in future to relax our selection criteria and extend the analysis to a much larger population. If successful, we might also be able to define the thickness of calcarine sulcus as a clinical predictor of visual ability.

Our results contribute to the developmental literature which, so far, demonstrates that thinner cortices relate to better global cognitive functioning, as well as improved functioning in domain-specific tasks (Squeglia, et al., 2013). Any irregularities to typical thinning during neurodegenerative diseases, traumatic brain injury, or medical illness could have implications on later expected perceptual and behavioral functioning. Future research with a larger sample size using longitudinal data will shed light on the effect of cortical thinning on visual and other high-level functioning in the congenital patient population.

ACKNOWLEDGMENT

This research was supported by the European Research Council under the European Union's (H2020) - ERC Advanced "Spatio-temporal mechanisms of generative perception" Grant N. 832813 — GenPercept (M.C.M.) and by the European Union's Horizon 2020 Research and Innovation Programme under the Marie Sklodowska-Curie grant agreement number 641805 (A.B.), by the Italian Ministry of University and Research under the project PRIN2017 (M.C.M) and Italian Ministry of Health 2017.

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In this manuscript we present evidence of a reliable correlation between Cortical Thickness of primary visual cortex and Flow Motion Sensitivity in PVL patients.

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