



## Brain lesion scores obtained using a simple semi-quantitative scale from MR imaging are associated with motor function, communication and cognition in dyskinetic cerebral palsy

Olga Laporta-Hoyos<sup>a,b,c</sup>, Simona Fiori<sup>b</sup>, Kerstin Pannek<sup>c</sup>, Júlia Ballester-Plané<sup>a,h,i</sup>, David Leiva<sup>d</sup>, Lee B. Reid<sup>c</sup>, Alex M. Pagnozzi<sup>c</sup>, Élica Vázquez<sup>e</sup>, Ignacio Delgado<sup>e</sup>, Alfons Macaya<sup>f</sup>, Roser Pueyo<sup>a,h,i,\*</sup>, Roslyn N. Boyd<sup>g</sup>

<sup>a</sup> Departament de Psicologia Clínica i Psicobiologia, Universitat de Barcelona, Barcelona, Spain

<sup>b</sup> IRCCS Fondazione Stella Maris, Pisa, Italy

<sup>c</sup> Australian e-Health Research Centre, Commonwealth Scientific and Industrial Research Organisation, Brisbane, Australia

<sup>d</sup> Departament de Psicologia Social i Psicologia Quantitativa, Universitat de Barcelona, Barcelona, Spain

<sup>e</sup> Servei de Radiologia Pediàtrica, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>f</sup> Grup de Recerca en Neurologia Pediàtrica, Vall d'Hebron Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>g</sup> Queensland Cerebral Palsy and Rehabilitation Research Centre, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

<sup>h</sup> Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain

<sup>i</sup> Institut de Recerca Sant Joan de Déu, Barcelona, Spain

### ARTICLE INFO

#### Keywords:

Dyskinetic cerebral palsy  
Communication  
Intellectual functioning  
Visuoperception  
Ventral posterior lateral thalamus  
Frontal lobe

### ABSTRACT

**Purpose:** To characterise brain lesions in dyskinetic cerebral palsy (DCP) using the semi-quantitative scale for structural MRI (sqMRI) and to investigate their relationship with motor, communication and cognitive function.

**Materials and methods:** Thirty-nine participants (19 females, median age 21y) with DCP were assessed in terms of motor function, communication and a variety of cognitive domains. Whole-head magnetic resonance imaging (MRI) was performed including T1-MPRAGE, T2 turbo spin echo (axial plane), and fluid attenuated inversion recovery images (FLAIR). A child neurologist visually assessed images for brain lesions and scored these using the sqMRI. Ordinal, Poisson and binomial negative regression models identified which brain lesions accounted for clinical outcomes.

**Results:** Brain lesions were most frequently located in the ventral posterior lateral thalamus and the frontal lobe. Gross ( $B = 0.180, p < .001$ ;  $B = 0.658, p < .001$ ) and fine ( $B = 0.136, p = .003$ ;  $B = 0.540, p < .001$ ) motor function were associated with global sqMRI score and parietal involvement. Communication functioning was associated with putamen involvement ( $B = 0.747, p < .028$ ). Intellectual functioning was associated with global sqMRI score and posterior thalamus involvement ( $B = -0.018, p < .001$ ;  $B = -0.192, p < .001$ ). Selective attention was associated with global sqMRI score ( $B = -0.035, p < .001$ ), parietal ( $B = -0.063, p = .023$ ), and corpus callosum involvement ( $B = -0.448, p < .001$ ). Visuospatial and visuoperceptive abilities were associated with global sqMRI score ( $B = -0.078, p = .007$ ) and medial dorsal thalamus involvement ( $B = -0.139, p < .012$ ), respectively.

**Conclusions:** Key clinical outcomes in DCP are associated with specific observable brain lesions as indexed by a simple lesion scoring system that relies only on standard clinical MRI.

### 1. Introduction

Dyskinetic cerebral palsy (DCP) is the second largest cerebral palsy (CP) group comprising between 3 and 15% of CP cases (Himmelmann et al., 2009). Motor disturbances are the primary component of CP, but

the main drivers of reduced quality of life tend to be other factors (Laporta-Hoyos et al., 2017a). Communication is impaired in 25% of all CP cases (Novak et al., 2012) which influences quality of life (Colver et al., 2015). Furthermore, almost 50% of the CP population have intellectual disability (Novak et al., 2012) which has been reported to be

**Abbreviations list:** Cerebral palsy, (CP); Dyskinetic cerebral palsy, (DCP); Fluid attenuated inversion recovery images, (FLAIR); Gross motor function classification system, (GMFCS); Magnetic resonance images, (MRI); Semi-quantitative scale for brain structural MRI, (sqMRI)

\* Corresponding author at Passeig de la Vall d'Hebron, 171, 08035 Barcelona, Spain.

E-mail address: [rpueyo@ub.edu](mailto:rpueyo@ub.edu) (R. Pueyo).

<https://doi.org/10.1016/j.nicl.2018.06.015>

Received 1 March 2018; Received in revised form 4 May 2018; Accepted 12 June 2018

Available online 14 June 2018

2213-1582/ Crown Copyright © 2018 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

associated with psychological and social functioning as measured by the Strengths and difficulties questionnaire (Parkes et al., 2008). Specific neuropsychological impairments such as visuospatial, visuo-perceptive, memory and executive functions have also been described (Straub and Obrzut, 2009), some of which seem to impair quality of life (Laporta-Hoyos et al., 2017a).

Studies that have utilised qualitative categorical descriptions of computed tomography and magnetic resonance images (MRI) have suggested that the most frequent brain abnormalities observed in DCP may be in the basal ganglia and thalamus, which in some cases are accompanied by periventricular leukomalacia, but some patients are without any apparent brain injury (Aravamuthan and Waugh, 2016; Benini et al., 2013; Himmelmann and Uvebrant, 2011; Krägeloh-Mann and Cans, 2009; Monbaliu et al., 2015; Towsley et al., 2011). These findings have provided critical insights, but the literature currently lacks quantitative analyses for moderately sized DCP cohorts. Quantitative neuroimaging studies in DCP have shed light on the pathogenesis of different CP subtypes (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b; Yoshida et al., 2011) but their translatability to routine clinical settings is limited. Ideally, such findings are best translated into clinical practice in a manner that utilises tools and imaging that clinicians are already familiar with. The semi-quantitative scale for brain structural MRI (sqMRI) is one such tool (Fiori et al., 2015; Fiori et al., 2014). It has been tested for reliability (Fiori et al., 2014) and construct validity in unilateral CP (Fiori et al., 2015) and can be robustly scored despite some motion artefacts that are highly likely to occur in DCP.

Longitudinal studies exploring long-term consequences of early brain injury provide unique opportunities to uncover information that may aid development of prognostic models. Unfortunately, studies of this nature are highly costly to conduct, and can take years before imaging can be compared with developmental outcomes. Given that brain lesions in CP are not progressive (Rosenbaum et al., 2007), a cross-sectional study might elucidate the association between brain lesions and concurrent clinical outcomes in older children or adults with DCP. The purpose of the present cross-sectional study was to (A) characterise a moderate-sized sample of participants with DCP using the sqMRI scale (Fiori et al., 2014), and (B) investigate the relationship between sqMRI scoring and key clinical outcomes in CP: motor, communication and cognitive function. We hypothesised that the primary feature of the DCP patients would be a brain lesion of the basal ganglia and thalamus. The second hypothesis was that the severity of the brain lesion would be negatively associated with clinical outcomes.

## 2. Materials and methods

### 2.1. Participants

All procedures performed in the study were in accordance with the ethical standards of the 1964 Helsinki declaration. Ethical approval was obtained by the University of Barcelona's Institutional Ethics Committee, Institutional Review Board (IRB 00003099 assurance number: FWA00004225; <http://www.ub.edu/recerca/comissiobioetica.htm>) and the Hospital Universitari Vall d'Hebron. Written and verbal informed consents were obtained from all participants or their legal guardian.

This study included 39 participants (19 male with median age 20 years, 20 females with median age 22.5 years) recruited from two hospitals of Barcelona, and three other institutions. The inclusion criteria for the study were (A) clinical diagnosis of CP with predominant dyskinetic features, (B) older than 6 years, and (C) for the neuropsychological assessment, being able to understand instructions as evaluated by the Spanish grammar screening test (receptive part) (Toronto, 1973). Exclusion criteria were (1) presence of severe visual or auditory disability that precludes neuropsychological assessment, and (2) lack of an intelligible yes/no response system.

### 2.2. Magnetic resonance imaging

Magnetic resonance images (MRI) were acquired on a Siemens Magnetom TRIO 3T scanner (Erlangen, Germany). Fluid attenuated inversion recovery images (FLAIR) were acquired in 25 axial slices (9040 ms TR, 86 ms TE,  $0.43 \times 0.43$  mm, slice thickness 5.2 mm). High-resolution three-dimensional T1-weighted images were acquired in the sagittal plane with a MPRAGE sequence (1900 ms TR, 2.46 ms TE, inversion time 900 ms, voxel size  $0.7 \text{ mm} \times 0.7 \text{ mm} \times 1 \text{ mm}$ ). T2 turbo spin echo (axial plane) images (5150 ms TR, 103 ms TE, flip angle of  $120^\circ$ ,  $0.43 \times 0.43$  mm, slice thickness 5.2 mm) were acquired, also in 25 axial slices, where time permitted. Prior to scanning, 21 participants took either diazepam ( $n = 15$ ; 2.5–10 mg) or pentobarbital and propofol ( $n = 6$ ), supervised by a physician in accordance with the protocol reviewed by the ethics committee.

### 2.3. Scoring

The sqMRI scoring was performed by a child neurologist (SF) according to the procedure and calculation detailed in Fiori et al. (2014). Abnormalities on FLAIR images were crosschecked with the axial T2 images and sagittal T1 images when available. Briefly, this system provides scores by brain region, assigning progressively higher scores for increased lesion involvement, as assessed by inspection of structural images. Each periventricular, middle and cortico/subcortical layer of the frontal, parietal, temporal and occipital lobes was scored as 0 or 1, and summed to provide a score ranging from 0 to 3 for each lobe. All lobar scores were summed to provide a hemispheric score (range: 0–24). As in Fiori et al. (2014), the corpus callosum, cerebellum and basal-ganglia-and-brainstem were each scored. For the cerebellum, the score ranged from 0 to 3, by assigning 1 point to the involvement of each vermis, right and/or left hemisphere. For corpus callosum, the score ranged from 0 to 3, by assigning 1 point to the involvement of each anterior, middle and/or posterior corpus callosum. In the original paper, the basal-ganglia-and-brainstem score ranged from 0 to 5, by assigning 1 point to the involvement of each caudate, lenticular, posterior limb of internal capsule, thalamus and/or brainstem. In the present study including DCP, as we were interested in deep grey matter injury, we extended the latter score to also detail the specific involvement of the thalamic nuclei (anterior thalamus, ventral posterior lateral thalamus, medial dorsal thalamus, posterior thalamus). We also extended the lenticular involvement by detailing the involvement of globus pallidus and/or putamen. As in the original paper, we assigned a score of 1 to the involvement of each of the detailed structure, thus resulting in a larger score range for the basal-ganglia-and-brainstem of 0 to 9 on each side (right or left). In the present study, no lateralization was considered for lesion severity. We thus included in the statistical analysis the sum of right and left scores for lateralized measures. The sum of all the summary scores according to the original template (Fiori et al., 2014) provided a global score ranging from 0 to 40, ranged from 0 to 48 in the present study due to the revision of basal-ganglia-and-brainstem score. Brain lesion types were also classified by using the Krägeloh-Mann categories (Krägeloh-Mann, 2004) as these were common categorical descriptions used in previous studies (Himmelmann and Uvebrant, 2011; Krägeloh-Mann and Cans, 2009; Towsley et al., 2011).

### 2.4. Clinical measures

Gross and fine motor functions were classified according to the Gross motor function classification system (GMFCS) and the Manual ability classification system. Communication was assessed with the Communication function classification system. Intellectual functioning was measured using Raven's coloured progressive matrices (Raven et al., 2001). Four domains of executive functions were assessed:

- Attentional control: Inhibition and sustained attention using the Stop signal task (Cambridge Cognition, 1999). Selective visual and

verbal attention using the digit span (Wechsler, 2003; Wechsler, 1999) and the spatial span (Wechsler and Naglieri, 2006).

- Cognitive flexibility: Wisconsin card sorting test (Kongs et al., 2000).
- Goal setting: Stockings of Cambridge test (Cambridge Cognition, 1999).
- Information processing: Lexical verbal fluency test (Peña-Casanova et al., 2009).

Visual/verbal short and long term memory were assessed using the Pattern/Verbal recognition memory task (Cambridge Cognition, 1999). Benton's facial recognition test (Benton, 1994) and Benton's judgment of line orientation test (Benton, 1994) were used to assess visuo-perceptual and visuospatial abilities. The Peabody picture vocabulary test third edition (Dunn, 1997) was used to assess vocabulary. All clinical measures were assessed by two trained neuropsychologists (OLH and JBP).

### 2.5. Statistics

We examined relationships between each clinical measure and both (A) sqMRI global scores and (B) sqMRI subscores. A top-down approach was followed to find the best models. Specifically, a first model including all relevant predictors correlating with sqMRI scores (Supplementary Table 1) was estimated (Supplementary Table 2) and simplified by manually removing those predictors that yielded non-significant results and validated by inspecting information criteria and multicollinearity measures (Supplementary Information 1).

The sqMRI scores that were significantly correlated with motor and communication status (ordinal variables) (Supplementary Table 1) were entered into separate ordinal regression models to identify the best predictive sqMRI scores for each function. Proportional odds assumptions were checked for ordinal models. The sqMRI scores that showed significant correlations with cognitive function scores (count data) were entered into separate Poisson regression models to identify the best predictors (i.e. sqMRI sub-scores) for each cognitive domain. All statistical assumptions were assessed and binomial negative models were used when Poisson regression models condition of equidispersion was not met. Cook's distance was used to measure the influence of data points. Data points showing a Cook's distance  $> 4/(n-k-1)$  ( $n$  = number of participants,  $k$  = independent variables included in the model) were removed from the Poisson regression model. In instances where results remained substantially stable after removal of these points, the data points were included in the final model. Age was included as a covariate in all models considering cognitive functioning. The level of significance of the model predictors was set at  $p < .05$  after false discovery rate correction for multiple comparisons.

### 3. Results

From a total of 101 eligible participants, 39 (6-62y, 19 female) were included in the study (Fig. 1; Table 1).

#### 3.1. Characterization of participants with DCP using the sqMRI scale

Frequencies of the sqMRI scores included in the analyses are reported in Fig. 2, Supplementary Table 3 and Supplementary Table 4. The most frequent brain lesion location reported by the sqMRI scale was the ventral posterior lateral thalamus ( $n = 23$ ; 59%; Fig. 3A). Other lesions identified by the sqMRI scale were in the posterior ( $n = 14$ ; 36%), middle ( $n = 5$ ; 13%) and anterior ( $n = 5$ ; 13%) thalamus; posterior limb of internal capsule ( $n = 17$ ; 44%), putamen ( $n = 17$ ; 44%); globus pallidus ( $n = 3$ ; 8%); brainstem ( $n = 3$ ; 8%), and caudate nucleus ( $n = 2$ ; 5%).

Regarding hemispheric involvement, lesions frequently involved frontal lobe ( $n = 20$ ; 51%; Fig. 3B), followed by the parietal ( $n = 16$ ; 41%) and temporal lobes ( $n = 12$ ; 31%). Only 21% ( $n = 8$ ) of

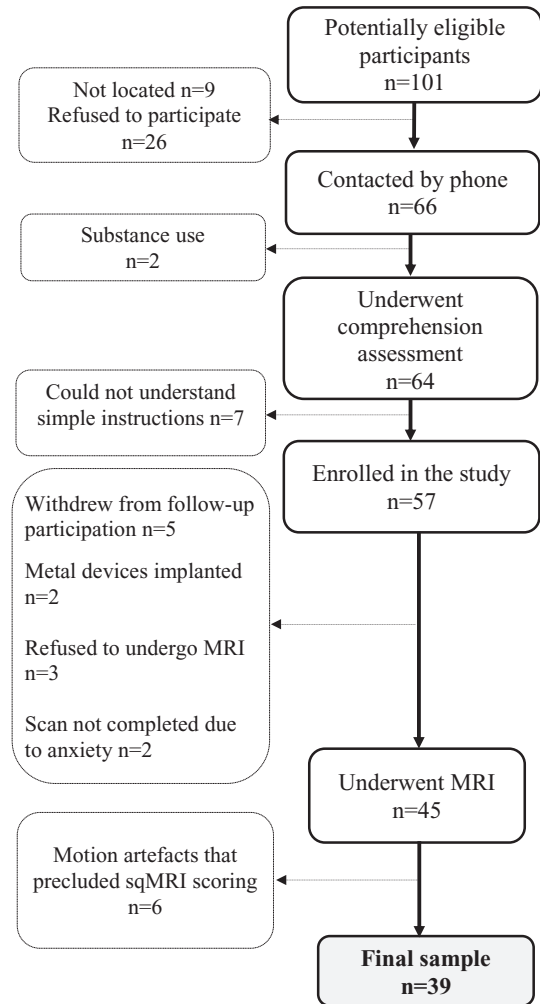


Fig. 1. Flowchart showing requirement process for participants.

participants presented a lesion involving the occipital lobe. Although frontal lesions were the second most frequent, their sqMRI score was generally lower ( $\leq 3.5$  out of 6 in all cases), indicating less severe lesions (in terms of extent) than those observed in the parietal lobe, where 59% of those with non-zero score had a score  $> 3.5$ . Interestingly, all participants, except eight who had no observable lesion (GMFCS: I  $n = 4$ , II  $n = 3$ , IV  $n = 1$ ; aetiology: unclassifiable  $n = 6$ , kernicterus  $n = 2$ ), presented with a lesion of the basal ganglia or thalamus. One third of participants with a visible brain lesion had lesions constrained to the basal ganglia and thalamus. Finally, no participant had an observable lesion in anterior corpus callosum or vermis.

#### 3.2. Association between sqMRI scoring and clinical outcomes

The final regression models examining the effects of sqMRI scores on clinical outcomes are presented in Table 2 and Fig. 4.

##### 3.2.1. Motor status

For clarity, results deriving from ordinal regression are reported henceforth using odds instead of log-odds. The odds of a higher GMFCS levels was 20% greater when the global sqMRI score increased by one unit ( $p < .001$ ). When the parietal sqMRI score increased by one unit, the odds of higher levels in GMFCS was 93% ( $p < .001$ ). Regarding fine motor function, the odds of higher levels in Manual ability classification system increased by 15% ( $p = .003$ ) for each unit increase in the global sqMRI score, whereas it increased 72% ( $p < .001$ ) as a result of a unit increase in parietal score (Fig. 5A).

**Table 1**  
Demographics and clinical data of dyskinetic cerebral palsy cohort ( $n = 39$ ).

Sex		19/20
n (female/male)		
Age		21 (13)/6–62
Median (interquartile range)/range		
Gestational age		3/5/31
n (< 32 weeks/32–36 weeks/ $\geq$ 37 weeks)		
Epilepsy status		26/10/3
n (no epilepsy/active/resolved)		
Type of lesion (Krägeloh-Mann categories, 2007)		23/8/0/8
n (CDGM/PWM/miscellaneous/normal)		
Aetiology, n		
HIE		15
Intra-cranial haemorrhage/infarction/hydrocephalus		5
Infection		1
Kernicterus		2
Unclassifiable		16
Motor distribution		
n (tetraplegia/hemiplegia/monoplegia)		32/6/1
Gross motor function (GMFCS) <sup>+</sup> , levels (n)		I (15); II (7); III (3); IV (5); V (9)
Manual ability (MACS) <sup>+</sup> , levels (n)		I (5); II (10); III (12); IV (3); V (9)
Communication (CFCS) <sup>+</sup> , levels (n)		I (15); II (16); III (4); IV (4); V (0)
		<b>Median (interquartile range)<sup>†</sup>/range<sup>†</sup>/n<sup>*</sup></b>
Intellectual functioning (RCPM)		29 (11)/12–36/39
Executive function	<b>Inhibition and sustained attention (SST)</b>	283 (16)/237–316/35
	<b>Selective verbal attention (Digit span)</b>	13 (8)/4–22/35
	<b>Selective visual attention (Spatial span)</b>	14 (8)/4–21/37
	<b>Cognitive flexibility (WCST)<sup>+</sup></b>	8 (7)/4–35/36
	<b>Goal setting (SOC)</b>	8 (3)/1–12/36
	<b>Information processing (Lexical verbal fluency)</b>	31 (18)/4–51/30
Visuosperception	<b>Visuospatial abilities (BJLOT)</b>	14 (8)/4–21/37
	<b>Visuosperceptual abilities (BFRT)</b>	13 (8)/4–22/39
Memory	<b>Visual short term (PRM)</b>	19.5 (5)/13–24/38
	<b>Verbal short term (VRM)</b>	23 (4)/13–24/38
	<b>Visual long term (PRM)</b>	8.5 (3)/3–12/38
	<b>Verbal long term (VRM)</b>	22 (4)/12–24/38
Vocabulary (PPVT-III)		136 (47)/45–182/39

BFRT: Benton's facial recognition test; BJLOT: Benton's judgment of line orientation test; CDGM: cortical and deep grey matter; CFCS: Communication function classification system; GMFCS: Gross motor function classification system; HIE: hypoxic-ischemic encephalopathy; MACS: Manual ability classification system; PPVT-III: Peabody picture vocabulary test-3rd; PRM: Pattern recognition memory; PWM: Periventricular white matter; RCPM: Raven's coloured progressive matrices; SOC: Stockings of Cambridge; SST: Stop signal task; VRM: Verbal recognition memory; WCST: Wisconsin card sorting test. +Higher scores indicate worse performance. † Raw scores. \*Despite the adaptations used (Supplementary table 5) missing data are due to the fact that some subjects present anarthria accompanied by very severe motor impairments that preclude using an appropriate response system for the test used.

### 3.2.2. Communication

The odds of higher Communication function classification system levels would increase 111% ( $p = .028$ ) as a result of a unit increase in the putamen score (Fig. 5B).

### 3.2.3. Cognition

A unit increase in the posterior thalamus sqMRI subscore was associated with a 17.47% decrease in the Raven's coloured progressive matrices score ( $B = -0.192$ ;  $p < .001$ ; Fig. 5C). This effect

contributed to the significant relationship between Raven's coloured progressive matrices scores and global sqMRI score (decrease of 1.78% per unit sqMRI increase;  $B = -0.018$ ;  $p < .001$ ).

Regarding executive functions, sqMRI scores were not associated with cognitive flexibility, goal setting, information processing, selective verbal attention or inhibition and sustained attention. By contrast, selective visual attention, measured by spatial span, was significantly associated with different models. The global model for spatial span indicated that a unit change in the sqMRI global score reduced the spatial span direct score by 3.44% ( $B = -0.035$ ;  $p < .001$ ). This appeared to be primarily driven by parietal and corpus callosum subscores, for which a unit increase would decrease the spatial span direct score by 6.11% ( $B = -0.063$ ;  $p = .023$ ) and 36.12% ( $B = -0.448$ ;  $p < .001$ ), respectively (Fig. 5D).

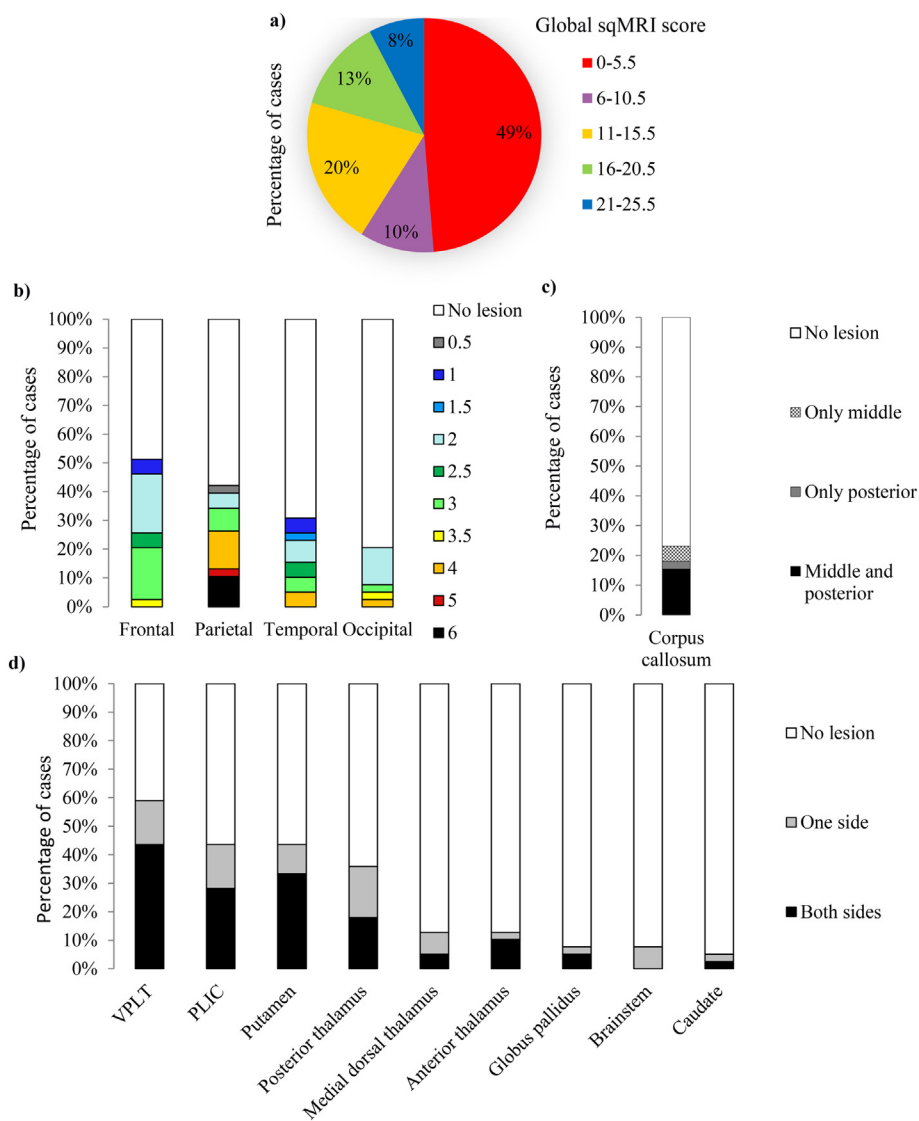
Visuospatial abilities were observed to decrease 7.5% as a result of a unit increase in the sqMRI global score ( $B = -0.078$ ;  $p = .007$ ) and visuosperceptive scores decreased by 12.98% as a result of a unit change in the medial dorsal thalamus score ( $B = -139$ ;  $p = .012$ ; Fig. 5E). Memory and vocabulary were not associated with any sqMRI score.

## 4. Discussion

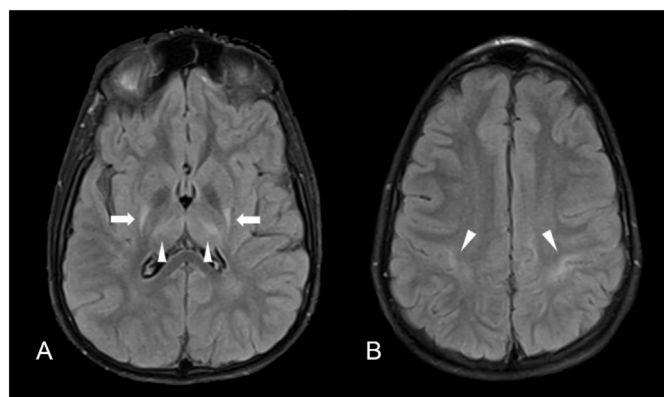
Overall, results indicate that (A) observable lesions in DCP most commonly occur in the lateral thalamus and frontal lobe, and (B) motor, communication and cognitive functioning are associated with brain lesion severity as measured by a simple lesion scoring system. By performing standardised sqMRI scoring, clinicians might use the weights from the presented models to predict several patient outcomes that can guide treatment.

In order to assist in the earlier detection of DCP, the frequency and location of brain lesions and their relationships with clinical outcomes should be understood. Previous neuroimaging studies of DCP have been based on qualitative analyses of pathogenesis (Himmelman and Uvebrant, 2011; Krägeloh-Mann and Cans, 2009; Towsley et al., 2011) or advanced neuroimaging protocols that cannot be easily utilised in a clinical context (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b; Yoshida et al., 2011). To enable clinical translation, in the present study brain lesions and their association with clinical outcomes have been characterized using a semi-quantitative scale for brain lesion severity on MRI, that is clinically accessible due to its relative simplicity and reliance only on standard clinical images. Basal ganglia and thalamus regions' involvement was evaluated in more detail than the original version of the sqMRI scale. Owing to the semi-quantitative scale's relatively accessible approach, the present study has a moderately good sample size considering the CP subtype and the wide range of cognitive assessments.

The present work reveals that the ventral posterior lateral thalamus is the most common brain lesion location in DCP. This is in agreement with the well-known pattern of brain involvement in diffuse hypoxic-ischemic injury of term neonates (Barkovich and Raybaud, 2005). The ventral posterior lateral thalamus has a fundamental role as a relay on S1 ascending projections influencing sensorimotor control (Chien et al., 2017; De Lafuente and Romo, 2005; Vazquez et al., 2012). The posterior thalamus also was frequently involved in our sample (36%). There are suggestions that the pulvinar critically supports an early visual pathway and plays a broad role in human cognition (Bridge et al., 2016). Congruent with these suggestions, in the present study posterior thalamic status was associated with intellectual functioning, as assessed by a visual reasoning task. By contrast, the medial dorsal thalamus and anterior thalamus were rarely impaired by lesions, but sufficiently so that medial dorsal thalamic status was associated with visuosperceptive abilities (evaluated by a facial recognition test). This is consistent with findings that medial dorsal thalamus is involved in familiarity detection (Kafkas and Montaldi, 2014) which seems to be influenced by face perception (Yan et al., 2017). Overall, regions involved by lesions in our group correspond to those reported in term children with hypoxic-



**Fig. 2.** Percentage of cases presenting different lesion severity according to sqMRI scores a) global score (maximum score of 40) to b) ranging from 0 to 6 for each lobar score (including right and left side) c) ranging from no lesion, middle and posterior lesion for corpus callosum and d) ranging from none, unilateral and bilateral lesion for basal ganglia, thalamus, brainstem and cerebellum. PLIC: posterior limb of internal capsule; VPLT: ventral posterior lateral thalamus.



**Fig. 3.** Axial FLAIR images of a 14 year old male, showing an example of the most common involvement observed, including ventral posterior lateral thalamus (A, arrowheads) and frontal perirolandic cortex (B, arrowheads). In this subject also putamina are involved (arrows).

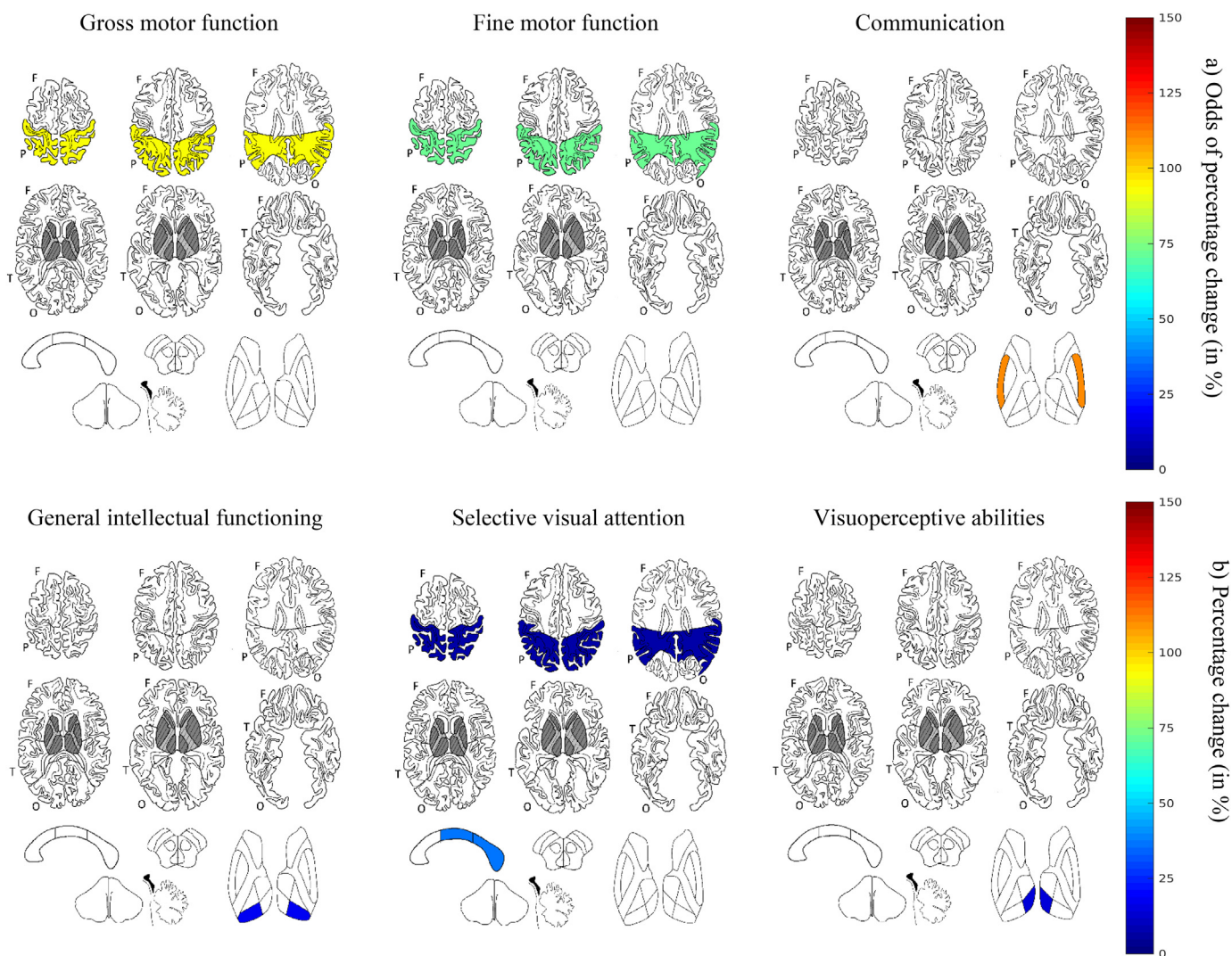
ischemic encephalopathy, kernicterus or other known etiopathogenetical factors which typically result in DCP (Graham et al., 2016; Krägeloh-Mann et al., 2002). A typical example of this is the involvement of basal ganglia–thalamus pattern mostly affecting the central grey nuclei and perirolandic cortex (Fig. 3). Each structure was, however, deliberately considered independently in the analyses.

With regards to cerebral lobes, results agreed with previous reports that white matter injury can occur in all cerebral lobes (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b). Frontal lobe damage was the second most common observable lesion (but the most common lobar involvement). This is consistent with the frequent abovementioned pattern of lesion reported in term neonates with hypoxic encephalopathy (Barkovich and Raybaud, 2005). Interestingly, although less frequent, parietal lobe lesions were more severe than frontal lobe lesions and were associated with poorer motor functioning. Of note, participants were diagnosed with CP with predominant dyskinetic features, thus lobar involvement might reflect the co-existence of spastic symptoms. This is consistent with the idea that sensory deficits

**Table 2**  
Final regression models showing the association between sqMRI scores, motor functioning, communication and cognitive domains.

Function assessed (test used)	sqMRI scores (predictors)	B	Std. Error	P	Omnibus test (global test)		AIC/BIC	
					Likelihood ratio chi-square	Degrees of freedom		
							Adjusted p	
Motor status <sup>o</sup>	Global model	Global score	0.180	0.050	< 0.001***	16.067	< 0.001***	–
	Subscores model	Parietal total	0.658	0.172	< 0.001***	18.041	< 0.001***	50.028/58.346
Fine motor function	Global model	Global score	0.136	0.045	0.003**	10.556	0.004**	–
	Subscores model	Parietal total	0.540	0.165	< 0.001***	12.482	< 0.001***	50.003/58.320
Communication <sup>o</sup>	Subscores model	Putamen	0.747	0.340	0.028*	5.119	0.033*	33.666/40.320
Intellectual functioning <sup>p</sup>	Global model	Global score	–0.018	0.005	< 0.001***	15.799	< 0.001***	–
	Subscores model	Posterior thalamus	–0.192	0.043	< 0.001***	21.752	< 0.001***	229.961/234.711
Executive function	ns							
	Inhibition and sustained attention (SST)							
Attentional control <sup>p</sup>	Global model	Global score	–0.035	0.008	< 0.001***	25.511	< 0.001***	–
	Subscores model	Parietal total	–0.063	0.028	0.023*	44.011	< 0.001***	191.770/197.991
Selective visual attention (Spatial span)	Global model	Corpus callosum	–0.448	0.094	< 0.001***	4.707	0.095	205.115/209.781
	Subscores model	Posterior thalamus	–0.128	0.065	0.049*			
Cognitive flexibility (WCST) <sup>b+</sup>	ns							
	Goal setting (SOC) <sup>p</sup>							
Information processing (Lexical verbal fluency) <sup>b</sup>	Global model	Global score	–0.023	0.010	0.019*	5.789	0.060	–
	Subscores model	Global score	–0.078	0.029	0.007**	7.010	0.036*	–
Visuospatial abilities (BJLOT) <sup>b</sup>	Global model	Global score	–0.139	0.055	0.012*	7.372	0.033*	241.630/246.620
	Subscores model	Medial dorsal thalamus						
Memory <sup>p</sup>	ns							
	Short term	Visual (PRM)						
Long term (PPVT-III)	ns							
	Verbal (VRM)							
Vocabulary <sup>b</sup>	ns							
	Verbal (VRM)							

BFRT: Benton's facial recognition test; BJLOT: Benton's judgment of line orientation test; CFCS: Communication function classification system; GMFCS: Gross motor function classification system; MACS: Manual ability classification system; PPVT-III: Peabody picture vocabulary test-3rd; PRM: Pattern recognition memory; RCPM: Raven's coloured progressive matrices; SOC: Stockings of Cambridge; sqMRI: Semi-quantitative scale for structural MRI; SST: Stop signal task; VRM: Verbal recognition memory; WCST: Wisconsin card sorting test. <sup>b</sup> Binomial negative model; <sup>p</sup> Poisson regression model; <sup>o</sup> Ordinal regression model; \*p ≤ .05, \*\*p ≤ .01; \*\*\*p ≤ .001 after false discovery rate correction for multiple comparisons in the global test. <sup>+</sup> Higher scores indicate worse performance. AIC and BIC values are only provided for subscores models.



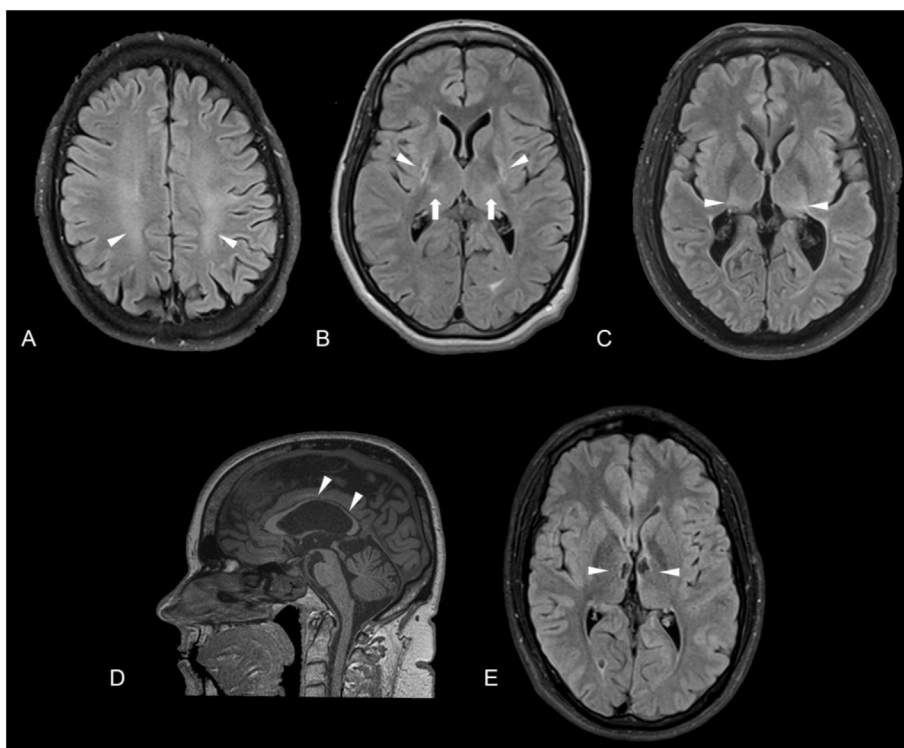
**Fig. 4.** An illustration of the results of the regression models obtained for the subscores regression models presented in Table 2. F: frontal, O: occipital, P: parietal, T: temporal. The colour bar indicates a) the percentage of odds change in each clinical outcome when the sqMRI score in this region increases by one unit b) the percentage change in clinical outcome when the sqMRI score in this region increases by one unit.

may alter motor coordination (Tsao et al., 2014). Additionally, more severe presentations in DCP have been reported to include cortical involvement (i.e. spastic symptoms) together with subcortical involvement (i.e. dyskinetic symptoms) (Monbaliu et al., 2017). Quantitative neuroimaging analyses previously reported associations between parietal structural connectivity and motor function in dyskinetic (Ballester-Plané et al., 2017), and in spastic CP (Arrigoni et al., 2016; Pannek et al., 2014; Tsao et al., 2015). The present study focused on motor severity in terms of GMFCS, rather than severity of dystonia which may explain why the association was not found with deep grey matter injury. Although quantitative neuroimaging studies report other associations between motor function and areas beyond the parietal lobe such as basal ganglia, thalamus and frontal cortex (Arrigoni et al., 2016; Ballester-Plané et al., 2017; Pannek et al., 2014; Tsao et al., 2015), at observable levels, these regions were not individually associated with motor functioning in the present study. A possible explanation for these differences with some of the studies above mentioned, might be due to the clinical measures used to assess motor outcome. Another reason may be that the sqMRI scale indexes the appearance of lesions on structural images, which are expected to be relatively static, whilst previous studies utilised measurements such as fractional anisotropy (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b; Yoshida et al., 2011), that may be affected by altered brain development and plasticity

(Deng et al., 2017). Finally, the association found between the severity of parietal injury and selective visual attention may be due to the involvement of the visual dorsal stream (Culham et al., 2006).

Despite the models here not relying on any form of prior knowledge, plausible associations between lesions in the remaining regions and clinical outcomes further add value to the potential clinical utilisation of the sqMRI. Specifically, abnormalities of the middle and posterior corpus callosum were associated with selective visual attention, a function this region has been associated with (Hines et al., 2002). Furthermore, damage occurring in the basal ganglia predominantly presented in the putamen was associated with communication ability. This aligns with a number of previous findings: that the putamen connects the basal ganglia with language regions (Ford et al., 2013), is heavily involved in semantic processes (Viñas-Guasch and Wu, 2017) and, when stimulated, induces dysarthria (Duffau, 2005).

Unexpectedly, no sqMRI score was associated with cognitive flexibility. Previous studies show that Wisconsin Card Sorting Test is sensitive to the white matter microstructural status and cortical thickness in DCP (Laporta-Hoyos et al., 2017a; Laporta-Hoyos et al., 2017b) but the present study implies that Wisconsin Card Sorting Test profiles might not be sensitive to macrostructural characteristics of observable lesions. For visuospatial abilities, global sqMRI score was the only score associated with performance, whilst in other domains global sqMRI



**Fig. 5.** Top row: Axial FLAIR images showing an example of the regions which showed an association with clinical measures. (A) Axial FLAIR: parietal white matter involvement (arrowheads); (B) Axial FLAIR: posterior putamina involvement (arrowheads); here with ventral posterior lateral thalamus involvement (arrows); (C) Axial FLAIR: posterior thalamic involvement (arrowheads); (D) Sagittal T1: thinning of middle and posterior corpus callosum (arrowheads); (E) Axial FLAIR: medial dorsal thalamus involvement (arrowheads). Images correspond to a (A) 50 year old male; (B) 21 year old female; (C) 42 year old male (D) 41 year old female and a (E) 17 year old male.

scores were less strongly associated than region-specific sqMRI scores. As such, it is recommended to use region-specific sqMRI scores when aiming to estimate any of the clinical outcomes assessed except for visuospatial domains. It is worthy of note that motor function and intellectual functioning have been shown to be associated with different observable lesions in the present study. This is interesting, as previous quantitative analyses that have relied on less regionally-specific methods, were unable to clearly differentiate which areas were involved with motor versus intellectual functioning (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b). Finally, further research with the revised scoring system for deep grey matter used is encouraged.

A limitation of the current work is the wide age range of participants assessed. Given that lesions are thought to be non-progressive, these results are promising, and encourage replication of the current findings in a longitudinal study in which imaging is performed during infancy and clinical outcomes assessed during later childhood and adolescence. Nevertheless, it is important to keep in mind that there have been years of plasticity and environmental factors that might have affected the structure-function relationship in this cohort. It must be also noted that people with severe communication difficulties cannot be included in a study of this nature, which indirectly precludes the inclusion of some participants at the highest GMFCS levels. Moreover, participants with higher GMFCS levels were less likely to be able hold still while undergoing the scan. These facts might have biased the cohort towards a less severe GMFCS motor level, which should be taken into account when considering the generalizability of our results to the whole spectrum of people with DCP. Furthermore, predominance of dystonia versus choreoathetosis was not considered in this study. As dystonia or choreoathetosis might have different neuroanatomical substrates, future studies including a comprehensive clinical assessment will be encouraged to clarify in more detail their neuroanatomical correlates. Finally, further studies are needed to assess the reliability of the updated version of the sqMRI scale used in the present study in order to support the generalizability of our results in different cohorts of people with DCP.

One major goal in CP research is the ability to provide early diagnoses and prognoses of outcomes, enabling enrolment of children into

early-intervention programs, which may lead to more effective motor, communication and cognitive functions. For neuroimaging tools to provide this service, they must not only demonstrate meaningful and plausible associations between measurements and clinical outcomes, but also do so in a manner that integrates easily with clinicians' facilities and expertise. Here we demonstrated that the clinically accessible sqMRI scale is associated with outcomes in DCP. Taking into account that CP disturbances in the brain are not progressive, this scoring may enable clinicians to determine future clinical outcomes associated with the early brain injury.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2018.06.015>.

## Acknowledgements

The authors wish to thank all participants and their families for their collaboration. We would also like to thank the association ASPACE and the Vigatans and ASDI centers for providing patients enrolled in this study, as well as UTAC service of the Faculty of Psychology at the University of Barcelona for their guidance in adapting tests. We further acknowledge Rosa Pasquariello for supervising the revision of the semi-quantitative scale. Finally, thanks to the University of Barcelona for supporting open access publication.

## Funding

This work was supported by the Ministerio de Ciencia e Innovación (grant code PSI2011/24386), by the Ministerio de Economía y Competitividad (PSI2016-75979-R AEI/FEDER, UE) and by Generalitat de Catalunya (2014SGR98). Roslyn Boyd is supported by a NHMRC Research Fellowship. Olga Laporta received a research grant from Ministerio de educación, cultura y deporte of the government of Spain (grant code FPU13/06435) and an Endeavour research Fellowship by the Australian Government (grant code 5240). Lee Reid and Alex Pagnozzi each are supported by an Advance Queensland Research Fellowship.



## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2018.06.015>.

## References

- Aravamuthan, B.R., Waugh, J.L., 2016. Pediatric neurology localization of basal ganglia and thalamic damage in dyskinetic cerebral palsy. *Pediatr. Neurol.* 54, 11–21. <http://dx.doi.org/10.1016/j.pediatrneurol.2015.10.005>.
- Arrigoni, X.F., Peruzzo, X.D., Gagliardi, X.C., Maghini, X.C., Colombo, X.P., Iammarrone, X.F.S., Pierpaoli, X.C., Triulzi, X.F., 2016. Whole-Brain DTI Assessment of white matter damage in children with bilateral cerebral palsy: evidence of involvement beyond the primary target of the anoxic insult. *Am. Soc. Neuroradiol.* 37, 1347–1353. <http://dx.doi.org/10.3174/ajnr.A4717>.
- Ballester-Plané, J., Schmidt, R., Laporta-Hoyos, O., Delgado, I., Zubiaurre-Elorza, L., Macaya, A., Pilar, P., de Reus, M.A., van den Heuvel, M.P., Pueyo, R., 2017. Whole-brain structural connectivity in dyskinetic cerebral palsy and its association with motor and cognitive function. *Hum. Brain Mapp.* 38, 4594–4612. <http://dx.doi.org/10.1002/hbm.23686>.
- Barkovich, J., Raybaud, C., 2005. *Pediatric Neuroimaging*. Lippincott Williams & Wilkins, New York.
- Benini, R., Dagenais, L., Shevell, M.I., 2013. Normal imaging in patients with cerebral palsy: what does it tell us? *J. Pediatr.* 162, 369–374. <http://dx.doi.org/10.1016/j.jpeds.2012.07.044>.
- Benton, A.L., 1994. *Contributions to Neuropsychological Assessment: A Clinical Manual*. vol. 2 Oxford University Press, New York.
- Bridge, H., Leopold, D.A., Bourne, J.A., 2016. Adaptive Pulvinar circuitry supports visual cognition. *Trends Cogn. Sci.* 20, 146–157. <http://dx.doi.org/10.1016/j.tics.2015.10.003>.
- Cambridge Cognition, 1999. *Limited Cambridge Neuropsychological Test Automated Battery*. Cambridge Cognition, Cambridge.
- Chien, J.H., Korzeniewska, A., Colloca, L., Campbell, C., Dougherty, P., Lenz, F., 2017. Human thalamic somatosensory nucleus (Ventral Caudal, Vc) as a locus for stimulation by INPUTS from tactile, noxious and thermal sensors on an active prosthesis. *Sensors (Basel)* 24, 17. <http://dx.doi.org/10.3390/s17061197>.
- Colver, A., Rapp, M., Eisemann, N., Ehlinger, V., Thyen, U., Dickinson, H.O., Parkes, J., Parkinson, K., Nystrand, M., Fauconnier, J., Marcelli, M., Michelsen, S.I., Arnaud, C., 2015. Self-reported quality of life of adolescents with cerebral palsy: a cross-sectional and longitudinal analysis. *Lancet* 385, 705–716. [http://dx.doi.org/10.1016/S0140-6736\(14\)61229-0](http://dx.doi.org/10.1016/S0140-6736(14)61229-0).
- Culham, J.C., Cavina-Pratesi, C., Singhal, A., 2006. The role of parietal cortex in visuo-motor control: what have we learned from neuroimaging? *Neuropsychologia* 44, 2668–2684. <http://dx.doi.org/10.1016/j.neuropsychologia.2005.11.003>.
- De Lafuente, V., Romo, R., 2005. Neuronal correlates of subjective sensory experience. *Nat. Neurosci.* 8, 1698–1703. <http://dx.doi.org/10.1038/nn1587>.
- Deng, F., Zhao, L., Liu, C., Lu, M., Zhang, S., Huang, H., Chen, L., Wu, X., 2017. Plasticity in deep and superficial white matter: a DTI study in world class gymnasts. *Brain Struct. Funct.* 223, 1849–1862. <http://dx.doi.org/10.1007/s00429-017-1594-9>.
- Duffau, H., 2005. The role of dominant striatum in language: a study using intraoperative electrical stimulations. *J. Neurol. Neurosurg. Psychiatry* 76, 940–946. <http://dx.doi.org/10.1136/jnnp.2004.045948>.
- Dunn, L.M., 1997. *Peabody Picture Vocabulary Test-Third Edition (PPVT-III)*. Circle Pines, American Guidance Services, MN.
- Fiori, S., Cioni, G., Klingels, K., Ortibus, E., Van Gestel, L., Rose, S., Boyd, R.N., Feys, H., Guzzetta, A., 2014. Reliability of a novel, semi-quantitative scale for classification of structural brain magnetic resonance imaging in children with cerebral palsy. *Dev. Med. Child Neurol.* 56, 839–845. <http://dx.doi.org/10.1111/dmcn.12457>.
- Fiori, S., Guzzetta, A., Pannek, K., Ware, R.S., Rossi, G., Klingels, K., Feys, H., Coulthard, A., Cioni, G., Rose, S., Boyd, R.N., 2015. Validity of semi-quantitative scale for brain MRI in unilateral cerebral palsy due to periventricular white matter lesions: relationship with hand sensorimotor function and structural connectivity. *NeuroImage Clin.* 8, 104–109. <http://dx.doi.org/10.1016/j.nicl.2015.04.005>.
- Ford, A.A., Triplett, W., Sudhyadhom, A., Gullett, J., McGregor, K., Fitzgerald, D.B., Mareci, T., White, K., Crosson, B., Weiss, K.L., 2013. Broca's area and its striatal and thalamic connections: a diffusion-MRI tractography study. *Front. Neuroanat.* 7, 8. <http://dx.doi.org/10.3389/fnana.2013.00008>.
- Graham, H.K., Rosenbaum, P., Paneth, N., Dan, B., Lin, J.-P., Damiano, D.L., Becher, J.G., Gaebler-Spira, D., Colver, A., Reddihough, D.S., Crompton, K.E., Lieber, R.L., 2016. Cerebral palsy. *Nat. Rev. Dis. Prim.* 15082. <http://dx.doi.org/10.1038/nrdp.2016.5>.
- Himmelmann, K., Uvebrant, P., 2011. Function and neuroimaging in cerebral palsy: a population-based study. *Dev. Med. Child Neurol.* 53, 516–521. <http://dx.doi.org/10.1111/j.1469-8749.2011.03932.x>.
- Himmelmann, K., McManus, V., Hagberg, G., Uvebrant, P., Krägeloh-Mann, I., Cans, C., Krägeloh-Mann, I., 2009. Dyskinetic cerebral palsy in Europe: trends in prevalence and severity. *Arch. Dis. Child.* 94, 921–926. <http://dx.doi.org/10.1136/adc.2008.144014>.
- Hines, R.J., Paul, L.K., Brown, W.S., 2002. Spatial attention in agenesis of the corpus callosum: shifting attention between visual fields. *Neuropsychologia* 40, 1804–1814.
- Kafkas, A., Montaldi, D., 2014. Two separate, but interacting, neural systems for familiarity and novelty detection: a dual-route mechanism. *Hippocampus* 24, 516–527. <http://dx.doi.org/10.1002/hipo.22241>.
- Kongs, S.K., Thompson, L.L., Iverson, G.L., Heaton, R.K., 2000. *Wisconsin Card Sorting Test – 64 Card Version*. Psychological Assessment Resources, Odessa.
- Krägeloh-Mann, I., 2004. Imaging of early brain injury and cortical plasticity. *Exp. Neurol.* 190 (Suppl.), 84–90. <http://dx.doi.org/10.1016/j.expneurol.2004.05.037>.
- Krägeloh-Mann, I., Cans, C., 2009. Cerebral palsy update. *Brain and Development* 31, 537–544. <http://dx.doi.org/10.1016/j.braindev.2009.03.009>.
- Krageloh-Mann, I., Horber, V., 2007. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev. Med. Child Neurol.* 49, 144–151. <http://dx.doi.org/10.1111/j.1469-8749.2007.00144.x>.
- Krägeloh-Mann, I., Helber, A., Mader, I., Staudt, M., Wolff, M., Groenendaal, F., Devries, L., Krägeloh-Mann, I., 2002. Bilateral lesions of thalamus and basal ganglia: origin and outcome. *Dev. Med. Child Neurol.* 44, 477–484.
- Laporta-Hoyos, O., Ballester-Plané, J., Póo, P., Macaya, A., Meléndez-Plumed, M., Vázquez, E., Delgado, I., Zubiaurre-Elorza, L., Botellero, V.L., Narberhaus, A., Toro-Tamargo, E., Segarra, D., Pueyo, R., 2017a. Proxy-reported quality of life in adolescents and adults with dyskinetic cerebral palsy is associated with executive functions and cortical thickness. *Qual. Life Res.* 26, 1209–1222. <http://dx.doi.org/10.1007/s11136-016-1433-0>.
- Laporta-Hoyos, O., Pannek, K., Ballester-Plané, J., Reid, L.B., Vázquez, E., Delgado, I., Zubiaurre-Elorza, L., Macaya, A., Póo, P., Meléndez-Plumed, M., Junqué, C., Boyd, R., Pueyo, R., 2017b. White matter integrity in dyskinetic cerebral palsy: relationship with intelligence quotient and executive function. *NeuroImage Clin.* 15, 789–800. <http://dx.doi.org/10.1016/j.nicl.2017.05.005>.
- Monbaliu, E., de Cock, P., Ortibus, E., Heyman, L., Klingels, K., Feys, H., 2015. Clinical patterns of dystonia and choreoathetosis in participants with dyskinetic cerebral palsy. *Dev. Med. Child Neurol.* 58, 138–144. <http://dx.doi.org/10.1111/dmcn.12846>.
- Monbaliu, E., Himmelmann, K., Lin, J., Ortibus, E., Bonouvrié, L., Feys, H., Vermeulen, R.J., Dan, B., 2017. Clinical Presentation and Management of Dyskinetic Cerebral Palsy. *Lancet. Neurol.* 16, 741–749. [http://dx.doi.org/10.1016/S1474-4422\(17\)30252-1](http://dx.doi.org/10.1016/S1474-4422(17)30252-1).
- Novak, I., Hines, M., Goldsmith, S., Barclay, R., 2012. Clinical prognostic messages from a systematic review on cerebral palsy. *Pediatrics* 130, e1285–e1312. <http://dx.doi.org/10.1542/peds.2012-0924>.
- Pannek, K., Boyd, R.N., Fiori, S., Guzzetta, A., Rose, S.E., 2014. Assessment of the structural brain network reveals altered connectivity in children with unilateral cerebral palsy due to periventricular white matter lesions. *NeuroImage Clin.* 5, 84–92. <http://dx.doi.org/10.1016/j.nicl.2014.05.018>.
- Parkes, J., White-Koning, M., Dickinson, H.O., Thyen, U., Arnaud, C., Beckung, E., Fauconnier, J., Marcelli, M., McManus, V., Michelsen, S.I., Parkinson, K., Colver, A., 2008. Psychological problems in children with cerebral palsy: a cross-sectional European study. *J. Child Psychol. Psychiatry Allied Discip.* 49, 405–413. <http://dx.doi.org/10.1111/j.1469-7610.2007.01845.x>.
- Peña-Casanova, J., Quiñones-Ubeda, S., Gramunt-Fombuena, N., Quintana-Aparicio, M., Aguilar, M., Badenes, D., Cerulla, N., Molinuevo, J.L., Ruiz, E., Robles, A., Barquero, M.S., Antúnez, C., Martínez-Parra, C., Frank-García, A., Fernández, M., Alfonso, V., Sol, J.M., Blesa, R., NEURONORMA Study Team, 2009. Spanish multicenter normative studies (NEURONORMA project): norms for verbal fluency tests. *Arch. Clin. Neuropsychol.* 4, 395–411. <http://dx.doi.org/10.1093/arclin/acp042>.
- Raven, J.C., Court, J.H., Seisdedos Cubero, N., 2001. *Raven Matrices Progressivas Escalas: CPM Color, SPM General, APM Superior*. TEA Ediciones, Madrid.
- Rosenbaum, P., Paneth, N., Leviton, A., Goldstein, M., Bax, M., Damiano, D., Dan, B., Jacobsson, B., 2007. A report: the definition and classification of cerebral palsy April 2006. *Dev. Med. Child Neurol.* 109 (Suppl.), 8–14.
- Straub, K., Obrzut, J.E., 2009. Effects of cerebral palsy on neuropsychological function. *J. Dev. Phys. Disabil.* 21, 153–157. <http://dx.doi.org/10.1007/s10882-009-9130-3>.
- Toronto, A.S., 1973. *Screening Test of Spanish Grammar*. Northwestern University Press, Evanston, IL.
- Towsley, K., Shevell, M.I., Dagenais, L., Consortium, R., 2011. Population-based study of neuroimaging findings in children with cerebral palsy. *Eur. J. Paediatr. Neurol.* 15, 29–35. <http://dx.doi.org/10.1016/j.ejpn.2010.07.005>.
- Tsao, H., Pannek, K., Fiori, S., Boyd, R.N., Rose, S., 2014. Reduced integrity of sensorimotor projections traversing the posterior limb of the internal capsule in children with congenital hemiparesis. *Res. Dev. Disabil.* 35, 250–260. <http://dx.doi.org/10.1016/j.ridd.2013.11.001>.
- Tsao, H., Pannek, K., Boyd, R.N., Rose, S.E., 2015. Changes in the integrity of thalamo-cortical connections are associated with sensorimotor deficits in children with congenital hemiplegia. *Brain Struct. Funct.* 220, 307–318. <http://dx.doi.org/10.1007/s00429-013-0656-x>.
- Vázquez, Y., Zainos, A., Alvarez, M., Salinas, E., Romo, R., 2012. Neural coding and perceptual detection in the primate somatosensory thalamus. *Proc. Natl. Acad. Sci.* 109, 15006–15011. <http://dx.doi.org/10.1073/pnas.1212535109>.
- Viñas-Guasch, N., Wu, Y.J., 2017. The role of the putamen in language: a meta-analytic connectivity modeling study. *Brain Struct. Funct.* 222, 3991–4004. <http://dx.doi.org/10.1007/s00429-017-1450-y>.
- Wechsler, D., 1999. *WAIS III: Escala de inteligencia de Wechsler para adultos-III manual técnico*. TEA Ediciones, Madrid.
- Wechsler, D., 2003. *Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV)*. The Psychological Corporation, San Antonio, TX.
- Wechsler, D., Naglieri, J.A., 2006. *Wechsler Nonverbal Scale of Ability (WNV)*. NCS Pearson, Inc.
- Yan, X., Young, A.W., Andrews, T.J., 2017. The automaticity of face perception is influenced by familiarity. *Atten Percept Psychophys.* 79, 2202–2211. <http://dx.doi.org/10.3758/s13414-017-1362-1>.
- Yoshida, S., Hayakawa, K., Oishi, K., Mori, S., Kanda, T., Yamori, Y., Yoshida, N., Hirota, H., Iwami, M., Okano, S., Matsushita, H., Imaging, B.D., 2011. Athetotic and spastic cerebral palsy: anatomic characterization based on diffusion-tensor imaging. *Radiology* 260, 511–520. <http://dx.doi.org/10.1148/radiol.11101783>.