Title

Cognitive, academic, executive and psychological functioning in children with spastic motor type cerebral palsy: Influence of extent, location, and laterality of brain lesions

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1. Introduction

Cerebral palsy (CP) is the most common physical disability in childhood with an estimated prevalence of 1.4 per 1000 live births in Australia (The Australian Cerebral Palsy Register (ACPR) Group, 2020). Spastic motor type CP comprises around 86% of CP cases (Smithers-Sheedy et al., 2016; Surveillance of Cerebral Palsy in Europe, 2002). In addition, children with CP often have impairments of cognition (1 in 2), language (6 in 10) (Mei et al., 2016) and behavioural disorders (Parkes et al., 2008; Sigurdardottir et al., 2010). Such comorbidities are major impediments to participation (Fauconnier et al., 2009), social functioning (Bottcher, 2010), and quality of life (Colver et al., 2015, 2014; Laporta-Hoyos et al., 2017; Majnemer et al., 2007), and may influence the efficacy of motor interventions (Fazzi et al., 2005; Kim et al., 2006; Reid et al., 2015). Furthermore, children with both CP and intellectual disability have a higher risk of mental health symptoms (Parkes et al., 2008) and a reduced 35 year survival rate than those without intellectual disability (Reid et al., 2018). Cognitive impairments contribute significantly to the lifetime economic costs of CP (Deloitte Access Economics, 2019).

Thirty to fifty percent of individuals with CP have an intellectual quotient (IQ) below 70 (Delacy and Reid, 2016; Fluss and Lidzba, 2020; Novak et al., 2012; Stadskeiv, 2020), however there is considerable variability (Numata et al., 2013; Stadskeiv et al., 2018). Epilepsy and lower motor functioning have consistently been associated with reduced cognitive functioning (Stadskeiv, 2020). Children with the spastic motor type tend to present better performance on verbal than on perceptual reasoning (Fluss and Lidzba, 2020; Stadskeiv, 2020). Delays in receptive and expressive language have also been reported (Choi et al., 2017; Hustad et al., 2014; Mei et al., 2016; Nordberg et al., 2015; Vos et al., 2014). Children with an average IQ may still face academic difficulties due to specific learning disabilities (Bottcher, 2010). Academic skills directly represent the real-life impact of cognitive dysfunctions (Fluss and Lidzba, 2020), and play a role in access to continued education and employment. Although reading ability tends to be grossly preserved in ambulant children, only 43% of children with hemiplegia, 38% with diplegia and 8% with quadriplegia achieve reading performance within the normal range (Gillies et al., 2018). Children with dysarthria are likely to present with poorer phonological awareness (Bishop et al., 1990; Card and Dodd, 2006; Hart et al., 2007), which impedes literacy development (Peeters et al., 2009). In children with unilateral CP, despite preserved IQ, academic attainment difficulties are frequent and more prevalent in the field of mathematics (Fluss and Lidzba, 2020). Children with unilateral or bilateral spastic CP present difficulties with proxy-reported executive function (EF) (Bottcher et al., 2010; Forsman and Eliasson, 2016; Hustad et al., 2018; Whittingham et al., 2014). Such difficulties appear consistently, even in children attending mainstream schools and those who are not intellectually impaired (Bottcher et al., 2010; Caillies et al., 2012; Di Lieto et al., 2017; Jenks et al., 2009; Kolk and Talvik, 2000; Li et al., 2014; Scheck et al., 2015).

Magnetic resonance imaging (MRI) contributes to the early diagnosis of CP (Novak et al., 2017), and helps to understand its pathological basis and relationship with clinical outcomes (Bax et al., 2006). The time burdens associated with acquisition and analysis of sophisticated quantitative neuroimaging studies, however, limit clinical adoption. In contrast, categorical descriptions of the lesion pattern (Himmelman et al., 2016; Krageloh-Mann and Horber, 2007) are easily conducted in the clinic but offer limited precision. The semi-quantitative scale for classification of structural brain MRI (sqMRI) is a valid and reliable alternative that systematically

assesses both the extent and the anatomical location of the brain lesion/s in people with CP (Fiori et al., 2015, 2014).

Studies that have explored the association between general intellectual functioning and brain structure in children with spastic motor type CP mostly used categorical descriptions of lesion patterns (Ahlin et al., 2017; Cioni et al., 1999; Himmelmann et al., 2021; Himmelmann and Uvebrant, 2011; Reid et al., 2018; Stadskleiv et al., 2018) and did not use standardized IQ measures. In children with spastic motor type CP, only three studies have investigated the relationship between general intellectual functioning and MRI characteristics other than the lesion pattern (Moll et al., 2021; Rai et al., 2013; S. M. Reid et al., 2015).

Neuroimaging studies of language functioning using a semi-quantitative approach have predominantly focused on basic communication skills including speech rather than more-complex verbal-related cognitive and/or academic skills such as vocabulary, reading and spelling. Brain lesion severity might be more useful for predicting language development than brain MRI categorization (Choi et al., 2017), and the global sqMRI score has previously been related with communication ability in a predominantly spastic motor type CP cohort (Coleman et al., 2016). In typically developing persons, language is predominantly processed in the left hemisphere, implying that it would be prudent to account for the laterality of brain lesions when investigating associations between brain characteristics and language (Corballis, 2012). Previous studies reported normal language function in children with right-sided hemiplegia (Frampton et al., 1998) and left-brain lesions (Muter et al., 1997) and similar degree of functional activation between right and left lateralized language functioning (Guzzetta et al., 2008; Staudt et al., 2002). This has been interpreted as evidence of functional equipotentiality. The brain's ability to reorganize, however, is likely imperfect: left sided lesions in children with CP have been associated with poorer communication skills (Coleman et al., 2016).

The association between proxy-reported behavioural manifestations of EF and quantitative brain measures has been studied in children with unilateral CP (Pagnozzi et al., 2016b). Neuroimaging studies taking a qualitative categorical approach have not found differences in Behaviour Rating Inventory of Executive Function (BRIEF) scores between patient groups displaying different lesion patterns but have found associations between task-based EF measures and focal frontal lesions (Crichton et al., 2020). Skranes et al. (2008) found that performance-based EF is related with ventricular dilatation, white matter reduction, and the total degree of brain abnormalities by using a modification of a semi-quantitative approach (Inder et al., 2003; Woodward et al., 2006).

To date, no study has examined the association between brain lesions and functioning on a broad spectrum of psychological outcomes by using the sqMRI scale in individuals with spastic motor type. Importantly, no imaging study has considered academic attainment. Potentially, examining relationships between the degree of lateralization (asymmetry) of brain lesions (rather than only left/right dichotomies) and complex verbal-related skills could help to increase our understanding of language reorganization after early brain injury.

The aim of this study was to determine which combination of clinical scores (encompassing sqMRI, motor functioning, and epilepsy status) is associated with psychological outcomes (cognitive, academic, and executive functioning as well as psychological adjustment) in children and adolescents with spastic motor type CP.

Specifically, we investigated associations between 1) the location and extent of brain lesions with psychological outcomes 2) the laterality of brain lesions and performance in verbal-related cognitive/academic outcomes. We hypothesized that the severity of the brain lesion would be negatively associated with clinical functioning, and that left sided brain lesions would be detrimental for verbal-related functions.

2. Materials and methods

We conducted a cross-sectional analysis of data pooled from two population-based cohorts recruited in Queensland, Australia, comparing sqMRI scores in a total of 101 participants with spastic CP with measures of cognitive and psychological functioning. The University of Queensland and Children's Health Queensland ethics committees granted ethical approval (HREC/14/QRCH/329; HREC/11/QRCH/35). Informed parental consent was obtained for all participants.

2.1. Participants

Participants were recruited as part of two cohort studies of participants with CP at the Queensland Cerebral Palsy and Rehabilitation Research Centre (Brisbane, Australia): the "Move it to improve it" (Mitii; recruitment period 2011 – 2014) (Boyd et al., 2013) and the "Comprehensive surveillance to PREDICT outcomes for school age children with CP" (PREDICT-CP; recruitment period 2016 – 2020) (Boyd et al., 2017). These studies included 8 – 18 year-old children and adolescents born in Queensland, physician-diagnosed CP with either any CP motor type (Boyd et al., 2017) or predominant spastic-type mild to moderate congenital hemiplegia (Boyd et al., 2013). Uncontrolled epilepsy was an explicit exclusion criterion for the Mitii study. Further inclusion and exclusion criteria are detailed in the study protocols. The present study includes participants who met the additional criteria: 1) presented with spastic CP motor type with unilateral or bilateral motor distribution; 2) completed any of the performance-based tests and proxy-reported questionnaires considered in the present study (see section 2.4 in methods); 3) underwent a 3T brain MRI as part of the Mitii or PREDICT-CP studies; 4) presented with observable brain lesions in the current or previous clinical brain MRI.

2.2. MRI acquisition

MRI data were acquired at study enrolment (Boyd et al., 2017, 2013) using a 3T Siemens Magnetom PRISMA (Predict-CP participants) or a 3T Siemens Trio (Mitii participants; Siemens, Erlangen, Germany). Imaging included 3D T1-weighted Magnetisation Prepared Rapid Gradient Echo (MPRAGE) and T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) acquisitions. FLAIR images were acquired to match reliability parameters of the sqMRI scale (Fiori et al., 2014).

2.3. Independent variables

2.3.1. sqMRI scores and laterality

The sqMRI scale scoring was performed by an MRI-trained neurologist (SF) according to the procedure and calculation detailed in (Fiori et al., 2014) with extension to detail the specific involvement of the different parts of the thalamic and lenticular nuclei as reported in a previous study (Laporta-Hoyos et al., 2018). In brief, this system scores severity of lesions by brain region, where progressively higher scores represent increased lesion

extension. Each of the four brain lobes is scored from 0 to 3 for each hemisphere. As detailed in in Fiori et al. (2014) three layers per lobe are considered when calculating the lobar scores: periventricular (including periventricular white matter), middle (including middle white matter) and cortico/subcortical (including grey matter). These are combined to provide a single score per lobe which includes both white and grey matter. Three sections of the corpus callosum (Figure 1 b), each half of the brainstem and eight deep brain regions (Figure 1 c) are scored with 1 each if they contain lesions. Additionally, the cerebellum is scored (ranging from 0 to 3). The global sqMRI score is the total sum of all scores, ranging from 0 to 48. In addition, brain lesion types were classified according to Krägeloh-Mann (Krägeloh-Mann, 2004) as per previous qualitative neuroimaging studies (Himmelmann and Uvebrant, 2011; Krägeloh-Mann and Cans, 2009; Towsley et al., 2011).

For aim 1, we explored the association between the location and extent of brain lesions with cognitive and psychological outcomes. Specifically, we used both (a) the global sqMRI score and (b) each individual regional score with left and right hemispheric scores combined (Figure 1 displays all regional scores considered in our analysis). The cerebellum contributed to the global sqMRI score but was not analysed as a regional score because only two participants showed involvement of this structure. For Aim 2, we undertook further analysis by calculating a lesion laterality index (Desmond et al., 1995) for brain regions whose lesions were identified as being significantly associated with verbal-related functioning in Aim 1. Laterality index ranged from -1 to 1 with a score approximating zero indicating a more bilateral lesion distribution; a score approaching 'one' indicated predominant right involvement and a score approaching 'negative one' indicated predominant left sided involvement.

2.3.2. Clinical measures

Gross motor function was classified by using the Gross Motor Function Classification System (GMFCS) (Palisano et al., 2008) and the ability to handle objects in daily life by the Manual Ability Classification System (MACS) (Eliasson et al., 2006). Motor distribution was classified for unilateral (including right and left) and bilateral (including diplegia, triplegia, and quadriplegia) clinical presentations (Surveillance of Cerebral Palsy in Europe, 2007). All classifications were made by paediatric physiotherapists (GMFCS, motor type) and occupational therapists (MACS). Presence of epilepsy was defined as having a formal diagnosis by a health professional as reviewed in the clinical history and/or reported by the parents (Boyd et al., 2017, 2013).

2.3.3. Outcomes: cognitive, academic, and executive functioning as well as psychological adjustment

For general intellectual functioning, both non-verbal and verbal intellectual functioning were assessed by a registered psychologist using measures of visual abstract reasoning (Raven's coloured progressive matrices, RCPM) (Raven et al., 2008) and receptive vocabulary (Peabody Picture Vocabulary Test Fourth edition, PPVT-IV) (Dunn and Dunn, 2007). To measure general intellectual functioning in CP, tests composed of one single task, free of response time requirements that use a multiple-choice format are the most appropriate (Ballester-Plané et al., 2016; Stadskleiv, 2020). The RCPM and the PPVT-IV are proxy IQ tests that meet these criteria and have been widely used in children with CP. While both tests provide a proxy IQ score, they measure different aspects of general intellectual functioning (nonverbal and verbal) and therefore can demonstrate divergence

in resulting proxy IQ levels (Ballester-Plané et al., 2016). The proxy IQ-scores (mean 100; standard deviation (SD) 15), controlling for age, were used in all analyses.

Academic attainment was assessed by a psychologist using the second edition of the Wechsler Individual Achievement Test (WIAT-II) (NCS Pearson, 2007), which indexes achievement across multiple academic domains. Word reading, spelling and numerical operations sub-tests were used in this study. Normal standard scores (mean 100; SD 15) controlling for age were used.

Behavioural manifestations of executive functioning in everyday life were measured by the parent report measure the BRIEF (Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, 2000). Normal standard T-scores for the global executive composite (mean 50; SD 10) controlling for age and sex were used. For the global executive composite T score, scores lower than 60 are considered to be within normal limits.

The Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997) completed by the parents was used to measure psychological adjustment including emotional, behavioural and socialization problems. The total difficulties score, a measure of overall psychological adjustment was used in all analyses.

All the above measures were used for Aim 1. As Aim 2 focussed on verbal-related functioning, analyses included only verbal proxy IQ measured by the PPVT-IV, and word reading and spelling achievement as measured by the WIAT-II.

2.3.4. Statistical analysis

The cognitive, academic, and executive functioning as well as psychological adjustment outcomes were treated as dependent variables. For Aim 1, the most predictive multivariable model was built for each of the outcomes. First, relationships between global sqMRI score and each outcome were examined using linear regression. The variables of unilateral or bilateral CP and global sqMRI scores were automatically included as covariables for control purposes, before motor function (GMFCS, MACS) and epilepsy were considered for inclusion as covariables. The best multivariable predictive model for each outcome was identified according to Bayesian information criterion (BIC) which identifies the model with the most explanatory power relative to its complexity (Izenman, 2008). Second, relationships between the regional sqMRI scores presented in Figure 1 and each outcome were similarly examined. Again, the best multivariable predictive model was identified according to BIC. Presentation of unilateral or bilateral CP was automatically included while each regional sqMRI score, motor function (GMFCS, MACS) and epilepsy were considered for inclusion as covariables. Middle and posterior corpus callosum scores were combined to avoid multicollinearity (a breach of statistical assumptions), while the anterior portion was considered separately. This is supported by evidence that the anterior third of the corpus callosum connects with high-order prefrontal areas while the middle and posterior thirds connect with temporo-parietal associative areas, as well as motor, somatosensory, auditory, and visual cortices (Raybaud, 2010; Tzourio-Mazoyer, 2016). These areas are therefore expected to play different roles in cognitive and psychological functioning outcomes.

For all models, assumptions of normality, linearity, and homoscedasticity were examined using residual scatterplots and histograms. Multicollinearity between variables was assessed using the variance inflation factor coefficient and checking the correlation matrix between included independent variables. When an unexpected Beta sign was found, additional checking for multicollinearity was undertaken whereby moderately correlated independent variables were removed singularly from the model and model findings checked for consistency. The Durbin-Watson test was used to check the lack of autocorrelation of the error terms and when values were between 1.5 and 2.5 the assumption was satisfied. 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 = number of independent variables included in the model) were temporarily removed from the model to check if the trend in the results remained stable. Missing data were handled using listwise deletion.

For Aim 2, to investigate the role of the laterality of brain lesion severity, two steps were taken. First, models from Aim 1 that considered verbal-related outcomes and that included statistically significant sqMRI scores were rerun, additionally including the laterality index of these scores. Second, standardised scores for each verbal-related cognitive/academic measure were compared between participants presenting left-sided and bilateral brain lesions using independent samples T tests.

Significance was set at $p < 0.05$ and corrected for multiple comparisons (Holm–Bonferroni). Data were analysed with a combination of the Statistical Package for the Social Sciences (SPSS, v27.0) (IBM Corporation, 2020) and Stats models v0.12.2 (statsmodels.org) in Python.

3. Results

3.1. Group characteristics

The present study includes 101 participants recruited as part of the PREDICT-CP ($n=45$) (Boyd et al., 2017) and Mitii ($n=56$) (Boyd et al., 2013). A flowchart showing selection process for participants included in the present study is presented in Figure 2. Demographic and clinical characteristics of the sample are presented in Table 1. Most participants did not present with epilepsy ($n=90$; 89%), had unilateral motor symptoms (80%) and were at the levels I of the GMFCS (58%) and II of the MACS (38%). Only those participants presenting observable brain lesions in a previous or current MRI were included in the present study. Periventricular white matter injury was the most common lesion pattern ($n=72$; 72%) followed by cortical and deep grey matter lesions ($n=23$; 23%).

Three (3%) participants presented with brain maldevelopment (Table 1 and Figure 2). Two participants are classified in Table 1 as presenting with normal MRI because their sqMRI score was 0 for the current MRI. These participants were included in the study because they met the inclusion criteria of presenting with observable brain lesion in the current or previous MRI. Specifically, one presented with a small signal abnormality in the left juxtacortical frontal area at a level which is not considered in the slices of the sqMRI template. This signal abnormality was consistent with the side of the hemiplegia and the participant is classified within the CDGM category in Table 1. The other presented with perinatal antecedents of hypoxic ischaemic

encephalopathy and, despite no signal abnormality being observable in the current MRI, a previous MRI at 37 months old presented with observable right-sided abnormalities consistent with the left-sided motor impairments. In Table 1, this participant is classified as presenting a normal MRI. The frontal lobe was most frequently involved followed by the parietal lobe, and then the PLIC (posterior limb of internal capsule) and corpus callosum (Figure 3).

Psychological outcomes are summarised in Table 2. More than half of the children presented with proxy IQ score equal or higher than 85 on the RCPM and PPVT-IV. In addition, more than half presented with standardised scores equal to or higher than 85 on the WIAT-II word reading and spelling and subtests. Numerical operation difficulties were more common, with 57.6% of children presenting a standardised score below 85 on that WIAT-II subtest. More than 50% of children presented with BRIEF and SDQ scores in the normal range.

3.2. Association between sqMRI scores and outcomes

Lateralisation of motor impairment (unilateral or bilateral) was included for control purposes in all models but did not reach statistical significance for any of the models (Tables 3 and 4 and Supplementary Tables 1 and 2). Similarly, the multivariable predictive models including the global sqMRI score as independent variable show that the global score is not statistically significantly associated with any outcome variable (Table 4 and Supplementary Table 1).

Given this, we will now present multivariable associations between the regional sqMRI scores (after considering motor functioning, and epilepsy status for inclusion as covariables) and the outcomes. For further information, the univariable associations between the global and regional sqMRI scores are presented in Supplementary Table 3.

3.2.1. General intellectual functioning: non-verbal and verbal proxy-IQ

The best multivariable predictive model for non-verbal proxy IQ as measured by the RCPM did not include any regional sqMRI score (Table 4 and Supplementary Table 2) and indicated that, as MACS level became more severe, non-verbal proxy IQ decreased compared to MACS level I (level II B=-10.3, 95% CI: -20.9, 0.3; level III B=-30.9, 95% CI: -46.9, -14.9).

Similarly, MACS was negatively associated with verbal proxy IQ as measured by the PPVT-IV (level II B=-5.9, 95% CI=-14.4, 2.5; III B=-29.7, 95% CI=-41.9, -17.5). The best multivariable model for verbal proxy IQ included three regional sqMRI scores with a unit increase in the parietal and medial dorsal thalamus scores implying decreases in verbal proxy IQ scores by 4.8 (95% CI=-8.9, -0.7) and 14.2 (95% CI=-26.3, -2.1) units, respectively. Conversely, each unit increase in temporal lobe scores implied an increase of 9.7 (95% CI=5.5, 13.9) units in verbal proxy IQ (Table 4, Figure 4 and Supplementary Table 2).

3.2.2. Academic attainment: word reading, spelling, and numerical operations

The best multivariable predictive model for word reading on the WIAT-II indicated that as manual ability on MACS level became more impaired, word reading scores decreased (level II $B=-7.5$, 95% CI=-18.6, 3.6; III $B=-34.9$, 95% CI=-51.4, -18.4). The occipital lobe score was also included in the model although it only bordered on significance, with a unit increase in this region corresponding to 4.1 (95% CI=-0.2, 8.4) units increase in the word reading score. The best multivariable predictive model for spelling on the WIAT-II did not include any regional sqMRI score and highlights the impact of being diagnosed with epilepsy, corresponding to a decrease of 29.2 (95% CI=-51.7, -6.7) units in spelling scores.

The best model for numerical operations on the WIAT-II indicated again the relevance of being diagnosed with epilepsy which implies a decrease of 26.4 (95% CI=-48.5, -4.2) units in numerical operations score. GMFCS was also negatively associated with numerical skills. The magnitude of difference between level I vs levels II and IV was similar ($B=-23.1$, 95% CI=-39.1, -7.2 and $B=-21.8$, 95% CI=-57.5, 14.0 respectively). For regional sqMRI scores included in this model, a unit increase in anterior corpus callosum corresponded to a 24.3 (95% CI= -49.6, 0.9) unit decrease in numerical operation scoring although this only bordered on significance.

3.2.3. Behavioural manifestations of executive functioning in everyday life

The best multivariable model for executive functioning emphasised the significance of being diagnosed with epilepsy which was associated with an increase of 11.7 (95% CI=5.1, 18.3) units in the BRIEF global executive composite scores. The model also included ventral posterior lateral thalamus (VPLT) scores with each unit increase indicating a decrease of 5.2 (95% CI=-9.7, -0.8) units in the BRIEF scores (i.e., better outcome).

The unexpected association between VPLT lesions and lower BRIEF scores was further explored by examining BRIEF scores of patients according to their epilepsy status and VPLT lesions status (the two significant variables included in the model). As presented in Figure 5, only 3 participants presented with epilepsy and no VPLT lesions, limiting our ability to draw conclusions with the model for this patient profile/subgroup. Across the remaining three profiles (1-Epilepsy and VPLT lesion, 2-No epilepsy and no VPLT lesion, 3-No epilepsy, and VPLT lesion), the model predicted that the worst clinical outcomes were associated with having both epilepsy and VPLT lesions. Among people without epilepsy, those with VPLT lesions typically scored with lower scores on the BRIEF than those without lesions (i.e. better outcome), with both means within the normative range (see Figure 5).

3.2.4. Psychological adjustment

The best multivariable predictive model for SDQ scores was not significant and did not include any sqMRI score, epilepsy, nor motor functioning variables.

Noteworthy, we re-run the above-mentioned MRI subregional models included in the paper, excluding these two participants who presented with a sqMRI score of 0. For all models, the variables which are significant remain as such.

3.3. Laterality of brain lesions and performance in verbal outcomes.

3.3.1. Association between regional sqMRI score laterality and verbal outcomes

Of the three models predicting verbal outcomes (verbal proxy IQ measured by the PPVT-IV and the word reading and spelling achievement subsets of the WIAT-II) only the model predicting verbal proxy IQ included a significant relationship with sqMRI scores; word reading and spelling models did not include a significant relationship with sqMRI scores and were therefore not further investigated.

Information about the laterality of the regional sqMRI scores included in the verbal proxy IQ model and the global sqMRI scores is presented in Figure 6. All lesions of the medial dorsal thalamus were in the left hemisphere, indicating that the negative association found with verbal proxy IQ was driven by only left-sided lesions in this region. As such, only the laterality indexes for the temporal and parietal lobe sqMRI scores were included in the model for verbal proxy IQ. The resulting model presented in Table 5 indicates that as the laterality index in the temporal lobe increases (i.e. the less the lesions were lateralized to the left temporal lobe), the higher the verbal IQ score ($B=10.9$ 95% CI=0.8, 21.0), while there was no association between verbal proxy IQ and parietal lobe laterality index ($B=0.1$ 95% CI=-9.2, 9.3). Among the 41 participants included in this model, only one participant presented with temporal lobe lesions circumscribed to the right temporal lobe and five had greater lesion load in the right temporal lobe than the left. However, twenty presented any lesion in the right temporal lobe.

3.3.2. Comparison of verbal functioning between participants presenting with bilateral or left-sided unilateral lesions

The global sqMRI score of brain lesion severity (ranging 0-48) was not significantly different between unilateral left-sided and bilateral brain lesion groups ($t=-0.2$; $p=0.84$), indicating that the groups were comparable in terms of brain lesion extent. Mean global sqMRI score in participants with unilateral lesions was 11.0 (SD=5.3) and 10.6 (SD=4.8) for participants with bilateral lesions. Consistently, participants with unilateral left-sided lesions presented with higher total left brain lesion extent (left hemisphere sqMRI score=10.1, SD=5.3) than those with bilateral lesions (left hemisphere sqMRI score=5.1, SD=2.8). The left hemisphere sqMRI score difference between groups was statistically significant ($t=-2.9$; $p=0.02$).

Scores for each verbal assessment were compared between participants presenting with unilateral left-sided ($n=10$) and bilateral brain lesions ($n=30$). Given that only four of the participants presented with unilateral right-sided lesions (Figure 6), this subgroup was not included in the analyses. On average, participants with bilateral lesions performed significantly better than those with unilateral left-sided lesions in all verbal-related domains (Supplementary Table 4). Specifically, the mean verbal proxy IQ score in participants with unilateral lesions was 86.8 (SD=14.4) whereas it was 102.0 (SD=14.7) in participants with bilateral lesions ($t=-2.8$; 95% CI=-26.1, -4.2). The mean word reading score on the WIAT-II was 71.6 (SD=24.8) in participants with unilateral lesions while it was 91.9 (SD=16.6) for those with bilateral lesions ($t=-2.4$; 95% CI=-38.6, -1.9). Finally, the mean spelling score on the WIAT-II was 73.7 (SD=22.4) for participants with unilateral and 90.2 (SD=18.2) for participants with bilateral lesions ($t=-2.3$; 95% CI=-30.7, -2.2).

4. Discussion

In a sample of Australian children and adolescents with spastic motor-type CP, we investigated which combination of clinical variables (brain lesion, gross motor functioning, manual ability, and epilepsy status) were associated with psychological outcomes (cognitive, academic, and executive functioning as well as psychological adjustment). Medial dorsal thalamus and parietal lobe lesions significantly accounted for poorer verbal proxy IQ on the PPVT-IV while temporal lobe lesions lateralized to the left hemisphere were associated with poorer verbal proxy IQ. In addition, in our sample, participants with bilateral lesions had similar total lesion load but lower left hemisphere lesion load than participants with left unilateral lesions, and presented with better functioning in all verbal-related domains including verbal proxy IQ and performance on the spelling and word reading subsets of the WIAT-II. When controlling for manual ability level (MACS), the association between occipital lobe scores and word reading bordered on significance. No sqMRI scores (global or regional) were associated with spelling performance after controlling for epilepsy. No sqMRI scores (global or regional) were significantly associated with non-verbal proxy IQ as measured by the RCPM after controlling for manual ability (MACS) level. There was a significant association between both GMFCS and epilepsy with numerical operations attainment, and a large but non-significant association between anterior corpus callosum and with numerical operations attainment. Among participants without epilepsy, both those without and with VPLT lesions presented with mean BRIEF scores within the normal range, however, those with VPLT lesions presented slightly lower (i.e. better clinical outcome) scores. Finally, no sqMRI scores nor any other variable considered were significantly associated with psychological adjustment.

The lack of association between non-verbal proxy IQ and regional or global sqMRI brain lesion severity scores reported here is consistent with a previous study including children with spastic CP that found no association between the extent of cerebral injury and intellectual disability (S. M. Reid et al., 2015). Our results support these previous findings by limiting analyses to participants with the same CP motor type and using a more detailed measure of IQ. In contrast, Moll et al. found that the extent of white matter damage and GMFCS level are prognostic factors for presenting with a non-verbal IQ ≤ 70 (Moll et al., 2021). The inconsistency between our findings and those of Moll et al.'s study (which also used a semiquantitative approach) may be due IQ being treated as continuous variable in our study, rather than applying an IQ cut-off. Another source of inconsistency could be that Moll et al. analysed the white and grey matter separately while in the present study lobar scores account for both grey and white matter altogether. During data exploration a significant univariable association was found between non-verbal proxy IQ and posterior thalamic injuries (Supplementary Table 3), which is consistent with our previous study in children and adults with dyskinetic CP (Laporta-Hoyos et al., 2018). This association was not found in our multivariable models due to the automated model selection approach. Specifically, this approach precludes two strongly co-linear variables both being included in the same model. For non-verbal proxy IQ, the automated approach selected MACS as an explanatory variable, which in turn precluded posterior thalamic injury from inclusion in the model due to its clear association with MACS.

In this study, no significant associations were found between the global sqMRI score and verbal proxy IQ, spelling or word reading. The only previous study with a similar approach reported associations between global sqMRI scores and parental reports of communication ability on the Communication and Symbolic Behavioral Scales Developmental Profile Infant-Toddler Checklist (Coleman et al., 2016). The apparent discrepancy may be

due to Coleman et al. using a broad parent-reported measure of communication ability whilst in the present study we utilized more specific performance-based assessments. In addition, our sample comprised older participants with correspondingly more developed language skills, milder CP, and lower and slightly more homogenous global sqMRI brain lesion severity scores. In similar study of children younger (3 – 7 years old) than assessed here the degree of periventricular white matter and deep gray matter lesion severity was significantly associated with receptive and expressive language (Choi et al., 2017). The discrepancy between the study of Choi et al. and the present one may be driven by the age difference between samples and the fact that we analysed participants with different lesion patterns together while Choi et al. stratified their patients into those presenting with periventricular white matter and those presenting with deep gray matter lesions.

When regional sqMRI scores were considered, we found that increases in parietal lobe and medial dorsal thalamus scores were associated with lower verbal proxy IQ. These findings are in alignment with a sophisticated neuroimaging study that reported that the superior longitudinal fasciculus and supramarginal gyrus were associated with both vocabulary and word reasoning performance on the Wechsler Preschool and Primary Scale of Intelligence-III (WIPPSI-III) subscales (Pagnozzi et al., 2016a). In addition, language learning has been associated with grey and white matter volumes in the inferior parietal lobes in the undamaged brain (Richardson and Price, 2009). Indices of damage to regions tightly connected with the thalamus (Middleton and Strick, 2000) have also been associated with word reasoning performance on the WIPPSI-III subscale in participants with CP (Pagnozzi et al., 2016b). Our previous study using the same measures did not find equivalent associations probably due to the different CP motor subtype studied, and different methodological approaches (Laporta-Hoyos et al., 2018).

When the temporal lobe laterality index is included in the verbal IQ model, results suggest that the unexpected positive association we found between temporal lobe sqMRI scores, and verbal proxy IQ was driven by right hemisphere scores. Specifically, the more the lesions were distributed toward the left temporal lobe, the poorer the verbal proxy IQ scores were. This must be interpreted considering that lesions balanced towards the right temporal lobe were less common than those balanced towards the left temporal lobe in our sample. Therefore, our conclusion would benefit from future work analysing a sample of a more even distribution of laterality indices. Conversely, in an earlier study, Coleman et al. (2016) did not find an association between lesional laterality index and overall communication skills, potentially for three reasons. Firstly, Coleman et al. assessed broader aspects of communication that included social and symbolic skills that are less likely to be lateralized. Secondly, the participants included in Coleman's study may have presented lesions in regions anatomically divergent from our patients. Finally, lesion laterality was only assessed by Coleman et al for the global sqMRI score whereas the present study found lateralization to be important specifically in the temporal lobe. The location of lesions plays a role in language lateralization (Guzzetta et al., 2008) and it has been reported that the more language functions shift to the right, the lower the cognitive and expressive language scores can be, although performance is typically still within the normal limits (Chilosi et al., 2019). After left-sided lesions, the right hemisphere can accommodate language to such a degree that everyday functions are preserved (Stadskleiv et al., 2018). That said, our results highlight that for more difficult language tasks, the laterality of lesions can indeed affect performance to some degree, as reported (Chilosi et al., 2019; Schwilling et al., 2012). The associations described here do not account for the fact that the type of lesion seems to influence

neuroplastic changes after early brain damage. That is, left cortical lesions tend to result in greater right hemispheric language dominance than left periventricular white matter lesions (Gaberova et al., 2019). In our study, we only accounted for the extent and location of the lesion in terms of cerebral lobe being involved considering white and grey matter together. Future studies with larger samples stratifying participants by type of lesion are likely able to provide a more complete picture of the relationship between early brain damage and verbal IQ.”

Occipital lobe sqMRI scores were included in the word reading model with the most explanatory power relative to its complexity, though its association with word reading did not reach significance. The relevance of the ventral occipito-temporal cortex for reading acquisition has been reported (Chyl et al., 2021). We speculate that our results, although in more mildly impaired participants, were also driven by similar mechanism as the relationship between temporal lobe lesions and verbal proxy IQ. Further studies using more detailed measures of brain microstructure assessed with diffusion MRI may enable better interpretation of our results.

In the present study, we found that brain lesions to the left hemisphere were more detrimental to language function than bilaterally distributed lesions, when the total lesion severity was comparable. Accordingly, Coleman et al. found that left sided lesions were associated with poorer communication skills (Coleman et al., 2016). Conversely, receptive and expressive language development were found to be significantly lower in children with bilateral compared with unilateral periventricular white matter lesions (Choi et al., 2017). Whether these results are truly divergent is difficult to assess as Choi et al. did not specify the hemisphere of the unilateral brain lesions, nor the severity of lesions: participants with bilateral involvement may have presented with more extended lesions. Our results are consistent with previous findings indicating that bilateral representation of language networks is associated with better word-learning performance (Catani et al., 2007). This should be interpreted in the context of our cohort, which was predominantly individuals with bilateral or left-hemispheric lesions. Taken together, our results highlight that language reorganization that takes place after early brain injury is likely complex and potentially affected by multiple aspects, including interactions between lesion characteristics (laterality, location, and extent) and clinical status (manual ability and epilepsy status).

The importance of fine motor functioning for numeracy and arithmetic in CP has been previously reported (van Rooijen et al., 2015). Van Rooijen et al., however, did not account for possible differences between gross motor capabilities and epilepsy status. In the present study in participants with spastic CP, gross motor functioning (GMFCS) was more relevant for the development of numerical operation skills than manual ability (MACS). The present study explored, for the first time, the association between brain lesions and arithmetic performance in participants with CP. Similar to a diffusion MRI study in typically developing children (Matejko and Ansari, 2015) we found associations between the corpus callosum status and numerical operation skills as measured on the WIAT-II. Although the association between corpus callosum status and numerical operation performance only bordered on significance, it was included in the model with the most explanatory power relative to its complexity. The corpus callosum forms a critical component of the neural networks recruited during high-order cognitive processes underlying arithmetic performance including attention and executive function (Bookstein et al., 2002; Dorion et al., 2002). While we found associations between numerical operation skills and the

anterior third of the corpus callosum in participants with CP, diffusion MRI studies in typically developing children suggested the relevance of the posterior parts of the corpus callosum (Matejko and Ansari, 2015). Our results are probably driven by the higher brain lesion load in the anterior portions of the brain in our sample.

Injury to the VPLT was unexpectedly associated with decreases in BRIEF scores (i.e., better performance) in the multivariable regression model, which also included epilepsy status. Participants without epilepsy typically had a BRIEF score in the normal range (<60). Interestingly, those with VPLT lesions typically had numerically slightly lower BRIEF scores than those without lesions (i.e. better clinical outcome) driving the statistical significance in our multivariable regression model. Consistently, a previous study identified that better BRIEF scores were associated with lower lenticular volumes and higher indicators of injury to the PLIC (Pagnozzi et al., 2016b), superior frontal gyrus, lenticular and caudate nucleus (Pagnozzi et al., 2016a). In one of these studies, lower thalamus volume was associated with poorer BRIEF scores (Pagnozzi et al., 2016b). We speculate that these divergent associations may be due to the involvement of different behaviourally relevant cortico-striato-thalamo-cortical circuits with origins in the prefrontal cortex. Specifically, three circuits involving these structures are known to play a role in EF aspects that are likely related to BRIEF scores. The dorsolateral circuit is predominantly involved in working memory, while the orbitofrontal circuit is involved in inhibitory control of impulses and interference (Fuster, 2002). Injury to the dorsolateral and orbitofrontal circuits are likely to result in behavioural differences, such as disruptive behaviour, which are likely to increase BRIEF scores. In contrast, the medial circuit is an important driver of motivational mechanisms (Fuster, 2002) with a likely decrease in BRIEF scores by reducing the behavioural responses linked to distraction and lack of impulse control. In other words, it is possible that these slightly lower scores in participants with mild thalamic lesions are due to a tendency to be more subdued in their daily activities, precluding disruptive behaviours.

Finally, no lesion scores were found to relate to child psychological adjustment, unlike the positive association found in a previous quantitative analysis (Pagnozzi et al., 2016b). This might be evidence that broader clinical tests require more detailed measures of brain characteristics that can index injury with a wider range of values, and/or capture non-observable abnormalities.

An important strength of our study is the standardized assessment of cognitive functions considering, for first time, academic achievement in word reading, spelling and numerical operations using the WIAT-II. Despite its role in everyday functioning of people with CP without intellectual disability, academic achievement has been underrepresented in studies exploring the associations between brain damage characteristics and clinical outcomes. Intellectual ability was not included in the models for academic achievement and so the extent to which IQ might explain the relationships found is unknown. A limitation of the current work is that the varying participant numbers for the different assessments, may have influenced the statistical power to identify associations. Moreover, the lack of children with fully right-sided brain lesions limits our ability to further explore the contribution of the right hemisphere to language related function. Finally, the sample was limited to children with spastic CP motor type but children with different lesion patterns were included in our models.

This is a limitation of our study as diverse lesion patterns have been reported to be associated with different clinical outcomes. This is a common challenge in CP research whereby analyses performed on subsamples partitioning by different lesion patterns are ideal but limited by the available sample size. Our models do not

therefore control for this aspect which may be associated with clinical outcomes such as intellectual impairment or epilepsy (Himmelmann et al., 2021).

5. Conclusion

In summary, our study identified associations between sqMRI scores of brain lesions and a proxy measure of verbal IQ as well as executive functioning in everyday life, after accounting for the effect of manual ability, and epilepsy diagnosis respectively. In addition, a relationship between sqMRI scores and numerical operations on the WIAT-II bordered on significance. Our results highlight the relevance of lesion lateralization for verbal cognitive functions. Given that brain lesions in CP are not progressive, the presented results indicate that sqMRI scoring may support personalised cognitive interventions and support planning for children with CP. A challenge for future studies is to standardise measures for cognitive assessment, enabling data pooling that may allow deeper investigations into the trends identified here.

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Figure 1. Representation of all the individual regional scores considered in the analysis (each in a different colour). Each regional sqMRI scoring is calculated as follows: a) Each lobe is scored from 0 to 6 (0 to 3 for each hemisphere), with lobar scores considering both grey and white matter; b) anterior, middle, and posterior corpus callosum scores from 0 (no lesion) to 1 (affected); c) Basal ganglia and brainstem scores 0 (no lesion), 1 (one side affected) or 2 (structure bilaterally affected). Middle and posterior corpus callosum scores were combined in statistical analysis. Key: CC, corpus callosum; PLIC, posterior limb of internal capsule.

Figure 2. Flowchart showing selection process participants included in the present study.

Key: BRIEF: Behaviour Rating Inventory of Executive Function; IQ: Intellectual quotient; MRI: Magnetic resonance imaging; PPVT-III: Peabody Picture Vocabulary Test-3rd; RCPM: Raven's Coloured Progressive Matrices; SDQ: Strengths and Difficulties Questionnaire; WIAT-II: Wechsler Individual Achievement Test.

Total sample n=101

Global sqMRI score

Sub-sample n=45
Participants from PREDICT-CP study included in the “General intellectual functioning” or “Academic attainment” models

Lobar scores

Basal ganglia and brainstem scores

Corpus callosum scores

Legend

Figure 3. Percentage of cases presenting different lesion severity according to the Global; lobar; basal ganglia and brainstem; and corpus callosum sqMRI scores. For global and lobar scores each colour/pattern represents a number in the sqMRI score, with higher numbers indicating higher lesion involvement. Key: LH: left hemisphere; RH: right hemisphere; PLIC: posterior limb of internal capsule; VPLT: ventral posterior lateral thalamus.

Figure 4. An illustration of the results of the linear regression models presented in Table 4 that include regional sqMRI scores. The colour bar indicates the standardized beta coefficients.

Figure 5. Boxplots of BRIEF scores divided by groups according to presenting epilepsy diagnosis (striped pattern) and lesions in the ventral posterior lateral thalamus (second and fourth boxes containing grey background). Numbers indicate mean (standard deviation). Key: BRIEF: Behaviour Rating Inventory of Executive Function.

Figure 6. Percentage of cases presenting bilateral, left hemisphere unilateral (LH), right hemisphere unilateral (RH) or no lesions according to the (a) global score and (b) regional sqMRI scores included in the best model for verbal IQ. Frequencies correspond to the sub-sample of people included in any verbal-related model (n=45).

Table 1. Demographics and clinical characteristics of the study sample

Sex n female/male	44 / 57
Age Mean (SD) / range	11 (2.1) / 6.6-17.4
Epilepsy status n no epilepsy/epilepsy	90 / 11
Motor distribution	
n unilateral (left/right side affected) / bilateral (diplegia/triplegia/quadruplegia)	81 (37/44) / 20 (15/2/3)
GMFCS, levels (n)	I (59); II (38); III (3); IV (1)
MACS, levels (n)	I (38); II (58); III (5)
Type of lesion	
n PWM / CDGM / brain maldevelopment / normal MRI	73 / 24 / 3 / 1*
sqMRI global score Mean (SD) / range	9.9 (5.7) / 0-21.5

Key: CDGM: cortical and deep grey matter; GMFCS: Gross motor function classification system; MACS: Manual ability classification system; PWM: Periventricular white matter; SD: standard deviations; * A participant presented with a sqMRI score of 0 and therefore were classified as 'normal MRI'. They were included in this analysis as they met the inclusion criteria of presenting with observable brain lesion in the current or previous MRI. Further information is available in Results section.

Table 2. Descriptive statistics of the outcome variables

			n (%)			
Test		Mean (SD) / range / n	≥85	71-84	≤70	
General intellectual functioning*	Non-verbal proxy IQ (RCPM)	89.8 (18.3) / 60-125 / n=45	29 (64.4)	7 (15.6)	9 (20)	
	Verbal proxy IQ (PPVT-III) ^{LR}	98.4 (16.0) / 60-130 / n=41	35 (85.4)	4 (9.8)	2 (4.9)	
Academic attainment	Word reading subtest (WIAT-II) ^{LR}	87.3 (20.8) / 46-120 / n=45	28 (62.2)	7 (15.6)	10 (22.2)	
	Spelling subtest (WIAT-II) ^{LR}	86.7 (19.6) / 40-121 / n=45	27 (60)	8 (17.8)	10 (22.2)	
	Numerical operations subtest (WIAT-II)	77.2 (20.9) / 41-106 / n=45	19 (42.2)	8 (17.8)	18 (40)	
Behavioural manifestations of executive functioning	Global executive composite (BRIEF)	57.9 (10.4) / 39-88 / n=98	≤59 normal	60-64 mildly elevated	65-69 potentially clinically elevated	≥70 clinically elevated
			53 (54.1)	17 (17.3)	16 (16.3)	12 (12.2)
Psychological adjustment	Total difficulties score (SDQ)	11.5 (6.2) / 1-30 / n=97	≤13 normal	14-16 slightly raised	17-19 high	20-40 very high
			60 (61.9)	17 (17.5)	9 (9.3)	11 (11.3)

Key: BRIEF: Behaviour Rating Inventory of Executive Function; PPVT-IV: Peabody Picture Vocabulary Test-4th; IQ: Intellectual quotient; RCPM: Raven's Coloured Progressive Matrices; SD: standard deviations; SDQ: Strengths and Difficulties Questionnaire; WIAT-II: Wechsler Individual Achievement Test; IQ: Intellectual quotient; ^{LR} Verbal-related cognitive functions. *According to the DSM-IV, IQ ≤70 and 71-84 were a diagnosis criterion for intellectual disability and borderline intellectual functioning, respectively. Both, DSM-IV and DSM-V require further criteria for the diagnosis of these disorders.

Table 3. Best multivariable models considering the global sqMRI score as independent variables.

Outcome	Independent variables	B (95% CI)	p	Model R ²
General intellectual functioning				
Non-verbal proxy IQ (n=45)	MACS (I) Reference			0.29
	MACS (II)	-10.1 (-20.9, 0.7)	0.07	
	MACS (III)	-30.4 (-46.9, -14.0)	0.001***	
	Unilateral motor type Reference			
	Bilateral motor type	-2.9 (-13.1, 7.3)	0.56	
	Global sqMRI score	-0.2 (-1.1, 0.8)	0.74	
Verbal proxy IQ (n=41) ^{LR}	MACS (I) Reference			0.33
	MACS (II)	-11.9 (-21.5, -2.2)	0.02*	
	MACS (III)	-26.7 (-50.0, -12.4)	0.001**	
	Unilateral motor type Reference			
	Bilateral motor type	2.5 (-6.6, 11.6)	0.58	
	Global sqMRI score	0.8 (-0.07, 1.6)	0.07	
Academic attainment				
Word reading (n=45) ^{LR}	MACS (I) Reference			0.32
	MACS (II)	-9.9 (-21.3, 1.6)	0.09	
	MACS (III)	-35.5 (-52.9, -18.1)	<0.001	
	Unilateral motor type Reference			
	Bilateral motor type	6.4 (-4.3, 17.2)	0.23	
	Global sqMRI score	0.4 (-0.6, 1.5)	0.39	
Spelling (n=45) ^{LR}	Diagnosis of epilepsy	-29.9 (-53.0, -6.9)	0.01**	0.15
	Unilateral motor type Reference			
	Bilateral motor type	0.9 (-10.5, 12.3)	0.87	
	Global sqMRI score	-0.2 (-1.3, 0.9)	0.70	
Numerical operations (n=45)	Diagnosis of epilepsy	-40.4 (-63.5, -17.3)	0.001***	0.24
	Unilateral motor type Reference			
	Bilateral motor type	-3.6 (-15.1, 7.8)	0.53	
	Global sqMRI score	-0.8 (-1.9, 0.4)	0.18	
Behavioural manifestations of executive functioning				
Global executive composite (n=98)	Diagnosis of epilepsy	10.7 (3.8, 17.6)	0.003**	0.10
	Unilateral motor type Reference			
	Bilateral motor type	0.6 (-4.5, 5.8)	0.81	
	Global sqMRI score	0.1 (-0.3, 0.4)	0.72	
Psychological adjustment				
Total difficulties score (n=97)	Unilateral motor type Reference			0.005
	Bilateral motor type	0.8 (-2.3, 4.0)	0.60	
	Global sqMRI score	0.1 (-0.2, 0.3)	0.64	

Key: B: unstandardized regression coefficient; CI: confidence interval; MACS: Manual ability classification System; IQ: Intellectual quotient; ^{LR} Verbal-related cognitive functions; * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001; n varies slightly between models as an effect of each subject having data available for the variables included in the model.

Table 4. Best multivariable models considering regional sqMRI scores as independent variables.

Outcome	Independent variables	B (95% CI)	p	Model R ²
General intellectual functioning				
Non-verbal proxy IQ (n=45)	MACS (I) Reference			
	MACS (II)	-10.3 (-20.9, -0.3)	0.06	
	MACS (III)	-30.9 (-46.9, -14.9)	<0.001***	0.30
	Unilateral motor type Reference			
	Bilateral motor type	-2.9 (-13.0, 7.2)	0.56	
Verbal proxy IQ (n=41) ^{LR}	MACS (I) Reference			
	MACS (II)	-5.9 (-14.4, 2.5)	0.16	
	MACS (III)	-29.7 (-41.9, -17.5)	<0.001***	
	Temporal lobe	9.7 (5.5, 13.9)	<0.001***	
	Parietal lobe	-4.8 (-8.9, -0.7)	0.02*	0.51
	Medial dorsal thalamus	-14.2 (-26.3, -2.1)	0.02*	
	Unilateral motor type Reference			
	Bilateral motor type	5.2 (-3.8, 14.3)	0.25	
Academic attainment				
Word reading (n=45) ^{LR}	MACS (I) Reference			
	MACS (II)	-7.5 (-18.6, 3.6)	0.18	
	MACS (III)	-34.9 (-51.4, -18.4)	<0.001***	0.30
	Occipital lobe	4.1 (-0.2, 8.4)	0.06	
	Unilateral motor type Reference			
Spelling (n=45) ^{LR}	Bilateral motor type	5.2 (-5.3, 15.7)	0.32	
	Diagnosis of epilepsy	-29.2 (-51.7, -6.7)	0.01**	
	Unilateral motor type Reference			0.11
	Bilateral motor type	1.0 (-10.3, 12.3)	0.86	
	Diagnosis of epilepsy	-26.4 (-48.5, -4.2)	0.02*	
Numerical operations (n=45)	GMFCS (I) Reference			
	GMFCS (II)	-23.1 (-39.1, -7.2)	0.01**	
	GMFCS (III)	8.9 (-12.3, 30.0)	0.40	
	GMFCS (IV)	-21.8 (-57.5, 14.0)	0.23	0.45
	Anterior corpus callosum	-24.3 (-49.6, 0.9)	0.06	
	Unilateral motor type Reference			
	Bilateral motor type	4.0 (-8.6, 16.5)	0.53	
Behavioural manifestations of executive functioning				
Global executive composite (n=98)	Diagnosis of epilepsy	11.7 (5.1, 18.3)	<0.001***	
	Ventral posterior lateral thalamus	-5.2 (-9.7, -0.8)	0.02*	0.16
	Unilateral motor type Reference			
	Bilateral motor type	-2.3 (-7.9, 3.4)	0.43	
Psychological adjustment				
Total difficulties score (n=97)	Unilateral motor type Reference			0.003
	Bilateral motor type	0.8 (-2.3, 3.4)	0.60	

B: unstandardized regression coefficient; CI: confidence interval; GMFCS: Gross motor function classification system; MACS: Manual ability classification System; IQ: Intellectual quotient; ^{LR} Verbal-related cognitive functions; * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001; n varies slightly between models as an effect of each subject having data available for the variables included in the model.

Table 5. Multivariable model for verbal IQ exploring the effect of laterality

Dependent variable	Independent variables	B (95% CI)	p	Model R ²
Verbal proxy IQ (n=41)	MACS (I) Reference			0.65
	MACS (II)	-4.4 (-12.6, 3.7)	0.28	
	MACS (III)	-26.3 (-38.2, -14.4)	<0.001***	
	Temporal lobe	98.7 (4.7, 12.8)	<0.001***	
	Parietal lobe	-4.0 (-7.9, -0.01)	0.49	
	Medial dorsal thalamus	-6.0 (-19.4, -7.6)	0.38	
	Unilateral motor type Reference			
	Bilateral motor type	3.8 (-5.3, 12.9)	0.41	
	Laterality index temporal lobe	10.9 (0.8, 21.0)	0.04*	
	Laterality index parietal lobe	0.06 (-9.2, 9.3)	0.99	

B: unstandardized regression coefficient; CI: confidence interval; MACS: Manual ability classification System; IQ: Intellectual quotient; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

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