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Brain magnetic resonance imaging is a predictor of bimanual performance and executive function in children with unilateral cerebral palsy

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ABBREVIATIONS

AHA	Assisting Hand Assessment
FVI	Focal vascular insults
WMI	White matter injury

AIM To examine the association between brain magnetic resonance imaging (MRI) characteristics and executive function and bimanual performance in children with unilateral cerebral palsy (CP).

METHOD Clinical MRI brain scans were classified as: (1) predominant pathological pattern (normal, white matter injury [WMI]; grey matter injury; focal vascular insults [FVI]; malformations; or miscellaneous); and (2) focal lesions (frontal, basal ganglia, and/or thalamus). Assessments included: (1) bimanual performance; (2) unimanual dexterity; and (3) executive function tasks (information processing, attention control, cognitive flexibility, and goal setting) and behavioural ratings (parent).

RESULTS From 131 recruited children, 60 were ineligible for analysis, leaving 71 children (47 males, 24 females) in the final sample (mean age 9y [SD 2y], 6y–12y 8mo). Brain MRIs were WMI (69%) and FVI (31%); and frontal (59%), thalamic (45%), basal ganglia (37%), and basal ganglia plus thalamic (21%). Bimanual performance was lower in FVI versus WMI

(p<0.003), and with frontal (p=0.36), basal ganglia (p=0.032), and thalamic/basal ganglia lesions (p=0.013). Other than information processing, executive function tasks were not associated with predominant pattern. Frontal lesions predicted attention control (p=0.049) and cognitive flexibility (p=0.009) but not goal setting, information processing, or behavioural ratings.

INTERPRETATION Clinical brain MRI predicts cognitive and motor outcomes when focal lesions and predominate lesion patterns are considered.

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What this paper adds

- Early brain magnetic resonance imaging (MRI) predicts bimanual performance and cognitive outcomes.
- Brain MRI may identify children requiring targeted interventions.
- Basal ganglia with/without thalamic lesions predicted bimanual performance.
- Frontal lesions were associated with attention control and cognitive flexibility.
- Brain MRI predominant patterns predicted motor, not cognitive outcomes, other than information processing.

[Main text]

Unilateral cerebral palsy (CP) is a motor impairment affecting one side of the body, caused by antenatal or perinatal insult to the developing brain. While the determining feature of CP is impaired motor function, CP is often associated with cognitive and developmental problems, including cognition.[1] Cognition, and particularly higher level executive function, in unilateral CP has rarely been scientifically studied. Motor and cognitive impairments arise from disrupted brain development and both impact on daily activity performance and participation in childhood tasks.[2]

Executive function is required for performance of daily activities. Executive functions form a set of self-regulatory behaviours necessary to select and sustain actions and guide behaviour within the context of task rules.[3–5] They emerge through childhood with the protracted neurodevelopment and late myelination of the prefrontal cortex, the anterior-most portion of the frontal lobes.[6] The prefrontal cortex is particularly vulnerable to early brain injury. However, disrupted executive function development in unilateral CP may arise from lesions at any point in the frontal–subcortical network (including white matter tracts, which disrupts projections between the prefrontal cortex and other brain areas).[7,8] Periventricular white matter injury (WMI), for example, can cause secondary changes to connected grey matter structures, particularly the thalamus and basal ganglia, but may also extend to cortical regions.[9] Further, the basal ganglia and/or thalamic lesions may impair focused attention and executive function.[10] Despite these various potential neuropathological pathways to executive dysfunction in CP, research has been limited.[11]

Only two studies have linked underlying brain lesions in unilateral CP and executive function.[12] Bilateral lesions were associated with poorer executive function performance versus unilateral lesions,[13] and parieto-occipital periventricular haemorrhagic infarction was related to behavioural executive dysfunction.[14] In children with spastic diplegic CP, early clinical MRI brain lesions associated with executive function (using a novel visual attention task) at 8 years of age were examined. Anterior and diffuse lesions were associated with greater executive dysfunction.[15] Straub et al. later surmised that this adds support for the neuro-anatomical correlates of executive function deficits within the frontal–collicular pathways and prefrontal lesions.[16] A growing body of research has associated brain abnormalities with bimanual performance in unilateral CP. Bimanual performance requires the spontaneous use of both hands together, where the dominant hand performs both fine and gross manipulations, and the non-dominant hand is used to stabilize objects.[17] However, magnetic resonance imaging (MRI) findings have been inconsistent. Basal ganglia and thalamic lesions on brain MRI have been associated with more impaired bimanual

performance in children with unilateral CP.[18] Using a larger sample of children with unilateral CP, Mailleux et al. found bimanual performance and unimanual capacity was associated with MRI of the brain depending on lesion type: children with deep grey matter lesions showed a close association between lesion location and extent, and hand function, whereas children with periventricular WMI did not.[19]

The aim of this study was to examine the association between early brain MRI characteristics and executive function and bimanual performance, as well as unimanual dexterity in children with unilateral CP. The objectives were to: (1) describe MRI characteristics (brain MRI patterns and presence/absence of focal lesions), and (2) explore whether MRI characteristics are associated with executive function or bimanual performance.

We hypothesized that: (1) WMI would be common and associated with more favourable cognitive and unimanual outcomes relative to other MRI brain patterns;[20] and (2) that frontal lesions would be associated with executive function, while specific subcortical focal lesions (thalamic and basal ganglia) would be associated with decrements in unimanual dexterity, and combined lesions would be associated with worse bimanual performance.

The current study is important for two reasons; first, cognitive and motor outcomes are both critical determinants of daily function, and, second, identifying children at risk of poor prognosis using clinical MRI could improve individualized care.

METHOD

Study design

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This was a prospective cross-sectional observational study, which incorporated retrospectively obtained MRI data (Trial registration: ACTRN12614000631606; date of retrospective registration 29th May 2014). The study was implemented across five Australian treatment centres (Monash Children's Hospital, Victoria; Royal Children's Hospital, Victoria; Cerebral Palsy Alliance, New South Wales; Lady Cilento Children's Hospital, Queensland; and Perth Children's Hospital, Western Australia), as previously described.[21]

Participants

Participants were children aged 6 to 12 years at the time of recruitment (July 2012–August 2015), presenting at the study sites. Inclusion criteria were a diagnosis of unilateral CP made by a medical specialist, sufficient cooperation, English language capacity, ability to attend

their local centre for behavioural assessments, and perinatal brain MRI. Children were ineligible if they had received either botulinum neurotoxin A injection or upper limb surgery within 3 or 12 months of recruitment respectively.

Eligible participants were identified by the lead investigator, or the child's doctor and therapists assigned to relevant clinics at each site. They were provided with an information letter before the child's clinic visit, and verbal information by their treating therapist at their clinic visit. Contact details of suitable families interested in participating were forwarded to the researchers. Once eligibility was confirmed, participants were recruited and provided written consent, including consent to access retrospective brain MRI data, in accordance with Human Research Ethics Committee-approved protocols.

Clinical and demographic data

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A clinical record form completed in collaboration with the parent/guardian captured confirmed topographical pattern and diagnosis of unilateral CP, side affected (left/right), demographic data (age, sex), child birth history (gestational age, birthweight), the presence of seizures (using the CP registry definition of seizure free being no seizures ≥2y without medication),[22] intellectual impairment, and comorbidities (blindness and bilateral deafness).

Classification tools

Children's functional motor and communication levels were classified using the Manual Ability Classification System,[23] Gross Motor Function Classification System (GMFCS),[24] and Communication Function Classification System.[25]

Brain MRI data

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Clinical brain magnetic resonance images were reviewed by one of two paediatric radiologists (JB, MD). The child's most recent scan was reviewed. The child's age at imaging was recorded. Neuroimaging patterns were retrospectively classified using an established protocol (Table S1, online supporting information) as either normal or fitting one of five predominant pathological patterns: WMI, grey matter injury, focal vascular insults (FVI), malformations, and miscellaneous patterns.[26] Mixed patterns were excluded because of lack of consensus regarding the classification of multiple patterns of injury.[27] Focal lesions were classified as present/absent across either hemispheres, for three regional areas: frontal, basal ganglia, and/or thalamus, using data from the same established protocols as above (Table S1). Bilateral WMI or bilateral focal lesions were recorded as bilateral lesions.

Behavioural data and executive functioning

Children completed a standardized child neuropsychological assessment, administered and scored by qualified psychologists. Assessments were completed across one or two appointments.

Executive function was assessed against four separate, but integrated, domains, specified in a developmental model,[28] using tasks that were minimally reliant on fine motor dexterity: (1) information processing (efficiency and speed of output) was measured using semantic word generation from the Developmental Neuropsychological Assessment, Second Edition;[29] (2) attention control (selectively attending to stimuli and inhibiting responses) was measured using the Sky Search DT task (decrement score, controlling for fine motor speed) from the Test of Everyday Attention for Children;[30] (3) cognitive flexibility (shifting between response sets, and process multiple sources of information concurrently) was measured using Inhibition Naming (combined score) from the Neuropsychological Assessment, Second Edition; and (4) goal setting (planning actions in advance and using an efficient and strategic approach to tasks) was measured using the Tower of London (total z-score).[31] Executive function tasks were scored using standardized criteria and analysed using age-referenced standard scores (mean 10 [SD 3]), unless specified. Higher scores indicate better functioning.

The Behaviour Rating Inventory of Executive Function is an 86-item questionnaire assessing behavioural manifestations of everyday executive function over the most recent 6 months, completed by parents at the child's appointment.[32] The Global Executive Composite was used in this study, standardized for age and sex (mean 50 [SD 10]). Higher scores reflect greater executive dysfunction.

Intellectual function

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Intellectual ability was measured using the General Ability Index, of the Wechsler Intelligence Scale for Children, Fourth Edition (mean 100 [SD 15]).[33] The General Ability Index is a valid substitute for full-scale IQ but is less sensitive to working memory and processing speed.[34]

Upper limb function

Upper limb assessments, detailed below, were administered and scored by experienced paediatric occupational therapists.

Bimanual performance

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Bimanual performance was measured using the Assisting Hand Assessment (AHA; version 5.0),[35,36] which assesses spontaneous use of the affected/assisting hand in bimanual activity for children with unilateral upper limb impairment. The AHA is a standardized, criterion-referenced measure with good psychometric properties.[35,36] The sum of raw scores (sum score) ranges from 20 (low ability) to 80 (high ability), which is converted to interval-level data using Rasch analysis. Rescaled logit-based AHA units range from 0 to 100.[35] Higher scores indicate greater bimanual performance. The AHA was video-recorded and retrospectively rated by certified occupational therapists.

Unimanual dexterity

The Box and Block Test is a standardized measure of unimanual dexterity, with demonstrated psychometric properties.[37] Age and sex norms are available for right and left hands.[38] Higher scores indicated greater unimanual speed and dexterity.

Executive function and upper limb function descriptive scores (mean, median, and interquartile range) are presented in Table S2 (online supporting information).

Statistical analysis

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The distribution of brain MRI lesion-predominant patterns in our sample was compared to a Victorian cohort of 442 children between 1999 and 2013, with unilateral CP (S. Reid, personal communication, 5th November 2017). Children with complete brain MRI and behavioural data (neuropsychological and fine motor) were included in the analysis. Group differences in standardized behavioural test scores for participants classified by (brain MRI pattern and focal lesions) were compared using parametric tests for continuous variables (Student's *t*-test, one-way analysis of variance, and medians tests) and χ^2 for categorical data.

Associations between brain MRI-predominant pattern, focal lesions (frontal, thalamus, and/or basal ganglia) and clinical outcome (executive function, bimanual performance, and unimanual capacity) were examined using multiple linear regressions and by boxplots. Covariates included side of hemiparesis (left/right), presence of active seizures (present/absent), bilateral lesion (present/absent), and gestational age. In executive function

models, general cognitive ability (Wechsler Intelligence Scale for Children, Fourth Edition General Ability Index) was included as an additional covariate. In unimanual dexterity models, child age at assessment was included as a covariate as scores increase with age.[39] A 5% level of significance and 95% confidence interval (CI) were reported across analyses. The variance inflation factor was calculated to inspect the degree of collinearity in all models. In order to test whether the effect of basal ganglia or thalamic lesions alone was significantly different to the effect of basal ganglia and thalamic lesions combined, standardized beta weights and their corresponding 95% CIs were estimated via bias-corrected bootstrap with the model adjusted for the same factors as in the model with unstandardized estimates. The comparison of estimates was then conducted using methods of CI overlaps suggested by Cumming,[40] who stated that in the event that CIs for two estimates overlap by less than 50%, the coefficient estimates would be considered statistically significantly different from each other (p<0.05). In the event of greater than 50% overlap of CIs, the conclusion is that p>0.05 and fail to reject the null hypothesis that estimates are different. Data were analysed using Stata Statistical Software version 15 (College Station, TX, USA).

RESULTS

From 131 children recruited to the study, 100 had MRI data available (Fig. S1, online supporting information). MRI brain predominant patterns were WMI (60%); FVI (27%); malformations (6%); grey matter injury or mixed abnormality (each 2%); miscellaneous lesions (0%), and normal (3%). This distribution of MRI brain lesion pattern was representative of Victorian cohort data for unilateral CP, although there were fewer malformations and miscellaneous lesions than expected (p=0.035 and p=0.034 respectively). MRI patterns with too few participants for analysis (i.e. <5; n=7) were excluded from the analysed sample, which included only 71 participants (WMI or FVI patterns only). Examples of magnetic resonance images classified according to the predominant pathological pattern or focal pathology are provided in Figure 1.

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Demographic information

Table S3 (online supporting information) summarizes the demographic, imaging, and clinical characteristics of the participants. Mean age was 9 years 2 months. About two-thirds were

males (66%) and were at Manual Ability Classification System level II, while just over half had right-sided hemiparesis.

Preliminary analysis

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Demographic (age at assessment, sex, or age at MRI acquisition) and functional abilities (Manual Ability Classification System, GMFCS) of children with WMI and FVI were comparable. However, those with WMI were born, on average, at an earlier gestational age, had a lower birthweight relative to those with FVI, and were more likely to exhibit bilateral lesions. Therefore, regression models included gestational age and bilateral lesions as covariates. Gestational weight was not included as a covariate owing to association with gestational age.

Children with focal lesions (frontal, thalamic, basal ganglia) did not differ with respect to demographic or key clinical characteristics to those without abnormality in the same area. However, children with basal ganglia lesions were less likely to be classified in GMFCS level I (58%) than those without (80%, p=0.044). Further, those with thalamic lesions were more likely than those without to exhibit bilateral lesions (p=0.048).

Main analysis

Brain MRI associations with executive function

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Figure 2 shows executive function by brain MRI lesion characteristics. Overall, MRI brain lesion pattern (FVI vs WMI) was not associated with differences in executive function, other than information processing (Table S4, online supporting information, adjusted models). Conversely, executive functions were associated with focal lesions as follows: frontal lesions were associated with lower attention control and cognitive flexibility, but not goal setting or information processing. Basal ganglia and thalamic focal lesions in isolation or combination were not associated with executive function performance. Parent-rated executive behaviour was not associated with predominant pattern or focal brain lesions.

Brain MRI associations with upper limb function

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Figures 3 and 4 show bimanual and unimanual outcomes by brain MRI predominant pattern and focal lesions. FVI predicted reduced bimanual performance (AHA scores) and dexterity

of both the affected and dominant hands, relative to WMI (Table S5, online supporting information, adjusted models). Bimanual performance and unimanual dexterity were associated with focal lesions as follows: frontal lesions were associated with reduced AHA scores and reduced dexterity of the non-dominant hand (but not dominant hand dexterity); thalamic lesions were associated with reduced dexterity in both hands; and basal ganglia lesions were associated with reduced upper limb performance across all measures. In addition to the unstandardized estimates presented in Table S5, standardized estimates were obtained to compare coefficients for the different lesion types. The estimated effect of basal ganglia alone on AHA was –0.23 (95% bias-corrected and accelerated CI –0.42 to 0.03), while that for thalamic lesions alone was –0.14 (95% bias-corrected and accelerated CI –0.37 to 0.08). The estimated effect of basal ganglia combined with thalamic lesions was –0.27 (95% bias-corrected and accelerated CI –0.47 to –0.06). Comparison of the single lesion standardized estimates to the combined lesion standardized estimates using Cumming's methods suggested that the presence of both basal ganglia and thalamic lesions had a similar effect on AHA as the presence of only one lesion.[41] However, the application of this rule needs to be interpreted with caution as its applicability, accuracy, and reliability beyond Cumming's examples has not been tested.

DISCUSSION

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This study is novel in examining the influence of MRI-identified brain lesions on executive function and bimanual performance in children with unilateral CP, using traditional categorizations of predominant pattern, in addition to the presence/absence of focal lesions. Executive function and upper limb performance were differentially associated with specific MRI characteristics.

The most common MRI brain lesion pattern was WMI followed by FVI. FVI was associated with reduced bimanual performance and worse dexterity in the non-dominant hand. This is consistent with previous research, documenting that children with a pure WMI pattern performed better than those with mixed lesions, or middle cerebral artery infarcts.[18]

MRI brain lesion pattern classification (WMI vs FVI) was relatively insensitive to executive function outcome, with the exception of information processing. Focal lesions were more strongly associated with specific executive function outcomes. Specifically, frontal pathology predicted reduced attention control and cognitive flexibility. Although we were not

able to specify the prefrontal cortex from the frontal lobes in the present study, these findings are broadly consistent with prior research, and the role of the prefrontal cortex in executive skills is well established.[41–43] Lack of concordance between child performances and parental behavioural ratings of executive function, and poor sensitivity of behavioural measures to frontal lesions has been noted,[44] and confirms our study findings.

Focal lesions of the basal ganglia and thalamus combined or of the basal ganglia alone were associated with lower bimanual performance (AHA). Hand function vulnerability to basal ganglia insult is consistent with several prior studies,[45,46] and is consistent with the findings of the present study. Holmefur et al.[18] reported that better bimanual performance was most closely associated with an absence of a concurrent lesion to the basal ganglia and thalamus, independent of the basic type of brain lesion. An interesting finding, requiring further validation, was the association between frontal pathology and reduced capacity in the non-dominant hand. Impaired hand function has previously been reported to be more common in children with CP with cortical/subcortical lesion compared to periventricular lesion.[47] Others have reported that associations between lesion location (and extent) and upper limb movement is influenced by the predominant pattern, with deep grey matter injury patterns demonstrating stronger associations between these factors relative to children with white matter lesion patterns.[48]

The limitations of the study include the small group size of MRI predominant patterns of grey matter injury, malformations, or miscellaneous lesions, requiring exclusion, meaning findings cannot be generalized to these children. Further, MRIs were classified using qualitative methods, which can lack specificity. For example, frontal pathology did not specify prefrontal cortex lesions and so may lack sensitivity to executive dysfunction. Also, we used retrospective clinical MRI scans, using available scanning protocols, taken on different types of scanners with different parameters, affecting uniformity of the scans for analysis. Also, MRI brain scans were taken when clinically indicated, at different ages and phases, for example acute versus chronic. We were also unable to specify the timing of brain injury, an important prognosticator for executive function outcomes,[49,50] possibly affecting upper limb outcomes.[51] We did not record the type of corticospinal tract wiring in this study, which, in combination with underlying lesion location/extent, has been shown to influence upper limb motor function.[52,53] Therefore, future studies should consider the potential contribution of corticospinal tract wring. Finally, executive function tasks were chosen requiring minimal fine motor dexterity; however, Tower of London performances could be

affected by slow cognitive or motor speed, and this study was not able to differentiate these two factors.

Implications

Classification of MRI brain lesion pattern was sensitive to bimanual performance and unimanual dexterity in this sample but was insensitive to executive function outcomes. Focal lesions were associated with both bimanual performance and executive function outcomes, suggesting that current pattern-based MRI classification protocols are enhanced by specifying focal brain lesions. The findings highlight the need for clinicians to have a clearer understanding about how MRI may predict children's functioning. Importantly, motor outcomes may become evident earlier in childhood relative to executive deficits that emerge later. Ultimately, early MRI may identify children at risk of cognitive/motor deficits and mobilize early intervention in order to optimize children's activity and participation outcomes.

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Supporting information

The following additional material may be found online:

Table S1: Magnetic resonance imaging classification of brain lesions.

Table S2: Performance of participants on executive function tasks and upper limb function measures.

Table S3: Characteristics of the children in study, by magnetic resonance imaging predominant pattern, and focal area of brain abnormality.

Table S4: Relationship between executive function outcomes and magnetic resonance imaging pattern or focal pathology.

Table S5: Relationship between motor outcomes and magnetic resonance imaging pattern or focal pathology.

Figure S1: Flow of participants through each stage study.

REFERENCES

1. Rosenbaum P, Stewart D. The World Health Organization International Classification of Functioning, Disability, and Health: a model to guide clinical thinking, practice and research in the field of cerebral palsy. *Semin Pediatr Neurol* 2004; **11**: 5–10.
2. Imms C, Adair B, Keen D, Ullenhag A, Rosenbaum P, Granlund M. 'Participation': a systematic review of language, definitions, and constructs used in intervention research with children with disabilities. *Dev Med Child Neurol* 2016; **58**: 29–38.
3. Mahone MM, Slomine BS. Manging dysexecutive disorders. In: Hunter S, Donders J editors. Pediatric neuropsychological intervention. New York: Cambridge University Press; 2007: 287–313.
4. Royall DR, Lauterbach EC, Cummings JL, et al. Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci* 2002; **14**: 377–405.
5. Litcher DG, Cummings JL. Frontal-subcortical circuits in psychiatric and neurological disorders. New York: Guilford Press, 2001.
6. Weierink L, Cunnington R, Vermeulen J, Bodimeade H, Boyd R. Brain structure-function relationship in relation to executive attention of children with congenital hemiplegia: a functional MRI study. *Dev Med Child Neurol* 2012; **54**(Suppl 5): 50.
7. Stuss DT, Alexander MP. Executive functions and the frontal lobes: a conceptual view. *Psychol Res* 2000; **63**: 289–98.
8. Denckla MB, Reiss AL. Prefrontal–subcortical circuits in developmental disorders. In: Krasnegor NA, Lyon GR, Goldman-Rakic PS, editors. Development of the prefrontal cortex: evolution, neurobiology, and behavior. Baltimore, MD: Brookes Publishing, 1997: 283–93.
9. Scheck SM, Pannek K, Fiori S, Boyd RN, Rose SE. Quantitative comparison of cortical and deep grey matter in pathological subtypes of unilateral cerebral palsy. *Dev Med Child Neurol* 2014; **56**: 968–75.

10. Mirsky AF. The neuropsychology of attention: elements of a complex behavior. In: Perecman E, editor. Integrating theory and practice in clinical neuropsychology. Hillsdale, NJ: Lawrence Erlbaum, 1989: 75–91.

11. Bottcher L. Children with spastic cerebral palsy, their cognitive functioning, and social participation: a review. *Child Neuropsychol* 2010; **16**: 209–28.

12. Weierink L, Vermeulen RJ, Boyd RN. Brain structure and executive functions in children with cerebral palsy: a systematic review. *Res Dev Disabil* 2013; **34**: 1678–88.

13. Pirila S, van der Meere JJ, Rantanen K, Jokiluoma M, Eriksson K. Executive functions in youth with spastic cerebral palsy. *J Child Neurol* 2011; **26**: 817–21.

14. Roze E, Van Braeckel KN, van der Veere CN, Maathuis GB, Martijn A, Bos AF. Functional outcome at school age of preterm infants with periventricular hemorrhagic infarction. *Pediatrics* 2009; **123**: 1493–500.

15. Schatz J, Craft S, White D, Park TS, Figiel GS. Inhibition of return in children with perinatal brain injury. *J Int Neuropsychol Soc* 2001; **7**: 275–84.

16. Straub K, Obrzut JF. Effects of cerebral palsy on neuropsychological function. *J Dev Phys Disabil* 2009; **21**: 153–67.

17. Kimmerle M, Mainwaring L, Borenstein M. The functional repertoire of the hand and its application to assessment. *Am J Occup Ther* 2003; **57**: 489–98.

18. Holmefur M, Kits A, Bergstrom J, et al. Neuroradiology can predict the development of hand function in children with unilateral cerebral palsy. *Neurorehabil Neural Repair* 2013; **27**: 72–8.

19. Mailleux L, Klingels K, Fiori S, et al. How does the interaction of presumed timing, location and extent of the underlying brain lesion relate to upper limb function in children with unilateral cerebral palsy? *Eur J Paediatr Neurol* 2017; **21**: 763–72.

20. Himmelmann K, Uvebrant P. Function and neuroimaging in cerebral palsy: a population-based study. *Dev Med Child Neurol* 2011; **53**: 516–21.

21. Hoare B, Ditchfield M, Thorley M, et al. Cognition and bimanual performance in children with unilateral cerebral palsy: protocol for a multicentre, cross-sectional study. *BMC Neurol* 2018; **18**: 63.

22. Delacy MJ, Reid SM. Profile of associated impairments at age 5 years in Australia by cerebral palsy subtype and Gross Motor Function Classification System level for birth years 1996 to 2005. *Dev Med Child Neurol* 2016; **58**: 50–6.

23. Eliasson AC, Krumlinde-Sundholm L, Rösblad B, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: Scale development and evidence of validity and reliability. *Dev Med Child Neurol* 2006; **48**: 549–54.

24. Palisano R, Rosenbaum P, Walter S, Russell DJ. Gross Motor Function Classification System for cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.

25. Hidecker MJC, Paneth N, Rosenbaum PL, et al. Developing and validating the Communication Function Classification System for individuals with cerebral palsy. *Dev Med Child Neurol* 2011; **53**: 704–10.

26. Leonard JM, Cozens AL, Reid S, Fahey MC, Ditchfield MR, Reddihough DS. Should children with cerebral palsy and normal imaging undergo testing for inherited metabolic disorders? *Dev Med Child Neurol* 2011; **53**: 226–32.

27. Reid SM, Dagia CD, Ditchfield MR, Carlin JB, Reddihough DS. Population-based studies of brain imaging patterns in cerebral palsy. *Dev Med Child Neurol* 2014; **56**: 222–32.

28. Anderson P. Assessment and development of executive function (EF) during childhood. *Child Neuropsychol* 2002; **8**: 71–82.

29. Korkman M, Kirk U, Kemp S. NEPSY-II. San Antonio, TX: Harcourt Assessment, 2007.

30. Manly T, Anderson V, Robertson I, Nimmo-Smith I. The Test of Everyday Attention for Children. London: Thames Valley Test Company, 1999.

31. Anderson P, Anderson V, Lajoie G. The tower of London test: Validation and standardization for pediatric populatons. *Clin Neuropsychol* 1996; **10**: 54–65.

32. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Resources, 2000.

33. Wechsler D. WISC – IV Australian Administration and Scoring Manual. London: Harcourt Assessment, 2003.

34. Raiford SE, Weiss LG, Rolfhus E, Coalson D. WISC-IV Technical Report #4. Available at: https://images.pearsonclinical.com/images/assets/WISC-IV/80720_WISCIV_Hr_r4.pdf (accessed 23 June 2018).

35. Holmefur M, Krumlinde-Sundholm L. Psychometric properties of a revised version of the Assisting Hand Assessment (Kids-AHA 5.0). *Dev Med Child Neurol* 2016; **58**: 618–24.

36. Krumlinde-Sundholm L, Eliasson AC. Development of the Assisting Hand Assessment: a rasch-built measure intended for children with unilateral upper limb impairments. *Scand J Occup Ther* 2003; **10**: 16–26.

37. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the box and block test of manual dexterity. *Am J Occup Ther* 1985; **39**: 386–93.

38. Mathiowetz V, Federman S, Wiemer D. Box and blocks test of manual dexterity: Norms for 6-19 year olds. *Can J Occup Ther* 1985; **52**: 241–5.

39. Canny ML, Thompson JM, Wheeler MJ. Reliability of the Box and Block Test of manual dexterity for use with patients with fibromyalgia. *A Am J Occup Ther* 2009; **63**: 506–10.

40. Cumming G. Inference by eye: reading the overlap of independent confidence intervals. *Stat Med* 2009; **28**: 205–20.

41. Anderson PJ. Assessment and development of executive function (EF) during childhood. *Child Neuropsychol* 2010; **8**: 71–82.

42. Jacobs R, Anderson V. Planning and problem solving skills following focal frontal brain lesions in childhood: analysis using the Tower of London. *Child Neuropsychol* 2002; **8**: 93–106.

43. Tsujimoto S. The prefrontal cortex: functional neural development during early childhood. *Neuroscientist* 2008; **14**: 345–58.

44. Anderson VA, Anderson P, Northam E, Jacobs R, Mikiewicz O. Relationships between cognitive and behavioral measures of executive function in children with brain disease. *Child Neuropsychol* 2002; **8**: 231–40.

45. Holmström L, Vollmer B, Tedroff K, et al. Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy. *Dev Med Child Neurol* 2010; **52**: 145–52.

46. Forssberg H, Eliasson AC, Redon-Zouitenn C, Mercuri E, Dubowitz L. Impaired grip-lift synergy in children with unilateral brain lesions. *Brain* 1999; **122**: 1157–68.

47. Feys H, Eyssen M, Jaspers E, et al. Relation between neuroradiological findings and upper limb function in hemiplegic cerebral palsy. *Eur J Paediatr Neurol* 2010; **14**: 169–77.

48. Mailleux L, Simon-Martinez C, Klingels K, et al. Structural brain damage and upper limb kinematics in children with unilateral cerebral palsy. *Front Hum Neurosci* 2017; **11**: 607.

49. Anderson VA, Jacobs R, Spencer-Smith M, et al. Does early age at brain insult predict worse outcome? Neuropsychological implications. *J Pediatr Psychol* 2010; **35**: 716–27.

50. Anderson VA, Spencer-Smith M, Coleman L, et al. Predicting neurocognitive and behavioural outcome after early brain insult. *Dev Med Child Neurol* 2014; **56**: 329–36.

51. Diamond A. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child Dev* 2000; **71**: 44–56.

52. Simon-Martinez C, Jaspers E, Mailleux L, et al. Corticospinal tract wiring and brain lesion characteristics in unilateral cerebral palsy: determinants of upper limb motor and sensory function. *Neural Plast* 2018; **2018**: 2671613.

53. Holmström L, Vollmer B, Tedroff K, et al. Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy. *Dev Med Child Neurol* 2010; **52**: 145–52.

54. Reid SM, Dagia CD, Ditchfield MR, Reddihough DS. Grey matter injury patterns in cerebral palsy: associations between structural involvement on MRI and clinical outcomes. *Dev Med Child Neurol* 2015; **57**: 1159–67.

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Figure legends

Figure 1: Example magnetic resonance imaging brain axial T2-weighted images, including (a) deep white matter injury, (b) focal vascular injury, (c) focal vascular injury in the frontal region, (d) symmetrical loss of volume of the thalmai and increased signal indicating gliosis, and (e) both basal ganglia and thalmai are infarcted. Note: isolated damage to the basal ganglia is not shown.

Figure 2: Boxplot of executive functioning across magnetic resonance imaging (MRI) pattern classification (white matter injury [WMI] vs focal vascular insults [FVI]) and focal lesions. [a]Focal lesions were classified as presence/absence of frontal thalamic, basal ganglia (BG), and thalamic and BG combined lesions. EF, executive functioning.

Figure 3: Boxplot of Assisting Hand Assessment (AHA) scores across magnetic resonance imaging (MRI) pattern classification (white matter injury [WMI] vs focal vascular insults [FVI]) and focal lesions. [a]Focal lesions was classified as presence/absence of frontal thalamic, basal ganglia (BG), and thalamic and BG combined lesions.

Figure 4: Boxplot of Box and Blocks Test scores across magnetic resonance imaging (MRI) pattern classification (white matter injury [WMI] vs focal vascular insults [FVI]) and focal lesions. [a]Focal lesions was classified as presence/absence of frontal thalamic, basal ganglia (BG), and thalamic and BG combined lesions.

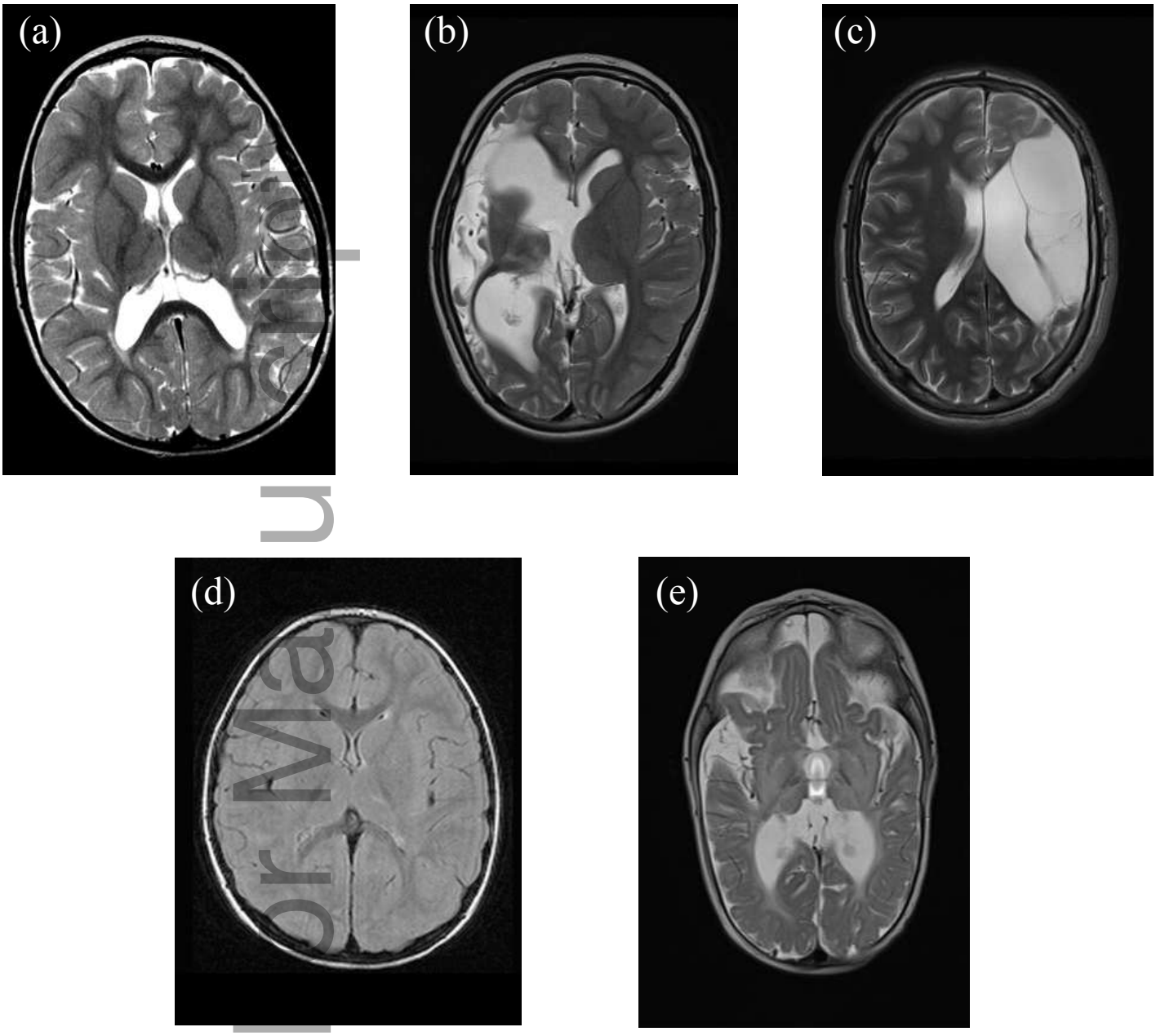
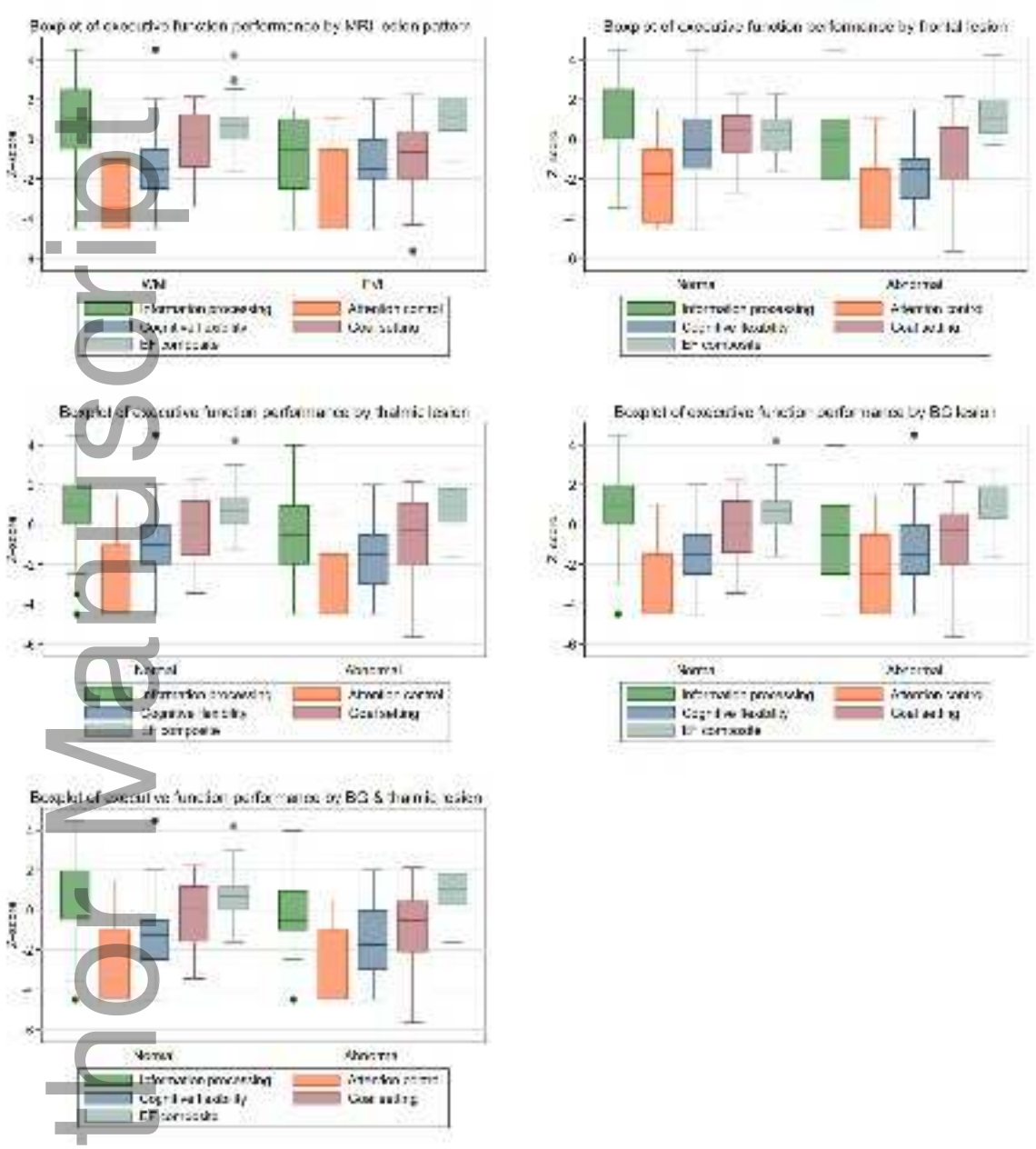


Figure 2 - Example MRI brain Axial T2-weighted images including (a) deep white matter injury, (b) focal vascular injury, (c) focal vascular injury in the frontal region, (d) symmetrical loss of volume of the thalmai and increased signal indicating gliosis, and (e) both basal ganglia and thalmai are infarcted. Note: isolated damage to the basal ganglia is not shown.

Figure 2 – Boxplot of executive functioning across magnetic resonance imaging (MRI) pattern classification (white matter injury [WMI] vs focal vascular insults [FVI]) and focal lesions. [a]



[a] Focal lesions were classified as presence/absence of frontal thalamic, basal ganglia (BG), and thalamic and BG combined lesions. EF, executive functioning.
MRI = Magnetic Resonance Imaging, WMI = White Matter Injury, FVI = Focal Vascular Injury, BG = Basal Ganglia

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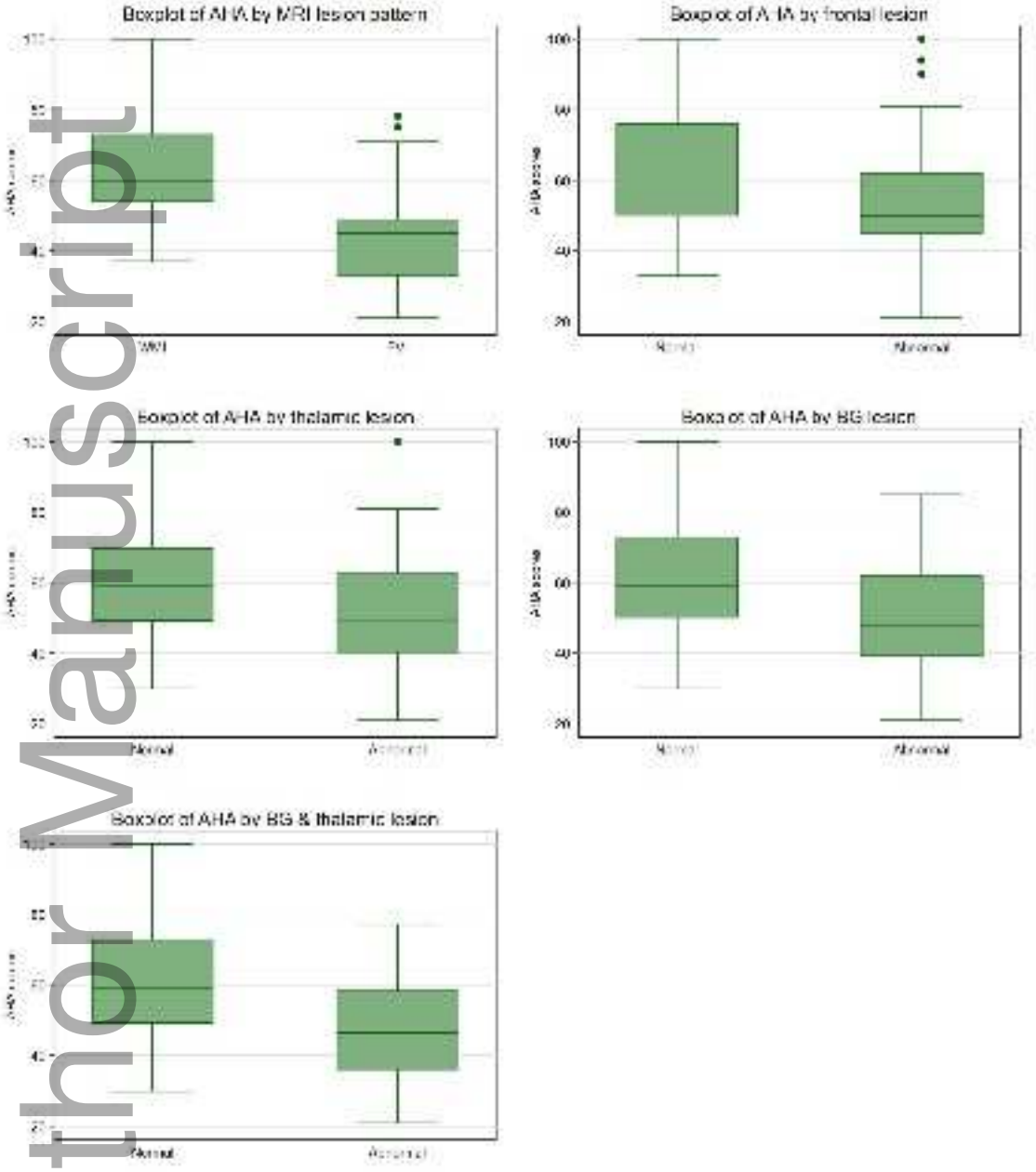
Figure 3 – Boxplot of Assisting Hand Assessment (AHA) scores across magnetic resonance imaging (MRI) pattern classification (white matter injury [WMI] vs focal vascular insults [FVI]) and focal lesions. [a]



[a] Focal lesions were classified as presence/absence of frontal thalamic, basal ganglia (BG), and thalamic and BG combined lesions.

AH = AHA-Assisting Hand Assessment, MRI = Magnetic Resonance Imaging, WMI = White Matter Injury, FVI = Focal Vascular Injury, BG = Basal Ganglia

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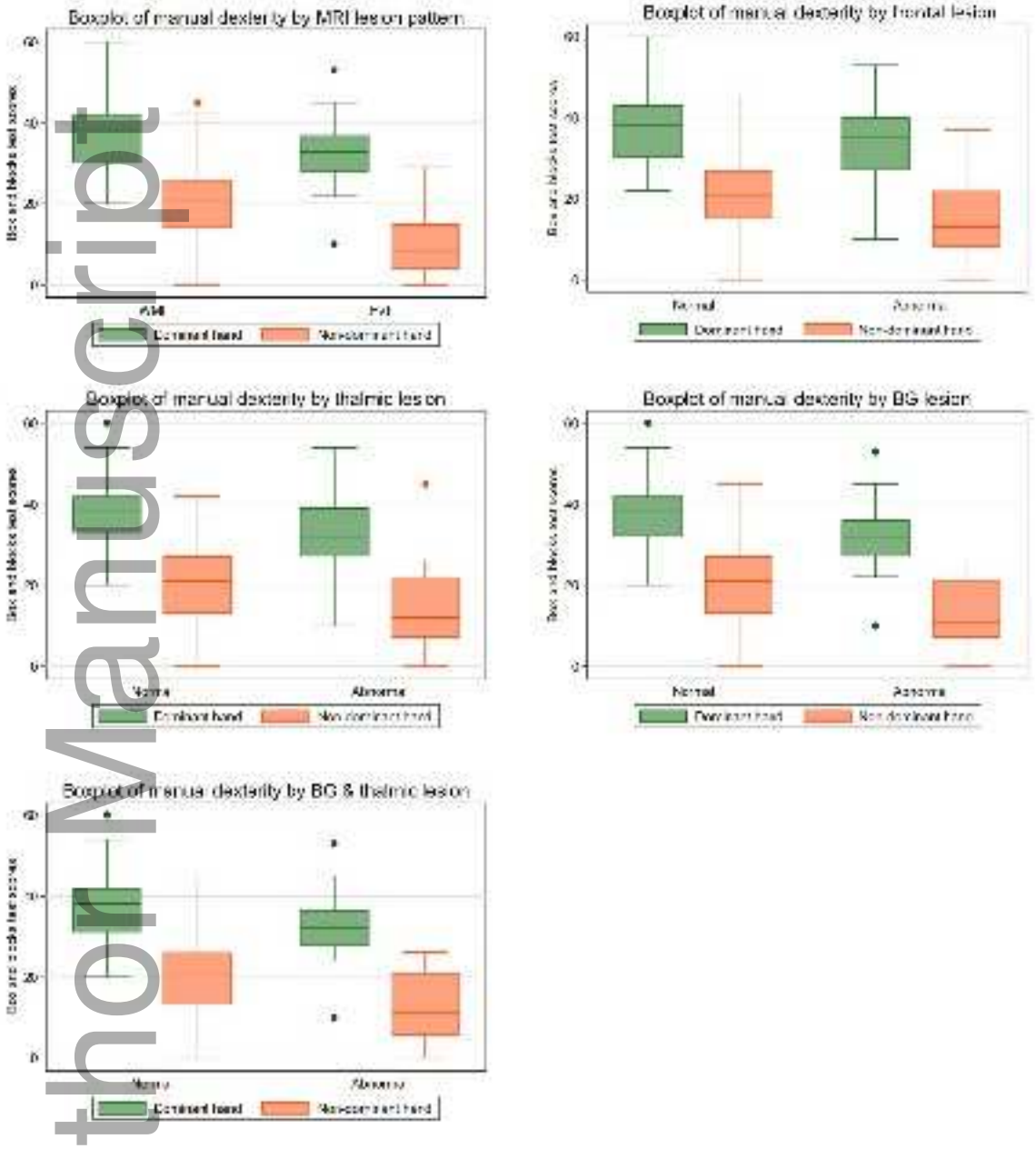
Figure 4 – Boxplot of Box and Blocks Test scores across magnetic resonance imaging (MRI) pattern classification (white matter injury [WMI] vs focal vascular insults [FVI]) and focal lesions. [a]



[a] Focal lesions were classified as presence/absence of frontal thalamic, basal ganglia (BG), and thalamic and BG combined lesions.

MRI – Magnetic Resonance Imaging, WMI – White Matter Injury, FVI – Focal Vascular Injury, BG – Basal Ganglia

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