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Neonatal motor functional connectivity and motor outcomes at age two years in very preterm children with and without high-grade brain injury

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ABSTRACT

Preterm-born children have high rates of motor impairments, but mechanisms for early identification remain limited. We hypothesized that neonatal motor system functional connectivity (FC) would relate to motor outcomes at age two years; currently, this relationship is not yet well-described in very preterm (VPT; born <32 weeks' gestation) infants with and without brain injury.

We recruited 107 VPT infants – including 55 with brain injury (grade III–IV intraventricular hemorrhage, cystic periventricular leukomalacia, post-hemorrhagic hydrocephalus) – and collected FC data at/near term-equivalent age (35–45 weeks postmenstrual age). Correlation coefficients were used to calculate the FC between bilateral motor and visual cortices and thalami. At two years corrected-age, motor outcomes were assessed with the Bayley Scales of Infant and Toddler Development, 3rd edition. Multiple imputation was used to estimate missing data, and regression models related FC measures to motor outcomes.

Within the brain-injured group only, interhemispheric motor cortex FC was positively related to gross motor outcomes. Thalamocortical and visual FC were not related to motor scores. This suggests neonatal alterations in motor system FC may provide prognostic information about impairments in children with brain injury.

1. Introduction

Preterm birth (<37 weeks' gestation) is the most common cause of motor disability in children. In the United States alone, approximately 500,000 infants are born preterm each year, representing about 10% of all live births (Frey and Klebanoff, 2016). Importantly, despite advances in neonatal care, a wide range of motor outcomes, including lifelong disability, still occur in surviving very preterm (VPT, ≤32 weeks' gestation) children (Balakrishnan et al., 2020; Dewan et al., 2019; Evensen et al., 2020; Johnson and Marlow, 2017), with high rates of cerebral palsy (CP, ~5–15%) and other forms of motor impairment (up to 70%) (Evensen et al., 2020). Further, children with motor disability, even when that disability is mild, experience increased rates of obesity, mental health problems, and decreased health-related quality of life that persist into adulthood (Cairney et al., 2010; Karras et al., 2019). Improved mechanisms for the identification of VPT children most likely to develop motor disabilities would allow for earlier and more targeted referrals to specialized clinical and therapy services and integration into the disability community.

Among VPT children, motor disability occurs most frequently in those who experience brain injury. This injury typically consists of high-grade intraventricular hemorrhage (IVH) and cystic periventricular

Abbreviations: FC, functional connectivity; VPT, very preterm; CP, cerebral palsy; IVH, intraventricular hemorrhage; cPVL, cystic periventricular leukomalacia; rs-fMRI, resting state functional magnetic resonance imaging; NICU, neonatal intensive care unit; BI, brain-injured; ROI, region of interest; MICE, multiple imputation with chained equations; UPT, uninjured preterm; L/RMC, left-right motor cortex; L/RVIS, left-right primary visual cortex; TC, thalamocortical; V1, primary visual cortex.

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leukomalacia (cPVL), which occur at a combined rate of ~15% in VPT infants (Stoll et al., 2015). Further, CP has been reported in up to 61% of VPT children with cPVL and 50% of children with intraparenchymal hemorrhage, as compared to 8% of VPT children with low-grade IVH and 4% of VPT children without brain injury (Beaino et al., 2010). Importantly, while there is some specificity regarding type of brain injury and specific forms of CP (Al Rifai and Al Tawil, 2015; Arnfield et al., 2013; Hayakawa et al., 1996; Lee et al., 2011; Okumura et al., 1997; Yoshida et al., 2011), there remains a wide range of motor outcomes (i.e., independently ambulatory, ambulatory with aids, non-ambulatory) even among brain-injured VPT children (Beaino et al., 2010), indicating that the appearance of injury on structural imaging studies only accounts for a relatively modest portion of this variance.

Resting-state functional MRI (rs-fMRI) affords unique potential to more precisely identify VPT children at greatest risk for motor disability. Using rs-fMRI data, measures of functional connectivity (FC) are calculated from the temporal correlations in low-frequency fluctuations in blood oxygen level dependent signal driven by intrinsic activity across the brain as measured when the subject is resting and not performing a task (Fox et al., 2005; Lowe et al., 1998). Because it requires no active participation and can assess the whole brain in a matter of minutes, this approach is ideal for use in neonates. Prior research has shown differences in FC across areas important for motor function in infants born preterm as compared to full term controls (Eyre et al., 2021; Gozdas et al., 2018; Smyser et al., 2016b), and differences in FC involving motor cortex have been linked to poorer motor function at age two years in uninjured VPT children (Toulmin et al., 2021). Further, cross-sectional research has found altered FC relationships involving somatomotor cortex in uninjured VPT adolescents (Wehrle et al., 2018) and thalamocortical FC (between somatomotor cortex and thalamus) in young adults with brain injury and CP (Burton et al., 2009; Lee et al., 2011). Finally, FC alterations have been associated with poorer motor outcomes in VPT preadolescents (Wheelock et al., 2018). However, these existing studies, which have been predominantly cross-sectional and/or not included both children with and without brain injury and/or not separated fine and gross motor domains (which are often treated by different professionals and may be affected to different degrees depending on the anatomic distribution of impairment), have not well characterized the full range of associations between neonatal FC and motor development in VPT children.

This study aims to address these gaps by examining the extent to which neonatal FC may improve understanding of early neural correlates of motor outcomes in early childhood above and beyond the presence/absence of perinatal brain injury among VPT infants. We hypothesized that stronger FC (i.e., higher correlation coefficients) within the motor system in the neonatal period will correlate with better motor outcomes at corrected-age two years in VPT children with and without brain injury. These associations were expected to be present across fine and gross motor domains.

2. Materials & methods

2.1. Participants

VPT infants (birth gestational age ≤30 weeks, n = 107) were recruited from the St. Louis Children's Hospital Level III Neonatal Intensive Care Unit from 2007 to 2016. The brain-injured (BI, n = 55) group included VPT children with grade III–IV IVH (Papile, 1978), cPVL, and/or post-hemorrhagic hydrocephalus based upon interpretation of clinical ultrasound studies obtained in the first weeks of life and MRI scans at/near term-equivalent postmenstrual age reviewed by a neuroradiologist (J.S.S.) and pediatric neurologist (C.D.S.), as defined by expert clinical opinion. VPT infants with brain injury were collapsed into a single BI group, as the sample size was too small to test the effects of specific injury types. The uninjured preterm (UPT, n = 52) group included infants with no injury or low-grade injury (grade I/II IVH [n = 5], non-cystic white matter injury [n = 10]). Exclusion criteria for both groups included parent unable to give informed consent, chromosomal/genetic abnormalities, and/or proven congenital infections. This study was approved by the Washington University Human Studies Committee. Parental written informed consent was obtained for all participants. The study was conducted in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki, 2008)*.

2.2. Medical risk scores

Infant medical records were prospectively reviewed and a medical risk index score (range: 0–10) was created from summing dichotomized (present = 1, absent = 0) factors: intrauterine growth restriction, did not receive antenatal steroids, received dexamethasone, oxygen supplementation at 36 weeks, necrotizing enterocolitis, confirmed sepsis, patent ductus arteriosus requiring medical or surgical treatment, retinopathy of prematurity requiring surgery, ≥3SD decrease in weight-for-length from birth to term-equivalent age, and >75th percentile for duration of parenteral nutrition (Lean et al., 2018).

2.3. Demographic stressor index

To describe the socioeconomic and life circumstances that may increase stress for the child's primary caregiver, a cumulative maternal demographic stressor index was assessed at NICU discharge and calculated using five demographic factors that were dichotomized (present = 1, absent = 0) and summed (0–5). Factors included age ≤18 years at time of delivery, Black race, no high school degree, public health insurance, and single-parent household (Hack et al., 1994; Mangin et al., 2017; Manley et al., 2015). Black race was included in the demographic stressor index to account for social and health inequities that result from experiencing structural and individual racism in America, particularly as the region of recruitment is heavily stratified by race (Bureau, 2010; Subramanian et al., 2005).

2.4. Neonatal MRI scanning and processing

UPT and BI neonates underwent MRI scanning at/near term-equivalent age (35–45 weeks postmenstrual age, mean 38.4 weeks). All neonates were scanned during natural sleep or quiet rest (Mathur et al., 2008). MRI scans were performed on a Siemens 3T Trio scanner (Erlangen, Germany) using an infant-specific head coil (Advanced Imaging Research, Cleveland, OH). Structural images were collected using a T2-weighted sequence (TR = 8600 ms; TE = 161 ms; voxel size 1 mm isotropic). The rs-fMRI data were collected using a gradient echo, echo planar image (*EPI*) sequence sensitized to T2* blood oxygen level-dependent (BOLD) contrast (TR = 2910 ms; TE = 28 ms; voxel size 2.4 mm isotropic; flip angle 90°; field of view 151 mm; matrix size 64 × 64). Each rs-fMRI run included 200 volumes (frames). A minimum of one run (9.6 min) was obtained in each infant, with additional runs acquired in a subset of participants depending upon tolerance, with a maximum of four runs.

The data were pre-processed using in-house software as described in prior work (Smyser et al., 2010, 2013). Magnetization inhomogeneity-related distortions were corrected using a mean field map technique (Gholipour et al., 2008). The tools used to perform image registration were a combination of in house 4dfp suite tools (4dfp.readthedocs.io) and FSL's (Jenkinson et al., 2012) applywarp. The T2-weighted image was affine registered to the cohort specific template (Smyser et al., 2016a) and the transformation matrix was saved. This transformation matrix (T2 → cohort template) was multiplied with the transformation matrix from cohort template to atlas space to create a one-step resample from subject specific T2 to atlas space. The rs-fMRI registration was performed in a similar fashion, creating volumetric time series with 3-mm isotropic voxels, combining motion correction and atlas transformation in a single resampling step. The rs-fMRI data were registered

to the subject-specific T2 and the transformation matrix was saved. This transformation matrix (rs-fMRI → subject T2) was multiplied with the T2 → atlas transformation matrix to generate a single step resample to atlas space. Additional preprocessing included regression of nuisance waveforms derived from rigid body motion correction, cerebrospinal fluid, and white matter regions, plus whole brain global signal. The data were high-pass filtered at 0.08 with a second-order Butterworth filter and spatially smoothed with a 6 mm kernel. Frames affected by sudden changes in head position (volume-to-volume head displacement $\geq$0.5 mm) were excluded from the rs-fMRI computations ("scrubbing") (Power et al., 2014). A minimum of five minutes of rs-fMRI data, excluding censored frames, was required for inclusion in the analysis.

Regions of Interest (ROIs) (Fig. 1) were selected to include key areas of the motor system, including bilateral motor cortex (Smyser et al., 2016b) and an area of the thalamus chosen specifically to maximize functional connectivity with motor cortex (Smyser et al., 2010). In the BI group, ROIs for the same brain areas were initially placed according to atlas coordinates and then adjusted to align with each infant's anatomy (Smyser et al., 2013). In order to check for widespread FC effects, a negative control was included. Because most other ROIs used in the BI group had known relationships to motor FC, ROIs in the bilateral primary visual cortex were used, as prior work had shown the visual network to have a lower magnitude correlation (positive or negative) with the motor network as compared to other functional networks in preterm infants (Smyser et al., 2016b). Any ROIs with mean BOLD fMRI intensities outside the typical range for gray matter, either due to individual differences in susceptibility inhomogeneity-related signal voids or incomplete coverage, were excluded from further analyses (Herzmann et al., 2018). ROI-ROI correlation coefficients were computed between the left and right motor cortex (L/R MC), thalamus and motor cortex (thalamocortical, TC – the mean of both pairs of ipsilateral thalamus-motor cortex ROI FC), and left and right visual cortex (L/R VIS), and Fisher z-transformed (Smyser et al., 2016b).

2.5. Motor outcomes

Motor outcomes were assessed at two years corrected-age using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III) (Bayley, 2006), which includes a standardized overall Motor Composite score (m = 100, SD = 15), as well as Fine Motor and Gross Motor subscale scores (m = 10, SD = 3). Assessments were conducted by highly trained members of the Washington University Intellectual and Developmental Disabilities Research Center or as part of clinical care. Psychometricians were blinded to each infant's birth history and injury status. At the assessment visit, a subset of children was also examined by a physician for cerebral palsy.

2.6. Statistical analysis

All statistical analyses were conducted in R. To estimate missing data, we used MICE (Multiple Imputation with Chained Equations) (van Buuren and Groothuis-Oudshoorn, 2011), with 100 imputations, well above the minimum number recommended for this analysis (von Hippel, 2020). Among the included participants for regression analyses, the number of originally missing values that were substituted with values obtained by multiple imputation ranged from 2% to 43% per variable, which was considered acceptable (Dong and Peng, 2013; Madley-Dowd et al., 2019) as they were not suspected of being Missing Not at Random.

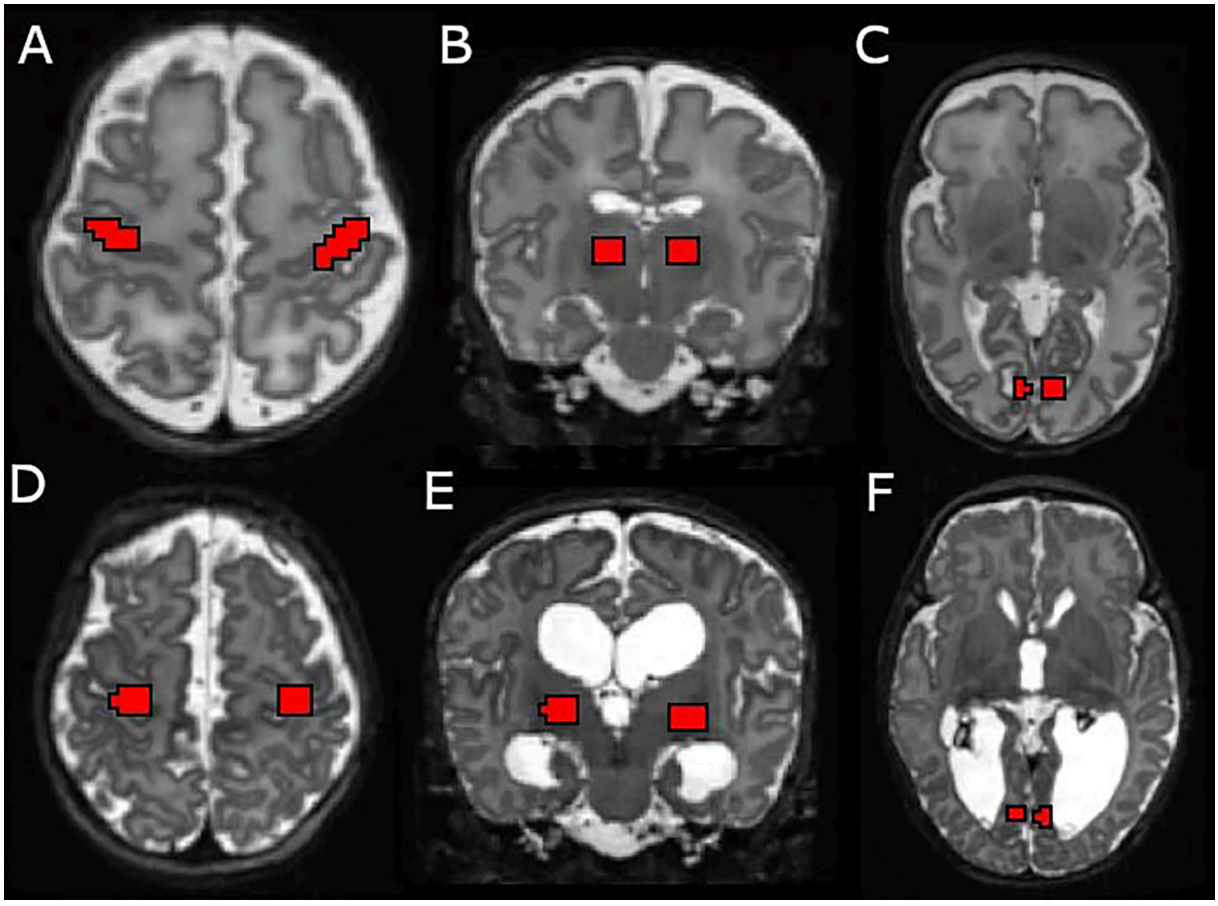

Fig. 1. Regions of interest. Representative images of the motor cortex (A, D), thalamus (B, E), and visual cortex (C, F) ROIs in an uninjured VPT infant brain (A, -C) and an injured VPT infant brain (D-F).

While only children with FC data were used in the final reported analyses, a larger pool of VPT children with data for any of the key variables (e.g., Bayley-III scores, medical risk scores) were used to inform the imputation, which also included additional measures of brain injury, more detailed medical risk information, and additional outcome measures.

Between-groups differences in demographics, FC values, and motor outcome scores were assessed using Mann-Whitney *U* tests for continuous variables due to non-normal distributions and Fisher exact tests for categorical data. Regression models robust to outliers related FC values to Bayley-III Gross Motor and Fine Motor scores. To address a floor effect in the Bayley-III scaled scores due to very poor performance in a subset of BI infants, raw scores were used with age at assessment included as a covariate in regression models. To account for twins/triplets, we ran the analyses both with all children and with only including one child from each set of multiples. Results did not differ, so those presented here are for the full cohort. FC values and Bayley raw scores were grand-mean z-scored to yield more interpretable model intercepts and slopes.

The analyses first examined which components of the motor system were most related to motor outcomes across domains in the whole cohort. Next, a dichotomous brain injury categorical variable (representing the two groups) and a group × FC interaction term were added to allow regression models to examine within-group brain-behavior relationships (thereby assessing effects of FC above and beyond injury grouping) and interaction effects. Finally, analyses were run with birth gestational age and medical risk scores added as covariates to assess whether FC was adding information beyond these two measures.

The demographic stressor index was not independently associated with FC or motor outcome measures in this cohort and so was not included in any analyses (all p's > 0.05). Postmenstrual age at scan was not significantly associated with any of the FC measures and so was also not included in the analyses. Finally, the amount of low-motion FC data was not used as a covariate in the models. While the injured group was allowed longer scan times, often resulting in a higher absolute number of low-motion frames, within each group there was no relationship between number or percent of low-motion frames and Bayley scores across all domains.

Data and analysis scripts are available upon request.

3. Results

3.1. Sample demographics

Of the 107 VPT infants with high-quality, low-motion FC data, 87 (40 UPT, 47 BI) completed follow-up assessment at corrected-age two years. The BI children had lower gestational age at birth, higher medical risk composites, were older at scan and two-year assessment, and had lower Bayley-III Fine, Gross, and Composite Motor Scores, as well as Cognitive and Language Composite Scores than the UPT group (Table 1). There were no differences in Bayley-III scores between psychometricians. Fine and gross motor scaled scores were significantly correlated ($r = 0.66$, $p < .01$). Among the children included in the main analyses, neither brain injury status, gestational age at birth, medical risk index, nor demographic stressor index were related to loss to follow-up at age 2 years.

3.2. Between-groups differences in neonatal functional connectivity

At term-equivalent age, the BI group showed lower left-right motor cortex ($p < .01$) and left-right visual cortex ($p < .01$) FC values relative to the UPT group (Table 2).

3.3. Whole cohort analysis

In whole-cohort models, none of the FC measures were significantly related to motor outcomes.

Table 1
Demographic and clinical description of the cohort.

	Uninjured Group Mean (SD)	Brain-injured Group Mean (SD)
Total N	52	55
Sex Assigned at Birth	20 M, 32 F	31 M, 24 F
Race (parent-report)	24 Black 3 Asian 2 Biracial 23 White	29 Black 1 Asian 1 Biracial 24 White
Gestational Age at Birth (weeks)**	26.7 (1.6)	25.4 (1.9)
Postmenstrual Age at Scan**	37.6 (1.3)	39.1 (2.5)
Medical Risk Composite**	1.6 (1.5)	3.0 (2.0)
Brain Injury		30 Grade III/IV IVH 16 IVH surgery 9 Cystic PVL
Demographic Stressor Index	2.7 (1.5)	2.7 (1.6)
Age at 2-year Assessment (months)**	29.0 (3.9)	30.6 (3.4)
Bayley-III Cognitive Composite Score**	89.0 (10.4)	79.4 (14.1)
Bayley-III Receptive Language Scaled Score	8.1 (2.4)	6.8 (3.1)
Bayley-III Expressive Language Scaled Score*	8.8 (2.4)	6.9 (3.3)
Bayley-III Language Composite Score*	91.3 (13.5)	81.7 (17.8)
Bayley-III Fine Motor Scaled Score**	8.3 (2.0)	5.8 (2.7)
Bayley-III Gross Motor Scaled Score**	7.5 (2.0)	4.0 (2.5)
Bayley-III Motor Composite Score**	87.6 (10.3)	69.7 (13.6)
Definite or Probable CP at age 2 years**	2/35 (6%)	26/36 (72%)

*p <.05, **p <.01.

Table 2
Fisher Z-transformed correlations.

	Uninjured group mean (SD)	Brain-injured group mean (SD)	p-value
L/R MC	0.81 (0.30)	0.69 (0.20)	<0.01
TC	0.24 (0.17)	0.29 (0.14)	0.08
L/R VIS	0.78 (0.23)	0.50 (0.25)	<0.01

Group differences tested with Mann-Whitney *U* test.

3.4. Within-group effects analysis

Within the BI group, L/R MC FC was positively related to Bayley-III Gross Motor raw scores ($\beta = 0.36$, $p < .05$), but not Bayley-III Fine Motor raw scores. Unlike in the BI group, L/R MC FC was not related to either gross or fine motor scores in the UPT group. There was a significant FC × Injury group interaction effect in the gross motor model ($\beta = 0.41$, $p < .05$) (Table 3, Fig. 2). Neither the TC nor the negative control L/R VIS FC demonstrated a relationship with motor scores. The L/R MC FC effect on gross motor outcomes and the interaction effect persisted when birth gestational age and medical risk scores were added to the models. For results with Bayley Cognitive and Language scales, see Supplementary Materials and Supplementary Table S1.

4. Discussion

The current study findings show that within the BI group, higher magnitude positive neonatal L/RMC FC values were uniquely related to improved gross motor outcomes at two years corrected-age. There were more children with low gross motor than fine motor scores, which may have allowed the models to better capture deficits in this area. This was different from the uninjured group in which there was no relationship

Table 3
Regression models with injury groups.

ROI group	Outcome measure	Parameter	Est (SE)
Left/Right Motor Cortex	Bayley-III Gross Motor Raw Score	**L/R MC FC (BI)**	**0.36* (0.17)**
		L/R MC FC (UPT)	−0.03 (0.11)
		Age at Assessment	**0.18* (0.09)**
		Brain Injury	**0.65** (0.18)**
		Brain Injury × FC	**0.41* (0.20)**
	Bayley-III Fine Motor Raw Score	L/R MC FC (BI)	0.34 (0.17)
		L/R MC FC (UPT)	−0.05 (0.10)
		Age at Assessment	**0.24* (0.10)**
		Brain Injury	**0.54** (0.19)**
		Brain Injury × FC	0.37 (0.21)

*p <.05, **p <.01, both are in bold

between neonatal FC and motor outcome. Additionally, this difference across BI and uninjured groups was statistically significant, as evidenced by the interaction effect. Similar to prior work in this cohort (Lean et al., 2018), social adversity was not related to motor outcomes, and therefore, it was unsurprising that it was found to also be unrelated to motor system FC. These findings provide longitudinal evidence that differences in motor system FC in infants with brain injury may reflect neuropathological processes underlying the development of motor problems in early childhood.

Prior literature has shown that FC in the motor system is affected, both in its strength and distribution, by early brain injury. Previous work has indicated that individuals with perinatal brain injury have reduced magnitude of FC in the motor system as shown in children with CP (Qin et al., 2018), and more diffuse motor FC (i.e., somatomotor cortex showed more widespread functional connectivity with itself and/or less clear somatotopic organization) both in neonates (Duerden et al., 2019) and in adults with PVL and spastic diplegic CP (Burton et al., 2009; Lee et al., 2011). While the current study did not assess the distribution of the motor system FC, we did find that injured children who had a stronger correlation between left and right motor cortex activity in the neonatal period had higher motor scores at follow-up. These children may have had less severe injury, as there is variation even within the category of high-grade brain injury (there were too few children with each injury type to assess this directly), and/or may have compensated for their injury. Indeed, prior human and animal model work on stroke has shown increased interhemispheric sensorimotor FC in the months immediately after injury to be a potential marker of compensation and/or associated with improved motor outcomes (van Meer et al., 2010; Zhang et al., 2016). Stronger functional measures of correlated activity between left and right motor cortex may, therefore, be capturing a combination of reduced injury severity and early compensation that then lead to better motor development.

We did not find relationships between thalamocortical FC and motor outcomes. While the extant literature is limited, earlier work suggests that thalamocortical FC is more related to outcomes in children with better motor function and/or to performance on more difficult tasks. For example, neonatal thalamocortical FC was found to be related to 2-year Bayley motor scores in a VPT cohort that included few (n = 7) children with brain injury and whose mean Bayley motor scores were similar to the general population (Toulmin et al., 2021). In contrast, the current study cohort had mean scores ~1 SD below the population average even in the uninjured children, and the injured children averaged ~1 SD lower still. This distinction is particularly relevant when using the Bayley-III, as the assessment tasks change to meet the child's ability, so our cohort would have been performing different tasks with potentially lower demands on higher-order motor function from a cohort of 2-year-olds with typical motor abilities. In another study comparing motor outcomes of VPT and term-born control children at age 12 years, not only did term-born children have significantly higher scores for all of the motor measures, but thalamocortical FC was only associated with performance in the term-born group (Wheelock et al., 2018). Therefore, TC FC may be more related to outcomes in children with typically developing motor abilities.

Interestingly, motor cortex FC was not correlated with motor outcomes in the uninjured children. This absence of a relationship may be due to the relatively narrow range of motor outcomes in the uninjured group. Children with milder motor impairments, as are more common in uninjured VPT children, are often not identified on assessments early in life. It may also be that the key brain disruptions affecting motor development in these children lie elsewhere. Nevertheless, it suggests

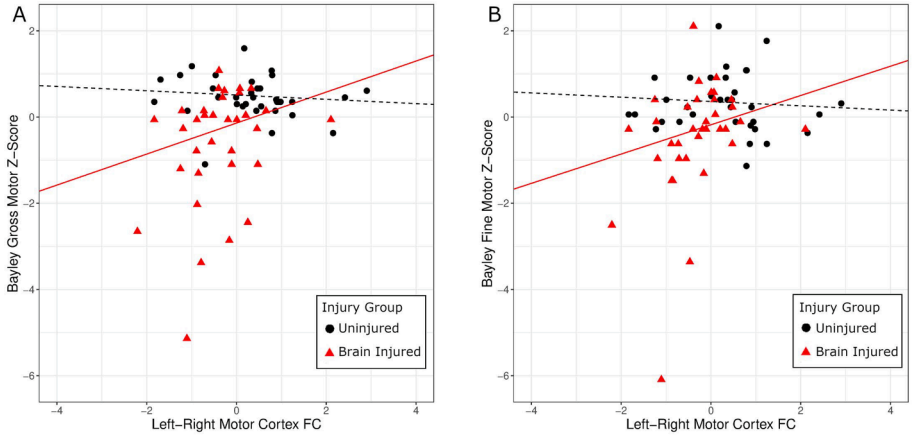

Fig. 2. Motor cortex FC and motor outcomes. Regression models of effects of Left/Right Motor Cortex FC (A, B) on Bayley-III Gross (A) and Fine (B) Motor scores. Lines are from the pooled regression models, while points are from the observed data set. For gross motor, the injured group shows a significant relationship (β = 0.36, p <.05), while the uninjured group does not. The FC × Injury Group interaction is also significant (β = 0.41, p <.05) for gross motor.

that our findings in the BI group may not generalize to uninjured infants and that motor cortex FC may be a less reliable predictor of two-year motor outcome in uninjured infants. In a study using a meta-analysis approach, motor scores at age two years were found to only account for 12% of variance in later motor scores in VPT children without CP (Luttikhuizen dos Santos et al., 2013), suggesting that longer follow-up is needed to better identify children with emerging motor difficulties that may become more prominent and/or stable in later childhood. Future work may include additional brain areas, such as the basal ganglia and/or cerebellum, greater specificity of types and degrees of brain injury in larger samples, and longer-term follow-up into school-age.

4.1. Strengths & limitations

Strengths of this study included its high-quality imaging data with stringent motion correction and a unique cohort of VPT children, including a large proportion with brain injury, with detailed clinical information and standardized motor assessment. Limitations of this study included its modest sample size (though comparable to other similar studies in this population) and an insufficient ability to assess for effects of additional factors, such as the type and intensity of early intervention therapies which may alter relationships between neonatal measures and later outcomes, due to the extent of data collected.

4.2. Conclusion

Stronger FC within the motor system is associated with better early childhood motor outcomes in VPT children with brain injury. The developmental processes linking early brain function and later motor outcomes may differ in children with and without brain injury. This may lead to better tools to help parents set expectations for their child, access appropriate therapies, and integrate into the disability community, as appropriate. Additional work is needed to extend these findings into middle childhood and further examine motor system developmental trajectories in both typically and atypically developing populations.

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CRediT authorship contribution statement

Peppar E.P. Cyr: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Rachel E. Lean:** Conceptualization, Methodology, Funding acquisition, Data curation, Writing – review & editing, Supervision. **Jeanette K. Kenley:** Software, Data curation, Visualization, Writing – review & editing. **Sydney Kaplan:** Software, Data curation. **Dominique E. Meyer:** Software, Data curation, Writing – review & editing. **Jeffery J. Neil:** Conceptualization, Supervision, Writing – review & editing. **Dimitrios Alexopoulos:** Data curation. **Rebecca G. Brady:** Conceptualization, Writing – review & editing. **Joshua S. Shimony:** Resources, Funding acquisition, Data curation, Writing – review & editing. **Thomas L. Rodebaugh:** Formal analysis, Supervision. **Cynthia E. Rogers:** Conceptualization, Methodology, Funding acquisition, Resources, Writing – review & editing, Supervision. **Christopher D. Smyser:** Conceptualization, Methodology, Funding acquisition, Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103260.

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