Mechanical ventilation duration, brainstem development and neurodevelopment in preterm children: a prospective cohort study

Mireille Guillot, MD[1]; Ting Guo, PhD[1]; Steven Ufkes, MSc[1]; Juliane Schneider, MD[2]; Anne Synnes, MDCM, MHSc[3]; Vann Chau, MD[1]; Ruth E. Grunau, PhD[3]; Steven P. Miller, MDCM, MAS[1]

Affiliations:
[1]Department of Pediatrics (Neurology), University of Toronto and the Hospital for Sick Children, Toronto, Canada
[2]Department of Women-Mother-Child (Neonatology), University Hospital Center and University of Lausanne, Lausanne, Switzerland
[3]BC Children's Hospital Research Institute, Vancouver, British Columbia, Canada; Department of Pediatrics (Neonatology), University of British Columbia and BC Women's Hospital and Health Centre, Vancouver, British Columbia, Canada

Address correspondence to: Steven P. Miller, Department of Pediatrics (Neurology), University of Toronto and the Hospital for Sick Children, Toronto, Ontario, Canada; Neurosciences & Mental Health, SickKids Research Institute, Toronto, Ontario, Canada
555 University Avenue, Toronto, Ontario, M5G 1X8, Canada
Telephone: (416) 813-6659
Electronic address: steven.miller@sickkids.ca

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Abbreviations:
BPD: bronchopulmonary dysplasia
FA: fractional anisotropy
GA: gestational age
MAGeT: Multiple Automatically Generated Templates
NEC: necrotizing enterocolitis
PMA: post-menstrual age
ROP: retinopathy of prematurity
TBSS: tract-based spatial statistics
TCV: total cerebral volume
TEA: term-equivalent age
WM: white matter
WMI: white matter injury

Abstract

Objectives: In children born preterm, determine the association of mechanical ventilation duration with brainstem development, white matter maturation, and neurodevelopmental outcomes at preschool age.

Study design: This prospective cohort study included 144 neonates born at <30 weeks' gestation (75 males, mean gestational age 27.1 weeks, SD 1.6) with regional brainstem volumes automatically segmented on MRI at term-equivalent age (TEA). The white matter maturation was assessed by diffusion tensor imaging and tract-based spatial statistics. Neurodevelopmental outcomes were assessed at 4.5 years of age using the Movement-ABC2 (M-ABC2), and the Wechsler Primary and Preschool Scale of Intelligence, 4th Ed., full-scale IQ. The association between the duration of mechanical ventilation and brainstem development was validated in an independent cohort of children born very preterm.

Results: Each additional day of mechanical ventilation predicted lower motor scores (0.5 point decrease in the M-ABC2 score by day of mechanical ventilation, 95% CI -0.6 to -0.3, P<0.0001). Prolonged exposure to mechanical ventilation was associated with smaller pons and medulla volumes at TEA in 2 independent cohorts, along with widespread abnormalities in white matter maturation. Pons and medulla volumes at TEA predicted motor outcomes at 4.5 years of age.

Conclusions: In very preterm neonates, prolonged mechanical ventilation is associated with impaired brainstem development, abnormal white matter maturation, and lower motor scores at preschool age. Further research is needed to better understand the neural pathological mechanisms involved.

Introduction

Despite advances in the neonatal medical care over the last decades, bronchopulmonary dysplasia (BPD) continues to be one of the most frequent complications of prematurity, affecting approximately 40% of neonates born before 28 weeks gestational age (GA).(1) Historically, survivors with BPD were described as having impaired development early in life, which typically evolved into global dysfunction, affecting their cognitive, motor and behavioural abilities in childhood.(2–7) Identifying the brain changes and the associated modifiable clinical risk factors leading to poorer functioning in children with BPD is crucial for informing prognosis, potential treatments and interventions.

Bronchopulmonary dysplasia is a heterogeneously defined diagnosis, based on respiratory status at a specific time point, which is problematic when used as an endpoint for prognostication. Instead, ventilation strategies can be reliably measured, modified and customized for individual preterm neonates to aim for better outcome. As such, exposure to mechanical ventilation is an important risk factor, which is potentially modifiable, in the pathway to BPD and adverse outcomes.(8–12) A recent retrospective study of ventilated preterm neonates showed that prolonged mechanical ventilation was associated with poorer neurodevelopmental outcomes at 18-24 months.(13) Yet, the consequences of prolonged ventilation on development at preschool age remain to be determined.

The neuropathologic substrate leading to impairment in preterm neonates with respiratory illness is not completely understood. Previous studies demonstrated that smaller brain volume, abnormal white matter microstructure and delayed brain maturation were associated with adverse neurodevelopmental outcomes in neonates with lung disease.(14–17) From early preclinical studies, we recognize that prolonged exposure to mechanical ventilation and hyperoxia are associated with abnormal brainstem development.(18,19) However, in earlier brain imaging studies, the brainstem, a crucial brain structure for respiratory control, was not addressed.

The objectives of this contemporary prospective cohort study of preterm neonates with advanced serial brain imaging were to determine the association of mechanical ventilation duration in the neonatal period with: 1) brainstem regional volumes at term, and 2) white matter development, as well as 3) neurodevelopmental outcomes at preschool age.

Methods

Study Population

Neonates born between 24 and 32 weeks GA at British Columbia's Children's & Women's Hospital were recruited to a large prospective study over a seven-year period (April 2006 to September 2013).(20–25) Only those born before 30 weeks GA were considered in this study given the decreased exposure to mechanical ventilation in neonates born after 30 weeks GA and the low risk of BPD in these older neonates.

Neonates were included if regional brainstem volumes on MRI at term-equivalent age (TEA) were successfully quantified. Neonates were excluded if they had congenital infection, genetic syndrome or ultrasound evidence of large parenchymal hemorrhagic infarction (>2 cm). The Clinical Research Ethics Board at the University of British Columbia and Children's & Women's Hospital approved the study protocol. Written informed consent from the parent or legal guardian was obtained for each neonate.

Clinical Data Collection

Clinical data regarding prenatal, perinatal and postnatal information were collected by systematic chart review. Based on the most commonly used definition, BPD was defined as the need for supplemental oxygen beyond 36 weeks post-menstrual age (PMA).(26–28) Ventilation data included days of mechanical ventilation (i.e. invasive ventilation involving endotracheal intubation, which includes high frequency and conventional ventilation), days on non-invasive ventilation (i.e. support that provides positive end-expiratory pressure such as high flow nasal cannula, CPAP or BiPAP), and days on supplemental oxygen. Other clinical characteristics included histologic chorioamnionitis defined by clinical pathology assessment, Apgar score and a Neonatal Resuscitation Score reporting on the amount of resuscitation at birth from 0 (no intervention) to 5 (endotracheal intubation with positive pressure ventilation and medication).(29) Neonatal complications included necrotizing enterocolitis (NEC) stage ≥2(30), multiple infections, defined by ≥3 infectious episodes in accordance with our previous report(24), and retinopathy of prematurity (ROP) stage ≥3.(31) Maternal level of education, categorized into three groups: completed primary/secondary school, undergraduate degree and postgraduate degree(25), was considered to reflect socioeconomic status.

Magnetic Resonance Imaging

Neonates underwent brain MRI early in life when clinically stable (mean 32.1 weeks PMA, SD 2.7) and again at TEA (mean 40.4 weeks PMA, SD 2.8). The MRI scans were acquired without sedation, using a Siemens 1.5T Avanto scanner (Erlangen, Germany). An experienced neuroradiologist blinded to the clinical history assessed the images for intraventricular hemorrhage ≥ grade 2(32) and cerebellar hemorrhage. White matter injury (WMI) identified on early T1-weighted images were quantified in volumes and normalized as the percentage of total cerebral volume (TCV), as previously reported.(33)

Automatic segmentation of brainstem

Segmentation of brainstem regional volumes (midbrain, pons and medulla) was performed with MAGeT-Brain (Multiple Automatically Generated Templates) pipeline.(34) Requiring only a small number of manually labelled atlases, MAGeT-Brain is a well-established method that has been widely applied to robustly segment different brain structures in various populations.(33–35) Manual segmentations of brainstem regional volumes on 5 TEA T1-weighted images were acquired and used as atlases that are propagated to an intermediate template library to serve as multiple atlases to segment all images.(34,36) The anatomical landmarks for midbrain, pons and medulla were described previously.(37) The automatically segmented brainstems (see Figure 1 (online) for example) were individually reviewed for quality assurance and manual corrections were applied to 14 (10%) images.

Diffusion tensor imaging

MRI diffusion tensor imaging and tract-based spatial statistics (TBSS) analysis were used to assess the white matter microstructural development.(38) The white matter skeleton resolved with TBSS extended caudally to the level of the pons. Detailed methods have been previously described.(21) Fractional anisotropy (FA) is a diffusion tensor imaging parameter which increases with white matter maturation.(39,40) Four age-appropriate fractional anisotropy (FA) templates thresholded at FA>0.15 were created according to the PMA at scan (<30 weeks (n=28), 30–33 weeks (n=72), 34–36 weeks (n=25), and 37–41 weeks (n=84)). Voxelwise regression analyses were performed on the 2 largest groups (30–33 weeks and 37–41 weeks) to assess the association of FA and mechanical ventilation duration, adjusting for GA at birth and

PMA at scan. Family-wise error correction for multiple comparisons was performed using threshold-free cluster enhancement.(41)

Neurodevelopmental Outcomes

Neurodevelopmental outcomes were assessed at age 4.5 corrected years by experienced staff in the Neonatal Follow-up Program, blinded to the imaging findings. Cognitive outcome was assessed in 113 children with the Wechsler Primary and Preschool Scale of Intelligence, 4th Edition , which provides the Full Scale IQ (mean 100, SD 15).(42) Four children were unable to complete testing due to severe cognitive impairment and were imputed with a score of 49.

Motor function was assessed in 113 children by an experienced occupational therapist, with the Movement Assessment Battery for Children, 2nd Edition (M-ABC2).(43) The M-ABC2 evaluates 3 components of motor performance: manual dexterity, aiming and catching, and balance.

Statistical Analysis

Statistical analysis was performed using Stata V.15.1 (StataCorp, College Station, Texas). Participant characteristics were compared using the Pearson’s chi-squared test for categorical variables and Student’s t-test for continuous variables. Descriptive statistics are presented with means and standard deviation (SD). We categorized the neonates into 2 groups (low vs. prolonged mechanical ventilation) to identify potential clinical confounders. Prolonged ventilation was defined as >28 days of mechanical ventilation. For all subsequent analysis, days of mechanical ventilation were used as a continuous variable.

The association between days of mechanical ventilation and neurodevelopmental outcomes was tested with univariable and multivariable linear regression accounting for GA at birth, WMI volume, and cerebellar hemorrhage. In clinical studies and experimental models, preterm WMI is strongly associated with ischemia and infections(24,44); as such, the volume of WMI was used as the mediating variable for these vary pathways. The linearity assumption was confirmed by the normal distribution of residuals, the absence of cut-off point using locally weighted scatterplot smoothing and the homogeneous variances of residuals.

We used univariable and multivariable linear regression models to examine the association between the number of days of mechanical ventilation and brainstem regional volumes, accounting for GA at birth, PMA at scan, TCV, and WMI volume. Subsequently, the relationships between brainstem regional volumes and neurodevelopmental outcomes were assessed with linear regression models accounting for TCV and WMI volume. A significance threshold of $p<0.05$ was used for all statistical analysis.

Independent Cohort Validation

We validated our hypothesis regarding the relationship between days of mechanical ventilation and brainstem regional volumes at TEA by combining the data from the original cohort with an independent cohort of 48 neonates born <30 weeks GA (both exposed and not exposed to mechanical ventilation) and admitted to the NICU of the University Hospital in Lausanne (Switzerland) between February 2011 and May 2013 (cohort previously described(35,45,46)) . As shown in Table 1 (online), GA at birth, birth weight and use of antenatal corticosteroids were similar in neonates from the validation cohort (Lausanne) and neonates from the primary cohort (Vancouver). However, neonates in the validation cohort differed from the primary cohort by their shorter duration of mechanical ventilation (mean 4.7 days of mechanical ventilation (SD 7.6) vs. 22.1 days (SD 25.1) in the primary cohort, P<0.0001), their longer duration of non-invasive ventilation (mean 45.9 days (SD 18.2) in the validation cohort vs. 27.2 days (SD 17.4) in the primary cohort, P<0.0001) and their lower incidence of BPD (15% in the validation cohort vs. 32% in the primary cohort, P=0.02). The brainstem regional volumes of the validation cohort were automatically segmented on their brain images at TEA (mean PMA at scan 40.9 weeks, SD 1.7) using the same technique (MAGeT-Brain) used for the primary cohort.

Results

Of the 234 very preterm neonates (112 males (48%), mean GA at birth 27.9 weeks (SD 2.2)) included in the original cohort, 187 (80%) were born before 30 weeks GA.

As shown in Figure 2 (online only), among the 187 neonates <30 weeks, 150 (80%) had ventilation data available and MRI performed at TEA. Brainstem segmentation was not performed on 6 scans due to motion artifact. A total of 144 neonates (75 males (52%), mean GA at birth 27.1 weeks (SD 1.6)) were included in the analysis, 46 (32%) were diagnosed with BPD and 117 (82% of survivors) were followed up to 4.5 years corrected age. There were no significant differences among the clinical characteristics of the neonates with and without TEA MRI, nor with children lost to follow-up.

Mechanical ventilation duration: clinical characteristics and association with adverse preschool age motor scores

As summarized in Table 2, neonates with prolonged mechanical ventilation were born earlier compared to neonates with low ventilation exposure (mean GA at birth 25.6 weeks vs. 27.8

weeks, P<0.001), had lower Apgar score (mean Apgar score at 5 minutes 6 vs. 7, P<0.001) and needed slightly more extensive resuscitation at birth (mean Neonatal Resuscitation Score 3.8 vs. 3.2, P=0.005). Neonates exposed to prolonged ventilation were also sicker during the neonatal period (NEC in 14.6% vs. 1%, P=0.001, severe ROP in 43.8% vs. 7.3%, P<0.001, and multiple infection in 66.7% vs. 17.7%, P<0.001), and more likely to develop cerebellar hemorrhage (39.5% vs. 14%, P=0.001). Of the 47 neonates with WMI, 4 had cystic periventricular leukomalacia concurrent with the largest WMI volumes (Table 2).

The number of days of mechanical ventilation in the neonatal period was associated linearly with preschool age motor outcomes (Figure 3). In the univariable regression analysis, each 10 days-period of mechanical ventilation was associated with a decrease of 4.6 points in the M-ABC2 score at 4.5 years of age (95% CI -6.1 to -3.3, P<0.0001). This association was unchanged when accounting for GA at birth, WMI volume, and cerebellar hemorrhage (-5.0 points in the M-ABC2 score per 10 days-period of mechanical ventilation, 95% CI -6.9 to -3.2, P<0.0001). Including dexamethasone cumulative dose (mg/kg) and sex in the model did not affect the relationship between days of mechanical ventilation and motor scores (-4.6 points in the M-ABC2 score per 10 days-period of mechanical ventilation, 95% CI -6.9 to -2.3, P<0.0001). However, the number of days on non-invasive ventilation was not associated with motor outcomes. Interestingly, in univariable and multivariable analysis, both days of mechanical ventilation and days on non-invasive ventilation were not associated with cognitive outcomes. The impact of very brief exposure to mechanical ventilation was not explored as only a small number of neonates were exposed to mechanical ventilation for a day or less (n=15) or not at all (n=13).

Considering that the recruitment was conducted over a 7 year-period, the timing of recruitment was examined in the analyses by comparing 2 epochs (neonates recruited before 2009 (n=80) vs. after 2009 (n=64)). While the duration of mechanical ventilation did not differ between the 2 epochs (mean of 24 days in neonates recruited before 2009, vs. 20 days in neonates recruited after 2009, P=0.32), the duration of non-invasive ventilation was longer in neonates born after 2009 (mean of 27 days of non-invasive ventilation in neonates recruited before 2009, vs. 38 days in neonates recruited after 2009, P<0.001). Importantly, there was no interaction between timing of recruitment and outcomes for neurodevelopmental outcomes and brainstem regional volumes (P>0.1).

Association of mechanical ventilation duration with brainstem regional volumes

The number of days of mechanical ventilation was significantly associated with smaller pons and medulla volumes at TEA (Table 3). The relationship was attenuated when adjusted for GA at birth, PMA at scan, TCV and WMI volume in multivariable regression analysis. The association was not modified by including cerebellar hemorrhage in the model. No signal changes in the brainstem were apparent on diagnostic brain imaging, even in cases of very restricted brainstem growth.

Similarly, in the validation cohort of preterm neonates from Lausanne who were exposed to significantly less mechanical ventilation, there was a comparable association between the number of days of mechanical ventilation and smaller pons and medulla at TEA (in adjusted models, for pons volume: ß=-4.6 mm^3 per day of mechanical ventilation, P<0.001, for medulla volume: ß=-1.3 mm^3 per day of mechanical ventilation, P=0.03). As shown in Table 1 (online), TEA MRI were obtained at the same GA period in both cohorts (mean of 40.9 weeks (SD 1.7) in the validation cohort vs. 40.4 weeks (SD 2.8) in the primary cohort, P=0.32). Notably, brainstem regional volumes were similar in both cohorts (Table 1, online).

Mechanical ventilation duration predicted impaired white matter development

As shown in Figure 4, the TBSS analysis of the preterm MRI completed at 30–33 weeks GA showed only very minimal diffusion anisotropy changes in association with mechanical ventilation duration. In contrast, in scans performed at 37–41 weeks GA, the number of days of mechanical ventilation was negatively associated with widespread FA changes in the white matter tracts, including the midbrain and pons.

Brainstem regional volumes predicted preschool-age motor scores

Pons and medulla volumes at TEA positively predicted motor function at 4.5 years of age (Table 4, online only). After adjusting for TCV at TEA and WMI volume, an increase of $0.1cm^3$ in the volume of the pons was associated with an increase of 2 points in the M-ABC2 total score, while an increase of 0.1 cm^3 in the medulla volume corresponded to a 5 points M-ABC2 total score increase.

Discussion

Mechanical ventilation duration and neurodevelopmental outcomes

In this prospective contemporary cohort of neonates born very preterm, every additional day of mechanical ventilation predicted lower motor scores at preschool age. Our data are consistent with other contemporary reports demonstrating the increased risk for adverse motor outcomes in preterm neonates exposed to prolonged mechanical ventilation.(13,47) Similarly, a subset of the ELGAN study including 915 extremely preterm neonates showed a strong association between the severity of respiratory disease in the neonatal period and motor performance at 2 years.(48) Moreover, the duration of non-invasive ventilation was not associated with adverse outcomes, which suggest that limiting the use of mechanical ventilation in favor to non-invasive ventilation strategies can potentially improve outcomes in very preterm neonates.

Mechanical ventilation duration and brain changes

In this prospective cohort study of very preterm neonates, we make the novel observation that the brainstem is implicated in the relationship between exposure to mechanical ventilation and impaired motor development at preschool age. This association was observed in 2 independent cohorts from different countries: one with high exposure to mechanical ventilation (Vancouver, Canada) and the other with restricted use of mechanical ventilation (Lausanne, Switzerland). The brainstem, critical for respiratory control and motor function, undergoes rapid development during the third trimester and may be more vulnerable to injury during this time period.(49) While several clinical studies have shown the negative impact of respiratory illness on total brain growth at term(14,15,35), there is a paucity of research regarding brainstem volume in the preterm neonates. Consistent with the findings from 2 other groups(50,51), we demonstrated that the duration of mechanical ventilation was strongly associated with the brainstem size at term age. Importantly, smaller pons or medulla at term age correlated with lower motor scores at preschool age.

Smaller brainstem and underlying mechanisms

We considered three possible pathogenic mechanisms leading to smaller pons and medulla at term in preterm neonates receiving mechanical ventilation. First, it may result from ***abnormal brain myelination***. From preclinical studies, we recognize that prolonged exposure to mechanical ventilation leads to increased brain damage, particularly involving a decrease in oligodendroglia, white matter (WM) and subsequently, volume loss.(52) As such, the reduced volumes of the pons and the medulla, two structures with abundant WM, may be related to the disrupted maturation of WM progenitor cells, which in turn leads to subsequent myelination failure, thus explaining the disrupted growth. This hypothesis is in keeping with our findings showing concurrent adverse changes in white matter development on TBSS analysis and impaired brainstem growth at TEA in neonates exposed to prolonged mechanical ventilation. Importantly, the white matter microstructural changes were not observed on preterm MRI, which suggests an evolving process over time and a possible window of opportunity for interventions promoting WM development. Such interventions could include improving nutrition in the first 2 weeks of life, which was recently shown to attenuate the negative association of mechanical ventilation with brain growth.(35)

Second, the brainstem hypoplasia may be secondary to the *degeneration of the WM tracts* associated with supratentorial WMI. Similarly to the strong association reported between cerebellar growth failure and cerebral WMI, pontine hypoplasia has been linked to supratentorial lesions, particularly periventricular leukomalacia.(50,53,54) The corticospinal tract, the main descending motor tract in the ventral brainstem, may be more susceptible to cerebral injury due to its anatomical pathway.(53) Thus, a degeneration process affecting principally the corticospinal fibers would contribute to the motor impairment associated with abnormal brainstem development. Yet, neonates exposed to prolonged mechanical ventilation did not exhibit more supratentorial WMI compared to their counterparts with low ventilation exposure. In our study, because of their critical illness, the early scan for preterm neonates with prolonged mechanical ventilation was acquired at significantly later GA. However, punctate WMI is better identified in the first weeks of life(33,55), which could have contributed to underestimate the severity of WMI in the prolonged ventilation group.

Third, the impaired brainstem development might be secondary to *focal necrotic changes* due to hypoxia-ischemia, hyperoxia, and hypocarbia during a crucial period for brain development. These conditions are recognized as important contributors in the pathogenesis of *pontosubicular necrosis*, a distinct type of selective neuronal injury affecting, among others, the neurons of the base of the pons.(18,56,57) This neuropathology finding has not previously been correlated with diagnostic imaging changes.

Alternatively, abnormal brain development in neonates exposed to prolonged mechanical ventilation may start as early as in the delivery room, as reflected by the need for more intensive resuscitation in this group. While antenatal insult might also be considered as a potential mechanism in the pathway to impaired brainstem development, the brainstem is relatively preserved in existing experimental models of hypoxic-ischemic brain injury and in human imaging studies.(54,58) The design of the study did not allow us to determine the antenatal predictors.

Limitations

Mechanical ventilation duration is closely linked to multiple other risk factors with possible impact both on brain development and neurodevelopmental outcomes. In our cohort, neonates exposed to prolonged mechanical ventilation were more likely to have other comorbidities such as NEC, multiple infections and ROP. Therefore, several pathways of brain injury likely coexist and might not have properly been considered. Additionally, data related to intermittent hypoxic episodes, nutrition, compromised respiratory function after NICU discharge and rehospitalization later in life, which may be important modifiers of preschool outcomes, were not available. Nonetheless, with the strong association demonstrated between mechanical ventilation duration, adverse brain development and impaired motor function, minimizing exposure to mechanical ventilation should be part of the strategies to optimize preterm care.

Conclusion

Preterm neonates exposed to prolonged mechanical ventilation are at high risk of developing adverse motor outcome at preschool age. Prolonged mechanical ventilation is associated with impaired white matter maturation and abnormal brainstem development at term age, which predicts adverse motor outcomes at preschool age. Future studies are needed to better determine the neural pathological mechanisms involved and longer term outcomes of the vulnerable preterm population exposed to prolonged mechanical ventilation.

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Figure Titles and Legends

Figure 1: MAGeT-Brain segmentation of the brainstem

The colors represent the regional brainstem segmentation: purple = midbrain, brown = pons, green = medulla.

Figure 2: Participant Flowchart

Segmentation could not be robustly completed in 6 scans due to motion artifact

Figure 3: Relationship of days of mechanical ventilation in the neonatal period and motor scores at 4.5 years of age in children with and without BPD

Abbreviation: BPD, bronchopulmonary dysplasia

Figure 4: TBSS analysis of preterm MRI (30 – 33 weeks GA) and term MRI (37 – 42 weeks) showing the association of days of mechanical ventilation with minimal FA changes early in life and widespread FA changes at term

Voxelwise regression analyses adjusting for GA at birth and PMA at scan.

Abbreviations: TBSS, tract-based spatial statistics; GA, gestational age; FA, fractional anisotropy

Table 1 online

Table 1 Demographics and clinical characteristics of neonates 24 – 30 weeks GA by cohort

Characteristics	Vancouver cohort (n = 144)	Lausanne cohort (n = 48)	P value
Male	75 (52.1)	21 (43.8)	0.32
Antenatal corticosteroids	128 (89.5)	42 (87.5)	0.70
GA at birth, wk	27.1 (1.6)	27.4 (1.3)	0.18
Birth weight, g	964 (259)	914 (229)	0.23
Non-invasive ventilation, days	31.0 (18.2)	45.9 (18.2)	<0.0001
Mechanical ventilation, days	22.1 (25.1)	4.7 (7.6)	<0.0001
Dexamethasone, no. exposed	38 (26.4)	7 (14.6)	0.09
BPD	46 (31.9)	7 (14.6)	0.02
Brain Imaging			
Age at TEA MRI	40.4 (2.8)	40.9 (1.7)	0.32
Midbrain volume at TEA, mm^3	2236 (334)	2236 (342)	0.99
Pons volume at TEA, mm^3	2723 (556)	2767 (436)	0.63
Medulla volume at TEA, mm^3	1332 (206)	1321 (252)	0.77

No, (%) or mean (SD)

Table 2

Table 2 Demographics and clinical characteristics of neonates 24 – 30 weeks GA for low vs. prolonged mechanical ventilation exposure

Characteristics		No. available for analysis	Low ventilation (≤28 days) (n = 96)	Prolonged ventilation (>28 days) (n = 48)	P value
Prenatal					
Male		144	48 (50)	27 (56.3)	0.48
Antenatal corticosteroids		143	90 (93.8)	38 (80.9)	0.02
Antenatal $MgSO_4$		144	25 (26)	6 (12.5)	0.06
Histologic chorioamnionitis		139	39 (41.5)	18 (40.0)	0.87
Maternal level of education	Primary/secondary school	128	13 (15.5)	7 (15.9)	0.90
	Undergraduate degree		57 (67.9)	31 (70.5)	
	Postgraduate degree		14 (16.7)	6 (13.6)	
Postnatal					
GA at birth, wk		144	27.8 (1.4)	25.6 (1.1)	<0.001
Birth weight, g		144	1055 (234)	782 (206)	<0.001
Apgar score at 5 min		142	7 (2)	6 (2)	<0.001
Resuscitation score		143	3.2 (1.2)	3.8 (1.0)	0.005
CPAP, days		144	20.1 (14.4)	16.1 (11.4)	0.09
Mechanical ventilation					
High frequency ventilation, days		144	0.9 (3.8)	10 (12.0)	<0.001
Conventional ventilation, days		144	5.8 (6.9)	42.8 (18.1)	<0.001
NEC stage ≥2		144	1 (1)	7 (14.6)	0.001
ROP stage ≥3		144	7 (7.3)	21 (43.8)	<0.001
Multiple infections		144	17 (17.7)	32 (66.7)	<0.001
Dexamethasone, no. exposed		144	4 (4.2)	34 (70.8)	<0.001
Caffeine, no. exposed		144	95 (99.0)	47 (97.9)	0.62
Brain Imaging					
Age at early MRI		136	31.2 (2.2)	34.2 (2.6)	<0.001
Age at TEA MRI		144	40.6 (2.7)	40.1 (2.9)	0.36
IVH grade 2-4 *(early MRI)*		136	30 (31.3)	19 (39.6)	0.16
Cerebellar hemorrhage *(early MRI)*		136	13 (14)	17 (39.5)	0.001
WMI volume, mm^3, % TCV *(early MRI)*		131	0.08 (0.3)	0.02 (0.05)	0.26
TCV, cm^3, *(TEA MRI)*		144	351.2(6.2)	312.4(6.0)	<0.001
Brainstem volume, mm^3, *(TEA MRI)*		144			
Midbrain volume			2292 (344)	2124 (285)	0.004
Pons volume			2849 (553)	2469 (475)	<0.001
Medulla volume			1379 (201)	1239 (185)	<0.001

No, (%) or mean (SD)

Abbreviations: $MgSO_4$, magnesium sulfate; GA, gestational age; wk, week; g, grams; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; TEA, term-equivalent age; IVH, intraventricular hemorrhage; WMI, white matter injury; TCV, total cerebral volume

Table 3 Association between days of mechanical ventilation and brainstem regional volumes at TEA

	Unadjusted			Adjusted[a]		
	Days of mechanical ventilation ß coefficient	**95% CI**	**P value**	**Days of mechanical ventilation ß coefficient**	**95% CI**	**P value**
Midbrain, TEA volume, mm^3	-2.9	-5.0, -0.7	0.009	-1.2	-2.8, 0.3	0.13
Pons, TEA volume, mm^3	-7.3	-10.8, -3.8	<0.001	-5.8	-8.3, -3.4	<0.001
Medulla, TEA volume, mm^3	-2.7	-3.9, -1.4	<0.001	-1.6	-2.5, -0.6	0.002

[a]Models adjusting for GA at birth, PMA at scan, total cerebral volume and white matter injury volume

Table 4 online

Table 4: TEA pons and medulla volumes in relation to motor outcomes at 4.5 years of age in the primary cohort

	Predictor Variable	Unadjusted			Adjusted[a]		
		ß coefficient	95% CI	P value	ß coefficient	95% CI	P value
M-ABC2 total score	Pons volume (mm^3)	0.009	0.001, 0.02	0.02	0.02	0.001, 0.04	0.04
	Medulla volume (mm^3)	0.025	0.005, 0.05	0.01	0.05	0.006, 0.09	0.02

Abbreviations: TEA term-equivalent age

[a]Models adjusting for total cerebral volume at TEA and white matter injury volume

Figure 1 online
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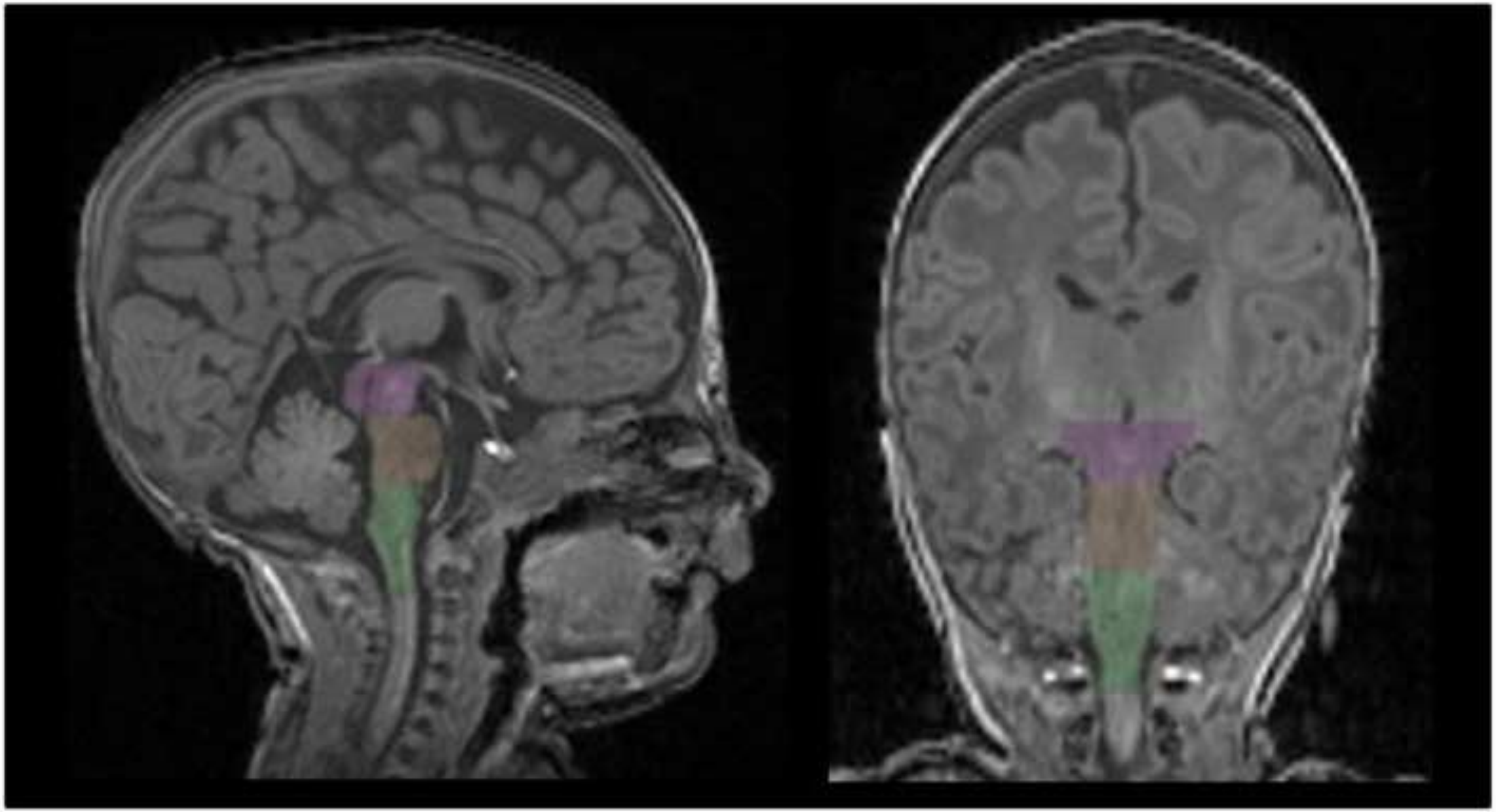
Figure 1 MAGeT-Brain segmentation of the brainstem



The colors represent the regional brainstem segmentation: purple = midbrain, brown = pons, green = medulla.

Figure 2 online

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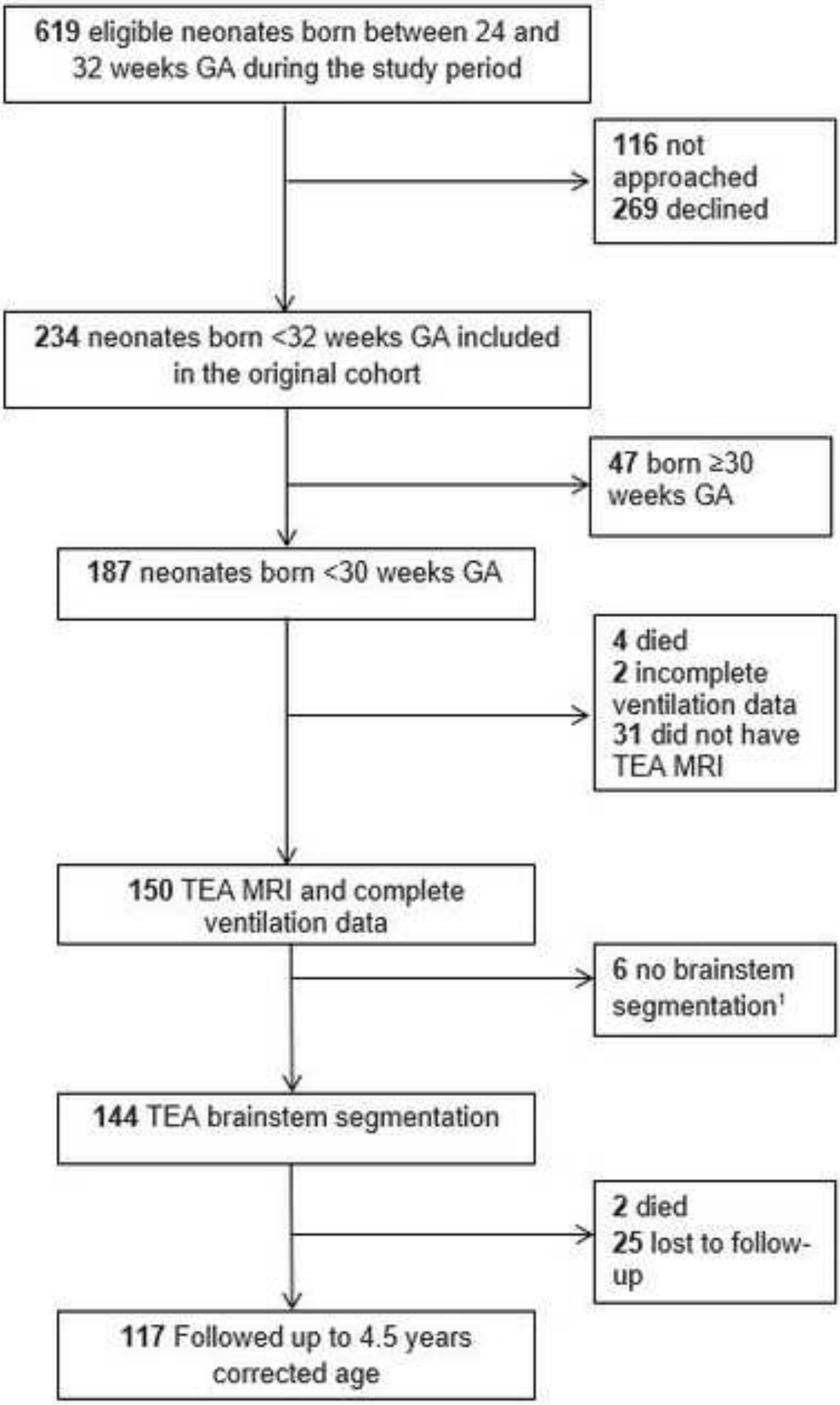
Figure 2: Participant Flowchart



[1]Segmentation could not be robustly completed in 6 scans due to motion artifact

Figure 3
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Figure 3 Relationship of days of mechanical ventilation in the neonatal period and motor score at 4.5 years of age in children with and without BPD

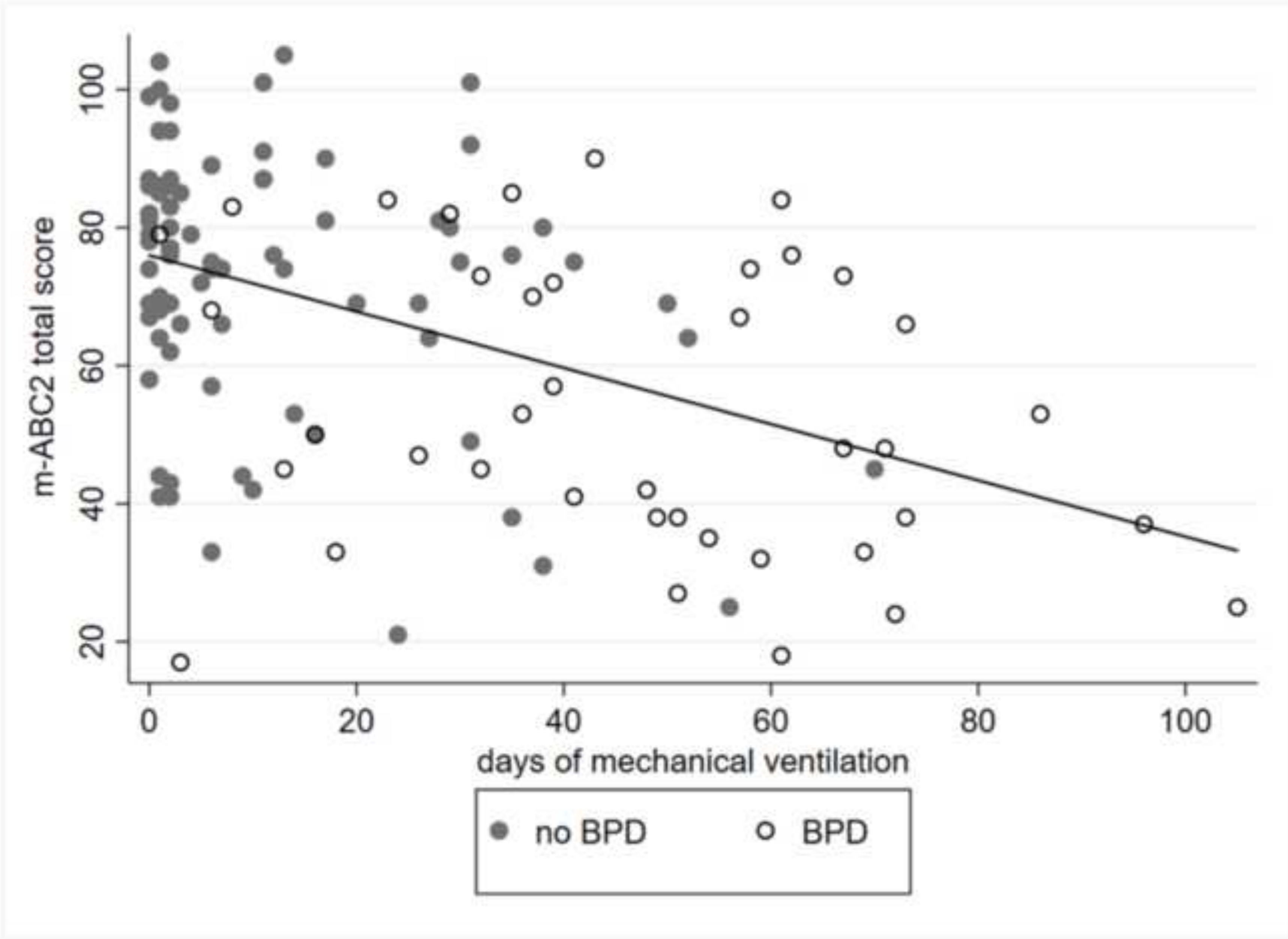

Figure 4
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Figure 4 TBSS analysis of preterm MRI (30 – 33 weeks GA) and term MRI (37 – 42 weeks) showing the association of days of mechanical ventilation with minimal FA changes early in life and widespread FA changes at term