Invasive Procedures in Preterm Children: Brain and Cognitive Development at School Age

WHAT’S KNOWN ON THIS SUBJECT: Greater numbers of invasive procedures from birth to term-equivalent age, adjusted for clinical confounders, are associated with altered brain microstructure during neonatal care and poorer cognitive outcome at 18 months’ corrected age in children born very preterm.

WHAT THIS STUDY ADDS: Altered myelination at school age is associated with greater numbers of invasive procedures during hospitalization in very preterm children without severe brain injury or neurosensory impairment. Greater numbers of invasive procedures and altered brain microstructure interact to predict lower IQ.

abstract

BACKGROUND: Very preterm infants (born 24–32 weeks’ gestation) undergo numerous invasive procedures during neonatal care. Repeated skin-breaking procedures in rodents cause neuronal cell death, and in human preterm neonates higher numbers of invasive procedures from birth to term-equivalent age are associated with abnormal brain development, even after controlling for other clinical risk factors. It is unknown whether higher numbers of invasive procedures are associated with long-term alterations in brain microstructure and cognitive outcome at school age in children born very preterm.

METHODS: Fifty children born very preterm underwent MRI and cognitive testing at median age 7.6 years (interquartile range, 7.5–7.7). T₁ and T₂ weighted images were assessed for the severity of brain injury. Magnetic resonance diffusion tensor sequences were used to measure fractional anisotropy (FA), an index of white matter (WM) maturation, from 7 anatomically defined WM regions. Child cognition was assessed using the Wechsler Intelligence Scale for Children—IV. Multivariate modeling was used to examine relationships between invasive procedures, brain microstructure, and cognition, adjusting for clinical confounders (eg, infection, ventilation, brain injury).

RESULTS: Greater numbers of invasive procedures were associated with lower FA values of the WM at age 7 years (P = .01). The interaction between the number of procedures and FA was associated with IQ (P = .02), such that greater numbers of invasive procedures and lower FA of the superior WM were related to lower IQ.

CONCLUSIONS: Invasive procedures during neonatal care contribute to long-term abnormalities in WM microstructure and lower IQ. Pediatrics 2014;133:412–421

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ABBREVIATIONS
CI—confidence interval
DTI—diffusion tensor imaging
FA—fractional anisotropy
FSIQ—full scale intelligence quotient
GA—gestational age
IQR—interquartile range
PRI—perceptual reasoning index
PSI—processing speed index
SNAP-II—Score for Neonatal Acute Physiology
VCI—verbal comprehension index
WISC—Wechsler Intelligence Scale
WM—white matter
WMI—working memory index

Ms Vinall assisted with the acquisition of data and statistical analyses, contributed to the interpretation of the data, and provided critical review of the manuscript; Drs Miller and Synnes contributed to the interpretation of the data and provided critical review of the manuscript; Drs Bjornson and Poskitt assisted with the acquisition of data, contributed to the interpretation of the data, and provided critical review of the manuscript; Mr Fitzpatrick assisted with the acquisition of data and provided critical review of the manuscript; Dr Brant conducted statistical analyses and provided critical review of the manuscript; Dr Cepeda provided critical review of the manuscript; Dr Grunau conceptualized and designed the study, contributed to the interpretation of the data, and provided critical review of the manuscript; and all authors approved the final manuscript as submitted.

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(Continued on last page)
Advances in neonatal care have greatly improved survival of infants born very preterm (≤32 weeks’ gestational age [GA]); however, cognitive impairment may have increased among children with birth weight ≤800 g.1–3 Even in the absence of severe disability (eg, blindness, nonambulatory cerebral palsy, IQ <70), cognitive problems and school difficulties are common among children born very preterm.4–6

Infants born very preterm undergo frequent invasive procedures during neonatal care. Greater numbers of invasive procedures, adjusted for clinical confounders, are associated with abnormal brain development up until term-equivalent age7,8 and altered functional cortical activity at school age.9 Moreover, higher numbers of invasive procedures have been found to be associated with poorer cognitive outcome at 18 months’ corrected age in children born very preterm.10 However, the relationship between the number of invasive procedures and long-term alterations of brain microstructure and cognitive outcomes in children born very preterm remains unknown.

The current study examined whether the number of invasive procedures during neonatal care was associated with white matter (WM) microstructure at age 7 years and whether the number of invasive procedures and measures of brain microstructure interact to predict cognitive outcome at school age in children born very preterm.

METHODS

This study was approved by the University of British Columbia/Children’s and Women’s Health Centre of British Columbia Research Ethics Board. Parental written informed consent and child assent were obtained.

Participants

Fifty children born very preterm (≤32 weeks’ GA) recruited from the NICU of the BC Children’s & Women’s Hospitals between February 2001 and July 2004 underwent MRI at median age 7.6 years (interquartile range [IQR], 7.5–7.7) as part of an ongoing study on the effects of neonatal pain on neurodevelopment of children born very preterm.10,11 Children were excluded if they had a major congenital anomaly, major neurosensory impairment (legally blind, nonambulatory cerebral palsy, sensorineural hearing impairment), or severe brain injury evident on neonatal ultrasound (periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage; Fig 1).

Neonatal Medical Chart Review

Neonatal data were acquired from medical chart review performed from birth to term-equivalent age or discharge (whichever came first) by a neonatal research nurse. We defined the number of invasive procedures as every attempt at a procedure as listed in Table 1, from birth to term-equivalent age, adjusted for clinical confounders (eg, illness severity on day 1 [Score for Neonatal Acute Physiology SNAP-II])12, days of mechanical ventilation, confirmed infection, morphine exposure).

MRI

Children were scanned at a median age of 7.6 years (IQR, 7.5–7.7). A Siemens 1.5 Tesla Avanto magnet, standard 12-channel head coil, and VB 18 software were used to obtain the following sequences: 3-dimensional T1-weighted spoiled gradient recalled acquisition (repetition time [ms] 18/echo time [ms] 9.2/field of view [mm] 256/slice thickness [mm] 1/gap [mm] 0/matrix 256 × 256) and T2-weighted images axial fast spin echo (4030/90/220/3/1 512 × 354) and axial fluid attenuation inversion recovery (8900/87/220/5/1 256 × 154). Neuroradiologist KJP, blinded to the child’s medical history, assessed these images for brain injury (ie, evidence of cerebellar hemorrhage, ventriculomegaly, or moderate to severe WM injury, as described previously).13

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a MRI technique that can be used to characterize the spatial distribution of water diffusion in each voxel (3-dimensional pixel) of the image as an ellipsoid, providing a measure of regional brain microstructural development.14 The size, shape, and orientation of the ellipsoid are given by eigenvalues (λ1, λ2, and λ3); λ1 corresponds to axial diffusion and is considered to reflect axonal integrity.15 λ2 and λ3 correspond to radial diffusion and reflect myelin integrity.15 Fractional anisotropy (FA), a measure of overall directionality, reflects the variance of λ1, λ2, and λ3. DTI was acquired with a multirepetition, single-shot echo planar sequence with 12 gradient directions (7800/82/256/2/0/128 × 128), 3 averages of diffusion weighting 700 (b value). DTI parameters of FA, λ1, λ2, and λ3 were obtained from 7 bilateral regions of interest in the WM (Fig 2), consistent with our neonatal studies.8,16 Intrarater reliability, based on the repeated analysis of a random 20% of regions of interest, was comparable with previously published findings (FA mean difference of −0.002 [Bland–Altman limits of agreement, −0.011 to 0.007]).8,16

Cognitive Testing

At age 7 years, IQ was measured by using the standardized Wechsler Intelligence Scale for Children–4th Edition (WISC-IV),17 which includes 4 index scores that make up the Full Scale IQ (FSIQ): Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed.

Statistical Analyses

Statistical analyses were performed by using Stata 9.2 (StataCorp, College Station, TX). Normality plots were examined,
and skewed variables (number of invasive procedures, days on mechanical ventilation, morphine exposure, FA values, and age at scan) were log transformed. IQ, GA, birth weight, and illness severity on day 1 of the included and excluded preterm infants were compared by using \( t \) tests or \( \chi^2 \), when appropriate. Multivariate analyses were adjusted for confounders: GA, size at birth (small for gestational age versus appropriate for gestational age), illness severity on day 1, days of mechanical ventilation, morphine exposure, infection, gender, age at scan, and concurrent brain injury. A generalized estimating equation was used to examine whether the number of invasive procedures was associated with FA at age 7 years in an initial pain model. This model was repeated for the axial and radial axes. The pain model was extended to include variables for surgery and fentanyl exposure (surgery model), and corticosteroids and midazolam (steroid model). The regression coefficients for these models are reported as effect sizes. FA values were then grouped a priori into superior WM (anterior, middle, and posterior subcortical WM) and WM tracts (genu and splenium of the corpus callosum, posterior limb of the internal capsule, optic radiations), and group means were used for analysis. Generalized linear modeling was used to examine whether the number of invasive procedures interacted with FA values from either the superior WM or WM tracts to predict FSIQ.

RESULTS

Participant Characteristics

Of the 131 eligible children contacted for the 7-year follow-up (Fig 1), 22 refused to participate and 7 withdrew, so that 102/131 (78%) were seen at school age. One child diagnosed with autism was excluded, leaving 101 children in this study. Of the 101 who returned for follow-up (psychometric assessment) at median age 7.6 years (IQR, 7.5–7.8), 58 (57%) parents and children consented/assented to an MRI. Research scans were available only on weekdays after 4 PM, and booking limitations affected study consents for MRI. Scans were not completed for 3 of the participants, and 3 were of poor quality because of motion artifact. Moreover, 2 children were missing either neonatal or follow-up data. Therefore, data from 50 children born very preterm were included in the current study. Importantly, the FSIQ of the children included \((n = 50)\) did not differ from that of the other 51 children who returned for 7-year follow-up (95% confidence interval \([CI]\), \(-7.18\) to 3.86, \(P = .55\)). Moreover, children included in the current study did not differ in GA.
(95% CI, −1.40 to 0.44, \( P = .30 \)), birth weight (95% CI, −187.33 to 147.52, \( P = .81 \)), or early illness severity (95% CI, −2.81 to 5.73, \( P = .50 \)) from the children who returned for follow-up or from the 81 infants in the original sample (95% CI, −1.10 to 0.63, \( P = .39 \); CI, −134.99 to 194.17, \( P = .72 \); and 95% CI, −2.50 to 5.73, \( P = .44 \); respectively).

Among the 50 children with imaging data at age 7 years, exposure to higher numbers of invasive procedures (median 122; IQR, 81–210) was associated with lower GA, higher illness severity on day 1, more days on mechanical ventilation, and a greater exposure to surgery, infection, dexamethasone, and morphine compared with children exposed to lower numbers of procedures (median 46; IQR, 30–55) (Table 2). Among the 101 children born very preterm who returned for follow-up at 7 years, exposure to higher numbers of invasive procedures (median 127; IQR, 87–200) were also associated with increased exposure to midazolam and fentanyl and a significantly lower FSIQ compared with children exposed to lower numbers of procedures (median 43; IQR, 32–52) (Table 3).

Number of Invasive Procedures in Relation to WM Microstructure at Age 7 Years

Children born very preterm exposed to a greater numbers of invasive procedures in the NICU had lower FA values at age 7 years (effect size = −0.02, \( P = .01 \); CI, −0.04 to −0.005) after adjusting for confounders (GA, birth weight, illness severity on day 1, days of mechanical ventilation, morphine exposure, infection, gender, age at scan, and concurrent brain injury) (pain model, Table 4). Infants who received the lowest number of invasive procedures (ie, 10 invasive procedures) had 7% higher FA values than infants who underwent the highest number of invasive procedures (ie, 267 invasive procedures). The relationship between the number of invasive procedures and FA of the WM was driven by the radial diffusion axes (\( \lambda_2 \) and \( \lambda_3 \); effect size = 0.05; CI, 0.01 to 0.09; \( P = .01 \)), such that greater numbers of invasive procedures from birth to term-equivalent age were associated with higher radial diffusion values. In contrast, the number of invasive procedures was not associated with the axial diffusion axis (\( \lambda_1 \); effect size = −0.05; CI, −0.15 to 0.06; \( P = .38 \)). Neither adjustment for surgery and fentanyl nor corticosteroids and

### Table 1: Invasive Procedures in the NICU

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection*</td>
<td>Umbilical artery catheter insertion</td>
</tr>
<tr>
<td>Chest tube insertion*</td>
<td>Umbilical venous catheter insertion</td>
</tr>
<tr>
<td>Pleural tap*</td>
<td>Lumbar puncture reservoir tap*</td>
</tr>
<tr>
<td>Peripheral artery line insertion*</td>
<td>Brainz needle insertion*</td>
</tr>
<tr>
<td>Peripherally inserted central line insertion or removal*</td>
<td>Heel poke (including glucometer pokes)*</td>
</tr>
<tr>
<td>Penrose insertion or removal*</td>
<td>Suprapubic bladder tap*</td>
</tr>
<tr>
<td>Abscess drained*</td>
<td>Catheter insertion for urine collection</td>
</tr>
<tr>
<td>Peripheral intravenous catheter sited or resited*</td>
<td>Venous blood collection*</td>
</tr>
<tr>
<td>Endotracheal tube prong change or retaping</td>
<td>Glycerin suppository</td>
</tr>
<tr>
<td>Nasogastric tube insertion</td>
<td>Orogastric tube insertion</td>
</tr>
<tr>
<td>Healon or Wydase for intravenous burns</td>
<td>Insuffion device site change*</td>
</tr>
<tr>
<td>Pericentesis*</td>
<td>Endotracheal or nasopharyngeal intubation*</td>
</tr>
</tbody>
</table>

Each attempt was counted.

* Skin-breaking procedures: The Pearson correlation between all procedures listed in this table and the skin-breaking procedures denoted by an asterisk was \( r = 0.99 \) for the 50 children born very preterm. The results of this study were the same whether the number of invasive procedures or the number of skin-breaking procedures was entered into the model.
midazolam signifi-
antly changed the results of the pain model (surgery and steroid models, Table 4).

**Number of Invasive Procedures Interacts With the Superior WM to Predict FSIQ at Age 7 Years**

The interaction between number of invasive procedures and FA values of the superior WM was significantly associated with FSIQ \( B = 412.18; P = .46; CI, 1106.38 \text{ to } 497.94 \).

**DISCUSSION**

This is the first study, to our knowledge, to show that greater numbers of invasive procedures during neonatal care are associated with altered WM microstructure at school age in children born very preterm, after accounting for degree of prematurity, systemic illness, drug exposures, and concurrent brain injury. Specifically, in 7-year-olds without severe brain injuries or major neurosensory impairment, a higher number of invasive procedures during NICU care was associated with an increase in radial diffusion values at age 7 years, suggestive of abnormal myelination.

Morphine did not appear to ameliorate or exacerbate the effects of the number of invasive procedures on the microstructural integrity of the WM. Greater numbers of invasive procedures and
which share common neural substrates (see Supplemental Information). Subsequently, infants born very preterm have lower tactile thresholds and become sensitized to repeated tactile and skin-breaking stimulation. Repeated stimulation of physiologically immature neurons can lead to excitotoxic damage and increased neuronal cell death.

### Table 3: Characteristics of Children Who Returned for Follow-Up at Age 7 Years

<table>
<thead>
<tr>
<th>Neonatal Characteristics</th>
<th>Lower Number of Invasive Procedures, Median 43, IQR 32–52</th>
<th>Higher Number of Invasive Procedures, Median 127, 87–200</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk), median (IQR)</td>
<td>29.9 (27.5–31.7)</td>
<td>31.6 (29.3–32.4)</td>
<td>27.7 (26.3–29.3)</td>
</tr>
<tr>
<td>Small for gestational age, n (%)</td>
<td>10 (10)</td>
<td>4 (8)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Illness severity on day 1 (SNAP-II), median (IQR)</td>
<td>9 (0–19)</td>
<td>5 (0–9)</td>
<td>16 (8–25)</td>
</tr>
<tr>
<td>Invasive procedures (n), median (IQR)</td>
<td>73 (43–129)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td>17 (17)</td>
<td>1 (2)</td>
<td>16 (31)</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>24 (24)</td>
<td>2 (2)</td>
<td>23 (45)</td>
</tr>
<tr>
<td>Mechanical ventilation (days), median (IQR)</td>
<td>2 (0–10)</td>
<td>0 (0–0)</td>
<td>9 (3–31)</td>
</tr>
<tr>
<td>Dexamethasone or hydrocortisone, number exposed (%)</td>
<td>8 (8)</td>
<td>0 (0)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Total morphine exposure (g/kg), median (IQR), number exposed (%)</td>
<td>0.0 (0.0–0.8)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.6 (0.1–1.8)</td>
</tr>
<tr>
<td>Total midazolam exposure (g/kg), median (IQR), number exposed (%)</td>
<td>49 (49)</td>
<td>6 (12)</td>
<td>43 (84)</td>
</tr>
<tr>
<td>Total fentanyl exposure (μg/kg), median (IQR), number exposed (%)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
</tr>
<tr>
<td>Child Characteristics</td>
<td>n = 101</td>
<td>n = 49</td>
<td>n = 51</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>50 (50)</td>
<td>19 (39)</td>
<td>31 (61)</td>
</tr>
<tr>
<td>Age at follow-up (y), median (IQR)</td>
<td>7.6 (7.5–7.8)</td>
<td>7.6 (7.5–7.7)</td>
<td>7.6 (7.5–7.8)</td>
</tr>
<tr>
<td>WISC-IV FSIQ, median (IQR)</td>
<td>100 (81–110)</td>
<td>104 (94–114)</td>
<td>95 (87–108)</td>
</tr>
<tr>
<td>WISC-IV VCI, median (IQR)</td>
<td>98 (83–108)</td>
<td>99 (85–114)</td>
<td>98 (89–104)</td>
</tr>
<tr>
<td>WISC-IV PRI, median (IQR)</td>
<td>100 (82–116)</td>
<td>104 (96–117)</td>
<td>100 (88–110)</td>
</tr>
<tr>
<td>WISC-IV PSI, median (IQR)</td>
<td>97 (88–110)</td>
<td>99 (81–110)</td>
<td>94 (88–108)</td>
</tr>
<tr>
<td>WISC-IV PSL, median (IQR)</td>
<td>94 (85–105)</td>
<td>100 (90–113)</td>
<td>88 (83–89)</td>
</tr>
</tbody>
</table>

> 1 child was missing neonatal data, and 2 children did not have neonatal infection data.

### Table 4: Higher Number of Invasive Procedures Was Associated With Lower FA at Age 7 Years

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Pain Model, n = 50</th>
<th>Surgery Model, n = 50</th>
<th>Steroid Model, n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of invasive procedures</td>
<td>Effect Size</td>
<td>CI</td>
<td>P</td>
</tr>
<tr>
<td>GA</td>
<td>-0.02</td>
<td>-0.04 to -0.005</td>
<td>.01</td>
</tr>
<tr>
<td>Small for GA</td>
<td>-0.001</td>
<td>-0.004 to 0.003</td>
<td>.71</td>
</tr>
<tr>
<td>Illness severity</td>
<td>&lt;0.001</td>
<td>-0.0004 to 0.001</td>
<td>.57</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>-0.003</td>
<td>-0.02 to 0.01</td>
<td>.70</td>
</tr>
<tr>
<td>Postnatal infection</td>
<td>0.009</td>
<td>-0.004 to 0.016</td>
<td>.16</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.002</td>
<td>-0.001 to 0.007</td>
<td>.71</td>
</tr>
<tr>
<td>Age at scan</td>
<td>-0.19</td>
<td>-0.47 to 0.08</td>
<td>.17</td>
</tr>
<tr>
<td>Brain injury</td>
<td>-0.009</td>
<td>-0.02 to 0.002</td>
<td>.10</td>
</tr>
<tr>
<td>Surgery</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Morphine exposure</td>
<td>0.008</td>
<td>-0.007 to 0.02</td>
<td>.28</td>
</tr>
<tr>
<td>Fentanyl exposure</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Midazolam</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

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Previously, it has been demonstrated that a higher number of invasive and stressful procedures was associated with delayed WM maturation in infants born very preterm both during NICU care and at term-equivalent age.\(^7,8,25\) Higher numbers of invasive procedures are associated with lower stress hormone cortisol responses at 32 weeks’ postmenstrual age and higher levels at 8 and 18 months’ corrected age.\(^{26,27}\) Brain regions rich in glucocorticoid receptors (e.g., prefrontal cortex) are particularly vulnerable to the effects of ongoing stress.\(^{28,29}\) This may explain why the number of invasive procedures and the subcortical WM, rather than the WM tracts, predicted IQ at 7 years. Preoligodendrocytes actively develop between 24 and 40 weeks’ gestation to form mature, myelinating oligodendrocytes.\(^{30}\) However, during this peak developmental period, preoligodendrocytes are sensitive to reactive oxygen, nitrogen species, and cytokines secreted by microglia.\(^{31–35}\) Neonatal hypoxia–ischemia and neuroinflammation lead to the activation of astrocytes and microglia, which induces myelin deficiency, associated with long-term cognitive problems.\(^{30,36}\) Similarly, pain also induces both oxidative stress and inflammatory reactions.\(^{37,38}\) Therefore, greater exposure to invasive procedures in the NICU may arrest the development of pre-myelinating cells.

In this study, we could not discern why the strongest association with invasive procedures was observed with the subcortical WM, rather than with WM tracts. Myelination first appears in the central WM tracts, therefore the subcortical WM may have been more enriched in progenitor stages of the oligodendrocyte lineage in contrast with the WM tracts. Alternatively, the subcortical and central WM tracts may have been similarly affected, but the latter had greater potential for recovery.

Another important consideration involves the distribution of opioid receptors. Electrical stimulation of the periaqueductal gray and rostroventral medulla, regions responsible for the release of opioids within the spinal cord, does not result in the inhibition of the pain signal in rat pups until postnatal day 21.\(^{39,40}\) Repeated invasive procedures during this maturational period of the descending inhibitory system may lead to hyperinnervation of the periaqueductal gray and rostroventral medulla, thereby altering their functional integrity.\(^{41}\) Inflammatory pain in neonatal rats has been found to increase the adult endogenous opioid tone.\(^{42}\) Therefore, repeated exposure to invasive procedures in the NICU may lead to chronically elevated opiate peptides, affecting the integrity of the subcortical WM, which connects to the periaqueductal gray, a region rich in opioid receptors.

Invasive procedures may also have indirectly affected the neonatal brain. Greater numbers of invasive procedures were associated with slower growth,\(^{43}\) and slower growth during neonatal care was associated with delayed cerebral cortical maturation in infants born very preterm.\(^{44}\) FA values reach the noise floor in the cortical gray matter by approximately 36 weeks’ postmenstrual age,\(^{44,45}\) due to neuronal maturation, synaptogenesis, and the disappearance of radial glial cells.\(^{46–50}\) Therefore, we could not examine the long-term effects of the number of invasive procedures on the DTI measures of cortical gray matter. Future studies using alternative methods for quantifying neuronal integrity...
The results of this article are a first step in understanding the relationship between the number of invasive procedures in the NICU and altered WM and IQ at school age, in very preterm children who escaped major brain injury and neurosensory impairment, after adjusting for other risk factors associated with prematurity. Given the apparently limited efficacy of morphine in preventing adverse effects of repeated invasive procedures, it is important to continue to examine methods for pain management. Reducing pain during neonatal care may help optimize brain development and improve cognitive outcomes in this vulnerable population.

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Invasive Procedures in Preterm Children: Brain and Cognitive Development at School Age

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