Boston Children's Hospital
Until every child is well

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TEACHING HOSPITAL

Brain injury in preterm infants and predicting outcomes

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The challenge of predicting outcomes in preterm infants

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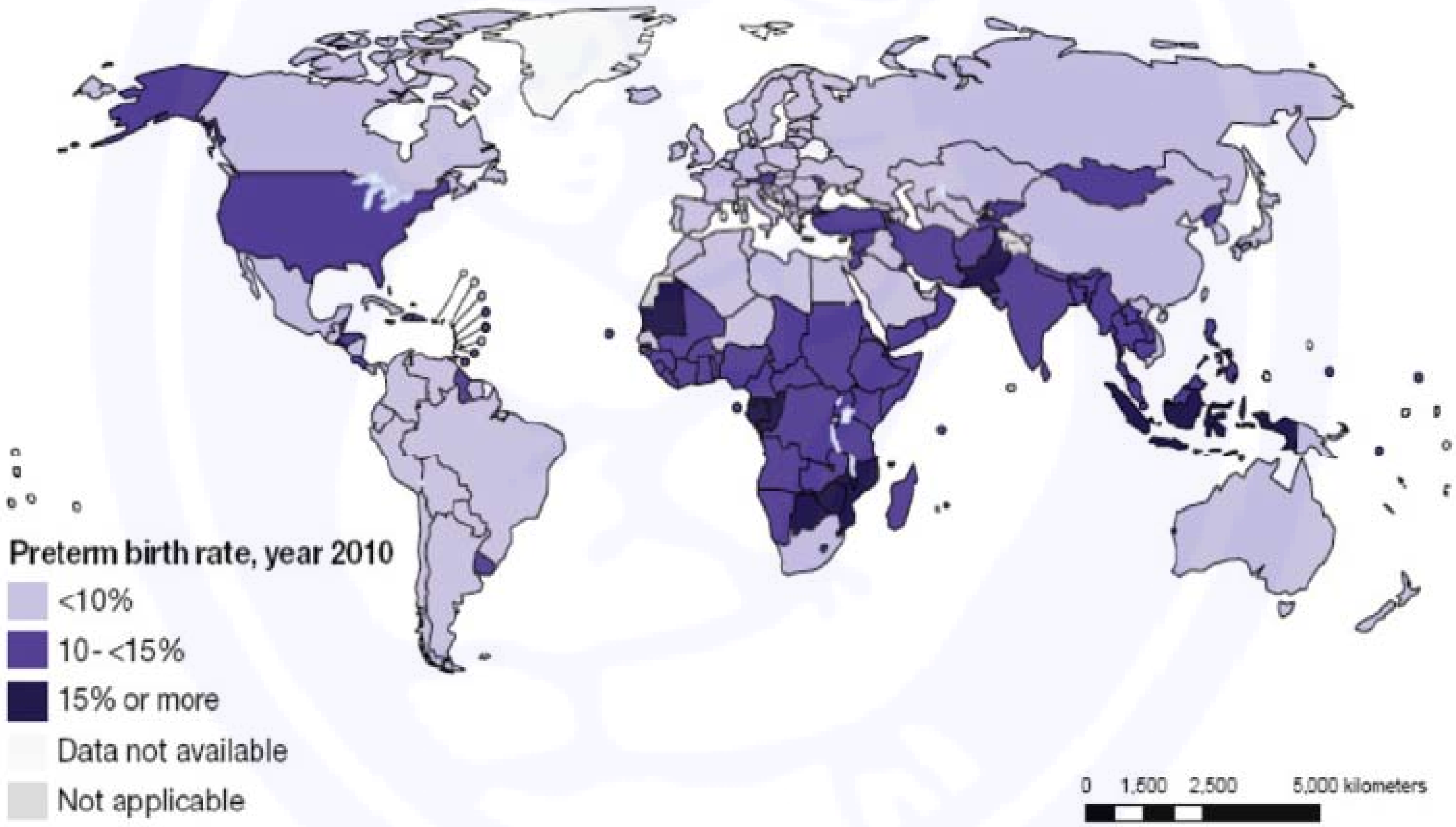
Disclosures

- I have no conflicts of interest or financial disclosures related to today's talk.

Epidemic of preterm birth



World Health Organization 2012; Blencowe et al., Reproductive Health, 2013

Numbers/Nomenclature

- ~4 million live births in US
- ~400,000 (preterm <37 weeks)
- ~60,000 (>32 weeks, VLBW<1500 grams)

- Certain populations more vulnerable
  - African American 13%, White 9%, Hispanic 9.1%

- Late preterm: 34-37
- Moderate preterm: 32-33 6/7
- Very preterm: 28-31 6/7
- Extremely preterm: <28 weeks

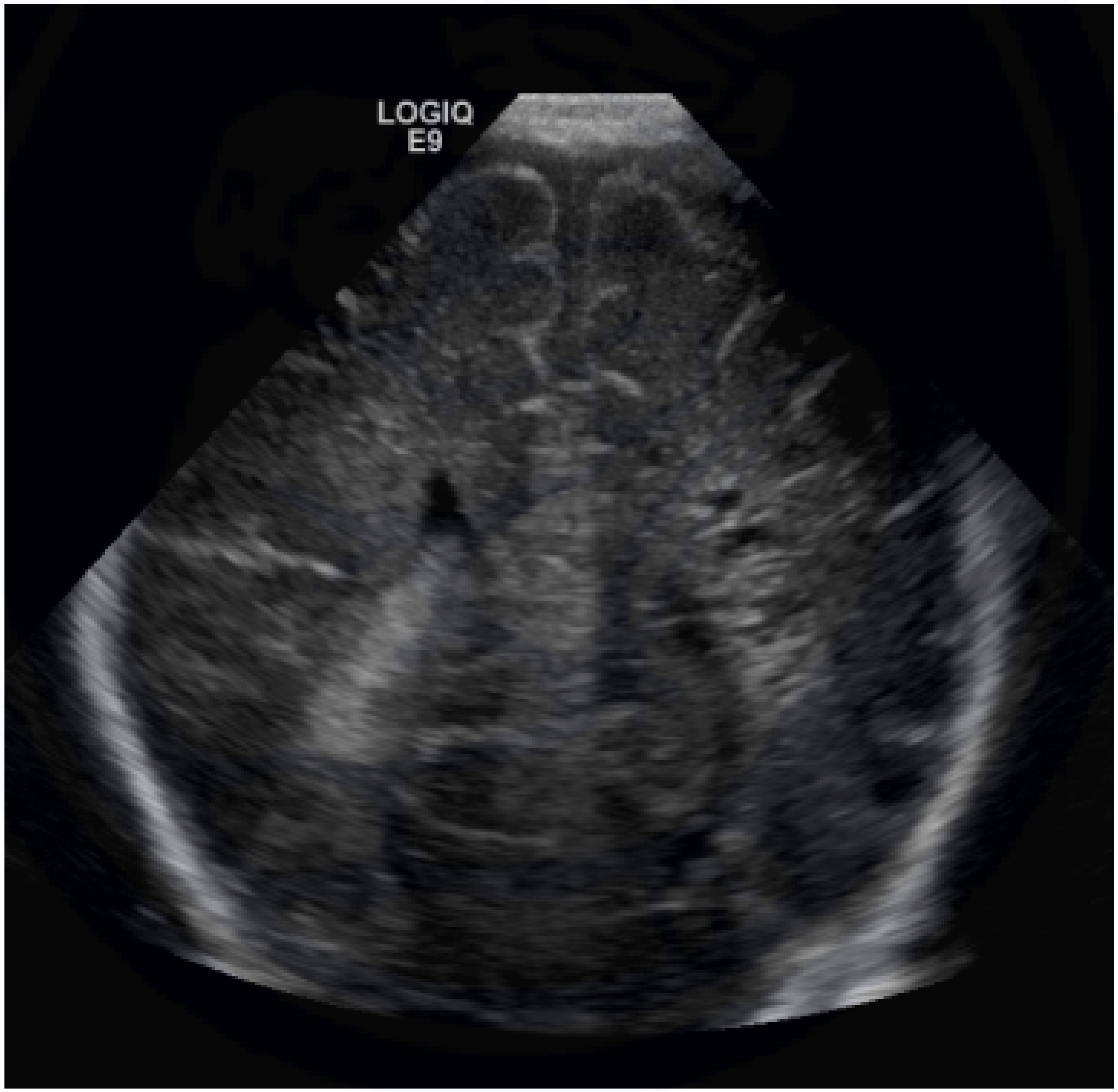
NICU Case 1

- Uncomplicated pregnancy, naturally conceived.
- 27 weeks gestation: preterm labor, bedrest, betamethasone, magnesium sulfate.
- Vaginal delivery at 29 week gestation after decreased fetal movements
- Birth weight 1365grams (60%), admitted to NICU.

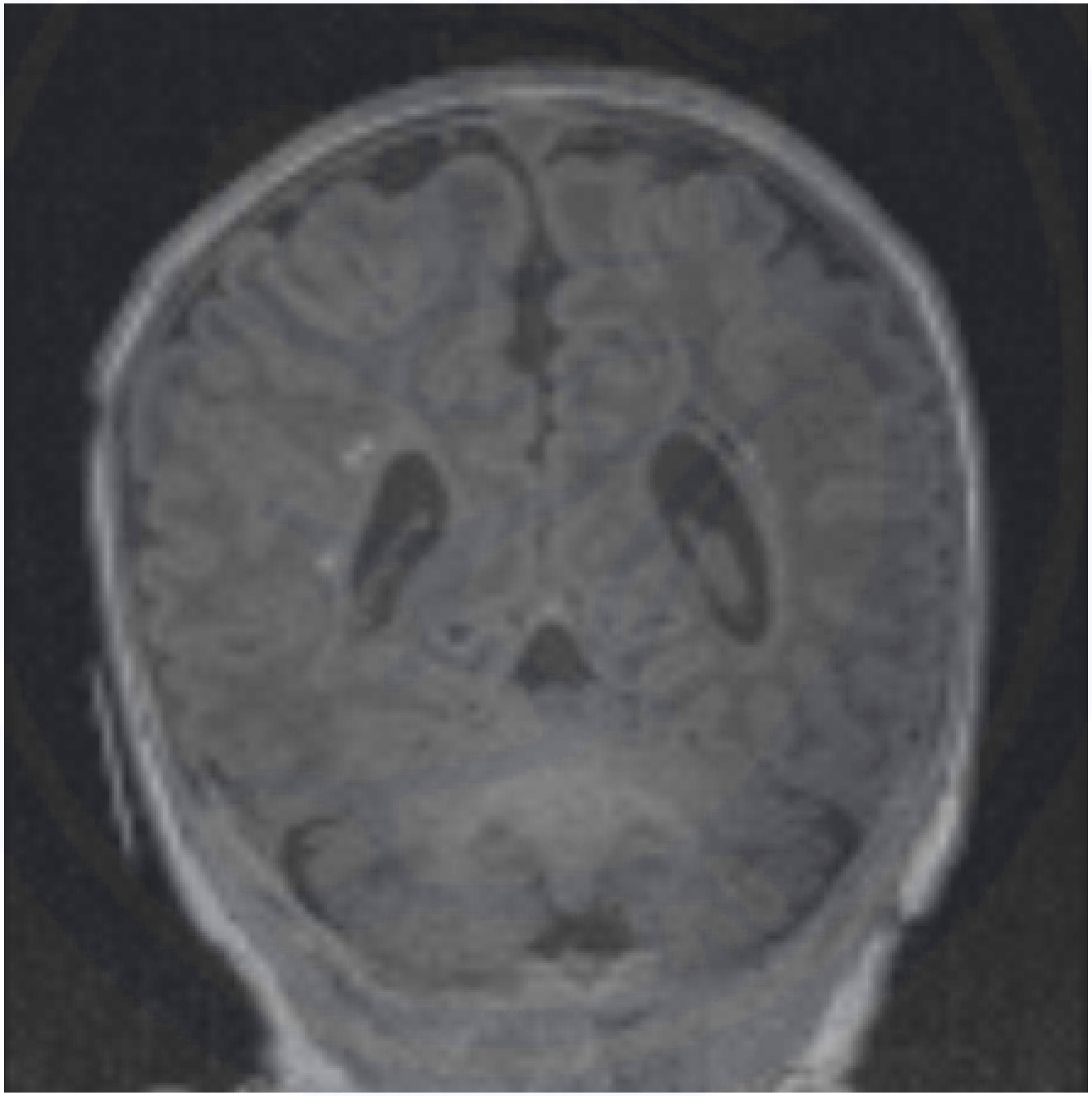
NICU Course

- Bubble CPAP with room air for 3 weeks
- Caffeine for apnea of prematurity
- Head ultrasound at 1 week of age unremarkable
- Eventually transferred to local community hospital
- Head ultrasound at 1 month of age….

Cystic PVL



Term MRI with cystic PVL



Outcome at age 3

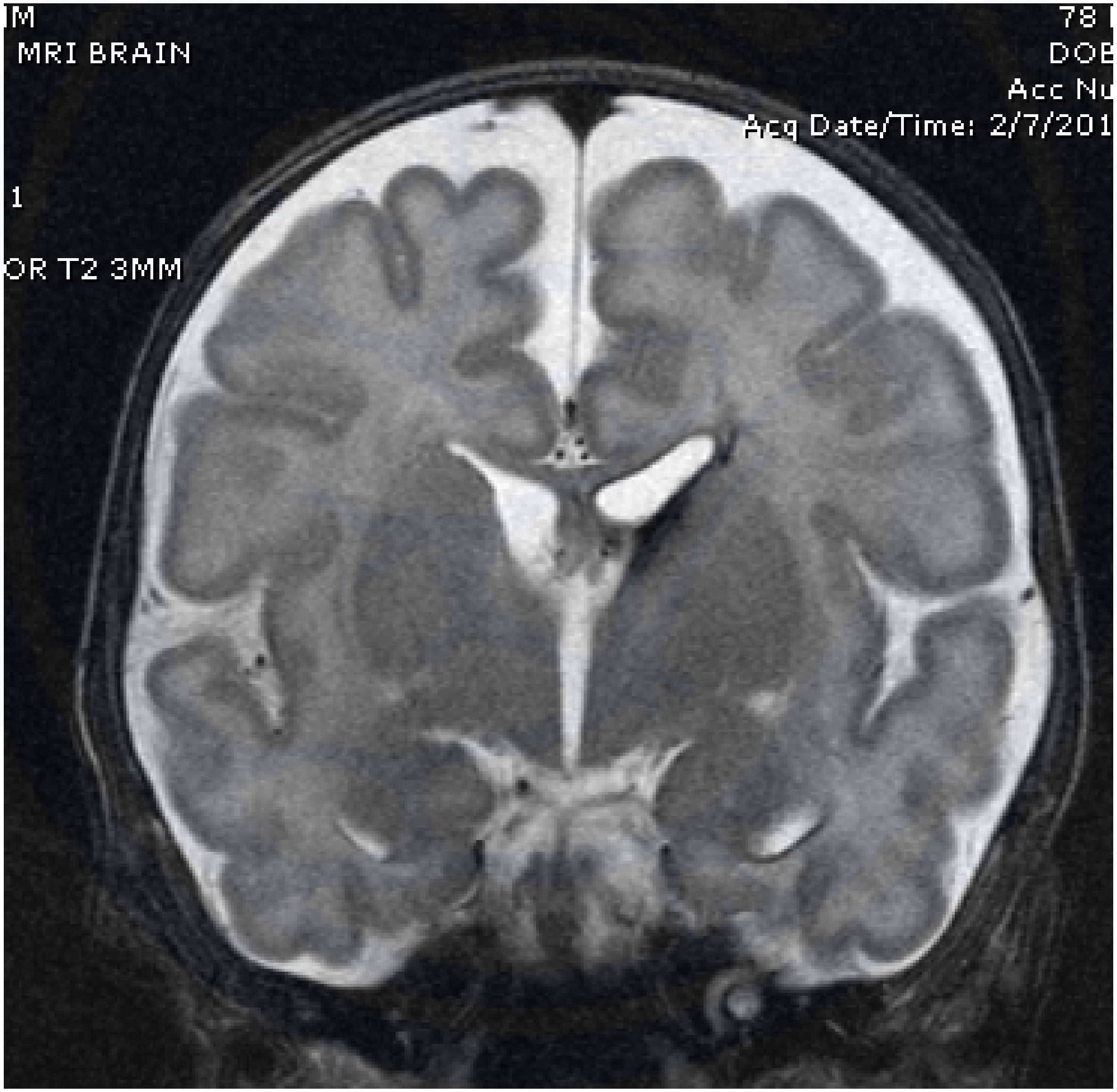
- Gross motor skills behind 14 months
- Fine motor skills behind 3 months
- Receptive language behind 12 months
- Expressive language behind 10 months
- Cognitive skills behind 12 months
- Social-interactions skills behind 18 months

- Receiving Botox for lower extremity spasticity, has AFOs

NICU Case 2

- Born at 29 weeks gestation
- IVH (grade 2, tiny amount of tissue involvement)
- CPAP 5 weeks, oxygen with feeds, chronic lung disease
- Feeding difficulties, oral aversion (g-tube now)

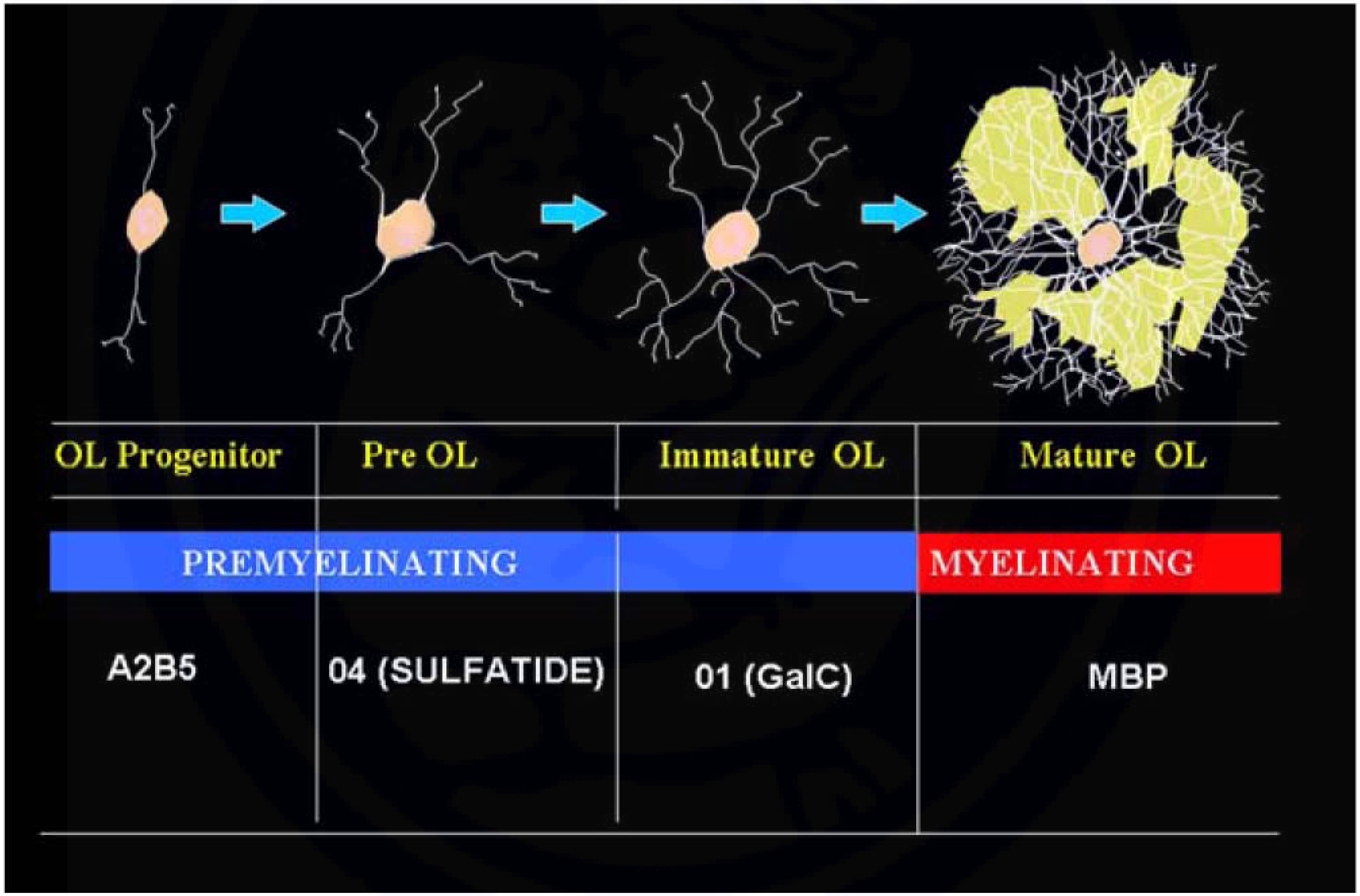
Case 2



Outcome at age 9 months

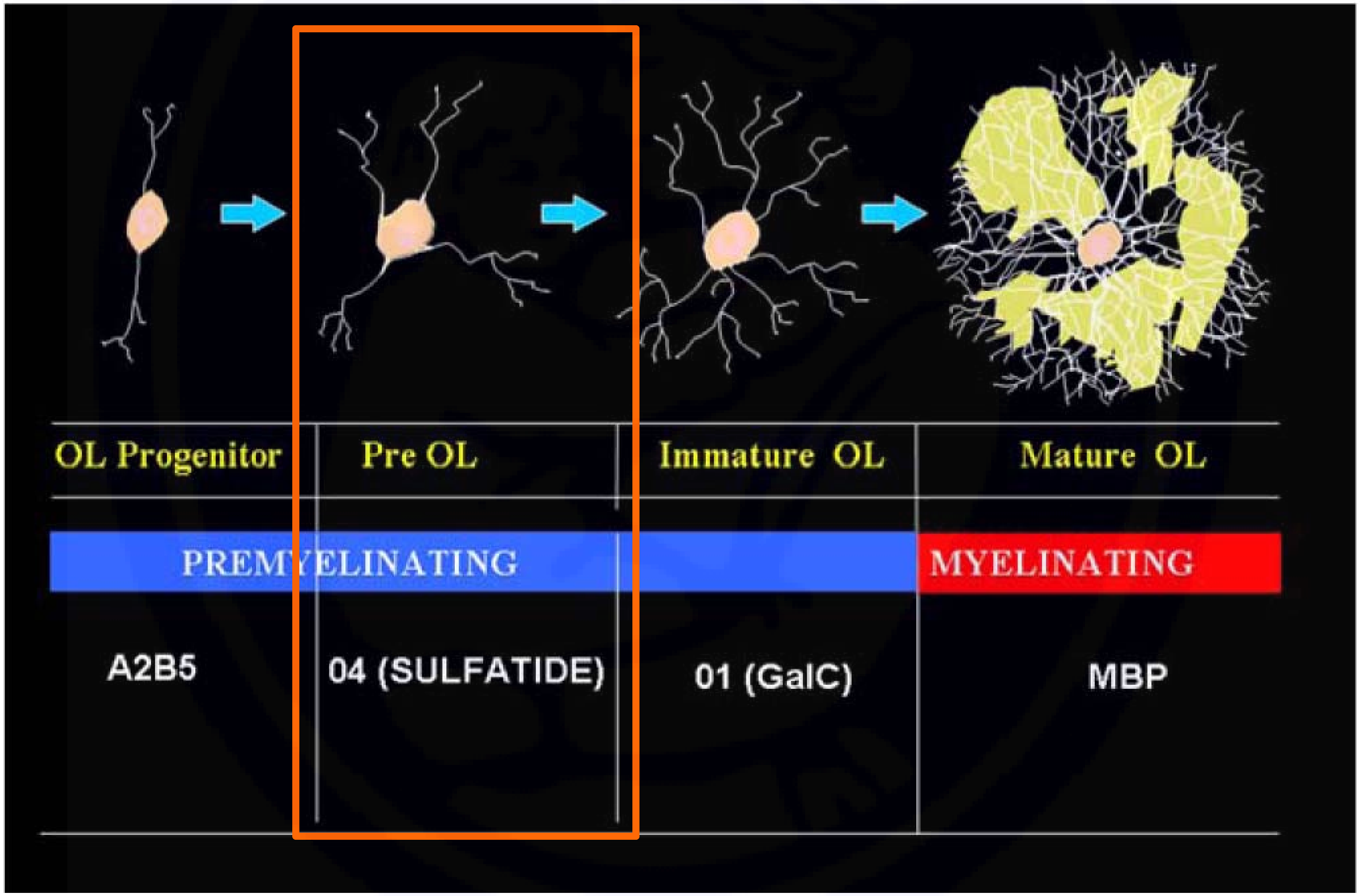
- Proximal muscle weakness
- Mildly increased muscle tone in the heel cords (left>right).
- Dyscoordinated suck
- Rolls, just starting to sit, babbles.
- Weekly EI (occupational therapy and feeding therapy)

Oligodendrocyte (OL) development



Volpe et al., International Journal of Developmental Neuroscience, 2011

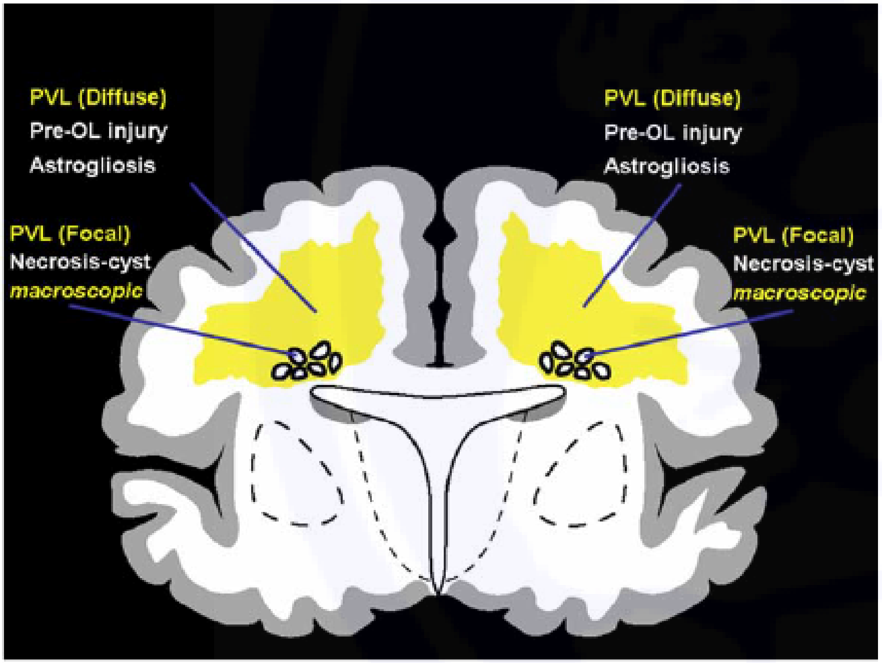
Oligodendrocyte (OL) development



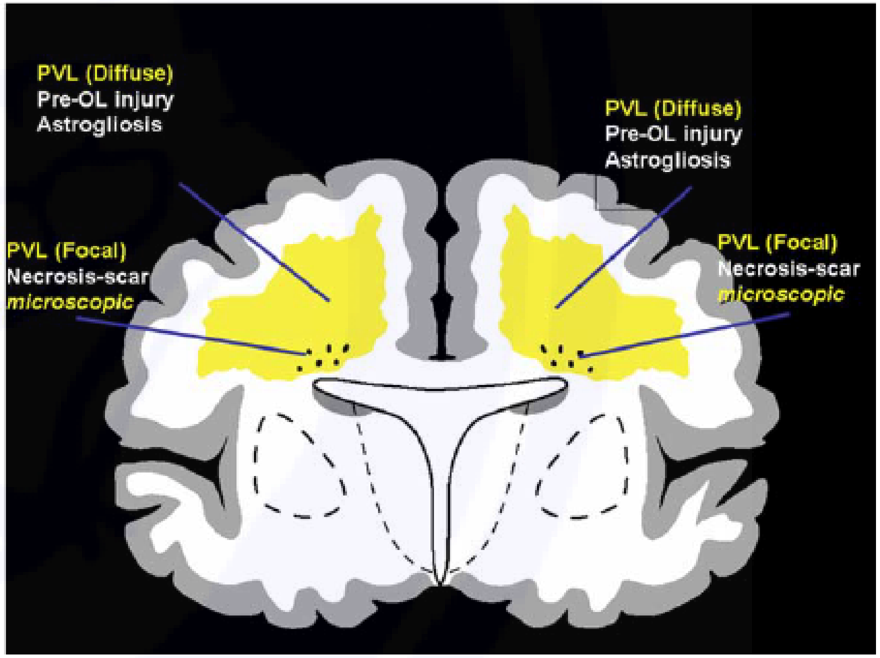
Volpe et al., International Journal of Developmental Neuroscience, 2011

White Matter Injury of Prematurity

Cystic PVL



Non-Cystic PVL

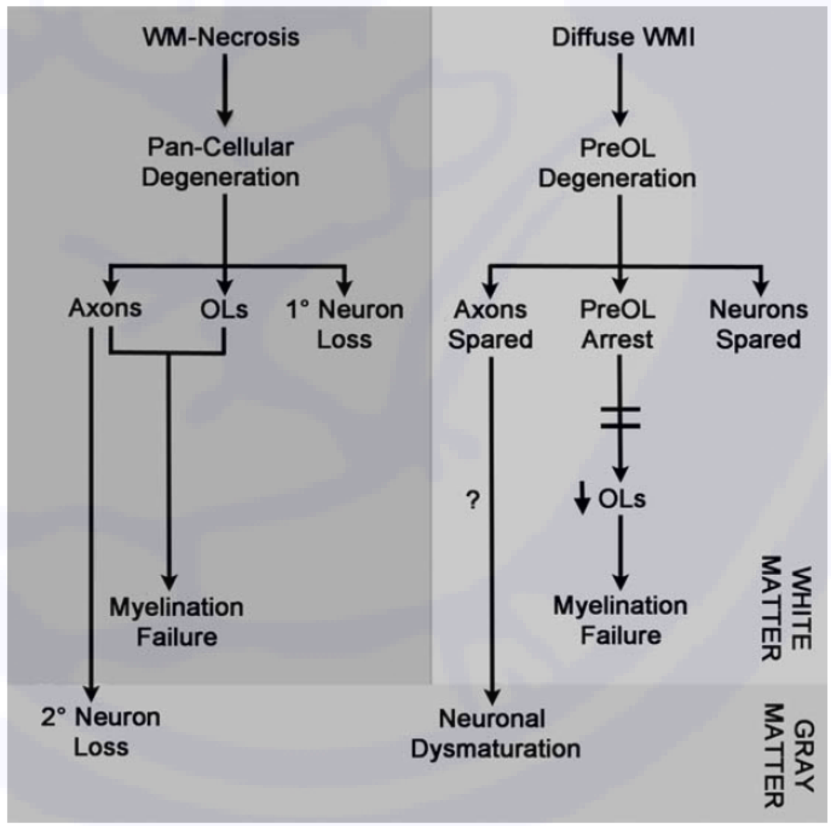


Volpe et al., International Journal of Developmental Neuroscience, 2011

Additional Reviews: Elitt & Rosenberg, *Neuroscience,* 2014; Rosenberg & Back, *Glia*, 2014 Volpe, JJ, *Pediatric Neurology*, 2017, Volpe, JJ, *Pediatric Neurology*, 2019.

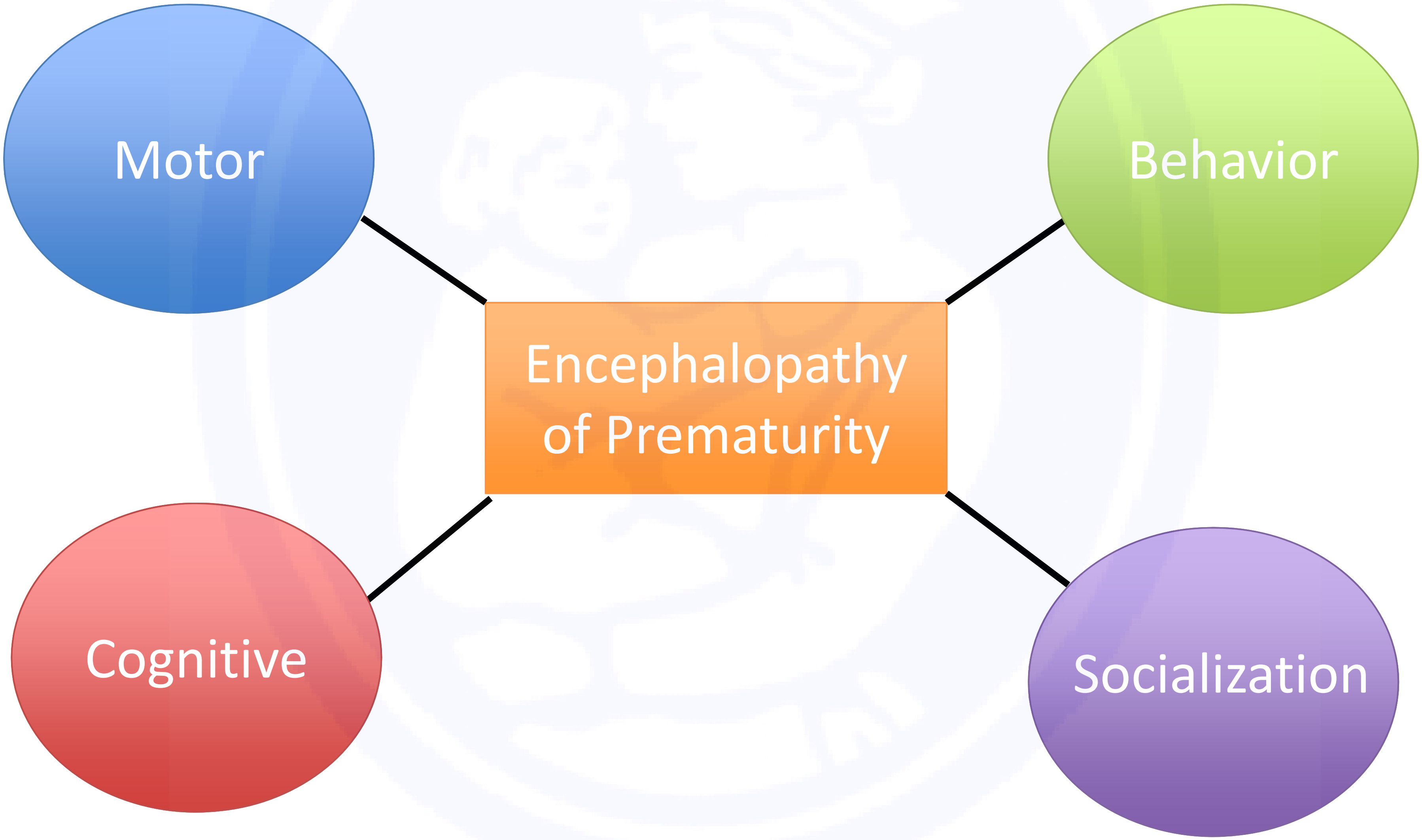
Encephalopathy of Prematurity

“A complex amalgam of destructive and developmental disturbances” involving axons and neurons, in addition to white matter”



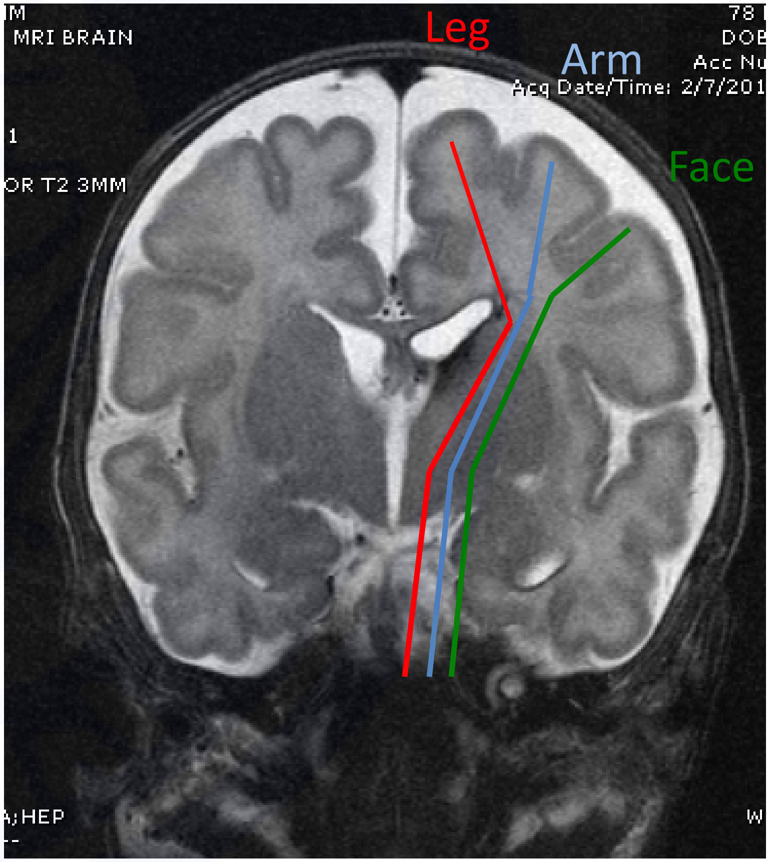
Volpe, JJ, *Neurology of the Newborn*, 6th Edition; Back & Miller, *Annals of Neurology*, 2014

Types of Disabilities



Motor Disabilities

- Spastic Diplegia (lower>upper extremities)
  - Often in association with cystic PVL
  - Incidence decreasing
  - Now ~2-3%, although some populations ~10%.



Hamrick et al., *J. Pediatrics*, 2004; Gano et al., *J. Pediatrics*, 2015; Van Haastert et al., *J. Pediatrics*, 2011; Hafstrom et al., *Pediatrics*, 2018

Motor Disabilities

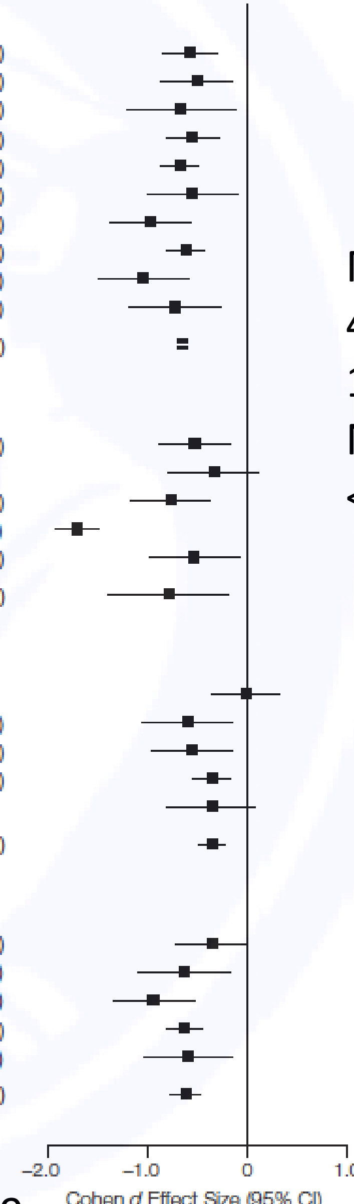
- Developmental coordination disorder
  - Balance
  - Coordination
  - Visual motor integration
  - Manual dexterity
  - Ball skills
  - Fine motor skills

  - ~50% of preterm infants <32 weeks gestation
  - Impairments persist into adulthood

Edwards et al., , *Journal of Developmental and Behavioral Pediatrics*, 2011.
Spittle & Orton, *Seminars in Fetal & Neonatal Medicine*, 2014

Figure 2. Effect Sizes and Heterogeneity Statistics for the Movement Assessment Battery for Children Ordered by Age at Assessment

Source	Age at Assessment, y	Effect Size (95% CI)
Overall score		
Hoff Esbjørn et al,[52] 2006	5	−0.57 (−0.84 to −0.30)
Johnson et al,[17] 2005	5	−0.50 (−0.85 to −0.15)
Jakobson et al,[53] 2006	5-6	−0.66 (−1.21 to −0.10)
Jongmans et al,[54] 1996	6	−0.55 (−0.82 to −0.27)
Cooke and Foulder-Hughes,[19] 2003	7	−0.67 (−0.86 to −0.49)
Rademaker et al,[16] 2004	7-8	−0.55 (−1.00 to −0.09)
Goyen and Lui,[56] 2009	8	−0.97 (−1.38 to −0.55)
Davis et al,[18] 2007	8	−0.61 (−0.80 to −0.42)
Powls et al,[3] 1995	12-13	−1.03 (−1.48 to −0.58)
Skranes et al,[55] 2007	15	−0.72 (−1.18 to −0.27)
Combined effect size		−0.65 (−0.70 to −0.60)
Heterogeneity: $Q=7.13$; $P=.62$; $I^2=0\%$		
Balance skills		
Johnson et al,[17] 2005	5	−0.51 (−0.86 to −0.16)
Rademaker et al,[16] 2004	7-8	−0.31 (−0.76 to 0.14)
Goyen and Lui,[56] 2009	8	−0.75 (−1.16 to −0.35)
Davis et al,[18] 2007	8	−1.68 (−1.89 to −1.46)
Skranes et al,[55] 2007	15	−0.51 (−0.96 to −0.06)
Combined effect size		−0.77 (−1.08 to −0.45)
Heterogeneity: $Q=60.40$; $P<.001$; $I^2=93\%$		
Ball skills		
Johnson et al,[17] 2005	5	0.00 (−0.35 to 0.35)
Rademaker et al,[16] 2004	7-8	−0.59 (−1.04 to −0.14)
Goyen and Lui,[56] 2009	8	−0.54 (−0.94 to −0.15)
Davis et al,[18] 2007	8	−0.34 (−0.53 to −0.16)
Skranes et al,[55] 2007	15	−0.35 (−0.79 to 0.10)
Combined effect size		−0.34 (−0.40 to −0.27)
Heterogeneity: $Q=5.88$; $P=.21$; $I^2=32\%$		
Manual dexterity		
Johnson et al,[17] 2005	5	−0.36 (−0.71 to −0.01)
Rademaker et al,[16] 2004	7-8	−0.62 (−1.08 to −0.17)
Goyen and Lui,[56] 2009	8	−0.94 (−1.35 to −0.52)
Davis et al,[18] 2007	8	−0.63 (−0.82 to −0.44)
Skranes et al,[55] 2007	15	−0.59 (−1.04 to −0.14)
Combined effect size		−0.62 (−0.69 to −0.55)
Heterogeneity: $Q=4.46$; $P=.35$; $I^2=10\%$		



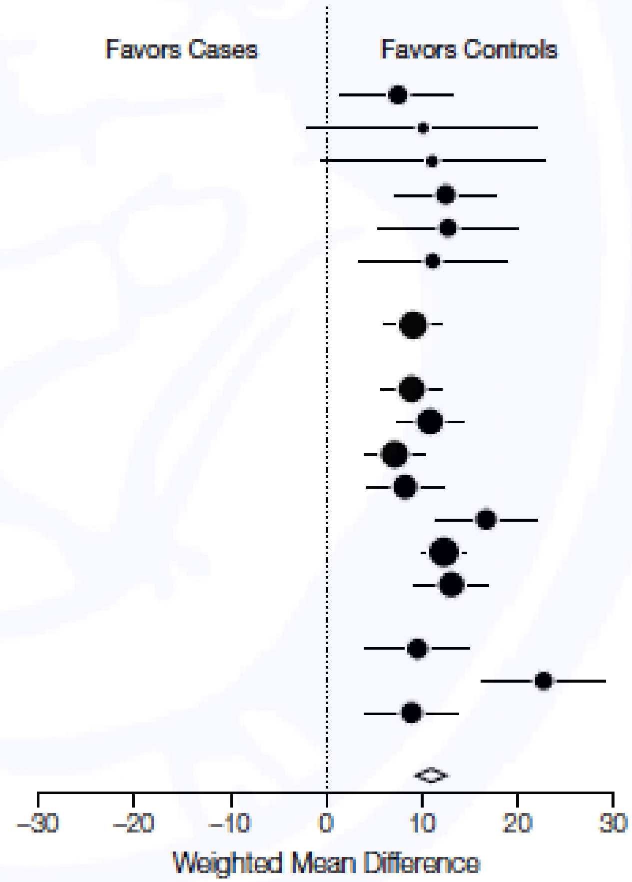
Meta-Analysis
41 articles
1992-2009
N=9653,
<32 weeks gestation

de Kieviet et al., *JAMA*, 2009.

Cognitive-IQ

Figure 1. Random-Effects Meta-analysis Comparing Cognitive Test Scores Between Cases and Controls

Source	Weighted Mean Difference (95% CI)
Lloyd et al,[23] 1988	7.40 (1.55 to 13.25)
Portnoy et al,[24] 1988	10.00 (−2.07 to 22.07)
McDonald et al,[25] 1989	11.00 (−0.91 to 22.91)
Smith and Knight-Jones,[26] 1990	12.40 (6.90 to 17.90)
Teplin et al,[27] 1991	12.70 (5.24 to 20.16)
Sommerfelt et al,[5] 1993	11.00 (3.26 to 18.74)
Levy-Shiff et al,[28] 1994	9.00 (6.03 to 11.97)
Hall et al,[29] 1995	
Study 1	8.80 (5.74 to 11.86)
Study 2	10.70 (7.24 to 14.16)
Sommerfelt et al,[30] 1995	7.00 (3.86 to 10.14)
Botting et al,[31] 1998	8.10 (4.18 to 12.02)
Stjernqvist and Svenningsen,[32] 1999	16.70 (11.36 to 22.04)
Wolke and Meyer,[33] 1999	12.20 (9.80 to 14.60)
Saigal et al,[34] 2000	13.00 (9.19 to 16.81)
Taylor et al,[35] 2000	
Study 1	9.40 (3.88 to 14.92)
Study 2	22.70 (16.31 to 29.09)
Rickards et al,[36] 2001	8.80 (3.87 to 13.73)
Overall	**10.85 (9.23 to 12.47)**

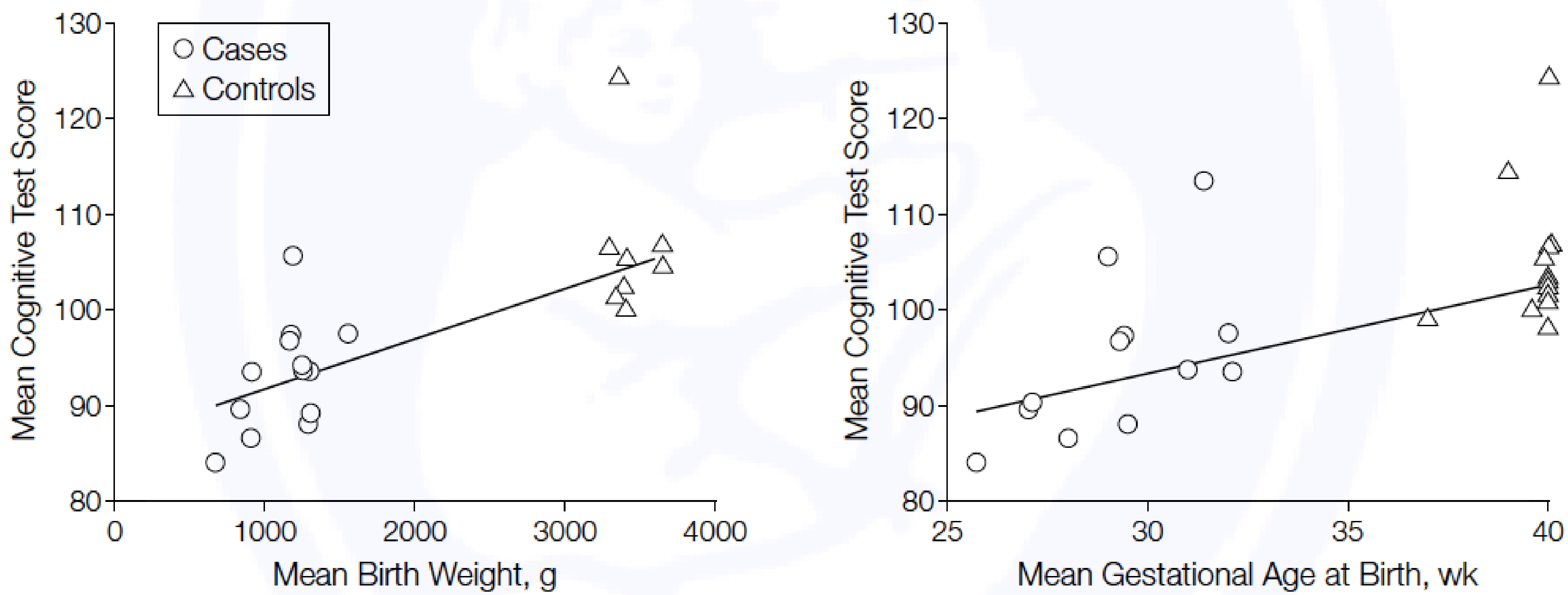


Meta-Analysis
15-16 studies
1980-2001
<37 weeks
N=1556 cases
N=1720 controls

Bhutta et al., JAMA, 2002

Cognitive-IQ

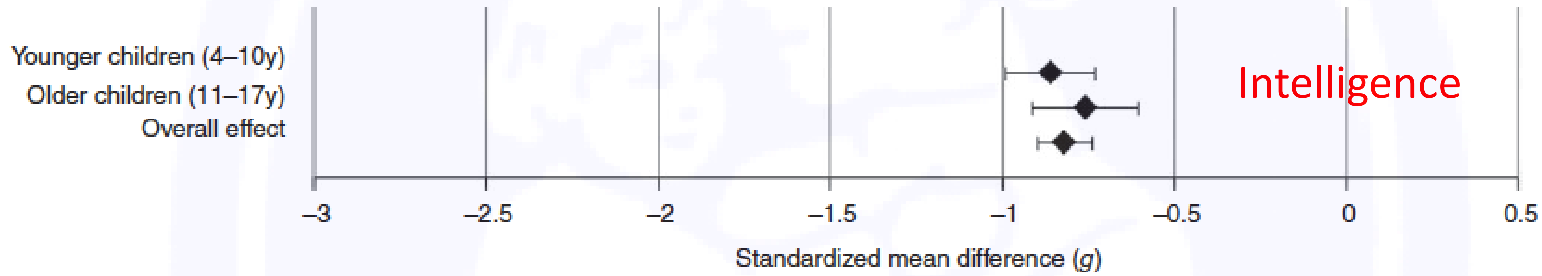
Figure 2. Correlations Between Mean Cognitive Scores, Birth Weight, and Gestational Age

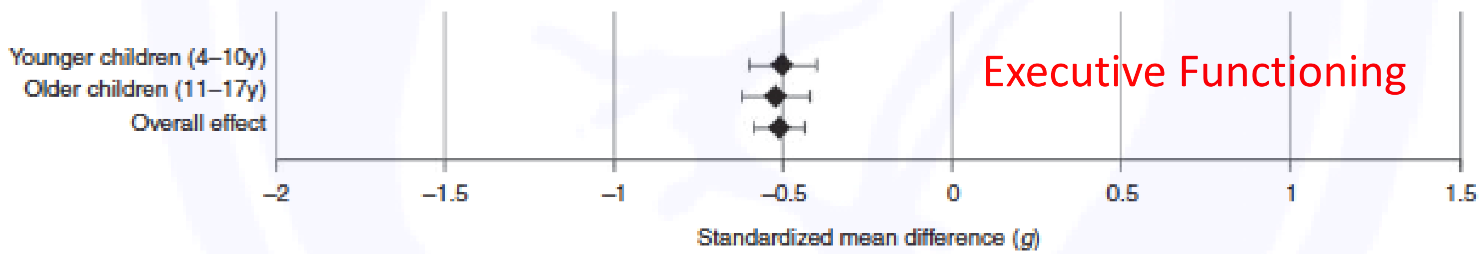


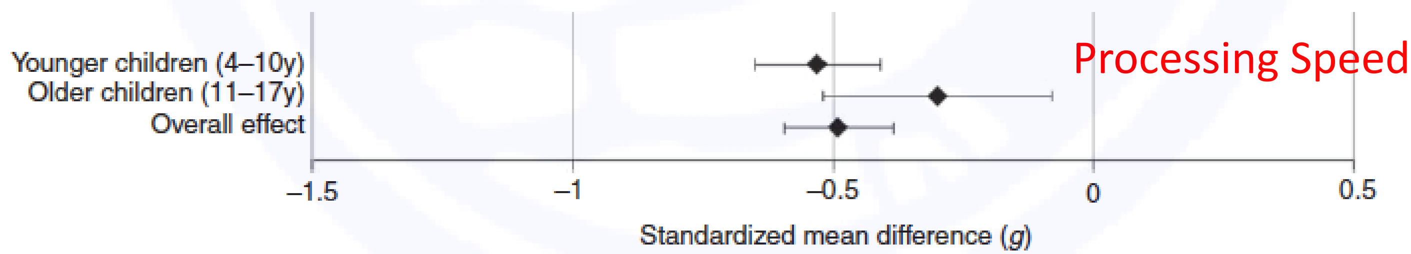
Bhutta et al., JAMA, 2002

Cognitive Disabilities

Meta-Analysis of 60 studies (2000's to present)
N=6163 preterm (<32 weeks), N=5471 term controls

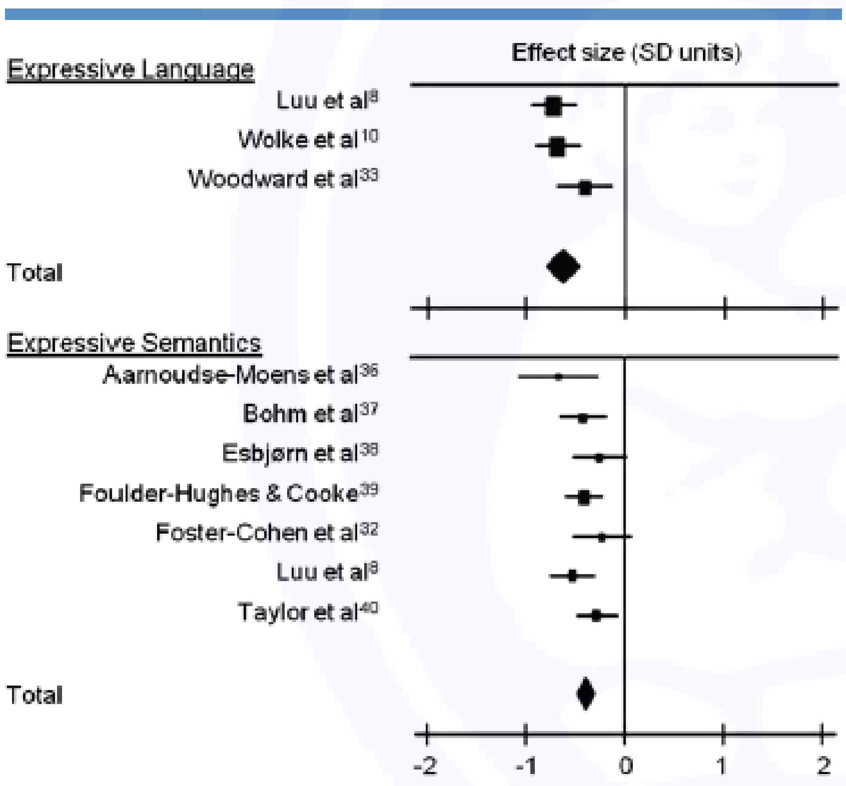


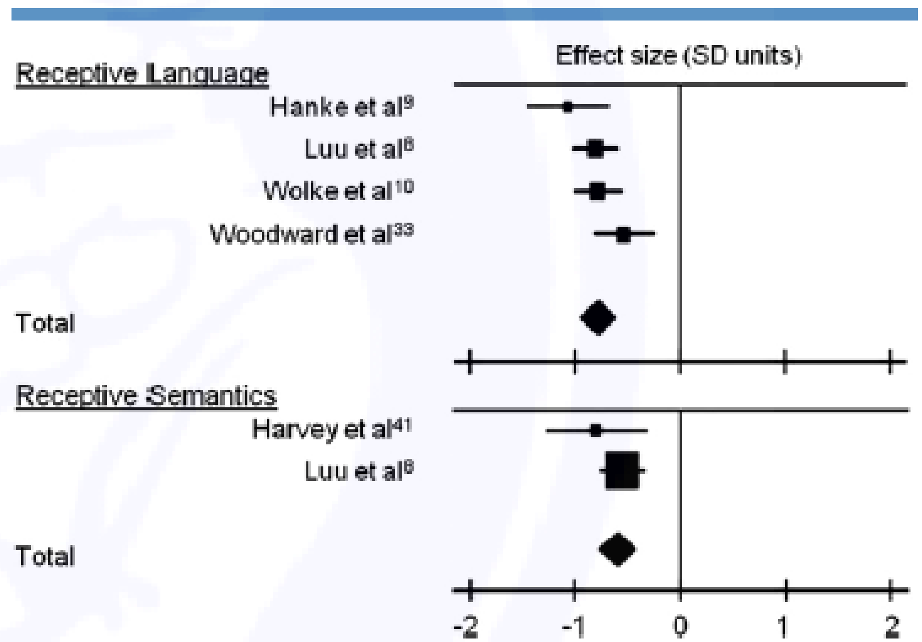




Brydges et al., *Developmental Medicine and Child Neurology*, 2018

Cognitive-Language





<32 weeks gestation vs term controls

Barre et al., *J. Pediatrics*, 2011

Review: Vohr, *Seminars in Fetal and Neonatal Medicine*, 2014

Cognitive-Learning Disabilities

TABLE 2 Cognitive and Academic Outcomes (Mean ± SD) for the EP/ELBW and T/NBW Cohorts at 8 Years of Age, Including Adjustment for Sociodemographic Variables and Neurosensory Impairment

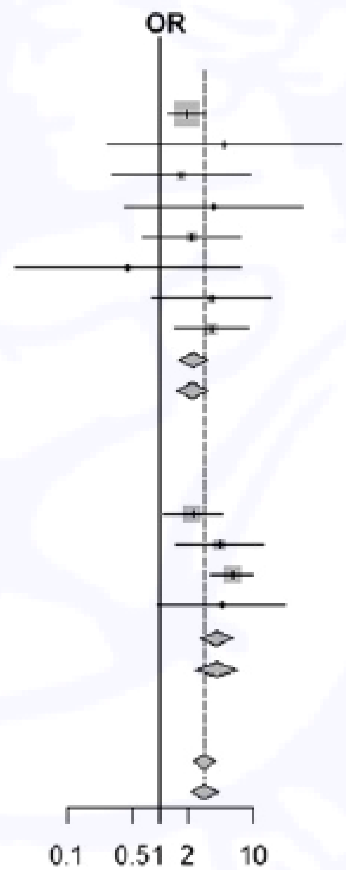
Outcome	EP/ELBW (n = 189)	Controls (n = 173)	Mean Difference (95% CI)	Adjusted Mean Difference 95% CI)[a]	Adjusted Mean Difference 95% CI)[b]
WISC-IV					
FSIQ	93.1 ± 16.1	105.6 ± 12.4	−12.5 (−15.5 to −9.5)*	−10.2 (−13.7 to −6.6)*	−8.8 (−12.2 to −5.3)*
Verbal comprehension	93.1 ± 14.3	103.2 ± 12.6	−10.2 (−13.0 to −7.4)*	−7.8 (−11.1 to −4.5)*	−7.0 (−10.2 to −3.9)*
Perceptual reasoning	95.9 ± 16.8	108.2 ± 12.8	−12.3 (−15.4 to −9.2)*	−10.1 (−13.9 to −6.4)*	−8.0 (−11.5 to −4.7)*
Working memory	94.0 ± 16.3	102.4 ± 12.9	−8.5 (−11.6 to −5.4)*	−7.1 (−10.9 to −3.4)*	−6.1 (−9.7 to −2.6)**
Processing speed	94.7 ± 15.9	101.1 ± 11.9	−6.4 (−9.4 to −3.5)*	−5.7 (−9.3 to −2.3)***	−4.3 (−7.7 to −1.0)***
WRAT3					
Reading	98.0 ± 16.1	105.5 ± 13.8	−7.6 (−10.7 to −4.4)*	−6.7 (−10.4 to −3)*	−6.7 (−10.4 to −3)*
Spelling	96.8 ± 15.2	104.2 ± 14.4	−7.5 (−10.6 to −4.3)*	−7.4 (−11.1 to −3.6)*	−7.7 (−11.5 to −4)*
Arithmetic	90.0 ± 16.9	99.1 ± 14.5	−9.2 (−12.5 to −5.8)*	−6.9 (−11 to −2.9)**	−6.8 (−10.9 to −2.8)**

<28 weeks, <1000grams, born 1997
N=~200

Hutchinson et al., *Pediatrics*, 2013

Attention-Deficit/Hyperactivity Disorder

Study	Preterm or LBW Events	Preterm or LBW Total	Controls Events	Controls Total	OR	95% CI	Weight (Fixed)	Weight (Random)
VP/VLBW								
Breeman, 2016	57	260	29	229	1.94	(1.19 to 3.15)	35.0%	24.0%
Cooke, 1999	19	87	0	8	4.84	(0.27 to 87.62)	1.0%	1.2%
Hatch, 2014	4	6	104	191	1.67	(0.30 to 9.35)	3.1%	3.4%
Indredavik, 2010	4	65	1	59	3.80	(0.41 to 35.04)	1.4%	2.1%
McNicholas, 2015	10	64	4	51	2.18	(0.64 to 7.40)	5.5%	6.3%
Murray, 2016	0	48	79	3535	0.45	(0.03 to 7.33)	3.1%	1.3%
Treyvaud, 2013	18	177	2	65	3.57	(0.80 to 15.82)	3.8%	4.4%
Woodward, 2016	20	100	7	107	3.57	(1.44 to 8.87)	7.9%	10.3%
Fixed effect model		807		4245	2.27	(1.59 to 3.26)	60.9%	--
Random effects model					2.25	(1.56 to 3.26)	--	52.9%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .82$								
EP/ELBW								
Burnett, 2014	30	204	11	153	2.23	(1.08 to 4.60)	15.6%	14.5%
Johnson, 2010	21	183	4	138	4.34	(1.45 to 12.96)	5.9%	7.6%
Scott, 2012	116	148	42	111	5.96	(3.44 to 10.30)	15.1%	21.0%
Van Lieshout, 2015	8	84	2	90	4.63	(0.95 to 22.48)	2.5%	3.9%
Fixed effect model		619		492	4.14	(2.79 to 6.15)	39.1%	--
Random effects model					4.05	(2.38 to 6.87)	--	47.1%
Heterogeneity: $I^2 = 34\%$, $\tau^2 = 0.098$, $P = .21$								
Fixed effect model		**1426**		**4737**	**3.00**	(2.31 to 3.92)	**100.0%**	**--**
Random effects model					**3.04**	(2.19 to 4.21)	**--**	**100.0%**
Heterogeneity: $I^2 = 17\%$, $\tau^2 = 0.0537$, $P = .27$								



N=1787, 12 studies, <32 or <28 weeks

Franz et al., *Pediatrics*, 2018

Autism/Social Communication

- 10% of preterm infants (<28 weeks gestation) screen positive on M-CHAT (twice expected rate) Kuban et al, *Pediatrics*, 2009.

- 2505 children <27 weeks gestation evaluated at 18-22 months with Brief Infant and Toddler Social and Emotional Assessment (BITSEA)
- 35% behavioral problems
- 26% deficits in socio-emotional competence

Peraltra-Carcelen et al., *Pediatrics*, 2017.

Are we doing better?

- Adams-Chapman et al., *Pediatrics*, 2018. Neonatal Network, <27 weeks, N=2113 (2011-2015)
  - Rate of moderate to severe NDI did not differ, but the rates of severe CP decreased, and mild CP increased.

- Spittle et al., *Pediatrics*, 2018. <28 weeks, 3 eras 1991-1992 (552), 1997 (297), 2005 (343) in Australia
  - Rate of motor impairment increased from 23%, 26%, 37% due to non-CP motor impairments

- Twilhaar et al., *JAMA Pediatrics*, 2018. Meta-Analysis, <32 weeks, 71 studies, 7152 preterm, 5155 controls.
  - no improvement in cognitive outcomes from 1990 to 2008.

- Linsell et al., *Arch Dis Child,* 2018. Cohort study, <28 weeks , 315 preterm, 160 term infant.
  - No evidence that impaired cognitive function in extremely preterm individuals materially recovers or deteriorates from infancy through to 19 years.

How to predict outcomes?

- Imaging?
- Serial Exams/Development Assessment?

How to predict outcomes?

- Imaging?
- Serial Exams/Development Assessment?

Is imaging the answer?

The Role of Neuroimaging in Predicting Neurodevelopmental Outcomes of Preterm Neonates

Soo Hyun Kwon, MD[a,1], Lana Vasung, MD, PhD[b,1], Laura R. Ment, MD[a,c], Petra S. Huppi, MD, PhD[b,*]

Kwon et al., *Clinics in Perinatology* 2013

Table 2
Prediction of neurodevelopmental outcomes with structural MRI

Study (Birth Years of Cohort)	Subjects (N)	Age at Birth (wk)	Age at Scan (wk)	Follow-up Age	MRI Findings and Outcomes	Odds Ratio	Diagnostic Value: CP or Motor Impairment PPV	CP or Motor Impairment NPV	MDI or FSIQ PPV	MDI or FSIQ NPV	NDI PPV	NDI NPV
GM and WM												
Jeon et al[33] (2004–2008)	126	<32	34–43	18–24 mo	Cystic PVL and PWML were associated with CP	19.6 (CPVL) 90.9 (PWML)	—	—	—	—	—	—
de Bruine et al[34] (2006–2007)	110	<32	40–44	24 mo	PWML and VD predicted motor delay PWML was associated with MDI scores[a]	18.38 (PWML) 4.57 (VD)	0.63[§]	0.97[§]	0.25[†]	0.95[†]	—	—
Skiold et al[35] (2004–2007)	107	<27	38–41	30 mo	Moderate-severe WM abnormalities associated with CP, lower cognitive and language scores[a]	—	0.5[§]	0.98[§]	—	—	—	—
Setanen et al[36] (2001–2006)	217	<32	Term	5 y	Extent of MRI abnormalities predicted neurodevelopmental impairment[b]	—	0.44[§]	0.99[§]	0.44	0.92	0.75	0.91
Munck et al[37] (2001–2006)	180	≤1500 g and <37	Term	24 mo	Major abnormalities on MRI were associated with lower MDI and NDI scores[a]	—	0.23[¶]	0.98[¶]	0.13	1	—	—
Spittle et al[40] (2001–2003)	227	<30	38–42	5 y	Severity of WM abnormalities was proportionally related to severity of motor impairment	19.4	0.34[§,¶]	0.91[§,¶]	—	—	—	—
Miller et al[78] (1998–2003)	86	<34	31–33	12–18 mo	Moderate-severe abnormalities associated with lower MDI scores[a]	—	—	—	0.31	0.94	—	—
Woodward et al[13] (1998–2000, 2001–2002)	167	<30	38–42	24 mo	WM and GM abnormalities were associated with adverse neurodevelopmental outcomes[a]	3.6 (cognitive delay) 10.3 (motor delay) 9.6 (CP)	0.31[§]	0.95[§]	0.31	0.89	—	—
Iwata et al[44] (1995–2001)	76	≤32	38–42	9 y	WM injury predicted low FSIQ,[c] CP, and requirements for special assistance at school GM abnormalities were not associated with any impaired outcome	8.3 (lower IQ) 7.0 (CP)	—	—	—	—	—	—

Kwon et al., *Clinics in Perinatology,* 2013

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Setanen et al[36] (2001–2006)	217	<32	Term	5 y	Extent of MRI abnormalities predicted neurodevelopmental impairment[b]	—	0.44[§]	0.99[§]	0.44	0.92	0.75	0.91
Munck et al[37] (2001–2006)	180	≤1500 g and <37	Term	24 mo	Major abnormalities on MRI were associated with lower MDI and NDI scores[a]	—	0.23[¶]	0.98[¶]	0.13	1	—	—
Spittle et al[40] (2001–2003)	227	<30	38–42	5 y	Severity of WM abnormalities was proportionally related to severity of motor impairment	19.4	0.34[§,¶]	0.91[§,¶]	—	—	—	—
Miller et al[78] (1998–2003)	86	<34	31–33	12–18 mo	Moderate-severe abnormalities associated with lower MDI scores[a]	—	—	—	0.31	0.94	—	—
Woodward et al[13] (1998–2000, 2001–2002)	167	<30	38–42	24 mo	WM and GM abnormalities were associated with adverse neurodevelopmental outcomes[a]	3.6 (cognitive delay) 10.3 (motor delay) 9.6 (CP)	0.31[§]	0.95[§]	0.31	0.89	—	—
Iwata et al[44] (1995–2001)	76	≤32	38–42	9 y	WM injury predicted low FSIQ,[c] CP, and requirements for special assistance at school GM abnormalities were not associated with any impaired outcome	8.3 (lower IQ) 7.0 (CP)	—	—	—	—	—	—

Kwon et al., *Clinics in Perinatology* 2013

Examples MRI & outcome discordance

- Woodward et al, *NEJM*, 2006
  - Infants <30 weeks gestation, n=167
  - 15% of patients without WMI----severe motor delay and CP at 2 years.

- Hintz et al, *Pediatrics*, 2015
  - Infants <28 weeks, n=480.
  - 4% without WMI had neurodevelopmental impairment, 3 of 18 infants with severe MRI abnormalities were unimpaired or mildly impaired

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Confusions in Nomenclature: "Periventricular Leukomalacia" and "White Matter Injury"—Identical, Distinct, or Overlapping?

Joseph J. Volpe MD *

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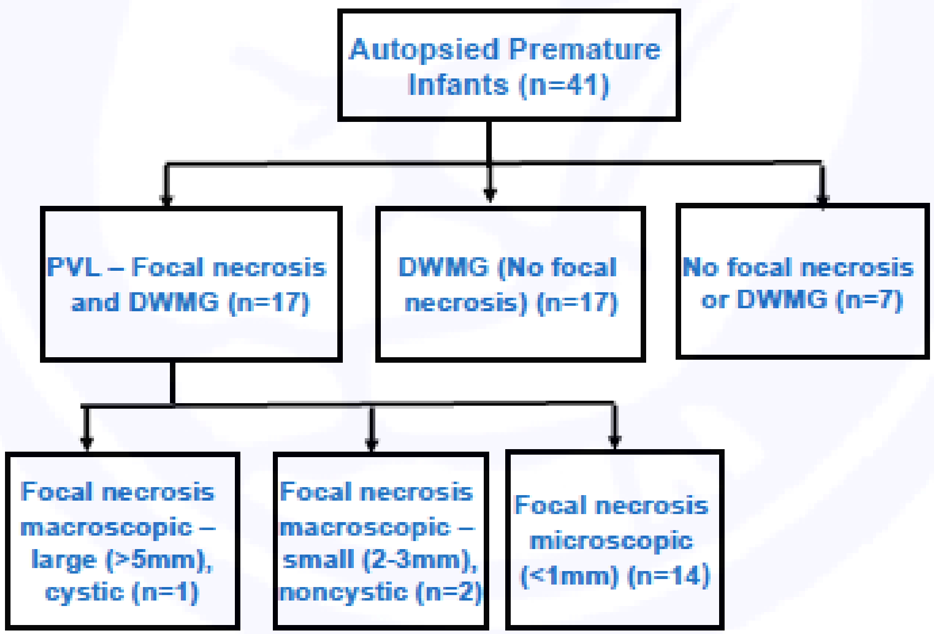

Data from Pierson et al., *Acta Neuropathol*, 2007

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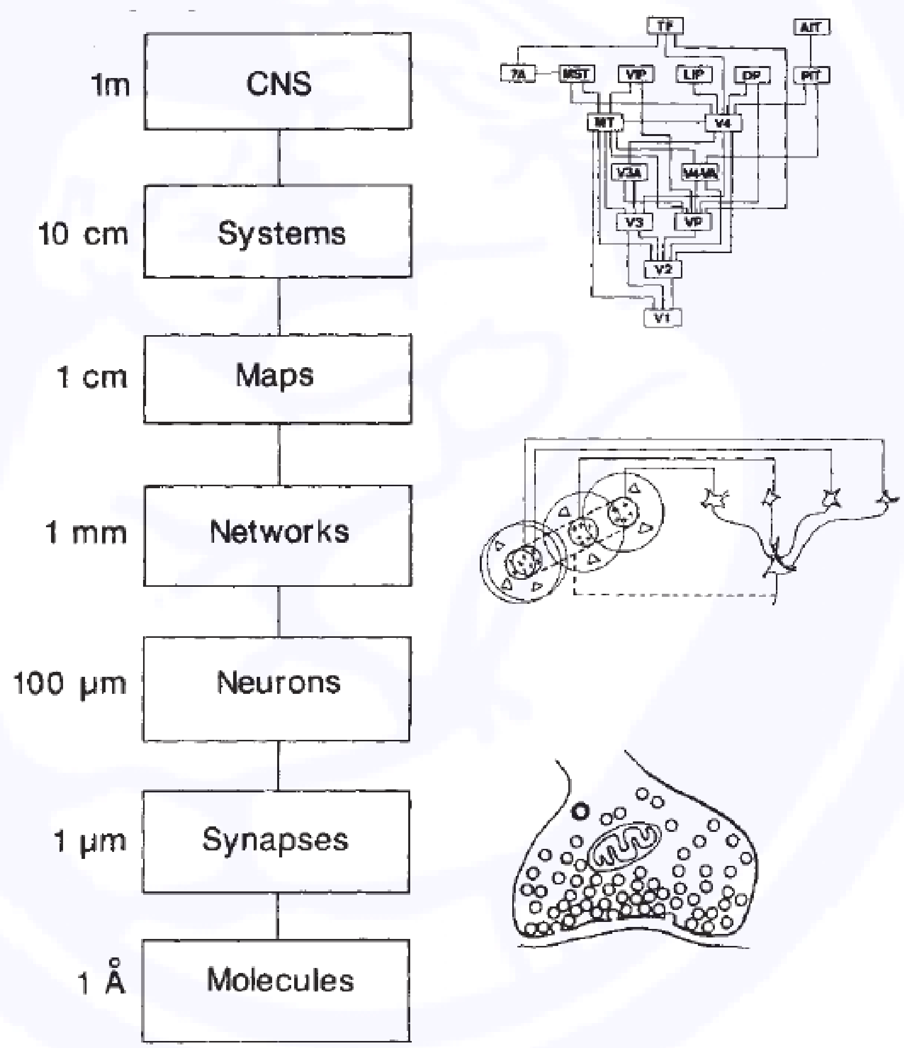
TABLE.
Spectrum of MRI-Demonstrated Cerebral White Matter Injury, Likely Neuropathological Correlates, and Proposed Nomenclature

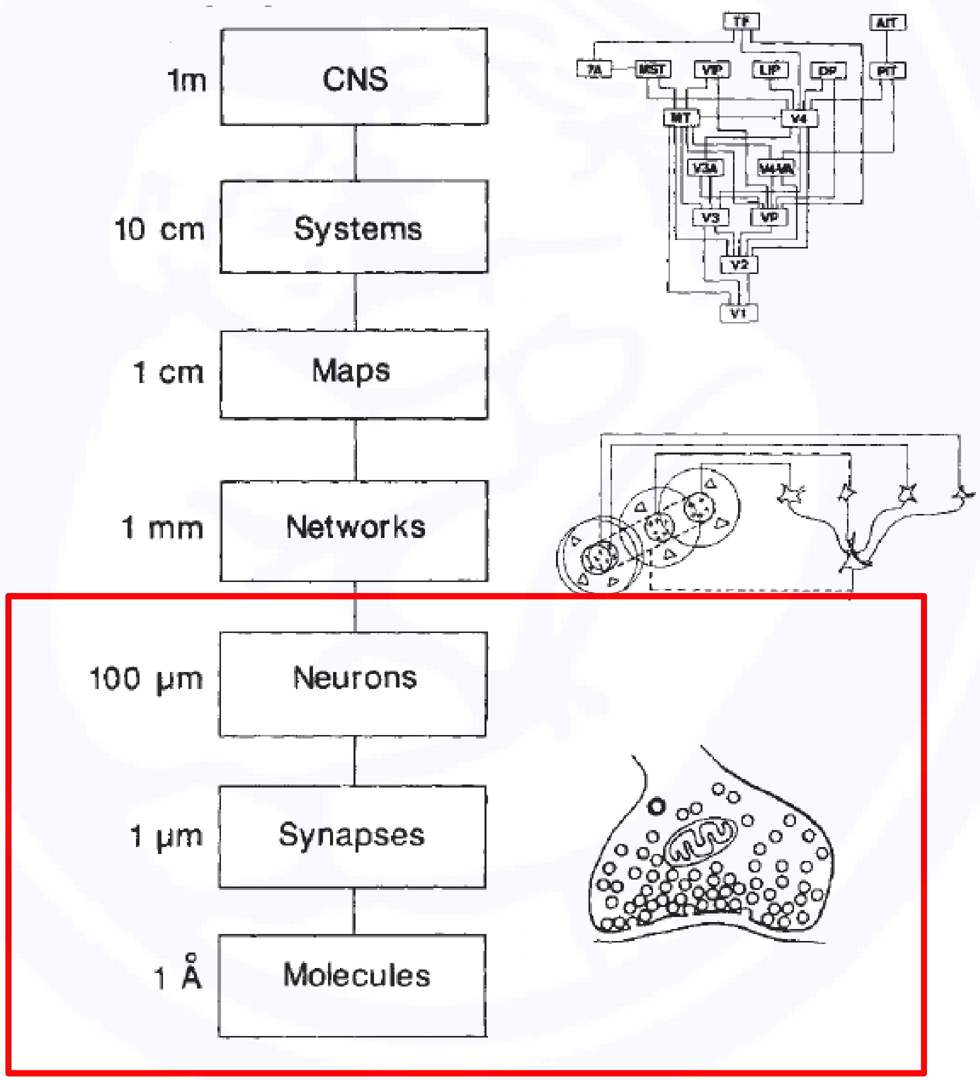
Proposed Nomenclature	Focal Periventricular Lesion	
	Neuropathology	Neuroimaging (MRI)
Severe WMI	Large necroses/cysts	"Cystic" lesions
Moderate WMI	Small necroses/glial scars	PWMLs
Mild/indeterminate WMI	Microscopic necroses	None
	or	
	No necroses	None

Abbreviations:
MRI = Magnetic resonance imaging
PWML = Punctate white matter lesion
WMI = White matter injury

What underlies the imaging findings?

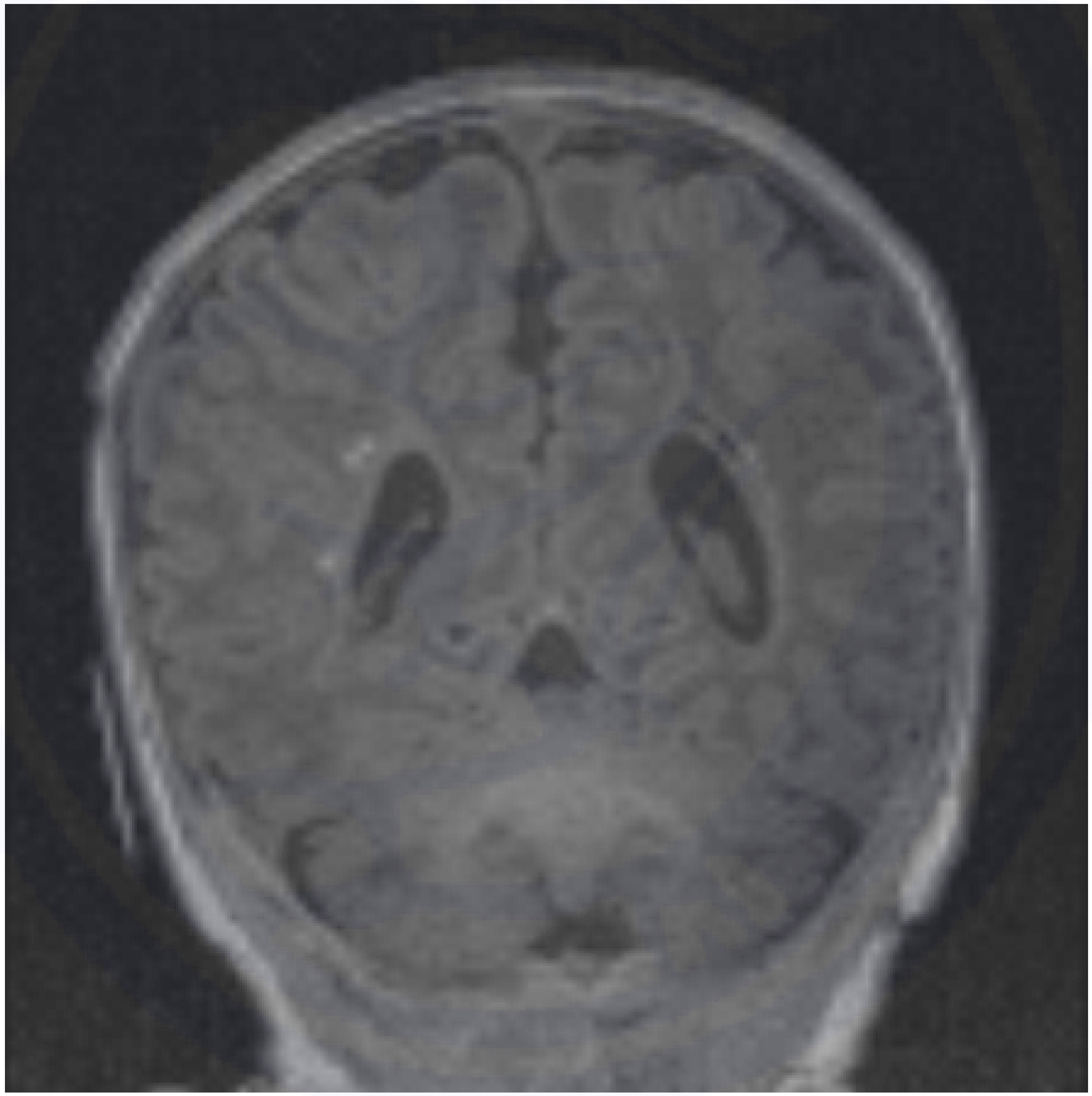


Sejnowski, *Nature*, 1991

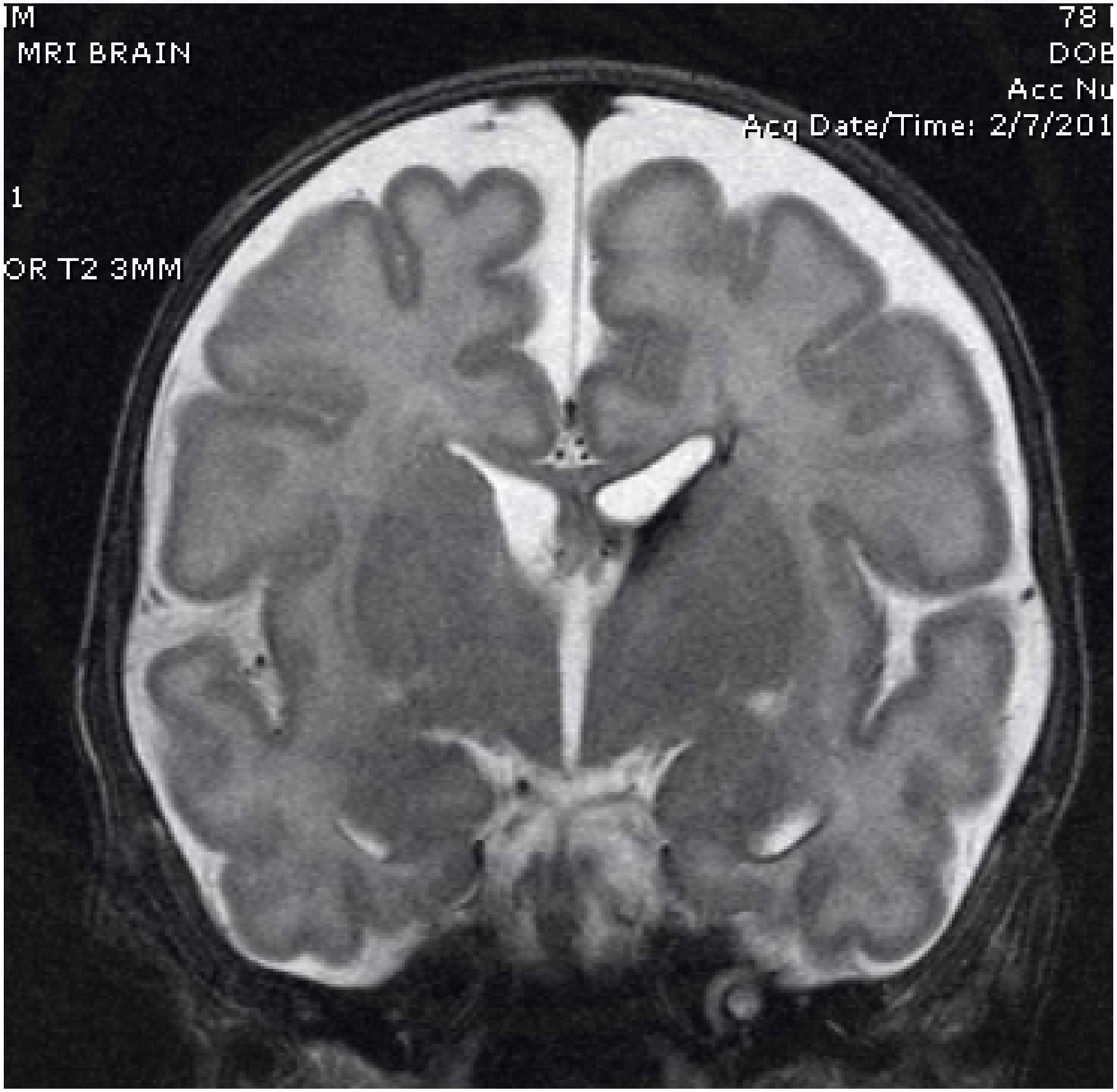


Sejnowski, *Nature*, 1991

Term MRI with cystic PVL



Case 2



Serial Assessment

- Wong et al., *Pediatrics*, 2016.
  - Meta-analysis, 24 studies, N=3133, <32 weeks, assessed 1-3 years and again at >5 years.
  - Early developmental assessment has poor sensitivity (55%) but good specificity (84%) and negative predictive value for school-age **cognitive** outcomes.
- Constantinou et al., *J. Perinatology*, 2007
  - N=130, <1500 grams, assessed general movements at 36wks, 52 wks. Bayley at 18 months.
  - NPV: 90%, PPV: 29-41% for **cerebral palsy**
- Erdei et al., *Pediatrics,* 2020.
  - N=103, <32 weeks, serial cognitive assessments at age 2, 4, 6, 9. 27% with mild cognitive impairment at age 12 that would have been missed at age 2.

What helps to maximize outcomes?

- Early Intervention
  - Spittle et al., *Cochrane Database Systemic Reviews*, 2015. 12 studies, meta-analysis
  - Improved cognitive outcomes at infancy and pre-school age, but effect not sustained at school age. Lots of heterogeneity between studies at infancy and school age.
  - Motor outcomes improved in infancy only. Little evidence of positive effect on long term motor outcomes (but only 2-3 studies)

Caveats

- Differences in clinical practice (interventions, surfactant, steroids, etc), resuscitation of peri-viable infants)
- Outcome studies are all delayed by 5-10 years (to allow for developmental assessments)
- Confounders: socio-economic status, maternal education, EI participation, changes in evaluation tools (Bayley II to Bayley III).

Summary

- White matter injury of prematurity is the major underlying pathology leading to encephalopathy of prematurity. Cystic forms have decreased over time.
- Preterm infants are at high risk for motor, cognitive, language, learning, behavioral, attention, social-communication deficits.
- Deficits persist to adulthood and there has been minimal progress in reducing cognitive deficits and non-CP motor deficits.
- MRI imaging alone is inadequate to predict outcomes and serial developmental monitoring is required.
- Early intervention is the only current treatment and has short term benefits on motor and cognitive deficits.