NIDCAP – Promise to Protect the Preterm Brain

David Schiff Memorial Lecture
Grand Rounds, Department of Pediatrics
University of Alberta Faculty of Medicine and Dentistry,
Royal Alexandra Hospital, Edmonton, Alberta Canada
19 October 2017

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Conflict of Interest Disclosure

I, Heidelise Als, PhD have no financial relationship with any commercial entity producing healthcare-related products and/or services.

I am a volunteer member of Board of Directors of the non-profit NIDCAP Federation International (NFI) and a Senior NIDCAP Master Trainer.

Key Collaborators

Neurology: FH Duffy, MD
Psychiatry: G McAnulty, PhD

S Butler, PhD

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N Weisenfeld, PhD
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Sridhar Vajapeyam, PhD

Robert Mulkern, PhD

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Harris Foundation Chicago, H Als, PhD
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H. Als, 2017

Many Other Collaborators Over the Years

Deborah Buehler, PhD
Rita Gibes, RN MSN
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Nikk Conneman, MD
Steven A. Ringer, MD
Richard Parad, MD, MPH
Elsa Sell, MD
Kathy Vandenberg, PhD
Petra Hüppi, MD and Linda Gilkerson, PhD

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The Challenge

- World-wide increase in prematurity rates:
- Thirteen million infants are born prematurely each year, i. e. 10% of all births.
- More than 50 % of children born preterm show later learning disabilities, attention deficits, behavior problems, emotional issues, and school failure.

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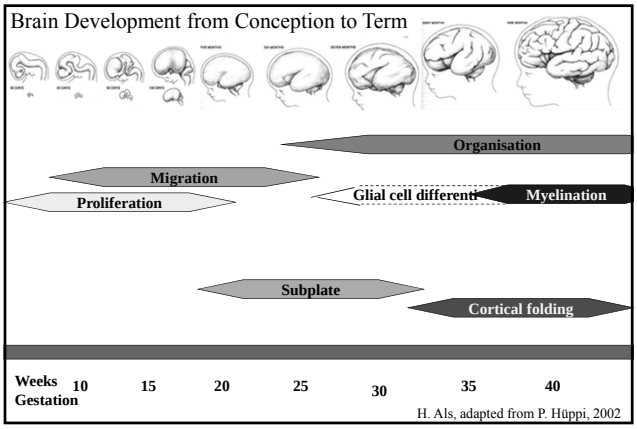
Brain Development from Conception to Term



H. Als, adapted from P. Hüppi, 2002

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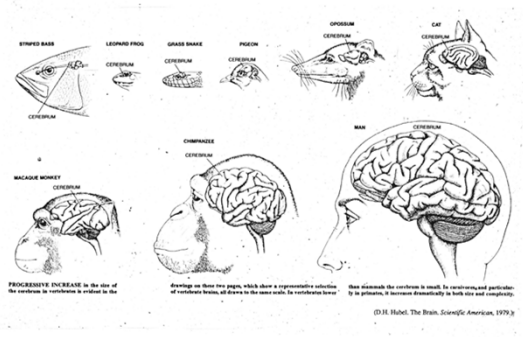
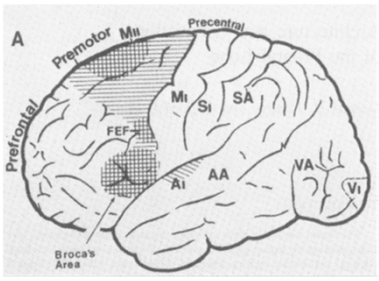
Phylogenetic Evolution of the Brain



D. H. Hubel, The Brain. Scientific American, 1979

H. Als 1979



Major Frontal Lobe Areas and Connections: AI-Primary Auditory Area; AA-Auditory Association Areas; SA-Somatosensory Association Areas; SI-Primary Somatosensory Area; MI-Motor Cortex; MII-Supplementary Motor Cortex; FEF-Frontal Eye Fields; VA-Visual Association Areas; VI-Primary Visual Area. Pandya DN, Barnes CL. (1987) Architecture and connections of the frontal lobe. In Perecman E (ed) *The Frontal Lobe Revisited.* Hillsdale, NJ: Lawrence Erlbaum.als,1991

Three Promised Environments

Hofer, 1985

The Mother's Womb, her Breast and Body, the Species' Social Group

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NICU Environment
Incubators and Machines
Parent Separation
Painful Touch
Many Hands

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Behavior

- Continuous expression of brain function
- Always available to be observed
- Guide for environment, interaction and care

Prematurely Yours , 1983

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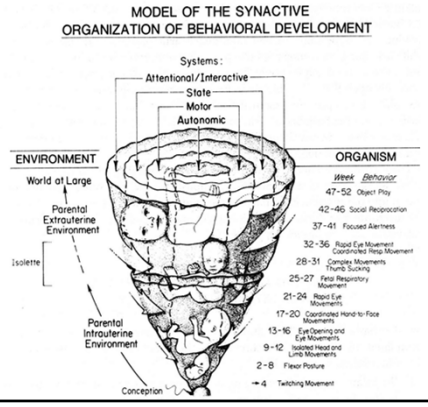

Als.H (1982). Toward a synactive theory of development: Promise for the assessment of infant individuality. *Infant Mental Health J 3(4), 229-243*

H. Als, 2017

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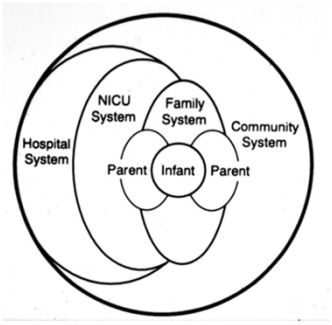
Synactive Model of Developmental Care



- NIDCAP

Newborn Individualized Developmental Care and Assessment Program

Als H (1992).Individualized, family-focused developmental care for the very low-birthweight preterm infant in the NICU. *Advances in Applied Developmental Psychology* (vol 6, pp. 341-388).

H. Als, 2017

Affectionate and Gentle Care

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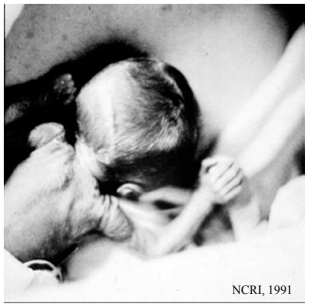
Peaceful and Assuring Intimacy



NCRI, 1991

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Collaborative Care, Parents and Professionals

Photos: S. Butler, with permission 2014

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Pleasurable Feeding, Nutrition and Nurturance

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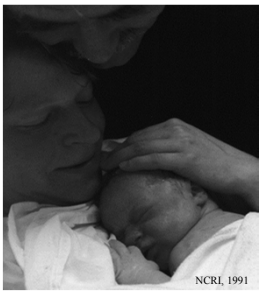
Safeguarding a quiet soothing environment for infant and family - growing security and trust



NCRI, 1991

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Goal: Continuous Assurance of

Protection
Predictability
Restfulness
Intimate Contact
Pleasure and Contentment

Als, H. and L. Gilkerson (1995). Developmentally supportive care in the neonatal intensive care unit. Zero to Three. 15: 1-10.

H. Als, 2017

Results of 15 NIDCAP Studies (10 RCTs)

Significant Reduction

- Ventilator Days
- Extra Oxygen Days
- Gavage Feeding Days
- Severity of BPD
- Incidence of IHV
- Weight Gain Problems
- Growth Problems
- Length of Hospital Stay*
- Age at Discharge*

Significant Improvement

- Neurobehavioral Functioning* (2 weeks*, 9 or 12 months*, 2, 3, & 8 years CA)
- EEG Coherence*: Better Frontal Lobe Engagement (2wCA & 8yCA)
- MRI*: Better White Matter Development in Frontal Lobe and Internal Capsule (2wCA)
- Parent Confidence and Competence

Ohlsson and Jacobs, Pediatrics, 2013; 131:3 e881-e893.

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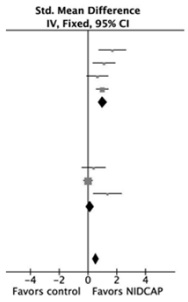
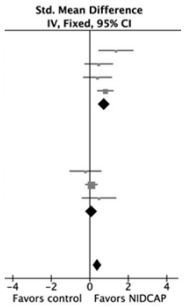
Bayley Mental Developmental Index at 9 or 12 mCA



H. Als, 2017

Ohlsson A, Jacobs SE. NIDCAP: A Systematic Review and Meta-analyses of Randomized Controlled Trials. Pediatrics, 2013; 131:3 e881-e893. Fig. 3

Bayley Psychomotor Developmental Index at 9 or12mCA



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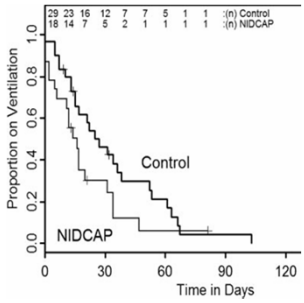
Ohlsson A, Jacobs SE. NIDCAP: A Systematic Review and Meta-analyses of Randomized Controlled Trial. Pediatrics, 2013; 131:3 e881-e893. Fig. 4

Peters KL et al. The Edmonton NIDCAP Trial

Pediatrics 2009;124:1009-1020



Significantly fewer days of mechanical ventilation

TABLE 6 Neurodevelopmental Outcomes at 18 Months

	n (%)		*P*
	NIDCAP (*N* = 51)	Control (*N* = 50)	
Any disability	5 (10)	15 (30)	.02
MDI score of <70	5 (10)	15 (30)	.02
CP	0 (0)	3 (6)	.11
Sensorineural hearing loss	0 (0)	2 (4)	.19
Visual impairment	0 (0)	0 (0)	NA
Severe disability	3 (6)	10 (20)	.03

Severe disability indicates ≥1 of MDI score of <55, CP, visual impairment, or sensorineural hearing loss; NA, not applicable.

Significantly better neuro-development at 18mCA

Als, 2017

Very High Risk Preterm Infants

< 29wGA, Ventilated > 24h/first 48h
Newborn Period to Age Eight Years CA
Health, Neurobehavior and EEG
n = 107 (51C; 56E)

H. Als, 2017

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Very High Risk Preterm Infants <29wGA; N=107
Medical Outcome Variables, 2wCA (1)

Variable	Control (n = 51)	Experimental (n = 56)	F*	*p*
Ventilator Days	48 (18)	27 (19)	8.37	**0.005**
Oxygen Days	106 (13)	60 (10)	5.36	**0.02**
Gavage Days	87 (95)	55 (31)	5.29	**0.03**
Hospital Days	128 (109)	84 (21)	7.93	**0.007**
Discharge Age (w, LMP)	44 (12)	39 (3)	8.70	**0.005**
Daily wt. gain to 2w CA (g)	20 (6)	23 (6)	7.52	**0.007**
Weight at 2w CA (kg)	3.12 (0.66)	3.39 (0.65)	4.57	**0.04**
Length at 2w CA (cm)	47.31 (3.6)	47.61 (3.8)	0.17	0.68
Head Circum. 2w CA (cm)	35.15 (2.2)	35.84 (2.1)	2.82	0.10
Ped Complication Scale	54.67 (6.7)	57.07 (6.9)	3.35	0.07

Means (SD). Corrected Age (CA). Brown-Forsythe One-Way Analysis of Variance: F*, 2-tailed; Note: *p (probability)* in bold ≤ .05 level.

McAnulty et al (2009) *Acta Paediatrica;* 98:1920-1926.

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Very High Risk Preterm Infants < 29wGA; N= 107
Medical Outcome Variables, 2wCA (2)

Variable	Control (n = 51)	Experimental (n = 56)	χ^2	*p*
Pneumothorax None, Present	37, 13	46, 10	1.03	0.31
Intraventricular Hemorrhage None, Grade 1/ 2/ 3/ 4	29, 8, 6, 3, 5	46, 2, 2, 6, 0	15.25	**0.004**
Bronchopulmonary Dysplasia None/ Stage I/ II/ III/ IV	8, 11, 12, 17, 3	9, 17, 24, 5, 1	12.68	**0.01**
Retinopathy of Prematurity None/ Stage I+II/ III/ IV+V	26, 23, 1, 1	31, 24, 1, 0	1.23	0.75

Chi Square Test: $\chi 2$, 2-tailed. Note: *p (probability)* in bold ≤ .05 level.

McAnulty et al (2009) *Acta Paediatrica;* 98:1920-1926.

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Very High Risk Preterm Infants < 29wGA; N = 107
APIB System Scores, 2wCA

Variable	C (n = 51)	E (n = 56)	F*	*p*
Autonomic system	6.67 (1.34)	5.55 (1.99)	20.78	**0.00001**
Motor system	6.62 (1.15)	5.46 (1.33)	23.29	**0.00001**
State system	5.87 (1.29)	5.02 (1.18)	12.77	**0.0005**
Attention system	7.19 (1.47)	6.68 (1.43)	3.26	0.07
Self-regulation system	6.61 (1.16)	5.62 (1.29)	17.63	**0.0001**
Examiner facilitation	7.03 (1.74)	5.93 (1.67)	11.08	**0.001**

Means (SD). Corrected Age (CA). Brown-Forsythe One-Way Analysis of Variance: F*, 2-tailed; Note: $p \leq .05$, bold. McAnulty et al (2009) *Acta Paediatrica;* 98:1920-1926.

Very High Risk Preterm Infants < 29wGA; N = 92
Bayley Scales of Infant Development, 9mCA

Variable	Control (n=42)	Experimental (n=50)	F*	*p*
MDI	96.55 (21.42)	116.24 (18.22)	22.24	**0.00001**
PDI	84.29 (19.24)	99.18 (17.30)	15.10	**0.0002**

Corrected Age (CA). Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI). Results Means (SD) MDI and PDI: Mean = 100; SD = 15. Brown-Forsythe One-Way Analysis of Variance: F*, 2-tailed. Chi Square Test: $\chi 2$, 2-tailed. Note: *p (probability)* in bold ≤ .05 level.

McAnulty et al (2009) *Acta Paediatrica ;* 98:1920-1926.

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Neuropsychological Factors at 8 YCA
< 29wGA High-Risk; C=11; E=11

Factors	*P* Value
Factor 1: Verbal and Language Abilities	0.40
Factor 2: Visual and Spatial EF Abilities	**0.01**
Factor 3: Automatized Verbal Abilities	0.60
Factor 4: Perceptual Organization and Visual Memory	0.68
Factor 5: Verbal Expression and Memory	0.14
Factor 6: School Achievement	0.31

MANOVA, $F^* = 2.52$; $df = 6, 15$; $\mathbf{P < .05}$

MANOVA, multivariate analysis of variance; *df,* degrees of freedom.

McAnulty et al, (2010) *Clinical Pediatrics;*49(3): 258 -270.

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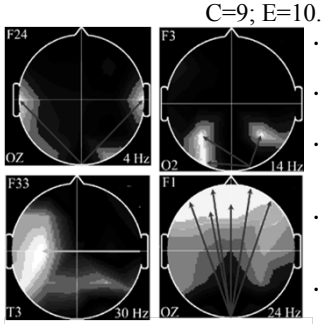
EEG Coherence Factors, <29wGA, at 8yCA.
C=9; E=10.



- Head in vertex view, nose above, left ear to left.
- Index electrode at lower left; frequency at lower right.
- Background color is loading on PCA: Blue=Decreased; Red-orange =Increased.
- Arrow color is E-group coherence: Green=decreased. Red=Increased;
- Index electrode at lower left; frequency lower right.

McAnulty et al, (2010) *Clinical Pediatrics;*49(3): 258 -270.

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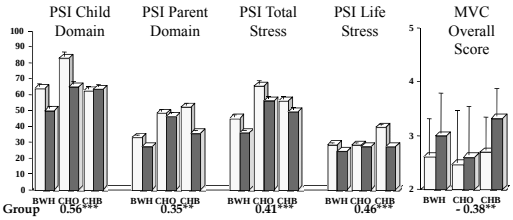
Family Outcome : *Parenting Stress Index (PSI)* and *Mother's View of the Child (MVC)* (n=77)
Very High Risk < 29wGA Preterm Infants at 2wCA

Control – Experimental : BWH 14-14; CHO 17-14; CHB 7-10



MANCOVA: Group: F=2.41; df=5,66; **p<.05.** Site: F=1.48; df=10,132; p<.15. G x S: F=0.57; df=10,132; p<.83 ; (* p<.05 ** p<.01 *** p<.001)

Als H, et al. A three-center randomized controlled trial of individualized developmental care for very low birth weight preterm infants. *J Dev Behav Pediatr.* 2003; 24(6):399-408.

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AGA Low-Risk Preterm-Born Infants (29-33wGA)
n = 30 (14 C; 16 E)
Newborn Period to Age Eight Years CA
Neurobehavior, EEG and MRI

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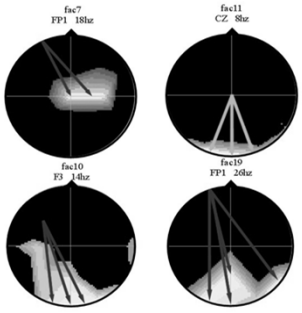
APIB System Scores 2wCA – AGA Preterm Infants (28-33wGA)

Variable	C (n = 14)	E (n = 16)	F*	*p*
Autonomic System	5.56 (1.41)	4.59 (1.26)	3.91	0.06
Motor System	6.29 (1.01)	4.70 (1.23)	15.02	**0.001**
State System	5.22 (1.34)	4.62 (0.90)	2.57	0.12
Attention System	6.91 (1.83)	6.54 (1.69)	0.32	0.58
Self-Regulation	6.11 (1.26)	4.94 (1.07)	7.31	**0.01**
Examiner Facilitation	6.89 (1.76)	5.74 (1.67)	3.37	0.08

Means (SD). Brown-Forsythe One-Way Analysis of Variance: F*, 2-tailed; $p \leq .05$ level.
Als et al, (2004) *Pediatrics;*113:846-857

Als, H. 2017

EEG Coherence Measures 2wCA AGA Preterm Infants



n=30
(14C; 16E)
29-33wGA
at Birth

Als et al (2004) *Pediatrics*; 113: 846-857

Wilks' Lambda=0.45; F=7.69; df=4,25; P = .0001
Coherence factor background: blue – negative / orange - positive;
Arrow Color E-Group: green - decreased / red - increased

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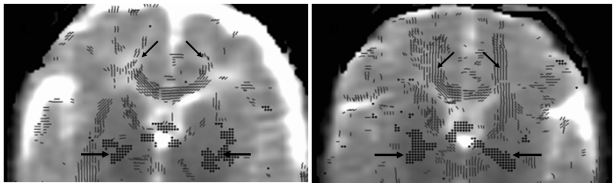
Diffusion Tensor Imaging at 2wCA
Low-Risk AGA Infants, 29-33wGA, n = 23 (8C; 15E)

Control Group Infant Experimental Group Infant



Anisotropy E1/E3 - Threshold ≥ 1.3
Black Arrows: Frontal White Matter
White Arrows: Internal Capsule, posterior limbs

Als et al (2004) *Pediatrics*; *113*:846-857

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Bayley Scales of Infant Development, 2nd Edition
Low-Risk AGA Infants, 28-33wGA, 9mCA

Variable	Control (n=13)	Experimental (n=11)	F*	*p*
MDI	94.85 (9.22)	109.55 (7.23)	19.14	0.0002
PDI	89.23 (14.88)	107.00 (9.28)	12.69	0.002
Orientation/Engagement	56.92 (27.97)	70.55 (21.62)	1.81	0.19
Emotional Regulation	39.31 (27.42)	66.91 (22.89)	7.22	0.01
Motor Quality	22.62 (21.57)	56.64 (31.05)	9.38	0.007
BRS Total Score	38.69 (23.04)	72.64 (16.13)	17.87	0.0004

MDI-Mental Developmental Index, PDI-Psychomotor Developmental Index, BRS-Behavior Rating Scales. Results: Means (SD); MDI, PDI: 100 (15). Brown-Forsythe One-Way Analysis of Variance: F*, 2-tailed. Chi Square Test: $\chi 2$, 2-tailed. Note: *p* (probability) in bold ≤ .05 level.
Als et al., (2004) *Pediatrics;*113:846-857

H. Als, 2017

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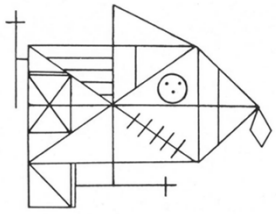
School Age (8-10yCA) Effectiveness of NIDCAP

Neuropsychological Functioning

Rey-Osterrieth Complex Figure



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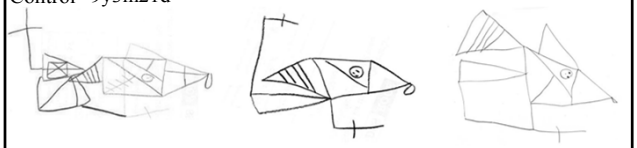
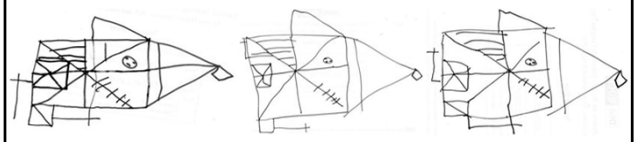
ROCFT: Copy Immediate Recall Delayed Recall

Control 9y3m21d



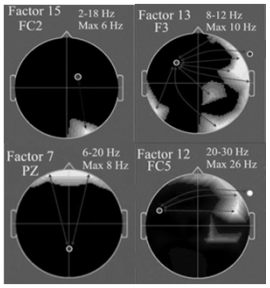
Experimental 8y4m22d



Low-Risk Preterm, 29-33wGA, School Age Outcome, H. Als, 2017
McAnulty et al. Journal of Clinical Neonatology, 2012; 1:184-194.

EEG Spectral Coherence, Low-Risk Preterms, 29-33wGA, at School Age

Control (8)
Experimental (15)



McAnulty et al. Journal of Clinical Neonatology, 2012; 1:184-194.

Head in vertex view, nose above, left ear to left.
Arrow color illustrates experimental group coherence:
green - decreased, red - increased.

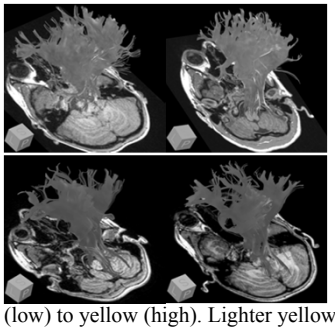
H. Als, 2017

Mean Diffusivity (MD) in Cortico-Spinal Tract - School Age

Low-Risk AGA
29-33wGA

Two Controls
L: 8y1m10d
R: 8y3m0d

Two Experimtls.
L: 8y3m21d
R: 9y6m20d



McAnulty et al Journal of Clinical Neonatology, 2012; 1:184-194.

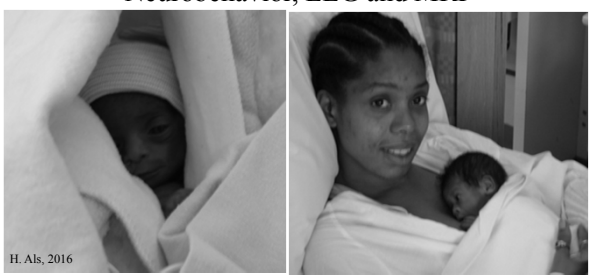
H. Als, 2017

Color code: red (low) to yellow (high). Lighter yellow and orange: higher measure of MD; darker orange and red: lower measure of MD

Severely IUGR High-Risk Preterm-Born Infants (29-33wGA) n = 30 (18 C; 12 E)

Newborn Period to Age Eight Years CA

Neurobehavior, EEG and MRI



H. Als, 2016

APIB System Scores 2wCA – IUGR Preterm Infants (*JPerinat*, 2011)

Variable	C (n = 18)	E (n = 12)	*p*
Autonomic System	6.86 (0.68)	5.54 (1.18)	**0.0003**
Motor System	6.93 (0.57)	5.89 (1.22)	**0.02**
State System	5.77 (1.33)	5.32 (0.59)	0.22
Attention System	7.61 (1.05)	7.36 (1.16)	0.55
Self-Regulation	6.90 (0.66)	6.01 (0.78)	**0.004**
Examiner Facilit.	7.81 (1.12)	6.79 (1.60)	0.07

MANOVA, F=5.95; *df=6,23*; *p*=0.0007. Brown-Forsythe ANOVA: F*.
p = probability, two-tailed. (Higher scores, poorer perfomance.)

H. Als, 2016

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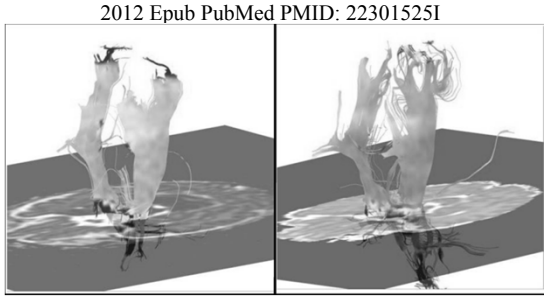
IUGR Preterm Infants (Study 2), J. Perinatology, 2012 Epub PubMed PMID: 22301525I



Control Infant | Experimental Infant

Mean diffusivity (MD) in corticospinal tract (internal capsule) at 42 wks PMA. Color coded from Red (Low MD → More mature fiber tracts) to Yellow (High MD → Less mature fiber tracts).

H. Als, 2016

Bayley Scales-II, IUGR, 9mCA (*JPerinat*, 2011)

Variable	Control (n = 18)	Experimental (n = 12)	*p*
MDI	90.06 (11.33)	102.83 (10.99)	**0.005**
< Mean - ≥ Mean	16 - 2	5 - 7	**0.01**[a]
PDI	82.48 (20.56)	92.25 (20.33)	0.21
< Mean - ≥ Mean	14 / 4	5 / 7	0.06[a]
BRS Total Score	21.26 (19.95)	34.08 (25.63)	0.17
WNL/Question./Non-Opt.	3 / 10 / 5	7 / 1 / 4	**0.02**[b]

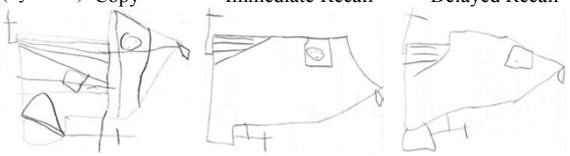
MDI, PDI and BRS Total Score, MANOVA, F = 3.11, df = 3,26, $p = 0.04$.
Brown-Forsythe ANOVA: F*; [a]Fisher Exact Test; [b]Pearson's Chi Square Test: $\chi 2$
p = probability, two-tailed.

H. Als, 2016, IUGR

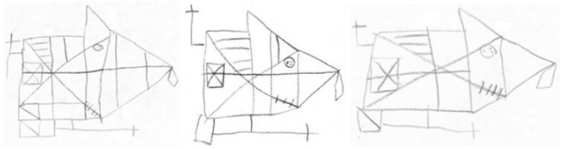
IUGR Preterm, 29-33wGA, School Age Outcome

ROCFT: Control (9y6m1d) Copy | Immediate Recall | Delayed Recall

McAnulty, et al. BMC Pediatrics, 2013; 13:25. PMID 23421857



Experimental (9y10m18d)



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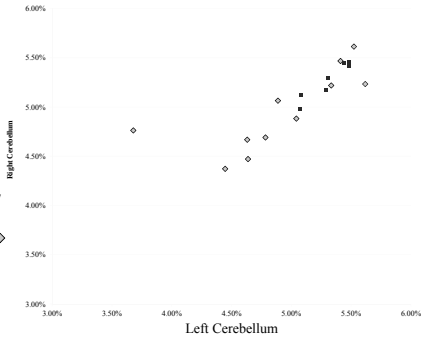
Cerebellar Volume as Percent of Parenchyma

School Age IUGR Preterms 29-33wGA

McAnulty, et al. BMC Pediatrics, 2013; 13:25. PMID 23421857

Control (11) ◇

Experimental (7) ■



H. Als, 2016

NIDCAP – Promise to Protect the Developing Brain

- Enhancement in experience mediated calmness and comfort (Protection of the NMDA *N-methyl-d-aspartate* axis, reduced toxic glutamate and free radical release, cell death).
- Assurance of steady blood flow (fewer hypoxemic events; reduction in intraventricular hemorrhage).
- Enhanced intimate contact and parenting (protective hormonal release – oxytocin) - enhanced social-emotional development.
- Assurance of darkness (enhanced melatonin release) – enhanced sleep and cognitive development.

H. Als, 2017

System-Wide Paradigm Shift, Culture Change, and Professional Role Transformation

Accountability and Excellence in the Care of

The Infant

The Family

The Staff & Professionals

The Environment.

NIDCAP Nursery Assessment and Certification Program (NNACP)
NFI - 2011

H. Als, 2017

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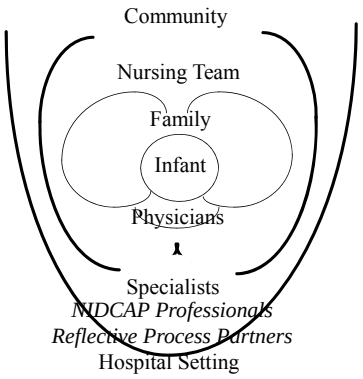
System Change - NIDCAP Developmental Care Model



H. Als, 2017

Summary Thoughts

Photo, I. Warren, with permission.

- One brain for life – all experience matters. *(Claudine Amiel-Tison)*
- It matters how we listen to the voice of each newborn and how we care for each newborn and each family.
- It matters how we care for one another and for ourselves.

H. Als, 20167

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