School Age Effects of the Newborn Individualized Developmental Care and Assessment Program for Medically Low-Risk Preterm Infants: Preliminary Findings

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ABSTRACT

Background: By school-age, even low-risk moderately preterm-born children show more neuro-cognitive deficits, motor impairments, academic underachievement, behavioral problems, and poor social adaptation than full-term peers. **Aim:** To evaluate the outcomes at school-age for moderately preterm-born children (29-33 weeks gestational age), appropriate in growth for gestational age (AGA) and medically at low-risk, randomized to Newborn Individualized Developmental Care and Assessment Program (NIDCAP) or standard care in the Newborn Intensive Care Unit. At school-age, the experimental (E) group will show better neuropsychological and neuro-electrophysiological function, as well as improved brain structure than the control (C) group. **Materials and Methods:** The original sample consisted of 30 moderately preterm-born infants (29 to 33 weeks), 23 (8C and 15E) of them were evaluated at 8 years of age, corrected-for-prematurity with neuropsychological, EEG spectral coherence, and diffusion tensor magnetic resonance imaging (DT-MRI) measures. **Results:** E-performed significantly better than C-group children on the Kaufman Assessment Battery for Children-Second Edition (KABC-II) and trended towards better scores on the Rey-Osterrieth Complex Figure Test. They also showed more mature frontal and parietal brain connectivities, and more mature fiber tracts involving the internal capsule and the cingulum. Neurobehavioral results in the newborn period successfully predicted neuropsychological functioning at 8 years corrected age. **Conclusion:** Moderately preterm infants cared for with the NIDCAP intervention showed improved neuropsychological and neuro-electrophysiological function as well as improved brain structure at school-age.

Key words:
Diffusion tensor magnetic resonance imaging, electroencephalogram, neuropsychological function, newborn individualized developmental care and assessment program, prematurity, school-age, spectral coherence

INTRODUCTION

Preterm compared to full-term children perform more poorly in working memory, planning, visual spatial organization, and mental flexibility,[1,2] and are over-represented among early intervention and special education service recipients.[3] Early brain-based differences[4,5] contribute to long-term disabilities. Poor executive function appears related to basal ganglia/cerebellar volume reduction and sub-cortical white matter circuit disruptions between frontal, striatal, and thalamic regions.[6,7] Cumulative effects of medical complications[8] are compounded by the Newborn Intensive Care Unit (NICU) experience (exposure to bright lights, heightened sound, frequent interventions), which alters brain development.[9-11] The Newborn Individualized Developmental Care and Assessment Program (NIDCAP)[12] provides a system of NICU care and environmental structure that supports preterm infants' early brain development. Several randomized, controlled NIDCAP trials reported significant neurobehavioral and neuro-electrophysiological improvement for high-risk preterm infants.[13-20] School-age follow-up studies[21,22] showed continued significant neurodevelopmental improvement. The current study tests NIDCAP-effectiveness into school-age for medically low-risk, appropriate for gestational age (AGA), moderately preterm infants and evaluates prediction by

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newborn-period neurobehavioral measures of school-age neuropsychological performance.

MATERIALS AND METHODS

Study design and ethics

Children born preterm, who had been studied in-NICU during a randomized control trial[23] (control-C and experimental-E), were assessed in follow-up at 8 years (y) of age corrected-for-prematurity (CA). The study protocol was approved by the hospital's Institutional Review Board for Research with Human Subjects. All school-age assessment personnel (neuropsychology, interviews, EEG, and MRI) were kept blind to original subject group assignments.

Subjects

The original sample[23] consisted of 30 study infants (14C; 16E), recruited from the 46-bed level-III NICU, with an inborn population at a large urban tertiary care center. Family selection criteria included: Maternal age >14 years; no major medical or psychiatric illness, chronic medication treatment, and/or history of substance abuse; telephone accessibility; and English-language facility. Infant criteria included: Gestational birth-age 28 weeks 4 days (d) to 33 weeks 3 days; 5-minute Apgar >7; at birth AGA (5^{th}-95^{th} percentile)[24] in weight and head circumference; normal initial cranial ultrasound (s), MRI, and/or electroencephalogram (EEG); <72 hours ventilator and/or vasopressor support; prenatal care; absence of congenital/chromosomal abnormalities, congenital/acquired infections, prenatal brain lesions, and seizures. Of the 30 subjects, 23 (8C; 15E) returned at school-age [Figure 1].

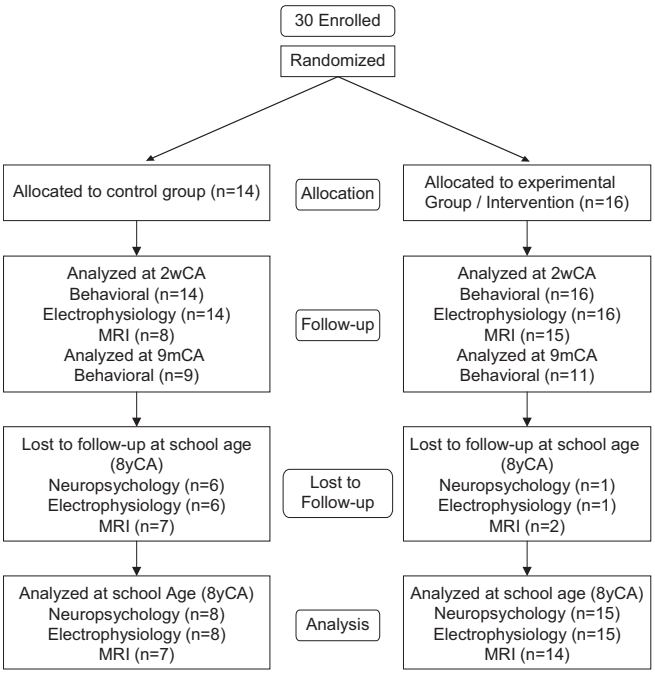

Figure 1: Consort chart

Summary of newborn intervention and study results

E-infants received NIDCAP[12] from NICU-admission to 2 weeks corrected age. C-group care was the study NICU's standard care. At 2 weeks corrected age, E-infants showed significantly better neurobehavioral functioning (Assessment of Preterm Infants' Behavior-APIB[25]), increased brain functionality (EEG) with increased frontal to occipital brain connectivities,[4] and improved brain structure (MRI) with more mature internal capsule and frontal white matter fiber tracts. The relationship among neurobehavior, EEG, and MRI was significant. Nine-months corrected age E-group neurodevelopmental functioning (Bayley Scales of Infant Development, Second Edition[26]) was significantly improved.

Primary and secondary school-age hypotheses

Significant E-group-favoring effects were hypothesized for visual-spatial planning, executive function and working memory, spectral coherence increase between long-distance bi-hemispheric frontal and parietal brain system, and improved fiber tract development in internal capsule and optic radiations. Significant relationships were hypothesized among school-age neuropsychological function, spectral coherence, and diffusion-tensor magnetic-resonance-imaging, and between newborn neurobehavioral and school-age neuropsychological function.

Sample description

Newborn background information was compared between the children who returned for school-age follow-up and those who did not. Newborn background information was also compared between returning school-age C-and E-group children. School-age anthropometric, medical, and academic history indices were measured or obtained by parent interview.[27] Parent-IQ, reportedly correlating with child functioning,[28] was measured with the Kaufman Brief Intelligence Test, Second Edition (KBIT-2),[29] yielding a Verbal IQ, Non-Verbal IQ, and Mental Processing Composite (Mean-*x*: 100; standard deviation-SD: 15). Should parent-IQ, hypothesized to be comparable between groups, correlate with child-IQ, all outcome measures would be corrected for parent-IQ.

School-age neurodevelopmental outcomes

Neuropsychological measures

The small sample size necessitated limited neuropsychological assessment. An experienced neuropsychologist performed the Kaufman Assessment Battery for Children, Second Edition (KABC-II)[30] yielding a Mental Processing Composite Index (x=100; SD=15),

four Scale Indexes, (Sequential, Simultaneous, Planning, Learning), and two language subscales (Expressive Vocabulary, Verbal Knowledge); the Woodcock-Johnson III Tests of Achievement (WJIII)[31] with two Standard Cluster Scores (x=100; SD=15) (Broad Reading-Letter/Word Identification, Reading Fluency, Passage Comprehension; Academic Skills-Letter/Word Identification, Calculation, Spelling); and the Rey-Osterrieth Complex Figure Test (Rey),[32-34] Copy, Immediate Recall and Delayed (20 minutes) Recall conditions assessing gestalt integration, executive function, spatial planning, and memory. The Rey Developmental Scoring System[35,36] yields per condition 3 mutually exclusive scores, Organization; Structural Elements Accuracy; and Incidental Elements Accuracy.

Neurophysiological measures

EEG and MRI studies were conducted within 1 week of neuropsychological testing. A pediatric EEG-technologist collected thirty-two-channel EEG at a 256 Hz sampling rate (with 1-50 Hz bandpass filtering with 60 Hz mains filter) for 12 minutes of Eyes Closed alert state EEG. Paroxysmal eye, muscle, and body movements were visually identified and excluded. Figure 2 shows standard EEG electrode names and positions [Figure 2]. Analysis used the Laplacian reference-electrode-free format, sensitive to underlying cortex and insensitive to deep/remote EEG sources.[37] Residual eye blink/movement artifacts were removed with source component techniques.[38,39] (BESA™ software package). Spectral analysis, including

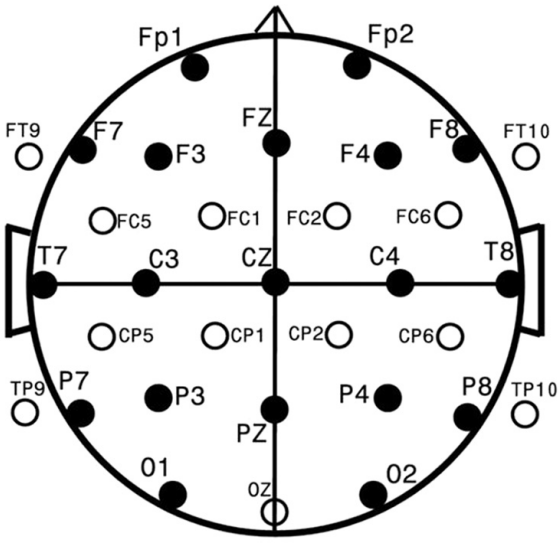

Figure 2: Standard EEG electrode names and positions. Head in vertex view, nose above, left ear to left. EEG electrodes: Z: Midline: FZ: Midline Frontal; CZ: Midline Central; PZ: Midline parietal; OZ: Midline occipital. Even numbers, right hemisphere locations; odd numbers, left hemisphere locations: Fp: Frontopolar; F: Frontal; C: Central; T: Temporal; P: Parietal; O: Occipital. The standard 19, 10-20 electrodes are shown as black circles. An additional subset of 17, 10-10 electrodes are shown as open circles

spectral coherence calculation,[40] was performed (Nicolet™ software package). Two Hz/data point (16 points/32 Hz) spectral resolution for 32 channels yielded 7936 individual coherence variables. Remaining low amplitude, artifactual contributions were removed by multivariate regression analysis,[41] utilizing signals proportional to known artifact sources. Coherence variable number was reduced by using in-house-developed[42] principal components analysis software suited to factoring large asymmetrical matrices. Forty coherence factors, previously created on an independent age-comparable normative sample (n=219) and reflecting 48% of total coherence variance,[43,44] were formed on the current school-age subjects utilizing the previous principal-components-analysis-generated rule. Given the sample size, the first 20 factors were utilized in the subsequent analyzes.

Neurostructural measures

Diffusion-tensor-MRI evaluated underlying brain structure by quantitative assessment of brain connectivity to delineate relevant white matter pathways and measure myelination and axon integrity parameters. Data were acquired at 3Tesla (Siemens Tim Trio, Siemens, Erlangen, Germany) with an MR imager using a 32-channel head coil. High spatial resolution echo-planar diffusion-weighted images were acquired (24 cm FOV, matrix 128 × 128, 2 mm thick contiguous slices). Geometric distortion from magnetic susceptibility differences was minimized with a short echo time (TE=78 ms) and parallel imaging (iPAT 2). Thirty b=1000 s/mm² images were acquired at directions evenly spaced on the sphere along with 5 baseline (b=0) images. Diffusion tensors were reconstructed, and 5 major fiber pathways were identified with a previously validated automated procedure.[45] Summary diffusion scalar measures of mean diffusivity, axial diffusivity, radial diffusivity, and fractional anisotropy were averaged in a streamline-density-weighted fashion.[46] along 5 major pathways: Arcuate Fasciculus (connecting posterior brain areas with Broca's area involved in complex language processing[47]); Corpus Callosum (thick white nerve band deep within the brain connecting the two hemispheres, supporting their communication and activity coordination); Cingulum (tracts receiving inputs from thalamus and neocortex; projecting to the entorhinal cortex; integral to limbic system; involving emotion, learning, memory, and executive function); Internal Capsule (massive white matter layer, major route inter-connecting cerebral cortex with brainstem and spinal cord); and Optic Radiations (axons carrying visual information from lateral geniculate nucleus relay neurons of thalamus to visual cortex). Children were scanned unsedated, awake, watching a cartoon or movie. Broad language processing tracts (arcuate fasciculus)[48] and early-developing basic hemispheres-connecting structures

were thought to be least affected by NIDCAP; cingulum, internal capsule, and optic radiations related to memory, executive function, and visual-motor processing were hypothesized to be improved for E-children.

Data analysis

The Biomedical Data Package 2007™ (BMDP)[49] supported statistical analyzes. Continuous variables were submitted to univariate analysis of variance (ANOVA) (BMDP-7D).[50] In cases of unequal variance, the Browne-Forsythe test of variance (F*) was used. Categorical variables were submitted to Fisher's exact probability test (FET) for 2 × 2, and Pearson's Chi-square (χ^2) test for all other multiple row by column arrays.[49,51] Two-tailed values of $P<0.05$ were considered statistically significant. Sample sizes provided 80% power to detect large between-group-effects, generally effect sizes >1.0.[52] Analyzes included stepwise discriminant analysis (BMDP-7M) for the neuropsychological, electrophysiological, and neurostructural domains; Wilks' lambda[53] and jack-knifed[54,55] classification for ascertainment of two-group classification success per domain and across domains; canonical correlation analysis (BMDP-6M) to explore relationships among the neuropsychological, electrophysiological, and neurostructural domains at school-age, and between newborn and school-age neurobehavioral domains.

RESULTS

Sample

Newborn background for subjects with versus without school age follow-up

The subjects who returned for school-age follow-up were sicker at birth than those who did not return [Table 1].[56-59] Moreover, the school-age E-group had significantly lower 5-minute Apgar scores than the C-group [Table 2].[56-59] This biased results against the E-group.

School-age background including parent IQ

C-and E-school-age groups were comparable in age-at-testing, parent-IQ,[29] and anthropometric, medical, and demographic characteristics. E-children's head circumferences were somewhat larger [Table 3]. Parent Mental Processing Composite and non-verbal IQ[29] correlated significantly with Child Simultaneous Processing[30] (r=0.4309, P=0.05; r=0.4231, P=0.05,

Table 1: Anthropometric, medical, and demographic background variables, participating vs. lost to follow-up subjects*

Variable	Returned n=23	Non-return n=7	P
Gestational age at birth	31.31 (1.46)	32.14 (1.26)	0.168
Birthweight (g)	1623 (243)	1891 (354)	0.098
Birthweight (%)	38.96 (19.63)	48.29 (19.55)	0.259
Head circumference (cm)	28.85 (1.54)	29.64 (1.71)	0.303
Head circumference (%)	42.96 (25.38)	44.29 (25.34)	0.905
Apgar ratings: 1 minute	7.09 (1.16)	7.29 (2.06)	0.814
Apgar ratings: 5 minutes	8.00 (0.74)	8.71 (0.49)	0.01
Days on oxygen, no.	11.30 (19.18)	2.00 (4.00)	0.039
SNAPPE-II†‖[56]	8.09 (11.29)	0.00 (0.00)	0.003
NTISS[57]	13.04 (5.61)	9.86 (4.02)	0.119
Obstetric complications scale[58]	63.65 (9.95)	79.29 (16.53)	0.049
Mother's age (years)	33.35 (6.13)	27.71 (6.47)	0.068
Prenatal corticosteroids, yes/no†	17/5	4/0	0.555
Vaginal deliveries, yes/no†	6/17	4/3	0.181
Patent ductus arteriosus, yes/no†	3/20	0/7	1.00
Surfactant, yes/no†	8/14	1/3	1.00
Gender, no. males/females†	14/9	5/2	1.00
Caucasian, black, hispan, others‡	19/2/0/2	4/1/1/1	0.253
Firstborn, laterborn, no†	13/10	4/3	1.00
Socio-economic status (I and II; III; IV and V)[59]‡	17/5/1	4/2/1	0.572
Parents married/attached, yes/no†	23/0	7/0	–
Umbilical flow (reversed/absent/normal)‡	0/0/23	0/0/7	–

Results are means and (standard deviations) unless otherwise noted. Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F, †Fisher's exact test, ‡‖Student's *t*-test and †Pearson's Chi square: χ^2. P=Probability. All probabilities are two-tailed

Table 2: Anthropometric, medical, and demographic background variables, children seen at follow-up, control vs. experimental group*

Variable	Control n=8	Experimental n=15	P
Gestational age at birth	31.39 (1.61)	31.27 (1.43)	0.854
Birthweight (g)	1571 (258)	1650 (239)	0.485
Birthweight (%)	29.50 (20.09)	44.00 (18.05)	0.112
Head circumference (cm)	28.69 (1.69)	28.93 (1.51)	0.746
Head circumference (%)	36.25 (20.66)	46.53 (27.56)	0.327
Apgar ratings: 1 minute	7.38 (1.30)	6.93 (1.10)	0.432
Apgar ratings: 5 minutes	8.38 (0.52)	7.80 (0.78)	0.047
Days on oxygen, no.	9.38 (15.79)	12.33 (21.22)	0.710
SNAPPE-II[56]	4.29 (6.24)	9.87 (12.81)	0.185
NTISS[57]	12.00 (3.02)	13.60 (6.63)	0.437
Obstetric complications scale[58]	61.75 (8.07)	64.67 (10.95)	0.477
Mother's age (years)	34.25 (5.70)	32.87 (6.49)	0.605
Prenatal corticosteroids, yes/no†	7/0	10/5	0.135
Vaginal deliveries, yes/no†	1/7	5/10	0.369
Patent ductus arteriosus, yes/no†	1/7	2/13	1.00
Surfactant, yes/no†	4/3	4/11	0.343
Gender, no. males/females†	5/3	9/6	1.00
Caucasian, black, hispan, others‡	5/2/0/1	14/0/0/1	0.103
Firstborn, laterborn, no†	4/4	9/6	0.685
Socioeconomic status (I and II; III; IV and V)[59]‡	6/2/0	11/3/1	0.743
Parents married/attached, yes/no†	8/0	15/0	–
Umbilical flow (reversed/absent/normal)‡	0/0/4	0/0/1	–

Results are means and (standard deviations) unless otherwise noted. Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F, †Fisher's exact test, and †Pearson's Chi square: χ^2. P=Probability. All probabilities are two-tailed

respectively). Therefore, all outcome measures were residualized by partial correlation and multivariate regression analysis (BMDP-6M) for Parent IQ.

Neurodevelopmental school-age outcome

Neuropsychological results

All subjects (8C; 15E) completed neuropsychological testing. E-performed significantly better than the C-children on KABC-II Composite Index Simultaneous Processing and on subtest Rover; subtest Triangles showed a trend [Table 4]. Both subtests assess planning, decision-making, executive function, and visual-spatial processing. The groups performed comparably on the WJ-III Broad Reading and Academic Skill Clusters [Table 5], as well as on the 9 Rey scores. However, on the Rey, Basal Level and Organization (Immediate Recall), along with Incidental Accuracy (Delayed Recall), showed a trend towards favoring E-over C-children [Table 6], indicating that E-children showed somewhat better overall gestalt integration, visual-motor planning, visual gestalt and detail memory, and executive function. Figure 3 shows a C-and an E-child's sample drawings. The KABC-II Simultaneous Processing and Rey differences are reminiscent of the earlier school-age study results for high-risk preterms[22] and the poorer

Table 3: Anthropometric, medical, and demographic variables at time of evaluation*

Variable	Control (C) (*n*=8)	Experimental (E) (*n*=15)	*P*
Metric			
Weight, kg	30.41 (8.44)	30.23 (5.67)	0.958
Height, cm	132.31 (7.39)	134.44 (7.59)	0.524
Head circumference, cm	52.63 (0.88)	53.37 (0.95)	0.079
Percentiles			
Weight percentile	65.88 (30.01)	70.93 (20.49)	0.678
Height percentile	63.63 (25.87)	80.27 (19.05)	0.186
Head circumference percentile	57.63 (18.76)	73.60 (18.24)	0.070
Age at testing, years	8.42 (0.84)	8.41 (0.97)	0.967
Mother's IQ			
Verbal	105.00 (13.73)	106.57 (15.43)	0.805
Non-verbal	105.88 (15.26)	112.36 (13.18)	0.328
Composite	106.00 (14.01)	109.93 (11.01)	0.505
Gender: Male/Female	5/3	9/6	1.00†
Handedness	7/0/1	13/0/2	1.00†
Special school services, yes/no	3/5	10/5	0.221†
Disability diagnoses, yes/no	3/5	4/11	0.657†
Hearing loss, yes/no	1/7	0/15	0.348†
Mother's education level (HS/College/Grad)	2/5/1	2/8/5	0.508‡
Income (<50 K/50-75 K/>75 K)	2/0/5	2/1/12	0.571‡
Ethnicity (Caucasian/Black/Hispan/Other)	5/2/0/1	14/0/0/1	0.103‡

Results are means and (standard deviations) unless otherwise noted. Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F, †Fisher's exact test, and ‡Pearson's Chi square: χ^2. *P*=Probability

Table 4: Kaufman assessment battery for children, second edition

Variable	Control (*n*=8)	Experimental (*n*=15)	*P*
Index scores (mean=100, sd=15)			
Mental processing index	108.02 (19.36)	117.19 (11.96)	0.250
Simultaneous processing	99.99 (13.98)	116.94 (11.04)	0.012
Sequential processing	99.29 (14.77)	106.65 (13.88)	0.265
Planning ability	110.22 (19.31)	115.29 (14.12)	0.520
Learning ability	113.43 (14.37)	111.30 (12.45)	0.729
Subtests (scaled score: Mean=10, sd=3)			
Number recall	9.64 (2.90)	10.66 (2.16)	0.400
Word order	10.09 (2.31)	11.55 (2.84)	0.202
Story completion	12.06 (3.01)	12.57 (1.89)	0.678
Pattern reasoning	11.32 (3.24)	12.63 (2.89)	0.354
Atlantis	13.63 (2.40)	12.73 (2.48)	0.411
Rebus	11.08 (2.64)	11.23 (2.26)	0.893
Rover	9.11 (2.59)	12.34 (2.12)	0.011
Triangles	10.83 (3.10)	13.02 (3.01)	0.125
Expressive vocabulary	12.11 (3.14)	12.41 (2.90)	0.831
Verbal knowledge	12.80 (1.82)	13.57 (2.37)	0.397

Results are means (SD). Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F*, two-tailed. *P*=Probability

Table 5: Woodcock-Johnson III

Variable	Control (*n*=8)	Experimental (*n*=15)	*P*
Word identification	111.15 (8.92)	107.39 (8.72)	0.395
Reading fluency	106.34 (15.03)	107.03 (16.14)	0.827
Math calculation	101.77 (8.50)	104.99 (6.68)	0.365
Spelling	109.17 (9.06)	107.38 (11.88)	0.626
Passage comprehension	107.31 (8.73)	104.90 (7.94)	0.745
Broad reading	109.95 (12.30)	107.76 (11.85)	0.798
Academic skills	110.09 (7.99)	107.75 (9.18)	0.602

Results are means (SD). Mean=100; standard deviation 15. Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F* two-tailed

Table 6: Rey-Osterrieth complex figure test

Variable	Control (*n*=8)	Experimental (*n*=15)	*P*
Copy basal level	1.90 (0.90)	1.86 (0.76)	0.916
Copy organization score	4.31 (2.05)	4.97 (2.06)	0.478
Copy structural accuracy score	22.36 (2.98)	22.41 (3.13)	0.967
Copy incidental accuracy score	35.78 (3.87)	34.85 (6.25)	0.667
Immediate recall basal level	1.49 (0.70)	2.00 (0.91)	0.152
Immediate recall organization score	3.30 (1.95)	4.71 (2.61)	0.159
Immediate recall structural accuracy score	16.09 (5.19)	17.82 (3.84)	0.424
Immediate recall incidental accuracy score	24.34 (5.47)	26.75 (6.15)	0.348
Delayed recall basal level	1.51 (0.68)	1.59 (0.76)	0.794
Delayed recall organization score	3.12 (1.78)	3.53 (2.33)	0.642
Delayed recall structural accuracy score	15.04 (4.79)	17.58 (4.52)	0.237
Delayed recall incidental accuracy score	24.41 (5.33)	28.04 (5.86)	0.152

Results are means (SD). Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F*, two-tailed. *P*=Probability

visual-spatial planning, executive and memory functions reported for preterms without intervention.[60,61]

Discriminant analysis (10 KABC-II, 7 WJ-III subtests, 9 Rey-measures) identified 3 KABC-II (Rover, Atlantis, and Triangles) and 2 Rey (Organization/Immediate and Delayed Recall) measures that showed significant C-from E-group differentiation [Table 7]. Misclassified were 2 C-and 3 E-subjects.

Neurophysiological results

All school-age subjects completed neurophysiological assessment. Coherence-Factor-15 showed significantly decreased E-over C-group connectivity (P=0.001) between the right medial posterior frontal and right occipital regions from 2-18 Hz. This suggests release of frontal-associative cortex from overly-restricted visual-motor integration, freeing it for higher level functions. Factor-13 showed a trend towards significant group difference (P=0.112) [Figure 4]. Factor-13 (8-12 Hz, i.e., alpha), a broad, long-distance, and interhemispheric set of connectivities, demonstrated strong E-over C-group enhancement of left frontal lobe (typically dominant in motor and sensory processing functions) connectivity with multiple distant regions, especially in the contra-lateral hemisphere, suggesting better information and processing flow to and from left frontal lobe, indicative of better visual-spatial and broad high level judgment, planning, and executive control functions.

Discriminant analysis identified 3 coherence factors [Figure 4] significantly differentiating C-from E-children [Table 8]. Jackknifed classification success utilizing the 3 factors showed 91.3% correct subject classification.[54,55] The factors included Coherence-Factor-7, increased for the E-subjects, a long distance bi-hemispheric factor (6-20 Hz) connecting parietal-associative regions with bilateral prefrontal cortex, consistent with more mature prefrontal cortex connectivities underlying organization, planning and executive function; Factor-12, (20-30 Hz), involving, similar to Factor-13, E-group connectivity increase of left lateral-frontal

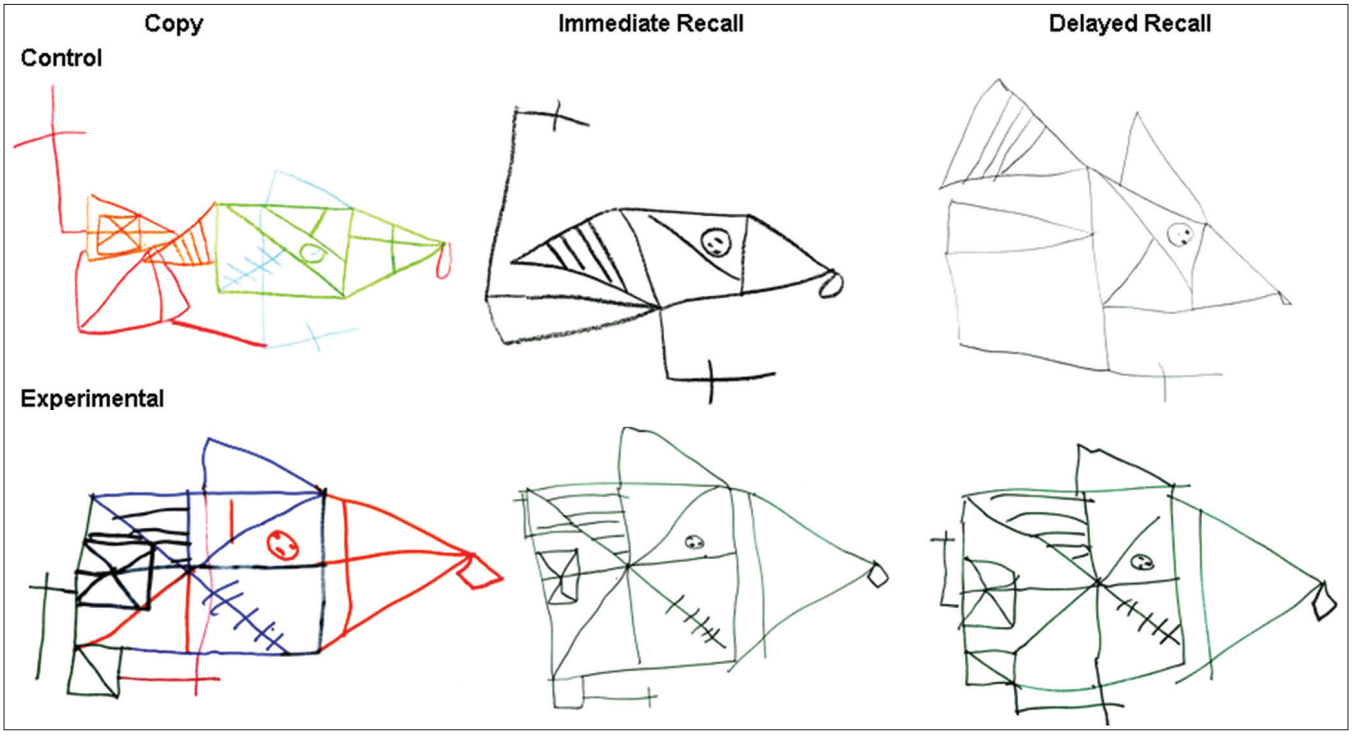

Figure 3: Rey-Osterrieth complex figure. The figure represents sample drawings from 2 study children, 1 from the Control group, a 9 year 3 month old born at 31 w 1 d GA; and 1 from the Experimental group, a 8 year 4 month old born at 31 w 4 d GA. The conditions displayed are from left to right: Copy, Immediate Recall, and Delayed Recall

Table 7: Discriminant function analysis of neuropsychological measures

Jackknifed classification matrix KABC-II Rover, KABC-II Atlantis, KABC-II Triangles, Rey-Osterrieth-Immediate Recall Organization, Rey-Osterrieth-Delayed Recall Organization	Correct classification (%)	Control (n=8)	Experimental (n=15)
Control (C) group	75.0	6	2
Experimental (E) group	80.0	3	12
Total	78.3	9	14

Wilks' lambda=0.4238; df=5,17; F=4.62; P=0.008

Table 8: Discriminant function analysis of EEG coherence factors

Jackknifed classification matrix coherence factors 7, 12, 15	Correct classification (%)	Control (n=8)	Experimental (n=15)
Control (C) group	75.0	6	2
Experimental (E) group	100.0	0	15
Total	91.3	6	17

Wilks' lambda=0.3420; df=3,19; F=12.19; P=0.0001

regions to homologous, broader, right lateral-frontal and anterior-temporal regions, likely sub-serving working memory; and again Factor-15, as interpreted above. These factors misclassified only 2 C-subjects.

Overall, the successful group-discriminating factors highlighted two increased bi-hemispheric, connectivities from left frontal to broad temporal and parietal regions and one decreased connectivity, freeing up frontal system function, mirroring earlier results.[22,23,62] NIDCAP, for this population, appears to have increased connectivities strongly supportive of broad executive and complex planning functions as well as of working memory.

Brain structural results

Twenty-one (7 C; 14 E) subjects completed MRI study. For internal capsule and optic radiation, as hypothesized, E-showed a significantly stronger trend towards lower diffusivity (mean and radial diffusivity) than C-children. Internal capsule, axial diffusivity was also lower. The cingulum also showed significantly lower E-than C-group mean and radial diffusivity and a trend towards lower axial diffusivity; and the arcuate fasciculus showed a trend towards lower mean and radial diffusivity [Table 9]. Higher E-than C-group fractional anisotropy was observed only at the trend level for the cingulum. Other structures differed in the direction favorable to the E-group. Marginal fractional anisotropy findings were possibly due to the small sample [Table 10 and Figure 5].

Discriminant function analysis accessing all 20 diffusion-tensor-MRI variables identified 3 measures, corpus callosum radial diffusivity, cingulum fractional anisotropy, and internal capsule radial diffusivity, which significantly differentiated C-from E-children [Table 11]. Two C-and 2 E-subjects were misclassified. Despite reduced sample, diffusion-tensor-MRI successfully differentiated the groups.

Classification success utilizing all three neurodevelopment domains

When examining the relative group classification power of the 3 neurodevelopmental domains, discriminant analysis identified 2 coherence factors (15, 12) and 3 neuropsychological variables including KABC-II Triangles (measuring planning, decision-making,

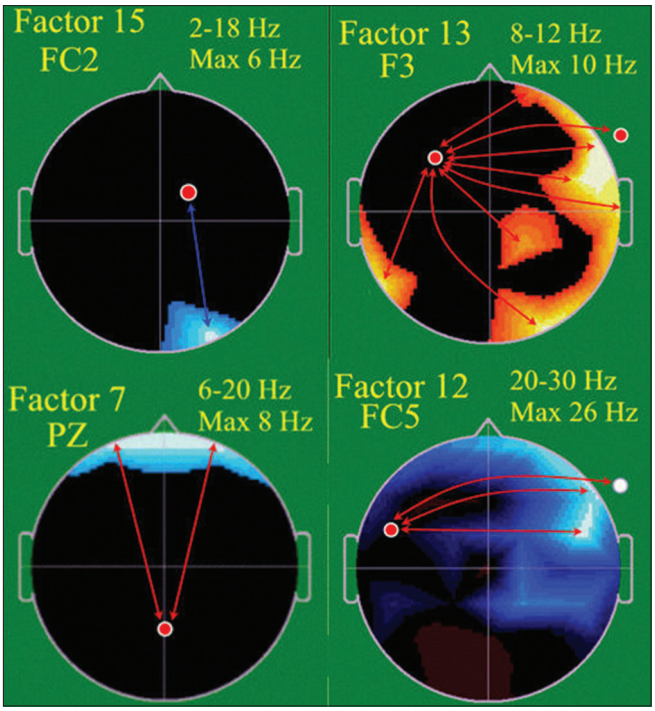

Figure 4: EEG Spectral coherence factors at school age, Control (C) (n = 8), Experimental (E) (n = 15). Head shown in vertex view, nose above, left ear to left. EEG frequency and coherence electrodes shown above head. Arrow color illustrates experimental group coherence; green = decreased, red = increased

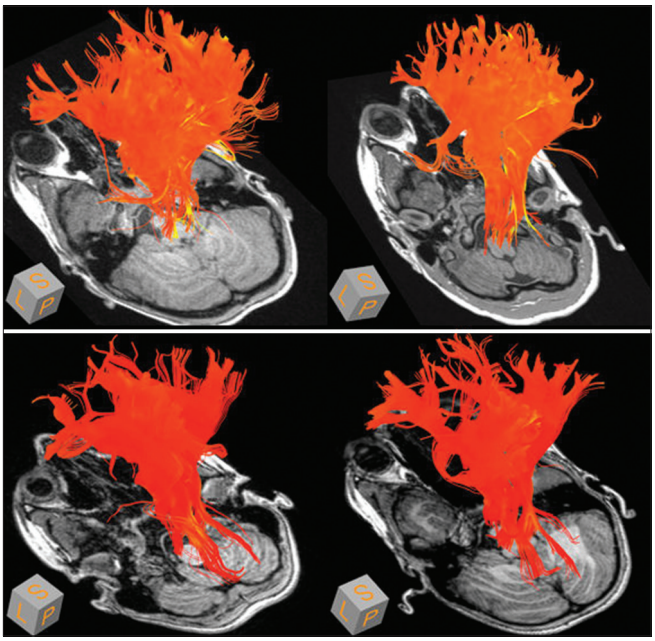

Figure 5: Mean diffusivity in cortico-spinal tract (internal capsule) at 8 years. Control children, top row, experimental children, bottom row. Mean diffusivity rendered onto trajectories of the cortico-spinal tract, and color coded from red (low) to yellow (high). (Yellow and brighter orange: Higher measure of mean diffusivity; darker orange and red: Lower measure of mean diffusivity

Table 9: Diffusion tensor magnetic resonance imaging, diffusivity measures (C=7; E=14)

Region/structure	Mean diffusivity			Radial diffusivity			Axial diffusivity		
	C	E	*P*	C	E	*P*	C	E	*P*
Arcuate fasciculus	0.80611 (0.02728)	0.76375 (0.07771)	0.084	0.63155 (0.03007)	0.59156 (0.06166)	0.060	1.15520 (0.05335)	1.10811 (0.11392)	0.213
Corpus callosum	0.88534 (0.04024)	0.85136 (0.11945)	0.349	0.63606 (0.05445)	0.60964 (0.08700)	0.406	1.38391 (0.05366)	1.33481 (0.18768)	0.377
Cingulum	0.85688 (0.05646)	0.79280 (0.08366)	0.054	0.68937 (0.05043)	0.63069 (0.06417)	0.037	1.19192 (0.07194)	1.11703 (0.12390)	0.098
Internal capsule	0.82637 (0.05426)	0.75758 (0.09043)	0.044	0.62717 (0.06232)	0.56541 (0.06299)	0.054	1.22477 (0.04196)	1.14191 (0.15091)	0.074
Optic radiation	0.89192 (0.03702)	0.83721 (0.11442)	0.122	0.67495 (0.03385)	0.62551 (0.07852)	0.059	1.32584 (0.05666)	1.26062 (0.18755)	0.248

Control (C), Experimental (E). Results are means and (standard deviations). Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F*, two-tailed. *P*=Probability

Table 10: Diffusion tensor magnetic resonance imaging factors for fractional anisotropy, (C=7; E=14)

Region	Fractional anisotropy		
	C	E	*P*
Arcuate fasciculus	388.07959 (29.38460)	398.08455 (19.93337)	0.437
Corpus callosum	464.41046 (41.35731)	470.11942 (16.56078)	0.736
Cingulum	349.31719 (15.35546)	362.83961 (14.71934)	0.078
Internal capsule	413.64815 (36.79636)	429.87629 (27.24274)	0.328
Optic radiation	422.41086 (24.36161)	433.86651 (21.90850)	0.316

Control (C), Experimental (E). Results are means and (standard deviations). Statistical analyzes used are Brown-Forsythe univariate analysis of variance: F*, two-tailed. *P*=Probability

Table 11: Discriminant function analysis of diffusion tensor magnetic resonance imaging measures

Jackknifed classification matrix corpus callosum radial diffusivity, cingulum fractional anisotropy, internal capsule radial diffusivity	Correct classification (%)	Control (*n*=7)	Experimental (*n*=14)
Control (C) group	71.4	5	2
Experimental (E) group	78.6	2	12
Total	76.2	7	14

Wilks' lambda=0.5749; *df*=3,17; F=4.191; *P*=0.02

Table 12: Discriminant function analysis of neuropsychological, EEG and diffusion tensor magnetic resonance imaging measures

Jackknifed classification matrix coherence factor 15, coherence factor 12, KABC-II triangles, Rey-Osterrieth-Immediate Recall Organization, Rey-Osterrieth-Delayed Recall Organization	Correct classification (%)	Control (*n*=7)	Experimental (*n*=14)
Control (C) group	71.4	5	2
Experimental (E) group	85.7	2	12
Total	81.0	7	14

Wilks' lambda=0.2430; *df*=5,15; F=9.35; *P*=0.0003

executive function, and visual-spatial processing) and Rey Organization-Immediate and Delayed Recall (assessing gestalt integration, executive function, spatial planning, and memory) measures which significantly differentiated C-from E-children [Table 12]. Two C-and 2 E-subjects were misclassified. Classification success was highly significant despite small sample size. Thus, overall, the EEG measures were most successful in discriminating C-from E-children.

Relationship between neuropsychological and spectral coherence measures

Canonical correlation between the discriminant-analysis-identified neuropsychological measures (KABC-II Rover, Atlantis, Triangles; Rey Immediate/Delayed Recall Organization Scores) and spectral coherence factors (12, 7, 15) showed a significant relationship (Bartlett's test, χ^2=38.01, *df*=15, *P*<0.0160). One canonical variable described the relationship. KABC-II subtest Atlantis (memory storage/retrieval of verbal information) and Rey Organization-Delayed Recall (long-term storage retrieval of visual-spatial content and executive function) as well as Coherence Factors-12 and-7 correlated highest with the canonical variable. Thus, better verbal and executive function, spatial organization, planning, and memory were associated with stronger broad bilateral frontal and parietal connectivities.

Relationship between spectral coherence and diffusion-tensor-MRI measures

Canonical correlation between the discriminant-analysis-identified Coherence Factors-7,-12, and-15 and the diffusion-tensor-MRI measures, (corpus callosum radial diffusivity, cingulum fractional anisotropy, and internal capsule radial diffusivity) was marginally significant (χ^2=14.79, *df*=9, *P*=0.0968). One canonical variable described the relationship. Variables correlating significantly with the canonical variable included Coherence Factors-15 (positive) and-7 (negative), and cingulum fractional anisotropy (positive), and internal capsule radial diffusivity (negative). Thus, measures of integrated central parietal and bilateral frontal connectivities coupled with frontal system functioning unhampered by restrictive visual motor input were associated with better-developed cingulum and internal capsule fiber tracts.

Relationships between newborn and school-age neurobehavioral function

Canonical correlation showed a significant relationship between the 8 newborn APIB/Prechtl factor scores[23] and

4 KABC-II[30] Scale Indexes (Sequential, Simultaneous, Planning, Learning) (χ^2=46.19, *df*=32 *P*=0.0501). One canonical variable described the relationship. APIB/Prechtl-Factor-3 (reactivity and hypersensitivity) and KABC-II Simultaneous Scale Index correlated significantly with the canonical variable. Newborns, who were less hypersensitive and over-reactive, had better KABC-II Simultaneous Scale scores at school age. Canonical correlation also identified a highly significant relationship (χ^2 = 137.64, *df*=96, *P*=0.0034) between the APIB/Prechtl factor scores[23] and 12 school-age Rey[32] measures. One canonical variable described the relationship. APIB/Prechtl-Factors-2 (broad motor organization) and-3 again, (see above) correlated significantly with the canonical variable as did Rey Organization-Copy and Basal Level-Immediate Recall. Thus, the better organized motorically and less hyper-reactive/hypersensitive the newborn, the better the school-age child's overall Rey-production in Copy and Immediate Recall. The relationship between newborn neurobehavioral and 8-year neuropsychological function was strong and internally consistent.

DISCUSSION

Results reported, consistent across the 3 domains tested, support the hypothesis that NIDCAP enhances low-risk AGA moderately preterm infants' long-term neurodevelopment, specifically complex planning, executive function, memory, and simultaneous non-verbal mental processing. E-children showed significantly better neurobehavioral functioning at 2 weeks corrected age[23] and better simultaneous processing and complex planning, memory, and executive function at school-age. Similarly, E-children at 2 weeks corrected age showed a pattern of increased long-distance connectivities between occipital and frontal regions,[23] and at school-age increased bilateral and across-midline broad frontal and parietal connectivities and release from overly connected visual-motor function. The NIDCAP experience supports better-differentiated brain connectivity development. Better developed connectivities between frontal systems and the parietal systems appears more conducive to better mental control, executive and memory functions.[63] This is reflected in Factor-15, supportive of frontal associative cortical functions, and Factor-13, supportive of mental processing, memory, executive function, attention to spatial relationships/location, responsivity to object shape, size, and orientation, and visual spatial working memory.[64,65]

The school-age neurostructural findings corroborated the neuropsychological and neurophysiological findings. Diffusion-tensor-MRI, which at 2 weeks corrected age showed improved E-group right and left internal capsule and frontal white matter tracts[23] showed at school-age improved internal capsule, cingulum, optic radiation, and arcuate fasciculus fiber tracts.

This is the first report of school-age NIDCAP-effectiveness for low-risk AGA moderately preterm infants in terms of neuropsychological, electrophysiological, and brain-structural development. Results are internally consistent. NIDCAP is directed towards reliable reduction in stressful experiences and consistent return to base and restfulness to assure the infants' opportunities for continued behavioral re-integration of experiences, the foundation for increasingly well-differentiated modulation of function and the growth of well-differentiated brain-connectivities.

Not all children returned for follow-up testing. It appears that the children who were more compromised at birth with lower Apgar scores at 5 minutes and higher SNAPPE-II, a newborn illness severity and mortality risk score, returned for school-age assessment. Moreover, the returning experimental group children were differentially sicker (lower Apgar scores at 5 minutes) in the newborn period than the returning control children. This emphasizes even more the effectiveness of the in-NICU NIDCAP intervention in improving neurodevelopmental outcomes at school-age.

Interpretation of findings, nevertheless, requires caution. The study's most serious limitation is the small sample size. Substantiation by larger, longitudinal school-age follow-up studies is necessary to corroborate the result presented. Advances in newborn intensive care since the time of study also may have implications for result interpretation. The mechanisms underlying NIDCAP effectiveness remain to be discovered. The cost-effectiveness of NIDCAP, as compared to other in-NICU interventions,[66] remains to be evaluated.

The long-term goal of the research is the wider dissemination of the NIDCAP approach.

Given the encouraging findings, preterm infants and their families benefit when those responsible for NICU care are knowledgeable and well-educated in early brain development and provide opportunities for individualized developmental care. The highly dependent, sensitive, and rapidly developing preterm infants and their hopeful and vulnerable parents have little choice but to fully trust NICU staff. Professionals and NICU systems must live up to and warrant this trust.

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