

Supplemental Appendix

Title: Effects of Intraventricular Hemorrhage on White Matter Microstructural Changes at Term and Early Developmental Outcomes in Infants Born Very Preterm

Authors: Weihong Yuan^{1,6}, Leanne Tamm^{2,6}, Karen Harpster^{3,6}, Mekibib Altaye^{4,6}, Venkata Sita Priyanka Illapani⁵, Nehal A. Parikh^{2,5,6}

Affiliations

¹Pediatric Neuroimaging Research Consortium, Division of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

²Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

³Division of Occupational Therapy and Physical Therapy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

⁴Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

⁵Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

⁶University of Cincinnati College of Medicine, Cincinnati, OH, United States

CORRESPONDING AUTHOR: Nehal A. Parikh, DO, MS, Email: Nehal.Parikh@cchmc.org

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Supplemental Methods

General Movement Assessment (GMA) – The GMA is a non-invasive evaluation aimed to identify neurological issues that are predictive of CP and/or other developmental disabilities. In the present study, GMA assessed at 3 months corrected age was classified as normal or abnormal (absent fidgety movements) according to the quality of spontaneous movement patterns.

Assessment for high risk for Cerebral Palsy (CP) Diagnosis – The evaluation was based on HINE, GMA, and global structural MRI scores. Infants were labeled as having high risk for CP based on the presence of moderate-severe injury based on structural MRI and abnormal GMA and/or HINE (score <57).

Supplemental Results

GMA & High Risk for CP: Four out of the 40 patients in the Low Grade IVH group were classified as having an abnormal GMA. The frequency of occurrence of abnormal GMA findings based on GMA in the High Grade IVH group was 2 out of 14, comparable to that in the Low Grade IVH group (Fisher's Exact test, $p=0.64$). In the Low Grade IVH group, 4 out of 41 patients were labeled as having high risk for CP. The frequency of occurrence was not significantly different from that in the High Grade IVH group (4 out of 14, Fisher's Exact test, $p=0.18$).

Among the five IBQ-R-S ratings that presented marginally significant group differences (i.e., $p<.10$) between Low Grade IVH and High Grade IVH (Smiling and Laughing, Low Intensity Pleasure, Cuddliness, Sadness, and Approach), significant within-group correlations were found between DTI metrics and two ratings: Smiling and Laughing and Low Intensity Pleasure. As shown in **Figure S1.A**, there was a significant positive correlation between Smiling and Laughing and FA in the Low Grade IVH group in white matter involving genu and body of corpus callosum and right anterior corona radiata. There was also significant inverse correlation between Smiling and Laughing and MD, AD and RD (**Figure S1.B-C**, respectively, $p<0.05$, TFCE corrected) in the High Grade IVH group in white matter areas involving genu and body of corpus callosum, left superior corona radiata, and cingulum (bilateral). For Low Intensity Pleasure, a significant correlation was found only in the High Grade Group; there was a significant positive correlation between Low Intensity Pleasure and MD (involving genu, body, and splenium of corpus callosum, and bilateral cingulum (**Figure S2.A**) and between Low Intensity Pleasure and RD (involving genu, body, and splenium of corpus callosum, left superior corona radiata, right posterior corona radiata, and bilateral cingulum, **Figure S2.B**), and a significant inverse correlation between Low

Intensity Pleasure and FA (involving body of corpus callosum, **Figure S2.C**) in the High Grade IVH group.

The size of the areas with significant within-group correlation between DTI and IBQ-R-S rating for Smiling and Laughing and Low Intensity Pleasure for individual anatomical regions can be found in **Table S3**.

Supplemental Figures & Figure Legends

Figure S1. White matter areas in patients with significant correlation between DTI at term and IBQ-R-S Smiling and Laughing scores at 3 months corrected age ($p < 0.05$, TFCE corrected).

Covariates included age at MRI and sex. (A) Positive correlation between FA and Smiling and Laughing scores in the Low Grade IVH Group; (B) Positive correlation between MD and Smiling and Laughing scores in the High Grade IVH Group; (C): Positive correlation between AD and Smiling and Laughing scores in the High Grade IVH Group; (D) Positive correlation between RD and Smiling and Laughing scores in the High Grade IVH Group.

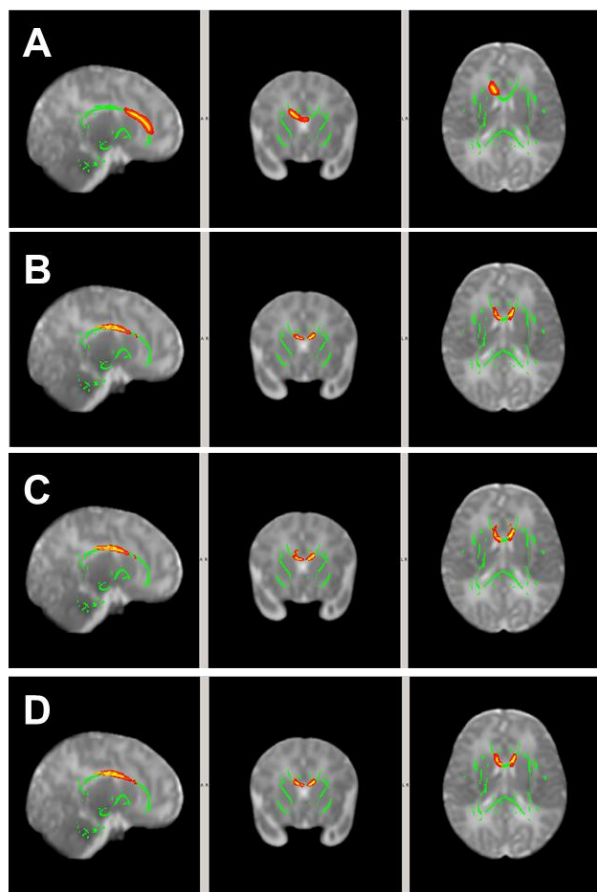
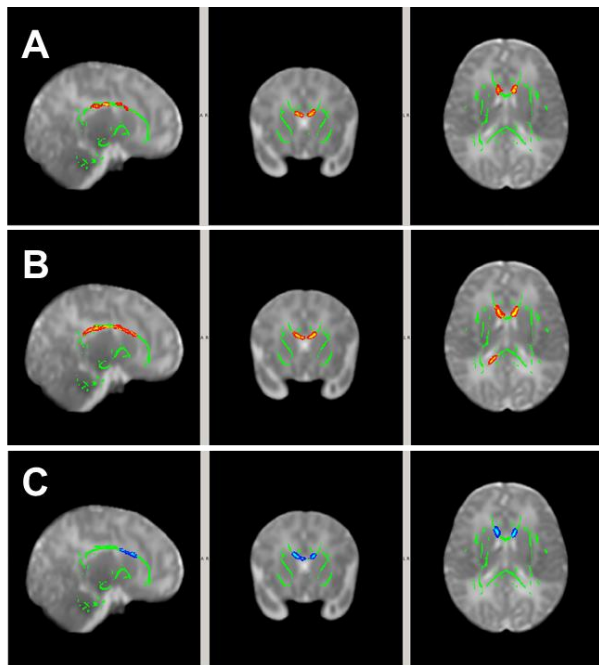


Figure S2. White matter areas in patients with a significant correlation between DTI at term and IBQ-R-S Low Intensity Pleasure scores at 3 months of age ($p < 0.05$, TFCE corrected). Covariates included age at MRI and sex. (A) Positive correlation between MD and Low Intensity Pleasure scores in the High Grade IVH Group; (B) Positive correlation between RD and Low Intensity Pleasure scores in the High Grade IVH Group; (C): Negative correlation between FA and Low Intensity Pleasure scores in the High Grade IVH Group.



Supplemental Tables

Table S1: Size of white matter area (in number of voxels) with significant difference between the Low Grade IVH and High Grade IVH groups.

	FA	MD	AD	RD
	Low Grade > High Grade	Low Grade < High Grade	Low Grade < High Grade	Low Grade < High Grade
gCC	35	45	51	46
bCC	1474	1830	1657	1937
sCC	332	90	19	409
ACR R	0	61	94	0
ACR L	0	0	46	0
SCR R	0	133	229	0
SCR L	22	138	387	139
PCR R	11	5	24	40
PCR L	37	84	140	94
PTR R	0	0	0	5
PTR L	82	0	0	253
C R	0	114	147	63
C L	11	255	292	219
Total	2004	2755	3086	3205

Note: All statistical significance was tested at level $p < 0.05$ (corrected for multiple voxel comparisons). Covariates included age at MRI and sex. **Abbreviations:** FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity; gCC = genu of corpus callosum; bCC = body of corpus callosum; sCC = splenium of corpus callosum; ACR = anterior corona radiata; SCR = superior corona radiata; PCR = posterior corona radiata; PTR = posterior thalamic radiation; C = cingulum; R = right; L = left.

Table S2: Size of white matter area (in number of voxels) with significant within group correlations between DTI and HINE or IBQ-R-S Fear ratings							
	FA vs. HINE (pos.)	RD vs. HINE (neg.)	FA vs. HINE (pos.)	FA vs. Fear (pos.)	MD vs. Fear (neg.)	AD vs. Fear (neg.)	RD vs. Fear (neg.)
	Low Grade	Low Grade	High Grade	High Grade	High Grade	High Grade	High Grade
gCC	234	0	0	25	36	30	39
bCC	911	0	438	1030	1292	1174	1341
sCC	26	1	521	0	252	220	301
ACR R	687	0	0	0	0	0	0
ACR L	185	0	0	0	0	0	0
SCR R	280	0	0	0	55	0	2
SCR L	313	17	42	70	99	94	98
PCR R	33	0	0	0	67	0	68
PCR L	23	199	341	0	0	0	0
PTR L	0	12	1	0	0	0	0
EC R	112	0	0	0	0	0	0
C R	0	0	0	0	92	134	82
C L	0	0	0	82	182	216	178
Total	1814	264	1343	1207	2075	1868	2109

Note: All statistical significance was tested at level $p < 0.05$ (corrected for multiple voxel comparisons). Covariates included age at MRI and sex.

Abbreviations: FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity; pos. = positive correlation; neg. = negative correlation; gCC = genu of corpus callosum; bCC = body of corpus callosum; sCC = splenium of corpus callosum; ACR = anterior corona radiata; SCR = superior corona radiata; PCR = posterior corona radiata; PTR = posterior thalamic radiation; EC = external capsule; C = cingulum; R = right; L = left; IBQ-R-S = Infant Behavior Questionnaire - Revised, Short Version

Table S3: Size of significant area located in different white matter regions in the analyses of within group correlations between DTI and IBQ-R-S Smiling and Laughing and Low Intensity Pleasure ratings

	FA vs. SMIL (pos.)	MD vs. SMIL (pos.)	AD vs. SMIL (pos.)	RD vs. SMIL (pos.)	FA vs. LIP (neg.)	MD vs. LIP (pos.)	RD vs. LIP (pos.)
	Low Grade	High Grade	High Grade	High Grade	High Grade	High Grade	High Grade
gCC	341	19	24	19	5	24	5
bCC	244	1054	1133	1056	420	966	429
sCC	0	0	2	0	26	292	0
PLIC R	0	0	0	0	0	0	0
ACR R	99	0	0	0	0	0	0
SCR L	0	101	114	87	0	38	0
PCR R	0	0	0	0	0	13	0
PCR L	0	0	0	0	0	0	0
EC L	0	0	0	0	0	0	0
C R	0	80	123	72	18	26	0
C L	0	174	225	164	95	144	0
Total	684	1428	1621	1398	564	1503	434

Note: Note: All voxel-wise statistical significance was tested at level $p < 0.05$ (corrected for multiple voxel comparisons). Covariates included age at MRI and sex. **Abbreviations:** FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity; pos. = positive correlation; neg. = negative correlation; gCC = genu of corpus callosum; bCC = body of corpus callosum; sCC = splenium of corpus callosum; PLIC = posterior limb of internal capsule; ACR = anterior corona radiata; SCR = superior corona radiata; PCR = posterior corona radiata; PTR = posterior thalamic radiation; EC = external capsule; C = cingulum; R = right; L = left; IBQ-R-S = Infant Behavior Questionnaire, Revised, Short Version; SMIL = Smiling and Laughing score; LIP = Low Intensity Pleasure score.

Table S4: Size of white matter area (in number of voxels) with significant interaction effect of IVH severity on DTI vs. outcome relationship.

	MD vs. HINE	FA vs. Fear	MD vs. Fear	AD vs. Fear
gCC	0	430	65	45
bCC	0	1651	1827	1692
sCC	0	908	543	312
ACR R	274	107	27	27
ACR L	0	125	0	0
SCR R	0	1	231	226
SCR L	0	116	140	142
PCR R	0	217	369	344
PCR L	0	7	2	31
PTR R	0	224	147	126
PTR L	0	90	134	0
SS R	0	34	0	0
EC R	15	0	0	0
C R	0	0	105	133
C L	0	1	253	279
Total	289	3911	3843	3357

Note: Covariates included age at MRI and sex. **Abbreviations:** FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity; gCC = genu of corpus callosum; bCC = body of corpus callosum; sCC = splenium of corpus callosum; ACR = anterior corona radiata; SCR = superior corona radiata; PCR = posterior corona radiata; PTR = posterior thalamic radiation; SS = sagittal stratum; EC = external capsule; C = cingulum; R = right; L = left; HINE = Hammersmith Infant Neurological Examination; IBQ-R-S = Infant Behavior Questionnaire, Revised, Short Version.