



Early Trajectory of White Matter Development in Nonsyndromic Craniosynostosis Compared to Neurotypical Infants: A Three-Site Diffusion Tensor Imaging Study

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BACKGROUND AND OBJECTIVES

- Nonsyndromic craniosynostosis (NSC)** is the isolated premature fusion of one or more cranial sutures
- Growing evidence links NSC to neurocognitive deficits including impairments in attention, language, and motor function
- Restricted skull growth may disrupt critical periods of brain development, and early surgical correction is the standard of care

- Diffusion tensor imaging (DTI)** provides insight into white matter microstructural development through quantitative metrics including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).

- Objectives:** To compare white matter tract development in infants with surgically corrected NSC to normally developing controls, and to assess how surgery affects white matter maturation.

METHODS

Study Design & Population

- Sixteen NSC patients underwent unsedated pre- and postoperative MRI across three academic centers (Yale, Vanderbilt, Arkansas; 2013–2023)
- Age-matched controls (n=47) were obtained from the LifeSpan Baby Connectome Project.

DTI Acquisition & Processing

- DTI data were acquired at 3T across all sites (30–99 gradient directions).
- A uniform processing pipeline was applied: tensor fitting via FSL dtifit, registration to UNC EBDS infant template, and extraction of FA, MD, AD, and RD across JHU white matter atlas tracts (Figure 1).

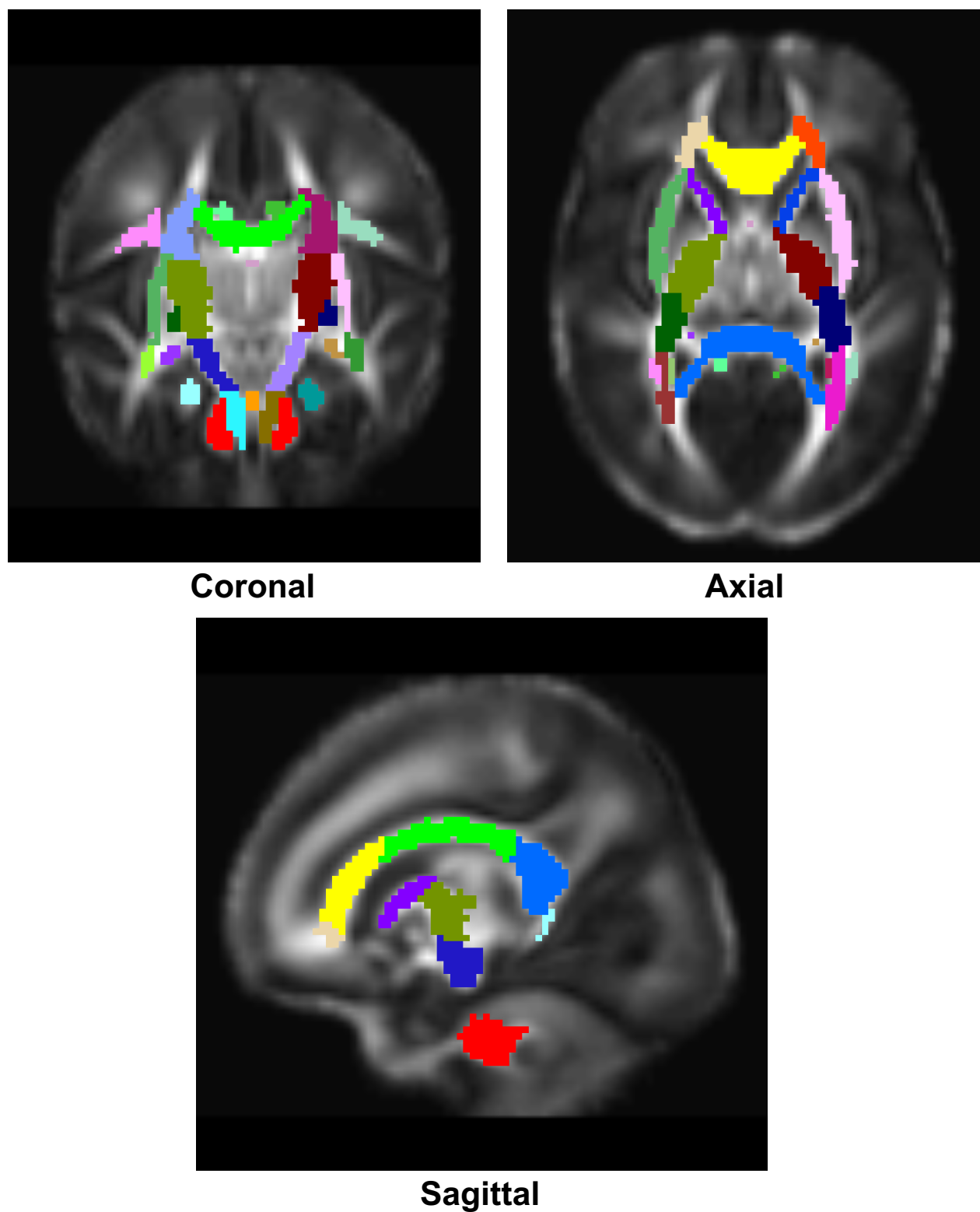


Figure 1. Representative DTI with JHU white matter tractography atlas overlay.

Statistical Analysis

- Baseline preoperative differences in diffusion parameters were compared between patients and controls.
- Linear mixed-effects models (LME) assessed longitudinal change in diffusion parameters between NSC patients and controls.
- Subgroup analyses compared CVR-only patients vs. controls and assessed suture-type and surgical approach differences.
- P-values corrected with Benjamini-Hochberg (adjusted p<0.05).

RESULTS

Patient Cohort

- 16 NSC patients (50% sagittal, 25% metopic, 19% unicoronal, 6% sag/met); 62% male
- Mean age at surgery: 5.3 ± 1.4 mo.
- Surgical approach: 81% CVR, 12% spring, 6% strip
- Control cohort: 47 BCP subjects (n=24 pre-op matched, n=32 post-op matched)

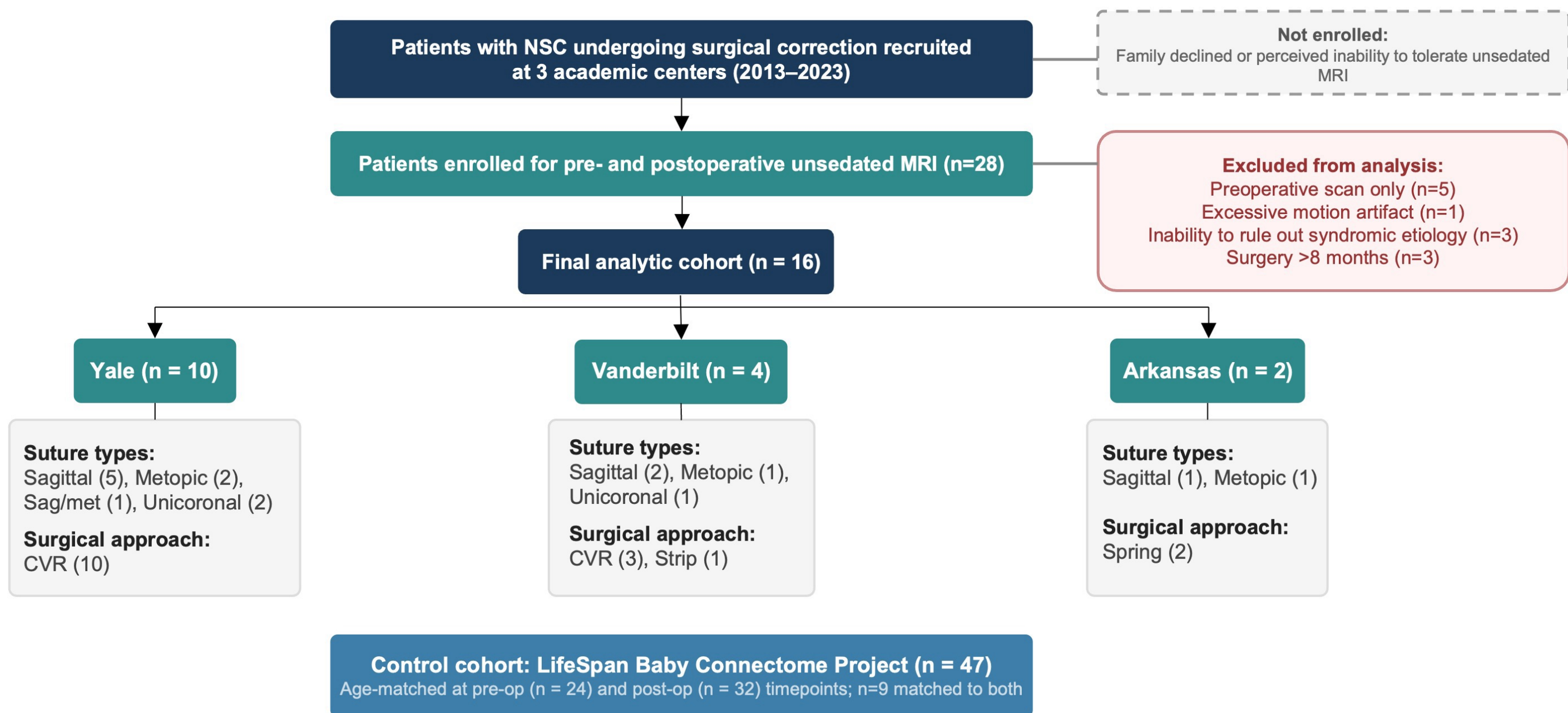


Figure 2. Study enrollment and analytic cohort flow diagram.

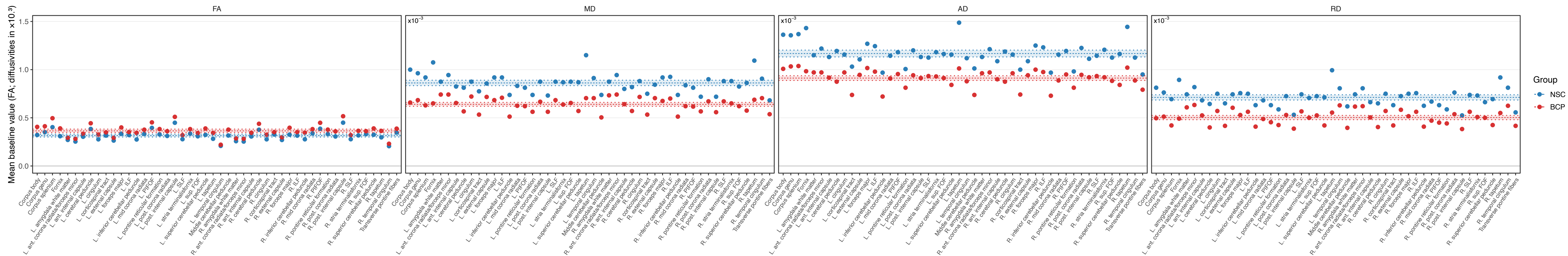


Figure 4. Baseline parameter values for all white matter tracts for NSC and BCP patients. Dashed lines and shading represent mean parameter value $\pm$ 95% CI across all white matter tracts for each cohort.

Longitudinal Findings

- LME models revealed significantly greater decreases in MD, AD, and RD in NSC patients vs. controls across multiple tracts
- Key tracts with significant differences included: corpus callosum splenium, corona radiata, SLF, external capsule, cingulum, internal capsule, forceps major, ILF, and amygdala WM (Figure 5, Table 1).
- No significant differences between suture types or surgical approaches.

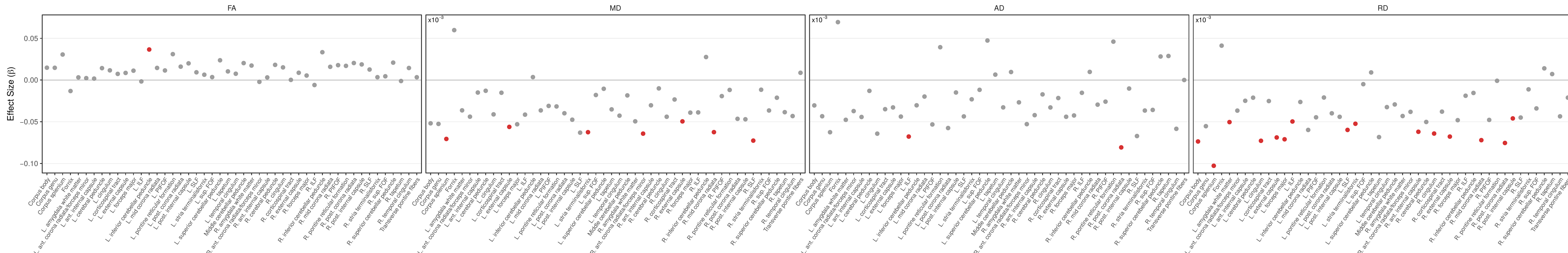


Figure 5. Effect sizes (β) for longitudinal diffusion changes in NSC vs. controls. Red = adjusted p<0.05.

Baseline Differences

- NSC patients showed numerically higher global MD, AD, and RD and lower FA compared to BCP controls at both pre- and postoperative timepoints (Figures 3 and 4)

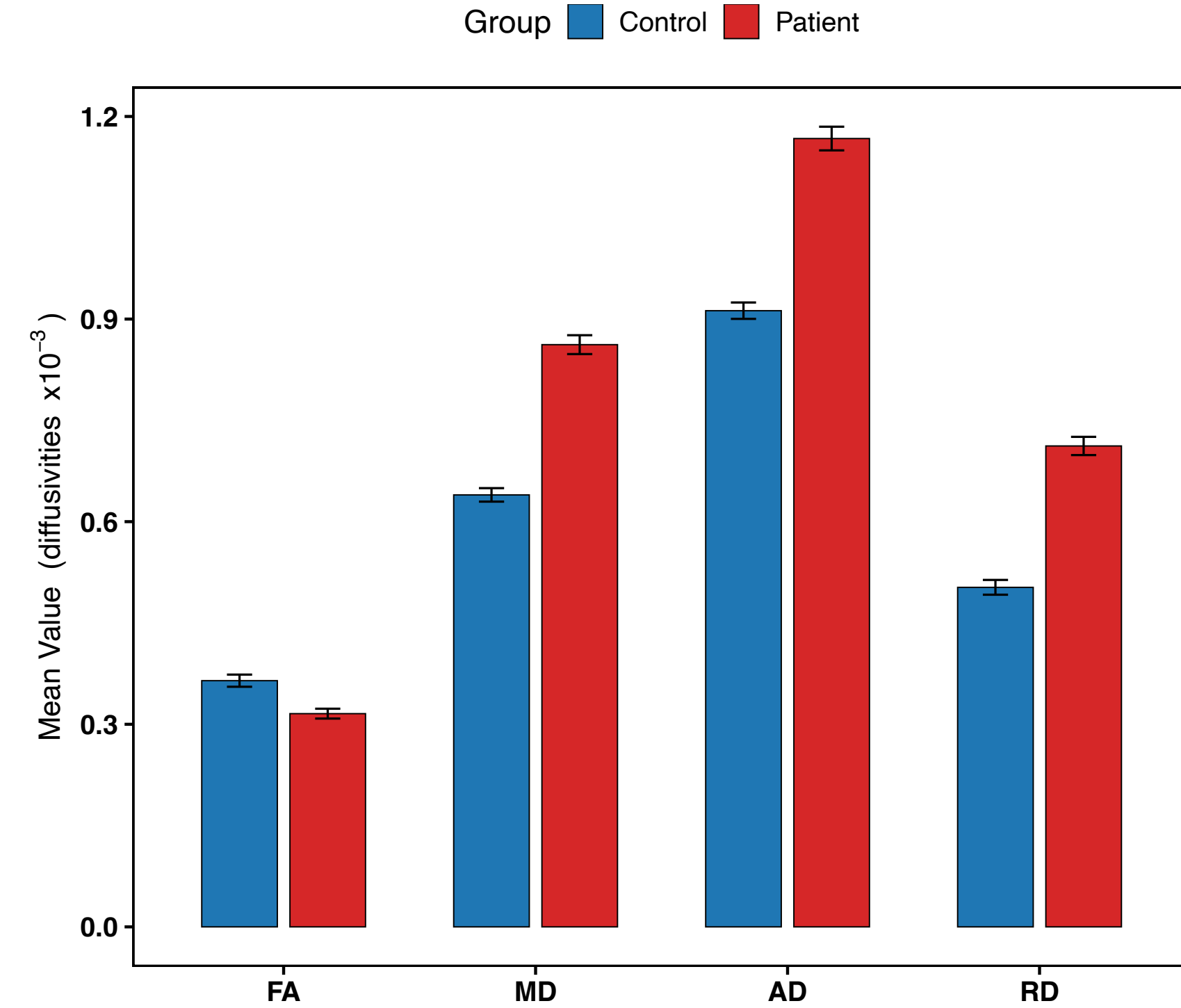


Figure 3. Baseline parameter values across all white matter tracts for NSC and BCP patients.

RESULTS

Table 1. White matter tracts with significant differences in longitudinal change between NSC patients and controls, with subgroup analyses by surgical approach. Effect size β is for the linear-mixed effects model group*timepoint term.

		All NSC (n=16)		CVR (n=13)		Strip/Spring (n=3)	
Param.	White Matter Tract	β	P adj	β	P adj	β	P adj
FA	L. inferior cerebellar peduncle	+0.037	0.040	—	—	—	—
AD	L. ILF	-6.8×10 ⁻⁴	0.048	-7.6×10 ⁻⁴	0.022	—	—
AD	R. post. corona radiata	-8.1×10 ⁻⁴	0.048	—	—	—	—
MD	Corpus callosum, splenium	-7.1×10 ⁻⁴	0.031	-8.1×10 ⁻⁴	0.010	—	—
MD	R. external capsule	-4.9×10 ⁻⁴	0.031	-4.6×10 ⁻⁴	0.045	—	—
MD	R. mid corona radiata	-6.2×10 ⁻⁴	0.031	-6.4×10 ⁻⁴	0.032	—	—
MD	R. SLF	-7.3×10 ⁻⁴	0.031	-7.3×10 ⁻⁴	0.023	—	—
MD	L. external capsule	-5.6×10 ⁻⁴	0.033	-4.9×10 ⁻⁴	0.046	—	—
MD	L. stria terminalis/fornix	-6.3×10 ⁻⁴	0.036	-6.3×10 ⁻⁴	0.045	—	—
MD	R. ant. corona radiata/FM	-6.4×10 ⁻⁴	0.039	-7.0×10 ⁻⁴	0.010	—	—
MD	R. post. internal capsule	—	—	-6.0×10 ⁻⁴	0.010	—	—
MD	R. amygdala white matter	—	—	-6.3×10 ⁻⁴	0.032	—	—
MD	L. post. internal capsule	—	—	-5.4×10 ⁻⁴	0.046	—	—
MD	L. temporal cingulum	—	—	—	—	-6.5×10 ⁻⁴	0.001
RD	Corpus callosum, splenium	-10.3×10 ⁻⁴	0.002	-10.4×10 ⁻⁴	0.002	—	—
RD	L. external capsule	-6.9×10 ⁻⁴	0.002	-6.6×10 ⁻⁴	0.003	—	—
RD	R. ant. internal capsule	-6.2×10 ⁻⁴	0.002	-6.1×10 ⁻⁴	0.004	—	—
RD	R. external capsule	-6.8×10 ⁻⁴	0.002	-7.6×10 ⁻⁴	<0.001	—	—
RD	R. mid corona radiata	-7.2×10 ⁻⁴	0.004	-7.5×10 ⁻⁴	0.005	—	—
RD	L. forceps major	-7.1×10 ⁻⁴	0.006	-6.9×10 ⁻⁴	0.005	—	—
RD	L. cingulum	-7.3×10 ⁻⁴	0.014	-6.9×10 ⁻⁴	0.019	—	—
RD	R. post. corona radiata	-7.5×10 ⁻⁴	0.014	-8.8×10 ⁻⁴	0.005	—	—
RD	L. SLF	-6.0×10 ⁻⁴	0.019	-5.8×10 ⁻⁴	0.019	—	—
RD	R. post. internal capsule	-4.6×10 ⁻⁴	0.019	-4.4×10 ⁻⁴	0.029	—	—
RD	L. ILF	-5.0×10 ⁻⁴	0.022	—	—	—	—
RD	R. cingulum	-6.4×10 ⁻⁴	0.022	-7.1×10 ⁻⁴	0.005	—	—
RD	L. stria terminalis/fornix	-5.2×10 ⁻⁴	0.031	—	—	-9.0×10 ⁻⁴	0.005
RD	Corpus callosum, body	-7.4×10 ⁻⁴	0.034	—	—	—	—
RD	L. amygdala white matter	-5.0×10 ⁻⁴	0.045	-4.8×10 ⁻⁴	0.035	—	—
RD	R. corticospinal tract	—	—	-5.8×10 ⁻⁴	0.019	—	—
RD	R. amygdala white matter	—	—	-4.8×10 ⁻⁴	0.029	—	—
RD	R. PIFOF	—	—	-5.4×10 ⁻⁴	0.048	—	—

DISCUSSION

- NSC patients exhibited higher baseline global diffusivity (MD, AD, RD) compared to controls.
- Following surgical correction, patients showed significantly greater decreases in diffusivity across major association, commissural, and projection tracts, suggesting partial normalization of white matter development.

- Affected tracts serve cognitive (SLF, external capsule), motor/sensory (internal capsule), emotional (cingulum, amygdala), and interhemispheric (corpus callosum) functions, consistent with neurocognitive domains previously reported as affected in NSC.

- No differences were observed between suture types or surgical approaches (CVR vs. strip/spring), suggesting global white matter dysfunction in NSC rather than localized effects. Genetic factors may contribute independently to white matter differences.

CONCLUSIONS

- NSC patients show greater baseline diffusivity vs. controls, suggesting altered baseline white matter microstructure.
- Following surgery, patients show significantly greater decreases in MD, AD, and RD across multiple major WM tracts, potentially reflecting accelerated maturation.
- Findings are consistent across suture types and surgical approaches, supporting a global mechanism.
- DTI shows promise as a biomarker for tracking white matter development in craniosynostosis.

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