

Supplementary material

Figure S1. Longitudinal changes in premature infants' microstructural diffusivities, from 33- to 40-wGA, averaged per RSN and scaled by the largest observed change per metric. a-b) Microstructural DKI metrics delta (Δ) change, including mean (MK), radial (RK) and axial kurtosis (AK); c-d) DTI metrics delta (Δ) change, including mean diffusivity (MD) and fractional anisotropy (FA); e-f) SMT metrics delta (Δ) change, including intra-neurite volume fraction (intra), intrinsic diffusivity (diff), extra-neurite mean diffusivity (extraMD) and extra-neurite transverse diffusivity (extraTrans).

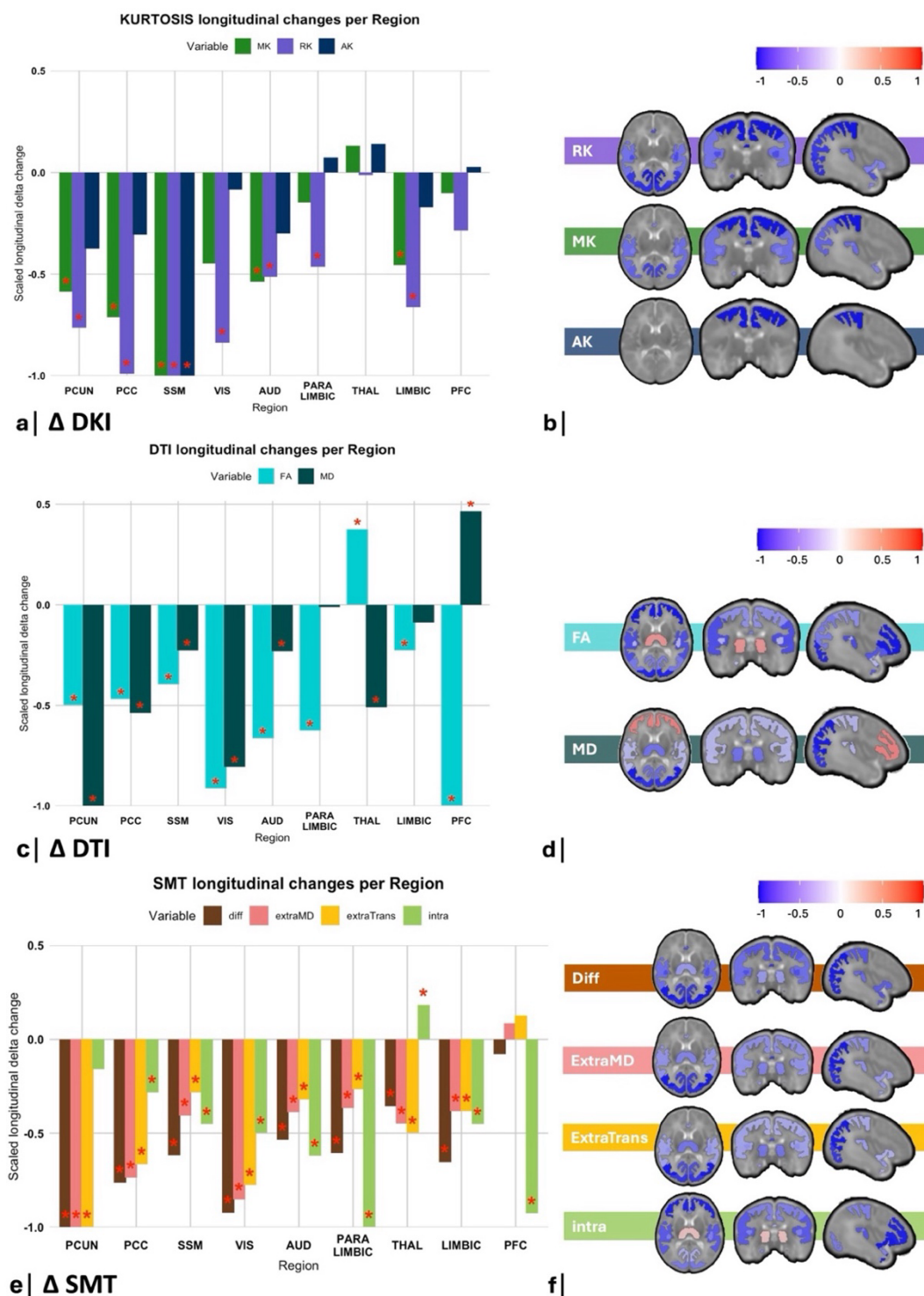
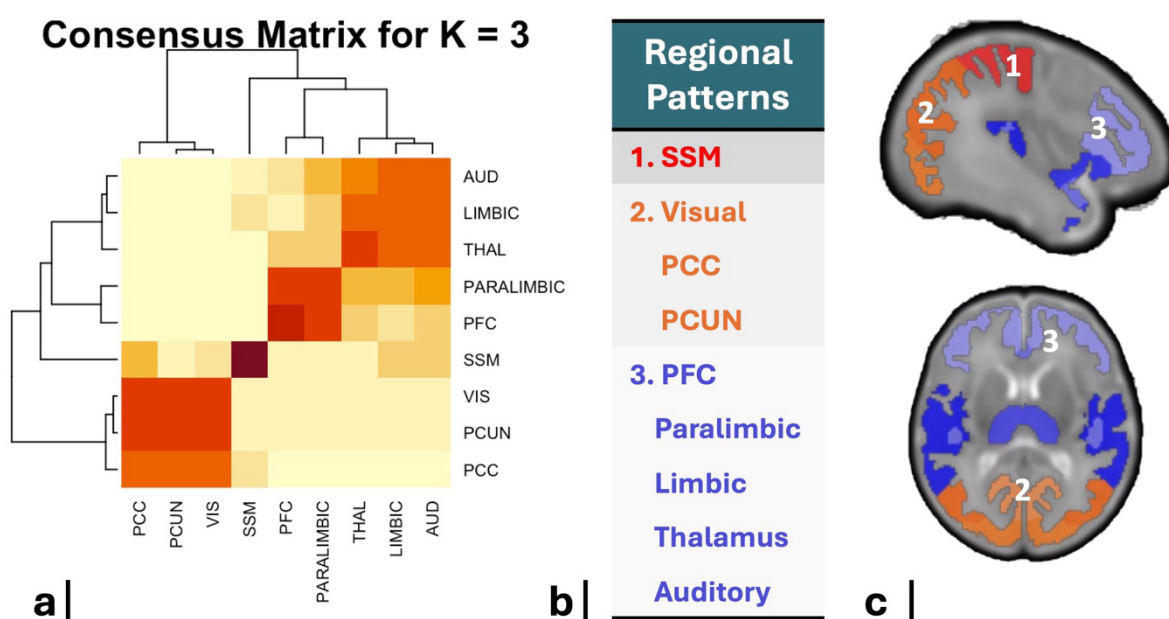


Figure S2. Results from the consensus clustering of the combined 9 distinct diffusion microstructural measures delta changes over time. a) Heatmap depicting the regional maturational patterns from 33- to 40-wGA, with rows and columns representing the RSNs and color intensity in each cell reflecting the composite changes over time of the microstructural metrics. b) Composition of the identified 3 regional patterns of microstructural delta changes (pattern 1: SSM; pattern 2: Visual, PCC and PCUN; pattern 3: PFC, Paralimbic, Limbic, Thalamus and Auditory). c) Brain plots illustrating the 3 distinct regional patterns depicted by the consensus clustering analysis, color-coded according to regional pattern (red = pattern 1, orange = pattern 2, blue = pattern 3).



To better understand the spatio-temporal patterns of cortical microstructural maturation across the various RSNs, occurring from 33- to 40-wGA, we have combined the longitudinal changes of all the diffusion microstructural measures across the different dMRI models (DTI, DKI and SMT) and performed a consensus clustering analysis ($k=3$).

Microstructural diffusivities were clustered using ConsensusClusterPlus function (k-means base algorithm and Euclidean distance) in R (4.4.1), to identify stable clusters of regional diffusivities. The optimal number of clusters was determined using the elbow method, based on the within-cluster sum of squares (WCSS).

Three distinct regional microstructural maturational patterns were identified, aligning with the central-to-peripheral and posterior-to-anterior known gradients in brain maturation, aligning with the brain myelination order of Kinney (Kinney et al., 1988). Microstructure cluster 1 and 2 are similar to BOLD SD cluster 1, whereas Microstructure cluster 3 is similar to BOLD SD cluster 2.

Table S3. Gene Ontology enrichment of genes that increased significantly more in cluster 1 than 2 from mid- to late-fetal period, using background reference set (5,287 genes).

		Reference set		
		Fetal gene markers (n=5287)		
GO term [†]	Description	Enrichment	FDR	Genes
GO:0007272	ensheathment of neurons	6.15	0.00001*	CD9; CLDN11; COL6A1; ERBB3; MAG; MAL; MBP; MOBP; NKX6-2; PLLP; PLP1; PMP22; TNFRSF1B; UGT8
GO:0042063	gliogenesis	2.85	0.01796*	APCDD1; CD9; COL6A1; ERBB3; GPR17; GPR183; GPR37L1; IL6ST; MAG; MAL; MOBP; NKX6-2; PLP1; TNFRSF1B
GO:0043062	extracellular structure organization	3.58	0.01796*	CAV1; CAV2; COL18A1; COL5A2; COL6A1; EFEMP2; LAMC1; SLC39A8; TNFRSF1B; VWA1
GO:0045229	external encapsulating structure organization	3.58	0.01796*	CAV1; CAV2; COL18A1; COL5A2; COL6A1; EFEMP2; LAMC1; SLC39A8; TNFRSF1B; VWA1
GO:0019221	cytokine-mediated signaling pathway	3.61	0.00797*	CAV1; CD74; F3; GPR17; IFI27; IL6ST; IRF1; MX1; OAS2; PADI2; PTPRC; SP100; TNFRSF1B
GO:0050817	coagulation	4.10	0.01351*	ACTN1; CAV1; CD9; CSRP1; F3; IL6ST; MMRN1; NFE2L2; PAPSS2; STXBP3
GO:0042060	wound healing	3.04	0.01365*	ACTN1; CAV1; CD9; CSRP1; ELK3; ERBB3; F3; GATA2; HBEGF; IL6ST; MMRN1; NFE2L2; PAPSS2; STXBP3
GO:0097191	extrinsic apoptotic signaling pathway	3.84	0.01548*	BAG3; CAV1; ERBB3; IFI27; MAL; PTPRC; SH3RF1; SP100; STK3; TNFRSF1B
GO:0033002	muscle cell proliferation	3.86	0.01796*	APOD; CALCRL; CAV2; EFEMP2; HBEGF; IGFBP5; JUN; NDRG2; PTGS2
GO:0050878	regulation of body fluid levels	3.55	0.00797*	ACTN1; CAV1; CD9; CSRP1; EMP2; F3; IL6ST; MMRN1; NFE2L2; OAS2; PAPSS2; STXBP3; WFS1

*p<0.05 after correction for multiple comparisons

[†] top 10 terms with 'fetal gene markers' background set are listed

Table S4. Effect of preterm birth on BOLD variability and cortical microstructure at TEA per region. Metrics include: BOLD variability (BOLD SD), Mean Kurtosis (MK), Radial Kurtosis (RK), Axial Kurtosis (AK), Mean Diffusivity (MD), Extra-neurite Mean Diffusivity (ExtraMD), Extra-neurite Transverse Diffusivity (ExtraTrans), intrinsic diffusivity (Diff). Numbers in bold indicate significant results between groups that survived FDR correction ($p \leq 0.05$).

Cortical region	Metric	Mean measurement (95% CI)		Group-effect
		VPT	FT	p-value (FDR adjusted)
Precuneus	BOLD SD	16.5 (14.3-18.8)	17.6 (14.9-20.3)	0.51
	MK	0.42 (0.39-0.45)	0.37 (0.33-0.41)	0.039*
	RK	0.41 (0.37-0.43)	0.33 (0.27-0.38)	0.016*
	AK	0.46 (0.44-0.48)	0.45 (0.42-0.47)	0.66
	MD	0.0017 (0.0016-0.0018)	0.0014 (0.0013-0.0015)	< 0.001***
	ExtraMD	0.0018 (0.0017-0.0019)	0.0015 (0.0014-0.0016)	< 0.001***
	ExtraTrans	0.0017 (0.0016-0.0018)	0.0014 (0.0013-0.0015)	< 0.001***
	Diff	0.0021 (0.0019-0.0022)	0.0017 (0.0016-0.0018)	< 0.001***
Posterior Cingulate Cortex	BOLD SD	13.6 (12.1-15.0)	18.6 (15.1-22.1)	0.02*
	MK	0.43 (0.41-0.46)	0.39 (0.36-0.42)	0.03*
	RK	0.40 (0.37-0.43)	0.33 (0.28-0.38)	0.016*
	AK	0.50 (0.44-0.47)	0.49 (0.47-0.51)	0.66
	MD	0.0014 (0.0013-0.0015)	0.0013 (0.0012-0.0014)	< 0.001***
	ExtraMD	0.00159 (0.0015-0.0016)	0.0014 (0.0013-0.0015)	< 0.001***
	ExtraTrans	0.00149 (0.0014-0.0015)	0.0013 (0.0012-0.0014)	< 0.001***
	Diff	0.0018 (0.0017-0.0019)	0.0016 (0.0015-0.0017)	< 0.001***
Sensorimotor	BOLD SD	10.0 (8.6-11.5)	12.9 (10.3-15.6)	0.09
	MK	0.47 (0.44-0.50)	0.42 (0.37-0.47)	0.05*
	RK	0.44 (0.41-0.48)	0.35 (0.29-0.41)	0.015*
	AK	0.52 (0.50-0.55)	0.52 (0.49-0.56)	0.85
	MD	0.0018 (0.0017-0.0019)	0.0013 (0.0012-0.0014)	< 0.001***
	ExtraMD	0.0019 (0.0018-0.002)	0.00146 (0.0014-0.0015)	< 0.001***
	ExtraTrans	0.0018 (0.0017-0.0019)	0.00136 (0.0013-0.0014)	< 0.001***
	Diff	0.0022 (0.0020-0.0023)	0.0017 (0.0015-0.0018)	< 0.001***
Visual	BOLD SD	16.7 (14.9-18.5)	23.1 (18.9-27.2)	0.02*
	MK	0.42 (0.39-0.45)	0.36 (0.32-0.40)	0.03*
	RK	0.39 (0.35-0.42)	0.31 (0.25-0.36)	0.015*
	AK	0.48 (0.45-0.50)	0.47 (0.45-0.48)	0.66
	MD	0.0015 (0.0014-0.0015)	0.0013 (0.0012-0.0014)	0.005**
	ExtraMD	0.0016 (0.0015-0.0017)	0.0015 (0.0014-0.0016)	0.005**
	ExtraTrans	0.0015 (0.0014-0.0016)	0.0014 (0.0013-0.0015)	0.001**
	Diff	0.0018 (0.0017-0.0019)	0.0017 (0.0015-0.0018)	0.02*
Auditory	BOLD SD	10.7 (9.2-12.1)	14.8 (12.3-17.4)	0.02*
	MK	0.46 (0.44-0.49)	0.41 (0.36-0.45)	0.03*
	RK	0.45 (0.42-0.48)	0.38 (0.30-0.42)	0.015*
	AK	0.50 (0.48-0.52)	0.48 (0.46-0.51)	0.57
	MD	0.0016 (0.0015-0.0017)	0.0014 (0.0013-0.0015)	< 0.001***
	ExtraMD	0.0018 (0.0017-0.0019)	0.0015 (0.0014-0.0016)	< 0.001***
	ExtraTrans	0.00167 (0.0016-0.0017)	0.00144 (0.0014-0.0015)	< 0.001***
	Diff	0.0021 (0.0020-0.0022)	0.0017 (0.0016-0.0018)	< 0.001***
Paralimbic	BOLD SD	11.4 (10.1-12.8)	13.2 (10.4-15.8)	0.30
	MK	0.46 (0.43-0.48)	0.39 (0.34-0.44)	0.03*
	RK	0.43 (0.40-0.46)	0.34 (0.28-0.40)	0.015*
	AK	0.49 (0.47-0.52)	0.47 (0.43-0.50)	0.49
	MD	0.0017 (0.0016-0.0018)	0.0014 (0.0013-0.0015)	< 0.001***
	ExtraMD	0.00185 (0.0018-0.0019)	0.00157 (0.0015-0.0016)	< 0.001***

Thalamus	ExtraTrans	0.0017 (0.0016-0.0018)	0.00148 (0.0014-0.0015)	< 0.001***
	Diff	0.0021 (0.0020-0.0022)	0.0018 (0.0017-0.0019)	< 0.001***
	BOLD SD	11.5 (9.8-13.1)	19.5 (16.5-22.5)	< 0.001***
	MK	0.38 (0.35-0.41)	0.33 (0.28-0.38)	0.099
	RK	0.33 (0.29-0.37)	0.26 (0.20-0.33)	0.06
	AK	0.44 (0.42-0.47)	0.43 (0.39-0.47)	0.66
	MD	0.00123 (0.0012-0.0013)	0.00117 (0.0011-0.0012)	0.007
	ExtraMD	0.00135 (0.0013-0.0014)	0.00123 (0.0011-0.0012)	< 0.001***
	ExtraTrans	0.00127 (0.0012-0.0013)	0.00117 (0.0011-0.0012)	< 0.001***
Limbic	Diff	0.0015 (0.0014-0.0016)	0.0013 (0.0012-0.0014)	< 0.001***
	BOLD SD	10.7 (9.2-12.2)	13.5 (10.8-16.3)	0.11
	MK	0.44 (0.41-0.47)	0.39 (0.34-0.43)	0.03*
	RK	0.40 (0.37-0.43)	0.32 (0.26-0.37)	0.015*
	AK	0.51 (0.49-0.53)	0.48 (0.46-0.51)	0.49
	MD	0.00156 (0.0014-0.0016)	0.00136 (0.0013-0.0014)	< 0.001***
	ExtraMD	0.00176 (0.0017-0.0018)	0.0015 (0.0014-0.0016)	< 0.001***
	ExtraTrans	0.0016 (0.0015-0.0017)	0.0014 (0.0013-0.0015)	< 0.001***
	Diff	0.0020 (0.0019-0.0021)	0.0018 (0.0017-0.0019)	< 0.001***
Prefrontal Cortex	BOLD SD	16.8 (13.2-20.4)	19.8 (15.6-24.0)	0.30
	MK	0.47 (0.44-0.50)	0.41 (0.36-0.46)	0.03*
	RK	0.45 (0.41-0.48)	0.35 (0.28-0.41)	0.015*
	AK	0.51 (0.49-0.54)	0.50 (0.47-0.54)	0.66
	MD	0.00188 (0.0018-0.0019)	0.0014 (0.0013-0.0015)	< 0.001***
	ExtraMD	0.0020 (0.0019-0.0021)	0.00156 (0.0015-0.0016)	< 0.001***
	ExtraTrans	0.0018 (0.0017-0.0019)	0.0014 (0.0013-0.0015)	< 0.001***
	Diff	0.0022 (0.0022-0.0024)	0.00146 (0.0014-0.0015)	< 0.001***

Figure S5. Flow chart of participant selection

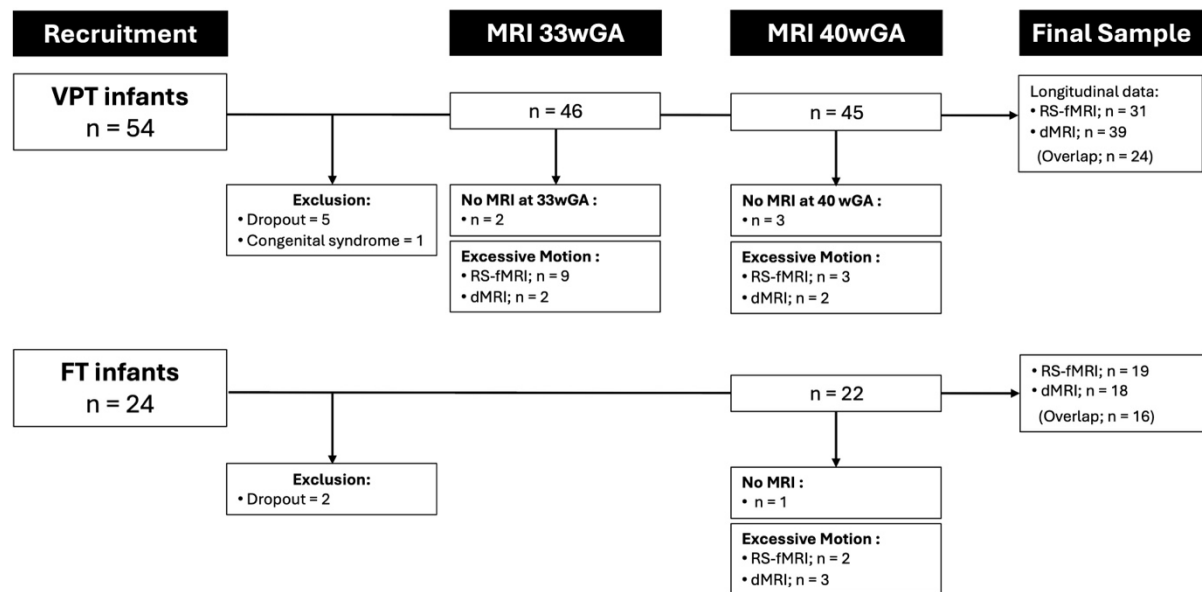


Figure S6. Components obtained from the data-driven ICA group analysis

