Supplementary Information: Neonatal brain dynamic functional connectivity in term and preterm infants and its association with early childhood neurodevelopment

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Supplementary Tables

Supplementary Table S1 | Association of global dynamic features (synchrony and metastability) with PMA, PND at scan, and preterm birth, using the M-CRIB atlas.
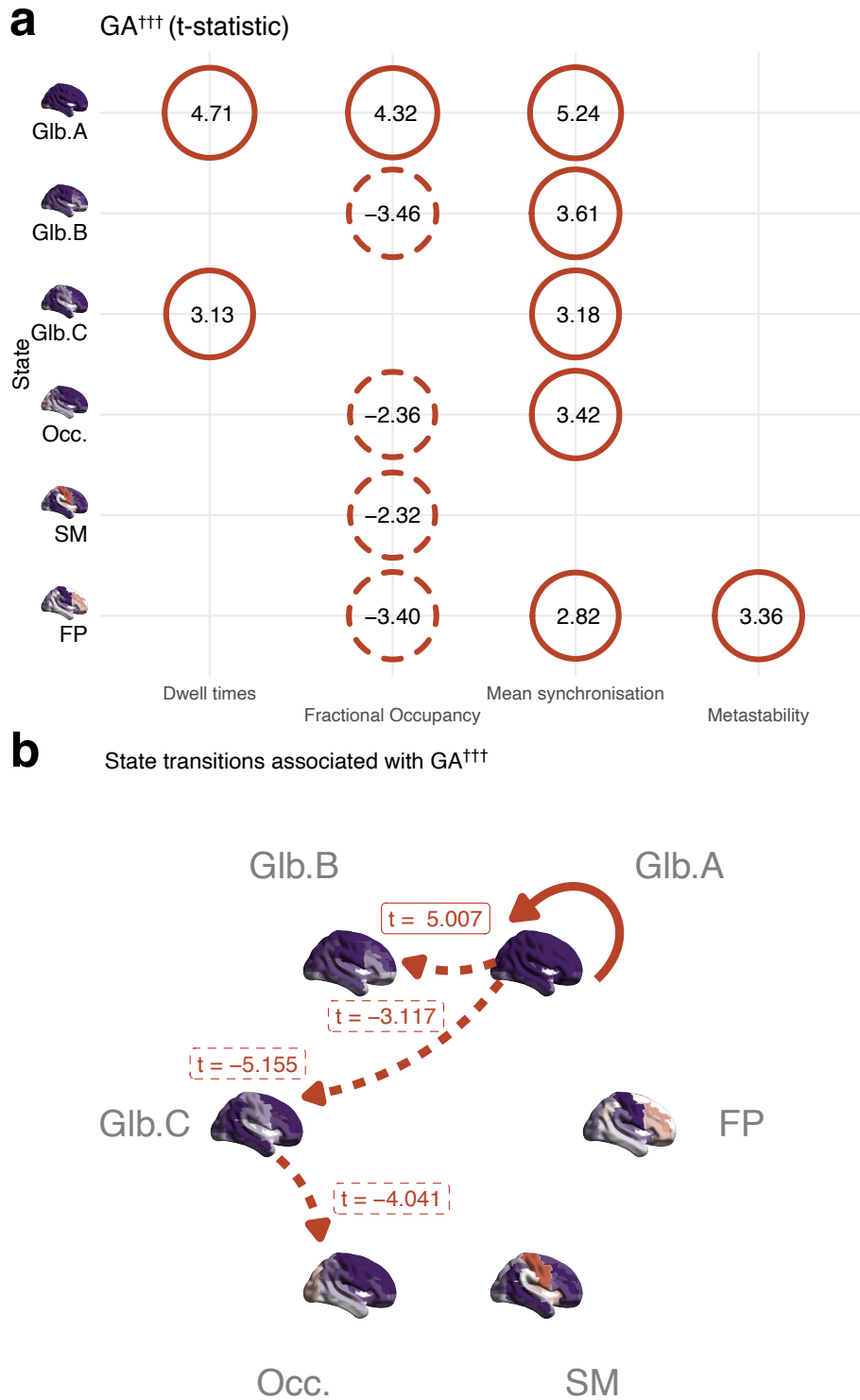
	Term ($n = 324$)				Term vs Preterm ($n = 390$)			
	PMA at scan		PND at scan		Term ($n = 324$)	Preterm ($n = 66$)	Cohen's D	p-value††
	$t^{\dagger}$	p-value†	$t^{\dagger}$	p-value†	[mean (S.D.)]			
Mean synchronisation	-0.173	0.862	1.370	0.172	0.53 (0.08)	0.48 (0.08)	0.628	$p < 0.001$*
Metastability	0.753	0.448	-2.330	0.019*	0.20 (0.02)	0.19 (0.02)	0.480	$p < 0.001$*

†GLM1 (including 324 term-born babies): $y \sim \beta_0 + \beta_1 PMA + \beta_2 PND + \beta_3 Sex + \beta_4 Motion$ outliers (FD). ††GLM2 (including 324 term-born and 66 preterm-born babies): $y \sim \beta_0 + \beta_1 Preterm\text{-}born + \beta_2 PMA + \beta_3 Sex + \beta_4 Motion$ outliers (FD). p-values obtained with a two-sided permutation test. * Indicates results surviving FDR multiple comparison correction with α error at 5%). PMA: Postmenstrual age. PND: Postnatal days.
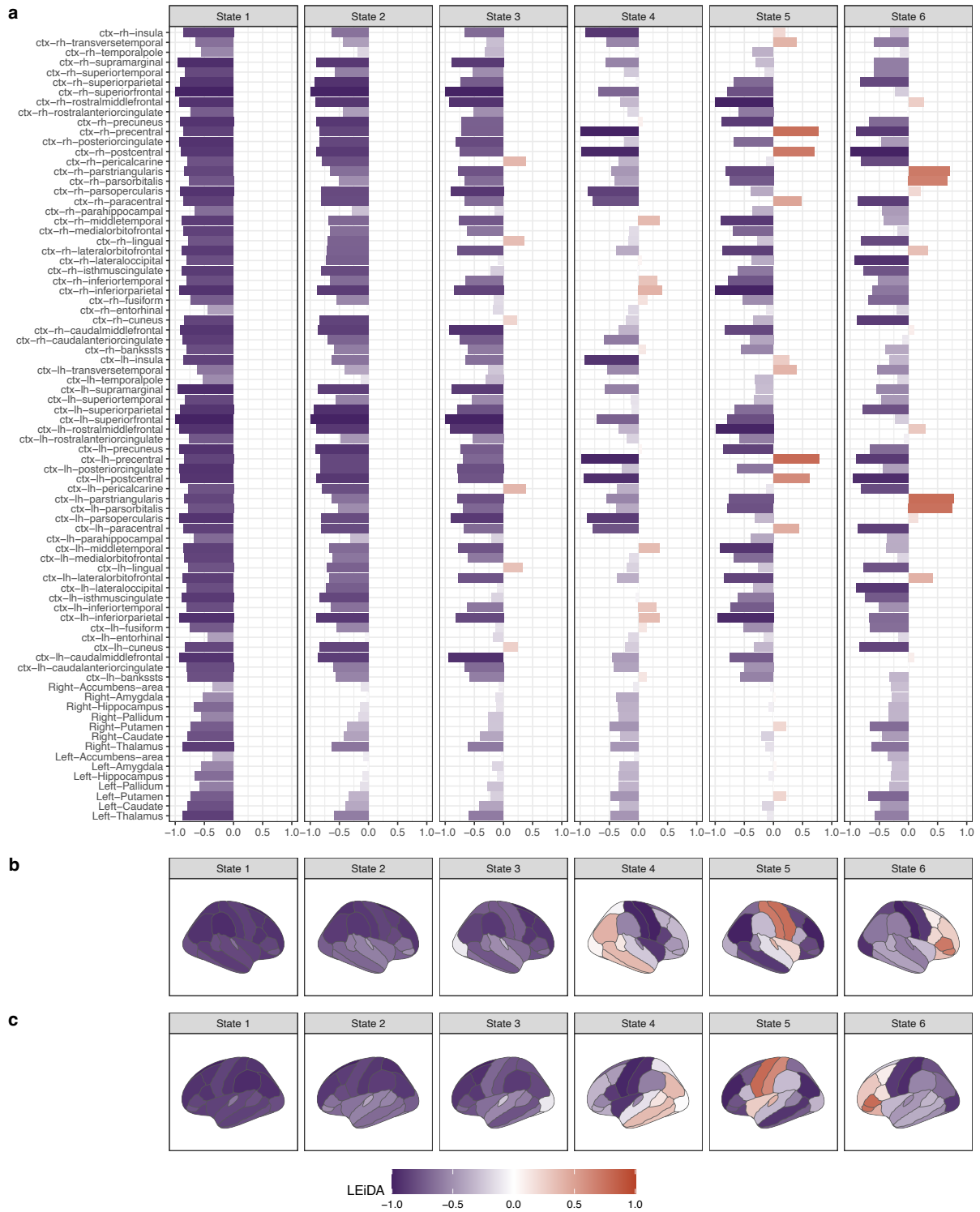
Supplementary Figures
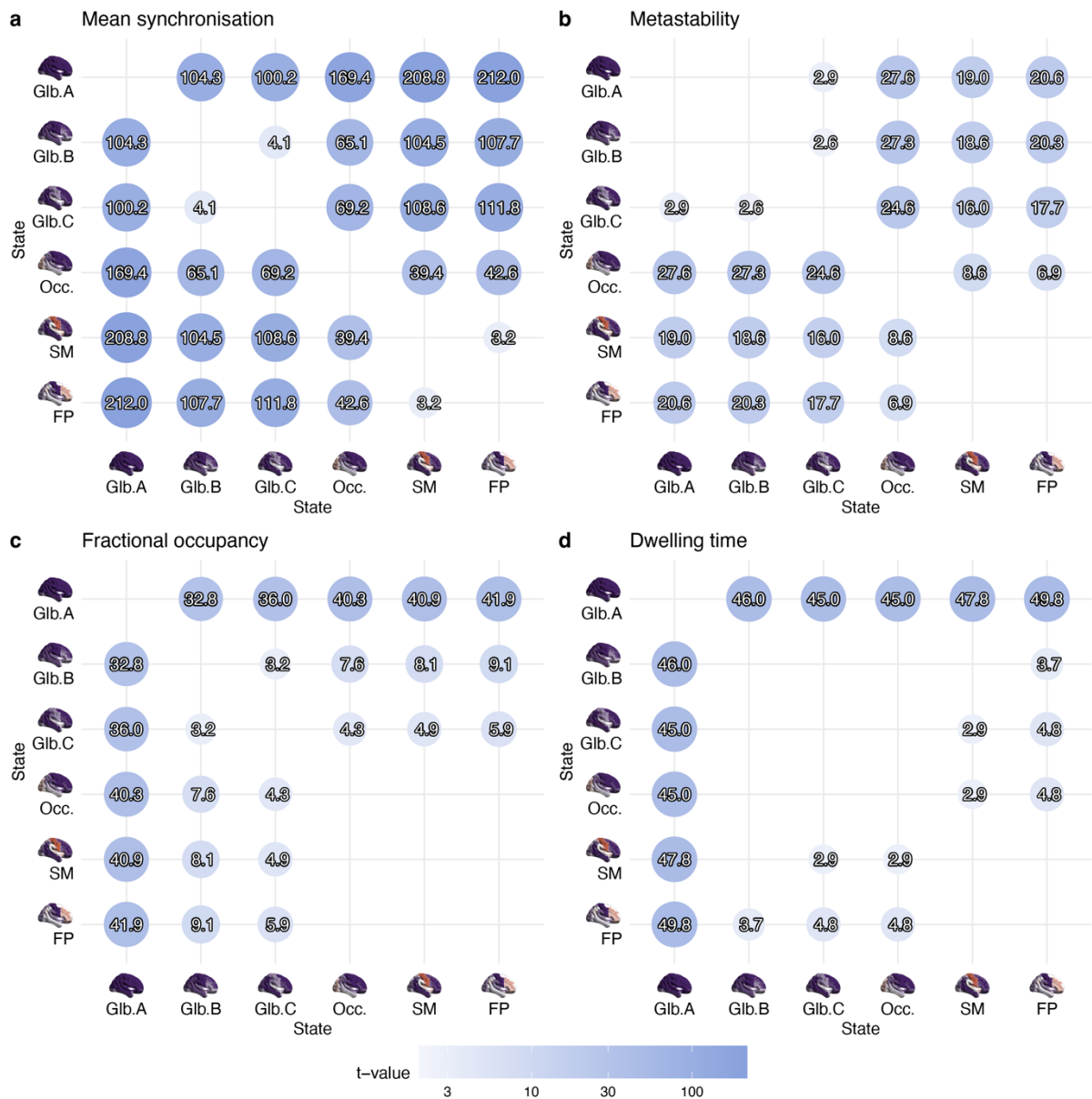
Supplementary Figure S1 | ANOVA two-sided post-hoc tests (n = 324) for **(a)** Mean synchronisation, **(b)** Metastability, **(c)** fractional occupancy, and **(d)** dwell times. Glb.: Global. Occ.: Occipital. SM: Sensorimotor. FP: Frontoparietal.

a GA††† (t-statistic)

	Dwell times	Fractional Occupancy	Mean synchronisation	Metastability
Glb.A	4.71	4.32	5.24	
Glb.B		−3.46	3.61	
Glb.C	3.13		3.18	
Occ.		−2.36	3.42	
SM		−2.32		
FP		−3.40	2.82	3.36

b State transitions associated with GA†††

Glb.B   Glb.A

t = 5.007

t = −3.117

t = −5.155

Glb.C   FP

t = −4.041

Occ.   SM

Supplementary Figure S2 | Association of GA at birth with modular features of neonatal brain dynamics (n = 390). (a) Summary of associations between each of the four metrics (dwell times, fractional occupancy, mean synchronisation, metastability) and GA at birth. **(b)** Association of state transitions probabilities and GA at birth. †††GLM3 (including 324 term-born and 66 preterm-born babies): $y \sim \beta_0 + \beta_1 GA + \beta_2 PMA + \beta_3 Sex + \beta_4 Motion\ outliers\ (FD)$. * p < 0.05. ** p < 0.01. *** p < 0.001. Glb.: Global. Occ.: Occipital. SM: Sensorimotor. FP: Frontoparietal. PMA: Postmenstrual age. PND: Postnatal days. GA: Gestational age.

Supplementary Figure S3 | Brain states in neonates using M-CRIB atlas. (a) LEiDA vectors for each of the six brain states identified in the neonatal brain using M-CRIB parcels. **(b)** Representation of LEiDA on brain surfaces (right side view). **(c)** Representation of LEiDA on brain surfaces (left side view).
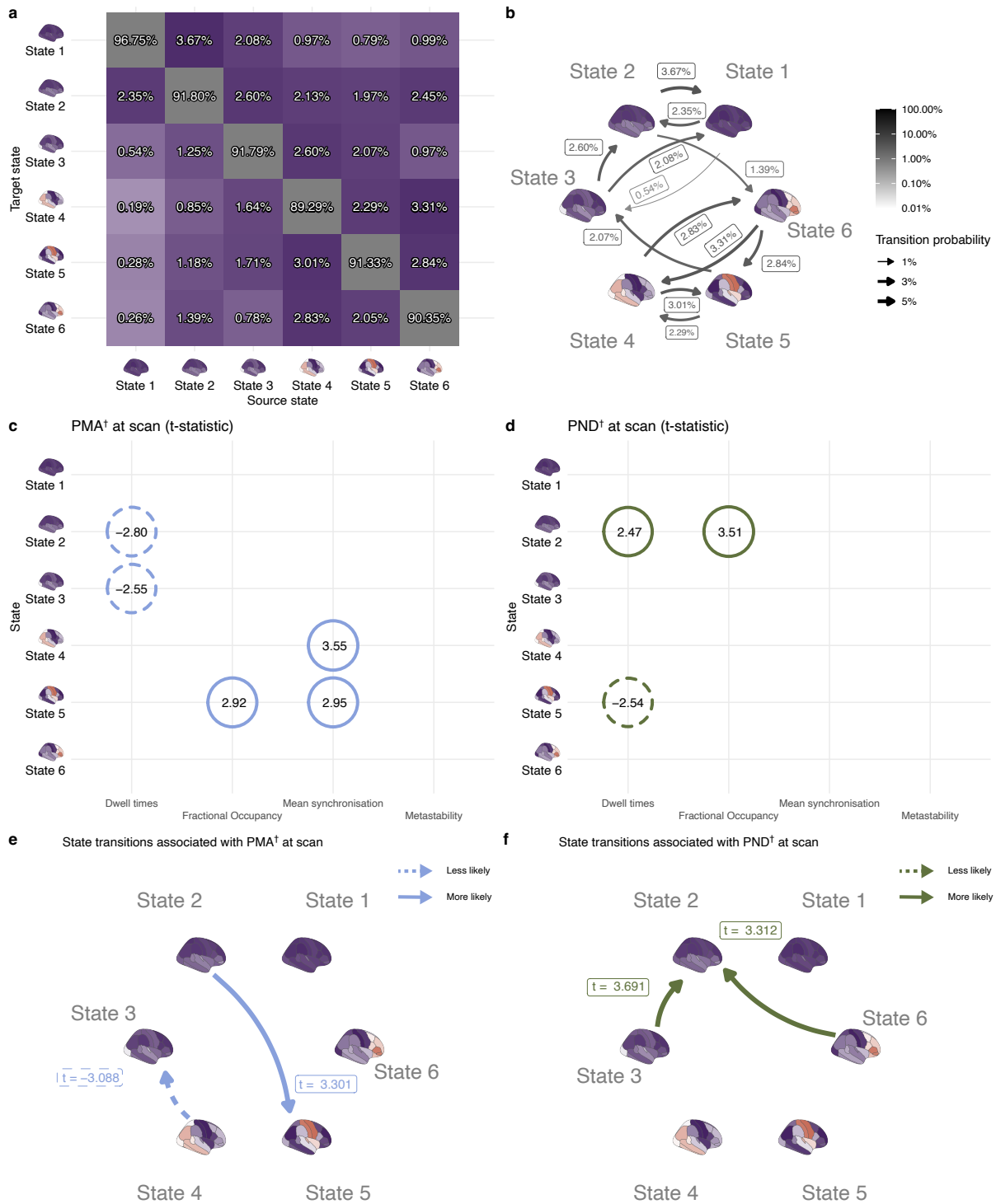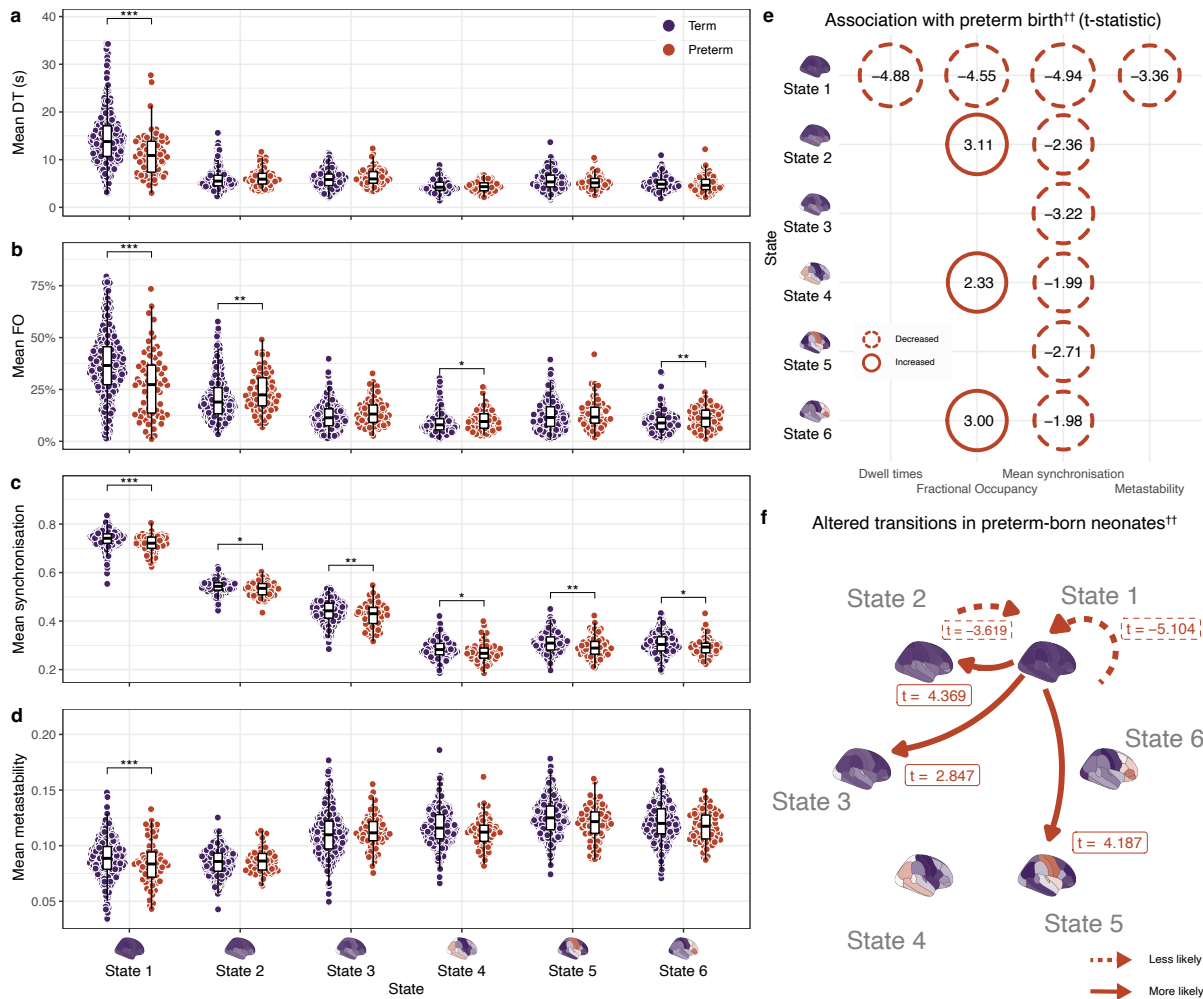
Supplementary Figure S4 | Brain dynamics in term-born neonates (n = 324) (M-CRIB atlas).
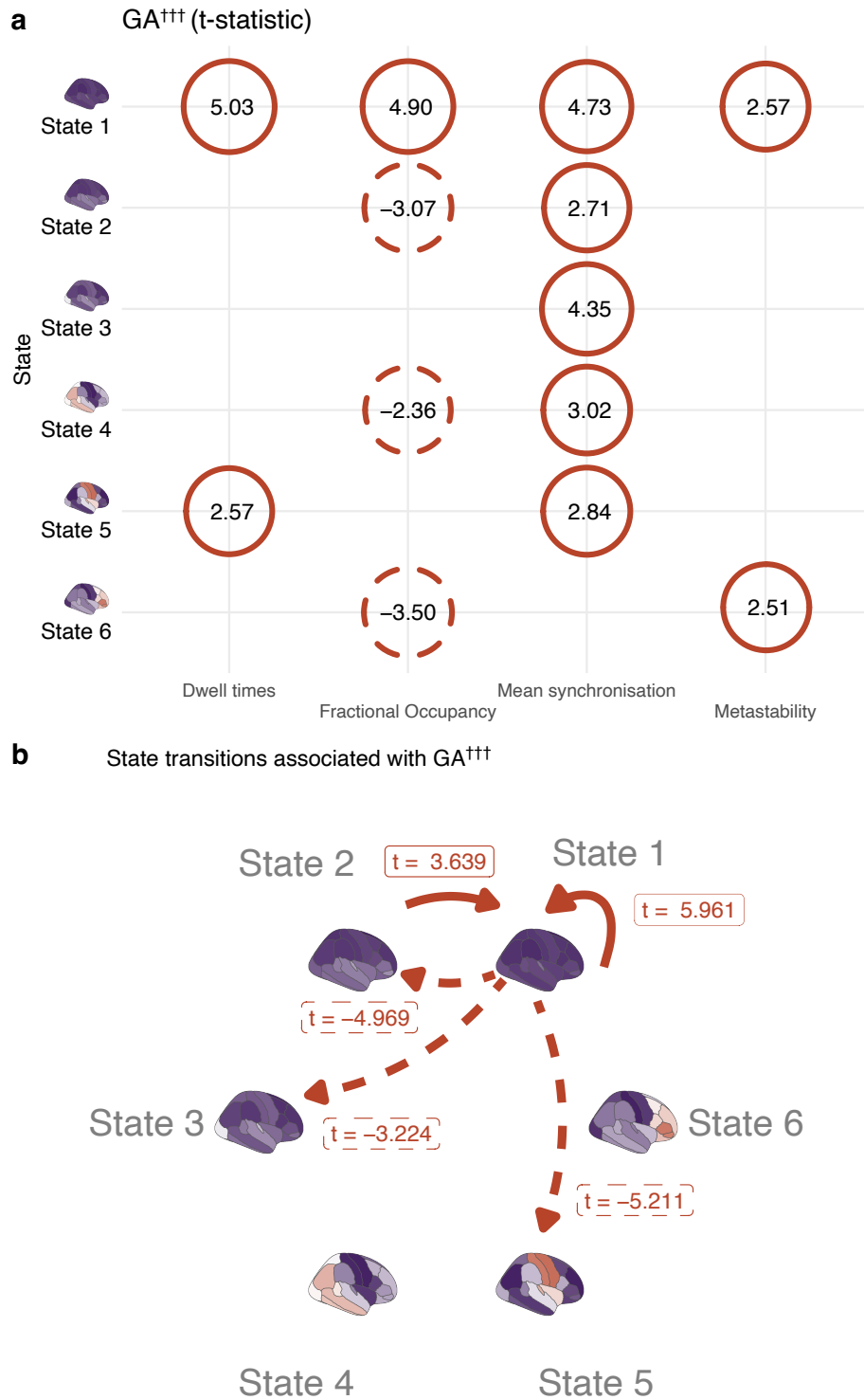(**a**) All transitions including dwelling state transitions. (**b**) Main transitions (top 12) between states excluding dwelling sequences. (**c**) Summary of brain state features significantly associated with PMA at scan. (**d**) Summary of brain state features significantly associated with PND at scan. (**e**) Summary of significant correlations between state transitions probabilities and PMA at scan. (**f**) Summary of significant correlations between state transitions probabilities and PND at scan. [†]GLM1 (including 324 term-born babies): $y \sim \beta_0 + \beta_1 PMA + \beta_2 PND + \beta_3 Sex + \beta_4 Motion$ outliers (FD). Values shown in **c** and **d** indicate t-statistics. All significant associations (two-sided permutation test) shown in this figure survive FDR multiple comparison correction with α error at 5%. PMA: Postmenstrual age. PND: Postnatal days.

Supplementary Figure S5 | Brain dynamics in preterm-born neonates (M-CRIB atlas).
(**a**) Mean dwell times (DT). (**b**) Mean fractional occupancy (FO). (**c**) Mean synchronisation.
(**d**) Metastability. (**e**) Summary of significant associations with preterm birth (**f**) Association of
state transitions probabilities and preterm birth. [†]GLM1 (324 term-born babies): $y \sim \beta_0 + \beta_1 PMA + \beta_2 PND + \beta_3 Sex + \beta_4 Motion\ outliers\ (FD)$. [††]GLM2 (324 term-born and 66 preterm-
born babies): $y \sim \beta_0 + \beta_1 Preterm\text{-}born + \beta_2 PMA + \beta_3 Sex + \beta_4 Motion\ outliers\ (FD)$. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$ obtained with a two-sided permutation test. Values shown in
e indicate t-statistics. Boxplots showing 0th, 25th, 50th, 75th and 100th centiles. Outliers
defined when value larger than 1.5*IQR + 75th centile. All significant associations highlighted
survive FDR multiple comparison correction with α error at 5%. PMA: Postmenstrual age.
PND: Postnatal days. DT: Dwell time. FO: Fractional occupancy.

a GA††† (t-statistic)

State 1: 5.03, 4.90, 4.73, 2.57
State 2: −3.07, 2.71
State 3: 4.35
State 4: −2.36, 3.02
State 5: 2.57, 2.84
State 6: −3.50, 2.51

Dwell times · Fractional Occupancy · Mean synchronisation · Metastability

b State transitions associated with GA†††

State 2 → State 1: t = 3.639
State 1: t = 5.961
t = −4.969
t = −3.224
t = −5.211

State 3, State 4, State 5, State 6

Supplementary Figure S6 | Association of GA at birth with modular features of neonatal brain dynamics (M-CRIB atlas). (**A**) Summary of associations between each of the four metrics (dwell times, fractional occupancy, mean synchronisation, metastability) and GA at birth. (**B**) Association of state transitions probabilities and GA at birth. †††GLM3 (including 324 term-born and 66 preterm-born babies): $y \sim \beta_0 + \beta_1 GA + \beta_2 PMA + \beta_3 Sex + \beta_4 Motion$ outliers (FD). * p < 0.05. ** p < 0.01. *** p < 0.001. Occ.: Occipital. SM: Sensorimotor. FP: Frontoparietal. PMA: Postmenstrual age. GA: Gestational age.
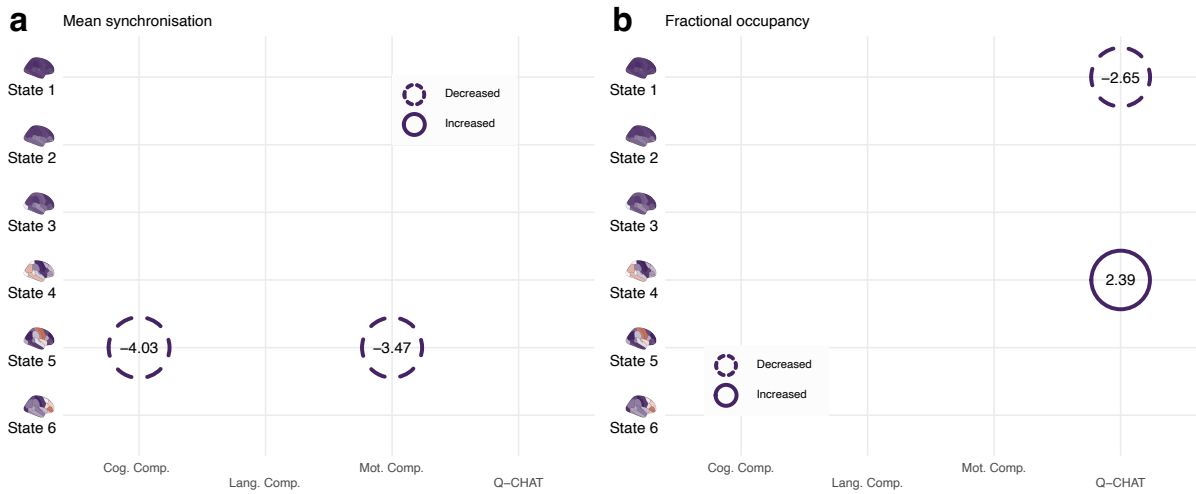
Supplementary Figure S7 | Summary of associations of brain state features with neurodevelopmental outcomes at 18 months corrected age (M-CRIB atlas). Association of average (**a**) mean synchronisation and (**b**) fractional occupancy in each of the six defined brain states during perinatal period with cognitive (Cog. Comp), language (Lang. Comp.) and motor (Mot. Comp) Bayley-III composite scores and Q-CHAT scores. GLM3 (257 term-born and 48 preterm-born babies for Bayley-III; and 254 term-born and 46 preterm-born babies for Q-CHAT): $y \sim \beta_0 + \beta_1 GA + \beta_2 PMA + \beta_3 Sex + \beta_4 Motion\ outliers\ (FD) + \beta_5[Corrected\ age\ at\ assessment] + \beta_6[Assessed\ component] + \beta_7[Index\ of\ multiple\ deprivation]$. Values shown in in both panels indicate t-statistics. All significant associations (two-sided permutation test) highlighted survive FDR multiple comparison correction with α error at 5%. PMA: Postmenstrual age. GA: Gestational age. Cog.: Cognitive. Lang.: Language. Mot.: Motor. Comp.: Component. Q-CHAT: Quantitative Checklist for Autism in Toddlers.
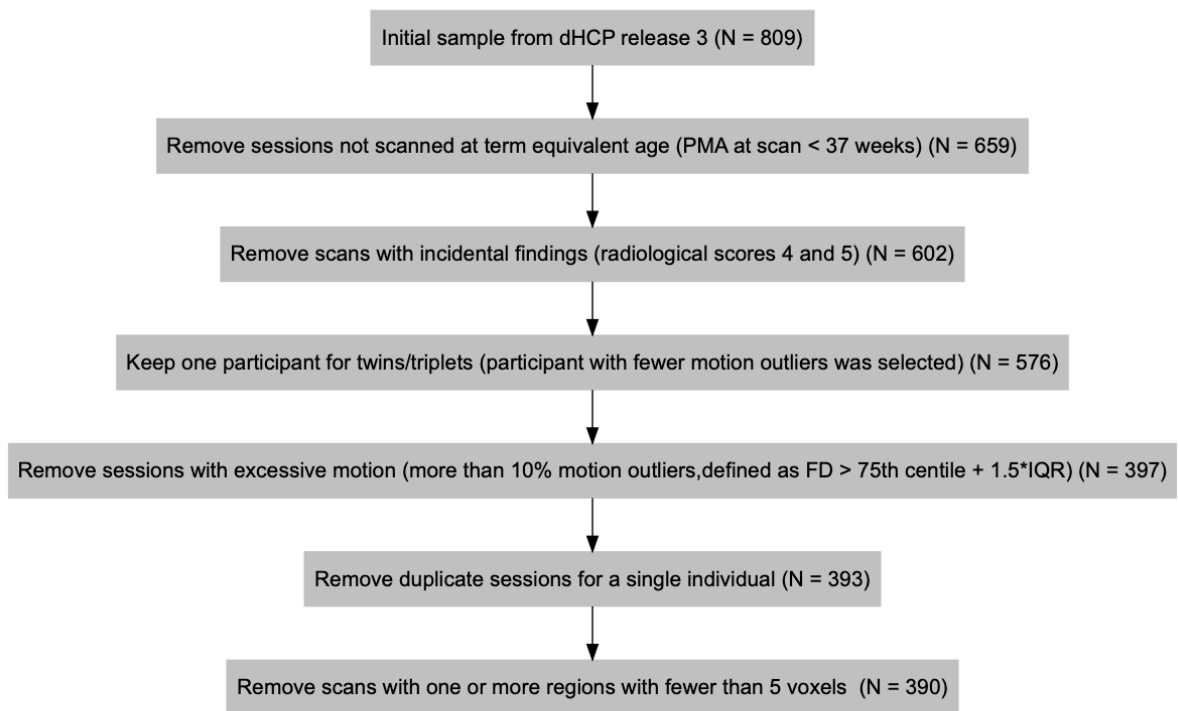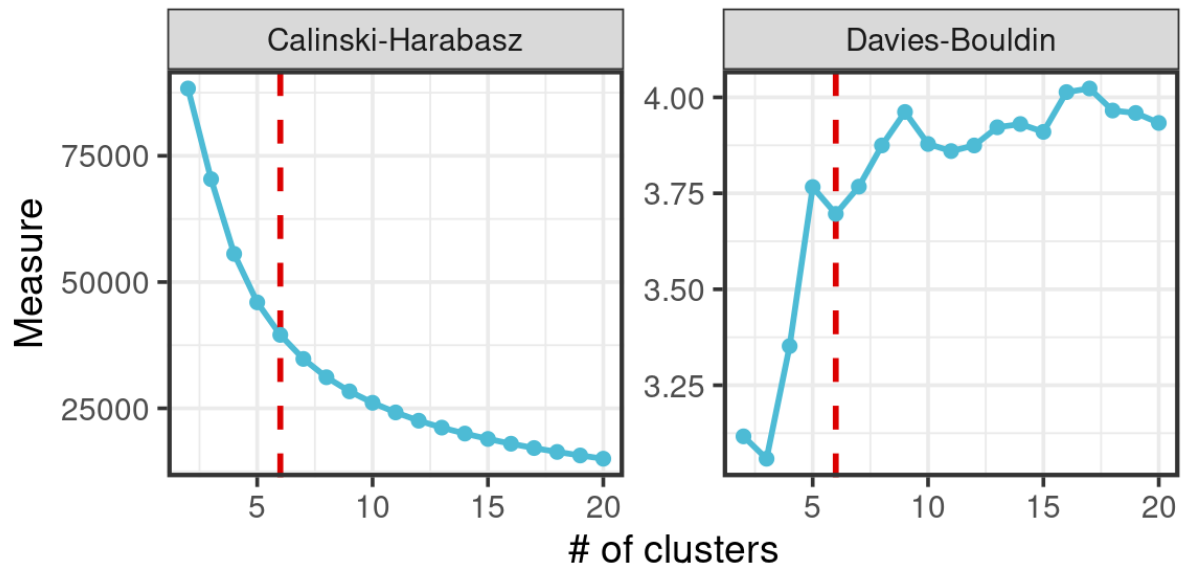
Supplementary Figure S8. Exclusion criteria flowchart.
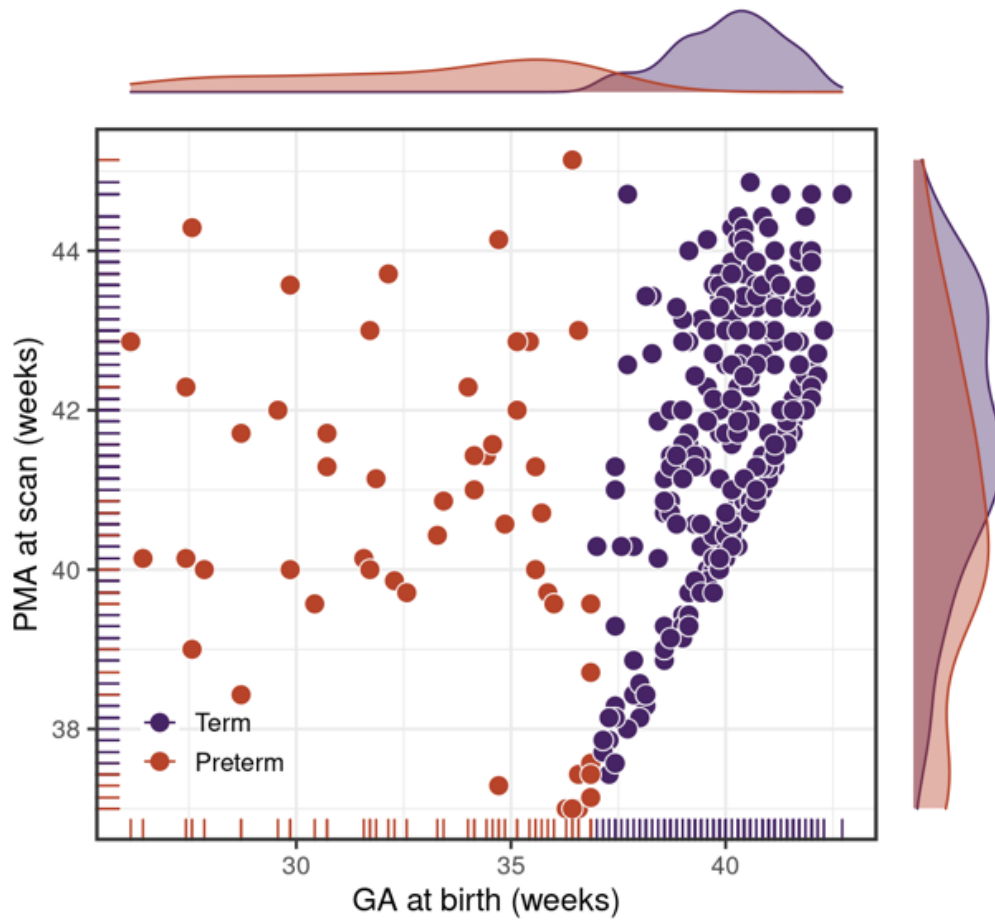
Supplementary Figure S9. Distribution of gestational age (GA) at birth and postmenstrual age (PMA) at scan for the participants included in this study.

Supplementary Figure S10. Ideal number of clusters according to Calinski-Harabasz and Davies-Bouldin methods.

Supplementary Results: Association of neonatal brain regional brain dynamics with PMA at scan and GA at birth using an alternative brain parcellation (M-CRIB atlas)

The six brain states obtained with the alternative M-CRIB neonatal atlas were compatible with the ones obtained for the AAL atlas (Supplementary Figure S3), with three global synchronisation states and three more regionally constrained. States 1, 2 and 3 obtained with the M-CRIB atlas were consistent with global synchronisation states obtained with the AAL atlas. The M-CRIB's State 4 featured some of the structures present in Occipital state, State 5 featured similar structures to the sensorimotor state, and State 6 was concordant with FP state obtained from AAL.

In term-born babies, PMA at scan is associated with increased mean synchronisation in State 4 ($t = 3.6$; $p < 0.001$) and State 5 ($t = 2.9$; $p = 0.003$); and fractional occupancy in State 5 ($t = 2.9$; $p = 0.002$). PMA is also associated with reduced dwell times for States 2 ($t = -2.8$; $p = 0.004$) and 3 ($t = -2.6$; $p = 0.012$). Transitions from State 2 to State 5 increased ($t = 3.3$; $p = 0.001$) and transitions from State 4 to State 3 decreased ($t = -3.1$; $p = 0.003$) with PMA. Also, in term-born babies, PND is associated with increases in dwell times ($t = 2.5$; $p = 0.012$) and fractional occupancy ($t = 3.5$; $p < 0.001$; and reduced dwell times for State 5 ($t = -2.5$; $p = 0.012$). Transitions from States 3 and 6 to State 2 also increased with PND ($t = 3.7$; $p < 0.001$ and $t = 3.3$; $p = 0.002$, respectively). SM and State 5 exhibit compatible associations with PMA and PND (Supplementary Figure S4).

Preterm-birth is associated with reduced dwell times for State 1 ($t = -4.9$; $p < 0.001$); reduced fractional occupancy for State 1 ($t = -4.5$; $p < 0.001$); reduced mean synchronisation for the States 1 ($t = -4.9$; $p < 0.001$), 2 ($t = -2.4$; $p = 0.018$), 3 ($t = -3.2$; $p = 0.002$), 4 ($t = -2.0$; $p = 0.047$), 5 ($t = -2.7$; $p = 0.007$), and 6 ($t = -2.0$; $p < 0.05$); and reduced metastability for Stage 1 ($t = -3.0$; $p = 0.003$). We have also found an association with increased fractional occupancy for States 2 ($t = 3.1$; $p = 0.002$), 4 ($t = 2.3$; $p = 0.019$), and 6 ($t = 3.0$; $p = 0.003$). Transitions from State 2 to State 1 ($t = -3.6$; $p < 0.001$) and dwelling sequences of State 1 ($t = -5.1$; $p < 0.001$) are reduced in preterm birth. Transitions from State 1 to State 2 ($t = 4.4$; $p < 0.001$); State 1 to State 3 ($t = 2.8$; $p = 0.005$); and State 1 to State 5 ($t = 4.2$; $p < 0.001$) increased with preterm birth (Supplementary Figure S5 and Supplementary Figure S6).

Developmental outcomes in cognitive ($t = -4.0$; $p < 0.001$) and motor ($t = -3.5$; $p < 0.001$) components of Bayley-III show negative associations with mean synchronisation for State 5. Moreover, higher Q-CHAT scores were associated with reduced fractional occupancy for State 1 ($t = -2.7$; $p = 0.008$) and increased fractional occupancy ($t = 2.4$; $p = 0.017$), see Supplementary Figure S7 for a summary. The results for Mean synchronisation for State 5 are compatible with those shown in AAL atlas (SM state), as well as fractional occupancy and Q-CHAT for State 1.