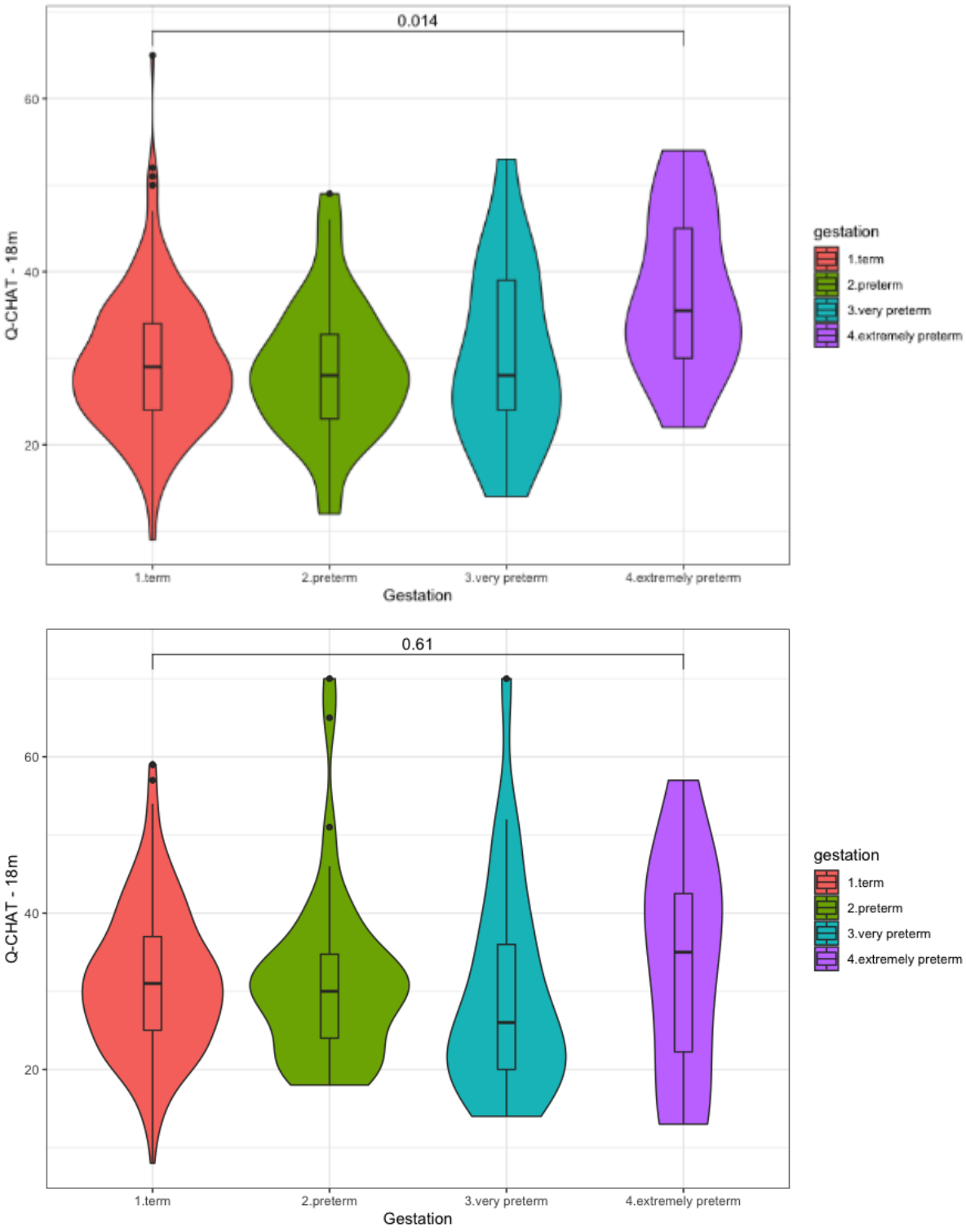
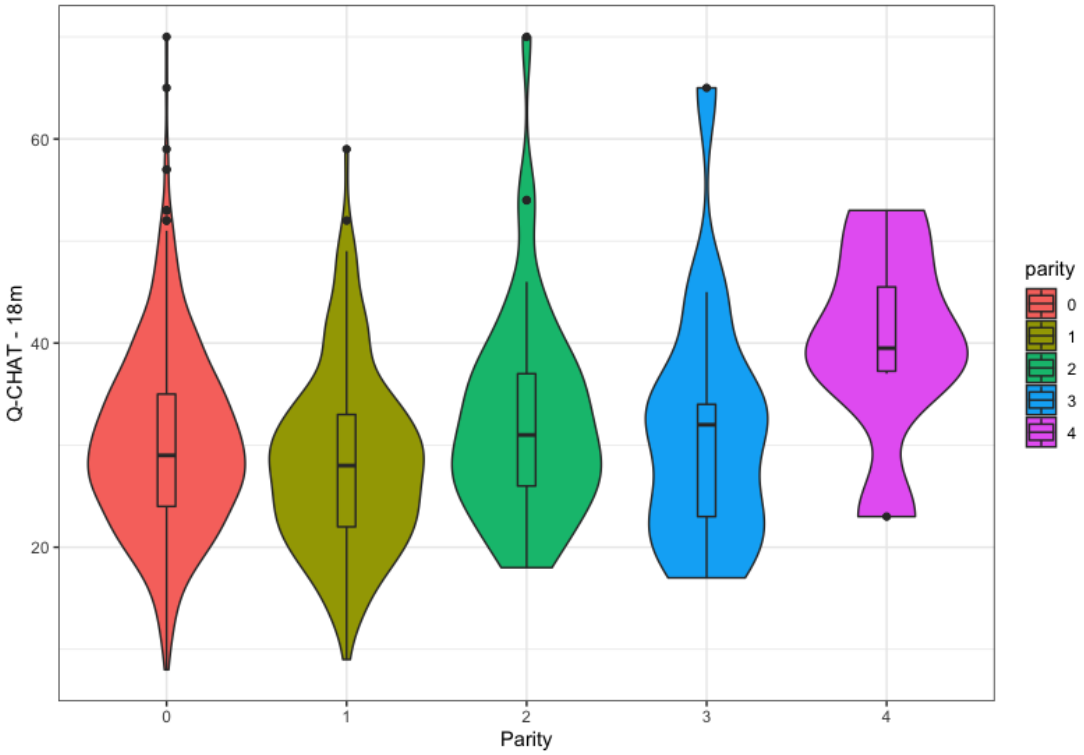
Supplementary Material



Supplementary Figure 1: Autistic traits and prematurity. Only females (top panel) show a significant increase in Q-CHAT in extremely preterm cases (p-value is student's t-test).



Supplementary Figure 2: Autistic traits on Q-CHAT and maternal parity. No significant differences were found, when comparing pairwise or linearly via regression.

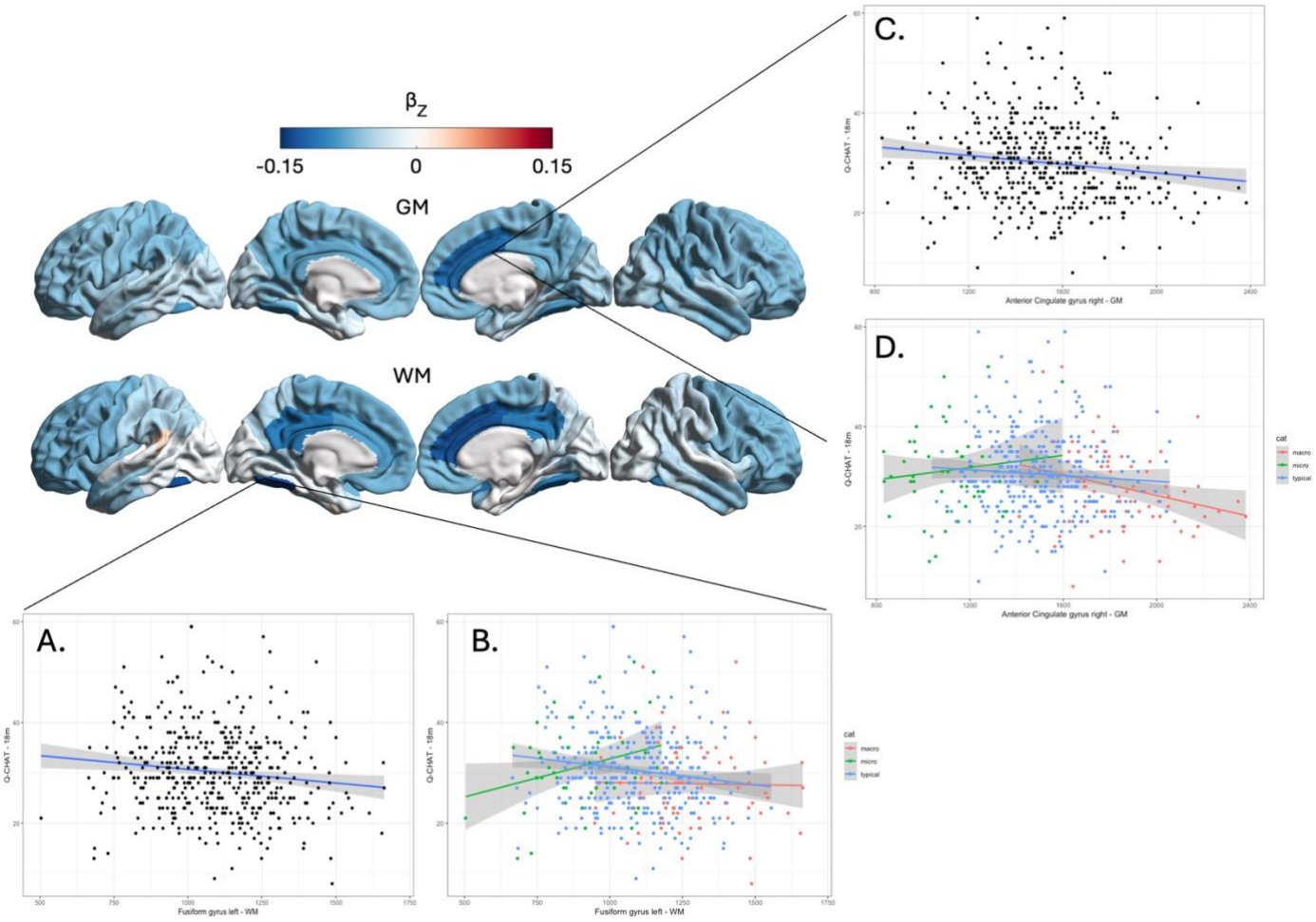
Supplementary Table 1: Maternal and infant characteristics in the subset of the dHCP cohort in which brain volume was studied in association to Q-CHAT (n=454), based on specific exclusion criteria outlined in the main text.

	Mean (SD)	**Effect size for Q-CHAT**	**95% CI**	**p - value**
Maternal age	33.67 (4.74)	r=-0.142	-0.231 – -0.051	0.002*
Paternal age	36.16 (6.03)	r=-0.054	-0.147 - 0.039	0.252
Maternal parity	n-0=365 n-1=140 n-2=46 n-3=16 n-4=4 n-5=3	r=-0.030	-0.12 – 0.06	0.533
Gestational age at birth	39.61 (1.99) weeks	r=-0.010	-0.100- 0.085	0.879
Birth Weight	3.33 (0.59) kg	r=-0.05	-0.140 – -0.045	0.305
Age at Q-CHAT	19.2(2.16) months	r=-0.58	-0.149 - 0.034	0.217

Model 2 identified regions that interacted with the total brain volume effect on Q-CHAT at a nominal level of significance (Table 4). These included anterior cortical regions, such as the right anterior cingulate (both WM and GM), right anterior temporal lobe and structures such as the amygdala and the subthalamic nuclei bilaterally. Their interactions with TBV were negative, indicating that they were non-additive with TBV on Q-CHAT scores (Suppl Table 4). This was further supported by post-hoc categorisation based on TBV, with infants at the lower centiles showing positive trends for an association to Q-CHAT scores, compared to the higher TBV centiles (Suppl Figure).

Suppl Table 2: Nominally associated regions in the dHCP that interacted with total brain volume in their association to Q-CHAT. None passed FDR-corrected of statistical significance. Model also included birth weight and age at Q-CHAT (data not shown, all non-significant)).r is partial coefficient of each variable in multiple regression.

	dHCP Model 2	**Regional volume**	**TBV**	**Regional x TBV**	**Sex**	**Maternal age**
GM	Anterior cingulate gyrus (R – GM)	r=0.112	r=0.053	r=-0.112	r=0.117	r=-0.124
		p=0.018	p=0.268	p=0.018	p=0.013	p=0.009
	Amygdala (R)	r=0.100	r=0.074	r=-0.111	r=0.120	r=-0.122
		p=0.035	p=0.119	p=0.019	p=0.011	p=0.010
	Subthalamic nucleus (L)	r=0.116	r=0.047	r=-0.100	r=0.116	r=-0.116
		p=0.015	p=0.323	p=0.035	p=0.014	p=0.015
	Subthalamic nucleus (R)	r=0.094	r=0.057	r=-0.098	r=0.120	r=-0.119
		p=0.047	p=0.229	p=0.039	p=0.011	p=0.012
WM	Post. fusiform gyrus (L – WM)	r=0.102	r=0.065	r=-0.110	r=0.122	r=-0.121
		p=0.032	p=0.170	p=0.021	p=0.010	p=0.011
	Ant. cingulate gyrus (R – WM)	r=0.102	r=0.058	r=-0.106	r=0.120	r=-0.125
		p=0.032	p=0.222	p=0.025	p=0.011	p=0.008
	Thalamus (low intensity part - R)	r=0.122	r=0.041	r=-0.111	r=0.112	r=-0.115
		p=0.010	p=0.382	p=0.019	p=0.018	p=0.015
	Anterior lateral temporal lobe (R - WM)	r=0.095	r=0.038	r=-0.098	r=0.116	r=-0.115
		p=0.045	p=0.422	p=0.039	p=0.014	p=0.015



Suppl Figure 3: Atlas showing effect sizes of association to Q-CHAT of the interaction term that included postnatal total brain volume and the volumes of each cortical grey matter (GM) and white matter (WM) region in the dHCP, regardless of statistical significance. (A and C): Fusiform gyrus (left – WM) and anterior cingulate (right – GM) were associated negatively with Q-CHAT at a nominal level of statistical significance, (B and D): when considering TBV as a categorical variable, infants in lower centiles (category 'micro'< (meanTBV- SD)) show evidence of positive associations, indicating an opposite interaction with TBV in predicting later autistic traits.

Suppl Table 3: Matching of brain regions in the dHCP that were nominally associated with Q-CHAT scores, to regions that were studied in the CHILD ROI association analysis. Segmentation methods were based on the 'drawEM' template for dHCP and STA31 template for CHILD.

Nominally associated brain segments in the dHCP with Q-CHAT scores	**Equivalent regions for ROI in CHILD**
Anterior lateral temporal lobe (R - WM)	Mid. Temporal Pole (R)
	Sup. Temporal Pole (R)
Posterior medial-inferior temporal gyri (R – WM)	Mid. Temporal Gyrus (R)
	Inf. Temporal Gyrus (R)
Amygdala (R)	Amygdala (R)
Posterior parahippocampal gyrus (L-GM)	Parahippocampal gyrus (L)
Posterior parahippocampal gyrus (R-WM)	Parahippocampal_R
Subthalamic nucleus (R)	Subthalamic Nucleus (R)
Anterior cingulate gyrus (R – GM)	Ant. Cingulum (R)
Anterior cingulate gyrus (R – WM)	
Subthalamic nucleus (L)	Subthalamic Nucleus (L)
Thalamus (low intensity part - R)	Thalamus (R)
Thalamus (low intensity part - L)	Thalamus (L)
Lateral occipitotemporal & posterior fusiformis gyrus (L – WM)	Fusiform Gyrus (L)
Lateral occipitotemporal & anterior fusiformis gyrus (L - GM)	
Lateral occipitotemporal & anterior fusiformis gyrus (R)	Fusiform Gyrus (R)
Frontal lobe (R-WM)	Frontal_Mid_R
	Frontal_Sup_R
Brainstem spanning the midline	Midbrain_L
	Midbrain_R

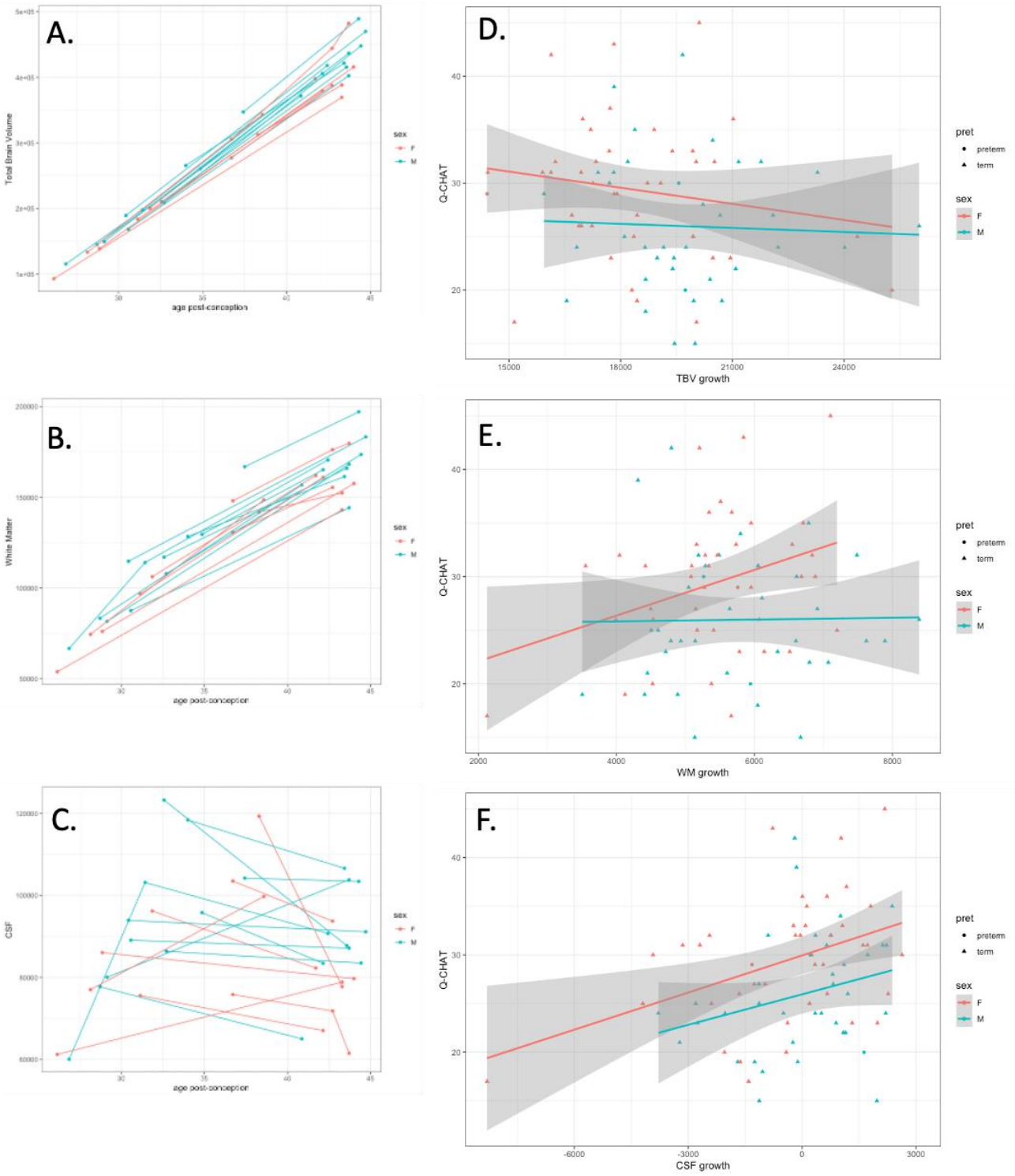
Supplementary Table 4: In CHILD, ROI analysis (Model 1) found no associations between the selected regions and autistic traits after controlling for TBV at either nominal or FDR-corrected level of significance.

Region	Regional volume	TBV	Sex	Maternal age	Age at Q-CHAT
Temporal_Pole_Sup_R	-0.443	-0.242	-0.074	-0.185	-0.443
	0.075	0.349	0.778	0.478	0.075
Frontal_Sup_R	-0.366	0.033	-0.110	-0.208	-0.366
	0.148	0.901	0.675	0.423	0.148
Thalamus_R	-0.325	-0.170	0.006	-0.061	-0.325
	0.203	0.515	0.982	0.817	0.203
Cingulum_Ant_R	0.219	-0.439	-0.032	-0.062	0.219
	0.398	0.078	0.901	0.813	0.398
Temporal_Mid_R	-0.217	-0.243	-0.030	-0.118	-0.217
	0.402	0.347	0.910	0.653	0.402
Temporal_Inf_R	-0.207	-0.198	-0.019	-0.079	-0.207
	0.425	0.447	0.942	0.763	0.425
Amygdala_R	0.204	-0.501	-0.051	-0.182	0.204
	0.433	0.041	0.846	0.485	0.433
Temporal_Pole_Mid_R	-0.177	-0.409	0.037	-0.190	-0.177
	0.496	0.103	0.889	0.466	0.496
Thalamus_L	-0.108	-0.328	-0.018	-0.127	-0.108
	0.681	0.198	0.946	0.626	0.681
Frontal_Mid_R	0.105	-0.407	-0.026	-0.170	0.105
	0.690	0.105	0.921	0.514	0.690
Subthalamic_Nuc_R	-0.099	-0.436	-0.065	-0.139	-0.099
	0.706	0.080	0.804	0.593	0.706

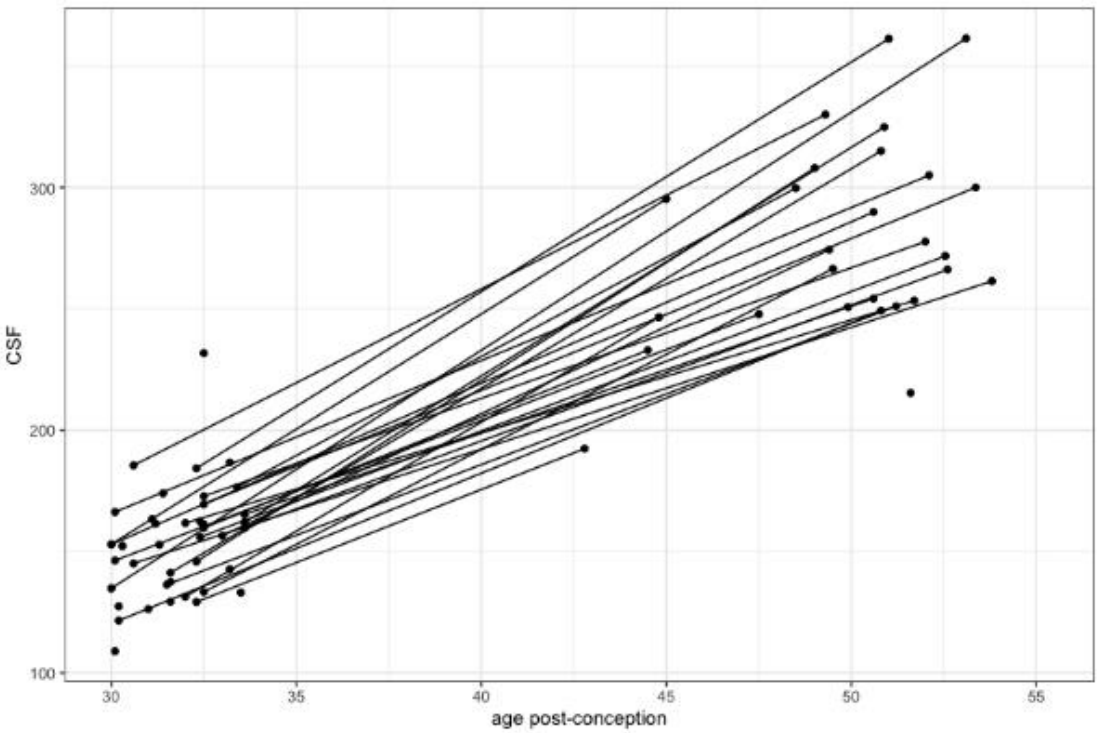
Subthalamic_Nuc_L	-0.098	-0.398	-0.061	-0.146	-0.098
	0.709	0.114	0.816	0.576	0.709
ParaHippocampal_L	0.074	-0.410	-0.043	-0.164	0.074
	0.778	0.102	0.870	0.528	0.778
Fusiform_L	0.069	-0.371	-0.056	-0.165	0.069
	0.793	0.143	0.831	0.526	0.793
ParaHippocampal_R	0.019	-0.429	-0.030	-0.145	0.019
	0.942	0.086	0.908	0.580	0.942

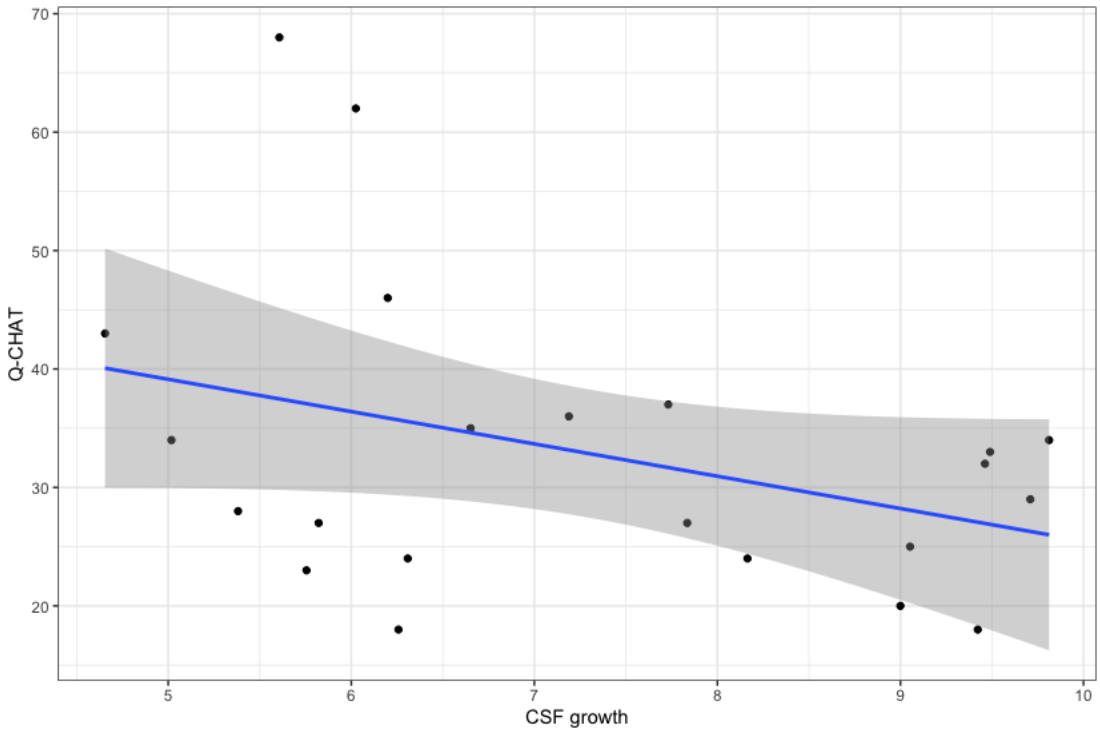
Supplementary Table 5: Fetal global brain metrics of individuals scanned prenatally but not postnatally in the dHCP, and their association to Q-CHAT scores at 18 months. Additional covariates (data not shown) included fetal age at the time of scan in gestational weeks and birth weight.

Q-CHAT	**TBV**	**Sex**	**Age at Q-CHAT**	**Maternal age**	**Age at scan**
dHCP,	r=-0.21	r=0.23	r=-0.10	r=0.02	r=0.20
n=106	p=0.102	p=0.076	p=0.432	p=0.864	p=0.135
Adjusted R-squared: 0.0367, p-value: 0.228					
Q-CHAT	**Grey Matter**	**Sex**	**Age at Q-CHAT**	**Maternal age**	**Age at scan**
dHCP,	r=-0.16	r=0.20	r=-0.10	r=0.02	r=0.13
n=106	p=0.232	p=0.123	p=0.443	p=0.899	p=0.318
Adjusted R-squared: 0.016, p-value: 0.335					
Q-CHAT	**White Matter**	**Sex**	**Age at Q-CHAT**	**Maternal age**	**Age at scan**
dHCP,	r=-0.15	r=0.21	r=-0.10	r=-0.00	r=0.13
n=106	p=0.243	p=0.110	p=0.438	p=0.972	p=0.319
Adjusted R-squared: 0.015, p-value: 0.342					
Q-CHAT	**CSF**	**Sex**	**Age at Q-CHAT**	**Maternal age**	**Age at scan**
dHCP,	r=-0.20	r=0.17	r=-0.13	r=-0.01	r=0.12
n=106	p=0.123	p=0.186	p=0.313	p=0.935	p=0.358
Adjusted R-squared: 0.032, p-value: 0.250					



Supplementary Figure 4: Linked total brain measurements for individuals scanned both prenatally and postnatally in the dHCP, together with rates of change regressed over Q-CHAT scores.





Supplementary Figure 5: Perinatal CSF change in CHILD and association with Q-CHAT.