Prenatal exposure to perfluoroalkyl substances predicts multimodal brain structural and functional outcomes in children aged 5 years: a birth cohort study

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Summary

Background Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are ubiquitous persistent organic pollutants associated with adverse health outcomes in humans. Although they are associated with autism spectrum disorder and behavioural outcomes, whether PFAS affect brain development is unclear. We aimed to characterise the relationship between maternal PFAS and brain structure and function in typically developing children.

Methods This study was set within the FinnBrain Birth Cohort Study, a prospective observational study that enrolled mothers from three clinics in Turku, Finland, during their first trimester of pregnancy. Maternal serum samples at gestational week 24 were analysed for PFAS by mass spectrometry and, at age 5 years, children were assessed through structural, diffusion-weighted, and functional MRI. Whole-brain voxel-level and vertex-level maps of grey matter volume, white matter fractional anisotropy and mean diffusivity, and cortical thickness and surface area were combined to compute ten independent components. Data were analysed by correlation network, elastic net regression, and multivariate linear regression with multiple testing correction.

Findings Pregnant mothers were enrolled into the birth cohort study between Dec 1, 2011, and April 30, 2015, and study visits at age 5 years took place between Oct 1, 2017, and March 31, 2020. This analysis involved 51 mother–child dyads for whom maternal PFAS concentrations and structural MRI data for the child were available. PFAS concentrations in maternal serum samples were mostly 0–1 ng/mL. Maternal perfluorononanoic acid (PFNA; R^2=0·13, β=0·39 [95% CI 0·09–0·69], p_{adj}=0·024) and linear perfluorooctanoic acid (PFOA; 0·13, 0·36 [0·09–0·63], p_{adj}=0·022) linearly predicted a multimodal component dominated by corpus callosal integrity, whereas branched perfluorohexanesulphonic acid (PFHxS; R^2=0·12, β=0·31, p_{adj}=0·036) and branched PFOA (R^2=0·14, β=0·36, p_{adj}=0·016) predicted a component comprising mainly occipital cortex volume and surface area. Branched perfluorooctanesulphonic acid predicted hypothalamic microstructure (R^2=0·10, β=0·29, p=0·026). PFNA, linear PFOA, and branched PFOA are associated with increased functional connectivity in the right precentral gyrus, whereas branched PFHxS predicts decreased connectivity in the intracalcerine cortices. Associations were not influenced by sex assigned at birth, but were related to PFAS chemical structure.

Interpretation We show an association between prenatal PFAS exposure and brain developmental outcomes in children. These findings are pertinent given the ubiquitous circulation of PFAS in humans and the extreme environmental persistence of these substances.

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Introduction

Polyfluoroalkyl and perfluoroalkyl substances (PFAS) are anthropogenic compounds containing at least one fully fluorinated methyl or methylene carbon atom.[1] Because of their amphipathic properties, PFAS have been widely used since the mid-20th century to manufacture products resistant to water, oil, and heat or electrical conductivity. However, in the early 2000s, these compounds began to generate controversy after reports that three PFAS species are ubiquitously present in human serum samples,[2] and that the most widely used of these, perfluorooctanesulphonic acid (PFOS), accumulates in the environment through biomagnification and is present in diverse avian and marine species around the world.[3] PFAS have since attracted considerable public, political, and academic interest, leading to their status as persistent organic pollutants. Given their extreme environmental persistence, PFAS are present in the air, soil, and surface water, and humans are exposed through occupation (eg, firefighters and manufacturers), close contact with a polluted water source, or simply as a result of the presence of PFAS in all drinking water and foodstuffs, especially seafood.[4,5] Multiple PFAS are now present in more than 95% of humans,[6] with half-lives typically in the range of 2–5 years.[7]

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Research in context

Evidence before this study

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are well documented to circulate ubiquitously in humans and to cross the placental and blood–brain barriers with high efficiency. Although they are currently associated with various adverse health outcomes, including effects on immune system development and fetal metabolism, emerging research is beginning to implicate PFAS in brain development. We searched PubMed and Google Scholar from database inception to May 1, 2025, for articles written in English, using the search terms ("PFAS" OR "per-fluoroalkyl" OR "per-fluoroalkyl substance" OR "PFNA" OR "PFOS" OR "PFHxS" OR "PFOA") AND ("brain" OR "brain development" OR "neurodevelopment" OR "MRI" OR "neuroimaging" OR "neurodevelopmental disorder" OR "cognition"). Maternal and perinatal PFAS increase the risk of diagnosis or traits of autism spectrum disorder, whereas the evidence for cognitive outcomes is mixed: many studies report no association or, more commonly, the findings differ substantially by PFAS, sex, age, and study and statistical design. Only two studies to date have examined any brain outcomes in relation to maternal PFAS: one in a sample of Taiwanese adolescents aged 13–16 years, the results of which were published between 2023 and 2025, and the other in Canadian children aged 2–6 years, with results published in 2025. Both studies reported associations between maternal PFAS and brain structural outcomes in offspring, particularly white matter microstructure.

Added value of this study

To our knowledge, this study is the first to comprehensively examine the association between prenatal (maternal) PFAS and multiple brain structural and functional outcomes in offspring at a whole-brain, voxel-wise, and vertex-wise level; the second to examine brain structural outcomes in young children in the context of maternal PFAS; the first to study the hypothalamus in this context, which has the highest accumulation of PFAS in the brain; and the first to consider the role of the chemical structure of PFAS on brain structural and functional outcomes in offspring. We measured multiple linear and branched PFAS in the serum of pregnant mothers and assessed their children at age 5 years using MRI. To comprehensively explore the relationship between prenatal PFAS exposure and the brain, we examined all the main brain tissue parameters simultaneously by computing ten components via linked independent component analysis. Using multiple robust statistical techniques, we show that specific maternal PFAS strongly and linearly predict two multimodal brain structural components, the microstructures of the hypothalamus and the corpus callosum, and brain functional connectivity. Associations were not influenced by sex assigned at birth but were related to the chemical structure of the PFAS, and were robust against confounders, outliers, and multiple testing.

Implications of all the available evidence

Maternal PFAS concentrations during pregnancy were found to strongly predict multiple brain structural outcomes in offspring at age 5 years, including the microstructures of the corpus callosum and hypothalamus and the occipital cortical volume, as well as brain functional connectivity. The associations are specific to the given chemical compound, in line with previous findings on cognitive and diagnostic outcomes. Our data are consistent with a high degree of transplacental transfer of PFAS from the mother to the fetus and with their implication in autism spectrum disorder. Specifically, perfluorooctanoic acid and perfluorononanoic acid have previously been reported to increase the risk of autism spectrum disorder whereas perfluorohexanesulphonic acid decreased the risk and perfluorooctanesulphonic acid was not associated, and we observed consistent effects for these PFAS in terms of occipital cortical volume and brain functional connectivity. This study sits within an emerging body of evidence that shows an association between prenatal and perinatal PFAS exposure and brain structure and function in children and adolescents. Collectively, this evidence suggests that PFAS could influence human brain development even at low concentrations in the general population, which is particularly concerning given their ubiquitous presence in pregnancies globally.

PFAS concentrations in the general population are linked to various adverse health outcomes, most notably immunosuppression,[8] effects on thyroid endocrine physiology[9] and on the synthesis and circulation of cholesterol and bile acids,[10] and metabolic dysfunction-associated steatotic liver disease.[11] Pregnant mothers are particularly vulnerable to PFAS, which increase the risk of low birthweight[12] and preterm birth.[13] As a consequence of their interaction with maternal physiological systems, PFAS might therefore affect the fetal brain, although changes in maternal bile acid concentrations are more likely to act indirectly, via modulation of the gut–brain axis and the permeability of the blood–brain barrier, than to have a direct effect.[14] There is also a clear mechanism by which PFAS can directly reach the developing nervous system and interfere with cellular developmental processes. PFAS use bile acid transporters in the gut, hijacking enterohepatic circulation to stay in the body.[15] Notably, the placenta expresses these same transporters highly,[16] and PFAS have a corresponding high degree of transplacental transfer to the fetus.[17,18] PFAS cross the blood–brain barrier and accumulate in the cerebrospinal fluid and brain parenchyma;[19,20] in vitro, they elicit neurotoxicity and gliotoxicity[21] and regulate the morphology and differentiation of human neural progenitor cells and synaptogenesis.[22] By mid-gestation, PFAS interfere with metabolism in the fetal liver,[23] but their effects on the fetal brain are unknown.

Reports since 2021 have implicated maternal and perinatal PFAS in the diagnosis or traits of autism spectrum disorder and attention-deficit hyperactivity disorder, although in many instances the evidence is mixed.[24–26] Behavioural and cognitive outcomes in children are

inconsistent, differing substantially by chemical compound, the sex and age of the children, and by the study design and statistical methods used.[27,28] Neuroimaging studies are beginning to examine the effects of maternal PFAS on the brain, and have so far identified associations with brain microstructure—mainly white matter integrity—in children aged 2–6 years and adolescents aged 13–16 years.[29–31] However, a comprehensive analysis of the relationship between prenatal PFAS and multiple brain structural and functional outcomes in children at a whole-brain, voxel-wise, and vertex-wise level has, to our knowledge, not been reported.

We hypothesised that PFAS affect human neurodevelopment, via these direct or indirect pathways, resulting in an observable association with childhood brain structure and function. Here we characterise the associations between maternal PFAS and multimodal brain structural components (encompassing all whole-brain tissue parameters at once), hypothalamic microstructure, and brain functional connectivity, in typically developing children aged 5 years. We examined the whole brain and did not anticipate associations to cluster in any one region, except for the hypothalamus, which has the highest accumulation of PFAS in the brain because of its contact with the cerebrospinal fluid.[22] Owing to sex-specific associations of maternal PFAS with behavioural outcomes in children[27] and sex differences in neurodevelopmental trajectories,[32] we adjusted for sex assigned at birth and explored sex-specific associations.

Methods

Study design and participants

This study is ancillary to the FinnBrain Birth Cohort Study, a prospective observational study that enrolled mothers from three clinics in Turku, Finland, during their first trimester of pregnancy between Dec 1, 2011, and April 30, 2015. Recruitment to the cohort has been described previously.[33] This ancillary study involved a subset of mother–child dyads for whom both maternal PFAS concentrations during gestation and structural MRI data for the child at age 5 years were available. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (VARHA/57/180/2011 for initial enrolment and blood sample collection, VARHA/31/180/2011 for MRI at age 5 years, and VARHA/18203/13.02.02/2023 for additional data collected for this study). All participants provided written, informed consent for themselves and on behalf of their children.

Procedures

Study visits have previously been described in detail.[34–36] Variables considered in this study were maternal age, pre-pregnancy BMI, education, income, smoking status, alcohol consumption, gravidity, and parity; and offspring's gestational age at birth, birthweight, sex assigned at birth, and age at scan (appendix p 2). Between Oct 1, 2017, and March 31, 2020, children attended a study visit at age 5 years, which included an MRI scan to study brain structure and function and a strengths and difficulties questionnaire (SDQ) on socioemotional development to study behavioural domains.[37]

PFAS and other analytes

A maternal blood sample was collected at gestational week 24 and stored at –80°C until further analysis. A panel of 31 PFAS, as well as bile acids, were measured in these samples by ultra-high-performance liquid chromatography quadrupole time-of-flight mass spectrometry on an Agilent 1290 Infinity LC system coupled with 6545 QTOFMS, interfaced with a dual jet stream electrospray ion source (Agilent Technologies, Santa Clara, CA, USA; appendix pp 2–3). Data were processed with MZmine version 2.53[38] and compounds were quantified by six-point calibration. C-reactive protein (CRP) was measured by an enhanced immunoturbidimetric assay (Thermo Fisher Scientific, Helsinki, Finland), thyroid-stimulating hormone by a sandwich chemiluminescence immunoassay (LIAISON, DiaSorin, Saluggia, Italy), and thyroxine by a solid-phase antigen luminescence technique (LIAISON, DiaSorin, Saluggia, Italy).

MRI acquisition and processing

MRI data were acquired on a Siemens MAGNETOM Skyra Fit 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a Head/Neck 20 receiver coil, and included the following sequences: sagittal T1 magnetisation prepared rapid gradient echo, T2 turbo spin echo, diffusion tensor imaging, and a 7-min functional MRI (fMRI) sequence (appendix pp 3–5). T1-weighted MRI data were pre-processed with CAT12 to generate cerebral grey matter volume maps, diffusion tensor imaging data were pre-processed using FSL version 5.0.9 and tract-based spatial statistics to generate fractional anisotropy and mean diffusivity maps representing white matter microstructure, and cortical reconstructions were done with FreeSurfer analysis suite version 6.0, which generated maps of cortical thickness and surface area. Whole-brain voxel-level and vertex-level maps of grey matter volume, white matter fractional anisotropy and mean diffusivity, and cortical thickness and surface area were combined using FSL's linked independent component (IC) analysis to compute ten independent components representing the sources of most biological variation across all modalities simultaneously, indexed in order of the total anatomical variance they explain. These multimodal components were the primary outcome of the study. Secondary structural outcomes were the mean fractional anisotropy of the body of the corpus callosum and the mean diffusivity of the hypothalamus. Regional homogeneity of blood-oxygen-level-dependent (BOLD) signal intensity was calculated on the basis of Kendall's coefficient of concordance over a target voxel and its neighbours, and these regional homogeneity maps were used as a measure of functional connectivity.

For **CAT12** see https://neuro-jena.github.io/cat/

For **FSL** see https://fsl.fmrib.ox.ac.uk/fsl/docs/#/

For the **FreeSurfer analysis suite** see https://surfer.nmr.mgh.harvard.edu/

See **Online** for appendix

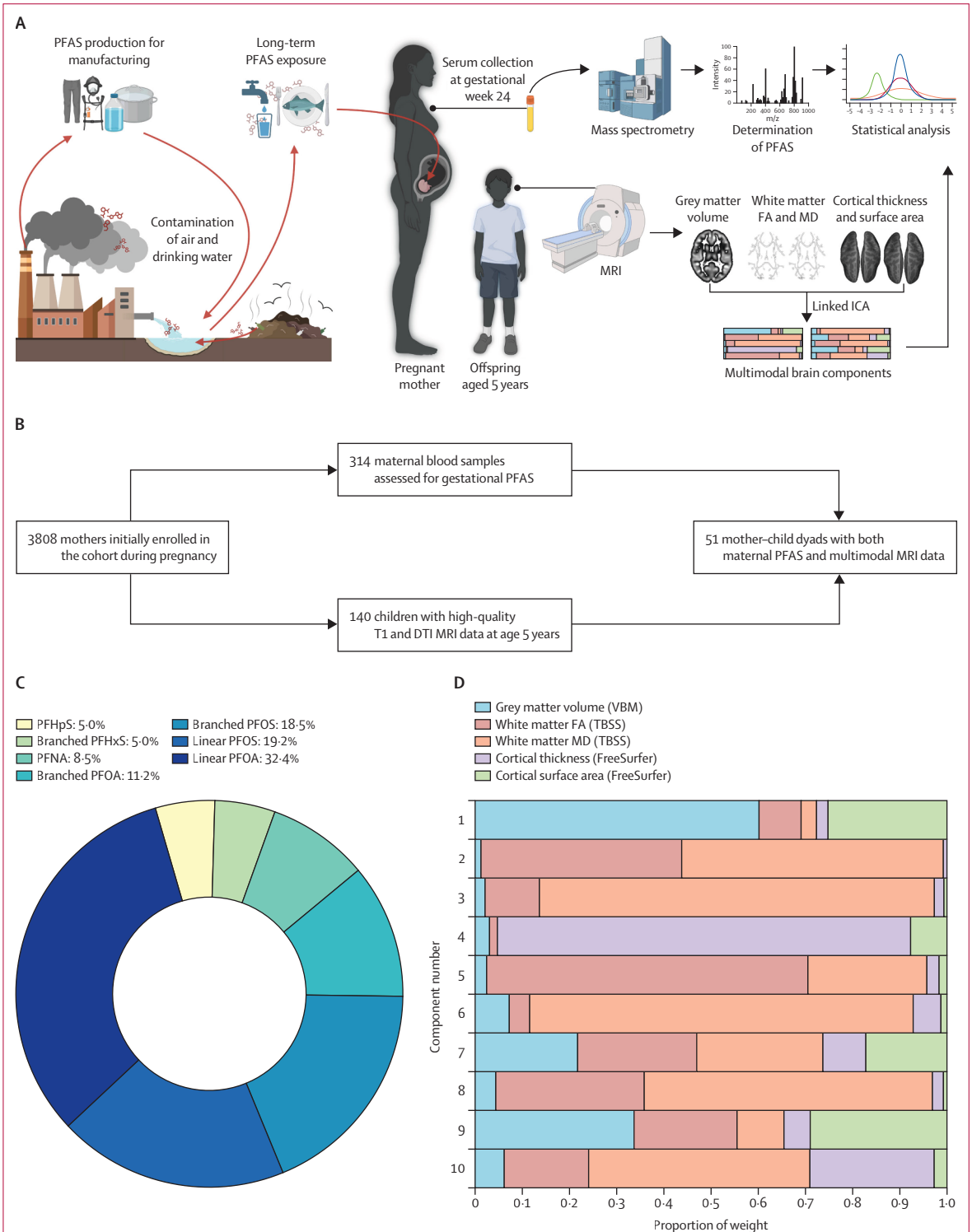
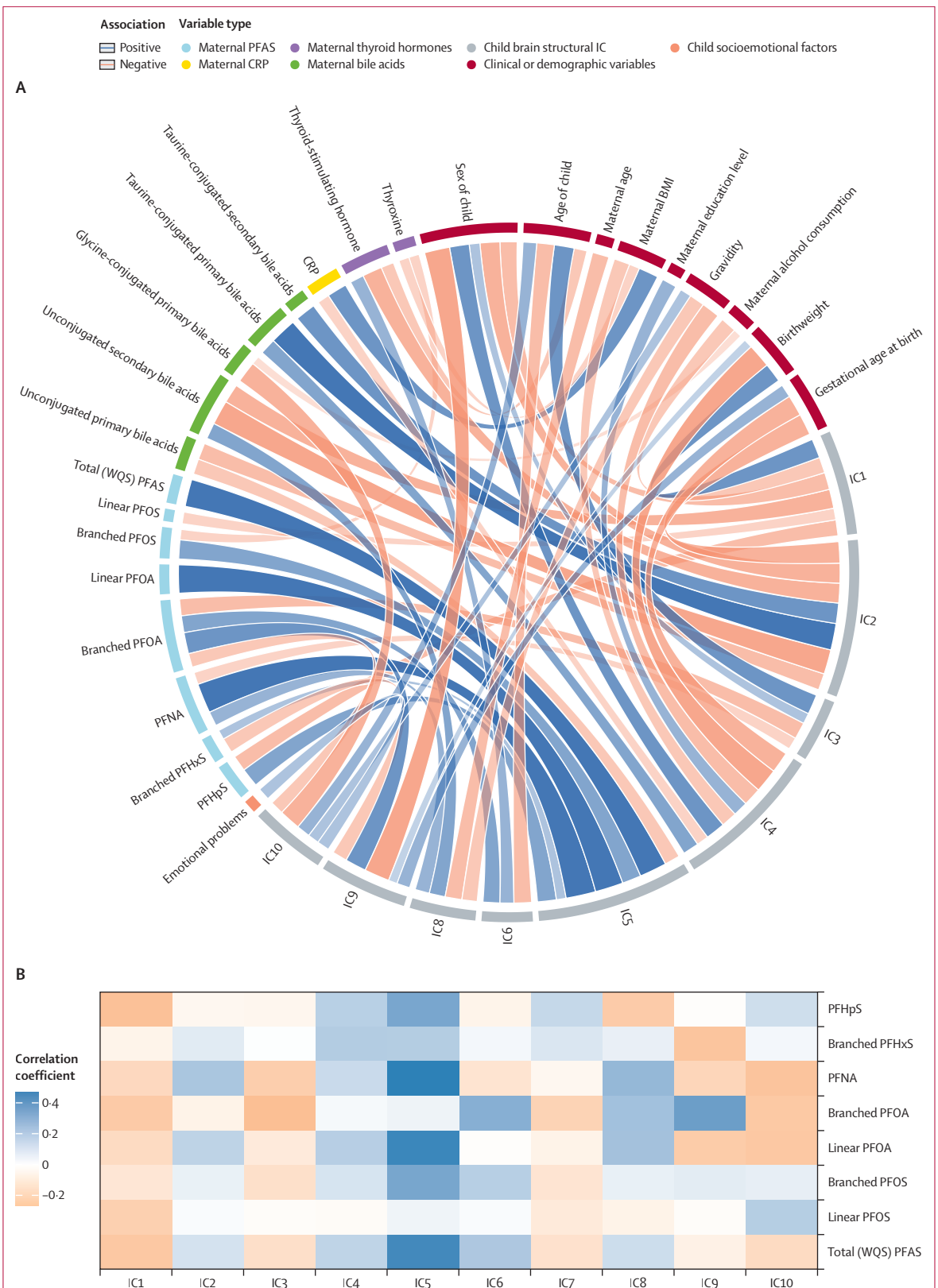


Figure 1: **Study design and summary of brain structural independent components**
(A) Schematic summary of the study design (created with BioRender.com). (B) Flow chart showing the subset of participants from the FinnBrain Birth Cohort Study included in the present study. (C) The contribution of each of the seven measured PFAS to total PFAS exposure, calculated by weighted quantile sums regression. Data are from 314 maternal blood samples. (D) Modality weighting of the ten brain structural independent components. Data are from the MRI scans of 140 children. FA=fractional anisotropy. ICA=independent component analysis. MD=mean diffusivity. PFAS=perfluoroalkyl and polyfluoroalkyl substances. PFHpS=perfluoroheptanesulphonic acid. PFHxS=perfluorohexanesulphonic acid. PFNA=perfluorononanoic acid. PFOA=perfluorooctanoic acid. PFOS=perfluorooctanesulphonic acid. TBSS=tract-based spatial statistics. VBM=voxel-based morphometry.

	Maternal PFAS (n=314)	Multimodal MRI (n=140)	Maternal PFAS and structural MRI (n=51)	Maternal PFAS and functional MRI (n=34)
Age at MRI scan (years)	NA	5·4 (0·1)	5·4 (0·1)	5·4 (0·1)
Sex of offspring				
Male	160 (51%)	73 (52%)	27 (53%)	14 (41%)
Female	154 (49%)	67 (48%)	24 (47%)	20 (59%)
Gestational age at birth (weeks)	40 (1·3)	39·7 (1·7)	40·1 (1·23)	40·1 (1·1)
Birthweight (g)	3589 (443)	3536 (501)	3578 (440)	3542 (464)
Maternal age (years)	31·1 (4·2)	30·5 (5·4)	30·4 (4·3)	30·5 (4·5)
Maternal pre-pregnancy BMI (kg/m^2)	24·8 (4·7)	24·1 (4·0)	23·8 (3·5)	23·5 (3·9)
Gravidity				
0	139 (44%)	65 (46%)	26 (51%)	17 (50%)
1	92 (29%)	38 (27%)	13 (25%)	8 (24%)
2	52 (17%)	20 (14%)	6 (12%)	5 (15%)
≥3	31 (10%)	17 (12%)	6 (12%)	4 (12%)
Parity				
0	187 (60%)	84 (60%)	36 (71%)	23 (68%)
1	93 (30%)	37 (26%)	9 (18%)	6 (18%)
2	29 (9%)	15 (11%)	6 (12%)	5 (15%)
≥3	5 (2%)	4 (3%)	0	0
Maternal smoking				
No	283 (90%)	134 (96%)	48 (94%)	33 (97%)
Yes, until pregnancy was known	20 (6%)	4 (3%)	2 (4%)	1 (3%)
Yes, continued when pregnancy was known	11 (4%)	2 (1%)	1 (2%)	0
Maternal alcohol consumption				
No	250 (80%)	100 (71%)	36 (71%)	24 (71%)
Yes, until pregnancy was known	48 (15%)	28 (20%)	11 (22%)	6 (18%)
Yes, continued when pregnancy was known	16 (5%)	12 (9%)	4 (8%)	4 (12%)
Maternal monthly income				
€0–1000	53 (17%)	22 (16%)	10 (20%)	6 (18%)
€1000–1500	49 (16%)	10 (7%)	3 (6%)	3 (9%)
€1500–2000	115 (37%)	48 (34%)	15 (29%)	10 (29%)
€2000–2500	61 (19%)	42 (30%)	16 (31%)	8 (24%)
€2500–3000	24 (8%)	13 (9%)	6 (12%)	6 (18%)
>€3000	12 (4%)	5 (4%)	1 (2%)	1 (3%)
Maternal education level				
Basic	44 (14%)	16 (11%)	5 (10%)	4 (12%)
Secondary	40 (13%)	16 (11%)	6 (12%)	5 (15%)
Higher	230 (73%)	108 (77%)	40 (78%)	25 (74%)
Maternal PFAS concentrations (ng/mL)				
Perfluoroheptanesulphonic acid	0·044 (0·032–0·063)	NA	0·044 (0·032–0·063)	0·045 (0·033–0·062)
Branched perfluorohexanesulphonic acid	0·036 (0·026–0·050)	NA	0·036 (0·026–0·050)	0·034 (0·023–0·037)
Perfluorononanoic acid	0·031 (0·021–0·048)	NA	0·031 (0·021–0·048)	0·032 (0·018–0·056)
Linear perfluorooctanoic acid	0·257 (0·157–0·391)	NA	0·257 (0·157–0·391)	0·291 (0·150–0·381)
Branched perfluorooctanoic acid	0·0009 (0·0004–0·0018)	NA	0·0009 (0·0004–0·0018)	0·0008 (0·0005–0·0021)
Linear perfluorooctanesulphonic acid	0·131 (0·076–0·204)	NA	0·131 (0·076–0·204)	0·124 (0·073–0·201)
Branched perfluorooctanesulphonic acid	0·161 (0·101–0·241)	NA	0·161 (0·101–0·241)	0·151 (0·090–0·248)

Data are mean (SD), n (%), or median (IQR). Percentages might not sum to 100 owing to rounding. PFAS=perfluoroalkyl and polyfluoroalkyl substances.

Table: **Participant characteristics**


Association
Positive
Negative
Variable type
Maternal PFAS
Maternal CRP
Maternal thyroid hormones
Maternal bile acids
Child brain structural IC
Clinical or demographic variables
Child socioemotional factors
A
Thyroid-stimulating hormone
Taurine-conjugated secondary bile acids
Taurine-conjugated primary bile acids
Glycine-conjugated primary bile acids
Unconjugated secondary bile acids
Unconjugated primary bile acids
Total (WQS) PFAS
Linear PFOS
Branched PFOS
Linear PFOA
Branched PFOA
PFNA
Branched PFHxS
PFHpS
Emotional problems
CRP
Thyroxine
Sex of child
Age of child
Maternal age
Maternal BMI
Maternal education level
Gravidity
Maternal alcohol consumption
Birthweight
Gestational age at birth
IC1
IC2
IC3
IC4
IC5
IC6
IC8
IC9
IC10
B
Correlation coefficient
0·4
0·2
0
−0·2
PFHpS
Branched PFHxS
PFNA
Branched PFOA
Linear PFOA
Branched PFOS
Linear PFOS
Total (WQS) PFAS
IC1
IC2
IC3
IC4
IC5
IC6
IC7
IC8
IC9
IC10

Statistical analysis

Statistical analyses were conducted using R statistical software version 4.4.0 in RStudio version 2024.04.0+735. For analyte concentrations below the limits of detection, data were half-minimum imputed then $\log_2$-transformed. Missing covariate data (BMI for one participant) were imputed with a single non-parametric imputation (appendix p 11). No batch effect was observed for PFAS; for bile acids, it was removed by quantile normalisation (appendix p 24). Categorical variables were factorised and continuous variables, including PFAS concentrations, were autoscaled. Full details of all statistical models are provided in the appendix (pp 5–7). Associations between maternal PFAS concentrations and offspring brain structure were examined by correlation network analysis, filtered by non-spurious associations using a non-rejection rate of 0·15, and by ten-fold nested cross-validated elastic net regression. Candidates were chosen for hypothesis testing by multivariate linear regression adjusted for sex, age, and additional confounders that explained the most variance in each of the respective maternal PFAS (appendix p 16). Unless otherwise indicated, p values were corrected for multiple testing by a modification of the family-wise error rate, which accounts for the non-independence of tests by calculating the effective number of tests based on principal components decomposition of their correlation matrix.[39] All R^2, standardised β coefficient, and p values represent the partial value for the maternal PFAS in fully covariate-adjusted models after multiple testing correction. Any PFAS associated with structural outcomes were then tested for association with functional connectivity using SPM12, with a cluster-forming threshold of $p<0·005$ and a cluster-level, family-wise error-rate-corrected threshold of $p<0·05$. All significant associations were further explored by sex–interaction analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 3808 mothers and 3837 children initially recruited to the FinnBrain Birth Cohort Study between Dec 1, 2011, and April 30, 2015, this analysis involved 51 mother–child dyads for whom maternal PFAS concentrations during gestation and MRI data of the child at age 5 years (obtained between Oct 1, 2017, and March 31, 2020) were available; 34 of these dyads had data from fMRI scans (figure 1A, B). All mothers were White and had higher socioeconomic status than that of the FinnBrain cohort overall (table, appendix p 13). Seven PFAS were detected in the majority of maternal blood samples: perfluoroheptanesulphonic acid (PFHpS), branched perfluorohexanesulphonic acid (PFHxS), perfluorononanoic acid (PFNA), and the linear and branched forms of PFOS and perfluorooctanoic acid (PFOA), mostly at concentrations of 0–1 ng/mL (table, appendix p 15). Exposure to all PFAS was calculated by weighted quantile sums regression, weighted mostly by PFOA and PFOS (figure 1C). The strongest predictor of maternal PFAS was BMI, followed by gravidity and age, although this varied by PFAS (appendix p 16).

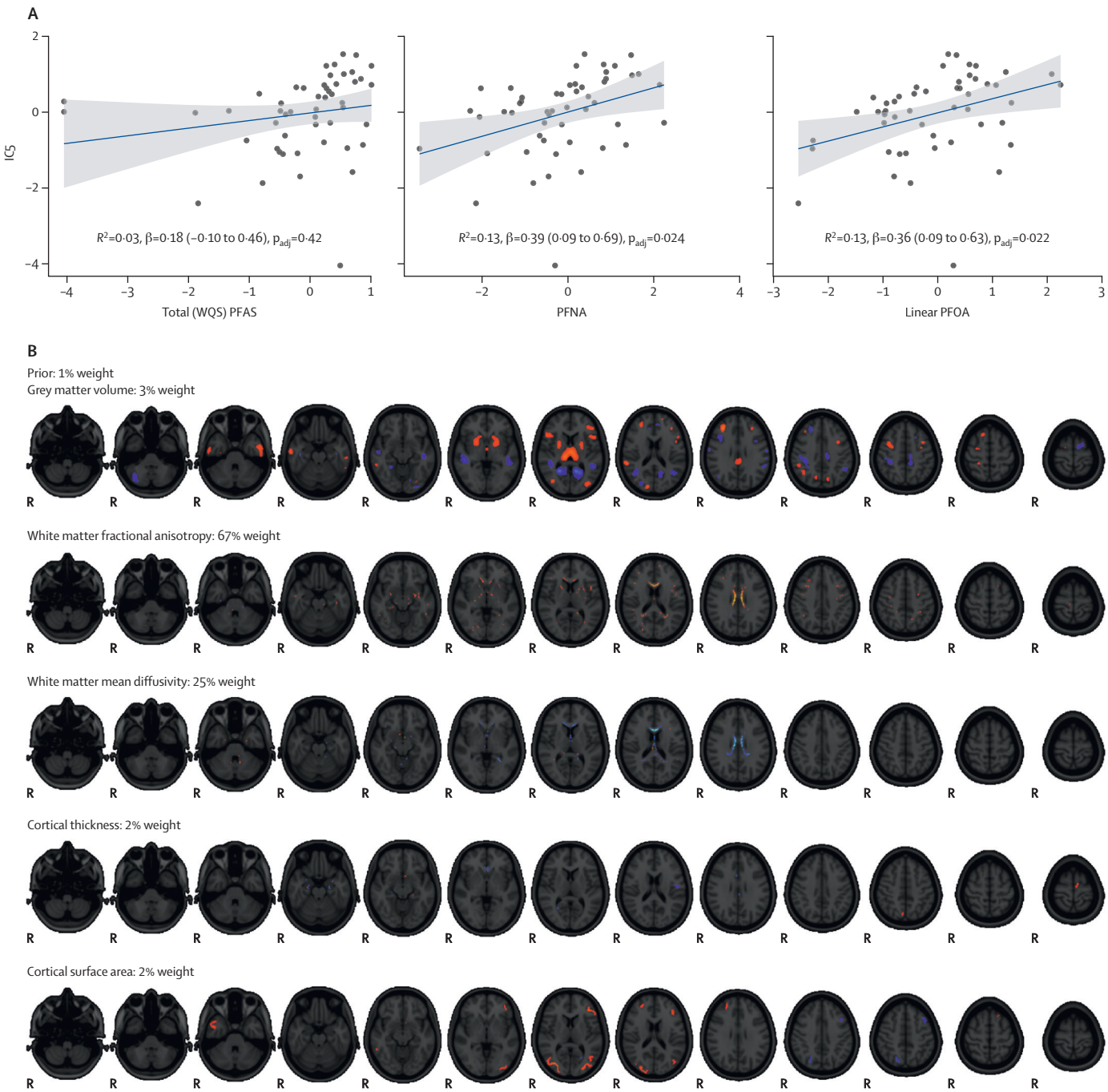
The mean age of the children at MRI scan was 5·4 years (SD 0·1). IC1 comprises mostly variation in grey matter volume, as reported in other samples.[40] The composition of all components is summarised in figure 1D. Participants were assigned a subject loading score for each component, representing how much they contribute to its variation. As a sensitivity analysis, when the analysis was rerun to generate n – 1 (nine) or n + 1 (11) components, the indexing, modality weighting, anatomical distribution, and subject loading scores remained almost identical (average correlation 0·974; appendix pp 21–23).

Correlations were calculated between all variable pairs. After the removal of spurious associations with a non-rejection rate of greater than 0·15, the remaining associations were projected as a circular correlation network (figure 2A). Maternal PFAS exhibited strong associations with offspring brain structural components but not with SDQ scores. No potential mediators—birthweight; gestational age at birth; or maternal concentrations of CRP, bile acids, or thyroid hormones—were associated with both PFAS concentrations and brain structural outcomes. Therefore, only the direct associations between PFAS and brain structure were explored further. PFAS with a carboxylic acid functional group had generally negative associations with brain outcomes; these associations were notably stronger than those of PFAS with a sulphonic acid group (t=3·47, p=0·0011). No such difference was observed between linear and branched PFAS (t=–0·49, p=0·62; appendix p 25). The component most strongly associated with maternal PFAS concentrations was IC5, which exhibited positive correlations with six of eight PFAS variables. Maternal PFNA (R^2=0·13, β=0·39 [0·09 to 0·69], p_{adj}=0·024) and linear PFOA (R^2=0·13, β=0·36 [0·09 to 0·63], p_{adj}=0·022), but not total PFAS (R^2=0·03, β=0·18 [–0·10 to 0·46], p_{adj}=0·42), positively and linearly predicted the value of IC5 (figure 3A), although the null association with total PFAS was driven by two outliers and, after their removal, this association was significant (p_{adj}=0·040; appendix p 26).

For **SPM12** see https://www.fil.ion.ucl.ac.uk/spm/software/spm12/

Figure 2: **Circular correlation network projection and correlations between brain structure and PFAS**

Spearman correlations were calculated pairwise for all variable pairs encompassing maternal PFAS, CRP, thyroid hormone, and bile acid concentrations; child socioemotional factors (from the strengths and difficulties questionnaire) and multimodal brain structural components; and potential confounding or mediating clinical and demographic factors; using data from 51 mother–child dyads. (A) Circos plot for all variable pairs. Associations were disregarded if the non-rejection rate was greater than 0·15. Positive associations are represented by blue edges, negative associations by orange edges, and the magnitude of the correlation coefficient is denoted by edge width and transparency. (B) Heat map of correlation coefficients between all brain structural components and maternal PFAS. CRP=C-reactive protein. IC=independent component. PFAS=perfluoroalkyl and polyfluoroalkyl substances. PFHpS=perfluoroheptanesulphonic acid. PFHxS=perfluorohexanesulphonic acid. PFNA=perfluorononanoic acid. PFOA=perfluorooctanoic acid. PFOS=perfluorooctanesulphonic acid. WQS=weighted quantile sums.



(Figure 3 continues on next page)

Unlike most other components, IC5 was notable for its heavy weighting by a single modality in a single brain region, namely fractional anisotropy in the body of the corpus callosum (figure 3B, C). After adjustment, only PFNA (R^2=0·09, β=0·32 [0·016 to 0·64], p_{adj}=0·037) significantly predicted tract mean fractional anisotropy (figure 3F, appendix p 28). We did not observe evidence of non-linear associations between total PFAS exposure and brain structural outcomes (appendix p 30). Overall, these findings suggest a potential influence of PFAS on white matter development.

We applied a cross-validated elastic net regression model to predict each component from all individual measured PFAS concentrations while controlling for sex, age, and

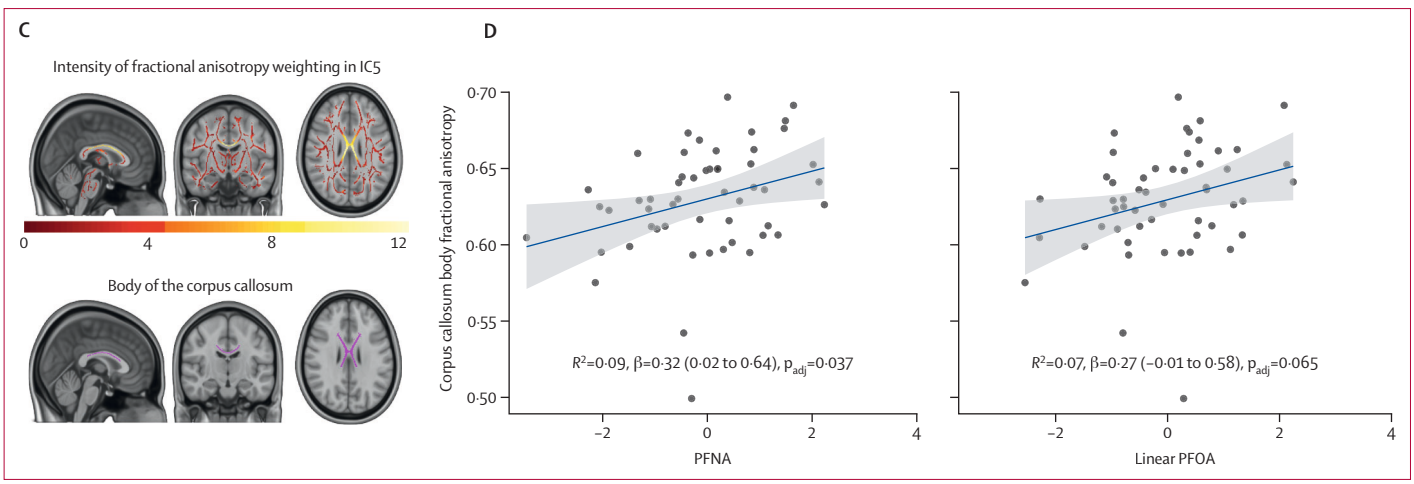


Figure 3: **Association of IC5 with maternal PFNA and linear PFOA**

(A) Associations between individual maternal PFAS and IC5. (B) Spatial distribution of each modality within IC5. (C) Spatial distribution of white matter fractional anisotropy in IC5 compared with the location of the body of the corpus callosum shown in pink. (D) Associations between individual PFAS and fractional anisotropy in the body of the corpus callosum. Statistics for A and D are from multiple linear regressions adjusting for the sex and age of the child and maternal confounders. p values are adjusted for multiple testing by Galwey modification of the family-wise error rate. Data are from 51 mother–child dyads. For A and D, the thick lines show the standardised regression coefficient β, the shaded areas represent the 95% CI, and individual data points are shown as dots. IC=independent component. PFAS=perfluoroalkyl and polyfluoroalkyl substances. PFNA=perfluorononanoic acid. PFOA=perfluorooctanoic acid. WQS=weighted quantile sums.

maternal confounders. Most models fit poorly, except for IC5 and, notably, two other components: IC4 (deviation ratio 0·31 [SEM 0·04]) and IC9 (0·45 [0·05]; figure 4A, appendix p 31). IC4 was not associated with the individual PFAS with the largest regularised coefficients: branched PFOA (R^2=0·02, β=–0·12 [95% CI –0·37 to 0·14], p_{adj}=0·38) or PFHpS (R^2=0·04, β=0·18 [–0·06 to 0·35], p_{adj}=0·18; appendix pp 32–34). The deviance explained in the IC4 model is therefore probably due not to PFAS but to the other covariates in the model, which are highly correlated with IC4 (figure 2A). Unlike IC4, IC9 is strongly and significantly predicted by the individual PFAS with the largest regularised coefficients: it is negatively associated with branched PFHxS (R^2=0·12, β=–0·32 [–0·58 to –0·06], p_{adj}=0·036) and positively associated with branched PFOA (R^2=0·14, β=0·36 [0·10 to 0·62], p_{adj}=0·016), but is not associated with branched PFOS (R^2<0·01, β=0·02 [–0·26 to 0·30], p_{adj}>0·99). These associations were not influenced by outliers (figure 4B, appendix p 35). There were larger coefficients for branched PFAS (t=1·54, p=0·13), although this difference was large only in the case of IC9 (t=3·35, p=0·066; appendix p 37). IC9 is composed mostly of increased posterior (occipital and cerebellar) grey matter volume and occipital cortical surface area (figure 4C), potentially implicating prenatal PFAS exposure in the development of posterior grey matter.

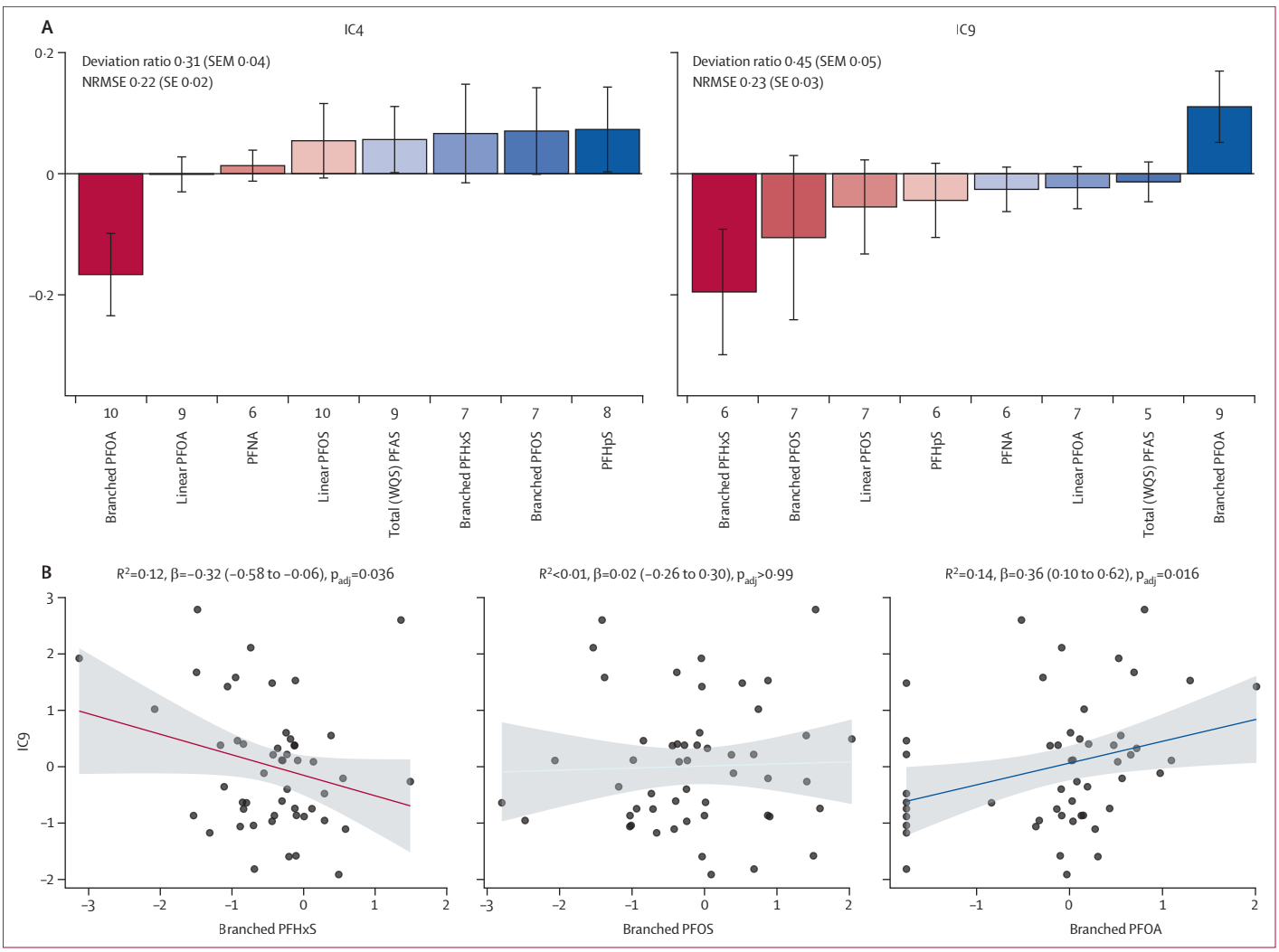
Branched PFOS had the largest negative correlation and branched PFHxS had the largest positive correlation with hypothalamic mean diffusivity (appendix p 38); only the association with branched PFOS (R^2=0·10, β=–0·29 [95% CI –0·57 to –0·041], p_{adj}=0·026) was significant. The deviation ratio for the elastic net regression model was 0·37 (SEM 0·021)—higher than that for any of the multimodal components except for IC9. PFAS with a sulphonic acid functional group contributed more to the predictive model than those with a carboxylic acid group (t=–4·05, p=0·014). Overall, PFAS predicted the microstructure of the hypothalamus, and to a greater degree than they did most multimodal structural outcomes.

IC5 was higher in children who had problems with peer relationships than in those who did not, although this association did not remain after false discovery rate (FDR) correction (p=0·017, p_{FDR}=0·10, appendix p 39), and neither IC5 nor IC9 differed according to scores in other socioemotional domains. All maternal PFAS that were associated with IC5 or IC9 significantly predicted BOLD-regional homogeneity in one cluster of the brain each. Three clusters were located in the right precentral gyrus, and showed a positive linear association between regional homogeneity and the respective PFAS. Conversely, branched PFHxS negatively predicted regional homogeneity in the bilateral intracalcerine cortices (figure 5A, B, appendix p 12). All clusters were in regions highly represented by the grey matter volume distribution in IC9: all cluster peak coordinates have IC9 grey matter values greater than 3·75 SD from the mean of all non-zero voxels (figure 5C, D), and therefore the structural and functional findings are highly congruent.

Sex interaction models revealed no sex-dependent effects in any association (appendix p 41).

Discussion

To our knowledge, the only two studies to date that have examined any brain outcomes in relation to prenatal PFAS exposure have reported associations in line with the findings presented here, particularly concerning alterations in the white matter integrity of offspring.[29,30] Our findings show notable regional specificity: the body of the corpus



(Figure 4 continues on next page)

callosum is the brain's largest white matter tract and undergoes substantial growth in childhood due to a high rate of myelination,[41] whereas the occipital lobe is the earliest cortical region to mature, reaching lifetime peak volume and thickness around the age of 5 years.[32] Given the dynamic growth of these regions early in life, they might be particularly sensitive to the effects of exogenous prenatal and perinatal factors, including PFAS. These regions might be developmentally interdependent, as the interhemispheric connections between the visual cortices through the corpus callosum are the longest in the brain. Therefore, if PFAS accelerate the growth of occipital grey matter, these fibres must be myelinated at a pace that matches that growth to maintain their correct functions, and this increased demand for myelination could explain the increase in callosal fractional anisotropy. These findings, and the functional association in the right precentral and bilateral intracalcerine cortices, suggest that prenatal PFAS are associated with primary sensory, visual, and association regions, and less so with frontotemporal parts of the brain.

We observed no evidence that the associations of PFAS with brain structure were mediated by the modulation of key maternal physiological systems or birth outcomes, although this study is not sufficiently powered to rule out these or other indirect pathways. The alternative mechanism is a direct effect on neurodevelopment, in which we would expect a degree of dose-dependency with a strong effect in the hypothalamus, because this structure has the highest relative PFAS accumulation owing to its contact with the cerebrospinal fluid[22]—this is consistent with our findings. The posterior cortical regions in particular were associated with maternal PFAS; these are the most well perfused regions of the brain[42] and would therefore receive relatively higher concentrations of circulating PFAS than other regions.

The association with brain outcomes was overall stronger for PFAS with carboxylic acid groups (linear and branched PFOA and PFNA) than for those with sulphonic acid groups (linear and branched PFOS, PFHpS, and branched PFHxS), except in the hypothalamus, where we observed

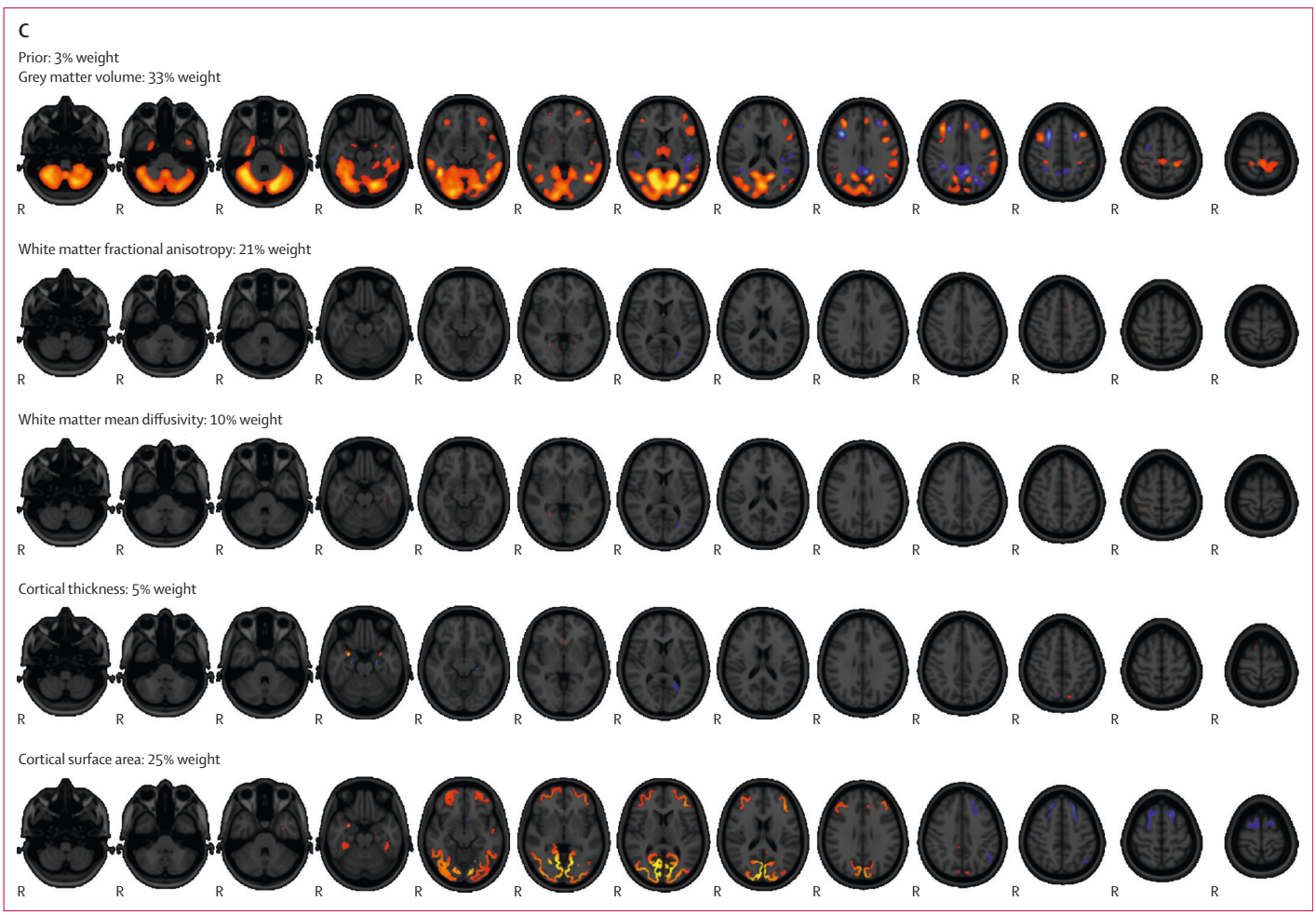


Figure 4: **Prediction of IC9 from maternal branched PFHxS and branched PFOA**

(A) Bar plots ordered by the regularised coefficients of each PFAS from ten-fold cross-validated elastic net regression models to predict the ten brain structural components from all maternal PFAS while controlling for sex, age, and all maternal confounders, shown for IC4 and IC9. Error bars indicate SE. The numbers above the PFAS indicate the number of folds for which that variable was included in the model. (B) Associations between individual maternal PFAS and IC9. The thick lines show the standardised regression coefficient β, the shaded areas represent the 95% CI, and individual data points are shown as dots. Statistics are from multiple linear regressions adjusting for the sex and age of the child and maternal confounders. p values are adjusted for multiple testing by Galwey modification of the family-wise error rate. Data are from 51 mother–child dyads (C) Spatial distribution of each modality within IC9. IC=individual component. NRMSE=normalised root-mean-square error. PFAS=perfluoroalkyl and polyfluoroalkyl substances. PFHpS=perfluoroheptanesulphonic acid. PFHxS=perfluorohexanesulphonic acid. PFNA=perfluorononanoic acid. PFOA=perfluorooctanoic acid. PFOS=perfluorooctanesulphonic acid. WQS=weighted quantile sums.

the opposite effect. This finding is in line with a direct effect on neurodevelopment, as carboxylates cross the placenta and enter the brain more efficiently than do sulphonates and are more likely to elicit toxic effects on developing neurons.[17–20]

These associations between PFAS and brain outcomes cannot be seen as unequivocally harmful or beneficial, as the literature on behavioural outcomes is highly variable and often differs by PFAS. A large case–control study reported that maternal PFOA and PFNA increased the risk of autism spectrum disorder, whereas PFHxS decreased the risk and PFOS was not associated. This result is in line with our own findings: branched PFHxS negatively predicts and branched PFOA positively predicts both the value of IC9 and regional homogeneity in a region strongly represented within IC9, whereas PFOS had no effect. This same result for each compound supports the notion that different PFAS elicit specific effects, and provides brain structural and functional corroboration of this diagnostic outcome. The implications of alterations to the microstructure of the hypothalamus can only be speculated; however, such alterations suggest that PFAS, as well as directly affecting metabolic pathways in the liver,[23] might interfere with central neuroendocrine regulation of metabolism. The maternal PFAS concentrations in our sample are low-to-normal for a typical Finnish or pregnant population,[11,13,24,27,43] and a key outstanding question is whether these linear associations persist at the increased concentrations found in individuals in high-exposure settings.

This study used a multidisciplinary approach and had some notable strengths, namely the prospective collection

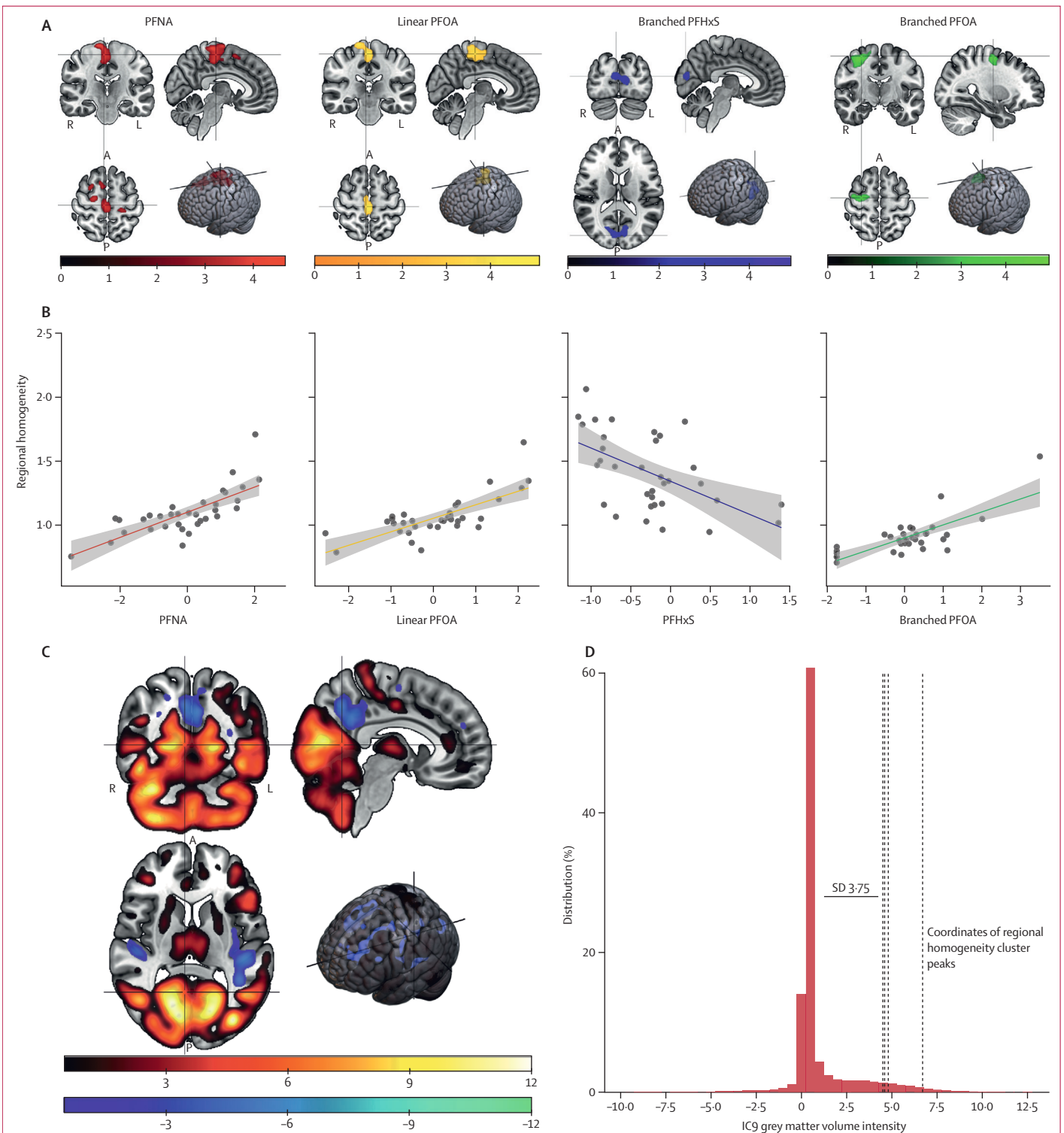


Figure 5: **Association of maternal PFAS with regional homogeneity of the BOLD signal**

Spatial maps were computed representing regional homogeneity of the BOLD signal across the grey matter. (A) Clusters with a significant association between each maternal PFAS and regional homogeneity. The colour bar represents *t* values within the cluster. (B) Scatter plots representing the association between PFAS and regional homogeneity within the clusters shown in A. The thick lines show the standardised regression coefficient β, the shaded areas represent the 95% CI, and individual data points are shown as dots. (C) Heat map of the spatial distribution of grey matter volume in IC9. (D) Distribution of IC9 grey matter volume intensities for all non-zero grey matter voxels. The dashed lines represent the value at the coordinates of the peak of each cluster for which regional homogeneity is significantly associated with PFAS. All clusters are significant ($p<0·05$) from voxel-wise analysis adjusting for the for the sex and age of the child and maternal confounders, with a cluster-forming threshold of $p<0·005$ and family-wise error correction for multiple testing. Data are from the fMRI scans of 34 children. A=anterior. BOLD=blood-oxygen-level dependent. fMRI=functional MRI. L=left. P=posterior. PFAS=perfluoroalkyl and polyfluoroalkyl substances. PFHxS=perfluorohexanesulphonic acid. PFNA=perfluorononanoic acid. PFOA=perfluorooctanoic acid. R=right.

of maternal serum samples and detection of multiple PFAS; the study of PFAS individually and as a mixture; and the acquisition and simultaneous evaluation of imaging data using multiple methods in a typically developing sample of young children. However, there are some important limitations, including confounding by maternal occupation, diet, and drinking water, which could not be robustly estimated in the current study; potential response errors in the SDQ; homogeneity of the sample and selection bias towards people of higher socioeconomic status, thereby limiting generalisability; and the observational design, which necessarily limits causal interpretations of the findings. The small sample size considerably limits the statistical power to detect small effect sizes, particularly in mediation analyses, and can lead to inflated effect sizes that are driven by few observations. Although we adjusted our models for confounders, corrected for multiple testing, and showed that most of our effect sizes were robust against outliers or other extreme observations, the small sample size is still a relevant limitation, and the R^2, standardised β coefficients with 95% CIs, and absolute p values should be considered simultaneously and with caution when interpreting the results. Finally, the high collinearity among PFAS makes disentangling their individual effects on the brain challenging. This issue was only partly addressed by the inclusion of a weighted sum of PFAS and elastic net regression models that include all PFAS simultaneously, and there could be additional synergistic, mixture, or even antagonistic effects between different PFAS.

The increasing public concern over PFAS has led to these substances being phased out since the early 2000s, and the European Commission (EC) and European Food Safety Authority continually regulate and monitor their concentrations in food and drinking water (EU directive 2020/2184 and EC recommendation 2022/1431). Consequently, circulating concentrations of these so-called legacy PFAS have been decreasing steadily since the early 2000s,[44] although in most instances only PFOS and PFOA have been phased out, and these have been replaced with now-ubiquitous emerging or alternative PFAS. We do not have sufficient data on the health consequences of these PFAS and, although several such compounds were analysed in our sample, they were present at concentrations below the limit of detection; further studies should therefore be conducted in settings with higher exposure. Meanwhile, legacy PFAS are still present in almost all humans and, owing to their environmental persistence—including an estimated presence of more than 1000 years in soil[45]—are expected to remain so for generations. The potential effects of PFAS on the brain are relevant not only for individuals who are highly exposed; rather, because PFAS are present in almost all pregnancies from conception and through all stages of development, consideration of their effects should also be integrated into our current understanding of brain development in the general population. Future studies should aim to replicate these analyses in independent, larger, and heterogenous populations, including those with high occupational or environmental PFAS exposure.

Contributors

AMD, MO, TH, LK, and HK conceptualised the study. TH, JJT, SK, HM, EPP, ESa, VK, AC, JDL, ESi, and AB developed the methods. AB carried out the investigation and presentation of results. MO, AMD, TH, and HK acquired funding. AMD, MO, LK, and HK were responsible for project administration. JJT, AMD, LK, and HK supervised the project. AB wrote the original draft of the manuscript, which was reviewed and edited by all other authors. AB and HK accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All R code used in the analysis is immediately and permanently available in a public GitHub repository (https://github.com/aaron-barron/TLPH-Maternal-PFAS-and-child-brain-outcomes) and archived by Zenodo (https://doi.org/10.5281/zenodo.16631478). Current EU and Finnish legislation on the protection of sensitive data and the informed consent given by the participants of the FinnBrain Birth Cohort Study do not allow for open data sharing. De-identified individual-participant data and an accompanying data dictionary can be shared via a trusted research environment upon request to the FinnBrain board at finnbrain-board@lists.utu.fi. Contact information for the board members and principal investigators of FinnBrain are listed on the project website at https://sites.utu.fi/finnbrain/en/contact/.

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