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ORIGINAL ARTICLE

The association between prenatal endocrine-disrupting chemical exposure and altered resting-state brain fMRI in teenagers

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Abstract

Many studies have reported that prenatal exposure to endocrine-disrupting chemicals (EDCs) can cause adverse behavioral effects or cognitive dysfunction in children. This study aimed to investigate a relationship of the concentration of prenatal EDCs and brain function in teenagers. We recruited 59 mother–child pairs during the third trimester of pregnancy, and collected and examined the concentration of EDCs, such as heavy metals, phthalates and perfluoroalkyl substances (PFASs), in maternal urine and serum. Resting-state functional magnetic resonance imaging (rs-fMRI) data were collected in teenagers 13–16 years of age, and fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo) were performed to find the association between maternal EDC concentrations and the functional development of the teenage brain. We found a correlation between MBP concentration and activity in the superior frontal gyrus, middle frontal gyrus, middle temporal gyrus and inferior temporal gyrus in the combined group of boys and girls. We also observed a correlation between MBzP concentration and activity in the anterior cingulum gyrus and insula in girls. We found a correlation between lead concentration and activity in the cuneus in the combined group. We also observed a correlation between MeHg concentration and activity in the superior temporal gyrus, caudate nucleus and putamen in the combined group. The PFOS results revealed a negative relationship between activity in the right putamen in boys, girls and the combined group after phthalate or heavy metals were applied as covariates. The PFNA results showed a negative correlation between activity in the left/right putamen and left caudate nucleus in boys, girls and the combined group after phthalate, heavy metals or PFOS were applied as covariates. We examined the correlations between maternal EDC concentrations and brain development and found that the associations with resting-state teenage brains in some circumstances are sex-related.

Keywords Endocrine-disrupting chemicals (EDCs) · Phthalate · Perfluoroalkyl substances (PFASs) · Heavy metal · Resting-state brain fMRI

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Introduction

The World Health Organization (WHO) defines endocrine-disrupting chemicals (EDCs) as follows: "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations". EDCs are widely used in our daily lives and are present in everyday substances such as soil, dust, air, drinking water, construction materials, vegetables, meat, fish and shellfish, food packaging, personal care products, toys, medical equipment, fire extinguishers, clothes, electronics, cleaners, etc. In daily life, people are inevitably exposed to EDCs, and long-term exposure affects human health and is a potential public health concern. According to previous studies, EDCs may cause different kinds of adverse health conditions in the human body, including reproductive dysfunction in men and women (Ankolkar and Balasinor 2016; Caserta et al. 2008; Fowler et al. 2012), cancer (Caserta et al. 2008; Cohn et al. 2007; Mallozzi et al. 2017), obesity (Braun 2017; Darbre 2017; Tang-Peronard et al. 2011), neurodevelopment dysfunction (Axelrad et al. 2007; Lanphear et al. 2005), etc. A study reported that the European Union (EU), through direct and indirect costs, has spent 157 billion euros on issues due to the medical burden and loss of productivity caused by EDCs. This accounts for 1.23% of the gross domestic product (GDP) of the EU (Trasande et al. 2015). Taiwan is facing a similar situation as the EU in sustaining the medical and economic burden caused by EDCs. However, current research mainly focuses on exposures during the early life or growth period; while, studies of EDC exposure during pregnancy are lacking.

In the past, many studies have focused on the effects of EDCs on neural development to characterize harm that EDCs cause in the nervous system. Currently, prevalently used and wide spread EDCs in Taiwan were considered including phthalate acid esters, perfluoroalkyl substances (PFASs), and the toxic metals. In animal experiments, perinatal exposure to heavy metal arsenic (As) reduces corticosterone receptor (CR) levels in the rat hippocampus, and lower levels of CR may lead to adverse effects on learning and memory (Martinez-Finley et al. 2009). Early exposure to PFASs causes abnormal behaviors such as reduced and/or absence habituation and hyperactivity in mice, and these effects were positively correlated with age (Johansson et al. 2008). Prenatal exposure to EDCs alters the structure of mouse brains, impairs cognitive function alters neurobehavior in offspring, and these changes were sex related (Li et al. 2013; Onishchenko et al. 2011; Rao Barkur and Bairy 2015).

There is a bunch of studies about the impact of EDCs on human cognitive function. Some cross-sectional and cohort studies observed that there was a negative correlation between maternal or infantile EDC concentrations and intelligence quotient (IQ), shown as higher EDC concentrations correlated with lower intelligence: We observed this association in the present cohort for PFASs (Wang et al. 2015), phthalates (Huang et al. 2019), and lead (Huang et al. 2012); others demonstrated for arsenic (Hamadani et al. 2011), cadmium (Jeong et al. 2015; Tian et al. 2009), lead (Schnaas et al. 2005; Wasserman et al. 1997), methylmercury (Lam et al. 2013), and Phthalate (Cho et al. 2010). These studies used the Wechsler intelligence scale to assess cognitive ability of subjects. The Wechsler intelligence scale is a comprehensive and detailed cognitive scale with different versions for each age of subject to evaluate diverse index scores including arithmetic, vocabulary, picture completion, etc. The Wechsler intelligence scale is one of the tools used to quantify the damage of EDCs on human cognitive function. Although numerous studies indicated that the impact is not serious, the loss of general intelligence represents a decrease in the high intelligence population and an increase the population with poor learning abilities. A study in the United States pointed out that individuals lose $13,030 USD in total lifetime income for each point decrease in IQ (Lien et al. 2016). Intelligence has a certain influence on the long-term societal developments. In addition to the harmful effects on cognitive function, there have also been many reports on abnormal behavior caused by EDCs. Some cross-sectional studies and cohort studies indicated that prenatal or infantile exposure to EDCs was associated with abnormal behaviors in children, such as anxiety, prosocial behavior, emotional problems, hyperactivity, etc. (Arbuckle et al. 2016; Høyer et al. 2015; Kippler et al. 2012; Kobrosly et al. 2014; Lien et al. 2015, 2016; Sioen et al. 2013; Whyatt et al. 2012). These studies used the child behavior checklist (CBCL), or strengths and difficulties questionnaire (SDQ) to assess children's behavior. However, none of these scales provide information of the effects of EDCs in the brain.

Two task-based fMRI studies have reported on the effects of EDCs in the brain. Childhood exposure to lead alters language function by changing neural structure. The investigators found that subjects with higher blood lead concentrations performed worse on language tasks and had reduced neural activity in their language area concomitant with recruitment of contralateral regions (Yuan et al. 2006). A study of maternal exposure to methylmercury (MeHg) and polychlorinated biphenyls (PCBs) reported abnormal brain activity in a high-exposure group compared to controls during photic stimulation and finger tapping tasks. After EDC exposure, subjects required more brain resources to complete these two simple tasks (White et al. 2011). These results provide evidence that EDCs affect brain function.

As neural developments occur in early days of fetal life and thereby particularly susceptible and vulnerable to various chemical insults. Our previous studies have shown that phthalate and PFAS endocrine disruptors may interfere the fetal programing via DNA methylation alterations (Chen et al. 2018; Kaushalet al. 2017; Miura et al. 2018). Such alterations might affect health in later life, so-called Fetal Origin of Health and Disease (DOHaD)—first published in Britain (Barker et al. 1990). The evidence was provided using an independent study of a birth cohort in the Netherlands (Roseboom et al. 2000).

There are only a handful of fMRI studies on early-life exposure to EDCs and brain development in children and adolescents. Previously, some task-based fMRI studies found that EDCs cause damage in the brain (Yuan et al. 2006; White et al. 2011), and several relevant recent studies on manganese exposure and exposure to polybrominated diphenyl ethers (de Water et al. 2018, 2019; Lao et al. 2017; Iannilli et al. 2016). However, there is no relevant research to establish the relationship between resting-state fMRI (rs-fMRI) results and EDCs. This study aimed to analyze the relationship between prenatal EDC concentrations and rs-fMRI connectivity from multiple angles in offspring of exposed mothers. The fractional amplitude of low-frequency fluctuations (fALFF) analysis provides a quantitative measure to calculate spontaneous brain activity, and the regional homogeneity (ReHo) can indicate the concordance or local homogeneity of the rs-fMRI signal in the brain. To analyze the relationship between prenatal EDC concentrations and rs-fMRI indices, multiple regression instead of widely used seed-based correlation analysis was used in the study. We sought to establish the necessary theoretical basis for future-related research. The fetus is in a sensitive period of neurodevelopment during pregnancy, and we assume that prenatal exposure to EDCs could cause adverse effects and indirectly affect the development of embryonic brains. EDCs have different toxicities and pathological mechanisms in the body because of their different molecular structures which could differentially influence health and brain regions. EDCs with similar structures or characteristics may have similar effects on specific functional areas of the brain. The study might help to provide hypothesis from a different perspective to explain how EDCs alter cognitive function and behavioral performance.

Materials and methods

Participants

The purpose of this cohort study is to explore the relationship between multiple prenatal factors and teenage brain function. We recruited 59 pregnant women in the middle of Taiwan from previous cohort study (Lien et al. 2015; Wang et al. 2015). The questionnaire, which included questions about basic demographics, dietary habits during pregnancy, and medical history, was completed after receiving a thorough description of this study. Urine and/or serum samples of pregnant women were collected during third trimester to determine levels of prenatal EDC exposure.

From July 2015 to August 2015, we gathered the teenage offspring (mean age was 13.95 ± 0.47 years) of the women described above to collect their brain imaging results from designated hospitals. We collected 59 rs-fMRI results (33 men, 26 women) from 3-T MRI machines in the Chung Shan Medical University Hospital. At this time, other questionnaires were completed by the women that included information on education level, vocation, family income, etc.

Participant inclusion and exclusion criteria

Pregnant women

All of the recruited women were 25–34 years old. They had no complications, such as eclampsia or pre-eclampsia, during pregnancy, during delivery, or after delivery. From December 2000 to November 2001, they all delivered at a designated medical center. The levels of prenatal EDC concentration in urine and/or serum should be sufficient for analysis of the results.

Teenagers

None of the teenage offspring had neurologic or psychiatric maladies, and they cooperated with instructions to remain still during scans.

EDC measurements

The central lab of National Institute of Environmental Health Sciences, National Health Research Institutes (NIEHS/NHRI) Taiwan has analyzed all the studied chemicals except for PFASs and methylmercury, which were completed in National Taiwan University (Lien et al. 2011), and the central lab of Chang Gung Medical Center following the clinical routine, respectively.

Urine samples were collected and analyzed using online solid-phase extraction (SPE) to extract the urine sample. Quantitative analysis was performed by liquid chromatography–electrospray ionization–tandem mass spectrometry (LC/MS/MS). The following phthalate metabolites were measured and in the final statistical analysis according to the previous outcomes for this cohort (Lien et al. 2015; Huang et al. 2019; Chen et al. 2018): monobutyl phthalate (MBP), mono-benzyl phthalate (MBzP), three di-(2-ethylhexyl) phthalate (DEHP)

metabolites, mono-2-ethylhexyl (MEHP), mono-2-ethyl-5-hydroxyhexyl (MEHHP) and mono-2-ethyl-5-oxohexyl phthalates (MEOHP). The intra-day variations of all seven urine phthalate metabolites were below 10%, with intra-day recoveries at 100 ± 20% at three different concentrations, 25%, 50% and 75%, of individual substance. The accuracy of the analytical approach was tested against two reference urine samples with different known phthalate metabolite concentrations. The samples were received from the laboratory inter-comparison program (www.g-equas.de) in 2006. In both concentrations, the relative errors (RE) of these five urinary metabolites were below 16%. The detection limits for MBP, MBzP, MEHP, MEHHP, and MEOHP were 1.6, 0.99, 0.55, 0.23, and 0.26 µg/L, respectively. The percentages of study participants with the urinary metabolites concentrations below their detection limits (DL) were 6.4% (3/47), 10.6%(5/47), and 2.1%(1/47) for MBzP, MEHHP, and MEOHP, respectively. No sample had the urinary MBP and MEHP concentrations below DL. If the levels of metabolites were below their detection limits (DL), they were assigned values equal to half of their DL.

Inductively coupled plasma mass spectrometry (ICP-MS) was performed to quantitate the urinary metals of cadmium (Cd), arsenic (As), and lead (Pb), and blood concentration of methylmercury (MeHg). Urinary Pb and Cd were quantified by Agilent 7700 × ICP-MS, (Agilent Technologies, USA). The spike recovery rate, blank sample, duplicate sample, and check sample measurement were measured every batch. Spike R (80–120%), blank sample (< 2MDL µg/L), duplicate sample (mean of relative error: < 20%), and check sample (recovery: 80–120%) measurements also have to pass our QC (quality control) criterion. Inter-laboratory comparisons were certified using the German external quality assessment scheme (G-EQUAS). The method detection limits (MDLs) for lead and cadmium were 0.022 and 0.066 µg/L, respectively. No sample had the urinary level below MDL. If the level was below MDL, MDL divided by the square root of 2 was imputed.

Arsenic exposure was the sum of four arsenic species to represent total inorganic exposure. The levels of the four species, arsenite, arsenate, monomethylarsonate (MMA) and dimethylarsinate (DMA), were measured using high-performance liquid chromatography (HPLC), to separate the species, coupled with inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS). The inter-assay coefficients of variation of all the samples were < 10%. Inter-laboratory comparisons were certified using the German External Quality Assessment Scheme (G-EQUAS), and we provided reference values of all the tested samples. The limits of detection (LOD) were 0.09, 0.05, 0.05, and 0.04 µg/L for arsenite, arsenate, MMA, and DMA, respectively, with corresponding proportions below LOD 29.4%, 45.7%, 1.3%, and 0%. When the level was under the LOD, the input level used was equal to the LOD divided by the square root of 2.

Urinary creatinine levels, used to estimate urine dilution in random urine samples, were measured using a Beckman Synchron LX20 auto-system (Beckman Coulter, Brea, CA, USA). The concentration of EDCs in urine was adjusted by normalizing to urinary creatinine.

Maternal serum samples collected in the third trimester were used to measure prenatal PFASs exposure (Lien et al. 2016). The serum collected in the hospital was centrifuged for 15 min and stored in a freezer at − 80 °C before being sent to the laboratory for analysis. After being thawed at room temperature, formic acid, methanol, and other solutions were added, and it was centrifuged. The instrument was an Agilent-1200 high-performance liquid chromatography system (Agilent, Palo Alto, CA, USA) coupled with a triple-quadrupole mass spectrometer (Sciex API 4000, Applied Biosystems, Foster City, CA, USA). The following perfluoroalkyl substances (PFASs) and heavy metals were measured: perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluoroundecanoic acid (PFUA), and perfluorododecanoic Acid (PFDoA) (Miura et al. 2018). The intra-assay coefficients of variation (CVs) for PFAS concentrations ranged from 0.83 to 7.94%, and the inter-assay CVs were 1.57–24.7%. The limit of quantitation values (LOQ) for serum PFASs were 0.45, 0.10, 0.11, 0.13, and 0.07 ng/mL for PFOA, PFNA, PFOS, PFUA, and PFDoA, respectively. The percentages of study participants with serum PFASs concentrations below LOQ were 21.3%(10/47), 6.4%(3/47), 6.4%(3/47), and 23.4%(11/47) for PFOA, PFNA, PFUA, and PFDoA, respectively. No sample had the serum PFOS concentration below LOQ. Serum PFASs concentrations under the limit of quantitation values (< LOQ) were recorded as half the LOQ value for analysis.

MRI data acquisition

The resting-state functional images in this experiment were collected using 3-T MRI scanners (Skyra, Siemens, Germany) with a 20-channel head–neck coil in the Chung Shan Medical University Hospital. Fifty-nine teenagers were instructed remain still, stay awake, close their eyes, and avoid thinking about specific thoughts during the scan. The rs-fMRI parameters were: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, number of slices = 28, field-of-view (FOV) = 250 × 250 mm^2, matrix size = 94 × 94, slice thickness = 4 mm, number of scans = 240, scan time = 8′08”.

Functional images preprocessing

The resting-state fMRI raw data were processed with Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Slice timing correction and realignment were preformed to correct for the different acquired times and head motions. The corrected images were spatially normalized to the Montreal Neurological Institute (MNI) template (each voxel was resampled to $3 \times 3 \times 3$ mm^3), and then the normalized images were smoothed with a Gaussian kernel of 6-mm full width at half maximum [FWHM = 6 mm]. Nuisance regression was then performed using six head motion parameters as covariates. In addition, the mean regional homogeneity analysis data were calculated prior to smoothing.

The Resting-State fMRI Data Analysis Toolkit (REST1.8, Lab of Cognitive Neuroscience and Learning, Beijing Normal University, China) was used to remove the linear trend of the functional data. We applied a 0.01–0.12-Hz band filter, and the mean fractional amplitude of low-frequency fluctuation (mfALFF) and mean regional homogeneity (mReHo) analyses were performed to calculate resting-state brain connectivity after removing physiological noises, such as cardiac and respiratory cycles. Structural image was segmented into gray matter, white matter, and CSF, and the white matter and CSF-masked fMRI signal were also used to remove the physiological noise.

Mean fractional amplitude of low-frequency fluctuations (mfALFF)

The fALFF analysis provides a quantitative measure to calculate spontaneous brain activity. The preprocessed resting-state data were transformed into a power spectrum using a fast Fourier transformation (FFT). The entire power spectrum range (0–0.25 Hz) was square-rooted at each frequency and then averaged across 0.01–0.12 Hz (default value was 0.01–0.08 Hz) at each voxel to obtain more fALFF values (Niazy et al. 2011). Previous studies suggested that the frequencies with important physiological information were in the range of 0.01–0.08 Hz (Cordes et al. 2001; Raichle et al. 2001). However, some research suggests that complex functional networks may be observed in the range of 0.1–0.12 Hz (Baria et al. 2011). Therefore, we extended the frequency range from 0.01 to 0.12 Hz to mitigate the influence of low-frequency drift and high-frequency physiological noise. fALFF is not sensitive to physiological noise compared to the ALFF method (Zou et al. 2008). Finally, the fALFF value of each voxel was divided by the mean fALFF value of each subject for standardization.

Mean regional homogeneity (mReHo)

The ReHo analysis was performed on a voxel-by-voxel basis using Kendall's coefficient of concordance (KCC) (Zang et al. 2004). ReHo uses KCC as an index to calculate the time series of a given voxel using those of its nearest neighbors (26 neighbors in this study). ReHo values between 0 and 1 are assigned to each voxel; values closer to 1 indicate higher concordance or local homogeneity. To measure ReHo, bandpass filtering (0.01–0.12 Hz) on the preprocessed images was performed, and the ReHo value of each voxel was divided by the mean value of the ReHo for standardization.

Statistical analysis

We used a multivariate linear regression to find the correlation between maternal EDC concentration and the neurodevelopment of teenage brain. A false discovery rate (FDR)-corrected *p*-value of less than 0.05 was considered as statistically significant. To reduce the impact from other confounders, family income and gender were selected and applied in the model as covariates. We also separated boys and girl in different groups to perform multivariate regression analyses in which family income was still included as a covariate. We determined the covariates by referring to other literatures (Satterthwaite et al. 2015; Tyan et al. 2017; Kobrosly et al. 2014; Lien et al. 2015; Messerlian et al. 2017; Whyatt et al. 2012). In addition, the relationship between PFOS/PFNA and the reward system arouse our interest, so we applied different concentrations of EDCs as covariates to separate the influences of other EDCs from that of PFOS and PFNA concentration and to rule out the impact of other EDCs on PFOS and PFNA results.

Results

EDC concentration in urine/serum samples

Urine/serum samples were taken from the pregnant subjects in this study according to methods described previously (Table 1). Arsenic (As) had the highest average concentration of the heavy metals. MBP had the highest average concentration of the phthalates (except for ΣDEHP which represents a number of phthalate metabolites). PFOS had the highest concentrations of the PFASs. From the concentration results, we observed that the standard deviation of each EDC was large. This indicated that the EDC levels were discretely distributed among pregnant women in this study and that may due to different lifestyles, diets, etc.

Table 1 EDC concentrations in urine/serum samples in pregnant women

EDCs	*n*	Mean	SD
Urine (μg/g creatinine)			
As	45	35.96	15.67
Cd	47	0.90	0.44
Pb	47	3.61	1.73
MBP	49	91.95	81.86
MBzP	49	17.90	12.59
MEHP	49	36.74	100.24
MEOHP	49	60.34	163.71
ΣDEHP	49	447.71	1154.64
Serum (ng/mL)			
MeHg	21	8.16	5.25
PFOA	47	2.93	4.31
PFOS	47	14.85	10.66
PFNA	47	1.70	1.85
PFUA	47	4.76	6.55
PFDoA	47	0.32	0.26

The average concentrations of arsenic (As) is the highest of the heavy metals. The average concentration of MBP is the highest of the phthalates (except for ΣDEHP which represents a number of phthalate metabolites). The average concentration of PFOS is the highest of the PFASs

ΣDEHP = The sum concentrations of three DEHP metabolites (MEHP, MEHHP, MEOHP), *SD* standard deviation

Phthalate exposure

In the mfALFF results for phthalate (Fig. 1a–d), we observed a lower mfALFF in teenagers with prenatal exposure to MBP in the right superior frontal gyrus and right middle frontal gyrus in the combined group of boys and girls ($p < 0.025$). There was a lower mfALFF in teenagers with prenatal exposure to MBzP in the left/right anterior cingulum gyrus in the girl group ($p < 0.015$). On the other hand, our mReHo results for phthalate (Fig. 1e–g) showed that in combined group of boys and girls, the MBP concentration during pregnancy was positively correlated with activity in the left middle temporal gyrus and left inferior temporal gyrus ($p < 0.015$). In the girl group, the MBzP concentration during pregnancy was inversely correlated with activity in the right insula ($p < 0.04$).

PFASs exposure

In the mfALFF results for PFASs (Fig. 2a–d), we observed a lower mfALFF in teenagers with prenatal exposure to PFOS in the right putamen and right insula in the combined group of boys and girls (0.015). There was a lower mfALFF in teenagers with prenatal exposure to PFOS in the right putamen and right pallidum in the boy group ($p < 0.01$). On the other hand, our mReHo results for PFASs (Fig. 2e–j) revealed in the combined group of boys and girls, the PFNA concentration during pregnancy was inversely related to activity in the left putamen, right putamen and left caudate nucleus ($p < 0.004$). In the boy group, the PFNA concentration during pregnancy was negatively correlated with activity in the left putamen, right putamen and left caudate nucleus ($p < 0.009$).

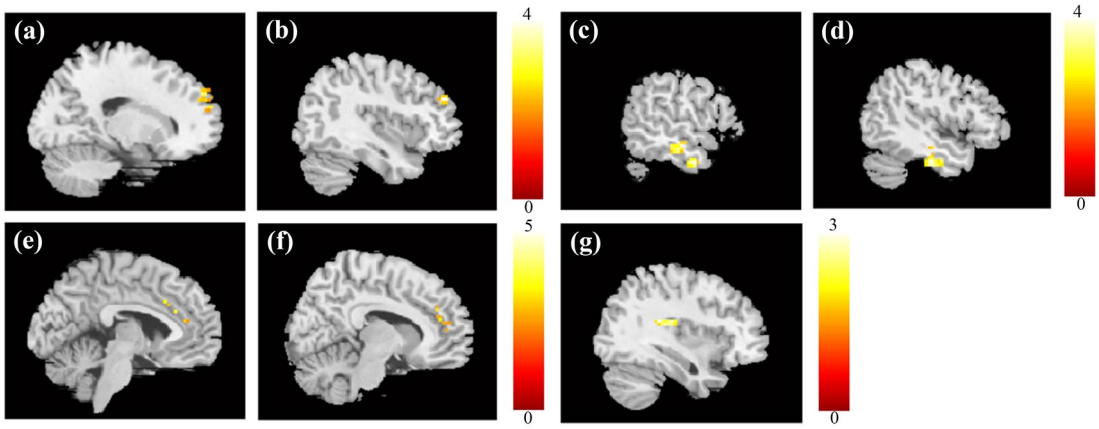

Fig. 1 mfALFF and mReHo results for MBP and MBzP. In the mfALFF results, we observed a correlation between MBP concentration and activity in the (**a**) right superior frontal gyrus and (**b**) right middle frontal gyrus, and a correlation between MBzP concentration and activity in the (**e**) left anterior cingulum gyrus and (**f**) right anterior cingulum gyrus in the girl group. In the mReHo results, we also observed a correlation between MBP concentration and activity in the (**c**) left middle temporal gyrus and (**d**) left inferior temporal gyrus in the combined group of boys and girls and a correlation between MBzP concentration and activity in the (**g**) right insula in the girl group

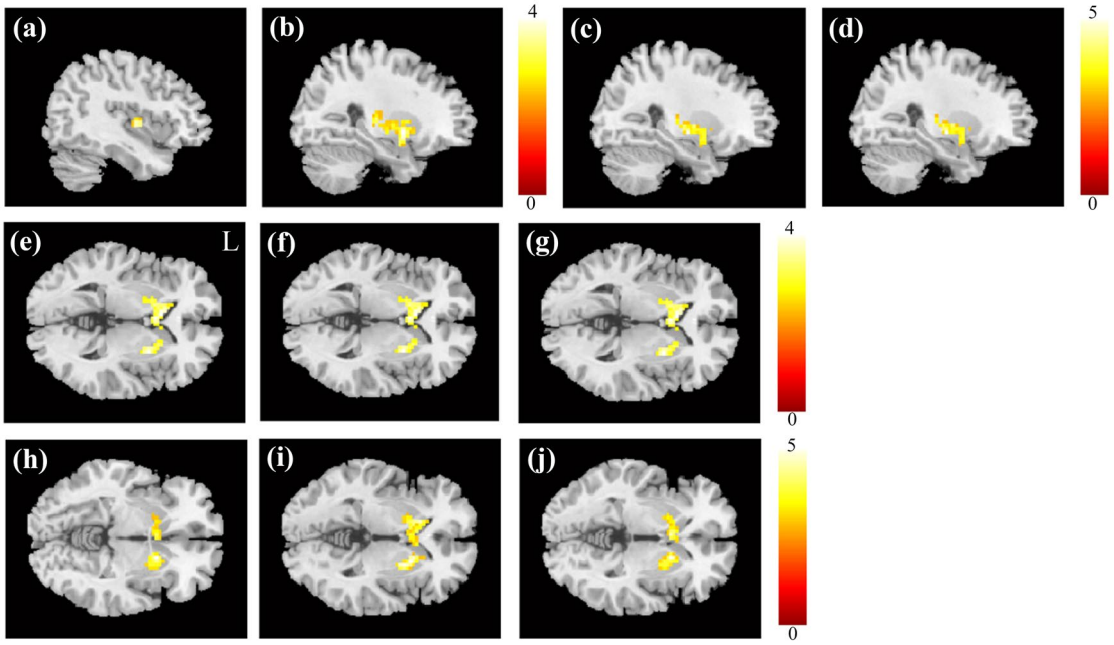

Fig. 2 mfALFF and mReHo results for PFOS and PFNA. In the mfALFF results, we observed a correlation between PFOS concentration and activity in the (**a**) right insula and (**b**) right putamen in the combined group of boys and girls, and the (**c**) right pallidum and (**d**) right putamen in the boy group. In the mReHo results, we also observed a correlation between PFNA concentration and activity in the (**e**) left caudate nucleus, (**f**) left putamen and (**g**) right putamen in the combined group of boys and girls and the (**h**) left caudate nucleus, (**i**) left putamen (**j**) and right putamen in the boy group

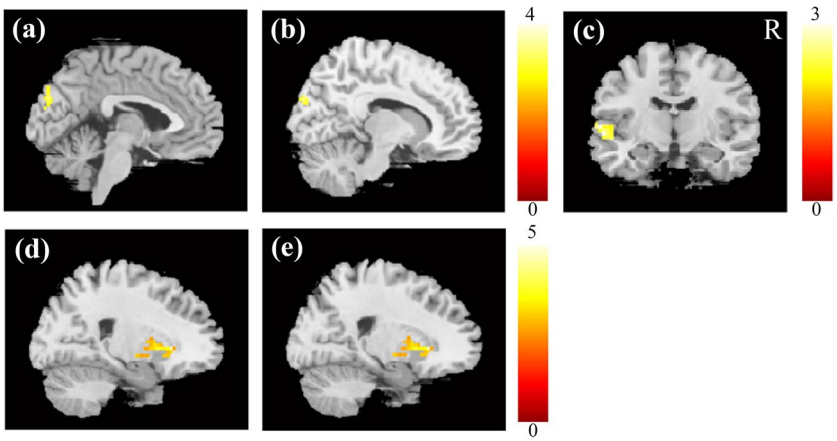

Fig. 3 mfALFF and mReHo results for lead and MeHg. In the mfALFF results, we observed a correlation between lead concentration and the activity in the (**a**) left cuneus and (**b**) right cuneus in the combined group of boys and girls and a correlation between MeHg concentration and activity in the (**c**) left superior temporal gyrus. In the mReHo results, we also observed a correlation between MeHg concentration and activity in the (**d**) right caudate nucleus and (**e**) right putamen in the combined group

Heavy metal exposure

In the mfALFF results for heavy metals (Fig. 3a–c), we observed a higher mfALFF in teenagers with prenatal exposure to lead in the left cuneus and right cuneus in the combined group of boys and girls ($p < 0.007$). There was a higher mfALFF in teenagers with prenatal exposure to MeHg in the left superior temporal gyrus in the combined group ($p < 0.025$). On the other hand, our mReHo results for heavy metals (Fig. 3d, e) showed that in the combined group of boys and girls, the MeHg concentration during pregnancy was negatively correlated with the right putamen and right caudate nucleus ($p < 0.021$).

PFOS and PFNA

Based on the significant negative correlation between PFOS concentration and activity in the right putamen in the combined group of boys and girls and in the boy group, and the significant negative correlation between PFNA concentration and activity in the left putamen, right putamen and left caudate nucleus in the combined group and the boy group, we added phthalates, heavy metals and PFOS (in PFNA) as covariates and performed multivariate linear regression to investigate the relationship between PFASs and other EDCs.

In the PFOS results (Fig. 4), there was a lower mfALFF in teenagers with prenatal exposure to PFOS in the right putamen and right insula in the combined group of boys and girls when using gender, family income and five phthalates as covariates ($p < 0.0125$). There was a lower mfALFF in teenagers with prenatal exposure to PFOS in the right putamen in the combined group when using gender, family income and three heavy metals as covariates ($p < 0.015$). There was a lower mfALFF in teenagers with prenatal exposure to PFOS was in the right putamen in the boy group when using family income and five phthalates as covariates ($p < 0.0125$). There was a lower mfALFF in teenagers with prenatal exposure to

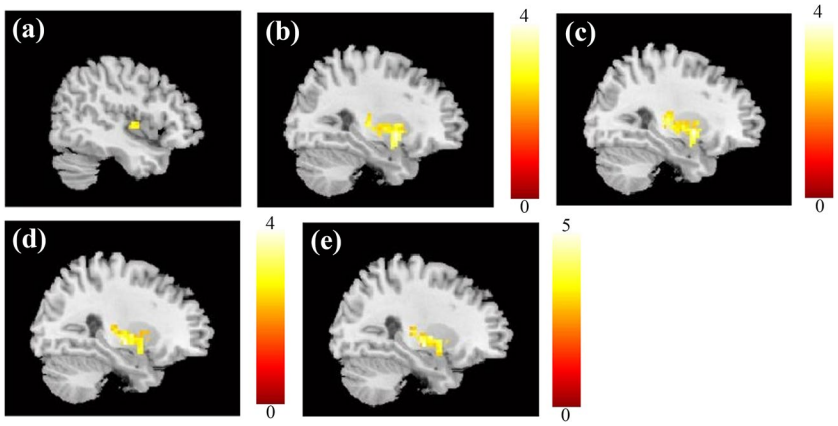

Fig. 4 The correlation between PFOS and mfALFF. PFOS showed a negative relationship with mfALFE results in the (**a**) right insula and (**b**, **c**) right putamen in the boys and girls combined group after application of (**a**, **b**) phthalate or (**c**) heavy metals as covariates. PFOS also showed a negative relationship with mfALFF in the right putamen in the boy group after application of (**d**) phthalate or (**e**) heavy metals as covariates

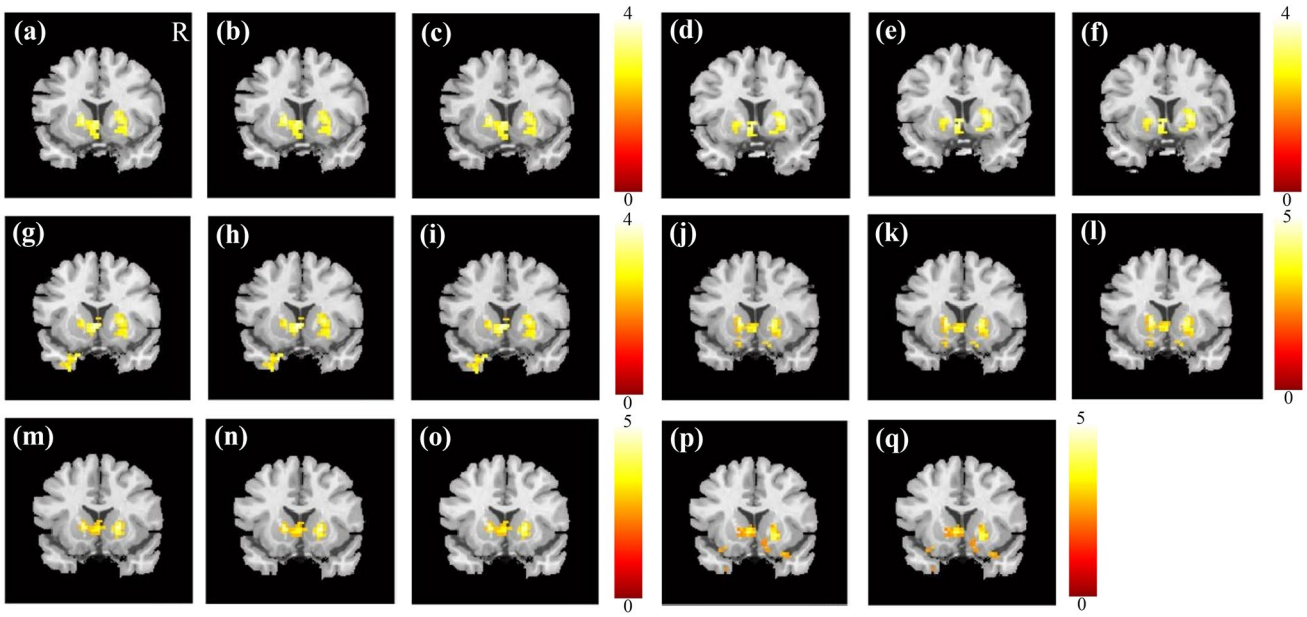

Fig. 5 The correlation between PFNA and mReHo. PFNA was negatively correlated with mReHo in the (**a**, **d**, **g**) left caudate nucleus, (**b**, **e**, **h**) left putamen and (**c**, **f**, **i**) right putamen in the boys and girls combined group after application of (**a**, **b**, **c**) PFOS, (**d**, **e**, **f**) phthalates and (**g**, **h**, **i**) heavy metals as covariates. PFNA was negatively correlated with mReHo of the (**j**, **m**, **p**) left caudate nucleus, (**k**, **n**) left putamen and (**l**, **o**, **q**) right putamen in the boy group after application of (**j**, **k**, **l**) PFOS, (**m**, **n**, **o**) phthalates and (**p**, **q**) heavy metals as covariates

PFOS in the right putamen in the boy group when using family income and three heavy metals as covariates ($p < 0.015$).

In the results for PFNA (Fig. 5), the PFNA concentration during pregnancy was inversely related to activity in the left putamen, right putamen and left caudate nucleus when using gender, family income and PFOS as covariates in the combined group of boys and girls ($p < 0.005$). The PFNA concentration during pregnancy was inversely related to activity in the left putamen, right putamen and left caudate nucleus when using gender, family income and five phthalates as covariates in the combined group ($p < 0.005$). The PFNA concentration during pregnancy was inversely related to activity in the left putamen, right putamen and left caudate nucleus when using gender, family income and three heavy metals as covariates in the combined group of boys and girls ($p < 0.01$). The PFNA concentration during pregnancy was inversely related to activity in the left putamen, right putamen and left caudate nucleus when using family income and PFOS as covariates in the boy group ($p < 0.005$). The PFNA concentration during pregnancy was inversely related to activity in the left putamen, right putamen and left caudate nucleus when using family income and five phthalates as covariates in the boy group ($p < 0.005$). The PFNA concentration during pregnancy was inversely related to the activity in the right putamen and left caudate nucleus when using family income and three heavy metals as covariates in the boy group ($p < 0.01$).

Overview

Our mfALFF and mReHo results showed significant correlations between different kinds of EDCs and several brain regions such as the frontal gyrus, temporal gyrus, anterior cingulum gyrus, cuneus, and especially regions of the reward system (Table 2). All of the corrected p-values were less than 0.05.

In addition, we added concentrations of other EDCs as covariates to investigate the relationship between PFASs and other EDCs (Table 3). The results were similar, and the PFOS and PFNA concentration still showed significant correlations with activity in the insula, caudate

Table 2 Significant correlations between the prenatal concentration of EDCs and activity in brain regions

Method	EDCs	L/R	Regions	MNI coordinates			Boys/Girls/Mix	±	Corrected *p* value
				x	*y*	*z*			
mfALFF	MBP	R	Middle frontal gyrus	40	42	27	Mix	–	0.025
			Superior frontal gyrus	18	56	27			
	MBzP	L	Anterior cingulum gyrus	– 5	40	16	Girls	+	0.02
		R		9	49	16			
	PFOS	R	Insula	41	– 3	1	Mix	–	0.015
			Putamen	27	– 2	– 5			
			Pallidum	27	– 11	– 3	Boys	–	0.01
			Putamen	27	1	– 5			
	Pb	L	Cuneus	– 3	– 85	26	Mix	+	0.007
		R		11	– 87	277			
	MeHg	L	Superior temporal gyrus	– 57	– 10	1	Mix	+	0.025
mReHo	MBP	L	Inferior temporal gyrus	– 47	– 19	– 30	Mix	+	0.015
			Middle temporal gyrus	– 56	– 19	– 15			
	MBzP	R	Insula	36	– 29	18	Girls	–	0.04
	PFNA	L	Caudate nucleus	– 11	17	2	Mix	–	0.004
		L	Putamen	– 16	8	2			
		R		26	3	2			
		L	Caudate nucleus	– 8	11	– 5	Boys	–	0.009
		L	Putamen	– 15	10	– 1			
		R		23	10	– 1			
	MeHg	R	Caudate nucleus	22	24	0	Mix	-	0.021
			Putamen	21	18	2			

There are significant correlations between different kinds of EDCs and several brain regions such as the frontal gyrus, temporal gyrus, anterior cingulum gyrus, cuneus, and especially regions of reward system. All of the corrected p-values were less than 0.01

L/R left/right; *Boys/Girls/Mix* Boy group/Girl group/Boys and girls mixed group; ± Positive/Negative correlation; *mfALFF* mean fractional amplitude of low-frequency fluctuations; *mReHo* = mean regional homogeneity; Cluster size = 100

Table 3 Results of prenatal PFOS and PFNA concentrations using different covariates

Method	EDCs	L/R	Regions	MNI coordinates			Boys/Girls/Mix	Covariates	Corrected *p* value
				x	*y*	*z*			
mfALFF	PFOS	R	Insula	41	− 3	1	Mix	Gender + family income	0.015
			Putamen	27	1	− 5			
			Insula	46	− 6	− 1	Mix	Gender + family income + phthalate	0.0125
			Putamen	28	1	− 1			
			Putamen	28	− 1	− 5	Mix	Gender + family income + heavy metal	0.015
			Pallidum	27	− 11	− 3	Boys	Family income	0.01
			Putamen	27	− 2	− 5			
			Putamen	27	3	3	Boys	Family income + phthalate	0.0125
			Putamen	27	2	− 3	Boys	Family income + Heavy metal	0.015
mReHo	PFNA	L	Caudate nucleus	− 11	17	2	Mix	Gender + family income	0.004
		L	Putamen	− 166	8	2			
		R		26	3	2			
		L	Caudate nucleus	− 5	11	− 4	Mix	Gender + family income + PFOS	0.005
		L	Putamen	− 18	11	− 3			
		R		26	11	0			
		L	Caudate nucleus	− 5	8	− 7	Mix	Gender + family income + phthalate	0.005
		L	Putamen	− 17	8	− 1			
		R		27	8	0			
		L	Caudate nucleus	− 7	12	− 3	Mix	Gender + family income + heavy metal	0.01
		L	Putamen	− 16	12	0			
		R		27	12	0			
		L	Caudate nucleus	− 8	11	− 5	Boys	Family income	0.009
		L	Putamen	− 15	10	0			
		R		23	10	− 1			
		L	Caudate nucleus	− 3	13	0	Boys	Family income + PFOS	0.005
		L	Putamen	− 16	13	1			
		R		20	13	− 5			
		L	Caudate nucleus	− 1	14	− 1	Boys	Family income + phthalate	0.005
		L	Putamen	− 16	14	1			
		R		20	14	− 3			
		L	Caudate nucleus	− 5	14	− 5	Boys	Family income + heavy metal	0.01
		R	Putamen	20	14	− 6			

The PFOS and PFNA concentrations were still significantly correlated with activity in the insula, caudate nucleus and, especially, the putamen after using different EDCs as covariates. The corrected p-values were less than 0.01

L/R left/right; *MNI* Montreal Neurological Institute; *Boys/Girls/Mix* Boys group/Girls group/Boys and girls mixed group; *mfALFF* mean fractional amplitude of low-frequency fluctuations; *mReHo* mean regional homogeneity; Cluster size = 100

nucleus and especially the putamen. The corrected p-values were less than 0.05.

Supplemental Table 1 showed the correlation level among the studied EDCs. As expected, the phthalate compounds tended to be correlated, and so as PFASs, and the metal of lead and cadmium. Thereby, animal testing would be necessary for the specific chemical effect because humans are exposed to the chemicals with similar routes and/or sources.

Discussion

Phthalate

Past studies have reported that prenatal exposure to phthalate could affect childhood behavior using several behavioral scales (Kobrosly et al. 2014; Lien et al. 2015). The results consistently indicated that pregnant women with

higher MBP concentrations had children with poor external behavior, such as delinquent and aggressive behavior, and these results were sex related in different studies. Messerlian et al. reported that higher MBP concentrations during pregnancy were associated with increased occurrences of aggressive behavior in boys (Messerlian et al. 2017). Whyatt et al. suggested a positive association between prenatal MBzP concentration and the anxiety and depression scores in girls at 3 years of age (Whyatt et al. 2012). The mfALFF results in our study showed that the MBP concentration during pregnancy in the combined group of boys and girls was negatively correlated with activity in the right superior frontal gyrus and right middle frontal gyrus (Fig. 1a, b). In the mReHo results, the concentration of MBP in the combined group was positively correlated with activity in the left middle temporal gyrus and left superior temporal gyrus in the left hemisphere (Fig. 1c, d). The frontal lobe is involved in executive functions, language, emotions and other higher functions. The temporal lobe is involved in visual memory, language comprehension, and emotion-related functions. Some studies have reported that abnormal frontal and temporal lobes are related to aggressive behavior (Ameis et al. 2014; Woermann et al. 2000). An activation likelihood estimation (ALE) meta-analysis by Raschle et al. pointed out that in people with aggressive behavior, the frontal gyrus, middle frontal gyrus, mid-temporal gyrus and inferior temporal gyrus showed lower activity levels than those of normal subjects (Raschle et al. 2015), which is consistent with our findings.

On the other hand, we found a negative correlation between the left/right anterior cingulum gyrus and MBzP concentration in the mfALFF results in the girl group (Fig. 1e, f). We also observed a negative correlation between activity in the right insula and MBzP concentration in girls in our mReHo analysis (Fig. 1g). Stein et al. reported that healthy subjects with high anxiety scores showed increased activity in their insula and amygdala when performing anxiety-related tasks (Stein et al. 2007). A diffusion tensor imaging (DTI) study also showed that the severity of anxiety disorders is associated with reduced fractional anisotropy (FA) values in the cingulum gyrus (Wang et al. 2016; Albaugh et al. 2017). These brain regions are all related to emotional feelings, which may be why we detected correlations in these regions.

PFASs

Maternal or childhood exposure to PFASs harms human neurodevelopment (Gump et al. 2011; Hoyer et al. 2015; Vuong et al. 2016). Gump et al. reported that childhood exposure to PFOS and PFNA causes impulsive behavior in ten-year-old children (Gump et al. 2011). In the mfALFF results in the boys and girls mixed group, there was a negative correlation between PFOS and activity in the putamen and insula in the right hemisphere (Fig. 2a, b). A lower mfALFF in teenagers with PFOS exposure was found in the pallidum and putamen of the right hemisphere in boys (Fig. 2c, d). In the mReHo results for the boys and girls mixed group and the boy group, we found a negative correlation between the PFNA and activity in the left/right putamen and left caudate nucleus (Fig. 2e–j). The putamen, insula, pallium and caudate nucleus are part of the reward system. Many studies reported the association between impulsive behavior and abnormal volume changes in those brain regions using voxel-based morphometry (VBM) analysis (Caravaggio et al. 2017; Dombrovski et al. 2012; Mackey et al. 2017; Tschernegg et al. 2015). These results implicated similar brain regions to those in our study. In addition, impulsive behaviors were more common in men (Weinstein and Dannon 2015). Therefore, this may be the reason why we only observed similar results in boys and not in girls.

In addition, we observed that the damage caused by PFOS and PFNA was concentrated in the reward system, especially in the putamen. Based on the original covariates (gender and family income), phthalates, heavy metals, or PFASs were added as extra covariates to investigate the effect of other EDCs on PFOS or PFNA effects. After the influences of phthalate and heavy metals were removed, we observed a significant negative correlation between PFOS and activity in the right insula and right putamen in the combined group of boys and girls and in the boy group (Fig. 4a–e), especially with right putamen (Fig. 4b–e). On the other hand, after we removed the influence of PFOS, phthalates or heavy metals, we observed a significant negative correlation with the left/right putamen and left caudate nucleus in the combined group and the boy group (Fig. 5). This was similar to the results before we removed other EDC factors (Fig. 2e–j). These PFOS and PFNA results indicated that the harms of phthalates, heavy metals and PFASs may be independent. The effect of EDCs on damaging brains during neurodevelopment was not synergetic. This evidence is consistent with our hypothesis. Further studies on the toxicological mechanisms of EDCs are required.

Heavy metal

The toxicity of lead in the human body has been reported from the past to the present (Farias 1998; Gundacker et al. 2010; Henriquez-Hernandez et al. 2017; Kranz et al. 2004; Storelli et al. 2010). Many of these studies are related to the exposure of lead during pregnancy or early childhood, which could cause negative effects on behavior and cognition, such as impaired language development, slower learning, and criminal activity in adults, etc. (Ernhart and Greene 1990; Nelson and Espy 2009; Wright et al. 2008). Some studies have pointed out that long-term lead exposure during

pregnancy or childhood causes adverse effects on children's attention span and may even be linked to attention-deficit/hyperactivity disorder (ADHD) (Neugebauer et al. 2015; Nicolescu et al. 2010; Sioen et al. 2013). In our results, a higher mfALFF in teenagers with prenatal exposure to lead was found in the cuneus of the left and right hemispheres (Fig. 3a, b). The cuneus is involved in basic visual processing, visual attention and spatial and non-spatial shifting attention (Corbetta et al. 1993; Hao et al. 2005; Le et al. 1998). Cuneus abnormalities are common in brains of ADHD patients (Park et al. 2016; Zhan et al. 2017). Other studies using ALFF and ReHo analysis have shown similar positive correlations with activity in cuneus (Alonso Bde et al. 2014; Wang et al. 2017).

MeHg is another EDC that has been extensively studied and has widely toxic effects. Previous studies reported that prenatal exposure to MeHg affects attention, memory, visuospatial and motor functions (Debes et al. 2006; Grandjean et al. 1997, 1998; Lam et al. 2013). The longitudinal study of Grandjen and Debes et al. recruited 1022 mother–child pairs, and then examined the association between prenatal MeHg concentration and intelligence, language and motor function at 7 and 14 years of age using different tests. They discovered that the concentration of MeHg during pregnancy is significantly related to poor performance in language, attention and memory in seven-year-old children (Grandjean et al. 1997). In fourteen-year-old children, the MeHg concentration during pregnancy was significantly related to the deterioration of language and attention performance (Debes et al. 2006). In our study, a higher mfALFF in teenagers with prenatal exposure to MeHg was found in the left superior temporal gyrus (Fig. 3c). The left superior temporal gyrus is also known as Brodmann area 22 (BA22). BA22 is not only involved in auditory components (Ahmad et al. 2003; Soderfeldt et al. 1997) but also plays an important role in semantic processing (Chou et al. 2006; McDermott et al. 2003). A VBM study suggested that left superior temporal stroke was associated with aphasia (Baldo et al. 2009). Another study observed a correlation between poor semantic processing and lower left superior temporal activation in healthy older subjects (Grossman et al. 2002). On the other hand, our mReHo results for the combined group of boys and girls showed that the right putamen and right caudate nucleus were negatively correlated with maternal MeHg concentration (Fig. 3d, e). A study indicated that exposure to MeHg during pregnancy affects children's working memory (Boucher et al. 2014). The putamen and caudate nucleus are responsible for rewarding the brain by directly regulating dopamine release (Gruber et al. 2006; Marklund et al. 2009). A retrospective study suggested that during the learning process, the brain rewards correct memory behaviors by releasing dopamine to indirectly influence memory (Grahn et al. 2009; Yu, FitzGerald, and Friston 2013). We hypothesize that exposure to MeHg affects these two brain regions and causes memory impairment in children.

However, some studies in the past indicated that prenatal exposure to MeHg did not impair emotion or motor functions in the adult (Davidson et al. 2011). Additionally, another study pointed out that prenatal exposure to MeHg does not adversely affect social or cognitive behavior in school-age children (Davidson et al. 2006; van Wijngaarden et al. 2013). The researchers suggested that the subjects' intake of MeHg was mainly through consumption of fish during pregnancy. Although fish contains MeHg which harms human health, they are also rich in nutrients such as vitamin E, omega-3 polyunsaturated fatty acids (n-3 PUFA), and docosahexaenoic acid (DHA) which are essential for normal brain development. These components reduce the harm of MeHg in the human body and even counteract the toxicity caused by MeHg, so that the fetus and children have normal neurological development. Further studies to explore the physiological mechanisms of MeHg that affect the human body are necessary.

Limitation

Although this research was carefully prepared, we are aware of its unavoidable limitations and shortcomings. First, our results only provide correlations between EDC concentrations during pregnancy and the functional changes in brain regions of their offspring. However, we cannot explain the mechanisms of EDC-induced damage. Therefore, further physiological studies are needed to explore the mechanisms of EDCs in the human body. Second, although we controlled some covariates such as gender and family income, other potential confounders, such as fetal and childhood EDC exposure and maternal exposure during the first and second trimesters, may also contaminate the results. We did not test if the fMRI results correlate with the duration of the gestation. Future research should consider these factors. Our investigation was directed to incorporate children's' IQ, CBCL, and probably attention-deficit/hyperactivity disorder (ADHD) as well (Ku et al. 2019) into the functional study.

Current literature on the mechanisms for the above EDCs results is scarce. A recent review demonstrated a focus on thyroid disruption for the various brain process effects, including neurogenesis, neural differentiation and migration, and neural connectivity (Ghassabian and Trasande 2018). The authors summarized the interference of hormonal signaling by EDCs' binding to thyroid receptors and modifying gene expression might be the major considerations. Others include the interference of the bio-synthesis, secretion, metabolism and transfer of the hormones especially during fetal and childhood exposure. Experimental designed studies

are warranted to further prove the underlying mechanisms at specific fetal stages.

The average exposure levels of the EDCs studied in the present study are in general comparable to other studies from daily life such as water and food intake (Chen et al. 2017; Rehman et al. 2018; Jian et al 2017). Thereby, such outcomes deserve the observations in other populations.

Conclusions

As far as we know, this is the first study to use resting-state fMRI to report the relationship between EDCs and brain resting activity. We used fALFF and ReHo analyses to detect the correlation between the maternal concentrations of multiple EDCs and activity in the brain regions of their offspring in resting state. This might help us to better understand the functional brain changes induced by EDCs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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