Environmental Pollution 231 (2017) 1112–1121

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Elevated lead levels from e-waste exposure are linked to decreased olfactory memory in children☆

Bo Zhang [a, 1], Xia Huo [c, 1], Long Xu [a], Zhiheng Cheng [a], Xiaowei Cong [a], Xueling Lu [a], Xijin Xu [a, b, *]

[a] *Laboratory of Environmental Medicine and Developmental Toxicology, and Guangdong Provincial Key Laboratory of Infectious Diseases, Shantou University Medical College, Shantou 515041, Guangdong, China*
[b] *Department of Cell Biology and Genetics, Shantou University Medical College, Shantou 515041, Guangdong, China*
[c] *School of Environment, Guangzhou Key Laboratory of Environmental Exposure and Health, Guangdong Key Laboratory of Environmental Pollution and Health, Jinan University, Guangzhou, Guangdong, 510632, China*

ARTICLE INFO

Article history:
Received 18 November 2016
Received in revised form
20 June 2017
Accepted 6 July 2017
Available online 9 August 2017

Keywords:
E-waste
Pb exposure
Children
Olfactory memory

ABSTRACT

Lead (Pb) is a developmental neurotoxicant and can cause abnormal development of the nervous system in children. Hence, the aim of this study was to investigate the effect of Pb exposure on child olfactory memory by correlating the blood Pb levels of children in Guiyu with olfactory memory tests. We recruited 61 preschool children, 4- to 7-years of age, from Guiyu and 57 children from Haojiang. The mean blood Pb level of Guiyu children was 9.40 μg/dL, significantly higher than the 5.04 μg/dL mean blood Pb level of Haojiang children. In addition, approximately 23% of Guiyu children had blood Pb levels exceeding 10.00 μg/dL. The correlation analysis showed that blood Pb levels in children highly correlated with e-waste contact ($r_s = 0.393$). Moreover, the mean concentration of serum BDNF in Guiyu children (35.91 ng/ml) was higher than for Haojiang (28.10 ng/ml) and was positively correlated with blood Pb levels. Both item and source olfactory memory tests at 15 min, 5 h and 24 h after odor exposure showed that scores were lower in Guiyu children indicative of reduced olfactory memory in Guiyu children. Olfactory memory tests scores negatively correlated with blood Pb and serum BDNF levels, but were positively associated with parental education levels. At the same time, scores of both tests on children in the high blood Pb level group (blood Pb levels > 5.00 μg/dL) were lower than those in the low blood Pb level group (blood Pb levels ≤ 5.00 μg/dL), implying that Pb exposure decreases olfactory memory in children. Our findings suggest that Pb exposure in e-waste recycling and dismantling areas could result in an increase in serum BDNF level and a decrease in child olfactory memory, in addition, BDNF might be involved in olfactory memory impairment.

1. Introduction

With the advance of science and technology around the world, the quality and performance of electronic equipment has continued to improve. Satisfying consumer needs, the continual updating of high-tech equipment at the same time has resulted in the accumulation electronic waste (e-waste), whose components have become major contaminants. E-waste includes the end-of-life electronics or electrical equipment for home or office, such as computers, printers, television sets, mobile phones, refrigerators, washing machines, and even large electrical products such as medical equipment and telecommunication equipment (Chen et al., 2011; Grant et al., 2013). To date, e-waste has become the fastest-growing stream of solid waste, the accumulation of which has caused serious environmental pollution and has become one of the most significant environmental health concerns (Heacock et al., 2016; Li et al., 2015; Tansel, 2017). Approximately 80% of the world's e-waste is imported into Asia, with as much as 90% being deposited in China (Chen et al., 2011; Hicks et al., 2005; LaDou and Lovegrove, 2008).

E-waste contamination mainly occurs in less developed

☆ This paper has been recommended for acceptance by Prof. W. Wen-Xiong.

* Corresponding author. Laboratory of Environmental Medicine and Developmental Toxicology, Shantou University Medical College, 22 Xinling Rd., Shantou, 515041, Guangdong, China.

E-mail address: xuxj@stu.edu.cn (X. Xu).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.envpol.2017.07.015
0269-7491/

countries, such as Nigeria or Ghana, and developing countries as India and China (LaDou and Lovegrove, 2008; Suk et al., 2016). In Guiyu, a small town in southern China and the biggest e-waste recycling and dismantling area in the world, the irregular disposal or recycling processes with e-waste is a major concern, for example the burning, acid leaching, roasting, dismantling and dumping of e-waste, resulting the release of heavy metals and organic pollutants to the surrounding air, water, and soil environment, contaminating food and threatening the health of local residents (Heacock et al., 2016; LaDou and Lovegrove, 2008; Lin et al., 2017; Ogunseitan et al., 2009; Schmidt, 2006; CS Wong et al., 2007; MH Wong et al., 2007; Wu et al., 2011; L Xu et al., 2015; Xu et al., 2013; X Xu et al., 2015; Yekeen et al., 2016; Yu et al., 2006; Zeng et al., 2016b).

As one of the major pollutants in e-waste recycling and dismantling, lead (Pb) is released by the dumping, roasting, burning and acid leaching of scrap electronic equipment such as Pb-contained circuit boards, batteries, and TVs, resulting in the liberation of pollutants into air, soil and water (Bi et al., 2015; CS Wong et al., 2007). The main routes of exposure for Pb are inhalation and ingestion (X Xu et al., 2015). Due to differences in physiology and habits, children are more susceptible to the adverse effects of Pb exposure than adults (Bellinger, 2004; Chen et al., 2011; Lidsky and Schneider, 2003; Zeng et al., 2016a). Previous studies showed that 1- to 6-year- old children living in primitive e-waste recycling areas have a higher burden of Pb compared to other toxicants, with mean blood Pb levels of 15.3 μg/dL, much higher than children from non-e-waste recycling and dismantling areas (Huo et al., 2007; Zhang et al., 2016; Zheng et al., 2008). The percentage of children with blood Pb levels exceeding 10 μg/dL is approximately 81.8%, which is much higher than the 37.7% found in non-e-waste recycling and dismantling areas, and continues to rise with age (Huo et al., 2007; Zheng et al., 2008). Several studies show that Pb impacts the nervous system of children who are at the critical period for neurodevelopment. Lower IQ performance, neuropsychological dysfunction, attention deficit hyperactivity disorder and impaired cognitive function as memory, language and executive function have all been demonstrated in Pb-exposed children. A prior study showed that 6- to 10-year-old children with blood Pb levels of 5–10 μg/dL exhibit mental decline, accompanied with attention disorders, and decreased memory and executive function (Bellinger, 2004, 2008, 2011; Lidsky and Schneider, 2003; Zhang et al., 2015). An increasing number of studies revealed that even Pb-exposed children with blood Pb levels less than 5 μg/dL are associated with intellectual impairment (Canfield et al., 2003; Chandramouli et al., 2009; Lanphear et al., 2005; Lucchini et al., 2012; Mazumdar et al., 2011; Miranda et al., 2007).

Brain derived neurotrophic factor (BDNF) has been shown to play an important role in nervous system development and synaptic plasticity, and the BDNF signaling system has been implicated in the processes of hippocampus-dependent learning and memory formation (Ninan, 2014; Zagrebelsky and Korte, 2014), which also can be observed in the induction and formation of olfactory memory (Tong et al., 2014). The production and release of BDNF have been shown to be activity-dependent, which can be modulated by N-methyl-D-aspartate (NMDA) receptors through the Ca^{2+} signaling pathway (Matsuda et al., 2009; Shieh et al., 1998; West et al., 2001). Modulating glutamate receptors by BDNF is thought to play an important role in hippocampal plasticity and memory formation (Fortin et al., 2012; Slipczuk et al., 2009). Deficiency of serum BDNF is associated with a reduction in spine density and dendritic complexity and in hippocampus volume (Erickson et al., 2010; von Bohlen und Halbach 2010). The insulin-like growth factor 1 (IGF-1) is a member of the insulin superfamily of peptides and is mainly produced by hepatocytes, contributing to circulating IGF-1 (Fernandez and Torres-Aleman, 2012). Serum IGF-1 entries into brain through brain vessels in an activity-dependent manner and affects neuronal plasticity and cognition (Nishijima et al., 2010). In addition, reduction of serum IGF-1 levels results in decreased hippocampal size and learning deficits (Lopez-Lopez et al., 2004; Trejo et al., 2007).

Olfactory memory is based on the recollection of odor in the associated context. Olfactory epithelium perceives the odor signal and *via* olfactory bulb projects inputs onto the piriform cortex, amygdala, and entorhinal cortex. Simultaneously, with the information from visual senses, olfactory information converges onto the orbitofrontal cortex, thalamus, hippocampus and insula cortex, allowing for the representation of the odor memory in the context in which it was experienced (Saive et al., 2014). Long-term potentiation (LTP), synaptic plasticity and neurogenesis mediated by NMDA receptors are involved in the molecular basis for formation and development of olfactory memory (du Bois and Huang, 2007; Tolias et al., 2005; Tong et al., 2014; Wang et al., 2011). Olfactory memory can be divided into two types: odor recognition memory (item memory) and odor associative memory (source memory) (Pirogovsky et al., 2006; Saive et al., 2014). Item memory is about the fact or content of an event, but source memory is the process of remembering the source or connection of events through specific projects or facts (Pirogovsky et al., 2006). According to the differences in storage time, olfactory memory can also be divided into short-term memory (STM), intermediate-term memory (ITM) and long-term memory (LTM) (Grimes et al., 2011; Tong et al., 2014).

To date, studies on the effects of lead on olfactory memory are few, and only in animal experiments. A recent study showed that Pb induces olfactory recognition memory impairment in rats (Flores-Montoya et al., 2015). There have been no epidemiological studies concerning the impairment of olfactory memory caused by Pb exposure. However it is clear that the relationship between lead exposure and impaired children's nervous system development is closely related. During the critical period of development, even low levels of Pb exposure may have adverse effects on mental development, and adverse effects on memory caused by low level Pb exposure may have profound effects on the health of a child's brain (Flores-Montoya et al., 2015). Pb blocks NMDA receptors which are essential for hippocampus-mediated learning and memory (Baranowska-Bosiacka et al., 2012; Gavazzo et al., 2008; Guilarte et al., 1995; Morris et al., 1982, 1986; Neal and Guilarte, 2013; Tsien et al., 1996). Therefore, we hypothesize that olfactory memory, which also depends on NMDA receptors, may be altered as a result of Pb-mediated neurotoxicity.

The aim of this study is to detect the level of Pb exposure and the olfactory memory in children from an e-waste recycling and dismantling area, to explore the effects of Pb exposure on children's olfactory memory, and to provide scientific basis for further study concerning the effect of lead exposure on both child nervous system development and the neurotoxicity of Pb.

2. Materials and methods

2.1. Study population

We recruited 118 preschool children approximately 6 years of age from Guiyu (n = 61) and Haojiang (n = 57), which was selected as the reference area for the similarities to Guiyu in population, cultural background and socioeconomic status, and furthermore without e-waste pollution. All children's parents or guardians gave written informed consent prior to enrollment. To collect the information as the general characteristics, health physiological, living and eating habits of children as well as dwelling environments, parental education level and jobs whether related to e-waste, a questionnaire was delivered to the parents or guardians. Collecting of blood samples and testing for olfactory memory in children were preformed after the children's parents or guardians provided the informed consent. The study protocol was approved by the Human Ethics Committee of Shantou University Medical College, China.

2.2. Determination of blood Pb

Peripheral blood were obtained from each child between 8:00–10:00 a.m. and collected in blood sample tubes containing anticoagulant, by trained nurses. The blood was stored at a −20 °C refrigerator until assay for Pb.

To determine blood Pb levels, 100 μL whole blood and 900 μL of 0.5% nitric acid were mixed and digested for 10 min at room temperature. The detection method for blood Pb levels was in accordance with our previous publication by graphite furnace atomic absorption spectrometry (GFAAS, Jena Zeenit 650, Germany) (Guo et al., 2010).

2.3. Measurement of serum BDNF and IGF-1 levels

The blood samples in anticoagulant-free tubes were clotted for 30 min at room temperature and then centrifuged for 15 min at 4 °C and 1000 g. Serum was aliquot and stored at −80 °C until assay.

Serum BDNF and IGF-1 concentrations were determined with Quantikine® quantitative sandwich ELISA kits (R&D Systems Inc., Minneapolis, MN, USA). All assays were performed according to the manufacturer's instructions. Assay sensitivities for BDNF and IGF-1 were 20 pg/mL and 0.056 ng/mL respectively. Respective intra- and inter-assay precision coefficients of variation for BDNF and IGF-1 were less than 6.2% and 4.3% within-assay, 11.3% and 8.3% between assays.

2.4. Alcohol sniff test

To assess the differences in olfactory threshold between Guiyu and Haojiang, we administered an alcohol sniff test (AST) (Pirogovsky et al., 2006). Children were first familiarized with the smell of a 70% isopropyl alcohol cotton ball, and then children were seated in an upright position. A standard tape measure was positioned downward from each child's nose and the child was asked to close his or her eyes and mouth, and breathe normally through the nose. The alcohol cotton ball was placed 30 cm below the nostrils and with each expiration the cotton ball was moved 1 cm closer to the nostrils until children detected the odor. The distance (cm) from the nose to the cotton ball was measured. This procedure was repeated three times and the mean distance was determined as the olfactory threshold for each child.

2.5. Olfactory memory test

The olfactory memory test included an odor recognition memory test (item test) and odor source memory test (source test). There were two phases in each test, namely the studying phase and testing phase, and the protocol was performed according to a previous study (Pirogovsky et al., 2006). A total of 24 odors were used in the test, 16 odors were used in the studying phase and 8 odors were used as the distractors during the item testing phase. Most of the odors were common household odors (Jones et al., 1978; Lesschaeve and Issanchou, 1996; Pirogovsky et al., 2006; Schab, 1991; Zucco and Tressoldi, 1989), including fruit, flowering plants, angiosperm, food, condiments and seasoning, which were presented in white opaque jars.

Wearing white lab coats, one male and one female experimenter were involved in presenting the stimuli only during the studying phase of the experiment. At the studying phase, children were instructed to smell a series of odors, each odor for 5 s. A total of 16 odors were presented in an alternating sequence, as the female experimenter presented the first odor and the second by the male experimenter, with finally each experimenter having presented 8 odors. Children did not know the subsequent process during the whole studying phase.

The testing phase, including an item test and source test, to separately assess item and source memory, were conducted by another experimenter and started 15 min (STM), 5 h (ITM) and 24 h (LTM) after studying. There were 16 trials at every time point, hence 8 for the item and 8 for the source test trials. During the item testing phase, child was presented once for 5 s with 1 odor selected randomly from the 16 odors previously presented and 1 distractor odor randomly selected from 8 odors not previously presented, and was asked to answer that which one was previously presented. This was repeated 8 times. Therefore, there were 8 remaining odors from the studying phase that were not used for the item testing trials. During the source testing phase, the child was presented once with 1 odor of the 8 remaining odors from the studying phase and asked to indicate if the male or the female experimenter presented it. The correct percentages of the item and source tests, which served as the scores of tests, were recorded for analysis.

2.6. Statistical analysis

Comparisons between the two populations were performed using an independent-sample *t*-test and chi-square test. Mean ± SE or mean ± SD were used to depict blood Pb levels, serum BDNF and IGF-1 levels, olfactory threshold, and scores of olfactory memory tests. Spearman correlation analysis was used to assess the relevant factors contributing to Pb exposure and the scores of olfactory memory tests. Univariate linear regression analysis was used to examine relationships between blood Pb levels and serum BDNF or IGF-1. The Hotelling T^2 test was carried out to examine the differences of olfactory memory between the two groups. All statistical analyses were performed with SPSS 19.0 and Graph Pad Prism 6.0 software. A $p < 0.05$ in a two-tailed test was considered as statistically significant.

3. Results

3.1. Characteristics of the study population

A total of 118 children were enrolled in the study (Table 1). The mean age of Guiyu children (n = 61) was 5.62 ± 0.66 years, and 5.88 ± 0.71 years of Haojiang children (n = 57) ($p < 0.05$). Guiyu children had a lower physical development level in terms of lower height ($p < 0.01$), weight ($p < 0.05$) and chest circumference ($p < 0.05$). Parents from Guiyu had a lower education level ($p < 0.01$) and lower monthly household income ($p < 0.01$), with a higher proportion of fathers whose work was related to e-waste ($p < 0.01$) as well. Moreover, Guiyu children had a higher risk of e-waste contact ($p < 0.01$).

3.2. Blood Pb levels and related factors

The mean blood Pb level in Guiyu children (9.40 ± 3.72 μg/dL, from 7.00 to 31.00 μg/dL) was higher than for Haojiang (5.04 ± 1.65 μg/dL, from 2.59 to 9.93 μg/dL) ($p < 0.01$). In addition, the proportion of Guiyu children with a blood Pb level exceeding 10.00 μg/dL was approximately 23% (Table 2).

Spearman correlation analysis was used to estimate whether certain factors were related with blood Pb level (Table 3). The results showed that blood Pb levels were positively associated with

Table 1

Descriptive statistics for the study population in Guiyu and Haojiang.

	Guiyu(n = 61)	Haojiang(n = 57)	*p* - value
Gender			0.708^{b}
Boys	38(62.3%)	33(57.9%)	
Girls	23(37.7%)	24(42.1%)	
Age (mean ± SD, years)	5.62 ± 0.66	5.88 ± 0.71	0.047^{a}/0.204^{b}
4	1(1.6%)	0(0.0%)	
5	26(42.6%)	18(31.6%)	
6	29(47.5%)	28(49.1%)	
7	5(8.2%)	11(19.3%)	
Height (mean ± SD, cm)	107.62 ± 5.97	112.53 ± 5.25	˂0.001^{a}
Weight (mean ± SD, kg)	17.47 ± 2.91	18.72 ± 2.86	0.020^{a}
Head circumference (mean ± SD, cm)	50.40 ± 1.68	50.19 ± 1.54	0.480^{a}
Chest circumference (mean ± SD, cm)	50.56 ± 2.77	51.80 ± 3.22	0.028^{a}
Father's educational level			˂0.001^{b}
Primary school	4(6.7%)	0(0.0%)	
Middle school	38(63.3%)	7(12.5%)	
Vocational school	9(15.0%)	13(23.2%)	
High school	5(8.3%)	11(19.6%)	
Undergraduate	4(6.7%)	25(44.6%)	
Mother's educational level			˂0.001^{b}
Primary school	13(21.7%)	1(1.8%)	
Middle school	33(55.0%)	10(17.5%)	
Vocational school	6(10.0%)	12(21.1%)	
High school	3(5.0%)	10(17.5%)	
Undergraduate	5(8.3%)	24(42.1%)	
Father' s work relating to e-waste			˂0.001^{b}
Yes	18(30.0%)	0(0.0%)	
No	42(70.0%)	56(100.0%)	
Mother' s work relating to e-waste			0.364^{b}
Yes	4(7.1%)	1(1.8%)	
No	52(92.9%)	55(98.2%)	
Child contact with e-waste			˂0.001^{b}
Yes	25(43.1%)	2(3.5%)	
No	33(56.9%)	55(96.5%)	
Monthly household income (yuan)			0.003^{b}
˂1500	4(7.7%)	0(0.0%)	
1500-3000	5(9.6%)	7(12.5%)	
3000-4500	14(26.9%)	9(16.1%)	
4500-6000	17(32.7%)	9(16.1%)	
˃6000	12(23.1%)	31(55.4%)	

Note: ^{a} analysis by independent-samples *t*-test. ^{b} analysis by chi-square test. $p < 0.05$ was considered statistically significant.

Table 2

Comparison of blood Pb levels in children between Guiyu and Haojiang.

	Guiyu (n = 61)	Haojiang (n = 57)	*p*-value
Blood Pb levels (mean ± SD, μg/dL)	9.40 ± 3.72	5.04 ± 1.65	«0.001^{a}/˂0.001^{b}
≤5	0 (0.0%)	31 (54.4%)	
5˂&≤10	47 (77.0%)	26 (45.6%)	
˃10	14 (23.0%)	0 (0.0%)	

Note: ^{a} analysis by independent-samples *t*-test. ^{b} analysis by chi-square test. $p < 0.05$ was considered statistically significant.

children having contact with e-waste, ventilation of housing, use of residence as a workplace, father's work related to e-waste, and child eating canned food and negatively correlated with age, child hand washing prior to food consumption, monthly household income, ventilation of housing, parental education levels, and the average time of the child eating dairy products and iron rich foods.

3.3. Serum BDNF, IGF-1 levels and the relationships to Pb

The mean concentration of serum BDNF in Guiyu children (35.91 ± 1.28 ng/ml) was higher than for Haojiang (28.10 ± 1.07 ng/ml) ($p < 0.001$) (Fig. 1). Moreover, there was no significant difference for the mean concentration of serum IGF-1 between Guiyu (170.41 ± 9.47 ng/ml) and Haojiang (153.90 ± 7.23 ng/ml) children ($t = -1.383$, $p > 0.05$).

Univariate linear regression analysis between blood Pb and BDNF levels showed that serum BDNF concentration was positively associated with blood Pb levels (B = 0.683, 95% CI: 0.211, 1.154, $p < 0.01$) (Table 4).

3.4. Differences in olfactory memory between Guiyu and Haojiang children

3.4.1. Comparison of olfactory threshold between the two groups

We measured child odor threshold prior to the olfactory memory tests. The results showed that there was no significant difference for olfactory threshold between Guiyu (8.02 ± 1.50 cm) and Haojiang (8.10 ± 1.82 cm) children ($t = 0.269$, $p > 0.05$).

3.4.2. Item and source test on Guiyu and Haojiang children

The scores of Guiyu children in item tests were 58.81 ± 2.60 (15 min), 53.48 ± 2.39 (5 h) and 55.94 ± 2.14 (24 h) respectively, all

Table 3
Spearman correlation analysis of factors related to blood Pb levels in children.

	Blood Pb levels (r_s)
Age	−0.255**
Gender	−0.043
Duration of outdoor play	−0.141
Child hand washing prion to food consumption	−0.422***
Chewing nail habit	0.129
Child contacting e-waste	0.393***
Sources of family drinking water	−0.019
Household tobacco smoke exposure	0.026
Monthly household income	−0.270**
Residence as workplace	0.297**
Ventilation of house	0.225*
Distance of residence from the nearest road	0.127
Number of e-waste workshops within 50 m of residence	0.139
Years of child residency in Guiyu	−0.129
Father's educational level	−0.449***
Mother's educational level	−0.480***
Father's work related to e-waste	0.301**
Mother's work related to e-waste	0.115
Average time of child eating dairy products	−0.253**
Average time of child eating bean products	0.028
Average time of child eating canned food	0.262**
Average time of child eating iron rich foods	−0.345***
Average time of child taking supplements with added calcium, iron or zinc	0.075
Average time of chil taking vitamin supplements	0.114

Note: $p < 0.05$ was considered statistically significant. r_s spearman correlation coefficient. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

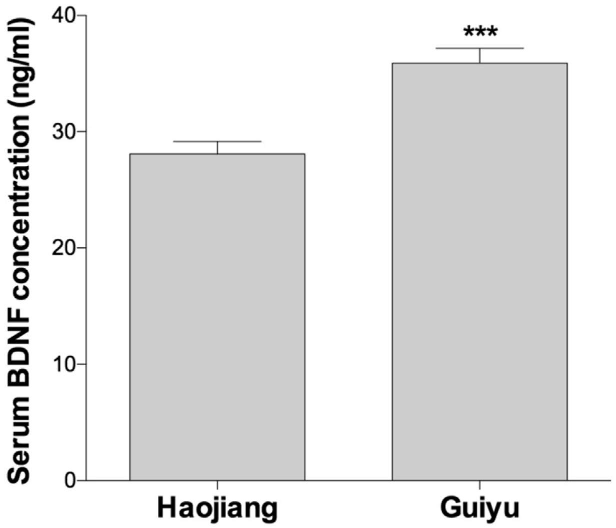

Fig. 1. Serum BDNF concentration in children from Guiyu were higher than that from Haojiang. Data are presented as mean ± SE. $p < 0.05$ was considered statistically significant. ***$p < 0.001$.

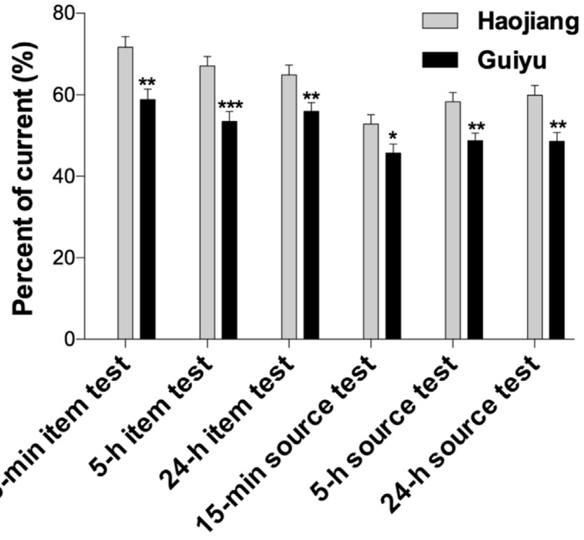

Fig. 2. Scores of olfactory memory tests in children from Guiyu were lower than that from Haojiang. Data are presented as mean ± SE. $p < 0.05$ was considered statistically significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 4
Univariate linear regression analysis of the association between blood Pb (μg/dL) and serum BDNF (ng/ml) levels in children.

	Serum BDNF concentration		
	B	95% CI for B	p-value
Blood Pb levels	0.683	0.211, 1.154	0.005

Note: $p < 0.05$ was considered statistically significant. B: unstandardized coefficients. CI: confidence interval.

significantly lower than the 71.68 ± 2.64 (15 min), 67.11 ± 2.31 (5 h) and 64.91 ± 2.37 (24 h) for Haojiang children. Additionally, the scores of Guiyu children in source tests were 45.70 ± 2.18 (15 min), 48.77 ± 1.84 (5 h) and 48.57 ± 2.21 (24 h), all significantly lower than the 52.85 ± 2.26 (15 min), 58.33 ± 2.26 (5 h) and 59.87 ± 2.44 (24 h) for Haojiang (Fig. 2).

Regarding the scores of item and source tests as two variables, the Hotelling T^2 test was performed to assess the differences in olfactory memory ability between Guiyu and Haojiang children. The results showed that the olfactory memory of Guiyu children was lower than that of Haojiang ($F = 8.060$, $p < 0.01$).

3.5. The association between Pb exposure and olfactory memory

Spearman correlation analysis showed that item test scores were negatively correlated with blood Pb levels, BDNF levels (5-h test only) and gender (5-h test only), and positively associated with parental education levels (Table 5). Except for the 24-h test,

Table 5
Spearman correlation analysis of factors related to olfactory memory test.

	Blood Pb levels	BDNF	Gender	Age	Father's educational level	Mother's educational level
5-min item	-0.260^{**}	-0.083	0.119	0.041	0.290^{**}	0.290^{**}
15-min source	-0.237^{**}	-0.124	0.240^{**}	-0.070	0.236^{**}	0.275^{**}
5-h item	-0.292^{**}	-0.235^{*}	-0.184^{*}	0.012	0.388^{***}	0.269^{**}
5-h source	-0.226^{**}	-0.187^{*}	0.006	0.261^{**}	0.199^{*}	0.180^{*}
24-h item	-0.163^{*}	-0.073	0.034	0.070	0.159^{*}	0.239^{**}
24-h source	-0.148	-0.155	0.069	0.027	0.003	0.036

Note: $p < 0.05$ was considered statistically significant. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

the source test scores were negatively correlated with blood Pb levels, and BDNF levels (5-h test only), but positively associated with gender (15-min test only), age (5-h test only) and parental education levels (Table 5).

3.6. *Effect of Pb exposure on olfactory memory*

To further investigate the effect of Pb exposure on olfactory memory, we defined blood Pb levels of less than or equal to 5 μg/dL as the low blood Pb level group, and blood Pb levels of more than 5 μg/dL as the high blood Pb level group (CDC, 2012), then regrouped the children from Guiyu and Haojiang for comparing the serum BDNF, IGF-1 levels and the scores of olfactory memory tests.

3.6.1. *Effect of Pb on serum BDNF and IGF-1 levels*

The mean concentration of serum BDNF in children from the high blood Pb level group (33.46 ± 1.06 ng/ml) was higher than children from the low blood Pb level group (28.20 ± 1.60 ng/ml) ($p < 0.05$) (Fig. 3). In addition, there was no significant difference for the mean concentration of serum IGF-1 between children from the high blood Pb level (164.25 ± 7.49 ng/ml) and from the low blood Pb level group (156.76 ± 9.24 ng/ml) ($t = -0.553$, $p > 0.05$).

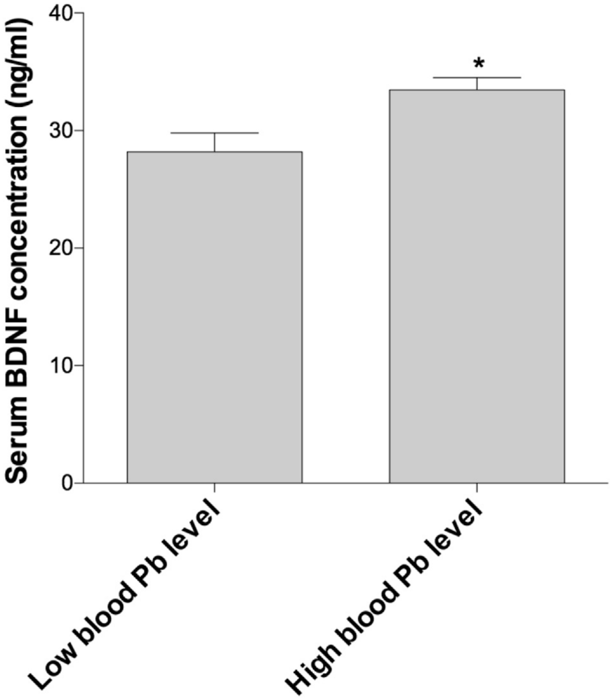

Fig. 3. Serum BDNF concentration in children from the high blood Pb level group were higher than from the low blood Pb level group. Data are presented as mean ± SE. $p < 0.05$ was considered statistically significant. $^{*}p < 0.05$.

3.6.2. *Comparison of children olfactory threshold between two groups*

The olfactory threshold did not show significant differences between high blood Pb level (8.09 ± 1.50 cm) and low blood Pb level (7.97 ± 2.06 cm) groups ($t = -0.304$, $p > 0.05$).

3.6.3. *Item and source test on children from the high blood Pb level and low blood Pb level groups*

Item test scores of children from the high blood Pb level group were 60.61 ± 2.15 (15-min test), 56.03 ± 2.01 (5-h test) and 57.62 ± 1.89 (24-h test), which were lower than the 77.42 ± 3.45 (15-min test), 71.37 ± 2.91 (5-h test) and 67.74 ± 2.94 (24-h test) scores of children from the low blood Pb level group. At the same time, the source test scores of children from the high blood Pb level group were 46.55 ± 1.85 (15-min test) and 51.44 ± 1.73 (5-h test), which were also lower than the 56.45 ± 2.83 (15-min test) and 58.87 ± 2.91 (5-h test) scores of children from the low blood Pb level group. There was no significant difference in the 24-h source test between children with high blood Pb levels (53.16 ± 2.00) and low blood Pb levels (56.45 ± 3.32) ($t = 0.848$, $p > 0.05$) (Fig. 4).

The Hotelling T^2 test showed that the ability of olfactory memory in children from the high blood Pb level group was lower than that in children from the low blood Pb level group ($F = 5.644$, $p < 0.01$).

4. Discussion

Referenced to previous research findings, children's blood Pb

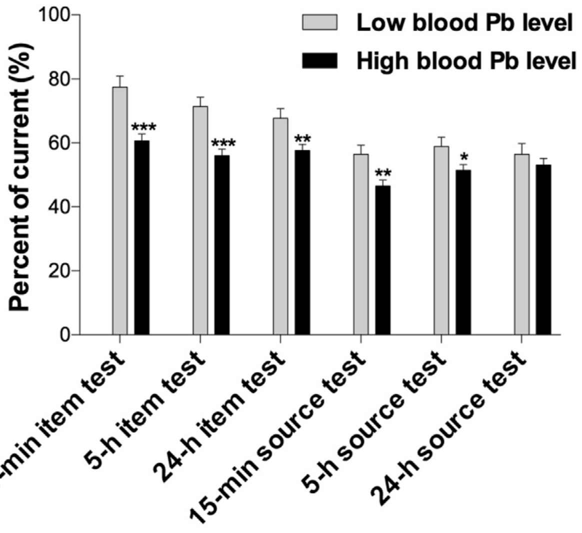

Fig. 4. Scores of olfactory memory tests in children from the high blood Pb level group were lower than from the low blood Pb level group. Data are presented as mean ± SE. $p < 0.05$ was considered statistically significant. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

levels in Guiyu showed a declining trend, which could been seen as well from the related factors to Pb exposure, as were converted to children contacting e-waste, ventilation of housing, residence as a workplace, father's work related to e-waste in our study from initial numbers of e-waste work-shops, location of child residence in Guiyu, duration of outdoor play, number of e-waste piles or recycling workshops around the house, parent's work related to e-waste, implying that the extent of environmental pollution caused by Pb from e-waste dismantling and the risk of children exposure to Pb were diminishing (Guo et al., 2014; Huo et al., 2007; Liu et al., 2011, 2014; Yang et al., 2013; Zhang et al., 2016; Zheng et al., 2008). Even though, local children still under the threaten of Pb exposure. In the current study, e-waste-exposed children had mean blood Pb levels of 9.40 μg/dL, with 23.0% of children exceeding 10 μg/dL. Moreover, physical development indices, for example height and weight, are lower than children in Haojiang. A recent study by our laboratory, in younger children, found lower mean blood Pb levels of 6.00 μg/dL in Guiyu children, and 3.92 μg/dL in Haojiang children (Zhang et al., 2016). Due to the consumption of canned foods by older children, the main reason the lower blood Pb levels in our prior study is likely due to the difference in child ages. In addition, since 3-to 7-year-olds are not as active as older children, younger children normally have outdoor activities within a small radius from the residence, and as a result have a low probability of e-waste contact.

Olfactory memory includes item memory and source memory, and can be divided into STM, ITM and LTM according to the difference in storage time. Hence, to explore the effect of Pb on child olfactory memory, we performed both item and source tests at 15 min, 5 h and 24 h after a 5-sec odor exposure. The results showed that for both item and source tests at all time points, scores for Guiyu children were lower than Haojiang children, suggesting that olfactory memory is affected by residence in Guiyu. Analysis of related factors shows that test scores negatively correlate with child blood Pb levels and positively associate with parental education levels, indicating that Pb exposure is a risk factor that could interfere with olfactory memory in children. Furthermore, since parents with higher education may pay more attention to children's early education and early intellectual development, children from such families may have been a better level of intellectual development, including memory, than children whose parents with lower education, thus Haojiang children showed higher scores of olfactory memory tests. On the other hand, parental education levels were negatively correlated with child blood Pb levels. Thus it can be seen that many factors lead to lower olfactory memory in Guiyu children. We also found that ability of olfactory memory in girls was better than in boys, meaning that there might be a gender difference in olfactory memory, which is similar with a recent study (Oleszkiewicz et al., 2016). The reason for the gender differences in olfactory memory may be that females usually more sensitive to odors compared with males and more important there are large differences in olfactory structures between females and males, resulting in a better olfactory performance in females (Ferdenzi et al., 2013; Garcia-Falgueras et al., 2006). Studies found that olfactory memory is better in adult females than in adult males (Choudhury et al., 2003; Larsson et al., 2003), and a positive correlation between odor identification performance and cortical thickness of an area around the entorhinal and piriform cortex in women is observed (Frasnelli et al., 2010). It was noted that test scores are positively associated with age. This provides evidence that during growth and brain development, child olfactory memory gradually strengthens, which makes age to be an influence factor for olfactory memory tests.

Due to the multi-component complexity of e-waste, there are many pollutants, in addition to Pb, that might affect child nervous system development in an e-waste recycling and dismantling area. Previous studies by our laboratory found blood Pb levels in children are higher than any other heavy metal developmental neurotoxicant tested, none of which have been reported to interfere with NMDA receptors thus far. To further determine the effect of Pb exposure on child olfactory memory, according to the blood Pb levels of children, we categorized children with blood Pb levels >5 μg/dL as having high blood Pb levels and ≤5 μg/dL as having low blood Pb levels, and then compared test scores. The results after the regrouping showed that the scores of both item and source tests at all time points, for children in the high blood Pb level group, were lower than the scores from the low blood Pb level group, indicating that Pb exposure may decrease child olfactory memory. Together, the findings above suggest that Pb exposure in e-waste recycling and dismantling areas result in decreased olfactory memory in children.

To investigate the biochemical effect indicators of impairment olfactory memory in Pb-exposed children, serum BDNF and IGF-1 were measured (Klein et al., 2011; Trejo et al., 2007). The results showed that the mean concentration of BDNF in children from the high blood Pb level group was higher than children from the low blood Pb level group. It is well known that at the early stage of olfactory memory process, odor learning induces glutamate release from the presynapse, which play a significant role in inducing of LTP and synaptic plasticity by postsynaptic NMDA receptor activation and especially downstream Ca^{2+} pathway (Tong et al., 2014). It has been proved that Pb inhibits the postsynaptic NMDA receptors, hence presynaptic glutamate release can not activate NMDA receptors normally (Morris et al., 1982, 1986). Furthermore, there is evidence that BDNF released from presynapse induced by depolarization in the learning process conversely has the presynaptic effect, enhancing neurotransmitter release from presynaptic terminals (Lohof et al., 1993). Together, in the olfactory memory process, a compensatory increasing of BDNF release from presynaptic terminals that resulted in more glutamate release appeared in Pb-exposed children, which could be proved by the positive correlation between serum BDNF and blood Pb levels. In addition, BDNF was negatively correlated with 5-h item and source test scores. It is notable that BDNF also plays a critical signaling role in LTM induction (Bekinschtein et al., 2008). Furthermore, new protein synthesis occurs in the ITM of 5-h olfactory memory, in which it is also a critical stage for BDNF synthesis relying CaMKII activated by Ca^{2+} at postsynaptic sites, during which BDNF play an important role in the olfactory memory formation (Bekinschtein et al., 2007; Bramham, 2008; Tong et al., 2014). Therefore, in the 5-h olfactory memory, deficiency of BDNF at the postsynaptic sites played the major role in the impairment olfactory memory in Pb-exposed children, which could be proved by partial correlation analysis between blood Pb levels and the scores of olfactory memory tests (data not shown), showing that there was no correlation between blood Pb levels and scores of olfactory memory test under variable controlled for BDNF, furthermore indicating that BDNF also contributed to short-term and long-term olfactory memory impairment, in addition to intermediate-term memory. Moreover, there was no significant difference for the mean concentration of IGF-1 between children from the high and low blood Pb level groups, suggesting that Pb might not disrupt the synthesis and secretion of IGF-1 from hepatocytes. In addition, there was no relation between serum IGF-1 levels and olfactory memory, indicating that IGF-1 was not involved in olfactory memory impairment.

Item and source memory rely on different brain structures: the medial temporal lobes, such as the entorhinal cortex and hippocampus, are critical to item memory, but the frontal lobes function in source memory (Craik et al., 1990; Janowsky et al., 1989;

Shimamura and Squire, 1987; Stark and Squire, 2000, 2003). Other reports show that the right anterior hippocampus plays an important role in the source memory (Goodrich-Hunsaker et al., 2009; Yeshurun et al., 2009). In these brain structures, NMDA receptor - dependent synaptic plasticity plays a significant role during the formation of olfactory memory (Kanter and Haberly, 1990; Lethbridge et al., 2012; Malenka and Nicoll, 1993; McNamara et al., 2008). The formation of olfactory memory is usually characterized by a continuous process of STM gradually transformed into LTM (Tong et al., 2014). The molecular mechanisms in formation of STM, ITM and LTM differ: STM mainly depends on presynaptic glutamate release, BDNF, NMDA receptors, α–amino–3–hydroxyl–5–methyl–4-isoxazole propionic acid (AMPA) receptors and activation of PKC and CaMKII, resulting in modification of synaptic proteins without new protein synthesis. For ITM, in addition to these processes, new protein synthesis occurs, from pre-existing mRNAs, after which LTM can form, in which the strengthening of new synapses occurs to form neural circuit (Grimes et al., 2011; Tong et al., 2014). It is believed that Pb disrupts the learning and memory processes of the brain by inhibiting the NMDA receptor (Baranowska-Bosiacka et al., 2012; Morris et al., 1986; Neal et al., 2011; Neal and Guilarte, 2013). According to the results, we speculate that Pb disrupt the NMDA receptors in olfactory memory related brain regions, such as the entorhinal cortex, hippocampus and the frontal lobes, causing abnormal upstream and downstream molecular event, for example phosphorylation of PKC or PKA, BDNF and Ca^{2+} signaling pathway, resulting in olfactory memory impairment.

The results of the present study suggest that Pb exposure could increase serum BDNF levels and decrease olfactory memory in children. The NMDA receptor plays a significant role in the formation and development of memory, and unfortunately is a target for Pb-mediated neurotoxicity. Hence future studies should be carried out to identify Pb-mediated alterations in the formation or the development of related brain areas related to olfactory memory. Furthermore, in addition to NMDA receptors, other ways in which Pb interferes with olfactory memory need to be explored and whether such adverse effects persist into adulthood as abnormalities of intellectual development.

5. Conclusion

The present study investigates the effect of Pb exposure on olfactory memory in 6-year-old children from e-waste polluted areas. The results of the current study suggest that Pb exposure in e-waste polluted areas results in an increase in serum BDNF levels and a decrease in child olfactory memory. Moreover, BDNF might be involved in olfactory memory impairment. The current study provides a scientific basis for further exploring the effect of Pb exposure on development of the nervous system in children.

Environmental pollution caused by e-waste recycling and dismantling still threatens the health of children, who are at a critical period of growth, despite recent reductions in environmental pollution. In order to eradicate the pollution caused by e-waste so that children can grow up healthily, the related government sectors in the e-waste input and output countries should implement stronger procedures for correct disposal and standardized recycling and dismantling of e-waste in the future.

Conflict of interest

Authors wish to declare that there is no conflict of interest.

Acknowledgments

This work was supported by the Natural Science Foundation of China (21577084) and the Postdoctoral Science Foundation of Shantou University Medical College. We would like to thank Dr. Stanley Lin for his constructive comments and English language editing. We are grateful to all the recruited children and their guardians for participating in this project.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2017.07.015.

References

Baranowska-Bosiacka, I., Gutowska, I., Rybicka, M., Nowacki, P., Chlubek, D., 2012. Neurotoxicity of lead. Hypothetical molecular mechanisms of synaptic function disorders. Neurol. i Neurochir. Pol. 46, 569–578.

Bekinschtein, P., Cammarota, M., Igaz, L.M., Bevilaqua, L.R., Izquierdo, I., Medina, J.H., 2007. Persistence of long-term memory storage requires a late protein synthesis- and bdnf- dependent phase in the hippocampus. Neuron 53, 261–277.

Bekinschtein, P., Cammarota, M., Katche, C., Slipczuk, L., Rossato, J.I., Goldin, A., et al., 2008. Bdnf is essential to promote persistence of long-term memory storage. Proc. Natl. Acad. Sci. U. S. A. 105, 2711–2716.

Bellinger, D.C., 2004. Lead. Pediatrics 113, 1016–1022.

Bellinger, D.C., 2008. Very low lead exposures and children's neurodevelopment. Curr. Opin. Pediatr. 20, 172–177.

Bellinger, D.C., 2011. The protean toxicities of lead: new chapters in a familiar story. Int. J. Environ. Res. public health 8, 2593–2628.

Bi, X., Liu, J., Han, Z., Yang, W., 2015. Lead in Chinese villager house dust: geographical variation and influencing factors. Environ. Pollut. 207, 183–189.

Bramham, C.R., 2008. Local protein synthesis, actin dynamics, and ltp consolidation. Curr. Opin. Neurobiol. 18, 524–531.

Canfield, R.L., Henderson Jr., C.R., Cory-Slechta, D.A., Cox, C., Jusko, T.A., Lanphear, B.P., 2003. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N. Engl. J. Med. 348, 1517–1526.

CDC, U.S., 2012. Low Level Lead Exposure Harms Children: a Renewed Call for Primary Prevention. Available: http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf.

Chandramouli, K., Steer, C.D., Ellis, M., Emond, A.M., 2009. Effects of early childhood lead exposure on academic performance and behaviour of school age children. Archives Dis. Child. 94, 844–848.

Chen, A., Dietrich, K.N., Huo, X., Ho, S.M., 2011. Developmental neurotoxicants in e-waste: an emerging health concern. Environ. health Perspect. 119, 431–438.

Choudhury, E.S., Moberg, P., Doty, R.L., 2003. Influences of age and sex on a microencapsulated odor memory test. Chem. Senses 28, 799–805.

Craik, F.I., Morris, L.W., Morris, R.G., Loewen, E.R., 1990. Relations between source amnesia and frontal lobe functioning in older adults. Psychol. Aging 5, 148–151.

du Bois, T.M., Huang, X.F., 2007. Early brain development disruption from nmda receptor hypofunction: relevance to schizophrenia. Brain Res. Rev. 53, 260–270.

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Heo, S., McLaren, M., et al., 2010. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J. Neurosci. Official J. Soc. Neurosci. 30, 5368–5375.

Ferdenzi, C., Roberts, S.C., Schirmer, A., Delplanque, S., Cekic, S., Porcherot, C., et al., 2013. Variability of affective responses to odors: culture, gender, and olfactory knowledge. Chem. Senses 38, 175–186.

Fernandez, A.M., Torres-Aleman, I., 2012. The many faces of insulin-like peptide signalling in the brain. Nat. Rev. Neurosci. 13, 225–239.

Flores-Montoya, M.G., Alvarez, J.M., Sobin, C., 2015. Olfactory recognition memory is disrupted in young mice with chronic low-level lead exposure. Toxicol. Lett. 236, 69–74.

Fortin, D.A., Srivastava, T., Dwarakanath, D., Pierre, P., Nygaard, S., Derkach, V.A., et al., 2012. Brain-derived neurotrophic factor activation of cam-kinase kinase via transient receptor potential canonical channels induces the translation and synaptic incorporation of glua1-containing calcium-permeable ampa receptors. J. Neurosci. Official J. Soc. Neurosci. 32, 8127–8137.

Frasnelli, J., Lundstrom, J.N., Boyle, J.A., Djordjevic, J., Zatorre, R.J., Jones-Gotman, M., 2010. Neuroanatomical correlates of olfactory performance. Exp. Brain Res. 201, 1–11.

Garcia-Falgueras, A., Junque, C., Gimenez, M., Caldu, X., Segovia, S., Guillamon, A., 2006. Sex differences in the human olfactory system. Brain Res. 1116, 103–111.

Gavazzo, P., Zanardi, I., Baranowska-Bosiacka, I., Marchetti, C., 2008. Molecular determinants of pb2+ interaction with nmda receptor channels. Neurochem. Int. 52, 329–337.

Goodrich-Hunsaker, N.J., Gilbert, P.E., Hopkins, R.O., 2009. The role of the human hippocampus in odor-place associative memory. Chem. senses 34, 513–521.

Grant, K., Goldizen, F.C., Sly, P.D., Brune, M.N., Neira, M., van den Berg, M., et al.,

2013. Health consequences of exposure to e-waste: a systematic review. Lancet Glob. health 1, e350–361.
Grimes, M.T., Smith, M., Li, X., Darby-King, A., Harley, C.W., McLean, J.H., 2011. Mammalian intermediate-term memory: new findings in neonate rat. Neurobiol. Learn. Mem. 95, 385–391.
Guilarte, T.R., Miceli, R.C., Jett, D.A., 1995. Biochemical evidence of an interaction of lead at the zinc allosteric sites of the nmda receptor complex: effects of neuronal development. Neurotoxicology 16, 63–71.
Guo, P., Xu, X., Huang, B., Sun, D., Zhang, J., Chen, X., et al., 2014. Blood lead levels and associated factors among children in guiyu of China: a population-based study. PloS one 9, e105470.
Guo, Y., Huo, X., Li, Y., Wu, K., Liu, J., Huang, J., et al., 2010. Monitoring of lead, cadmium, chromium and nickel in placenta from an e-waste recycling town in China. Sci. Total Environ. 408, 3113–3117.
Heacock, M., Kelly, C.B., Asante, K.A., Birnbaum, L.S., Bergman, A.L., Brune, M.N., et al., 2016. E-waste and harm to vulnerable populations: a growing global problem. Environ. Health Perspect. 124, 550–555.
Hicks, C., Dietmar, R., Eugster, M., 2005. The recycling and disposal of electrical and electronic waste in China - legislative and market responses. Environ. Impact Asses 25, 459–471.
Huo, X., Peng, L., Xu, X., Zheng, L., Qiu, B., Qi, Z., et al., 2007. Elevated blood lead levels of children in guiyu, an electronic waste recycling town in China. Environ. Health Perspect. 115, 1113–1117.
Janowsky, J.S., Shimamura, A.P., Squire, L.R., 1989. Source memory impairment in patients with frontal lobe lesions. Neuropsychologia 27, 1043–1056.
Jones, F.N., Roberts, K., Holman, E.W., 1978. Similarity judgments and recognition memory for some common spices. Percept. Psychophys. 24, 2–6.
Kanter, E.D., Haberly, L.B., 1990. Nmda-dependent induction of long-term potentiation in afferent and association fiber systems of piriform cortex in vitro. Brain Res. 525, 175–179.
Klein, A.B., Williamson, R., Santini, M.A., Clemmensen, C., Ettrup, A., Rios, M., et al., 2011. Blood bdnf concentrations reflect brain-tissue bdnf levels across species. Int. J. Neuropsychopharmacol. 14, 347–353.
LaDou, J., Lovegrove, S., 2008. Export of electronics equipment waste. Int. J. Occup. Environ. Health 14, 1–10.
Lanphear, B.P., Hornung, R., Khoury, J., Yolton, K., Baghurst, P., Bellinger, D.C., et al., 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ. Health Perspect. 113, 894–899.
Larsson, M., Lovden, M., Nilsson, L.G., 2003. Sex differences in recollective experience for olfactory and verbal information. Acta Psychol. 112, 89–103.
Lesschaeve, I., Issanchou, S., 1996. Effects of panel experience on olfactory memory performance: influence of stimuli familiarity and labeling ability of subjects. Chem. Senses 21, 699–709.
Lethbridge, R., Hou, Q., Harley, C.W., Yuan, Q., 2012. Olfactory bulb glomerular nmda receptors mediate olfactory nerve potentiation and odor preference learning in the neonate rat. PloS one 7, e35024.
Li, J., Zeng, X., Chen, M., Ogunseitan, O.A., Stevels, A., 2015. "Control-alt-delete": rebooting solutions for the e-waste problem. Environ. Sci. Technol. 49, 7095–7108.
Lidsky, T.I., Schneider, J.S., 2003. Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain J. neurology 126, 5–19.
Lin, X., Xu, X., Zeng, X., Xu, L., Zeng, Z., Huo, X., 2017. Decreased vaccine antibody titers following exposure to multiple metals and metalloids in e-waste-exposed preschool children. Environ. Pollut. 220, 354–363.
Liu, J., Xu, X., Wu, K., Piao, Z., Huang, J., Guo, Y., et al., 2011. Association between lead exposure from electronic waste recycling and child temperament alterations. Neurotoxicology 32, 458–464.
Liu, W., Huo, X., Liu, D., Zeng, X., Zhang, Y., Xu, X., 2014. S100beta in heavy metal-related child attention-deficit hyperactivity disorder in an informal e-waste recycling area. Neurotoxicology 45, 185–191.
Lohof, A.M., Ip, N.Y., Poo, M.M., 1993. Potentiation of developing neuromuscular synapses by the neurotrophins nt-3 and bdnf. Nature 363, 350–353.
Lopez-Lopez, C., LeRoith, D., Torres-Aleman, I., 2004. Insulin-like growth factor i is required for vessel remodeling in the adult brain. Proc. Natl. Acad. Sci. U. S. A. 101, 9833–9838.
Lucchini, R.G., Zoni, S., Guazzetti, S., Bontempi, E., Micheletti, S., Broberg, K., et al., 2012. Inverse association of intellectual function with very low blood lead but not with manganese exposure in Italian adolescents. Environ. Res. 118, 65–71.
Malenka, R.C., Nicoll, R.A., 1993. Nmda-receptor-dependent synaptic plasticity: multiple forms and mechanisms. Trends Neurosci. 16, 521–527.
Matsuda, N., Lu, H., Fukata, Y., Noritake, J., Gao, H., Mukherjee, S., et al., 2009. Differential activity-dependent secretion of brain-derived neurotrophic factor from axon and dendrite. J. Neurosci. Official J. Soc. Neurosci. 29, 14185–14198.
Mazumdar, M., Bellinger, D.C., Gregas, M., Abanilla, K., Bacic, J., Needleman, H.L., 2011. Low-level environmental lead exposure in childhood and adult intellectual function: a follow-up study. Environ. health a Glob. Access Sci. source 10, 24.
McNamara, A.M., Magidson, P.D., Linster, C., Wilson, D.A., Cleland, T.A., 2008. Distinct neural mechanisms mediate olfactory memory formation at different timescales. Learn. Mem. 15, 117–125.
Miranda, M.L., Kim, D., Galeano, M.A., Paul, C.J., Hull, A.P., Morgan, S.P., 2007. The relationship between early childhood blood lead levels and performance on end-of-grade tests. Environ. health Perspect. 115, 1242–1247.
Morris, R.G., Garrud, P., Rawlins, J.N., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297, 681–683.
Morris, R.G., Anderson, E., Lynch, G.S., Baudry, M., 1986. Selective impairment of learning and blockade of long-term potentiation by an n-methyl-d-aspartate receptor antagonist, ap5. Nature 319, 774–776.
Neal, A.P., Worley, P.F., Guilarte, T.R., 2011. Lead exposure during synaptogenesis alters nmda receptor targeting via nmda receptor inhibition. Neurotoxicology 32, 281–289.
Neal, A.P., Guilarte, T.R., 2013. Mechanisms of lead and manganese neurotoxicity. Toxicol. Res. 2, 99–114.
Ninan, I., 2014. Synaptic regulation of affective behaviors; role of bdnf. Neuropharmacology 76 (Pt C), 684–695.
Nishijima, T., Piriz, J., Duflot, S., Fernandez, A.M., Gaitan, G., Gomez-Pinedo, U., et al., 2010. Neuronal activity drives localized blood-brain-barrier transport of serum insulin-like growth factor-i into the cns. Neuron 67, 834–846.
Ogunseitan, O.A., Schoenung, J.M., Saphores, J.D., Shapiro, A.A., 2009. Science and regulation. The electronics revolution: from e-wonderland to e-wasteland. Science 326, 670–671.
Oleszkiewicz, A., Walliczek-Dworschak, U., Klotze, P., Gerber, F., Croy, I., Hummel, T., 2016. Developmental changes in adolescents' olfactory performance and significance of olfaction. PloS one 11, e0157560.
Pirogovsky, E., Gilbert, P.E., Murphy, C., 2006. Source and item memory for odors and objects in children and young adults. Dev. Neuropsychol. 30, 739–752.
Saive, A.L., Royet, J.P., Plailly, J., 2014. A review on the neural bases of episodic odor memory: from laboratory-based to autobiographical approaches. Front. Behav. Neurosci. 8, 240.
Schab, F.R., 1991. Odor memory: taking stock. Psychol. Bull. 109, 242–251.
Schmidt, C.W., 2006. Unfair trade: E-waste in africa. Environ. health Perspect. 114, a232–235.
Shieh, P.B., Hu, S.C., Bobb, K., Timmusk, T., Ghosh, A., 1998. Identification of a signaling pathway involved in calcium regulation of bdnf expression. Neuron 20, 727–740.
Shimamura, A.P., Squire, L.R., 1987. A neuropsychological study of fact memory and source amnesia. J. Exp. Psychol. Learn. Mem. Cognition 13, 464–473.
Slipczuk, L., Bekinschtein, P., Katche, C., Cammarota, M., Izquierdo, I., Medina, J.H., 2009. Bdnf activates mtor to regulate glur1 expression required for memory formation. PloS one 4, e6007.
Stark, C.E., Squire, L.R., 2000. Functional magnetic resonance imaging (fmri) activity in the hippocampal region during recognition memory. J. Neurosci. official J. Soc. Neurosci. 20, 7776–7781.
Stark, C.E., Squire, L.R., 2003. Hippocampal damage equally impairs memory for single items and memory for conjunctions. Hippocampus 13, 281–292.
Suk, W.A., Ahanchian, H., Asante, K.A., Carpenter, D.O., Diaz-Barriga, F., Ha, E.H., et al., 2016. Environmental pollution: an under-recognized threat to children's health, especially in low- and middle-income countries. Environ. health Perspect. 124, A41–A45.
Tansel, B., 2017. From electronic consumer products to e-wastes: global outlook, waste quantities, recycling challenges. Environ. Int. 98, 35–45.
Tolias, K.F., Bikoff, J.B., Burette, A., Paradis, S., Harrar, D., Tavazoie, S., et al., 2005. The rac1-gef tiam1 couples the nmda receptor to the activity-dependent development of dendritic arbors and spines. Neuron 45, 525–538.
Tong, M.T., Peace, S.T., Cleland, T.A., 2014. Properties and mechanisms of olfactory learning and memory. Front. Behav. Neurosci. 8, 238.
Trejo, J.L., Piriz, J., Llorens-Martin, M.V., Fernandez, A.M., Bolos, M., LeRoith, D., et al., 2007. Central actions of liver-derived insulin-like growth factor i underlying its pro-cognitive effects. Mol. Psychiatry 12, 1118–1128.
Tsien, J.Z., Huerta, P.T., Tonegawa, S., 1996. The essential role of hippocampal ca1 nmda receptor-dependent synaptic plasticity in spatial memory. Cell 87, 1327–1338.
von Bohlen, Halbach, O., 2010. Involvement of bdnf in age-dependent alterations in the hippocampus. Front. aging Neurosci. 2.
Wang, C.C., Held, R.G., Chang, S.C., Yang, L., Delpire, E., Ghosh, A., et al., 2011. A critical role for glun2b-containing nmda receptors in cortical development and function. Neuron 72, 789–805.
West, A.E., Chen, W.G., Dalva, M.B., Dolmetsch, R.E., Kornhauser, J.M., Shaywitz, A.J., et al., 2001. Calcium regulation of neuronal gene expression. Proc. Natl. Acad. Sci. U. S. A. 98, 11024–11031.
Wong, C.S., Wu, S.C., Duzgoren-Aydin, N.S., Aydin, A., Wong, M.H., 2007a. Trace metal contamination of sediments in an e-waste processing village in China. Environ. Pollut. 145, 434–442.
Wong, M.H., Wu, S.C., Deng, W.J., Yu, X.Z., Luo, Q., Leung, A.O., et al., 2007b. Export of toxic chemicals - a review of the case of uncontrolled electronic-waste recycling. Environ. Pollut. 149, 131–140.
Wu, K., Xu, X., Liu, J., Guo, Y., Huo, X., 2011. In utero exposure to polychlorinated biphenyls and reduced neonatal physiological development from guiyu, China. Ecotoxicol. Environ. Saf. 74, 2141–2147.
Xu, L., Huo, X., Zhang, Y., Li, W., Zhang, J., Xu, X., 2015a. Polybrominated diphenyl ethers in human placenta associated with neonatal physiological development at a typical e-waste recycling area in China. Environ. Pollut. 196, 414–422.
Xu, X., Zeng, X., Boezen, H.M., Huo, X., 2015b. E-waste environmental contamination and harm to public health in China. Front. Med. 9, 220–228.
Xu, X., Yekeen, T.A., Xiao, Q., Wang, Y., Lu, F., Huo, X., 2013. Placental igf-1 and igfbp-3 expression correlate with umbilical cord blood pah and pbde levels from prenatal exposure to electronic waste. Environ. Pollut. 182, 63–69.
Yang, H., Huo, X., Yekeen, T.A., Zheng, Q., Zheng, M., Xu, X., 2013. Effects of lead and cadmium exposure from electronic waste on child physical growth. Environ. Sci.

Pollut. Res. Int. 20, 4441–4447.

Yekeen, T.A., Xu, X., Zhang, Y., Wu, Y., Kim, S., Reponen, T., et al., 2016. Assessment of health risk of trace metal pollution in surface soil and road dust from e-waste recycling area in China. Environ. Sci. Pollut. Res. Int. 23, 17511–17524.

Yeshurun, Y., Lapid, H., Dudai, Y., Sobel, N., 2009. The privileged brain representation of first olfactory associations. Curr. Biol. 19, 1869–1874.

Yu, X.Z., Gao, Y., Wu, S.C., Zhang, H.B., Cheung, K.C., Wong, M.H., 2006. Distribution of polycyclic aromatic hydrocarbons in soils at guiyu area of China, affected by recycling of electronic waste using primitive technologies. Chemosphere 65, 1500–1509.

Zagrebelsky, M., Korte, M., 2014. Form follows function: bdnf and its involvement in sculpting the function and structure of synapses. Neuropharmacology 76 (Pt C), 628–638.

Zeng, X., Xu, X., Boezen, H.M., Huo, X., 2016a. Children with health impairments by heavy metals in an e-waste recycling area. Chemosphere 148, 408–415.

Zeng, X., Xu, X., Zheng, X., Reponen, T., Chen, A., Huo, X., 2016b. Heavy metals in pm2.5 and in blood, and children's respiratory symptoms and asthma from an e-waste recycling area. Environ. Pollut. 210, 346–353.

Zhang, R., Huo, X., Ho, G., Chen, X., Wang, H., Wang, T., et al., 2015. Attention-deficit/hyperactivity symptoms in preschool children from an e-waste recycling town: assessment by the parent report derived from dsm-iv. BMC Pediatr. 15, 51.

Zhang, Y., Huo, X., Cao, J., Yang, T., Xu, L., Xu, X., 2016. Elevated lead levels and adverse effects on natural killer cells in children from an electronic waste recycling area. Environ. Pollut. 213, 143–150.

Zheng, L., Wu, K., Li, Y., Qi, Z., Han, D., Zhang, B., et al., 2008. Blood lead and cadmium levels and relevant factors among children from an e-waste recycling town in China. Environ. Res. 108, 15–20.

Zucco, G.M., Tressoldi, P.E., 1989. Hemispheric differences in odour recognition. Cortex; a J. devoted study Nerv. Syst. Behav. 25, 607–615.