Neurotoxicology 71 (2019) 150–158

Contents lists available at ScienceDirect

Neurotoxicology

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

Full Length Article

Elevated lead levels from e-waste exposure are linked to sensory integration difficulties in preschool children

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ARTICLE INFO

Keywords:
E-waste
Cortisol
Lead exposure
Sensory integration disorder
Preschool children

ABSTRACT

Exposure to lead is associated with adverse effects on neurodevelopment. However, studies of the effects of lead on sensory integration are few. The purpose of this research is to investigate the effect of lead exposure on child sensory integration by correlating the blood lead levels of children with sensory processing measures. A total of 574 children, from 3 to 6 years of age, 358 from an electronic waste (e-waste) recycling town named Guiyu, and 216 from Haojiang, a nearby town with no e-waste recycling activity, were recruited in this study. The median blood lead level in Guiyu children was 4.88 μg/dL, higher than the 3.47 μg/dL blood lead level in Haojiang children ($P < 0.001$). 47.2% of Guiyu children had blood lead levels exceeding 5 μg/dL. The median concentration of serum cortisol, an HPA-axis biomarker, in Guiyu children was significantly lower than in Haojiang, and was negatively correlated with blood lead levels. All subscale scores and the total score of the Sensory Processing Measure (Hong Kong Chinese version, SPM-HKC) in Guiyu children were higher than Haojiang children, indicating greater difficulties, especially for touch, body awareness, balance and motion, and total sensory systems. Sensory processing scores were positively correlated with blood lead, except for touch, which was negatively correlated with serum cortisol levels. Simultaneously, all subscale scores and the total SPM-HKC scores for children with high blood lead levels (blood lead > 5 μg/dL) were higher than those in the low blood lead level group (blood lead < 5 μg/dL), especially for hearing, touch, body awareness, balance and motion, and total sensory systems. Our findings suggest that lead exposure in e-waste recycling areas may result in a decrease in serum cortisol levels and an increase in child sensory integration difficulties. Cortisol may be involved in touch-related sensory integration difficulties.

1. Introduction

Although child blood lead levels have fallen drastically among the general population (Burm et al., 2016; He et al., 2009; Hwang et al., 2004; Li et al., 2014, 2017; Lyle et al., 2006; Recio-Vega et al., 2012; Schnaas et al., 2004; Stromberg et al., 2008; Skerfving et al., 1986; Wheeler and Brown, 2013), lead exposure remains a problem in specific population clusters, for example in electronic waste (e-waste) recycling areas (Dai et al., 2017; Huo et al., 2007; Lin et al., 2017; Lu et al., 2018; Pascale et al., 2016; Wittsiepe et al., 2017; Zeng et al., 2017; Zhang et al., 2016). Exposure to lead can have adverse effects on neurodevelopment, including behavioral problems and sensory abnormalities in children (AbuShady et al., 2017; Bhattacharya and Linz, 1991; Bhattacharya et al., 1993; Lin et al., 2008; Liu et al., 2011; Gump et al., 2017; Liu et al., 2014; Mielke and Zahran, 2012; Nkomo et al., 2017; Sioen et al., 2013; Smith, 1985; Umar et al., 2017). Recent cross-

Abbreviations: ACTH, adrenocorticotropic hormone; CDC, Centers for Disease Control and Prevention; DSM, Diagnostic and Statistical Manual of Mental Disorders; EDTA, ethylenediaminetetraacetic acid; e-waste, electronic waste; GABA, gamma-aminobutyric acid; GHB, gamma-hydroxybutyrate; HPA axis, hypothalamic-pituitary-adrenal axis; IQR, interquartile range; r_s, Spearman's correlation coefficient; SD, standard deviation; SE, standard error; SPM-HKC, sensory processing measure-Hong Kong Chinese version; WHO, World Health Organization

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https://doi.org/10.1016/j.neuro.2019.01.004
Received 20 September 2018; Received in revised form 22 December 2018; Accepted 16 January 2019
Available online 18 January 2019

sectional surveys indicate that lead exposure produces adverse effects on sensory pathways, such as hearing loss, balance and vestibular dysfunction (Choi et al., 2012; Choi and Park, 2017; Min et al., 2012). Other epidemiological studies imply developmental lead exposure is associated with high-frequency hearing loss, increased average hearing thresholds, and decreased olfactory memory in children and adolescents (Liu et al., 2018; Shargorodsky et al., 2011; Zhang et al., 2017). Previous prospective studies have already shown that early life exposure (up to age 78 months) to lead detrimentally influences the maturation of postural balance of growing children. Postural balance is dependent on sensory integration elements associated with three afferents (vision, proprioception and vestibular systems), even though their exposure to lead had ceased (Bhattacharya et al., 2006, 2007). In a non-human primate model, it has been observed that developmental lead exposure induces tactile defensiveness, a sensory integration difficulty, definitively establishing causality (Moore et al., 2008).

Cortisol in humans is an important neuromodulator and is used as a biomarker of hypothalamic-pituitary-adrenal (HPA) axis function. The HPA axis plays an essential role in regulating neuroendocrine function by routinely translating environmental stimulation into hormonal signals to facilitate adaptation to environmental changes (Herman et al., 2003; Watts, 2005). It has been previously suggested that cortisol may act on arterioles and decrease perfusion in the thalamus (Gros et al., 2007; Strelzyk et al., 2012). Recent research has shown that the thalamus may play a broader role in cognition, as it amplifies and controls functional cortical connectivity and is prominent in multisensory processing (Cappe et al., 2012, 2009; Henschke et al., 2015, 2018; Schmitt et al., 2017; Tyll et al., 2011). In patients with high (low) corticosteroids, the thresholds for detection of auditory, olfactory and gustatory sensory systems were increased (decreased), indicating that cortisol levels can also modulate general sensations (Kuehl et al., 2010).

Sensory integration difficulties, also known as sensory processing disorder, comprise a condition in which multi-sensory integration is not processed appropriately in response to environmental requirements (Ayres and Robbins, 1979). It is a significant public health problem worldwide, with approximately 30% of American children and 21%–28% of Taiwanese preschool children developing sensory integration disorders (Elbasan et al., 2012; Lin et al., 2013). Children with sensory integration disorders can be severely maladaptive to benign sensory stimuli in daily life, including light stimulation to vision, sound stimulation to hearing, temperature stimulation to touch, and other such stimuli to proprioception and the vestibular system. Further magnifying the importance of this condition is the fact that affected individuals may not able to process real injury or pain in a hazardous environment, or cannot avoid meaningless signals in a normal environment (Baranek and Berkson, 1994). Sensory-integration therapy can modulate baseline cortisol levels toward normal ranges in children diagnosed with autism spectrum disorder (Devlin et al., 2011). Other work has shown that during acute treatment, acute phase schizophrenia patients show a significant decrease in sensorial integration difficulty scores and an increase in basal cortisol but a significant decrease in sensory integration difficulty scores, and a drop in basal cortisol occurs when treatment is successful (Ceskova et al., 2001). Therefore, we hypothesize that sensory integration may be involved in cortisol level.

Lead is a well-known neurotoxicant, and there is a close relationship between lead exposure and developmental impairment of the nervous system in children (Bellinger et al., 2016; Caito and Aschner, 2017; Ethier et al., 2012; Mahmoudian et al., 2009). However, the extent and mechanisms by which developmental lead exposure is associated with sensory integration-related behavioral problems in preschool children, in the absence of overt toxicological effects, remains unknown. The objective of this research is to explore the sensory integration of children living in an e-waste contaminated area, and to investigate the effects of lead exposure and HPA axis activity by measuring children's blood samples.

2. Materials and methods

2.1. Sample collection

A total of 574 children (3- to 6-years of age) from Guiyu (one of the world's largest e-waste destinations and recycling areas, n = 358) and Haojiang (a non-e-waste recycling area, n = 216) were recruited. Both places are towns in Guangdong Province, China, with a homologous cultural background, living habits, ethnicity and population. Blood samples were taken during the period from November to December 2017. Self-administered questionnaires were completed by the children's parents (or guardians) to collect information about general demographic characteristics, living environment, children's lifestyles and eating habits and medical and disease histories of parents and children. There were no children who had received or were receiving sensory integration therapy or any other treatment at the time of the assessment. Informed consents were accepted and signed by children's parents (or guardians). The ethical approval of this research came from the Human Ethics Committee of Shantou University Medical College, China.

2.2. Measurement of blood lead

Medical personnel collected peripheral venous blood (1–2 mL) from every child, in a trace metal-free vacuum blood collection tube, containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant, for blood lead measurement. Blood lead was measured by graphite furnace atomic absorption spectrophotometry (Jena Zeenit 650, Germany), as described in a previous publication (Guo et al., 2010). Blood lead measurements are expressed as micrograms of lead per deciliter of blood.

2.3. Measurement of serum cortisol level

Medical personnel collected peripheral venous blood (1–2 mL) from each child, in an early fasting state between 8:00-8:30 am, into a vacuum blood collection tube containing no additives. Blood allowed to clot. In the laboratory, blood samples was centrifuged at 1000 g for 15 min to isolate serum, then divided into aliquots of 100 μL and stored at −70 °C until assayed. Serum cortisol was assayed using competitive enzyme immunoassay kits (R&D Systems, Inc., Minneapolis, USA) according to the product's instructions. The cortisol assay had a sensitivity of 0.071 ng/mL.

2.4. Measurement of sensory integration

To assess the sensory integration of children in Guiyu and Haojiang, we used the Sensory Processing Measure-Hong Kong Chinese version (SPM-HKC) form (Lai et al., 2011). The SPM-HKC is a research version adapted from the Sensory Processing Measure (SPM) (Parham et al., 2007). The SPM has been widely used in Western countries to measure the sensory processing difficulty of children. This scale was translated into Chinese based on guidance for cross-cultural use of questionnaires (Lai et al., 2011; Su and Parham, 2002). The SPM-HKC has been validated against the Chinese Sensory Profile (Cheung and Siu, 2010) - the standardized questionnaire is the sensory profile (Dunn, 1999) - as both tests claim to measure the same sensory processing structure. The test items of the SPM-HKC cover typical behaviors and characteristics related to sensory processing (vision, hearing, touch, taste and smell, and body awareness, as well as balance and motion). From scores obtained for vision, hearing, touch, taste and smell, body awareness, and balance and motion processing difficulties, a score for total sensory systems is derived (Parham et al., 2007; Parham and Ecker, 2010). This score represents the extent of impairment (or difference) in sensory processing, with a higher score representing greater impairment. The SPM-HKC home form, that ranks the frequency of observed behaviors, was filled in by the children's parents or guardians. Each item was rated with one of four categories: never, occasionally, frequently, or always, corresponding to a numeric score of 1–4, respectively. An item-by-item analysis is allowed in the scale. Although sensory integration disorder is a term that is occasionally mentioned in the literature, it is not currently a mental illness that can be diagnosed alone in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Therefore, in this study, SPM-HKC was used only to compare the frequency of behavioral dissonance-related behaviors in children in the two areas (two groups).

2.5. Statistical analysis

The distributions of data of both predictors and outcomes were summarized with means, standard errors (SEs), percentiles, and histograms. All variables of demographic characteristics were expressed as the median [interquartile range (IQR)] for skewed distributions, mean ± one standard deviation (SD) for normal distributions, and percentage for enumeration data. Two-sample t-tests were performed to compare the differences of means between groups when the two variables were distributed normally and the Wilcoxon-Mann-Whitney test was used to determine the differences in medians between groups when the two sets of data were non-normally distributed. A chi-square test was used to determine whether there were significant differences between different categorical data.

Child blood lead concentration data were dichotomized at 5.00 μg/dL, the current United States Centers for Disease Control and Prevention (CDC) relative safety level, classifying the children from the two areas into a low blood lead level group and a high blood lead level group. Serum cortisol levels and blood lead were ln-transformed for the purposes of inference. Outliers and missing values were replaced by median values during analysis to ensure compatibility of the data.

Spearman's correlation coefficient (r_s) was used to express the relationship between factors associated with lead exposure and the scale score for SPM-HKC. The Wilcoxon-Mann-Whitney test was used to contrast serum cortisol levels and the SPM-HKC score between groups. Multiple linear regression analysis was used to explain the association between the ln-transformed blood lead levels and the ln-transformed serum cortisol levels in the children. Models of blood lead levels were run with and without adjustment for physiological factors (sex, height and weight) and social factors (current use of medications and monthly household income). Statistical analysis was performed with SPSS 22.0 (IBM Inc., Armonk, USA), GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, USA) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed tests used $P < 0.05$ as the significant level.

3. Results

3.1. Characteristics of the study population

Table 1 summarizes the demographic characteristics of the 574 participating children. The mean age of Guiyu children (n = 358) was 4.79 ± 0.87 years vs. 4.62 ± 0.98 years for Haojiang children (n = 216) ($P < 0.05$). A chi-square test showed that gender distribution was not different between Guiyu and Haojiang children ($P > 0.05$). Similarly, no difference between Guiyu and Haojiang children was found for family history of disease in terms of hypertension, diabetes, obesity and psychosis (all $P > 0.05$). However, significant differences were identified whereby the proportion of parents working on e-waste and children who contacted e-waste was higher in Guiyu than in Haojiang (both $P < 0.001$). Guiyu families resided closer to roads ($P < 0.001$) with more e-waste contamination within 50 m ($P < 0.001$) and less ventilation (all $P < 0.001$). The physiological and social factors of child height ($P < 0.001$), weight ($P < 0.001$), chest circumference ($P < 0.05$) and monthly household income ($P < 0.001$) in Guiyu were lower than those in Haojiang.

3.2. Blood lead levels and relative factors

The median blood lead in Guiyu children (4.88 μg/dL, range from 1.68 to 40.12 μg/dL) was higher than for Haojiang children (3.47 μg/dL, range from 1.68 to 27.48 μg/dL) ($P < 0.001$). Approximately 47.2% of Guiyu children had blood lead levels greater than the CDC relative safety threshold of 5 μg/dL. In contrast only 10.7% of Haojiang children ($P < 0.001$) exceeded the threshold. Around 5.3% of Guiyu children had level above the World Health Organization (WHO) level of concern of 10 μg/dL, in contrast to only 1.4% of Haojiang children ($P < 0.001$) (Table 2).

Spearman correlation analysis was performed to evaluate whether e-waste exposure factors were associated with blood lead levels in children from the e-waste polluted area (Table 3). The analysis showed that children's blood lead levels were positively correlated with touching e-waste ($r_s = 0.113$, $P < 0.01$), parental work related to e-waste ($r_s = 0.144$, $P < 0.01$ and $r_s = 0.097$, $P < 0.05$, respectively), living and working in the same place ($r_s = 0.165$, $P < 0.01$), more e-waste workshops in a residential radius of 50 m ($r_s = 0.091$, $P < 0.05$), years of child residency ($r_s = 0.261$, $P < 0.01$), house ventilation ($r_s = 0.084$, $P < 0.05$), and child eating fewer dairy products ($r_s = 0.234$, $P < 0.01$), and fewer vegetables and fruit ($r_s = 0.169$, $P < 0.01$). Blood lead levels were negatively related to child hand washing before food consumption ($r_s = -0.195$, $P < 0.01$), monthly household income ($r_s = -0.202$, $P < 0.01$), farther residence from the road ($r_s = -0.170$, $P < 0.01$), parental education levels ($r_s = -0.297$, $P < 0.01$ and $r_s = -0.292$, $P < 0.01$, respectively), parents changing clothes after work ($r_s = -0.209$, $P < 0.01$ and $r_s = -0.184$, $P < 0.05$, respectively) and fewer times the child spent eating canned products ($r_s = -0.163$, $P < 0.01$).

3.3. Differences in sensory integration between Guiyu and Haojiang children

The median SPM-HKC scores from Guiyu children (vs. Haojiang children) were 19.00 (vs. 18.00) for touch, 16.00 (vs. 14.00) for body awareness, 18.00 (vs. 16.00) for balance and motion and 90.00 (vs. 86.00) for total sensory systems. These scores were significantly higher across the board in Guiyu children. There was no significant difference in the subscale scores for vision (17.00 vs. 16.00, $Z = -1.195$, $P > 0.05$), hearing (11.00 vs. 11.00, $Z = -1.312$, $P > 0.05$) and taste and smell (9.00 vs. 9.00, $Z = -1.484$, $P > 0.05$) between Guiyu and Haojiang children. Regarding the subscale scores and the total score, the Wilcoxon-Mann-Whitney test showed that the sensory integration difficulties of Guiyu children were worse than that of Haojiang children (Fig. 1).

3.4. Association among serum cortisol, blood lead and sensory integration

The median (IQR) level of serum cortisol in Guiyu children [451.96 (381.75, 614.10) ng/mL] was lower than for Haojiang [593.61 (434.74, 1014.32) ng/mL] ($Z = -3.985$, $P < 0.001$) (Fig. 2).

Multiple linear regression analysis of blood lead levels and serum cortisol levels showed that the ln-transformed serum cortisol concentration was negatively associated with the ln-transformed blood lead levels in unadjusted linear model ($B = -0.139$, 95% CI: -0.268, -0.009, $P = 0.036$). These associations were maintained in the adjusted models ($B = -0.150$, 95% CI: -0.280, -0.019, $P = 0.025$ and $B = -0.138$, 95% CI: -0.272, -0.003, $P = 0.045$, respectively; Table 4).

Spearman correlation analysis showed that, excluding taste and smell, the subscale scores of sensory integration difficulties were positively correlated with blood lead levels. The scale score for touch were negatively correlated with serum cortisol levels (Fig. 3).

Table 1
Demographic characteristics of the Guiyu and Haojiang study populations.

	Haojiang (n = 216)	Guiyu (n = 358)	Statistics	*P* -value
Age (mean ± SD, years)	4.62 ± 0.98	4.79 ± 0.87	$t = -2.178$	0.030
3 years [n (%)]	31 (14.4)	31 (8.7)	$\chi2 = 5.446$	0.244
4 years [n (%)]	68 (31.5)	106 (29.8)		
5 years [n (%)]	74 (34.3)	139 (39.0)		
6 years [n (%)]	41 (19.0)	75 (21.1)		
7 years [n (%)]	2 (0.9)	5 (1.4)		
Gender			$\chi2 = 2.538$	0.111
Male [n (%)]	124 (57.4)	181 (50.6)		
Female [n (%)]	92 (42.6)	177 (49.4)		
Height [median (IQR), cm]	108.00 (102.00, 113.00)	105.00 (101.00, 110.00)	$Z = -3.397$	< 0.001
Weight [median (IQR), kg]	17.80 (15.60, 19.50)	16.50 (14.80, 18.10)	$Z = -4.840$	< 0.001
Head circumference (mean ± SD, cm)	49.74 ± 1.40	49.64 ± 1.47	$t = 0.799$	0.425
Chest circumference [median (IQR), cm]	51.35 (49.45, 53.85)	51.05 (49.35, 52.55)	$Z = -2.398$	0.017
Use of medications currently [n (%)]	15 (7.1)	41 (12.0)	$\chi2 = 3.391$	0.066
Family history of hypertension [n (%)]	69 (31.9)	97 (27.3)	$\chi2 = 1.390$	0.238
Family history of diabetes [n (%)]	26 (12.0)	51 (14.4)	$\chi2 = 0.624$	0.429
Family history of obesity [n (%)]	3 (1.4)	8 (2.3)	$\chi2 = 0.172$	0.678
Family history of psychosis [n (%)]	1 (0.5)	1 (0.3)	$\chi2 = 0.000$	1.000
Family member daily smoking [n (%)]			$\chi2 = 39.354$	< 0.001
Non-smoking	108 (50.0)	90 (25.8)		
˜2 cigarettes	27 (12.5)	44 (12.6)		
˜10 cigarettes	41 (19.0)	91 (26.1)		
˜20 cigarettes	30 (13.9)	82 (23.5)		
> 20 cigarettes	10 (4.6)	42 (12.0)		
Monthly household income (yuan) [n (%)]			$\chi2 = 36.550$	< 0.001
< 1500	1 (0.5)	11 (3.4)		
1500-3000	22 (10.2)	49 (15.1)		
3000-4500	36 (16.7)	93 (28.7)		
4500-6000	35 (16.2)	69 (21.3)		
> 6000	122 (56.5)	102 (31.5)		
Father's educational level [n (%)]			$\chi2 = 157.832$	< 0.001
Primary school	3 (1.4)	36 (10.3)		
Middle school	36 (16.7)	200 (57.3)		
Vocational school	34 (15.8)	39 (11.2)		
High school	33 (15.3)	39 (11.2)		
College/university	109 (50.7)	35 (10.0)		
Mother's educational level [n (%)]			$\chi2 = 130.325$	< 0.001
Illiteracy	0 (0.0)	1 (0.3)		
Primary school	5 (2.3)	52 (14.9)		
Middle school	50 (23.1)	198 (56.7)		
Vocational school	29 (13.4)	34 (9.7)		
High school	29 (13.4)	21 (6.0)		
College/university	103 (47.7)	43 (12.3)		
Paternal work associated with e-waste dismantling [n (%)]	0 (0.0)	71 (20.5)	$\chi2 = 50.574$	< 0.001
Maternal work associated with e-waste dismantling [n (%)]	0 (0.0)	14 (4.1)	$\chi2 = 9.016$	0.003
Child contact with e-waste [n (%)]	29 (13.5)	135 (38.3)	$\chi2 = 42.874$	< 0.001
Ventilation of house [n (%)]	214 (99.1)	346 (96.7)	$\chi2 = 30.172$	< 0.001
E-waste contamination within 50 m away from residence [n (%)]	2 (0.9)	91 (26.9)	$\chi2 = 63.760$	< 0.001
Distance of residence from road (m) [n (%)]			$\chi2 = 144.805$	< 0.001
< 10	11 (5.1)	126 (37.3)		
˜50	36 (16.7)	99 (29.3)		
˜100	53 (24.5)	72 (21.3)		
> 100	116 (53.7)	41 (12.1)		

Table 2
Comparison of blood lead levels in children between the two groups.

	Haojiang (n = 216)	Guiyu (n = 358)	Statistics	*P*-value
Blood lead level [median (IQR), μg/dL]	3.47 (3.00, 4.09)	4.88 (3.81, 6.02)	$Z = -10.367$	< 0.001
< 5.00 μg/dL [n (%)]	193 (89.4)	189 (52.8)	$\chi2 = 80.913$	< 0.001
5.00 ≤ & < 10.00 μg/dL [n (%)]	20 (9.3)	150 (41.9)		
≥ 10.00 μg/dL [n (%)]	3 (1.4)	19 (5.3)		

3.5. Sensory integration and serum cortisol between the high blood lead level and low blood lead level groups

To further study the effect of lead exposure on sensory integration, we compared SPM-HKC scores and serum cortisol levels. The children were classified into a low blood lead level group (children with blood lead ≤ 5 μg/dL) and a high blood lead level group (children with blood lead > 5 μg/dL). The median SPM-HKC scores from the high (vs. low) blood lead level children were 11.00 (vs. 11.00) for hearing, 19.00 (vs. 18.00) for touch, 16.00 (vs. 14.00 for body awareness, 18.00 (vs. 16.00) for balance and motion, and 90.00 (vs. 86.00) for the total sensory system). There were no significant differences in subscale scores for vision (17.00 vs. 16.00, $Z = -1.024$, $P > 0.05$) and taste and smell (19.00 vs. 18.00, $Z = -1.146$, $P > 0.05$) between children with high

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

	Blood lead levels (r_s)
Age	−0.003
Gender	−0.068
Duration of outdoor play	−0.071
Child hand washing prion to food consumption	**−0.195****
Habit of chewing nails	0.046
Child contact with e-waste	**0.113****
Sources of family drinking water	−0.027
Household tobacco smoke exposure	**0.234****
Monthly household income	**−0.202****
Residence as workplace	**0.165****
Home ventilation	**0.084***
Distance of residence from the nearest road	**−0.170****
Number of e-waste workshops within a 50-m radius of residence	**0.091***
Years of child residency	**0.261****
Father's educational level	**−0.297****
Mother's educational level	**−0.292****
Father's work related to e-waste	**0.144****
Mother's work related to e-waste	**0.097***
Father changing clothes after work	**−0.209****
Mother changing clothes after work	**−0.184****
Average number of times child ate dairy products	**0.234****
Average number of times child ate bean products	−0.035
Average number of times child ate vegetables and fruits	**0.169****
Average number of times child ate pickled foods	**0.207****
Average number of times child ate canned foods	**−0.163****
Average number of times child ate iron-rich foods	0.035

Note: significant *p*-values ($P < 0.05$) are marked in bold. $P < 0.05$ was considered statistically significant; r_s Spearman correlation coefficient. *$P < 0.05$, **$P < 0.01$.

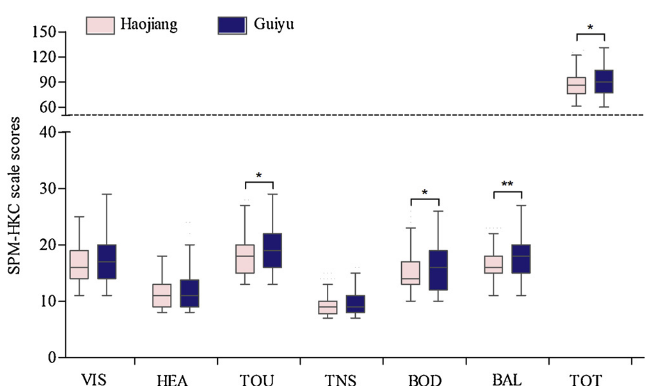

Fig. 1. SPM-HKC scores in Guiyu children are higher than Haojiang children.
Note: data are presented as median (IQR). Haojiang, n = 194; Guiyu, n = 220. VIS: vision; HEA: hearing; TOU: touch; TNS: taste and smell; BOD: body awareness; BAL: balance and motion; TOT: total sensory systems. $P < 0.05$ was considered statistically significant. *$P < 0.05$, **$P < 0.01$.

vs. low blood lead levels. Regarding the subscale scores and the total score, the Wilcoxon-Mann-Whitney test was conducted to compare the differences in SPM-HKC scale scores between the high and low blood lead level groups. The Wilcoxon-Mann-Whitney test showed that sensory integration differences of the high blood lead level group children were worse than that of children with low blood lead levels (Fig. 4). The median level of serum cortisol in children with high blood lead levels [446.33 (390.51, 629.38) ng/mL] was lower than in children with low blood lead levels [552.23 (409.15, 846.66) ng/mL] ($Z = -2.292$, $P < 0.05$) (Fig. 5).

4. Discussion

There are two main findings in the current study. First, children with high blood lead levels show significantly increased sensory integration difficulty scores (that is the degree of sensory integration disability) compared to children with low blood lead levels. Second, scores for touch-related sensory integration difficulty negatively correlated with reduced serum cortisol levels, which are associated with elevated lead levels.

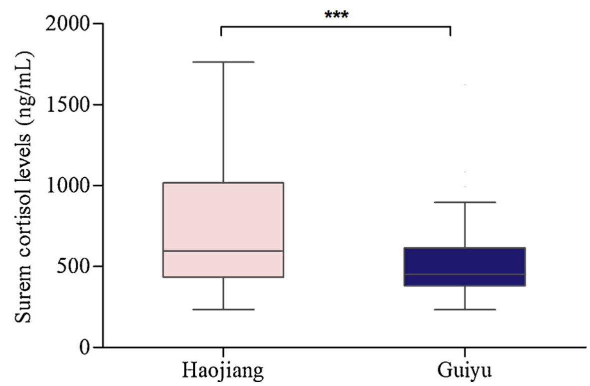

Fig. 2. Serum cortisol concentrations in Guiyu children are lower than Haojiang children.
Note: data are presented as median (IQR). Haojiang, n = 104; Guiyu, n = 108. $P < 0.05$ was considered statistically significant. ***$P < 0.001$.

Table 4
Multiple linear regression analysis of the association between the ln-transformed blood lead levels and the ln-transformed serum cortisol levels in children.

The ln-transformed blood lead levels	Change in the ln-transformed serum cortisol levels: *β*	B (95% CI)	*P*-value
Model			
Unadjusted	−0.144	**−0.139 (−0.268, −0.009)***	0.036
Physiological factors adjusted [a]	−0.156	**−0.150 (−0.280, −0.019)***	0.025
Physiological and social factors adjusted [b]	−0.145	**−0.138 (−0.272, −0.003)***	0.045

Note: significant *p*-values ($P < 0.05$) are marked in bold.
β: standardized coefficients; B: unstandardized coefficients; CI: confidence interval. [a] Model adjusted physiological factors for sex, height and weight. [b] Model adjusted physiological and social factors for sex, height, weight, current use of medications and monthly household income. Significant *p*-values ($P < 0.05$). *$P < 0.05$.

Our first finding, that elevated lead exposure is associated with an increase in children's sensory integration difficulty score, this implies that developmental lead exposure is a possible risk factor for sensory integration dysfunction. To explore the effect of lead on child sensory integration, the SPM-HKC home form was administered to parents or guardians. The results showed that Guiyu children scored higher than Haojiang children in all subscale scores of sensory integration difficulties, these results indicate that sensory integration is implied by living in e-waste exposure areas. All subscale scores of sensory integration difficulties for children with high blood lead levels were higher than for children with low blood lead level, this further illustates that lead is one of the risk factors. Our analysis of related factors shows that, except for taste and smell, scores for vision, hearing, touch, body awareness, balance and motion (corresponding to five sensory systems functioning - visual, auditory, tactile, proprioceptive, and vestibular), and total sensory systems, positively correlate with child blood lead.

We reviewed the literature on lead exposure associated with developmental changes in various sensory components. In a visual go/no-go task in Inuit children exposed to lead, blood lead concentrations

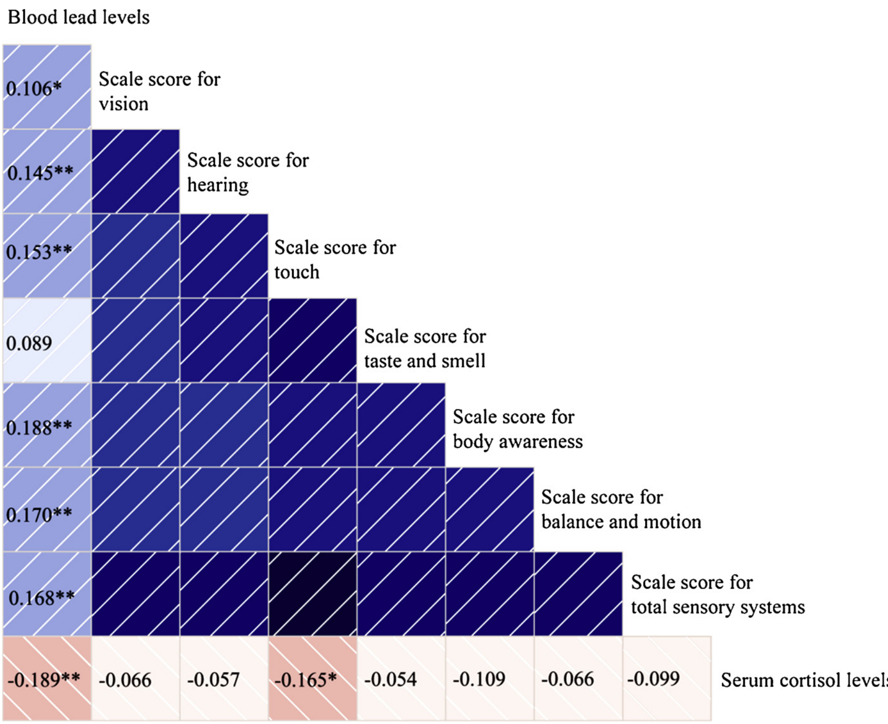

Fig. 3. Spearman correlation analysis of blood lead and serum cortisol levels related to SPM-HKC scores. Note: blue and the diagonal from the lower left to the upper right represents a positive correlation between two-variables of corresponding cell. Red and the diagonal from the upper left to the lower right represents a negative correlation of the two variables. A darker color (the higher saturation) indicates stronger relevance between two-variables of the corresponding cell. $P < 0.05$ was considered statistically significant. $^*P < 0.05$, $^{**}P < 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

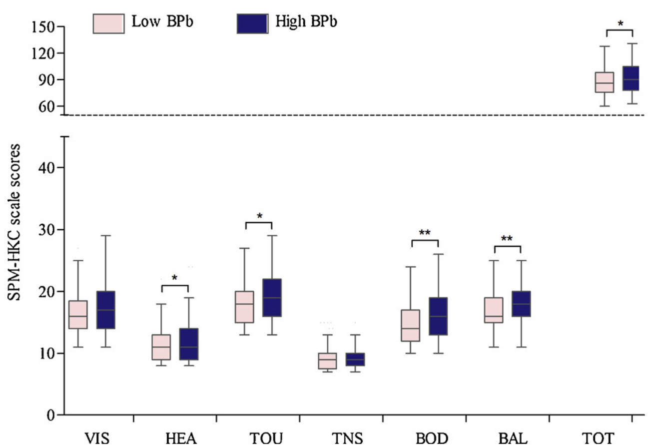

Fig. 4. SPM-HKC scale scores in children from the high BPb group are higher than those from the low BPb level group. Note: data are presented as median (IQR). Low BPb level group, n = 285; high BPb level group, n = 129. BPb: blood lead; VIS: vision; HEA: hearing; TOU: touch; TNS: taste and smell; BOD: body awareness; BAL: balance and motion; TOT: total sensory systems. $P < 0.05$ was considered statistically significant. $^*P < 0.05$, $^{**}P < 0.01$.

were associated with higher rates of false alarms and with decreased P3 amplitudes. The results suggest that lead exposure during childhood impairs children's ability to allocate the cognitive resources needed to correctly inhibit a prepotent response (Boucher et al., 2012). In prospective studies of postural balance, classic examples of sensory integration of three afferent systems (vision, proprioception and vestibular systems) necessary for the maintenance of postural balance, the results showed that early childhood lead exposure was associated with impairment in postural balance as measured with a microprocessor-based force platform system (Bhattacharya et al., 1995; Bhattacharya et al., 2006), and lead competes with calcium modifying postural muscle contractions and resulting in compromised postural balance. In infants with higher prenatal lead exposure during late-pregnancy, even comparatively low blood lead levels have been shown to be a risk factor for sensory function, delayed auditory and visual system maturation, this may demonstrate the role of low level of lead exposure in myelination in sensory system (Silver et al., 2016). In animal experiments, a recent study in mice, with altered development due to lead exposure, showed that a lead-related reduction in synaptic density within the lateral superior olive may cause auditory temporal processing loss (Park et al., 2016). More recently, a correlation has been found between occupationally-relevant lead exposure and reduced head stability in young adult CBA/CaJ mice, this indicates that lead exposure can lead to decreased vestibular function (Klimpel et al., 2017). Pharmacological magnetic resonance imaging analysis has found that enhancement of body awareness and resting-state limbic perfusion are properties of gamma-hydroxybutyrate (GHB), a GHB-/gamma-aminobutyric acid (GABA)-B receptor agonist, a drug of abuse (Bosch et al., 2017). Interestingly, the GABA-B receptor is also a potential target for lead ions, indicating that lead exposure may affect body awareness via the GABA-B receptor (Gorkhali et al., 2016). Children's sensory integration difficulties has been linked to attention deficit hyperactivity disorder and learning disability (Ayres, 1972; Mulligan, 1998). There are the most common mental illness and learning problems in children with lead poisoning. The mechanism of impairment (or difference) of developmental lead exposure for sensory integration still requires further research.

Our second finding is that elevated scores of touch-related sensory integration difficulties are associated with reduced serum cortisol levels, which are linked with elevated lead levels. Our analysis of factors related to sensory integration shows that, apart from taste and smell, scores for vision, hearing, touch, body awareness, and balance and motion, as well as total sensory systems, positively correlate with blood lead levels. Among them, the score for touch was negatively correlated with serum cortisol levels. We confirm that touch-related sensory integration often results from lead-induced neurotoxicity and may be modulated by cortisol level.

An earlier report showed that early postnatal exposure to lead can induce more negative reactions to tactile stimuli in rhesus monkeys, and provides evidence that developmental lead exposure is a cause of tactile defensiveness (Moore et al., 2008). Based on our research results, we believe that the HPA axis plays a potential role in lead-induced touch-related sensory integration. We tentatively interpret this

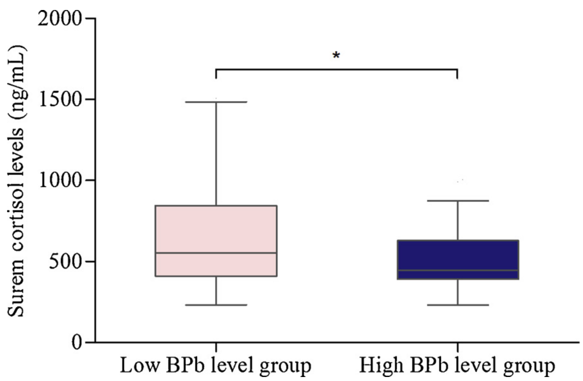

Fig. 5. Serum cortisol concentrations in the high BPb level group are lower than the low BPb level group. Note: low BPb level group, n = 147; high BPb level group, n = 65. Data are presented as median (IQR). $P < 0.05$ was considered statistically significant. *$P < 0.05$.

deduction, lead perhaps acts on the melanocortin 2 receptor, a G-coupled receptor located on the cell plasma membrane of the zona fasciculata of the adrenal cortex, and competitively inhibits binding of ACTH to the receptor, which reduces cortisol secretion (Fortin et al., 2012; Nishiyama et al., 1985). Low cortisol levels may attenuate glutamate inhibition, inhibition of GABA release and negative regulation of spinal glutamate transporters by glucocorticoid receptor-mediated effects (Kuehl et al., 2010). This may be the potential mechanism by which low cortisol alters the threshold of sensory regulation.

In the current research, we evaluated the influence of blood lead on the HPA axis in lead-exposed children in both Haojiang and Guiyu. Our data show that the median serum cortisol level is lower in children with high blood lead levels than those with low blood lead levels. As elevated blood lead levels are related with reduced serum cortisol levels, this suggests that lead exposure could alter HPA axis function, leading to lower than expected cortisol release. We know that when stressors or exposure to lead is chronic, the compensatory mechanism of the HPA axis may reach a depletion phase, resulting in lower cortisol levels and diminished induction, or even reduced response to pressure sources due to habituation (Grissom and Bhatnagar, 2009; Miller et al., 2007). The finding is consistent with previous reports showing baseline cortisol concentration is negatively associated with lead among occupationally-exposed populations, and correlates with a reduced cortisol awakening response among non-occupationally-exposed pregnant women (Braun et al., 2014; Cullen et al., 1984; Fortin et al., 2012; Gustafson et al., 1989). A similar study used the Short Sensory Profile test, and the result shows a negative relationship between morning cortisol and the stress survey schedule such that higher chronic stress were correlated with lower cortisol in autistic children. Greater impairment of sensory sensitivity, specifically the touch subdomain, was associated with lower afternoon cortisol in normal children (Corbett et al., 2009). This shows to some extent that tactile-related sensory integration may be modulated by cortisol level.

In our project, we used data from the same population to analyze simultaneously serum cortisol, blood lead levels and children's sensory integration difficulty scores. The results imply that elevated lead levels from e-waste exposure are an environmental risk factor for sensory integration difficulties in preschool children, and that the HPA axis may play a role in touch-related sensory integration caused by lead exposure.

Although we use reliable statistical methods to assess the contribution of serum cortisol concentrations, some limitations should be emphasized. Blood ACTH levels were not measured, and changes in ACTH levels would provide additional information to assess the mechanism of lead action on the HPA axis. Also, we did not collect nocturnal serum cortisol levels, which would permit comparison to the results of other studies. Although SPM-HKC is to some extent indicative of a child's state, in this study the SPM-HKC was used only to compare the frequency of behavioral dissonance between the two groups of children. Another limitation that needs to be acknowledged, we measured the scores of visual, vestibular and proprioceptive corresponding sensory integration disorders in children, we could not diagnose postural stability difficulties. Although animal experiments have proven that lead exposure induces tactile defensiveness, the causality between cortisol level and touch-related sensory integration difficulty remains unclear in this study. Future research is needed to determine the direction and extent of variable changes.

5. Conclusion

Our study explores the effect of lead on sensory integration in children from e-waste areas. The results suggest that elevated lead exposure is associated with greater sensory integration difficulties in children. Tactile-related sensory integration may be modulated by cortisol levels, which are modified by lead neurotoxicity.

In summary, this study supports the hypothesis that environmental lead exposure may increase the risk of sensory integration difficulties in children, and that the HPA axis plays a potential role in lead-induced tactile-related sensory integration. Future studies should explore the mechanism of lead exposure on sensory integration. This is a worldwide public health issue, and our findings support efforts to reduce environmental lead exposure to prevent or reduce children's sensory integration difficulties.

Conflict of interest

The authors declare that they have no conflict of interests.

Transparency document

The Transparency document associated with this article can be found in the online version.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21577084 and 21876065). We thank Western Psychological Services (WPS) Rights & Permissions, for they share SPM-HKC with us for academic use. We thank Dr. Stanley Lin for his constructive comments and English language editing for the manuscript. We are grateful to all the recruited children and their guardians for participating in this project.

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