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Altered executive function in the lead-exposed brain: A functional magnetic resonance imaging study

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ABSTRACT

Introduction: It is well known that lead exposure induces neurotoxic effects, which can result in dysfunction in a variety of cognitive capacities including executive function. However, few studies have used fMRI to examine the direct neural correlates of executive function in participants with past lead exposure. Therefore, this study aimed to investigate possible alterations in the neural correlates of executive function in the previously lead-exposed brain.
Methods: Forty-three lead-exposed and 41 healthy participants were enrolled. During the fMRI scans, participants performed two modified versions of the Wisconsin Card Sorting Task (WCST) differing in cognitive demand, and a task that established a high-level baseline condition (HLB).
Results: The neural activation of left dorsolateral prefrontal cortex was greater in healthy controls than in participants with lead exposure when contrasting the difficult version of the WCST with the HLB. Moreover, cortical activation was found to be inversely associated with blood lead concentration after controlling for covariates.
Discussion: These data suggest that lead exposure can induce functional abnormalities in distributed cortical networks related to executive function, and that lead-induced neurotoxicity may be persistent rather than transient.

1. Introduction

Occupational exposure to lead has declined steadily over the past 20 years (CDC, 2013), and thus present-day concerns center on the health effects of past exposure (Khalil et al., 2009; Schwartz et al., 2000). It is widely recognized that lead exposure has toxic effects on every organ system, especially the central nervous system. Lead-induced brain damage may result in a variety of neurological disorders, including mental retardation (Sanders et al., 2009), Alzheimer's disease, Parkinson's disease (Monnet-Tschudi et al., 2006), and schizophrenia (Opler et al., 2008). In addition, the neurotoxic effects of lead exposure may cause behavioral problems such as attention deficit hyperactivity disorder, juvenile delinquency, and criminality (Wright et al., 2008). In addition, lead can adversely affect general intellectual functioning (Sanders et al., 2009), visuospatial function (Weisskopf et al., 2007), and verbal learning and memory (Bleecker et al.,

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2005). Furthermore, recent studies have demonstrated that executive function may be at particular risk from lead-induced neurotoxicity (Canfield et al., 2004; Trope et al., 2001). Executive dysfunction can appear immediately after lead exposure, or be delayed (Sanders et al., 2009). Most studies of executive dysfunction have been performed in children, and only a few studies in adults have examined workers exposed to lead (Canfield et al., 2004; Trope et al., 2001; Sanders et al., 2009). Adult occupational exposure and childhood developmental exposure to lead result in different cognitive and behavioral outcomes (Sanders et al., 2009; NTP, 2012). Thus, studies on workers exposed to lead are needed to clarify lead neurotoxicity related to executive functions.

Executive function, one of the main functions of the prefrontal cortex, allows us to guide appropriate behavior contextually. The Wisconsin Card Sorting Task (WCST) has been used to examine executive dysfunction (Goldstein et al., 2004; Milner, 1963). During this task, the participants asked to match randomly drawn cards to reference cards in accordance with a rule of classification. Without notice, however, the rule is changed and the participant must switch from the previous rule to a new rule. Thus, the WCST involves a range of cognitive functions including working memory, set shifting, and error detection. There is mounting evidence of impairment on the WCST in patients with frontal cortex damage (Demakis, 2003; Goldstein et al., 2004; Mukhopadhyay et al., 2008; Stuss et al., 2000). Furthermore, most neuroimaging studies demonstrate that the WCST increases neural activation specific to executive function, especially in prefrontal cortex (Gonzalez-Hernandez et al., 2002; Lie et al., 2006; Nyhus and Barcelo, 2009). Recently, neuroimaging research has investigated the prefrontal cortex in relation to different cognitive components using several modified versions of the WCST (Lie et al., 2006; Monchi et al., 2001).

The present study is among the first to use fMRI to investigate direct neural processing in relation to executive function in persons exposed to lead. Therefore, this study aimed to elucidate the possible differences in the neural correlates of ongoing executive function between participants with past lead exposure and healthy controls. We employed two modified versions of the WCST, which differed in cognitive demand, and a high-level baseline condition (HLB) to compare neural processing between the two groups as a function of task complexity (Lie et al., 2006). Based on previous findings of lead-induced executive dysfunction (Canfield et al., 2004; Ris et al., 2004; Sanders et al., 2009; Trope et al., 2001), we hypothesized that participants with past lead exposure would show abnormal activity in distributed neural networks related to executive function during performance of the WCST relative to healthy controls. In particular, we hypothesized that a difference in neural processing related to executive function would be seen in the prefrontal cortex under conditions of high cognitive demand. Therefore, the difference would be seen with a difficult version of the WCST rather than with a simple version.

2. Methods

2.1. Participants

Of the 53 recruited subjects previously exposed to lead, 43 were women; therefore, only women were enrolled to eliminate sex as an important effect modifier. The fMRI data from 84 right handed participants, comprising 43 participants with past lead exposure (all female; mean age 60.1 ± 4.9) and 41 age-matched control participants (all female; mean age 58.3 ± 5.2) were included in the current study. We recruited retired former lead workers who had worked in plants producing lead batteries. Control participants were manual workers not exposed to lead or solvents, in other factories in the same geographic area in Korea. For cultural reasons, lead-based paints have never been used in homes in Korea; thus, all participants reported little or no exposure to lead-based paint residues. All participants had normal vision and had Korean as a first language. Study participants were recruited voluntarily and screened for the presence of any chronic medical illness or disorder. Participants were provided with $150 each for participation in the study as compensation for not being able to work for the several hours required for the examination and travel. All participants in the current fMRI study gave written, informed consent and the local Institutional Review Board approved the study protocols.

2.2. Determination of lead in whole blood

Blood lead content was measured in duplicate with a Zeeman background-corrected atomic absorption spectrophotometer (modelZ-8100; Hitachi, Tokyo, Japan) using the standard addition method of the National Institute of Occupational Safety and Health. Blood samples were diluted 1:10 with 1% Triton X-100 in distilled water using 0.5% ammonium phosphate as a modifier, and 15-μL aliquots of the diluted samples were injected onto the platform of the furnace (Kneip, 1988). All blood lead analyses were carried out by the Institute of Environmental and Occupational Medicine, Soonchunhyang University, a laboratory certified by the Korean Ministry of Labor. Since 1988, the institute has served as a reference laboratory for blood lead assessment in a Korean quality control and assurance program. It is licensed by the Ministry of Labor as a uniquely designated institute for nationwide occupational health services to lead-using industries. For the internal quality assurance and control aspects of our study, commercial reference materials were obtained from Bio-Rad (Lyphochek® Whole Blood Metals Control). The detection limit of the presently used method for blood lead determination was 0.60 μg/dL. No sample contained levels below the detection limit.

2.3. Clinical laboratories

The level of hemoglobin was determined using the cyanmet hemoglobin method (Beckman Coulter Inc., model Ac-T 8, United States), and hematocrit was measured using the capillary centrifugation method (Thomas and Collins, 1982). The level of zinc protoporphyrin (ZPP) was measured by a hematofluorometer (Aviv, United States) (Blumberg et al., 1977). The urinary amino levulinic acid (ALA) levels were determined according to the method of Tomokuni et al. (1992). Creatinine levels in urine were analyzed using the appropriate Sigma kit (St. Louis, Missouri, United States) (Heinegard and Tiderstrom, 1973).

2.4. Experimental paradigm

A modified version of the WCST was used as the experimental paradigm, with two different test variants (A and B) and a high-level baseline condition (HLB) in an efficient blocked design (Konishi et al., 2008; Lie et al., 2006). Task A was the most similar to the original Wisconsin Card Sorting Test (WCST) of those used in our experimental task. Participants were first given the control cue word "card" devoid of any information about the current sorting dimension. Participants were asked to identify the subsequent dimension, whether 'shape', 'color' or 'number', by trial and error and the use of feedback stimuli. Because each task A block consisted of 12 trials, a sorting dimension shift occurred once every six trials, resulting in one sorting dimension shift per task A block. As there were 3 task A blocks per experimental run and 3 sorting dimension shifts were experienced in task A blocks: the first shift (shape to number), the second shift (color to number), and the third shift (shape to color).