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Altered executive function in the welders: A functional magnetic resonance imaging study

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ABSTRACT

Chronic exposure to manganese (Mn) can lead to impairments in motor and cognitive functions. Several recent studies reported Mn-induced executive dysfunction. The present study compared the neural correlates of ongoing executive function of welders and healthy controls. Fifty-three welders and 44 healthy controls were enrolled. Participants were given functional magnetic resonance imaging (fMRI) scans and performed two modified versions of the Wisconsin Card Sorting Task (WCST) that differed in cognitive demand, and a task that established a high-level baseline (HLB) condition. Card Sorting Test and Word-Color Test were also used to assess executive performance. Neural activation of the bilateral superior-frontal cortex, right-inferior parietal cortex, and bilateral insula cortex were greater in healthy controls than in welders when contrasting the difficult version of the WCST with the HLB. There were also correlations between executive functions by the Card Sorting Test and Word-Color Test, and brain activation in the insula cortex using the WCST. Our results indicated that welders had altered neural processing related to executive function in the prefrontal cortex under conditions of high cognitive demand. Welders also had less activation of the insula cortex, a part of a larger network comprising the lateral prefrontal cortex and parietal cortex.

1. Introduction

Manganese (Mn) is the fourth most widely used heavy metal element in the world. Mn neurotoxicity (manganism), which is primarily a movement disorder that occurs following long-term exposure, can occur in Mn miners, welders, and those involved in ferroalloy processing (Chia et al., 1993; Myers et al., 2003; Stredrick et al., 2004; Bowler et al., 2006). Manganism can also occur in patients with chronic liver diseases such as liver cirrhosis or portal systemic shunt (Hauser et al., 1994; Krieger et al., 1995; Ikeda et al., 2000). Because of the obvious clinical features of manganism, diagnostic and epidemiological research of Mn neurotoxicity until the 1980s has focused on altered motor responses and movements. In the 1990s, studies of Mn-exposed workers focused on early neurobehavioral manifestations, such as early motor function deficits; the results from cognitive testing were inconsistent. More recent studies, especially since 2000, have reported dose-related cognitive deficits in welders exposed to Mn-containing fumes (Bowler et al., 2007a, 2007b; Chang et al., 2009). Moreover, numerous population-based studies reported cognitive deficits in children and adults exposed to environmental Mn from a variety of sources, including airborne particulate from industrial activities and mining, drinking water from aquifers, and Mn-based pesticides (Wasserman et al., 2006; Bowler et al., 2015). Several recent studies reported Mn-induced executive dysfunction (Chang et al., 2010a; Roels et al., 2012; Bowler et al., 2015).

Neuroimaging is changing from a morphological to a functional approach as new technologies develop. Recent studies have used functional neuroimaging modalities, including diffusion tensor imaging (DTI),

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and functional magnetic resonance imaging (fMRI), to evaluate the neurological consequences of exposure to neurotoxins (Weisskopf et al., 2007; Chang et al., 2010a, 2010b). Despite advances in these techniques, few studies have examined the neural correlates of Mn-induced cognitive impairment (Chang et al., 2010a). Our previous fMRI study indicated that welders had altered working memory processes during the 2-back verbal working memory task (Chang et al., 2010a). This task examines the neural basis of working memory process. In contrast, the Wisconsin Card Sorting Task (WCST) involves a range of executive functions including set shifting, decision-making, judgement, and working memory (Goldstein et al., 2004; Seo et al., 2015). For these reasons, we performed fMRI with the WCSTs to assess the neural correlates of Mn-induced executive function impairment in welders who had prolonged exposure to Mn.

Executive function, one of the main activities of the prefrontal cortex, guides appropriate behavior contextually. The WCST is widely used to examine executive dysfunction (Milner, 1963; Lezak, 2012; Bowler and Lezak, 2015; Seo et al., 2015). This task requires the participant to match randomly drawn cards to reference cards according to a sorting category of classification of color, shape and number. The sorting category would be changed after a certain number of consecutive correct decisions. Without notice, however, the sorting category is changed and the participant must switch from the previous category to a new sorting category. Thus, the WCST examines a range of cognitive functions including working memory, set shifting, perseveration, and error detection. There is mounting evidence that patients with frontal cortex damage have impaired performance on the WCST (Stuss et al., 2000; Goldstein et al., 2004; Mukhopadhyay et al., 2008; Lezak, 2012). Furthermore, most neuroimaging studies demonstrated that the WCST increases neural activation specific to executive function, especially in the prefrontal cortex (Lie et al., 2006; Nyhus and Barcelo, 2009; Seo et al., 2015). Recent neuroimaging research investigated the prefrontal cortex in relation to different cognitive components using WCST (Monchi et al., 2001; Lie et al., 2006).

The present study is among the first to use fMRI to investigate direct neural processing in relation to executive function in welders exposed to Mn. In particular, we compared the neural correlates of ongoing executive function of welders and healthy controls. We employed two modified versions of the WCST, which differed in cognitive demand, and a high-level baseline (HLB) condition to compare neural processing between the groups as a function of task complexity (Lie et al., 2006). Based on previous findings of Mn-induced executive dysfunction (Chang et al., 2010a; Menezes-Filho et al., 2011; Roels et al., 2012; Bowler et al., 2015), we hypothesized that welders would show abnormal activity in distributed neural networks related to executive function during performance of the WCST. Specifically, it was hypothesized that a main difference in neural processing related to executive function would be found in the prefrontal cortex during performance of the difficult version of the WCST with high cognitive demand.

2. Subjects and methods

2.1. Subjects

We recruited males older than 40 years, who were current full-time welders with more than 3 years of welding experience, from four factories that make mild steel blocks for shipbuilding in Korea. These welders were contract workers rather than regular factory employees. Over the past 10 years, these welders mainly performed gas metal arc welding (GMAW) using CO_2 as a shielding gas. Qualified industrial hygienists assessed exposure in the workplace, and welding was the only source of Mn in the workplace. Age-matched males who were non-welding production workers from the same workplaces and not exposed to other hazardous materials (*e.g.* paint) were recruited as controls. We selected these workers instead of office workers (who had no Mn exposure) because their socioeconomic and behavioral characteristics were more similar to those of welders. One welder with only primary school education (6 years of education or less) was excluded to avoid between-group differences in neurocognitive performance. Workers with recent histories of head injury, hand injury, or other physical impairments (*e.g.* history of chronic liver disease, iron deficiency anemia, carbon dioxide poisoning, stroke, depression, or seizure disorders) were excluded. Workers with specific, non-Mn-related physical conditions that could affect fMRI signals, such as trauma, hyperosmolar conditions, hypoxia, stroke, and tumors (Warakaulle and Anslow, 2003), were also excluded. Among all recruited workers, 2 welders and 2 control individuals did not complete all the examinations. Thus, 97 workers (53 welders and 44 controls) were included in the final analyses. All workers visited a university hospital during a weekend, and were examined at least 12 h after their most recent work shift. All participants completed questionnaires, provided blood samples, and underwent neurocognitive tests and fMRI examination on the day of this visit. All subjects were right-handed according to the Edinburgh handedness scale. After detailed explanation of the study design and potential risks, all subjects gave written informed consent. The Institutional Review Board (IRB) of Ulsan University Hospital approved the study protocol.

2.2. Exposure

We analyzed airborne Mn measurements that were taken twice yearly at each workplace since 2006. Airborne Mn released by the welding process was collected on mixed cellulose ester membrane filters (0.8 μm pore size, 37 mm diameter; SKC, USA) in personal air samplers (AirLite; SKC Inc., Eighty Four, PA, USA). All pumps were calibrated before and after use. Sampling was performed for at least 6 h, excluding break periods, with flow rates of 1~2.5 L/min. Samples were measured in a laboratory that performs quality control programs organized by the Korean Occupational Safety and Health Agency (KOSHA).

Analysis was performed using inductively coupled plasma atomic emission spectroscopy (ICP-AES; ULTI-MA2; Horiba Jobin Yvon, France) according to NIOSH analytical methods 7300 (NIOSH, 1994).

2.3. Questionnaires and blood measurements

Each individual completed a questionnaire and underwent blood sample collection during a single day. The questionnaire assessed basic demographic information including age, education level, tobacco use, alcohol consumption, use of medications, recent medical history, subjective symptoms, and job type, including the type and duration of welding. Each participant was asked detailed questions about his work history.

Blood was collected by venipuncture of the antecubital vein, with care taken to avoid contaminating the skin and equipment with workplace dust. Blood samples (2 mL) were drawn into standard commercial evacuated tubes containing sodium heparin. Mn levels were measured using a graphite furnace atomic absorption spectrophotometer (Varian AA240Z; Varian Techtron Pty, Victoria, Australia). Blood Mn was determined by flameless graphite furnace atomic absorption spectrophotometry (Spectra AA880-GTA 100, Varian, Australia) using the standard addition method (Baruthio et al., 1988; Baldwin et al., 1994). Briefly, aliquots (0.1 mL) of blood were diluted 20-fold with 0.1% (v/v) Triton X-100, and 15 μL samples were injected into the graphite furnace. All blood Mn analyses were performed in the Ulsan University Hospital laboratory, which passed the Quality Assurance Program for Mn operated by the Korea Occupational Safety and Health Agency (KOSHA). Commercial reference materials were used for internal quality assurance and control (Lyphochek1 Whole Blood Metals Control, Bio-Rad). The method detection limit for blood Mn was 0.16 μg/dL. All tested samples had Mn levels well above this limit.

Complete blood count, hemoglobin, and hematocrit were determined by DxH800 (Beckman Coulter Inc., Brea, CA, USA) using triplicate electrical impedance method. Liver function (aspartate aminotransferase,