Original Article

The Neural Alteration according to Cognitive Load on Working Memory by Organic-Solvent Exposures

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Organic solvents are known toxic effects like vertigo, behavioral obstacle, distracting, and peripheral neuropathy in neuron areas. However, there have been few studies how neurotoxic solvents-exposed workers are affected by the cognitive load of preceding working memory tasks. Therefore, we used fMRI as to measure the neural correlates of working memory impairment in occupational workers who had from chronic exposure to organic solvent. Twenty-nine solvent-exposed workers were included in this study. Each participant concluded the verbal N-back tasks (1- and 2-back) during the fMRI acquisition. Within-group analyses showed fronto-parietal networks were active in each condition. Direct comparisons between 1- and 2-back showed higher activation during the 2-back than 1-back. We found that increased activation of these regions at lower task demand is associated with increased cost of implementing.

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Key Words: Organic-Solvent exposure, Neurotoxicity, fMRI, Working memory

Introduction

Organic solvents are contained in volatile liquids, such as printing or dry cleaning agents, metal degreasing, and paint, and used in many industries. Therefore, occupational exposures are common in metal degreasing, paint stripping, and dry cleaning occupations. Some solvents have well-established neurotoxic effects, including dizziness, loss of consciousness, behavioral abnormalities, and peripheral neuropathy.[1,2] Certain solvents may cause motor system abnormalities.[3] Accumulated

or repeated exposures usually represent a chronic continuous diffuse injury to the brain resulting called chronic toxic encephalopathy (CTE). A variety of cognitive impairment is usually involved in the clinical manifestations of CTE.[3] Internationally, CTE is a recognized and established condition that results from immoderate occupational exposure to solvents via inhalation or skin contact. According to several researches, solvent-exposed workers are frequently showed significantly compromised attention, processing speed, and working memory deficits compared to demographically similar unexposed controls.[4,5]

The few neuroimaging studies to document neural structures affected by exposure to solvents demonstrated that solvents-exposed subjects showed significantly lower activation of anterior frontal areas and significantly worse performance on the working memory task than did controls.[6,7] Haut and colleagues studied the pattern of neural activation during verbal working memory in patients with solvent exposure using [15O] water positron emission tomography (PET).[6] They suggested that frontal dysfunction and compensatory can be related to use within anterior regions of the working memory system in pa-

tients with solvent exposure.

However, no investigations have directly examined that how solvents-exposed subjects are influenced by the cognitive load of a preceding working memory task. Accordingly, in this study, we used fMRI to evaluate the neural correlates of organic solvent induced memory impairment in occupational workers with subclinical dysfunction in working memory networks as a consequence of chronic exposure to this neurotoxicant. We supposed that memory functional deficits were related to an increased cognitive demand on the working memory system. Therefore, we performed fMRI experiments using the 1- and 2-back memory tasks to examine the behavioral significance of additionally recruited brain regions in the workers with chronic neurotoxicant exposure.
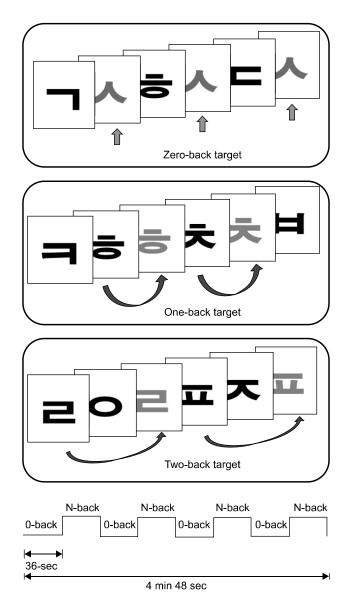
Materials and Methods

1. Subjects

A total 29 solvent-exposed workers were recruited in this study. The subjects were 45.07±6.0 year old and all were right-handed. We recruited active solvent-exposed workers who had worked in plants using organic solvents over 5 or more years. All subjects had normal vision and had Korean as the first language. They all agreed to participate in our fMRI study and provided written informed consent. The protocol used for this study was approved by the local Internal Review Board.

2. Verbal working memory task

The verbal N-back task was applied during the fMRI acquisition to investigate changes in neural recruitment and suppression as a function of increasing task load. N is an integer usually 0, 1, 2, or 3, requires on-line monitoring, updating, and manipulation of remembered information, and is therefore assumed to place great demands on a number of key processes within working memory.[7] In our implementation of the fMRI-compatible N-back task, participants were presented with a stream of letters and asked to respond when presented with target letters defined according to one of N prespecified conditions (in this case, three conditions referred to as 0-, 1-, or 2-back). In the control condition (0-back), participants were asked to identify the target letter "ㅅ" that was presented at the beginning of each trial block. In the N-back (N is 1 or 2)

condition, they had to permanently memorize the recently presented letters in order to press a button when a letter matched one that had been presented N letters before the present letter (Fig. 1). We used letters from the Korean alphabet as target cues. Stimuli were displayed using SuperLab (Cedrus Corp.,

Fig. 1. N-back task paradigm and schematic of block design. In the 0-back condition, participants were asked to identify the target letter "ㅅ" that was presented at the beginning of each trial block. In the N-back (N is 1 or 2) condition, they had to permanently memorize the recently presented letters in order to press a button whent a letter matched one that had been presented N letters before the present letter. The entire functional scanning run took approximately 4 min 48 sec.

version 4.5, San Pedro, CA). When SuperLab detects the MRI scan trigger, it immediately starts the N-back stimulus task. The stimuli were presented binocularly using a goggle-based system (modified SilentVision SV-7021 Fiber Optic Visual System, Avotec Inc., Stuart, FL) positioned on top of the head coil. Participants responded with their right index finger if a specific target appeared and with their middle finger if there was no match. To ensure that the participants understood the task demands, they received instructions and rehearsed before they entered the MRI suite. The experiment utilized a blocked design with two epochs for each of the two experimental conditions (4 epochs in total). Each stimulus letter was visible for 500 ms and was followed by a fixation cross that randomly appeared for 2500 or 3500 ms. Ten letters were presented in each epoch of trials, so that each epoch lasted 36 sec. The probability of a letter being a target was 31%. The entire functional scanning run took approximately 4 min 48 sec.

3. Functional magnetic resonance imaging

Blood oxygenation level dependent (BOLD) contrast was collected for each subject using a 3.0 T GE EXCITE scanner (Milwaukee, WI) equipped with a transmit-receive body coil and a commercial eight-element head coil array. T2*-weighted echo-planar imaging was used for fMRI acquisition. The following acquisition parameters were used in the fMRI protocol: echo time (TE)=40 ms, repetition time (TR)=3000 ms, field of view (FOV)=22×22 cm, acquisition matrix=64×64. Using a midsagittal scout image, 31 contiguous axial slices with 4 mm thickness were placed along the anterior-posterior commissure (AC-PC) plane covering the entire brain. A 3-dimensional T1-weighted anatomical scan was obtained using fast spoiled gradient echo (FSPGR) for structural reference. The following acquisition parameters were: TE=3 ms, TR=7.8 ms, flip angle (FA)=20°, FOW=25.6×25.6 cm, acquisition matrix=256×256, voxel size=1.0×1.0×1.0 mm³.

4. Functional image analyses

Image processing and statistical analyses for fMRI data were carried out using MATLAB (The Mathworks Inc., Natick, MA) and SPM8 (SPM; Wellcome Department of Imaging Neuroscience, London, UK; online at http://www.fil.ion.ucl. ac. uk). Data were converted from DICOM to NIFTII format,

processed using a slice timing correction with the first acquired slice to correct for temporal offsets in the acquisition of slices and spatially realigned and unwarped to the first image for correction movement and distortion. The mean fMRI volume and FSPGR were coregistered using mutual information, and normalized to the Montreal Neurological Institute (MNI) brain.[8] The normalized data were smoothed with isotropic Gaussian kernel of FWHM 8 mm. The pre-processed fMRI data were then entered into the first-level individual analysis by comparing fMRI activity during the N-back task with that during the 0-back (N-back>0-back). In the second-level within-in-group analysis, contrast images from the analysis of individual subjects were analyzed by one-sample t-tests, there by generating a random-effects model, allowing inference to the general population. And for the direct comparison between the conditions (2-back>1-backand 2-back<1-back), contrast images for the main effects were assessed using a two-sample t-test. The significant level of $p<0.01$ was used with correcting multiple comparisons by using the false discovery rate (FDR) method across the whole brain and clusters of fewer than 32 voxels were ignored.

5. Statistical analysis

We used t-tests to examine N-back accuracy and reaction time in solvent-exposed subjects. Pearson correlation analyses were used to determine the correlations between mean percentage changes in BOLD fMRI signals in the activation brain regions and working memory performance in individual subjects. All statistical analyses were performed using SPSS software. Statistical significance was defined at $p<0.05$.
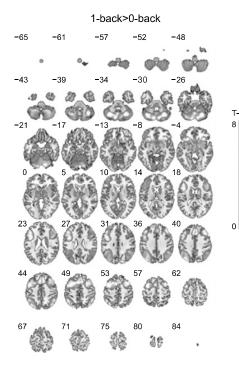
Results

1. General characteristics and N-back task performance

The demographic, clinical, and laboratory characteristics of the 29 organic solvent exposed workers are listed in Table 1. Moreover, reaction time and accuracy data for the N-back task collected during scanning for organic solvent-exposed subjects with standard deviation are presented in Table 1. The mean performance differences between the N-back tasks and 0-back control condition was inferior in the high-load-cognitive task (2-back) compared to that of the low-load-cognitive task

(1-back). The differences in reaction time between two cognitive loads were statistically significant ($p < 0.01$), except for task accuracy.

Table 1. Demographic, clinical, and laboratory characteristics of organic solvent-exposed subjects.

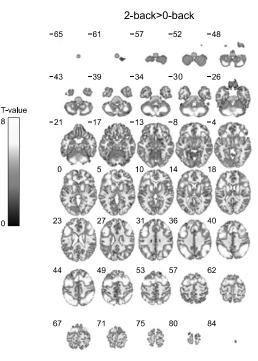|	N=29
Age (year)	45.07±6.0
Educational level n (%)	
No education	0 (0%)
Elementary school	0 (0%)
Middle school	5 (17.24%)
High school or more	24 (82.76%)
College	0 (0%)
Smoking (pack year)	14.72±10.57
Duration of exposure (year)	14.39±7.38
Alcohol year	19.51±10.80
Reaction time (msec)	
1-back	1286.9±3.2
2-back	1466.1±5.3
Task accuracy (%)	
1-back	75.9±2.7
2-back	74.2±1.7

Mean±SD.

2. Functional magnetic resonance imaging data

In the within-group analyses, the N-back working memory tasks revealted that a network of frontal and parietal cortical areas was active in both two conditions (1- and 2-back). The network included activations in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), inferior parietal cortex (IPC), precuneus, and cerebellum (Fig. 2). Direct comparisons between two conditions (1- and 2-back) showed that, during the 2-back working memory task, the organic solvent-exposed subjects showed higher activation than performing the 1-back working memory task in the bilateral DLPFC, IPC, and cerebellum (Fig. 3). No region showed significantly higher activation in the performing the 1-back task compared to the 2-back task.

3. Correlation analysis between mean percentage BOLD signal changes and task performance

The increased percentage BOLD signal change in the left inferior parietal cortex of the 1-back task compared to 0-back control condition showed a strong positive correlation (R=0.370, $p < 0.05$) with increased 1-back response time compared to

Fig. 2. Brain activation maps contrasted from 1- or 2-back minus 0-back task for all organic solvent-exposed subjects. The N-back working memory tasks revealted that a network of frontal and parietal cortical areas was active in both two conditions.
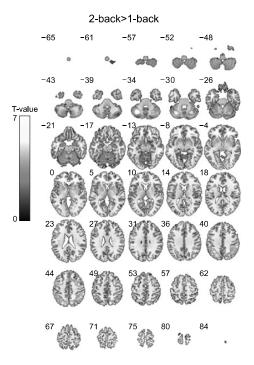
Fig. 3. Brain activation maps derived from direct comparison between 2-back task and 1-back task. During the 2-back task, the organic solvent-exposed subjects showed higher activation than performing the 1-back task in the frontal and parietal cortical areas. No region showed significantly higher activation in the performing the 1-back task compared to the 2-back task.

Fig. 4. Correlation between BOLD signal change and 1-back task performance (reaction time) (R=0.370, p<0.05).

0-back control condition (Fig. 4). For the high-load-cognitive task (2-back), however, such a positive trend was not founded for any of the activated brain areas.

Discussion

In this study, employing the N-back task with varying levels of load, our goal was to investigate activation patterns of cognitive load in individuals with chronic occupational exposure to solvent. As hypothesized, we found that solvent-exposed subjects exhibited significantly higher activation of the bilateral DLPFC, IPC, and cerebellum with increased cognitive demands during the N-back tasks. Our findings of higher activity in brain regions with increased cognitive demands is consistent with studies that increasing working memory processing load is generally associated with increased activation of that bilateral frontal and parietal cortexes.[9,10]

With increased cognitive demands during performance of the N-back tasks, the prefrontal cortex plays an essential role in
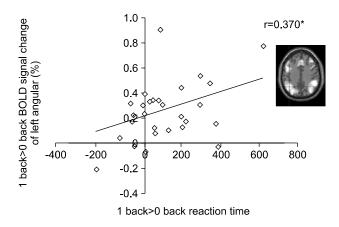
mediating the monitoring of online stimuli, conforming the information that is held in working memory to include the most recently presented stimulus,[7] The DLPFC is thought to support the executive or cognitive functions for manipulating and maintaining items in the working memory.[11] Furthermore, the left DLPFC is essential for allowing and guiding approach of verbal and spatial knowledge, while the right DLPFC is necessary for the manipulating information in a verbal and spatial reasoning contexts as well as allowing adaptive decision making.[12,13] Rypma and colleagues suggests that the increased brain activation with increased cognitive load in the DLPFC is the result of the strategic process of data compression.[14] Thus, our findings are in line with prior studies that have demonstrated the relationship between cognitive load and brain activation in the DLPFC.

Additionally, we found that solvent-exposed subjects exhibited significantly higher activation of the IPC with increased cognitive demands during the N-back tasks. Several neuroimaging studies have showed that the bilateral parietal cortices are engaged when verbal information must be remembered from short-term memory regardless of the type of verbal item (e.g., letter, words, or digits).[15-17]

We also found a positive association between increased reaction time on the 1-back task compared to 0-back task and increased percentage BOLD signal changes in the left inferior parietal cortex, while such a positive association was not founded for the 2-back task. This suggested that the increased recruitment of this region at lower task demand (1-back) is as-

sociated with increased cost for the performing that. However, at higher task demand (2-back), there are no relationship between the utilization of neural resources and the performing task because the neural activation in the solvent-exposed subjects approached a ceiling for the 2-back task.

Conclusion

In conclusion, employing the N-back task with varying levels of load, we investigated activation patterns of cognitive load in individuals with chronic occupational exposure to solvent. As hypothesized, we found that solvent-exposed subjects exhibited significantly higher activation of the bilateral DLPFC, IPC, and cerebellum with increased cognitive demands during the N-back tasks. Furthermore, we also found a positive association between increased reaction time on the 1-back task compared to 0-back task and increased percentage BOLD signal changes in the left inferior parietal cortex, while such a positive association was not founded for the 2-back task.

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유기용제에 노출된 직업군에서 보여진 작업 기억에서의 인지부하에 따른 신경학적 변화

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유기용제는 현기증, 행동장애, 주의산만, 말초신경증과 같은 신경 독성을 일으키는 물질로 잘 알려져 있다. 그러나, 이러한 신경 독성물질인 유기 용제에 노출된 근로자들이 작업 기억 기능을 수행할 때 인지 부하에 어떻게 영향을 받는지에 관해서 많이 연구가 되어오지 않았다. 따라서, 본 연구에서는 기능적인 자기공명영상을 이용하여 만성적으로 유기용제에 노출된 근로자들이 인지 부하에 따른 작업 기억 기능을 수행할 때 보여지는 신경 변화의 관계를 살펴보았다. 29명의 유기용제에 노출된 근로자들을 대상으로 언어적 작업 기억 기능(1-back and 2-back)을 수행시켰으며 낮은 인지 부하와 높은 인지 부하의 작업 기억 기능을 수행할 때, 인지 부하의 차이에 따라 활성화 되는 뇌 영역의 차이를 구하였다. 1-back의 반응속도가 증가함에 따라 좌측 하위 두정 피질에서의 뇌 활성화가 점점 증가하는 관계를 보였는데, 이러한 증가되는 양상이 더 높은 인지 부하인 2-back에서는 보여지지 않았다. 이를 통해, 인지 부하가 많이 걸릴수록 활성화 되는 뇌 영역이 많아지며, 유기용제에 노출된 근로자들은 어느 정도 낮은 인지 부하가 걸렸을 때는 그만큼의 뇌 활성화가 증가되는데, 높은 인지 부하가 걸리게 되면 더 이상 뇌 활성화가 증가되지 않고 한계에 다다르는 것을 알 수 있었다.

중심단어: 유기용제노출, 신경독성, 기능적 자기공명영상, 작업기억