

# Correlation between Car-driving Performance and Regional Brain Activity after Oral Administration of a Sedative Antihistamine

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### Introduction

Histamine H<sub>1</sub> receptor antagonists (antihistamines) are widely used for treatment of allergic disorders, and are well-known for their central side effects such as drowsiness and impaired psychomotor performance<sup>1)</sup>. Car-driving is closely connected with our everyday life. There are so many reports about the effects of antihistamines on car-driving performance but its mechanism has not been demonstrated yet. Recently, some functional MRI (fMRI) studies have been published on regional brain activities during simulated car-driving<sup>2-4)</sup>. Previously, we reported the rCBF changes during simulated car-driving after oral administration of d-chlorpheniramine, a sedative antihistamine, using positron emission tomography (PET) with [<sup>15</sup>O]H<sub>2</sub>O<sup>5,6)</sup>. In this report, we demonstrate additional results of correlation analysis between car-driving performances and the regional brain activity, such as car-driving.

### Materials and Methods

#### *Subjects*

Fourteen healthy male volunteers, ranging 20-25 years old (mean +/- SD :22.5 +/- 1.8), participated in the present study. All subjects were evaluated as right-handed based on the Edinburgh inventory and Chapman test. This study protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine. Written informed consent was obtained from each subject and the study was performed in compliance with

the relevant laws and institutional guidelines<sup>5,6</sup>).

### *Study design*

The present study was conducted as a single-blind crossover study. The subject was given one of a d-chlorpheniramine 6 mg repetab or a placebo before PET examination. The PET investigation started approximately 2 hours after oral administration of d-chlorpheniramine 6 mg and so did it for placebo. PET scans were performed for the following three conditions such as 1) resting, 2) active driving, and 3) passive driving as reported previously<sup>5,6</sup>.

### *Driving simulation*

A commercially-available software (Gekisoh 99, Twilight Express Co., Tokyo, Japan) was used for simulated car-driving task. The subjects were positioned in a PET scanner, wearing a head mount display (HMD: Glasstron PLM-A35, SONY, Tokyo, Japan). Subjects were instructed to drive according to video instructions projected onto the HMD. Afterward, driving performance was evaluated for the following five assessment items: 1) time, 2) number of crashes, 3) number of over-steering, 4) number of stop due to crashes, and 5) subjective sleepiness<sup>5</sup>.

### *PET measurements and data analysis*

The brain perfusion images were obtained using a 3D-acquisition PET scanner (SET 2400W, Shimadzu Co. Ltd., Japan). These images obtained were realigned, normalized and smoothed by Statistical Parametric Mapping (SPM) software. And then, the correlation analysis was performed between the regional brain activity and driving performance indices as well as sleepiness index in order to find the regions with positive and negative correlations in placebo and d-chlorpheniramine conditions, respectively (Not corrected for multiple comparisons:  $p < 0.001$ ).

## **Results**

All 14 subjects completed the entire investigation. In driving performance evaluation, “over-steering” showed significant difference between the placebo and d-chlorpheniramine conditions ( $p < 0.05$ ), but the difference of other items were not significant. Especially, there was no difference between placebo and d-chlorpheniramine on subjective sleepiness<sup>5</sup>.

The regions with significant negative correlation to the number of over-steering in placebo condition was found in the somatic sensory association (Brodmann's area 7: BA7) and the cingulate cortices (BA23, 30, 31 and 37), whereas in d-chlorpheniramine condition, significant negative correlation was observed in the primary motor cortex (BA4), frontal eye field (BA8), the visual association cortex (BA18 and 19) and the cingulate cortex (BA23) (Fig. 1). And the regions with significant positive correlation with "subjective sleepiness" in placebo condition was found in the premotor (BA6), the somatic sensory association (BA7), the prefrontal (BA9), the primary and secondary visual cortex (BA17, 18 and 19) and the cingulate cortices (BA30), whereas in d-chlorpheniramine condition, significant positive correlation was observed in the premotor (BA6), the somatic sensory association (BA7), the includes frontal eye field (BA8), the visual association cortex (BA19) and the cingulate cortex (BA24).

## **Discussion**

The aim of the current study was to perform correlation analysis between car-driving performance and regional brain activity. When drivers operate the steering wheel, they might recognize the road alignments through their eyes and perform steering. Significant negative correlation was observed in a placebo condition between the cingulate gyrus activity and the number of over-steering. This finding may suggest the involvement of the cingulate gyrus in visuospatial cognition. The results in a d-chlorpheniramine condition demonstrated a less-significant correlation. This result suggest that suppression of the cingulate gyrus activity due to d-chlorpheniramine was associated with the performance impairment in over-steering. The posterior cingulate gyrus might be playing an important role in visuospatial cognition.

In summary, our study shows that the oral administration of d-chlorpheniramine may affect the function of the cingulate gyrus. But, its mechanism can't explain by only their results. Thus, we will need to investigate on their mechanism.

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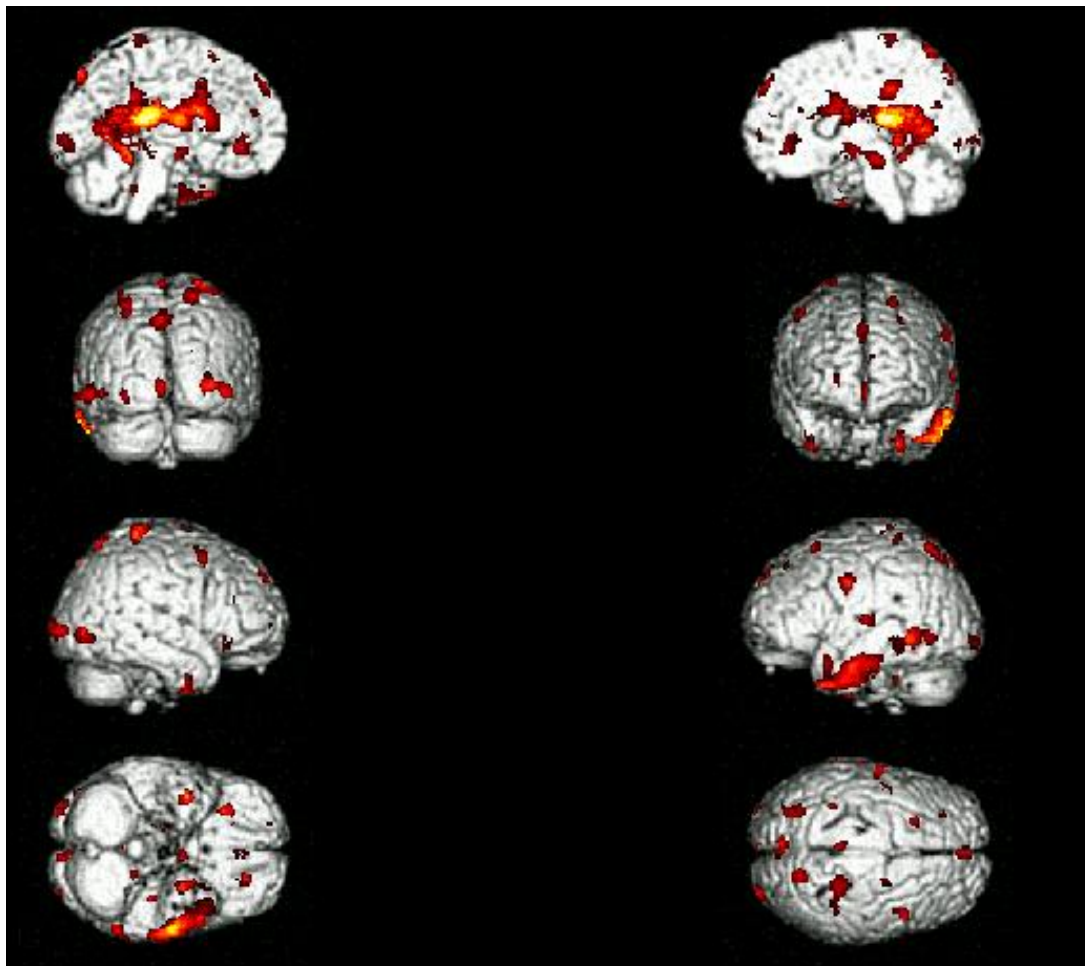


Figure 1. The regions with significant negative correlation with "over-steering" following placebo administration.