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HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2008; **23**: 139–150.
Published online 8 January 2008 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.909

Effects of a sedative antihistamine, D-chlorpheniramine, on regional cerebral perfusion and performance during simulated car driving†

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Objectives The sedative side effects of antihistamines have been recognized to be potentially dangerous in car driving, but the mechanism underlying these effects has not yet been elucidated to date. The aim of the present study is to examine regional cerebral blood flow (rCBF) responses during a simulated car-driving task following oral administration of D-chlorpheniramine using positron emission tomography (PET) and [^{15}O]H_2O, based on a single-blind cross-over study-design.

Methods Right-handed, healthy male volunteers ($n = 14$) drove a car in a simulated environment following oral administration of D-chlorpheniramine repetab 6 mg or placebo. Their rCBF was measured using PET with [^{15}O]H_2O in the following three conditions: (1) resting, (2) active driving, and (3) passive driving. All 'in-car' views during the simulated driving were videotaped and used for rating driving performance.

Results Performance evaluation revealed that the number of lane deviations significantly increased in the D-chlorpheniramine condition compared with the placebo condition ($p < 0.01$). Subjective sleepiness was not significantly different between the two drug conditions. The regions of diminished brain responses following D-chlorpheniramine treatment were detected in the parietal, temporal and visual cortices, and in the cerebellum. The regions of augmented rCBF responses were found in the orbitofrontal cortex and cerebellar vermis.

Conclusion These results suggest that D-chlorpheniramine tends to suppress visuo-spatial cognition and visuo-motor coordinating functions rather than attention and motor functions during car driving. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — antihistamine; impaired performance; cerebral blood flow; PET; car driving

INTRODUCTION

Car driving is one of our everyday tasks and is also a series of complex perceptual and psychomotor tasks that require the integration of various basic functions such as attention, visuo-spatial cognition, motor programming and control, and visuo-motor coordination (Theunissen *et al.*, 2004; Verster and Volkerts, 2004). Cognitive and psychomotor impairments following the administration of sedating drugs can lead to impairment of driving performance and increase a driver's risk of injury (Movig *et al.*, 2004; Seppala *et al.*, 1979). So far, a large number of studies have been conducted to determine the effects on driving behavior following administration of

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Received 15 May 2007
Accepted 26 October 2007

various psychoactive drugs, such as antidepressants (Ridout and Hindmarch, 2001; Ridout *et al.*, 2003a; Warrington, 1991), anxiolytics (Hindmarch *et al.*, 1977; van Laar *et al.*, 2001), analgesics (Sabatowski *et al.*, 2003; Vainio *et al.*, 1995), and antihistamines (Gengo and Gabos, 1987; Ridout *et al.*, 2003b; Tashiro *et al.*, 2005; Verster *et al.*, 2003; Weiler *et al.*, 2000) alone or in combination with alcohol (Koelega, 1995; Movig *et al.*, 2004; Ramaekers *et al.*, 2002; Seppala *et al.*, 1979; Weiler *et al.*, 2000). Antihistamines are widely used for treating various allergic disorders such as allergic rhinitis and dermatitis, and sedative antihistamines in particular significantly impair driving performance (Aso and Sakai, 1988; Ramaekers *et al.*, 1992; Ridout *et al.*, 2003b; Tashiro *et al.*, 2005; Theunissen *et al.*, 2004; Verster and Volkerts, 2004; Verster *et al.*, 2003; Weiler *et al.*, 2000).

Sedative antihistamines such as D-chlorpheniramine and diphenhydramine can readily cross the blood-brain barrier (BBB) and block histamine H_1 receptors (H_1Rs) in the histaminergic neuronal system of the brain, resulting in sleepiness, drowsiness, fatigue, and psychomotor disturbances that might result in car injury (Ridout *et al.*, 2003b; Theunissen *et al.*, 2004; Verster and Volkerts, 2004; Yanai and Tashiro, 2007). Neuro-receptor positron emission tomography (PET) studies using [^{11}C]doxepin have demonstrated that these sedative antihistamines occupy more than 50% of brain H_1Rs, which may considerably suppress the psychomotor functions of drivers (Okamura *et al.*, 2000; Tagawa *et al.*, 2001; 2006; Yanai and Tashiro, 2007; Yanai *et al.*, 1995, 1999). A simulated driving performance study by Weiler *et al.* (2000) demonstrated that sedative antihistamines had a greater impact on driving ability than alcohol. Ironically, these potentially dangerous sedative antihistamines are more easily available as over-the-counter drugs than newer less-sedating antihistamines (Tashiro *et al.*, 2005). These facts emphasize the importance of research activities to reveal the neural mechanisms of drug-induced sedation among drivers. In order to promote this line of research, it is of great help to know the functional neuroanatomy of car driving as demonstrated by a recent imaging technique (Calhoun *et al.*, 2002; Horikawa *et al.*, 2005; Jeong *et al.*, 2006; Uchiyama *et al.*, 2003; Walter *et al.*, 2001).

Car driving is such a complex task that various regions of the brain may be actively involved. Studies on imaging the neural correlates of car driving have just started compared with performance studies. Most recent imaging studies on car driving have employed a simulated driving task using functional magnetic resonance imaging (MRI) [fMRI] (Calhoun *et al.*, 2002; Uchiyama *et al.*, 2003; Walter *et al.*, 2001) and PET (Horikawa *et al.*, 2005). Walter *et al.* first examined regional cerebral blood flow (rCBF) responses during simulated car driving. They succeeded in visualizing the brain regions associated with vision, sensorimotor coordination, motor function as well as the cerebellum (Walter *et al.*, 2001). To the best of the authors' knowledge, however, neuroimaging studies using a car-driving task have not yet been carried out to elucidate the mechanism of antihistamine-induced impairment of driving performance, with the exception of a few studies on simple cognitive tasks (Mochizuki *et al.*, 2002; Okamura *et al.*, 2000).

The main purpose of the present study was to examine rCBF responses (ΔrCBF) in healthy volunteers during simulated car driving following the oral administration of D-chlorpheniramine, a typical sedative antihistamine, using PET with [^{15}O]H_2O.

SUBJECTS AND METHODS

Fourteen healthy Japanese male volunteers ranging from 20 to 25 years old (mean age $\pm$ SD: 21.9 $\pm$ 1.8 years old) were recruited to the present study. None of the participating subjects were under any medication nor had any previous history of allergic and neuropsychiatric disorders including sleep disturbances. There were no heavy smokers or habitual coffee drinkers among the subjects. The present protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, and written informed consent was obtained from each subject after thorough explanation of the whole procedure and possible risk of the experiment. Ingestion of caffeine, alcohol-containing drinks, nicotine, grapefruit juice, and any other supplement drinks was not permitted from the night before the testing day until the end of the study. All the subjects except for one enrolled in the present study have a valid driver's license and the mean duration of their driving history was 17.2 $\pm$ 13.0 months. All the subjects were evaluated as right-handed based on the results of Edinburgh inventory (Oldfield, 1971), Chapman test (Chapman and Chapman, 1987), and H. N. Handedness Inventory (Hatta and Kawakami, 1995).

EXPERIMENTAL DESIGN

The purpose of the present study is to examine the rCBF effects of D-chlorpheniramine, whose sedative effects have been repeatedly demonstrated by several groups (Hindmarch and Bhatti, 1987; Mochizuki *et al.*, 2002; Nicholson *et al.*, 1991; Starbuck *et al.*,

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2000; Tagawa *et al.*, 2001). The present study was conducted as a single-blind cross-over study. Each subject was given D-chlorpheniramine repetab (6 mg) or a lactobacteria tablet used as placebo in each study. The D-chlorpheniramine repetab was successfully used in our previous activation studies (Mochizuki *et al.*, 2002; Tagawa *et al.*, 2001) as well as the lactobacteria preparation, giving no statistical difference between pre- and post-administration in previous cognitive studies (Mochizuki *et al.*, 2002; Tagawa *et al.*, 2001, 2002; Tashiro *et al.*, 2002, 2004). The same subjects were studied for each drug at an interval of at least 6 days as a wash-out period. The order of drugs given to each subject was randomly assigned and balanced.

According to a previous report, the peak plasma drug concentration of orally administered D-chlorpheniramine is achieved 2 h post-administration (Peets *et al.*, 1972). Thus, the PET investigation was started approximately 2 h after the oral administration of the D-chlorpheniramine repetab, which was given to maintain its high plasma concentration for 2–3 h similarly as in a previous PET study (Tagawa *et al.*, 2002). In the present study, PET scan was started approximately 2 h post-administration of oral tablets (placebo or antihistamine), and a set of 6 PET scans was taken for approximately 1 h per condition. The whole scanning procedure was completed within 3 h post-administration.

The subjects were placed in the dorsal position on the PET coach with their knee on the knee rest, and they were requested to wear a head mount display (HMD: Glasstron PLM-A35, SONY, Tokyo, Japan) to enable them to watch the projected 'in-car' views of the outer world during driving (Figure 1). The steering wheel and acceleration pedal were attached at a suitable position so that the subjects were able to operate them easily and comfortably. This system lacked a brake pedal and the subjects were able to decrease driving speed by setting their foot away from the acceleration pedal. The intravenous infusion line for $[^{15}O]H_2O$ injection was inserted into a subject's right antecubital vein so as not to interfere with the handling of the steering wheel. For a simulated driving task, a commercial computer software was used (Gekisoh99, Twilight Express Co., Ltd, Tokyo, Japan) that operated on a Windows 95/98 operating system. A 'time trial mode' was employed in the present study to measure the total duration of driving from the 'start' to the 'goal' points, where there were three lanes in each side of the road with oncoming cars on the other side of the road but with no traffic signals and pedestrians. The subjects were requested to drive smoothly as in normal car driving, but also as fast as possible from the start to the goal point, avoiding collision and deadlocks. The in-car views during the simulated driving were all videotaped and were later used for rating each volunteer's driving performance. Further

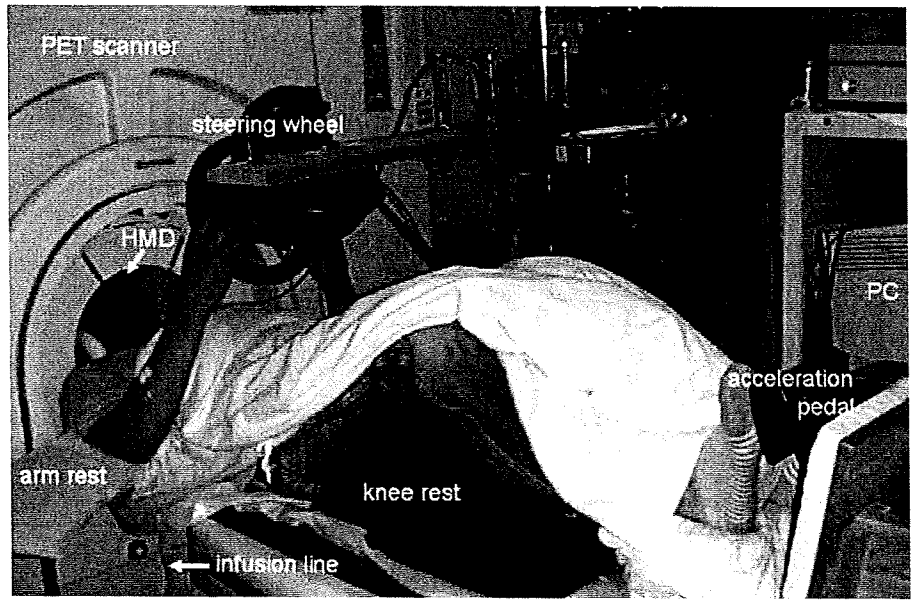

Figure 1. A picture of PET examination during a simulated car-driving task. Each subject wears a HMD monitor for driving. The driving simulator system was attached to a steering wheel and an acceleration pedal. The subject is injected with saline water containing $[^{15}O]H_2O$ via an infusion line inserted into the right antecubital vein

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DOI: 10.1002/hup

details regarding this program are already mentioned in our previous report (Horikawa *et al.*, 2005).

PET rCBF images were acquired under the following three conditions: (1) resting condition with the eyes closed, (2) active driving condition where the subjects were requested to drive on their own, and (3) passive driving condition where the subjects were requested to watch the changing in-car view that had been videotaped previously, with their hands and feet fixed on the steering wheel and acceleration pedal, respectively. Two sets of measurements were conducted for each drug condition, where the orders of driving conditions were the resting-active-passive order in the first session and the active-passive-resting order in the second session (Figure 2) in order to eliminate an order effect. However, the order of active and passive driving conditions was fixed since the recorded landscape during active driving was used for the presentation of the following passive driving measurement. A single session took approximately 200 s, where PET scanning commenced shortly after the radioactivity from the head of each subject exceeded 40 counts per second (cps) as measured using the PET system (nearly 30 s after the initiation of $[^{15}O]H_2O$) injection and lasted for 70 s. For the results, driving task continued for 40–90 s following the cessation of PET scanning. In general, all PET examinations were conducted during the daytime ranging within the period between 9:30 and 15:00.

Performance of the subjects was evaluated in terms of the following four criteria: (a) total duration (second) of driving from the start to the goal point, (b) number of collisions to oncoming cars or guard-rails, (c) number of lane deviations due to crossing a center line, and (d) number of deadlocks where driving speed becomes lower than 10 km/h. The performance variables in the present study were measured by two raters. These measurements were assessed by a rater and the results of the rating were cross-checked by another rater, producing the same results.

Additionally, subjective sleepiness was also evaluated before drug administration (placebo or D-chlorpheniramine) and just after each PET scanning, using the Stanford Sleepiness Scale (SSS) (Hoddes *et al.*, 1973) (Figure 2).

PET MEASUREMENTS

The rCBF images were obtained at the whole brain level using a PET scanner (SET 2400 W, Shimadzu Co., Ltd, Japan), with an average spatial resolution of 4.5 mm full-width at half-maximum and with a sensitivity of a 20 cm cylindrical phantom of 48.6 kcps/KBq ml in the three-dimensional (3D) mode. PET acquisition was performed for 70 s. Each subject was injected with $[^{15}O]H_2O$ of 157.8 ± 25.6 MBq (4.26 ± 0.69 mCi) on average through the antecubital vein for each scan. PET scans were started shortly after the

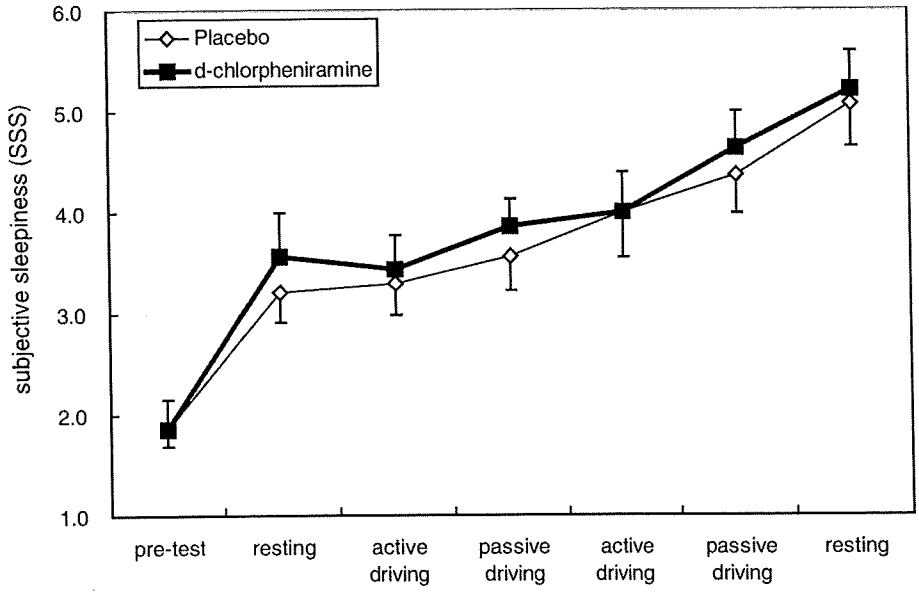

Figure 2. Subjective sleepiness measured using the SSS before oral administration of placebo or D-chlorpheniramine (pre-test) and just after each PET scanning (resting, active driving, and passive driving). There was no significant difference between the placebo and D-chlorpheniramine conditions throughout the whole examination. Error bars indicate the standard error of mean (SEM)

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DOI: 10.1002/hup

radioactivity from the head region could be detected and lasted for 70 s.

DATA ANALYSIS

Driving performance data

After the completion of all PET investigations, driving performance was rated for each volunteer. Statistical analysis of the variables for performance and sleepiness was performed to detect significant differences between placebo and D-chlorpheniramine treatments using the non-parametric Wilcoxon *rank sum* test, where $p < 0.05$ was set to be significant, because of the non-normal distribution of the driving performance data.

Brain image analysis

The rCBF images were processed and analyzed using a Statistical Parametric Mapping (SPM) software package (SPM99; Wellcome Department of Cognitive Neurology, London, U.K.) (Friston *et al.*, 1995). Before starting the analysis, intrasubject head movements were corrected (realignment), and then all images were stereotaxially normalized using linear and nonlinear transformations into a stereotaxic coordinate system (normalization to the standard brain space) (Talairach and Tournoux, 1988). The normalized images were then smoothed using a $12 \times 12 \times 12\,mm^3$ Gaussian filter (smoothing). The rCBF values were expressed as ml/dl/min, adjusted using proportional scaling and scaled to a mean of 50 ml/dl/min. A significant change in rCBF was evaluated according to the general linear model at each voxel. To test the hypotheses on specific rCBF changes, the estimates were compared using linear contrasts. The resulting set of voxel values for each contrast constitutes a statistical parametric map of the *t*-statistics.

To identify brain regions that are related to the simulated driving stimulus, rCBF images during active driving were compared with those during the resting and passive driving conditions. The *t*-value of each voxel was transformed into normally distributed Z-statistics. For each comparison, each voxel difference with a Z-value higher than 2.99, corresponding to $p < 0.001$ (uncorrected), was interpreted as significant. Additionally, each cluster including significant voxel differences and also having at least 10 voxels was interpreted as significant regional rCBF changes.

We further compared rCBF changes during active driving compared to the resting state between the D-chlorpheniramine and placebo conditions. We determined the localization of the peak activation related to the active driving condition as compared with the resting and passive driving conditions. Mean voxel values were calculated among the voxels including the peak and also those exceeding a threshold of $Z > 2.99$. The mean of these voxel values reflected rCBF since all voxel values in the rCBF images were scaled to a mean of 50 ml/dl/min. The rCBF changes (ΔrCBF) were compared between the D-chlorpheniramine and placebo conditions using paired *t*-test. A probability of less than 0.05 was considered to be statistically significant.

RESULTS

Driving performance

All 14 subjects completed the entire investigation. Performance evaluation revealed that the number of lane deviations significantly increased in the D-chlorpheniramine condition compared with the placebo condition (mean value $\pm$ SEM: 2.57 ± 0.60 vs. 6.36 ± 1.80, respectively: $p < 0.01$). All other measurements (duration of driving time and numbers of collisions and deadlocks) demonstrated

Table 1. Driving performance in D-chlorpheniramine and placebo conditions

				Percentile		
Measurement items	Drug	Mean	SEM	25	50	75
Driving duration (s)	Placebo	124.2	2.90	117.1	124.8	133.1
	D-chlorpheniramine	131.1	5.30	110.8	128.0	150.4
Crashes (times)	Placebo	3.68	0.40	2.75	3.75	4.88
	D-chlorpheniramine	5.54	1.10	1.88	4.00	6.25
Deadlocks (times)	Placebo	1.25	0.20	0.50	1.00	1.50
	D-chlorpheniramine	2.36	0.60	0.38	1.00	4.25
Excessive lane shifts[a] (times)	Placebo	2.57	0.60	0.38	1.50	4.63
	D-chlorpheniramine	6.36	1.80	1.38	2.50	10.50

[a] $p < 0.01$.

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DOI: 10.1002/hup

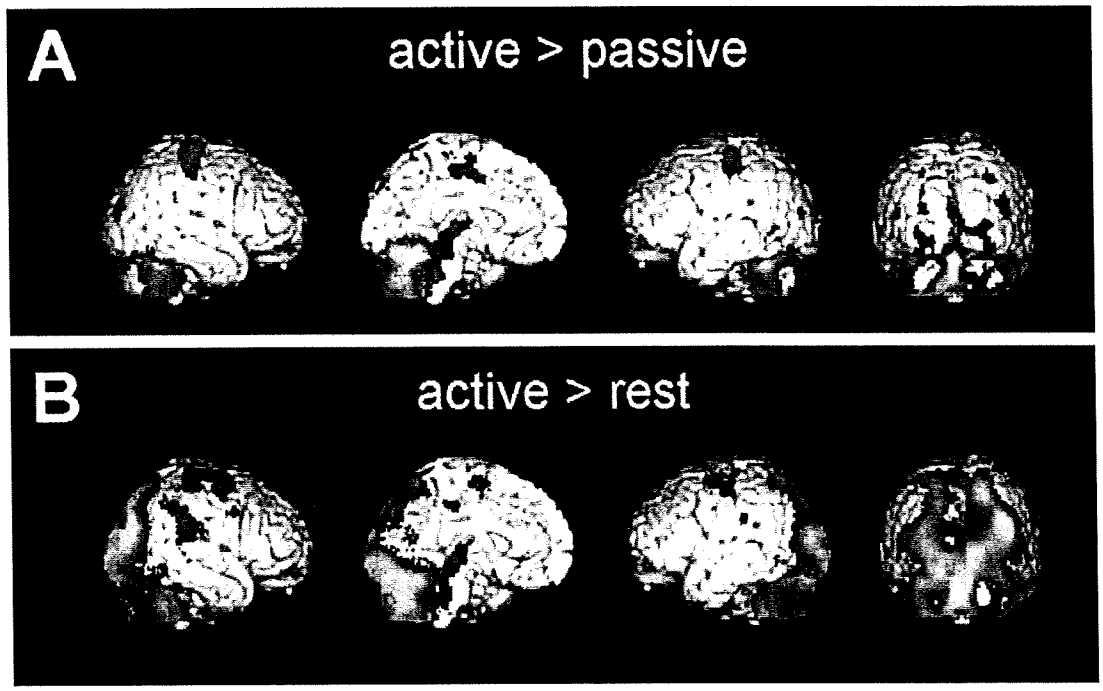

Figure 3. Brain regions significantly activated during the 'active' driving condition compared with the 'passive' driving condition (A). Brain regions significantly activated during the 'active' driving condition compared with the 'resting' condition (B). Statistically significant regions are superimposed onto standard MRI rendered images (statistical threshold: $p < 0.001$ uncorrected; minimum number of voxels, 10)

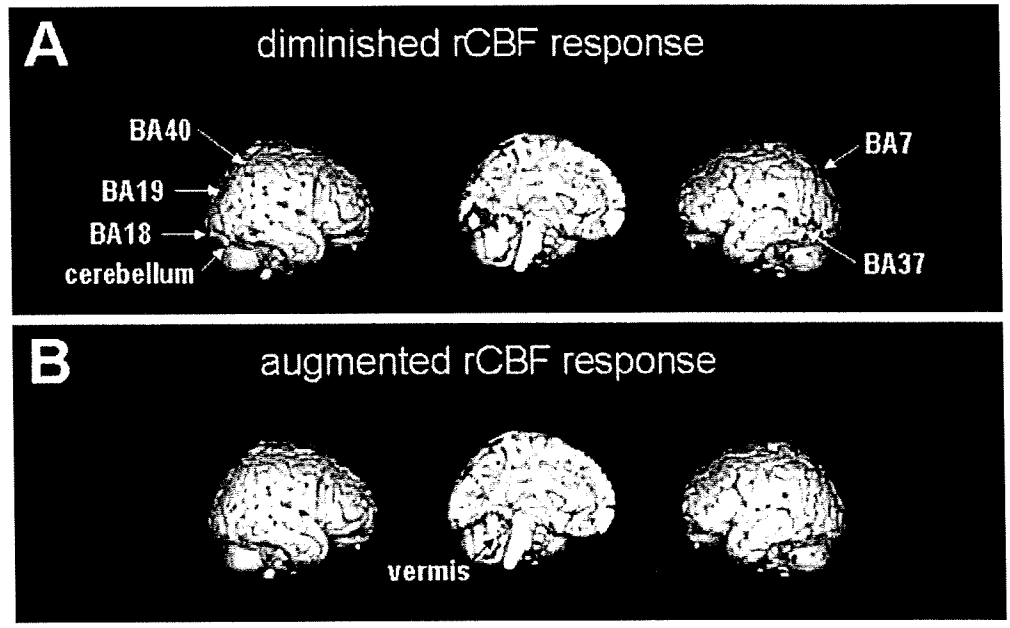

Figure 4. Brain images with augmented rCBF responses (A) and diminished rCBF response (B) following D-chlorpheniramine treatment. Statistically significant regions are superimposed onto standard MRI rendered images (statistical threshold: $p < 0.001$ uncorrected; minimum number of voxels; 10). Abbreviation: BA = Brodmann's area

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Table 2. Regions with diminished and augmented CBF responses in D-chlorpheniramine condition

Area		BA	Coordinate (x,y,z)	Z-score	t-value	Cluster size (voxels)
Diminished CBF response						
Parietal lobe						
Posterior parietal	Lt	7	−24, −80, 48	3.38	3.45	63
Supramarginal gyrus	Rt	40	58, −54, 48	3.08	3.13	22
Temporal lobe						
Inferior temporal	Lt	37	−64, −56, −4	3.14	3.20	18
Parahippocampal gyrus	Rt	35/36	24, −32, −8	3.09	3.15	62
Occipital lobe						
Visual association	Lt	18	−26, −74, −6	3.69	3.79	206
Visual association	Lt	18	−2, −94, 20	3.47	3.55	97
Visual association	Rt	18	18, −90, −12	3.37	3.45	101
Visual association	Rt	19	42, −82, 34	3.62	3.71	151
Cerebellar hemisphere	Rt		38, −84, −20	4.08	4.21	399
Augmented CBF response						
Frontal lobe						
Orbitofrontal	Rt	11	28, 36, −28	3.40	3.47	23
Cerebellar vermis			−10, −46, −22	3.23	3.30	45

D-chlorpheniramine's effects on impaired driving performance but were not significant (Table 1). Subjective sleepiness score was not significantly different between the placebo and D-chlorpheniramine conditions. Sleepiness score increased similarly in both drug conditions (Figure 2), which may have been induced by the present experiment setting in a dark room. Each performance score and the sleepiness scores did not correlate significantly.

Regional brain activity

Regions with increased rCBF during the active driving condition compared with the passive driving condition were detected in the primary sensorimotor [Brodmann's area (BA): BA4], premotor (BA6), cingulate (BA23/31), posterior parietal (BA7), temporal (BA37), and occipital (BA17–19) cortices and in the cerebellar hemisphere, midbrain, globus pallidus, and pulvinar of the thalamus (Figure 3). The regions with increased rCBF during the active driving condition compared with the resting condition covered nearly the same regions mentioned above, but in much wider areas additionally including the right orbitofrontal cortex (BA11) (Figure 3).

Next, the resting CBF images were compared between the D-chlorpheniramine and placebo conditions in order to examine the central effect of D-chlorpheniramine in the resting state. rCBF in the right parietal (BA7 and 40), bilateral temporal (BA21/22) and left occipital cortices (BA17 and 19) as well as in the caudate nucleus and cerebellum following D-chlorpheniramine treatment was higher than that in the same areas following placebo administration. Lower rCBF following D-chlorpheniramine treatment was observed in the bilateral frontal (BA6, 8, 10), right parietal (BA39), bilateral temporal (BA21 and 22), and bilateral insular cortices.

Finally, the regions with altered ΔrCBF ([active driving] − [resting]) compared with the resting condition were compared between the D-chlorpheniramine and placebo conditions. The regions with decreased ΔrCBF following D-chlorpheniramine treatment were detected in the bilateral parietal (BA7/40), temporal (BA36/37), and occipital cortices (BA17 and 19) (Table 2, Figures 4 and 5A–C). The regions with augmented ΔrCBF following D-chlorpheniramine administration were found in the orbitofrontal cortex and cerebellar vermis (Table 2, Figures 4 and 5D). No areas of statistically significant difference were detected by comparison of altered ΔrCBF ([active driving] − [passive driving]) compared with the passive driving condition.

DISCUSSION

Antihistamines are potentially dangerous agents to many drivers and, so far, a large number of studies have been conducted to determine their effects on driving behavior (Aso and Sakai, 1988; Ramaekers *et al.*, 1992; Ridout *et al.*, 2003b; Tashiro *et al.*, 2005; Theunissen *et al.*, 2004; Verster and Volkerts, 2004; Verster *et al.*, 2003; Weiler *et al.*, 2000). Their main therapeutic target in various allergic disorders is H_1Rs in the peripheral blood; however, some components of antihistamines can easily cross the BBB

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and block the H_1Rs of neurons in the brain. The histaminergic neuronal system plays important roles in maintaining arousal and attention, sleep–wake cycle, and learning and memory, and the blockade of H_1Rs may result in sedation characterized by symptoms such as sleepiness, drowsiness, fatigue, and psychomotor disturbances (Brown *et al.*, 2001; Yanai and Tashiro, 2007). In particular, sedative antihistamines such as D-chlorpheniramine and diphenhydramine significantly impair driving performance (Hindmarch, 1976; Qidwai *et al.*, 2002; RedBook, 1998; Ridout *et al.*, 2003b; Verster and Volkerts, 2004; Weiler *et al.*, 2000). The degrees of BBB permeability by antihistamines have been measured using PET and [^{11}C]doxepin in healthy volunteers termed as H_1R occupancy (Holgate *et al.*, 2003; Okamura *et al.*, 2000; Tagawa *et al.*, 2001; Tashiro *et al.*, 2004, 2006; Yanai and Tashiro, 2007; 1999). One of our previous studies demonstrated that a single oral administration of D-chlorpheniramine (2 mg) achieved approximately 49% H_1R occupancy and repetab (6 mg) achieved 53% (Tagawa *et al.*, 2001). Such high H_1R occupancy may considerably suppress psychomotor functions, sometimes manifesting a greater impact on driving ability than alcohol (Weiler *et al.*, 2000). Ironically, sedative antihistamines are more easily available over the counter than newer less-sedating antihistamines, and are still considered among the top-selling OTC drugs for allergic rhinitis (Hindmarch, 1976; Qidwai *et al.*, 2002; RedBook, 1998; Ridout *et al.*, 2003b; Verster and Volkerts, 2004; Weiler *et al.*, 2000). These facts may encourage researchers to exert more effort to elucidate the effects of sedative antihistamines on the neural correlates of car driving.

So far, neural correlates of car driving have been demonstrated using fMRI and PET and the reproducibility of the findings was demonstrated in the present study as well by comparing with the results of other studies (Calhoun *et al.*, 2002; Horikawa *et al.*, 2005; Uchiyama *et al.*, 2003; Walter *et al.*, 2001). Walter *et al.* (2001), who first applied fMRI to the measurement of regional brain activity during simulated driving, demonstrated brain activation in the visual and somatosensory cortices and cerebellum, by comparing active and passive driving conditions created in a simulated environment. Calhoun *et al.* (2002) confirmed the reproducibility of a car-driving study and further divided the car-driving task into several basic components such as visual perception, visual monitoring, vigilance, motor control, motor coordination, and error monitoring and inhibition, using independent component analysis. Uchiyama *et al.* (2003) obtained results similar to those reported by Walter and Calhoun, and additionally demonstrated a correlation between the rCBF response in the anterior cingulate and the driving performance in a driving task to maintain a safe distance from a leading car. In principle, both fMRI and PET with [^{15}O]H_2O measure hemodynamic responses and should produce basically the same results, having been confirmed by applying an identical protocol to identical subjects. Horikawa *et al.* (2005) confirmed the reproducibility of a simulation study scanned using PET and [^{15}O]H_2O. Later, the reliability of using a simulated driving task was partly confirmed by Jeong *et al.* (2006), who applied an actual car-driving task on a road for a PET study using [^{18}F]fluorodeoxyglucose that enabled PET scanning after completion of driving tasks. Their results were nearly the same as those of previous studies using fMRI and simulated driving tasks, demonstrating significant brain activation during active driving in the primary and secondary visual cortices, primary sensorimotor areas, premotor area, parietal association area, cingulate gyrus, thalamus, as well as in the cerebellum. Passive driving showed an almost similar activation pattern, lacking activations in the premotor area, and cingulate and parahippocampal gyri. Thus, the reliability of using a simulated driving system for elucidating neural correlates of car driving was partly confirmed, and it is possible that these simulation studies represent the neural correlates of car driving at least regarding cognitive aspects.

For the evaluation of impaired driving performance due to sedative antihistamines, various measures have been applied such as brake reaction time (Ramaekers and O'Hanlon, 1994; Ramaekers *et al.*, 1992; Verster *et al.*, 2003; Weiler *et al.*, 2000) and vehicle maintenance capability (Aso and Sakai, 1988; Ramaekers and O'Hanlon, 1994; Verster *et al.*, 2003; Weiler *et al.*, 2000) using either an actual or simulated car-driving task. The reaction time is a rather simple task and is mostly associated with basic psychomotor functions of attention, visual cognition, and motor output, mediated mainly by the anterior cingulate gyrus, and occipital and motor cortices, respectively. Vehicle maintenance capability seems to be more complex and can be divided into subcategories such as 'coherence', the ability to maintain a constant distance from a leading car that varied its speed randomly, and 'steering stability', the ability to maintain a constant position in a driving lane (Aso and Sakai, 1988). These tasks may require additional neural functions such as visuo-spatial cognition and visuo-motor coordination, which may require involvement of the temporo-parietal association cortex in addition to the basic

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components of a car-driving task (cingulate, visual, and motor cortices). A previous behavioral study reported that D-chlorpheniramine (6 mg) impaired steering stability (over-steering), where the steering angle was unnecessarily large (Aso and Sakai, 1988). A highway driving test revealed a significant increase in the standard deviation of lateral position (SDLP) following D-chlorpheniramine treatment. Subjective alertness score was also significantly lower following D-chlorpheniramine treatment than that following placebo treatment (Theunissen *et al.*, 2004). According to another study by Weiler *et al.* (2000), steering stability was impaired by both alcohol and diphenhydramine, whereas coherence ability was impaired following only the administration of diphenhydramine. In the present study, impairment of steering stability (number of lane deviations) was demonstrated following D-chlorpheniramine treatment.

As for the non-significant difference in subjective sleepiness scores between the placebo and D-chlorpheniramine conditions, it is important to mention that the PET experiment room was dimly lit during the whole scanning procedure, where spontaneous sleepiness was probably induced. This condition would be relevant to the result showing that the subjective sleepiness scores did not show a significant difference. Such variability would also be attributable to the level of task difficulty. It is suggested that the level of task difficulty in the present study was not very high. However, the effects of D-chlorpheniramine observed in the present study were less pronounced partly because D-chlorpheniramine was given as a sustained release formulation, or repetab, as used in a previous study by Theunissen *et al.* (2004). In addition, this result suggests that subjective sleepiness is not always a reliable measure of sedation.

A comparison of the ΔrCBF between the D-chlorpheniramine and placebo conditions revealed regions with significantly 'diminished' and 'augmented' rCBF responses following D-chlorpheniramine treatment (Figure 4). The regions of diminished rCBF responses were observed in the posterior parietal (BA7 and 40), temporal (BA35 and 37) and occipital regions (BA18 and 19) as well as in the cerebellar hemisphere, which can be linked to functional suppression due to D-chlorpheniramine. Thus, the present results suggest that D-chlorpheniramine suppresses neural activities associated with visuo-spatial cognition and visuo-motor coordination. In general, visual information projected onto the occipital cortex is transferred to the posterior part of the parietal cortex via the dorsal pathway for higher visual processing of motion and visuo-spatial information (Jueptner and Weiller, 1998). Based on these findings, the suppression of rCBF responses in the visual and temporo-parietal association areas following D-chlorpheniramine treatment seems to also be in accordance with the present performance results. In addition, the suppression of the occipital cortex and cerebellum also seems to be reasonable since the cerebellum plays an important role in optimizing motor output based on visual inputs. It is hard to explain the findings in the temporal cortex (BA21/22) that demonstrated both increased and decreased rCBF following D-chlorpheniramine treatment in comparison to that following placebo treatment. Probably, they were caused by a slight difference in the phonetic environment.

To the best of the authors' knowledge, however, there is as yet no imaging study that has elucidated the effects of sedative drugs on the neural correlates of car driving except for a few studies from Calhoun *et al.* (2004, 2005) that applied fMRI to evaluate the brain activity of alcohol-intoxicated drivers. Interestingly, they reported that marked CNS effects due to alcohol were observed only in the orbitofrontal and primary sensorimotor regions but not in the cerebellum, and visual and temporo-parietal regions that seemed to be essential for car driving (Calhoun *et al.*, 2004, 2005). Based on the findings that alcohol impaired steering stability but not coherence ability, it is suggested that alcohol tends to affect motor function more strongly than sedative antihistamines do and that coherence ability tends to be more easily affected by impairment of motor functions. It seems that regional CNS effects during driving are variable and drug- and dose-dependent, stressing the importance of clinical and pharmacological research studies.

The regions with significantly augmented rCBF responses were observed in the orbitofrontal cortex and cerebellar vermis. The cerebellar vermis and orbitofrontal regions seem to be activated possibly as part of the compensatory mechanism to maintain driving performance; however, the specific underlying mechanism remains to be investigated. In addition, subjective sleepiness score was not significantly different between the placebo and D-chlorpheniramine conditions in the present study, suggesting that subjective sleepiness is not necessarily a reliable index of sedation, as demonstrated by other performance studies.

In conclusion, we detected diminished and augmented regional brain responses especially in the occipital and parietal cortices and cerebellar regions following D-chlorpheniramine treatment. These findings suggest that D-chlorpheniramine may suppress

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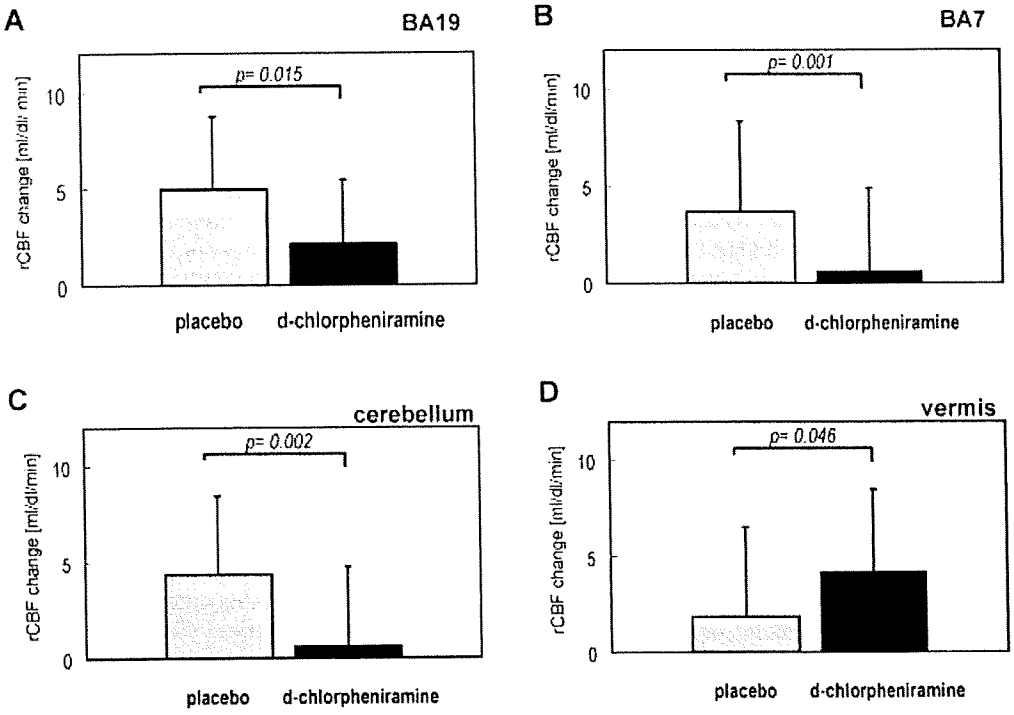

Figure 5. Comparisons of augmented rCBF responses in BA19 (A), BA7 (B) and the cerebellum (C) as well as diminished rCBF response in the cerebellar vermis (D) following D-chlorpheniramine treatment

brain functions particularly those associated with visuo-spatial cognition and visuo-motor coordination, which are essential in car driving. Non-invasive functional neuroimaging is potentially useful not only for elucidating the neural correlates of car driving but also for clarifying the brain mechanism underlying drug-induced impairments of driving performance.

Since the present study is the first attempt to combine simulated driving task and antihistamines, discussion on the limitations of the present study would be useful for replication. The present driving test was relatively short (approximately 150 s) and therefore it is possible that attention processes were not markedly influenced by D-chlorpheniramine as these processes were not affected using this protocol. Probably, the test length could account for the results showing no significant differences in the scores of driving performances and subjective sleepiness. In addition, the order of active and passive driving conditions was fixed partly because of the protocol used in the present study, where the videotaped in-car landscape was used for passive driving. The order effect could be further eliminated if the order of the active and passive driving conditions were balanced, although the present study has already given reasonable results. Since the repetab used in the present study may have slow releasing effects, the sedative effects were less outstanding than those of the immediate release formulation.

ACKNOWLEDGEMENTS

This work was in part supported by Grants-in-Aid for Scientific Research (Nos. 17390156 for K. Y. and 16790308 for M. T.) from the Japan Society of Promotion of Science (JSPS) and the Ministry of Education, Culture, Sports, Science and Technology in Japan, as well as by a grant from the Japan Society of Technology (JST) on research and education in 'molecular imaging'. The authors thank the volunteers for participating in the PET study and Ms Kazuko Takeda for attending to the needs of the volunteers.

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BRAIN RESEARCH 1172 (2007) 82–92

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Research Report

Brain activity associated with dual-task management differs depending on the combinations of response modalities

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ARTICLE INFO

Article history:
Accepted 24 July 2007
Available online 7 August 2007

Keywords:
Dual-task management
Combinations of response modalities
Premotor cortex
Parietal cortex

ABSTRACT

Several functional imaging studies have demonstrated the importance of fronto-parietal network in dual-task management. However, neural correlates underlying the difference in intensity of dual-task interference between the same and different response modalities remain unknown. Therefore, we investigated the relationship between brain activity associated with dual-task management and the combinations of response modalities. We used the dual-task requiring bilateral finger responses (DT-same condition) and that requiring finger and oral responses (DT-different condition) to visual and auditory stimuli. The right premotor cortex, precuneus and right posterior parietal cortex were significantly activated in the DT-same condition. The neural activities in the right premotor cortex significantly correlated to the delayed responses in the DT-same condition relative to the single-task conditions, indicating that the right premotor cortex is partly associated with dual-task management (i.e., the regulation of information flow). In addition, neural activity in this brain region was significantly higher in the DT-same condition than in the DT-different condition, suggesting that the difference in intensity between the same and different response modalities is partly associated with difference in the load on the premotor cortex between the DT-same and DT-different conditions. The significant activation of the parietal cortex also differed between the DT-same and DT-different conditions. These results demonstrate that brain activity associated with dual-task management differs depending on the combination of response modalities and that such a difference in brain activity, particularly in the right premotor cortex, might be partly associated with the difference in intensity of dual-task interference between the DT-same and DT-different conditions.

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doi:10.1016/j.brainres.2007.07.046

1. Introduction

Many researchers have been interested in how the human brain processes two things simultaneously (dual task) (Telford, 1931; Smith, 1967; Pashler, 1994; Sigman and Dehaene, 2005). In a dual-task condition, the response to each component task is slower than that in a single-task condition. In particular, the response to the second stimulus is often delayed when stimulus onset asynchrony (SOA) is reduced. Such delayed responses are explained by assuming of dual-task interference or the psychological refractory period (PRP) (e.g., Telford, 1931; Welford, 1952; Pashler, 1994). It is suggested that delayed responses in a dual-task condition are associated with the management of two concurrent tasks in the brain such as a coordination of information flow and a divided attention to two input modalities in preparation for dual-task execution (Baddeley, 1986; Pashler, 1994; De Jong and Sweet, 1994; De Jong, 1995; Tombu and Joliceur, 2003, 2005). The most accepted theory of dual-task interference is the bottleneck model. In this model, processing for response selection in one task is interrupted as long as that in the other task is carried out in the central stage (Pashler, 1994). Recently, functional neuroimaging techniques have been applied to clarify the neural mechanism associated with dual-task interference. Several researchers reported that the activities in the frontal and parietal cortices in dual-task conditions increase as compared to those in single-task conditions (D'Esposito et al., 1995; Herath et al., 2001; Szameitat et al., 2002; Erickson et al., 2005). It was also reported that neural activities in these brain regions in a dual-task condition were significantly higher than the summed neural activities in single-task conditions, indicating that some additional processing for dual-task management occurred in the frontal and parietal cortices (Schubert and Szameitat, 2003). Szameitat et al. (2002, 2006) suggested that the prefrontal and parietal cortices were associated with a coordination of information flow. Erickson et al. (2005) found that the right prefrontal cortex were associated with the preparatory processes such as dividing attention to two input modalities. Marois et al. (2006) observed that neural activities in the frontal and parietal cortices were sensitive to manipulation of dual-task costs. These previous neuroimaging studies suggested that the fronto-parietal network plays an important role in dual-task management. In these previous studies, the combinations of response modalities were common (finger–finger responses) (e.g., Herath et al., 2001; Szameitat et al., 2002; Erickson et al., 2005). However, dual-task interference occurs when the combination of response modalities is different (e.g., Pashler, 1990; Lien et al., 2005). Therefore, it remained unclear whether a common brain network managed dual tasks regardless of the combination of response modalities. In addition, the effect of response modalities on dual-task interference has long been discussed in psychological studies, because dual-task interference can be eliminated or markedly reduced when two tasks use very different responses (e.g., finger–oral responses). To explore this phenomenon, the multiprocessor model is proposed (e.g., Allport et al., 1972; Allport, 1979; McLeod, 1977). In this model, dual-task interference does not occur when responses differ, because independent cognitive systems are involved in the performance of two tasks. However, precise investigations by several researchers have showed that PRP effects occur when the combinations of response modalities are different (Pashler, 1990; Lien et al., 2005). At least, it can be said that the intensity of dual-task interference differs depending on the combination of response modalities. Ruthruff et al. (2001) also reported that the amount of decrease in dual-task interference after training was very large when

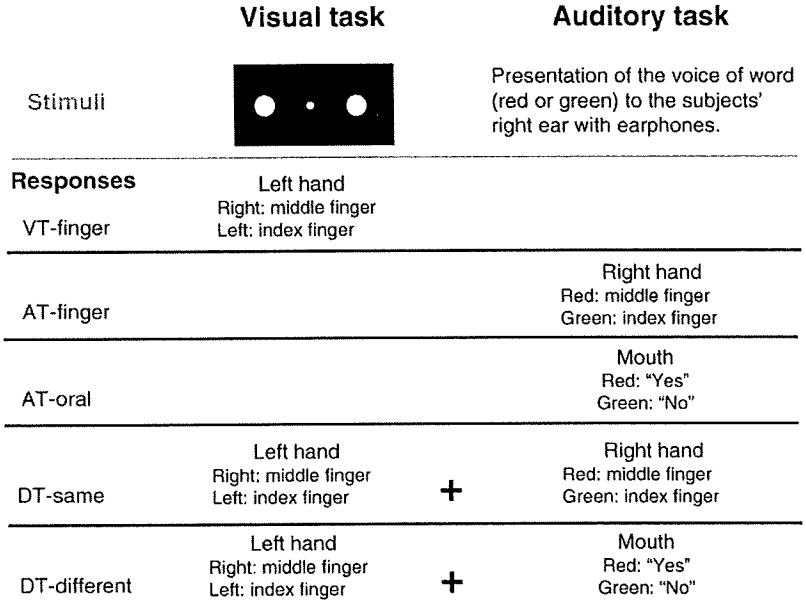

Fig. 1 – Protocol for dual and single tasks used in this study. The top row shows the stimuli used in the dual and single tasks. Each row below the top row shows response modalities.

the combination of response modalities was different as compared to when the combination was the same. One possible explanation for these phenomena is that the neural mechanism associated with dual-task management differs between the same and different responses. However, few neuroimaging studies have investigated this point. In this study, we employed two dual tasks: One was a combination of a visual task requiring finger responses and an auditory task requiring finger responses (the DT-same condition) (Fig. 1). The other was a combination of a visual task requiring finger responses and an auditory task requiring oral responses (the DT-different condition) (Fig. 1). We compared brain activity measured by positron emission tomography (PET) between these two dual-task conditions to investigate the relationship between brain activity associated with dual-task management and the combination of response modalities.

2. Results

2.1. *Behavioral data*

Fig. 2A shows the responses for the visual tasks requiring finger responses in the single-task (VT-finger) and dual-task (the DT-same and DT-different) conditions. Responses for the visual task in the DT-same and DT-different conditions were slower than those in the VT-finger condition. In particular, the delay in response for the visual task in the DT-same condition was significant. Fig. 2B shows the RTs for the auditory tasks requiring finger responses in the single-task (AT-finger) and dual-task (DT-same) conditions, whereas Fig. 2C shows the RTs for the auditory tasks requiring oral responses in the single-task (AT-oral) and dual-task (DT-different) conditions.

Table 1 – Accuracy of each task

	Visual task			Auditory task			
	VT-finger	DT-same	DT-different	AT-finger	DT-same	AT-oral	DT-different
Mean	98	98	98	97	96	96	94
SD	2	1	1	2	1	5	3

Responses to the auditory stimulus in the DT-same condition, but not in the DT-different condition, were significantly longer than those in the single-task conditions (Figs. 2B and C). To compare the intensity of dual task interference between the DT-same and DT-different condition, we calculated the difference of RT for each component task between the dual-task and single-task conditions (the RT change). Details are described in Section 4.9 Correlation analysis. The RT changes for the visual and auditory tasks were significantly larger in the DT-same condition than in the DT-different condition (Figs. 2D and E). No significant differences in accuracies for the visual and auditory tasks were observed between the dual-task and single-task conditions (Table 1).

2.2. *Brain regions related to each single-task*

Significant increases in the regional cerebral blood flow (rCBF) in the VT-finger condition relative to in the resting condition were observed in the right supplementary motor area (SMA), right motor cortex, left cerebellum and left auditory cortex (Fig. 3A and Table 2). On the other hand, brain regions that showed increased rCBFs in the AT-finger condition relative to the rCBFs in the resting condition were the left SMA, left motor cortex, right cerebellum, left auditory cortex and Broca area

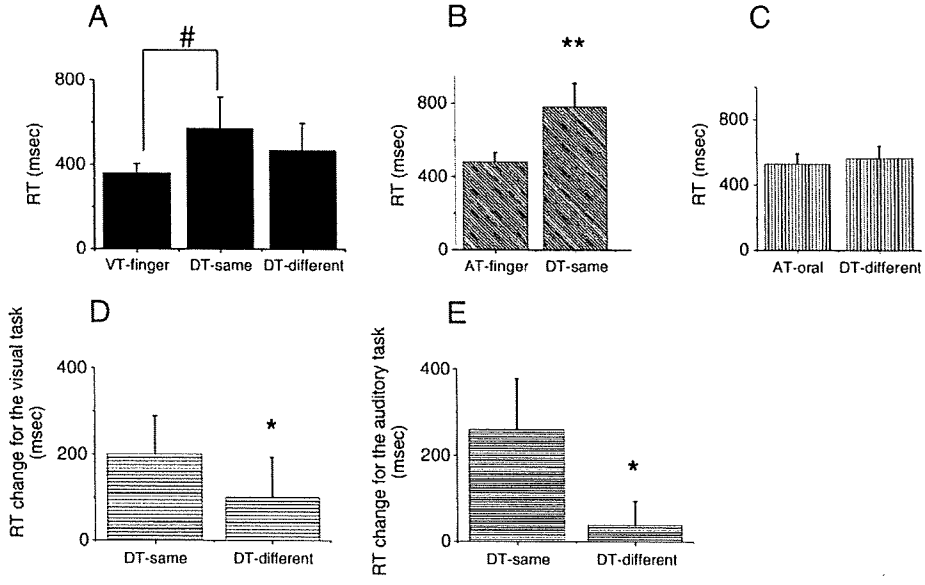

Fig. 2 – Comparison of subjects' performance between the dual and single tasks. (A) RTs for the visual task were compared between the DT-same, DT-different and VT-finger conditions. $^{\#}p<0.05$ (ANOVA followed by Scheffe's test). (B) RTs for the auditory task in the DT-same condition were compared to those in the AT-finger condition. (C) RTs for the auditory task in the DT-different condition were compared to those in the AT-oral condition. (D, E) Comparisons of RT changes between the DT-same and DT-different conditions (D: visual task; E: auditory task). $^{*}p<0.05$, $^{**}p<0.01$.

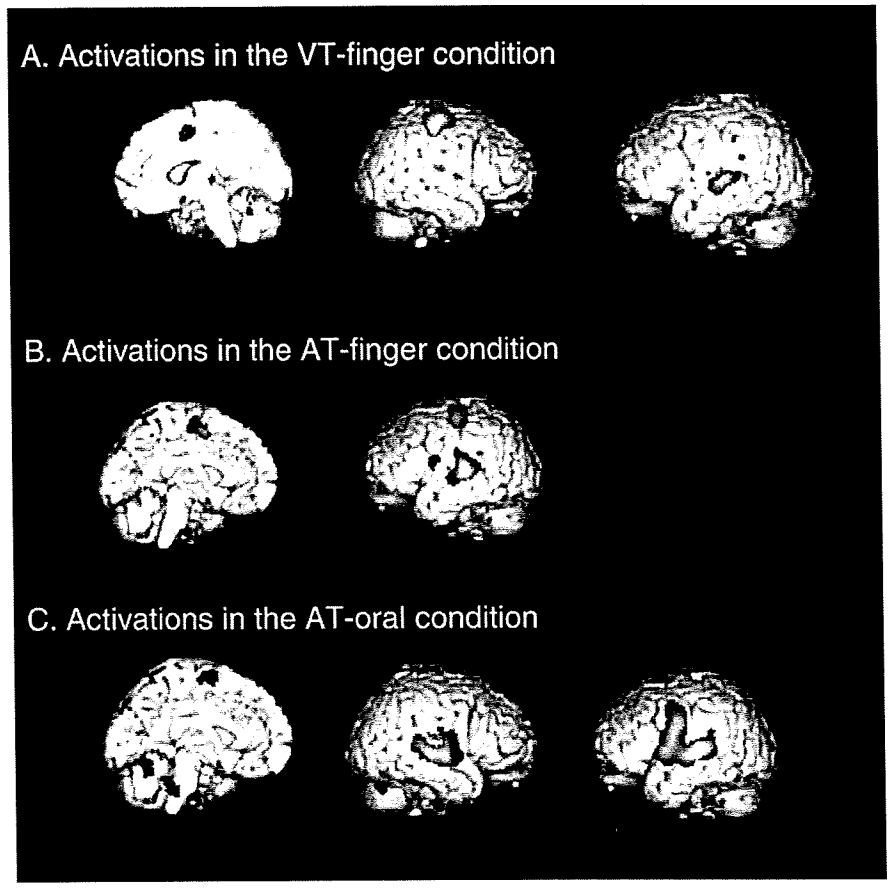

Fig. 3 – Brain regions activated in the single-task conditions as compared to in the resting condition: (A) VT-finger, (B) AT-finger and (C) AT-oral. The threshold for significant activation was FDR $p<0.05$.

(Fig. 3B and Table 3). We observed a significant brain activity in the Broca area, brain stem, right cerebellum, left SMA and bilateral auditory cortices in the AT-oral condition as compared to in the resting condition (Fig. 3C and Table 4). The brain regions activated in the VT-finger and AT-finger conditions were also activated in the DT-same condition. The brain regions associated with the VT-finger and AT-oral conditions were also activated in the DT-different condition. Their activities showed no significant difference between the single-task and dual-task conditions (Tables 2–4).

Table 2 – Brain regions related to VT-finger

Brain regions	Axes			Z scores	Activities	
	x	y	z		DT-different	DT-same
Right SMA	6	0	52	4.56	n.s.	n.s.
Right motor cortex	40	−20	60	6.76	n.s.	n.s.
Left auditory cortex	−56	−28	6	5.32	n.s.	n.s.
Left cerebellum	−16	−54	−22	5.13	n.s.	n.s.

Fourth column: Comparison of rCBF in each brain region between DT-same/DT-different conditions and VT-finger conditions.

2.3. *Dual-task-related activity in the DT-same and DT-different conditions*

The bilateral premotor cortices, precuneus and bilateral posterior parietal cortices were significantly activated in the DT-same condition as compared to in the resting condition (Table 5 and Fig. 4) and the right anterior parietal cortex and right posterior parietal cortex showed significant activations in the DT-different condition as compared to in the resting condition (Table 5 and Fig. 4). These brain regions were not activated in the single-task conditions. We calculated the rCBF changes by subtracting rCBF in the resting condition from

Table 3 – Brain regions related to AT-finger

Brain regions	Axes			Z scores	Activities
	x	y	z		
Left SMA	−6	2	52	5.32	n.s.
Left motor cortex	−40	−22	60	6.08	n.s.
Left auditory cortex	−56	−28	6	7.11	n.s.
Broca	−60	2	18	4.57	n.s.
Right cerebellum	18	−58	−22	4.46	n.s.

Fourth column: Comparison of rCBF in each brain region between DT-same and AT-finger conditions.

Table 4 – Brain regions related to AT-oral

Brain regions	Axes			Z scores	Activities
	x	y	z		
Broca	−60	−4	20	inf	n.s.
Brain stem	0	−38	−38	5.07	n.s.
Right cerebellum	38	−68	−30	4.94	n.s.
Left SMA	−8	−2	66	4.59	n.s.
Left auditory cortex	−58	−32	6	7.37	n.s.
Right auditory cortex	60	−10	−2	6.93	n.s.

Fourth column: Comparison of rCBF in each brain region between DT-different and AT-oral conditions.

those in each condition (DT-same, DT-different, VT-finger, AT-finger and AT-oral conditions). The rCBF changes in the left premotor cortex and left posterior parietal cortex in the DT-same condition showed no significant differences from the sum of the rCBF changes in the VT-finger and AT-finger conditions, while those in the other brain regions showed significant differences (Table 5).

2.4. *Comparison of brain activity between the DT-same and DT-different conditions*

A direct comparison of brain activity between the DT-same and DT-different conditions showed that the neural activities in the right premotor cortex, precuneus and right posterior parietal cortex were significantly higher in the DT-same condition than in the DT-different condition (Fig. 4, red brain regions), whereas those in the right anterior and posterior parietal cortices were significantly higher in the DT-different condition than in the DT-same condition (Fig. 4, green brain regions). We further investigated which brain regions observed in the dual-task conditions were associated with the delayed responses for each component task in the dual-task condition relative to those in the single-task condition. Interestingly, the rCBF changes in the right premotor cortex significantly correlated to the RT changes for the visual and auditory tasks in the DT-same condition (Fig. 4B). On the other hand, the rCBF change in the anterior parietal cortex was significantly proportional to the RT changes for the visual and auditory tasks in the DT-different condition (Fig. 4A). Although no significant activations of the left premotor cortex and left posterior parietal cortex were observed in the DT-different condition as compared to in the resting condition, a direct comparison of brain activity between the DT-different and DT-same conditions showed no significant difference in activity between these brain regions (Fig. 4). We also compared the rCBF changes in these brain regions between the DT-different condition and the single-task conditions (VT-finger and AT-finger conditions). The rCBF changes in the left premotor cortex and left posterior parietal cortex in the DT-different condition showed no significant difference from the sum of the rCBF changes in the VT-finger and AT-oral conditions [left premotor cortex (mean (SD)): DT-different: −1.3 (3.2), VT-finger+AT-oral: −2.3 (3.7), paired t-test: $p=0.89$; left posterior parietal cortex: DT-different: 0.6 (3.3), VT-finger+AT-oral: 0.7 (5.9), paired t-test: $p=0.81$]. In addition, we compared the rCBF changes in the right premotor cortex and right posterior parietal cortex between the DT-different condition and the single-task conditions [right premotor cortex: DT-different: 1.8 (4.8), VT-finger+AT-oral: 1.2 (4.8), paired t-test: $p=0.50$; right posterior parietal cortex: DT-different: −0.1 (3.3), VT-finger+AT-oral: −2.1 (7.1), paired t-test: $p=0.38$]. There were no significant differences between the rCBF changes in the DT-different condition and the sum of the rCBF changes in the VT-finger and AT-oral conditions.

3. Discussion

Psychological studies show that dual-task interference occurs in several combinations of response modalities. In particular, the intensity of dual-task interference differs between the same and different response modalities, indicating that dual-task management differs depending on the combination of response modalities. Recently, neuroimaging studies have been used to clarify the neural mechanism associated with dual-task interference and it has been found that the fronto-parietal network plays an important role in dual-task management. However, most previous studies used similar response combinations (finger–finger responses). Stelzel et al. (2006) used different response modalities (finger–oral responses). They reported that the effect of combinations of stimulus–response pairings (e.g., [visual–finger and auditory–oral pairings] vs. [visual–oral and auditory–finger pairing]) on dual-task interference was associated with the prefrontal cortex. Unfortunately, the neural mechanism associated with

Table 5 – Dual-task-related activations in DT-same and DT-different conditions

Brain regions	Axes			Z scores	Comparison of rCBF changes	
					rCBF changes (mean (SD))	
	x	y	z		Dual-task	Sum of single-tasks
DT-same condition						
Right premotor cortex	30	−12	60	7.13	5.0 (4.3)*	1.3 (6.2)
Left premotor cortex	−26	−10	60	4.42	1.2(3.5)	0.6 (5.5)
Right posterior parietal cortex	58	−30	38	7.72	2.8 (3.8)*	−2.3 (5.0)
Left posterior parietal cortex	−36	−50	62	6.55	2.8 (4.1)	1.7 (5.7)
Precuneus	4	−72	50	5.05	2.7 (4.4)*	−1.4 (6.9)
DT-different condition						
Right anterior parietal cortex	50	−24	40	4.86	2.7 (3.9)*	−0.8 (5.3)
Right posterior parietal cortex	26	−30	70	4.49	2.9 (4.3)*	−0.1 (6.6)

Comparison of rCBF changes: In the case of DT-same condition, the rCBF changes in DT-same condition were compared to the sum of the rCBF changes in VT-finger and AT-finger conditions (DT-same vs. VT-finger and AT-finger).
In the case of DT-different condition, the comparison was DT-different vs. VT-finger and AT-oral.
* Significant difference, $p<0.05$.

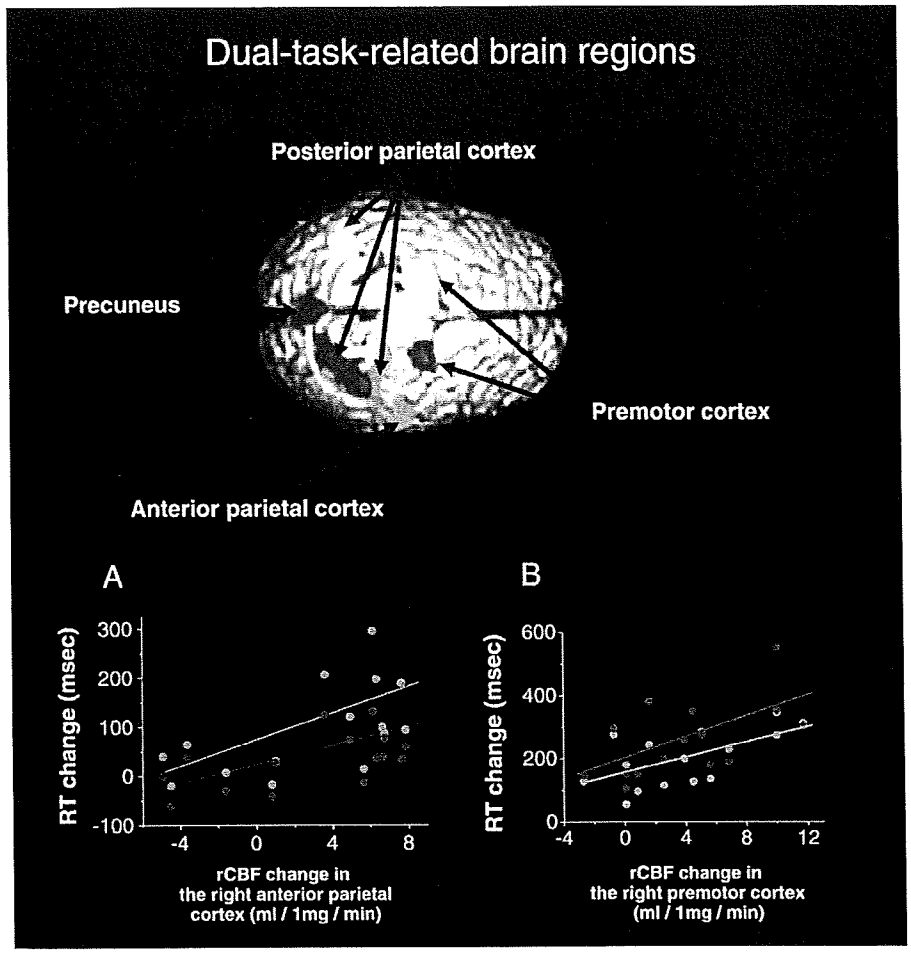

Fig. 4 – Dual-task-related activations in the DT-same and DT-different conditions. Brain regions significantly activated only in the DT-same and DT-different conditions were further classified into 3 types by comparing CBF images between the DT-same and DT-different conditions (threshold: FDR $p=0.05$). Brain regions whose neural activity was significantly higher in the DT-same condition than in the DT-different conditions are in red (Red: DT-same condition>DT-different condition). Green: DT-different condition>DT-same condition, Yellow: no significant differences between the DT-same and DT-different conditions. (A) Correlation between rCBF change in the right anterior parietal cortex and RT changes for visual and auditory tasks in the DT-different condition [Visual task (gray circles): $y=12x+60$, $r=0.6$ ($p=0.02$); Auditory task (red circles): $y=13x+7$, $r=0.57$ ($p=0.03$)]. Gray and red circles represent the visual and auditory tasks, respectively. (B) Correlation between rCBF change in right premotor cortex and RT changes in visual and auditory tasks in the DT-same condition [Visual task (gray circles): $y=13x+149$, $r=0.63$ ($p=0.01$); Auditory task (red circles): $y=16x+197$, $r=0.58$ ($p=0.02$)].

the effect of response modalities (e.g., finger–finger responses vs. finger–oral responses) on dual-task interference is still unclear. In this study, using PET, we investigated the relationship between brain activity associated with dual-task management and the combination of response modalities.

3.1. *Behavioral data*

The responses in component tasks in dual-task conditions were slower than that in the single-task conditions (Figs. 2A–C). In particular, the response delays were significantly longer in the DT-same condition than in the DT-different condition (Figs. 2D and E), indicating that the intensity of dual-task interference differed depending on the combination of response modalities. This result was analogous to those of previous psychological studies (Pashler, 1990; Lien et al., 2005). Dual-task interference is also affected by the manipulation of stimulus–response pairings. For example, dual-task interference in the incompatible condition (e.g., visual–oral and auditory–finger pairings) was larger than that in the compatible condition (e.g., visual–finger and auditory–oral pairings) (Hazeltine and Ruthruff, 2006). Stelzel et al. (2006) reported that the neural activity in the inferior frontal cortex activated in dual-task conditions was sensitive to the manipulation of stimulus–response modality compatibility. On the basis of this finding, they argued that the increased activity in the prefrontal cortex for the modality-incompatible dual-task reflects additional cognitive requirements for resolving the interference of mapping processes caused by an overlap of the neural systems involved in the processing of the component

tasks (Stelzel et al., 2006). Considering this finding, it might be that the larger interference in the DT-same condition than in the DT-different condition reflected an additional processing for or increased load in dual-task management in the DT-same condition.

3.2. *Imaging data*

As in previous studies (Herath et al., 2001; Szameitat et al., 2002; Erickson et al., 2005), we observed the significant activations of the bilateral premotor cortices and bilateral posterior parietal cortices in the DT-same condition (Fig. 4 and Table 5). As shown in Table 5, the rCBF changes in the left premotor cortex and left posterior parietal cortex in the DT-same condition were not significantly different from the sum of the rCBF changes in the single-task conditions (VT-finger and AT-finger conditions). Erickson et al. (2005) also reported that neural activities in the bilateral premotor cortices and bilateral parietal cortices associated with the component tasks significantly increased in a dual-task condition. This previous study and our result suggested that the significant activations of the left premotor cortex and left posterior parietal cortex in the DT-same condition were associated with the processing of two component tasks. On the other hand, the rCBF changes in the right premotor cortex and right posterior parietal cortex in the DT-same condition were significantly larger than the sum of the rCBF changes in the VT-finger and AT-finger conditions (Table 5). These results suggested that the right premotor cortex and the right posterior parietal cortex were associated not only with the processing of two component tasks. A similar result was also shown in a previous study (Schubert and Szameitat, 2003). Some additional processing for dual-task management might occur in these brain regions in the DT-same condition. In the DT-different condition, we observed no significant activations of the bilateral premotor cortices and bilateral posterior parietal cortices. However, a direct comparison of brain activity between the DT-same and DT-different conditions showed no significant difference in neural activity in the left premotor cortex and left posterior parietal cortex (Fig. 4). One possibility was that these brain regions were also activated in the DT-different condition. The rCBF changes in the left premotor cortex and left posterior parietal cortex in the DT-different condition were not significantly different from the sum of the rCBF changes in the VT-finger and AT-oral conditions (see Section 2.4 Comparison of brain activity between the DT-same and DT-different conditions). In addition, we also observed that the rCBF changes in the right premotor cortex and right posterior parietal cortex in the DT-different condition were not significantly different from the sum of rCBF changes in the VT-finger and AT-oral conditions (see Section 2.4 Comparison of brain activity between the DT-same and DT-different conditions). Jiang and Kanwisher (2003) reported that the brain regions associated with response selection such as the bilateral premotor cortices and bilateral parietal cortices were the same regardless of input (e.g., visual and auditory) and output modality (e.g., manual and oral). Considering the result of this previous study and our results, it might be that the bilateral premotor cortices and bilateral posterior parietal cortices were also associated with the processing of two component tasks in the DT-different conditions.

The neural activities in the right premotor cortex, precuneus and right posterior parietal cortex activated in the DT-same condition were significantly higher than those in the DT-different condition (Fig. 4). Several neuroimaging studies have shown that these brain regions are activated when subjects perform complex finger movements such as bimanual coordination (Sadato et al., 1996, 1997; Andre et al., 1999). Samuel et al. (1997) reported that abnormal activity in the premotor cortex and parietal cortex was associated with deteriorated bimanual coordination in patients with Parkinson's diseases. In addition, lesions in the premotor cortex and parietal cortex impair bimanual coordination (Kleisto, 1907, 1911; Serrien et al., 2001). These previous studies suggested that the right premotor cortex, precuneus and right posterior parietal cortex observed in the DT-same condition were associated with dual-task performance requiring finger–finger responses. In addition, as shown in Figs. 2D and E, the RT changes for the visual and the auditory tasks were significantly larger in the DT-same condition than in the DT-different condition, indicating that task difficulty such as the complexity of spatial mapping for response selection (Pashler, 1990) was different between the DT-same and DT-different conditions. Therefore, it might be that a difference in task difficulty between the DT-same and DT-different conditions was also included in the different activities in the right premotor cortex, precuneus and right posterior parietal cortex between these conditions. On the other hand, we observed significant activations in the right anterior parietal cortex and right posterior parietal cortex in the DT-different condition. The neural activities in the right anterior parietal cortex and right posterior parietal cortex in the DT-different condition were significantly higher than those in the DT-same condition and the sum of the rCBF changes in the VT-finger and AT-oral conditions (Fig. 4 and Table 5). In particular, we observed that the rCBF changes in the right anterior parietal cortex significantly correlated to the RT changes for the visual and auditory tasks in the DT-different condition (Fig. 4A). Yokochi et al. (2003) reported that the anterior parietal cortex was associated with hand–mouth coordination. The right anterior parietal cortex and right posterior parietal cortex observed in the DT-different condition might be associated with a dual-task performance requiring finger–oral responses. Several neuroimaging studies have shown that the frontal cortex and parietal cortex are associated with executive processes such as attentional and cognitive controls and working memory (Baddeley and Della Sala, 1996; Koechlin et al., 2000; Fletcher and Henson, 2001; Rowe et al., 2002; Koechlin et al., 2003). These processes are considered to play important roles in a dual-task performance (e.g., Baddeley, 1986; Erickson et al., 2005). Therefore, it was suggested that the enhanced activations in the right premotor cortex, precuneus and posterior parietal cortex observed in the DT-same condition and those in the anterior parietal cortex and posterior parietal cortex observed in the DT-different condition were partly associated with executive processes for dual-task management. On the other hand, Jiang et al. (2004) reported that the brain activity in short SOA (interference) was not significantly