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Functional brain mapping of actual car-driving using [^{18}F]FDG-PET

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Aims: This study aims at identifying the brain activation during actual car-driving on the road, and at comparing the results to those of previous studies on simulated car-driving. ***Methods:*** Thirty normal volunteers, aged 20 to 56 years, were divided into three subgroups, active driving, passive driving and control groups, for examination by positron emission tomography (PET) and [^{18}F]2-deoxy-2-fluoro-D-glucose (FDG). The active driving subjects (n = 10) drove for 30 minutes on quiet normal roads with a few traffic signals. The passive driving subjects (n = 10) participated as passengers on the front seat. The control subjects (n = 10) remained seated in a lit room with their eyes open. Voxel-based *t*-statistics were applied using SPM2 to search brain activation among the subgroups mentioned above. ***Results:*** Significant brain activation was detected during active driving in the primary and secondary visual cortices, primary sensorimotor areas, premotor area, parietal association area, cingulate gyrus, the parahippocampal gyrus as well as in thalamus and cerebellum. The passive driving manifested a similar-looking activation pattern, lacking activations in the premotor area, cingulate and parahippocampal gyri and thalamus. Direct comparison of the active and passive driving conditions revealed activation in the cerebellum. ***Conclusion:*** The result of actual driving looked similar to that of simulated driving, suggesting that visual perception and visuomotor coordination were the main brain functions while driving. In terms of attention and autonomic arousal, however, it seems there was a significant difference between simulated and actual driving possibly due to risk of accidents. Autonomic and emotional aspects of driving should be studied using an actual driving study-design.

Key words: positron emission tomography, FDG, statistical parametric mapping, car driving

INTRODUCTION

CAR-DRIVING is a combination of complex neural tasks such as attention, perception, integration of visual and somatosensory inputs, generation of motor outputs and action controls. Though the car-driving is not a difficult task for many experienced drivers, all drivers might sometimes encounter potentially-dangerous situations induced by cognitive and psychomotor deficits due to aging, neurological disorders,[1] psychoactive drugs such as alcohol and antihistamines,[2] and mobile phone use,[3] etc. Therefore, elucidation of the brain mechanism during car-driving is important and might lead to the development of an effective system to prevent accidents. Recently, Ott and colleagues first reported that impaired driving performance of demented patients was associated

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with hypoperfusion in the temporooccipital cortex measured by SPECT in the resting state.[1] Later on, new findings regarding neural activities during simulated car-driving have been demonstrated, using high resolution neuroimaging techniques such as functional magnetic resonance imaging (fMRI)[4–6] and positron emission tomography (PET).[7] Several investigators detected brain activations in the occipital and parietal regions bilaterally as neural substrates of simulated driving,[4–6] and a comparable result was obtained by using PET with [^{15}O]H_2O as well.[7] All of these results are, however, based on "simulated" driving tasks and until now no one can be sure that these brain activations are identical to those during actual driving. Therefore, we have aimed at elucidation of brain activation during actual car-driving using PET and [^{18}F]2-deoxy-2-fluoro-D-glucose (FDG), that has a unique property of "metabolic trapping" where neuronal activity during 30 to 60 min post-injection can be stored,[8,9] and at comparing the results of actual driving to those of other neuroimaging studies of simulated driving.[4–7]

MATERIALS AND METHODS

Subjects

Thirty healthy male volunteers, all right-handed, aged 20 to 56 years old, participated in the present study. All the subjects had held a driving license for at least 6 months. The study protocol was approved by the ethics committee and the clinical research committee using radioisotope, Tohoku University Graduate School of Medicine. Each subject provided a written informed consent for participation in the study after receiving sufficient explanation.

Task procedure

The subjects were divided into the following 3 groups: (1) the active driving group (n = 10; mean age ± S.D.: 35.8 ± 12.2 y.o.) who drove on an ordinary road; (2) the passive driving group (n = 10; mean age: 34.8 ± 13.1 y.o.) who remained seated on a front passenger seat during the driving experiment; and (3) the subjects belonging to the control group (n = 10; mean age: 32.7 ± 9.6 y.o.) who remained seated on a comfortable chair in a laboratory building, looking outside the windows. All subjects were kept in a fasting state for at least 5 hours before the study.

The subjects of the active driving group were requested to start driving an experimental car, with automatic transmission, shortly after intravenous injection of FDG. They were requested to keep driving for 30 min at an approximate speed of 40 km/h along a quiet driving route around Tohoku University Aoba-yama Campus (Fig. 1). The active-driving subjects were not informed of the details of the driving route in advance, and at each square they followed the directions of an investigator sitting on the rear seat. The passive-driving subjects followed the same protocol except that they were sitting on the front passenger seat simply looking at the landscape ahead of the car

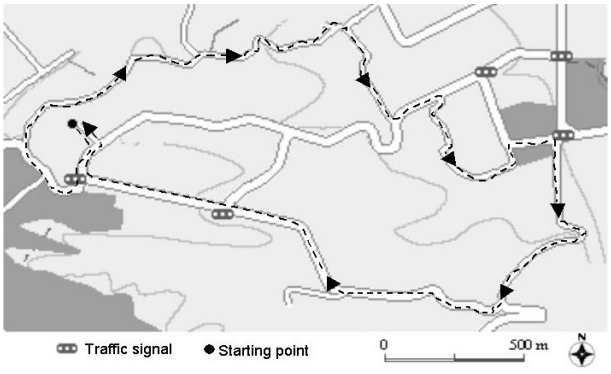

Fig. 1 A map of the driving route used in the present study.

throughout the driving experiment. The active and passive drivers were in the same experimental car during experiment, but they were not allowed to talk to each other. The control subjects were sitting on a soft chair similar to that of the experimental car for 30 min simply looking at the landscape outside and with their ears unplugged so that they could hear normal conversation around them. Following these tasks, PET scans started just after they emptied their bladders.

PET imaging acquisition

PET emission scan started approximately 45 minutes after FDG injection using an SET-2400W scanner (Shimadzu Inc., Kyoto, Japan), with spatial resolutions of 4.0, 4.0, and 4.5 mm at full-width-half-maximum (FWHM) in radial, tangential and axial directions, respectively. The axial field-of-view of the scanner was 200 mm. FDG was synthesized according to the Hammacher method.[10] The subjects' heads were fixed gently to the head-holder with a plastic spacer inflated with air to minimize the subjects' head movement. The mean radiological dose given to the subjects was 40.7 ± 7.4 MBq (1.1 ± 0.2 mCi). Three-dimensional emission scan was performed for 5 min and post-injection transmission scan was performed for 8 min using a ^{68}Ge/^{68}Ga external rotating line source for tissue attenuation correction. In the present protocol, a scan order was balanced by conducting 5 of the 10 experiments in an "active-passive" order and the other 5 experiments in a "passive-active" order. PET image data were transferred to a supercomputer at the Synergy Center, Tohoku University, for reconstruction into 128 × 128 × 63 matrices based on a filtered back-projection algorithm using the Colsher filter with an 8 mm cut-off frequency.[11,12]

Statistical analysis

Driving-related brain activation was examined using Statistical Parametric Mapping software package (SPM2, Wellcome Department of Cognitive Neurology, London, UK).[13,14] Brain images were anatomically normalized to a standard brain template (FDG-PET version adapted to

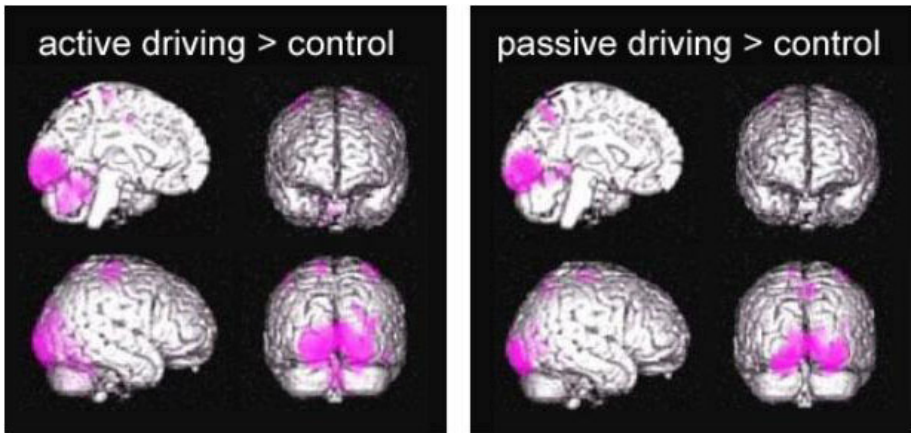

Fig. 2 The main effect of driving was tested by inter-group comparison between the active (*left*) or passive (*right*) driving (n = 10 for each) and control groups (n = 10). The statistical threshold: $p < 0.001$ (uncorrected).

Table 1 Brain areas activated by car-driving (driving > control)

Region	Active driving					Passive driving				
	side	Talairach			Z-score	side	Talairach			Z-score
		x	y	z			x	y	z	
Precentral gyrus (BA4)	L	−10	−26	68	3.40	R	36	−28	64	3.47
Precentral gyrus (BA6)	L	−10	−22	64	3.40					
Postcentral gyrus (BA3/1/2)	R	38	−27	57	4.20	R	42	−15	62	3.23
	L	−44	−18	52	3.40					
Primary visual cortex (BA17/18)	L	−2	−77	8	5.51	L	−8	−81	7	4.43
	R	32	−90	1	4.19	R	8	−76	4	4.84
Fusiform gyrus (BA19/37)	R	30	−48	−8	4.02	L	30	−88	−12	4.42
						R	30	−48	−8	3.31
Precuneus (BA7/31)	L	−10	−49	63	3.67	L	−4	−54	51	3.79
	R	24	−78	28	3.57					
Medial temporal gyrus (BA39)	R	36	−68	20	3.81	R	38	−73	22	3.54
Cingulate gyrus (BA24)	R	10	−7	41	3.27					
Parahippocampal gyrus (BA35)	L	−18	−36	−2	3.18					
Thalamus	R	16	−17	1	3.36					
Cerebellum	R	22	−51	−24	4.71	L	−22	−58	−12	3.98

The main effect of driving was tested by inter-group comparison between the active driving (n = 10) and control groups (n = 10). The statistical threshold is $p < 0.001$ (uncorrected).

the MNI-MRI template by Montreal Neurological Institute)[15] by linear (Affine) and non-linear transformations to minimize inter-subject anatomical variations using a SPM routine. The brain images were then smoothed using an 11 mm isotropic 3D Gaussian filter to increase the signal to noise ratio. Indices of global activity were modeled as a confounding covariate (after proportional scaling of the global brain activity to a physiologically realistic value of 50 m*l*/100 m*l*/min) using ANCOVA.[16] Linear contrasts were used to test for regionally specific differences between groups, producing *t*-statistic maps in Talairach standard space.[17] These *t*-statistics were transformed to corresponding Z maps, which constituted the statistical map (SPM-Z). The peak voxel-based significance of statistics was set at $p < 0.001$ ($Z > 3.18$) without corrections for multiple comparisons.

RESULTS

The plasma glucose level measured prior to FDG injection was within the normal range (mean blood glucose level ± S.D.: 101.2 ± 9.4 mg/d*l*). Significant brain activations in the active driving group compared with the control were found in the visual cortices (BA17–19), primary sensorimotor (BA1–4) areas, premotor area (BA6), parietal association area (precuneus), cingulate gyrus

Table 2 Brain areas deactivated by driving (driving < control)

Region	Active driving					Passive driving				
	side	Talairach			Z-score	side	Talairach			Z-score
		x	y	z			x	y	z	
Prefrontal gyrus (BA10)	R	34	61	−7	4.10	L	−32	61	8	3.36
	L	−2	63	−10	3.69	L	−28	56	1	3.17
Inferior frontal gyrus (BA45/47)	R	57	20	16	3.55	R	57	20	14	3.50
	L	−50	21	−1	3.94					
Postcentral gyrus (BA43)						R	57	−10	26	3.64
Orbital gyrus (BA11)	R	2	43	−19	4.48	R	2	31	−25	3.99
Medial temporal gyrus (BA21)	L	−46	3	−27	3.57					
	R	59	4	−20	3.38	R	61	0	−3	4.33
Subcallosal gyrus (BA25)	L	−8	17	−14	3.71	L	−12	19	−14	3.28
Cingulate gyrus (BA32)						L	−10	41	9	3.20

The main effect of driving was tested by inter-group comparison between the active driving (n = 10) and control groups (n = 10). The statistical threshold is $p < 0.001$ (uncorrected).

(BA24), parahippocampal gyrus (BA35) as well as in the thalamus and cerebellum (Table 1). Brain activations in the passive driving compared to the control looked similar to those of active driving (Table 1) except for the absence of activations in the premotor, cingulate, parahippocampal areas and thalamus.

Comparison of the active to passive driving (active > passive) demonstrated activations in the bilateral cerebellar hemispheres only (Right: 32, −48, −36; Z = 3.71; Left: −8, −52, −28; Z = 3.89). Comparison of the passive to active driving (active < passive) did not find any significant areas. Inverse comparisons of the control group to the active or passive driving group revealed deactivation in the bilateral frontal and temporal cortices and in the subcallosal/cingulate gyri (Table 2).

DISCUSSION

As mentioned in the introduction section, neural correlates of car-driving have been studied using a driving simulator and fMRI[4–6] or PET with $[^{15}O]H_2O$.[7] Walter and colleagues first demonstrated neural activation during simulated driving by comparing active and passive driving conditions,[4] following Ott and colleagues' report that first demonstrated a possible association between impaired driving performance and resting brain hypoperfusion measured by SPECT.[1] Later, groups including those of Uchiyama[6] and Horikawa[7] independently reported the brain regions associated with driving abilities, using a similar study-design as that of Walter et al.[4] In addition, Calhoun and colleagues first introduced independent component analysis (ICA) to their fMRI data of simulated driving[5] as well as virtual driving task to see not only the neural correlates of driving but also to observe the effects of alcohol on driving performance.[2,18]

A potential problem of using a driving simulator, however, is the fact that the degree of realism of driving is limited in simulated driving, as mentioned by Walter et al.[4] It is not yet known whether the results of simulated driving exactly represent the neural correlates of actual car-driving. For observation of actual driving, use of EEG has started much earlier though its spatial resolution is limited.[19–21] Thus, the present study is, as far as the authors know, the first to demonstrate neural correlates of actual car-driving using a high-resolution imaging technique such as PET. For this purpose, FDG is a radiotracer of choice that may allow PET scans following completion of driving tasks. Our previous work already confirmed the usefulness of FDG PET in the observation of regional brain activity conducted apart from a PET scanner such as that associated with running.[9]

The present study demonstrated several brain activations resembling those of the previous simulated-driving studies[4,5]; namely, the primary sensorimotor areas (BA3 and 4), premotor area (BA6), visual cortex (BA17–19), medial temporal cortex (BA39), precuneus (BA7/31) and cerebellum (Table 1). All of the all available neuroimaging studies, including four fMRI[2,4–6] and one PET study,[7] measured brain perfusion but not brain (glucose) metabolism. Similarity in the results of fMRI and $[^{15}O]H_2O$ PET measurements was already demonstrated by comparing the two activation results obtained by using the different methods but using the same protocol.[22] In addition, there is a coupling between hemodynamic response and glucose metabolism in human brain under a physiological condition.[23] Then, despite the methodological differences, we are allowed to roughly compare the present FDG results to those of previous perfusion studies in terms of the regional brain activity changes.[4–7] Similarity in the findings of fMRI and FDG PET has also been demonstrated by comparing the two activation results obtained by the different methods.[24] And the present study-setting, characterized by quiet traffic and small number of traffic lights, was similar to the average condition of previous simulation studies. This fact would further make the comparison to the previous studies easier.

The present findings are basically consistent with the previous fMRI[4,6] and PET[7] results obtained from contrasting active and passive driving conditions. During car-driving, a driver's brain may need to process various visual inputs regarding the complex scene of the surroundings including forward movements[25,26] to match the complex visual informaiton to the driver's own egocentric coordinates.[26,27] Such visuomotor coordination would require the action of temporo-parietal/-occipital regions[26,27] as well as the premotor area that generates appropriate motor outputs.[4,6,7] Especially, Uchiyama et al. reported significant activation of the premotor area probably due to a difficult visuomotor coordination task to keep a constant distance from a preceding car going at random speeds.[6] The activation in the cerebellum, being more extended in active than in passive driving, would suggest that the cerebellum also plays an important role in actual car-driving as well[7] (Table 1). Findings of deactivation during actual driving were also similar to those of the previous perfusion studies.[4,6,7]

In the present study, a comparison of the active driving to the control demonstrated activations in the primary sensory (BA1–3) and motor (BA4), and premotor (BA6, for motor programming) cortices. A comparison of the passive driving to the control demonstrated also activation in the sensory and motor cortices but not in the premotor area. It is easy to understand that the premotor area was activated only during active driving because the "motor programming" is an essential part of neural activity during active driving. As for the primary sensorimotor area, contrary to the authors' expectation, a direct comparison of the active to passive driving did not demonstrate a significant difference though there was a trend to more activation during active driving in the sensorimotor area. One possible reason for this result could be attributed to the fact that the involvement of muscle contraction is quite limited in active driving for simple steering (arms and hands) and pressing acceleration and brake pedals (a leg and foot). Second, during driving experiments, even passive drivers required contraction of muscles in legs, arms and hands and body trunk to keep their body posture against acceleration gravity and centrifugal forces, that would result in a certain amount of activation of the sensorimotor areas. This aspect would be one of the important differences between actual and simulated driving studies that has not been discussed previously.

Activations in the cingulate and parahippocampal gyri were observed during active driving in the present study (Table 1). None of these regions were activated in the studies by Walter et al. or Horikawa et al. that used relatively simple driving tasks.[4,7] Uchiyama et al., using a specific "keep-a-safe-distance" task, reported activation in the anterior cingulate, where hemodynamic responses significantly correlated to task performance.[6] These findings suggest that actual driving is more-strongly associated with cingulate activation since actual drivers must always be careful to keep safe distances not only from preceding cars but also pedestrians and guardrails etc. The activation in the parahippocampal gyrus seems to be also associated with attention and cognition during actual driving, since this region tended to be most active during active driving and less active during passive driving as revealed by ICA[5] but not by simple contrasting study-designs, suggesting that the activation in this region is relatively weak.

A possible disadvantage of FDG PET in comparison to fMRI would be radiation exposure not only to the subjects but also to the investigator. Based on the measurement by Cronin and colleagues (1999), irradiation from the driving subjects, injected with FDG, to the investigator sitting on the rear seat (supposed to be irradiated at a distance of 50 cm) for 30 min or so can be estimated as 4.88 μSv on average. Since active and passive drivers were sitting on front seats during the experiment, the irradiation to the investigator is roughly doubled (9.76 μSv per experiment). Thus, the estimated total irradiation (for 10 experiments) to the investigator would be 97.6 μSv, or 0.098 mSv.

In summary, the actual driving experiment demonstrated similar findings to those of simulated driving in spite of several differences in methodologies and protocols,[4,6,7] and the results suggested that visual perception and visuomotor coordination were the main brain functions during actual driving as well. As for autonomic responses, however, it seems there is a significant difference between simulated and actual driving conditions possibly due to the absence/presence of the possible risk of actual accidents. It seems that perceptive and visuomotor components can be studied by simulation, but other components of autonomic and emotional responses should be studied using actual driving, or at least a highly-sophisticated driving simulator that can imitate vibration and acceleration, etc. For drawing a definitive conclusion, the authors should indicate the importance of future replication where the same subjects undergo both actual and simulated driving using the same protocol.

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