


RESEARCH ARTICLE

Effects of levocetirizine and diphenhydramine on regional glucose metabolic changes and hemodynamic responses in the human prefrontal cortex during cognitive tasks

Asuka Kikuchi¹ | Fairuz Binti Mohammadi Nasir² | Akie Inami¹ | Attayeb Mohsen^{1,3,4} | Shoichi Watanuki¹ | Masayasu Miyake² | Kazuko Takeda¹ | Daigo Koike¹ | Takayasu Ito¹ | Junpei Sasakawa¹ | Rin Matsuda¹ | Kotaro Hiraoka¹ | Marcus Maurer⁵ | Kazuhiko Yanai^{1,3} | Hiroshi Watabe² | Manabu Tashiro¹ 

¹Division of Cyclotron Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan

²Division of Radiation Safety, Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan

³Department of Pharmacology, Tohoku University Graduate School of Medicine, Sendai, Japan

⁴Bioinformatics Project, National Institutes of Biomedical Innovation, Health, and Nutrition, Osaka, Japan

⁵Department of Dermatology and Allergy, Charité—Universitätsmedizin Berlin, Berlin, Germany

Correspondence

Manabu Tashiro, Division of Cyclotron Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai, Miyagi 980-8578, Japan.
Email: mtashiro@m.tohoku.ac.jp

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Abstract

Objective: Antihistamines often have sedative side effects. This was the first study to measure regional cerebral glucose (energy) consumption and hemodynamic responses in young adults during cognitive tests after antihistamine administration.

Methods: In this double-blind, placebo-controlled, three-way crossover study, 18 healthy young Japanese men received single doses of levocetirizine 5 mg and diphenhydramine 50 mg at intervals of at least six days. Subjective feeling, task performances, and brain activity were evaluated during three cognitive tests (word fluency, two-back, and Stroop). Regional cerebral glucose consumption changes were measured using positron emission tomography with [¹⁸F]fluorodeoxyglucose. Regional hemodynamic responses were measured using near-infrared spectroscopy.

Results: Energy consumption in prefrontal regions was significantly increased after antihistamine administration, especially diphenhydramine, whereas prefrontal hemodynamic responses, evaluated with oxygenated hemoglobin levels, were significantly lower with diphenhydramine treatment. Stroop test accuracy was significantly impaired by diphenhydramine, but not by levocetirizine. There was no significant difference in subjective sleepiness.

Conclusions: Physiological “coupling” between metabolism and perfusion in the healthy human brain may not be maintained under pharmacological influence due to antihistamines. This uncoupling may be caused by a combination of increased energy demands in the prefrontal regions and suppression of vascular permeability in brain capillaries after antihistamine treatment. Further research is needed to validate this hypothesis.

KEYWORDS

antihistamines, diphenhydramine, FDG-PET, levocetirizine, NIRS, sedation

1 | INTRODUCTION

Histamine plays important roles in various brain functions, such as arousal, attention, and cognition (Haas & Panula, 2003; Tashiro et al.,

2002; Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004). Brain histamine is synthesized in the tuberomammillary nucleus of the posterior hypothalamus. The neurons project axons to various brain regions that maintain neuronal activity through histamine H₁

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receptors (H_1 Rs). As a neurotransmitter, histamine plays major roles in maintaining vigilance and attention through H_1 Rs. During antihistamine use, blockade of histamine H_1 Rs may affect various aspects of performance in our day-to-day lives, which is why antihistamines often impair arousal and brain function in allergy patients (Casale et al., 2003; Church et al., 2010; Church & Maurer, 2012; Holgate et al., 2003).

Sedative antihistamines, such as diphenhydramine and *d*-chlorpheniramine, used to be the treatment of choice to manage allergic symptoms. However, they have adverse effects such as sedation and impairment of psychomotor performances. These adverse effects are mainly due to the ability of antihistamines to penetrate the blood-brain barrier, blocking neuronal transmission in the histaminergic nervous system in the brain. Such sedative antihistamines, which have the strongest sedative effects, are often ingredients of over-the-counter drugs for the common cold in many countries. Sedative antihistamines are so potent that they can even impair everyday tasks such as car driving (Ridout, Shamsi, Meadows, Johnson, & Hindmarch, 2003; Tashiro et al., 2005; Tashiro, Sakurada, et al., 2008). Therefore, newer generations of "mildly sedative" and "nonsedative" antihistamines have been introduced to improve patients' quality of life and avoid accidents.

Levocetirizine, the levo enantiomer of cetirizine, has recently been introduced in Japan as an antihistamine with minimal side effects. It has high affinity and selectivity for H_1 Rs, whereas the dextro enantiomer of cetirizine is inactive (Gillard, Van Der Perren, Moguilevsky, Massingham, & Chatelain, 2002). Levocetirizine 5 mg shows equivalent potency to cetirizine 10 mg and diphenhydramine 50 mg in terms of inhibiting histamine-induced wheals and flares (Clough, Boutsouki, & Church, 2001; Wang, Hanotte, De Vos, & Clement, 2001) but does not significantly affect performance in cognitive tests (Hindmarch, Johnson, Meadows, Kirkpatrick, & Shamsi, 2001), unlike diphenhydramine 50 mg (Gandon & Allain, 2002). In addition, levocetirizine 5 mg does not affect cognitive functions and car-driving performance (Verster, de Weert, et al., 2003; Verster, Volkerts, et al., 2003). Our recent study also showed that levocetirizine did not impair car-driving performance in young Japanese adults (Inami et al., 2016). A brain histamine H_1 R occupancy (H_1 RO) measure has been added as an objective measure to the Consensus Group on New-Generation Antihistamines (CONGA) (Holgate et al., 2003). This molecular neuroimaging technique has been used to measure brain H_1 RO using positron emission tomography (PET) and [^{11}C]doxepin, a potent antagonistic radioligand used to visualize the distribution of histamine H_1 Rs. Our previous study also determined a brain H_1 RO of approximately 8.1% after treatment with levocetirizine 5 mg (Hiraoka et al., 2015), whereas that after diphenhydramine 30 mg was 56.4% (Tashiro, Duan, et al., 2008). We have proposed that antihistamines be classified by H_1 RO values as sedative (>50%), mildly sedative (10–50%), and nonsedative (<10%). Thus, on the basis of its H_1 RO value of 8.1%, levocetirizine would be classified as a nonsedative antihistamine, which is why it is of academic and clinical interest to measure the sedative potential of levocetirizine using various methods.

Functional neuroimaging techniques are powerful tools for investigating regional brain activity. PET used to be regularly used to measure regional brain activities in terms of regional cerebral blood flow (rCBF) changes using radioactive water, [^{15}O]H₂O (H₂O PET). Our group determined the brain regions with increased and decreased rCBF during visual discrimination tasks before and after oral

administration of *d*-chlorpheniramine (Okamura et al., 2000; Mochizuki et al., 2002; Tashiro, Sakurada, et al., 2008). In addition, rCBF responses after antihistamine treatment have also been studied using near-infrared spectroscopy (NIRS). Tsujii, Yamamoto, Ohira, Saito, and Watanabe (2007) demonstrated decreased hemodynamic responses after ketotifen treatment during cognitive tasks in healthy adults.

Regional cerebral glucose consumption can also be used as an alternative index for measuring regional brain activity with [^{18}F] fluorodeoxyglucose (FDG)-PET. FDG molecules are trapped in activated cells through glucose transporters in the brain in proportion to tissue energy consumption. Thus, tissue glucose consumption can be a more direct index of regional brain activity than regional blood flow changes (due to brain capillary dilations) that follow metabolic changes (coupling). This method can also be applied to pharmacological studies, but such usage of FDG-PET has been rare. As far as we know, Molchan et al. (1994) were the first to use the "FDG double-injection" method to evaluate the effects of scopolamine on the brain of elderly subjects. One of the most important advantages of this method is that the regional brain activity for nearly 30 min after FDG injection can be summed and recorded based on the biochemical property called "metabolic trapping," where investigators can separate the "task" phase of FDG uptake from the "measurement" phase. This technique was first applied to healthy volunteers to observe regional brain activity during a natural running task in upright posture (Tashiro, Itoh, et al., 2001; Tashiro, Itoh, et al., 2008). Later, this technique was applied to studies of alternative therapies (Duan et al., 2007; Inami et al., 2017; Sugawara et al., 2012). In particular, Sugawara and colleagues applied the FDG double-injection method. This method is very useful because a study subject can complete two measurements in one session, whereas the usual protocol can require at least 2 days. The reliability and reproducibility of this method have been examined and confirmed (Murase, Kuwabara, Yasuhara, Evans, & Gjedde, 1996; Poulsen et al., 1997; Nishizawa et al., 2001). However, FDG-PET has never been applied to activation studies performed after antihistamine treatment.

One of the main aims of the present study was to investigate the regional brain activity during cognitive tasks after the administration of sedative and nonsedative antihistamines in terms of cerebral glucose metabolic changes, and we also examined its relationship with regional hemodynamic responses. As far as we know, no study has compared FDG-PET and NIRS findings, although H₂O PET and NIRS have been compared (Hock et al., 1997; Villringer et al., 1997). PET has high sensitivity and spatial resolution but poor temporal resolution, whereas NIRS has a high temporal resolution and measurement convenience. Therefore, the use of a NIRS system to compensate for the disadvantages of the PET system would be practical. We additionally studied the effects of sedative and nonsedative antihistamines on the performances of different cognitive tests in healthy Japanese volunteers.

2 | MATERIALS AND METHODS

2.1 | Subjects

Subjects were recruited through advertisements in Tohoku University campuses. The ethics committee of the University Graduate School

of Medicine approved the study protocol. Study subjects were treated according to the Guidelines for Good Clinical Practice and the Declaration of Helsinki and its 1996 amendments. Each subject was informed beforehand about the possible risks of radiation exposure and medical procedures during the examinations as well as the possible adverse effects of antihistamines. Written informed consent was obtained before the subjects were included in the study, and the subjects were paid to cover the costs related to the study.

Upon recruitment, the study candidates were screened for abnormalities in brain magnetic resonance imaging (MRI) T1 images. Study candidates with brain abnormalities on MRI and past histories of food and drug allergies, epilepsy, glaucoma, or prostatic hypertrophy were excluded. No subjects used concomitant medication or had a history of alcohol or drug abuse. Eighteen healthy Japanese volunteers (all men) participated in and completed the study. Their mean age \pm standard deviation was 21.7 ± 0.8 years. All subjects were trained on the cognitive test battery beforehand to become familiar with the test procedures.

2.2 | Study design

This study used a double-blind, placebo-controlled, three-way, cross-over design. Single doses of levocetirizine 5 mg, diphenhydramine 50 mg, and placebo (lactobacillus tablets) were administered orally with 100-ml water. These tablets were concealed in three envelopes labeled with the subject's ID (randomization number) and treatment period (1, 2, or 3). The test drug order was determined based on the Latin square method to eliminate the order effect. Treatment periods were separated by a washout period of at least six days. The first

PET scan (PET1) was performed in the resting state before oral administration (baseline), and the second PET scan (PET2) was done at 120 min post administration (Figure 1, top). Use of alcohol and any other drugs was prohibited the day before and on treatment days, and nicotine was prohibited 24 hr prior to the experiment and on treatment days. Products containing caffeine, grapefruit juice, or any supplement drink containing active agents, such as amino acids, vitamins, and catechin, were prohibited on treatment days. Only water was allowed during testing. Subjects had been instructed to have a sufficient amount of sleep (at least 7 hr) the night before the test days.

On the test day, subjects were requested to arrive at our center at 08:50 hr without eating breakfast. This was because subjects needed a fasting period of at least 5 hr for FDG-PET examinations in order to obtain clear images. Subjects were familiarized with the cognitive tasks by practicing the tasks for approximately 10 min using a shortened version of the task program. After a simple physical examination of blood pressure and pulse rate, an infusion line was inserted into the left antecubital vein of each subject. After the blood glucose level is checked, each subject was requested to sit on a chair in a relaxed position for 15 min (resting period). Then, the study subjects were moved to the test chamber, and an FDG-containing saline solution was injected into the subject at 09:20 hr through the left antecubital vein. The subject was asked to look at the center of a PC monitor fixed to the wall of the test chamber for another 30 min. The distance between the subjects' eyes and the monitor was approximately 90 cm. After a 30-min-long FDG uptake period in the resting state, the study subject moved to the adjacent PET room, and the baseline PET examination was initiated (PET1), which lasted for 30 min. Soon after the

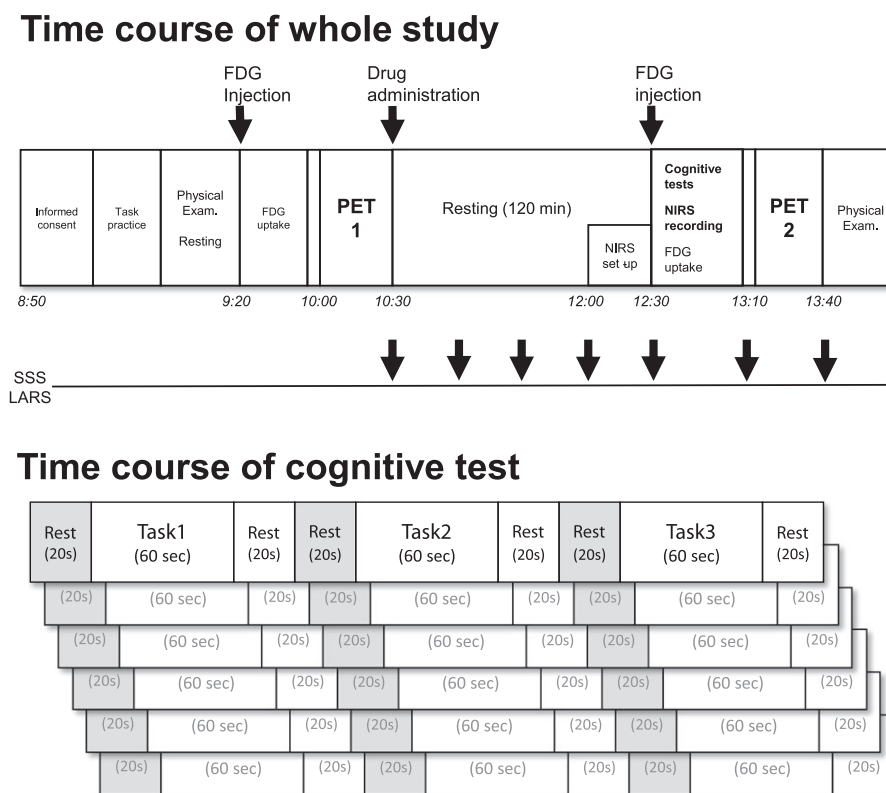


FIGURE 1 Schematic diagrams of the entire study protocol (top) and of the cognitive test protocol (bottom). FDG, [^{18}F]fluorodeoxyglucose; LARS, line analog rating scale; NIRS, near-infrared spectroscopy; PET, positron emission tomography; SSS, Stanford Sleepiness Scale

completion of the PET1 scan (at 10:30 hr), the subjects took the medication for each test day (Figure 1, top). After the oral administration of the test drug, the subjects spent approximately 90 min in a relaxed position. Then, NIRS probes were fixed to the scalp of each study subject, and the locations of all NIRS probes were recorded. At 120 min post drug administration (at 12:30 hr), another FDG-containing saline solution was injected into the study subject. Cognitive tests and NIRS measurements were initiated simultaneously (Figure 1, top). Shortly after completion of the cognitive tests and NIRS measurement, the second PET scan (PET2) was initiated (160 min after the drug administration; Figure 1, top). After PET2, the subject was again examined for physical problems.

The cognitive testing battery consisted of the word fluency test (Task1), two-back test (Task2), and Stroop test (Task3), all of which were prepared to activate the prefrontal cortex. Each of the three tasks took 60 s, and each task was separated by 20-s-long pretask and posttask resting phases (20 s for each). A session including the three tasks was repeated six times, taking 30 min in total (Figure 1, bottom). In the word fluency task (Task1), subjects were requested to generate and vocalize as many words as possible that started with specific Japanese phonetic characters (hiragana: e.g., “ta” and “ku”)

displayed on the monitor. A single-word fluency task session (60 s) consisted of a set of two tests for two different phonetic characters taking 30 s each. In the two-back test, the subject was instructed to press the “1” button when the onscreen illustration in the monitor was identical to the one presented before the previous one (match) and to press “2” when the onscreen illustration was different from the one presented before the previous one (no match; Figure 2, top). In the Stroop task, two Chinese characters (kanjis) were displayed on the monitor. The subject was instructed to press “1” when the “actual color” of the character displayed in the upper position matched the “meaning” of the character displayed in the lower position. In addition, the subject was instructed to press “2” when the “actual color” of the character displayed in the upper position did not match the “meaning” of the character displayed in the lower position (Figure 2, bottom).

2.3 | Assessment of subjective feelings

Assessment of subjective sleepiness was performed with the Stanford Sleepiness Scale (SSS) and the line analog rating scale (LARS; Figure 1, top). The SSS is a 7-point self-report measure of how alert an individual

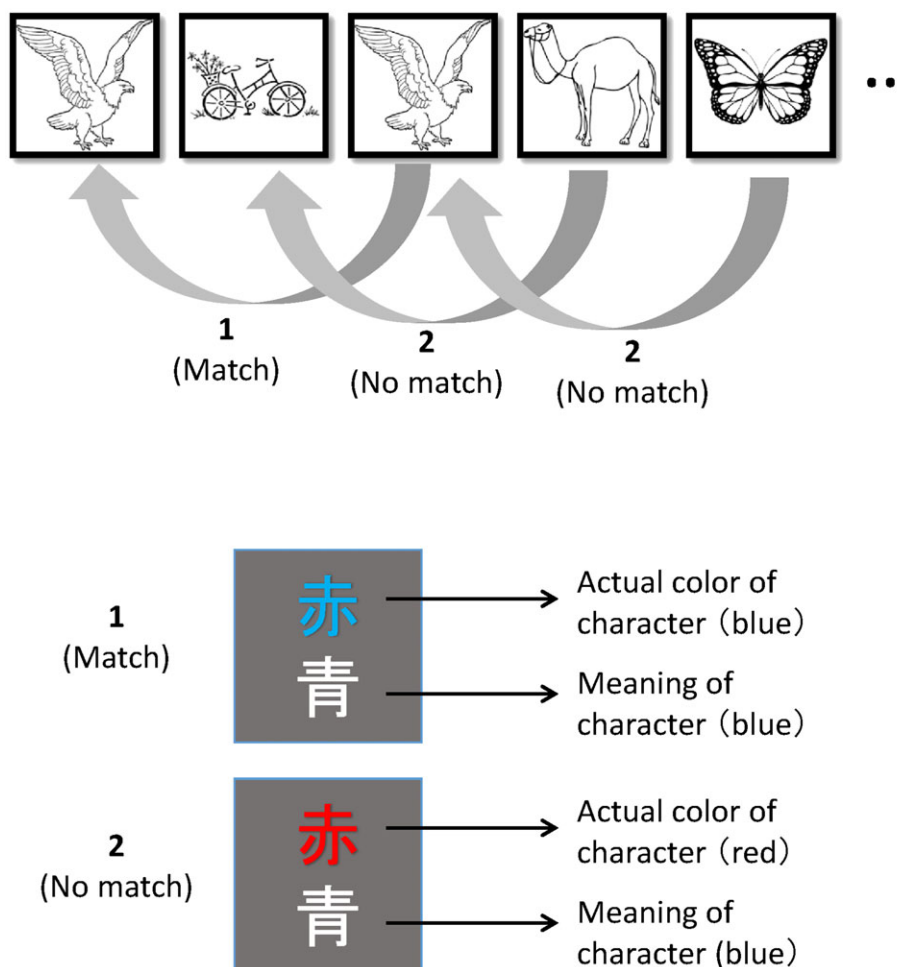


FIGURE 2 Schematic diagrams of the two-back test (top) and Stroop test (bottom). In the two-back test, the subject was instructed to press “1” when the onscreen illustration was identical to the one presented before the previous one (match) and to press “2” when the onscreen illustration was different from the one presented before the previous one (no match; top). In the Stroop task, the subject was instructed to press “1” when the “actual color” of the character presented in the upper position (blue) matched the “meaning” of the character presented in the lower position (blue) and to press “2” when the “actual color” of the character presented in the upper position (red) mismatched the “meaning” of the character presented in the lower position (blue; bottom)

feels (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973) and has been used in many of our studies (Inami et al., 2017; Mochizuki et al., 2002; Okamura et al., 2000). Subjects can report whether they feel active, vital, alert, wide awake, somewhat foggy, sleepy, or asleep by choosing a score. The higher the score, the drowsier and less alert the subject felt. In the LARS, subjects were asked to mark a series of 100-mm line analog scales, indicating their present state of sleepiness and fatigue. This method has also been used to measure various subjective effects such as sedation due to different psychoactive drugs (Hindmarch, 1975; Hindmarch, Shamsi, Stanley, & Fairweather, 1999; Ridout & Hindmarch, 2003; Ridout et al., 2003). The mean ratings of the scores were taken as a measurement of perceived sedation and fatigue (Sherwood & Hindmarch, 1993). As before, the higher the score, the drowsier or more tired the subject felt.

2.4 | [¹⁸F]Fluorodeoxyglucose positron emission tomography

2.4.1 | Positron emission tomography measurements

Each subject was scanned twice on each test day (FDG double-injection study). Subjects were first scanned in the “resting” control condition (PET1) and later in the “task” condition (PET2) to compare the regional brain metabolic changes due to antihistamines (Figure 1, top). Therefore, each subject underwent six PET examinations in total. In the resting condition, subjects, sitting in a quiet room with dim light, were requested to watch the center of the PC monitor for 30 min after the FDG injection (16.0 ± 0.7 MBq for PET1). In the second scan (PET2), shortly after the FDG injection (30.5 ± 1.1 MBq for PET2), they were requested to respond to sequential cognitive tasks with their voice or with their right index and middle fingers according to the instructions displayed on the PC monitor. Each PET brain scan was initiated shortly after the resting or task phases finished.

Brain scans were performed using the Eminence STARGATE PET scanner (Shimadzu Corp., Kyoto, Japan). The PET scanning covered the entire brain in one scan, taking 20 min for the emission scan and approximately 5 min for the transmission scan for tissue attenuation correction. Radiation exposure due to the series of six PET scans was estimated to be approximately 2.1 mSv. This amount is somewhat comparable with the annual environmental exposure of 2.4 mSv.

2.4.2 | Positron emission tomography image analysis

PET brain images were transformed into those representing standardized uptake values (SUVs), normalized by body weight and by injected radioactivity of FDG. These SUV images were analyzed to identify regional changes in glucose consumption using a software package, Statistical Parametric Mapping (SPM8; Functional Imaging Laboratory, London, UK; Friston et al., 1995; Friston, Frith, Liddle, & Frackowiak, 1991; Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). Positional errors between the two scans (PET1 and PET2 images) across the three drug treatments (in total, six images) were corrected within each subject (realignment). A PET2' image was produced to eliminate the effect of residual FDG radioactivity from the PET1 image by subtracting the PET1 image corrected with a decay coefficient from the PET2 image, based on the following equation:

$$PET2' = PET2 - PET1 \times \left(\frac{1}{2}\right)^{\frac{T_2 - T_1}{T_{1/2}}} \times \frac{A_1}{A_2},$$

where A_1 is the first injection dose activity, A_2 is the second injection dose activity, PET1 is the standard uptake value of image1, PET2 is the standard uptake value of image2, PET2' is the standard uptake value of image2', T_1 is the first scan start time, T_2 is the second scan start time, and $T_{1/2}$ is the half-life of ¹⁸F.

Then, an FDG brain template distributed by the Montreal Neurological Institute (MNI atlas; McGill University, Montreal, Canada) (Friston et al., 1995) was used for anatomical standardization (spatial normalization) of the PET1 and PET2' images by applying linear and nonlinear transformations to minimize the intersubject anatomical differences in gyral and functional anatomy. The spatially normalized data were smoothed using an isotropic Gaussian kernel of 12 mm for the x, y, and z axes to increase the signal-to-noise ratio.

Voxel-by-voxel analysis such as SPM is the standard tool for detecting regional changes in radioactivity levels in certain brain regions. The most popular contrast in these studies has been to compare “resting” with “task.” For statistical analysis, all “voxel” values were normalized to an arbitrary global (whole brain) mean value of 50 mg/100 ml/min by analysis of covariance to eliminate the effects of intersubject variability in global cerebral glucose metabolism. Repeated analysis of variance was applied to each voxel; only voxel clusters with voxels corresponding to $p < .05$ in a single test were maintained (corrected for multiple comparisons using Bonferroni correction). The statistical significance of a regional metabolic change was also given in Z scores. The Z score is, in general, the difference between the target group mean value (M_{target} ; the treatment condition in this study) and the control mean value (M_{control}), divided by the standard deviation (SD) of the control values ($[M_{\text{target}} - M_{\text{control}}]/SD_{\text{control}}$). The location of each statistical peak was identified by comparing the results with a coplanar stereotactic atlas of the human brain (Talairach & Tournoux, 1988). Statistically significant voxels were superimposed onto the standard MRI brain template images (Figure 3). Two contrasts were examined to demonstrate the regional increases and decreases in regional glucose consumption (Tables 1 and 2). In addition, regions of interest (ROIs) were also defined for bilateral prefrontal cortices such as Brodmann area (BA)9, BA10, and BA44/BA45 in PET images. The obtained ROI values were normalized by the whole brain mean value. Regional changes in glucose consumption were compared between the treatments (Figure 4).

2.5 | Near-infrared spectroscopy

During the cognitive tasks, hemodynamic responses were recorded as changes in oxygenated hemoglobin ($\Delta\text{oxy-Hb}$) concentrations in the frontal cortex using the OMM-3000 System (Shimadzu Corp.). This device uses near-infrared light at three different wavelengths (780, 805, and 830 nm). In the NIRS cap, light emitters (emitting probes) and detectors (receiving probes) were 3 cm apart. This apparatus can measure the relative concentrations of oxy-Hb. NIRS caps were positioned over the bilateral prefrontal regions, and the emitting and receiving probes were fixed (Figure 5, bottom left). The locations of these emitting and receiving probes as well as standard points on the

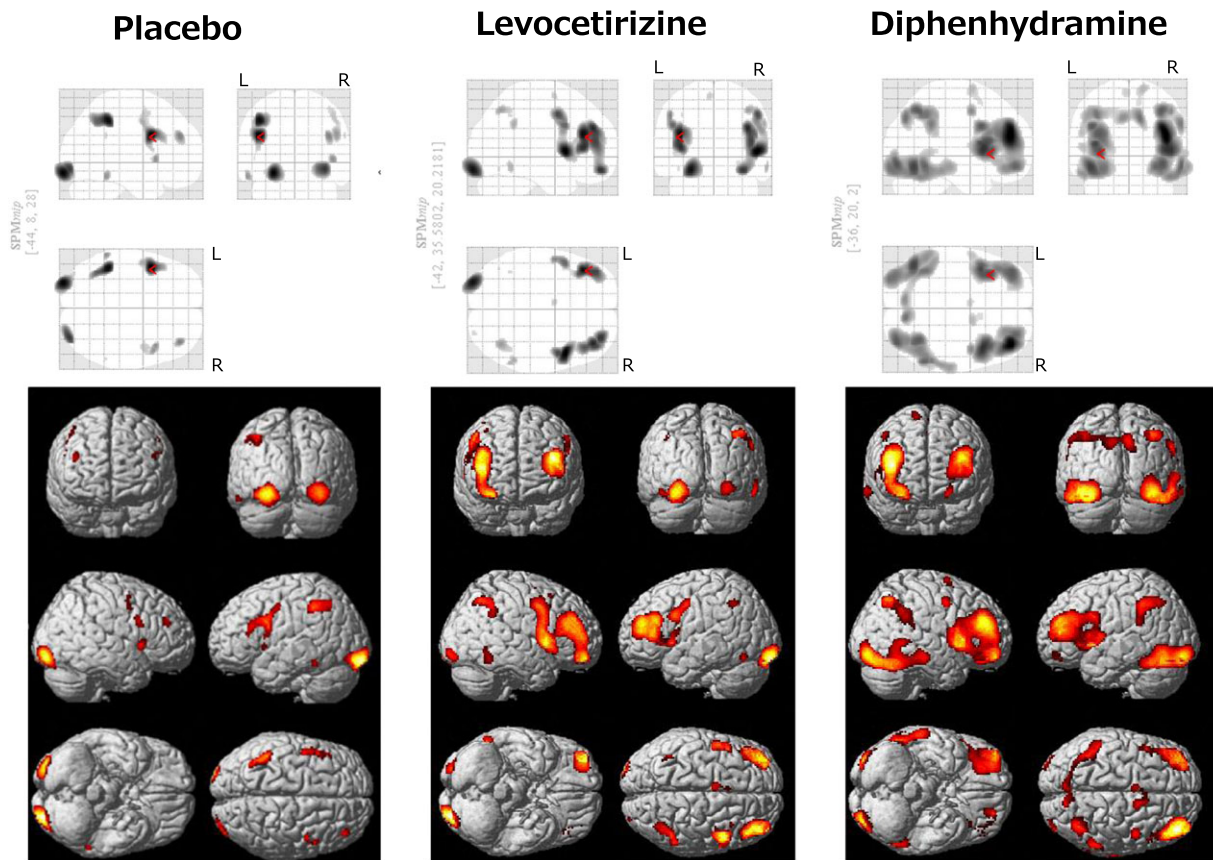


FIGURE 3 Results of voxel-by-voxel statistical parametric analysis of positron emission tomography images with [^{18}F]fluorodeoxyglucose. Statistically significant voxels are presented in the transparent standard brain space (glass brain, top) and superimposed onto the standard magnetic resonance imaging brain template images (bottom). The metabolic results of a voxel-by-voxel comparison of regional cerebral glucose metabolic images using statistical parametric mapping (SPM8; height threshold, $p < .05$, corresponding to z value >3.1 ; extent threshold 10 voxel minimum, with correction for multiple comparisons). L, left hemisphere; R, right hemisphere

head surface (Cz, Nz, Ar, and Al) were recorded using a magnetic 3D digitizer (FASTRAK; Polhemus Inc., Colchester, VT). The location of each logical channel was defined as the midpoint between the emitting and receiving probes (Figure 5, bottom). Near-infrared light absorption was measured with a time resolution of 1 s. In the present study protocol, the first cognitive task (word fluency task: Task1) was initiated after the pretask resting period (20 s) and lasted for 60 s; this was followed by other posttask and pretask resting periods (20 s each) and then the second task. Then, the second (two-back task: Task2) and third (Stroop task: Task3) tasks were assigned in a similar manner. Thus, the set of three cognitive tests was repeated six times (Figure 1, bottom). The cerebral hemodynamic response pattern was examined for each task and for each drug treatment condition.

2.5.1 | Near-infrared spectroscopy data analysis

For NIRS data analysis in the present study, we focused on the increase in oxy-Hb concentration, which is considered to be an estimate of regional brain activation. To see the spatial distribution of significant brain hemodynamic responses during cognitive tasks, regional activation was examined using the NIRS-SPM toolbox (Korea Advanced Institute of Science and Technology, Daejeon, Korea). After the original NIRS text data are converted into the NIRS-SPM format, 3D spatial information on the location of each channel, as obtained

using a 3D digitizer, was spatially registered to the standard brain template based on the Montreal Neurological Institute atlas (Okamoto et al., 2009; Singh, Okamoto, Dan, Jurcak, & Dan, 2005; Ye, Tak, Jang, Jung, & Jang, 2009). The oxy-Hb data were filtered with a low-pass filter (hemodynamic response function) to eliminate a high-frequency component that was regarded as noise. Later, significantly activated channels were detected using a general linear model based on hemodynamic functions by defining the onset time of each session of cognitive tasks (e.g., for Task1, onset = 20, 320, 620, 920, 1,220, and 1,520 s; duration = 60 s) in each individual subject (first-level analysis). In addition, the results of individual analyses were integrated into information of commonly activated channels in all subjects (group analysis). Stereotactic coordinates and statistical significances of activation were determined for Task1 activation with the threshold of $p < .05$, corresponding to t values > 1.7 for each subject (without correction for multiple comparisons: Figure 5, top and Table 3).

To examine the relationship between the increased regional glucose uptake and regional hemodynamic responses, we selected several prefrontal regions based on the SPM results of FDG-PET (e.g., bilateral BA9, BA10, and BA44/BA45). The NIRS channels spatially representing these regions (with a probability greater than 70%) were picked up based on the results of individual spatial registration as above (Okamoto et al., 2009; Singh et al., 2005; Tsuzuki et al., 2007; Ye et al., 2009). A low-pass filter (cutoff frequency: 0.1 Hz) was applied

TABLE 1 Regions of increased glucose consumption in comparison with the resting condition

Anatomical region	Hemisphere	Coordinates, mm			Brodmann area	Cluster equivalent	Voxel Z score
		x	y	z			
Placebo							
Inferior frontal gyrus	L	-44	8	28	44	582	6.25
Inferior frontal gyrus	R	48	12	28	44	170*	5.08
Middle frontal gyrus	R	40	42	28	9/46	96	5.27
Precentral gyrus	L	-50	-2	44	4/6	170*	4.97
Precentral gyrus	R	48	0	44	6	170*	4.77
Inferior parietal lobule	L	-44	-44	46	40	437	6.14
Inferior temporal gyrus	L	-58	-46	-18	37	44	5.11
Inferior occipital gyrus	L	-28	-98	-14	18	598	6.17
Inferior occipital gyrus	R	34	-90	-10	18	375	5.80
Insula	R	44	14	2		55	5.17
Levocetirizine							
Inferior frontal gyrus	L	-40	32	8	10/46	1,226	6.03
Inferior frontal gyrus	L	-48	10	32	44	205**	5.55
Middle frontal gyrus	L	-40	30	22	45/46	625*	6.29
Middle frontal gyrus	L	-38	44	24	9/10/46	625*	5.87
Middle frontal gyrus	R	38	42	28	9/46	625*	6.08
Medial frontal gyrus	L	-6	-2	62	6	18	4.75
Precentral gyrus	L	-52	-2	42	6	205**	5.32
Superior frontal gyrus	R	32	52	-16	11	625*	5.96
Inferior parietal lobule	R	56	-48	32	40	41	5.01
Superior parietal lobule	R	38	-64	48	40	114	5.12
Inferior temporal gyrus	L	58	-52	-14	37	21	4.92
Inferior occipital gyrus	L	-28	-96	-16	17/18	625*	6.28
Insula	R	48	10	4		2,396	6.44
Diphenhydramine							
Middle frontal gyrus	L	-36	46	22	9/10/46	2,634	7.03
Middle frontal gyrus	R	40	44	22	9/10/46	5,473*	65,535.00
Superior frontal gyrus	L	-4	-2	66	6	32	4.93
Superior frontal gyrus	R	14	2	68	6	120	5.32
Inferior frontal gyrus	R	42	14	6	44/45	5,473*	7.66
Precentral gyrus	R	46	0	46	4/6	128	6.26
Inferior parietal lobule	L	-38	-54	42	40	1,623	6.63
Superior parietal lobule	R	36	-62	46	7/40	1,063	6.99
Precuneus	L	-8	-76	38	7	128	6.13
Precuneus	R	12	-76	38	7	1,623	6.63
Supramarginal gyrus	R	58	-46	32	40	1,623	6.43
Inferior temporal gyrus	R	58	-54	-14	37	1,063	6.86
Fusiform gyrus	L	-46	-66	-14	19	2,264	7.42
Inferior occipital gyrus	L	-32	-90	-16	18	1,063	6.63
Inferior occipital gyrus	R	36	-86	-12	18/19	2,634	7.10
Insula	L	-40	10	10		4,002	7.36
Insula	L	-36	20	2		4,002	7.18
Cerebellum	L	-52	-52	-22		128	6.09
Cerebellum	R	46	-60	-24		1,623	6.36

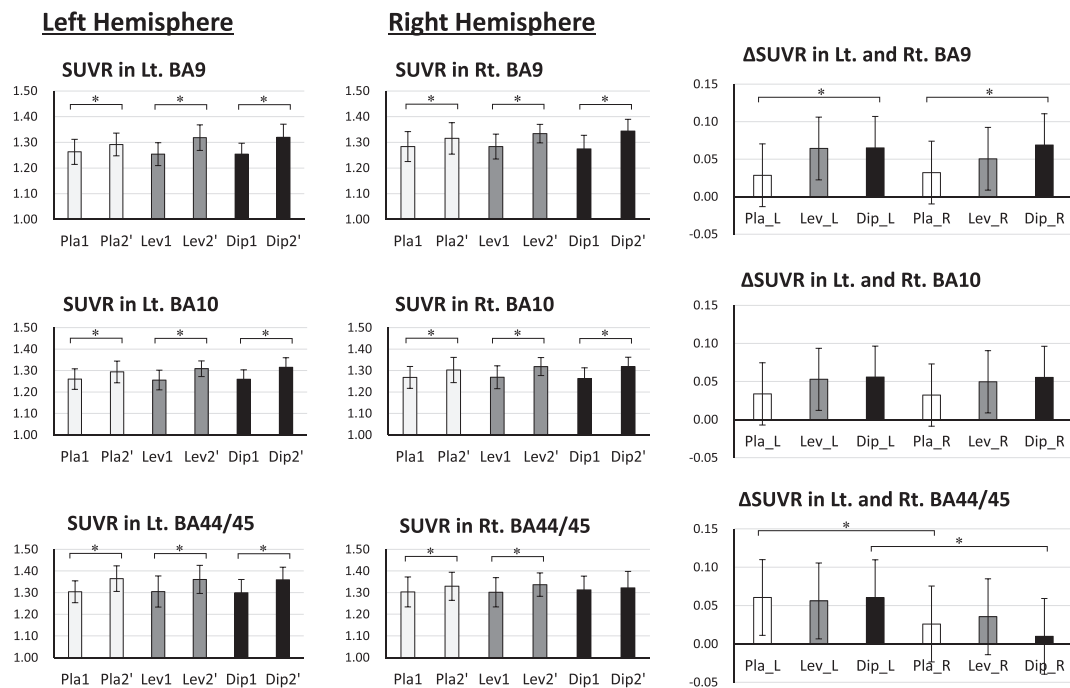
Note. These asterisks with the same cluster equivalent values indicate that these peaks belong to the same cluster, showing multiple high peaks within a single cluster.

to the oxy-Hb waveform data to attenuate a high-frequency component (Kreplin & Fairclough, 2013). The oxy-Hb data were also corrected for baseline offset (zero) to the task starting time ($t = 0$) and were transformed into Δ oxy-Hb data and were averaged to

demonstrate hemodynamic responses in bilateral prefrontal areas during the task for the three drug treatment conditions (Figure 6, left and middle). Δ oxy-Hb waveform values were averaged throughout the task phase (0–60 s) for statistical examination (Figure 6, right).

TABLE 2 Regions of decreased glucose consumption in comparison with the resting condition

Anatomical region	Hemisphere	Coordinates, mm			Brodmann area	Cluster equivalent	Voxel Z score
		x	y	z			
Placebo							
Inferior parietal gyrus	L	-22	-36	46	40	38	4.90
Occipital cortex	L	-12	-98	28	19	164	5.75
Occipital cortex	L	-18	-94	34	19		5.43
Cerebellum	L	-8	-60	-6		614	5.45
Cerebellum	R	18	-48	-50		14	4.64
Levocetirizine							
Posterior cingulate gyrus	L	-6	-56	10		3,246	6.32
Middle temporal gyrus	L	-64	0	-18	21	10	4.92
Occipital cortex	L	-8	-98	26	19	267	6.59
Occipital cortex	L	-14	-92	38			4.99
Cerebellum	L	-4	-48	-6			6.25
Cerebellum	R	26	-88	-40		13	4.75
Pons	L	-14	-18	-26			5.98
Diphenhydramine							
Postcentral gyrus	L	-64	-16	40	1-4	78	5.97
Postcentral gyrus	R	28	-30	60	1-4	932	5.59
Cerebellum	L	-44	-74	-48		26	4.99
Cerebellum	R	56	-52	-44		7	4.85
Pons	L	-2	-14	-22		9,260	6.88

**FIGURE 4** Results of region of interest analysis of positron emission tomography images with [¹⁸F]fluorodeoxyglucose. **p* < .05, ***p* < .001 for the post hoc Bonferroni test. SUVR, standardized uptake value ratio; BA, Brodmann's area; Lt., left; Rt., right; Pla, placebo; Lev, levocetirizine; Dip, diphenhydramine

2.6 | Statistics

For statistical analyses, we used SPSS 22.0 (Japanese version). For the subjective sedation, the SSS and LARS scores were both examined by applying nonparametric examinations such as the Friedman test and

Wilcoxon signed rank test (two-tailed; *p* ≤ .05). All results of cognitive tests, including word counts in word fluency tests and accuracy and reaction time in the two-back and Stroop tests, were also examined between drug treatments using nonparametric methods such as the Friedman test and Wilcoxon signed rank test (two-tailed; *p* ≤ .05).

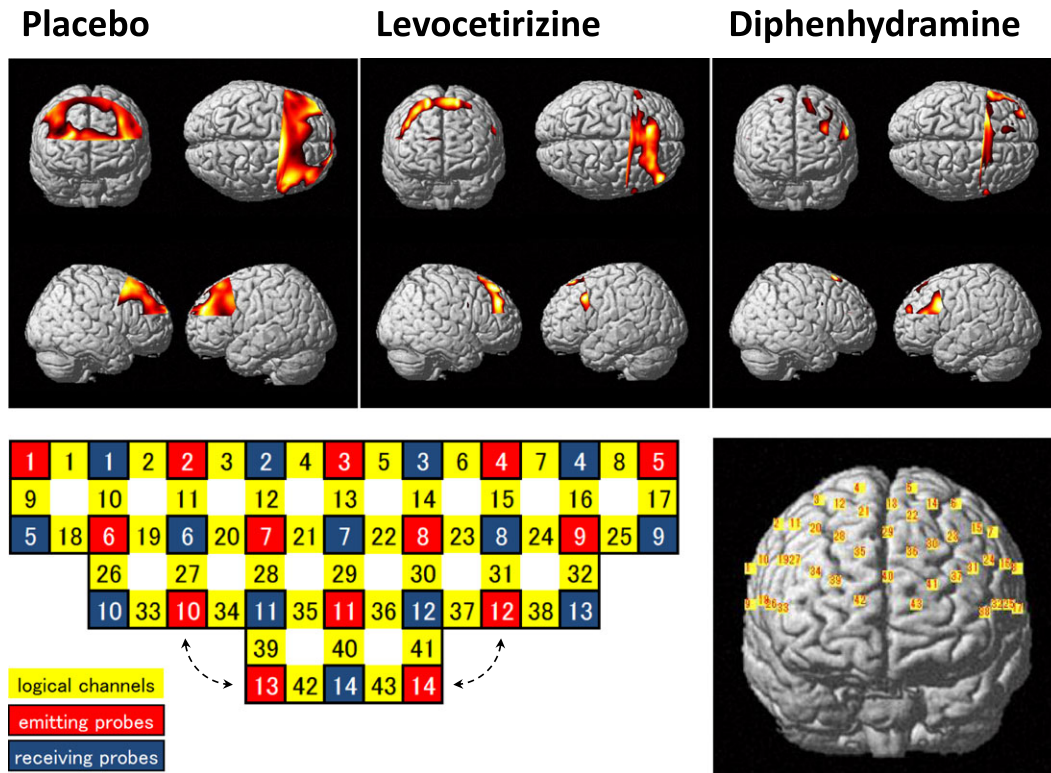


FIGURE 5 Results of statistical parametric analysis of near-infrared spectroscopy (NIRS-SPM). Statistically significant channel data are superimposed onto the standard magnetic resonance imaging brain template images (top; height threshold, $p < .05$, corresponding to t value > 1.7 , without correction for multiple comparisons). Locations of the emitting (red) and receiving (blue) probes and logical channels (yellow) are shown (bottom left). Dotted arrows indicate sutures to construct a cap. Locations of the channels superimposed onto the surface of standard brain template (bottom right)

TABLE 3 Suprathreshold regional increases in hemodynamic responses (activations)

Anatomical region	Hemisphere	Channels	Coordinates, mm			Brodmann Area (BA)	t-value		
			x	y	z		Placebo	Levocetirizine	Diphenhydramine
Middle frontal gyrus	L	No. 16	-56	15	33	44/9	3.050	1.966	2.590
Middle frontal gyrus	L	No. 24	-48	33	36	9	2.226	n.s.	n.s.
Middle frontal gyrus	R	No. 39	25	64	27	10	3.394	n.s.	n.s.
Middle frontal gyrus	L	No. 23	-30	37	49	8/9	2.859	n.s.	n.s.
Middle frontal gyrus	R	No. 20	35	35	49	8/9	3.118	2.392	n.s.
Superior frontal gyrus	L	No. 31	-40	45	34	9/46	3.299	n.s.	n.s.
Superior frontal gyrus	R	No. 27	44	43	33	9/46	2.623	2.300	n.s.
Superior frontal gyrus	L	No. 37	-29	56	31	9/10	1.819	n.s.	2.319
Superior frontal gyrus	R	No. 34	34	55	30	9/10	1.873	n.s.	n.s.
Superior frontal gyrus	R	No. 40	5	64	30	9/10	2.236	n.s.	n.s.
Superior frontal gyrus	L	No. 43	-11	71	18	10	3.774	n.s.	n.s.
Superior frontal gyrus	R	No. 42	16	71	19	10	3.080	1.911	n.s.
Superior frontal gyrus	L	No. 22	-10	40	57	8	2.008	2.034	n.s.
Superior frontal gyrus	R	No. 21	15	39	57	8	n.s.	1.928	n.s.
Superior frontal gyrus	L	No. 15	-42	23	52	8/6	2.570	1.219	1.739
Superior frontal gyrus	R	No. 11	46	22	51	8/6	3.859	n.s.	n.s.
Superior frontal gyrus	R	No. 12	26	25	61	8/6	2.403	2.266	n.s.
Superior frontal gyrus	L	No. 14	-20	26	63	6/8	3.115	1.965	n.s.
Superior frontal gyrus	R	No. 13	4	28	63	6/8	2.053	2.289	n.s.

Note. Statistical threshold: t value > 1.7 , that is corresponding to $p > .05$ (not corrected for multiple comparisons).

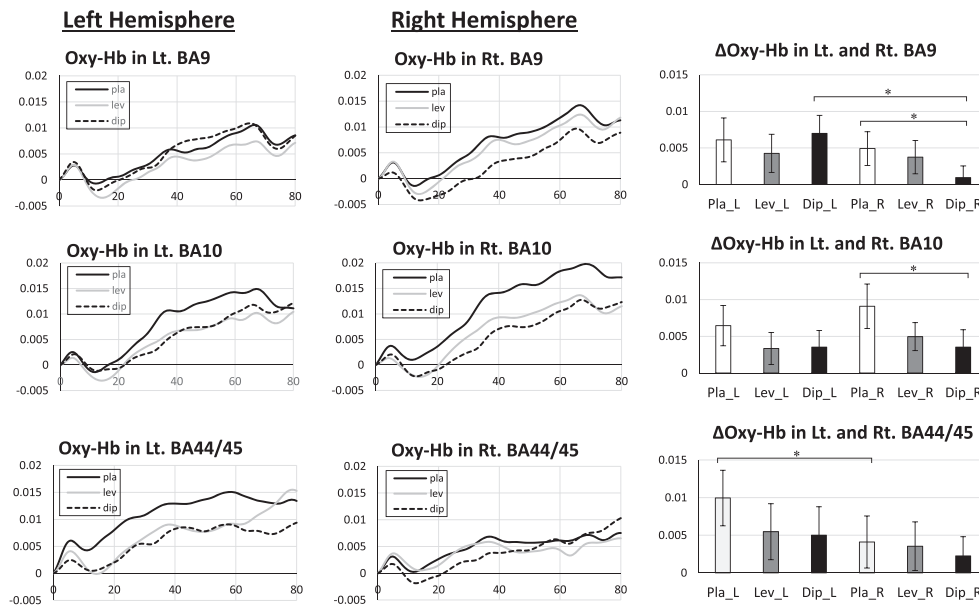


FIGURE 6 Changes in oxygenated hemoglobin (Δ oxy-Hb) waveforms showing cortical activation patterns during word fluency task (Task1) in BA9, BA10, and BA44/BA45 in the left and right hemispheres measured with near-infrared spectroscopy (left and middle columns). Results of statistical examination regarding the quantitative analysis of activation (right column). * $p < .05$, ** $p < .001$ for the post hoc Wilcoxon signed rank test. BA, Brodmann's area; Lt., left; Rt., right; Pla, placebo; Lev, levocetirizine; Dip, diphenhydramine; oxy-Hb, oxygenated hemoglobin

For the statistical analyses of PET images, the repeated analysis of variance was applied because a normal distribution and equal variance were confirmed. Significant findings were additionally examined by post hoc multiple pairwise treatment comparisons using a Bonferroni test (two-tailed; $p \leq .05$). For the statistical analyses of NIRS data, non-parametric examinations such as the Friedman test and Wilcoxon signed rank test (two-tailed; $p \leq .05$) were applied because normal distribution and equal variance were not confirmed. In addition, linear correlation between Δ oxy-Hb and Δ SUV ratio (SUVR) was also examined in BA9, BA10, and BA44/BA45 across individual subjects within each treatment condition and within each brain region, as well as for all subjects combined.

3 | RESULTS

3.1 | [18 F]Fluorodeoxyglucose positron emission tomography

FDG-PET analysis using SPM8 revealed significant regional brain changes in glucose consumption during the cognitive tasks (PET2') compared with the pretreatment resting images (PET1) for each drug treatment condition (Figure 3, Tables 1 and 2). These results showed some similarities to previous neuroimaging studies of word fluency tasks using the Japanese language (Dan et al., 2013; Kohmura et al., 2013). In the placebo treatment, increased glucose consumption was observed, mainly in the prefrontal cortex (BA9, BA44, and BA46) bilaterally, precentral gyrus (BA4 and BA6) bilaterally, left parietal and temporal cortices (BA37 and BA40), occipital cortex (BA18) bilaterally, and right insular cortex. Notably, the activation in BA44 (Broca's area) was more dominant in the left hemisphere than in the right, as indicated by higher Z values ($L/R = 6.25/5.08$, respectively) and larger cluster size

($L/R = 582/170$, respectively; Table 1, Figure 3). Decreased glucose metabolism was observed in the left inferior parietal gyrus, left occipital gyrus, and cerebellum (Table 2). With levocetirizine treatment, increased glucose consumption was observed in the prefrontal cortex (BA44, BA45, BA46, BA9, and BA10) bilaterally, right precentral gyrus (BA6), left parietal and temporal cortices (BA37 and BA40), occipital cortex (BA17/BA18) bilaterally, and right insular cortex (Table 1, Figure 3). Decreased glucose metabolism was observed in the left cingulate gyrus, left temporal gyrus, bilateral occipital gyrus, and pons (Table 2). With diphenhydramine treatment, an increased glucose consumption was observed in the prefrontal cortex (BA44, BA45, BA46, BA9, and BA10) bilaterally, precentral gyrus (BA4 and BA6) bilaterally, left parietal and temporal cortices (BA7, BA37, and BA40), occipital cortex (BA18/BA19) bilaterally, left insular cortex, and cerebellum bilaterally. The activation in BA9, BA10, and BA46 was more intense and extensive in the right hemisphere than in the left, as indicated by higher Z values ($L/R = 7.03/65,535.00$, respectively) and larger cluster size ($L/R = 2,634/5,473$, respectively) in the right hemisphere compared with the left (Table 1, Figure 3). Decreased glucose metabolism was observed in the bilateral postcentral gyrus and cerebellum (Table 2).

In addition, ROI analysis revealed that the SUVR values of PET2' images were significantly higher than those of PET1 images in the bilateral BA9 and BA10 and in the left BA44/BA45 after levocetirizine and diphenhydramine treatment (Figure 4, left and middle). A significant difference in Δ SUVR was observed in the bilateral BA9 regions, with the Δ SUVR values being significantly higher after diphenhydramine treatment than after placebo (Figure 4, right; left and right: $p = .018$ and $.010$, respectively). In BA44/BA45, the Δ SUVR values in the left hemisphere were significantly higher than those in the right hemisphere with placebo and diphenhydramine treatments (Figure 4, right; placebo and diphenhydramine: $p = .002$ and $p = .004$, respectively).

3.2 | Near-infrared spectroscopy data

NIRS-SPM analysis demonstrated the significant regional changes in brain hemodynamics during the cognitive tasks (during the word fluency task [Task1] following placebo treatment) compared with the baseline for each drug treatment condition (Table 3, Figure 5, top). With placebo treatment, increased hemodynamic responses were observed mainly in the bilateral frontal cortex (BA6, BA8, BA9, BA10, BA44, and BA46), basically showing similarities to previous NIRS studies of the word fluency tasks using the Japanese language (Dan et al., 2013; Kohmura et al., 2013). Notably, the significant activation in the left BA44/BA9 only (including Broca's area: channel 16) demonstrated that this activation was associated with the word fluency task (Table 3, Figure 5, top). With levocetirizine treatment, significant hemodynamic responses were observed in a less extensive area of the bilateral frontal cortex than those with placebo treatment (Table 3, Figure 5, top). With diphenhydramine treatment, significant hemodynamic responses were observed in much less extensive area in the left frontal cortex than those with placebo treatment (Table 3, Figure 5, top).

Temporal and quantitative aspects of hemodynamic responses were examined in the prefrontal regions that showed significant activation in FDG-PET (BA9, BA10, and BA44/45). Prefrontal activation ($\Delta\text{oxy-Hb}$) was much more prominent during Task1 than during the other tasks; thus, activation during Task2 and Task3 was much less prominent. In terms of temporal analysis, cortical activation patterns during Task1 in BA9, BA10, and BA44/45 were compared in both hemispheres (Figure 6). Basically, there was no clear difference in shape of $\Delta\text{oxy-Hb}$ waveforms between drug treatments (Figure 6, left and middle). In all treatment conditions, there was an initial small peak (at 5 s after task onset) in hemodynamic responses, and the highest peak was observed at 60–70 s after task onset. There were some significant differences between the hemispheres and between the treatment conditions, with the general trend for higher activation with placebo treatment than with antihistamine treatment (Figure 6, left and middle).

In terms of quantitative analysis, in the right hemisphere, $\Delta\text{oxy-Hb}$ values in BA9 and BA10 were significantly reduced after diphenhydramine treatment compared with placebo ($p = .018$ and $.035$, respectively; Figure 6, right). In the left hemisphere, there were no significant intertreatment differences. In addition, the right hemisphere showed a trend for higher hemodynamic responses as compared with the left hemisphere in BA10, whereas the left hemisphere showed a trend for higher hemodynamic responses as compared with the right hemisphere in BA44/BA45. Statistical analysis revealed a laterality in BA9 and BA44/BA45, with significantly higher $\Delta\text{oxy-Hb}$ in the left BA9 than in the right after diphenhydramine treatment ($p = .006$) as well as significantly higher $\Delta\text{oxy-Hb}$ in the left BA44/BA45 than in the right after placebo treatment ($p = .016$; Figure 6, right). There were no clear differences during Task2 and Task3. In addition, no significant linear correlation was detected between $\Delta\text{oxy-Hb}$ and ΔSUVR (FDG-PET) in bilateral prefrontal regions (BA9, BA10, and BA44/BA45).

3.3 | Performances in the cognitive tests

Performance in the Stroop test (accuracy) was significantly impaired after treatment with the sedative antihistamine (diphenhydramine

50 mg) compared with both the placebo ($p = .008$; Figure 7, top) and the levocetirizine treatment ($p = .001$; Figure 7, top). There was no significant difference between the accuracy results of the placebo and levocetirizine treatments (Figure 7, top). Another index for performance in the Stroop test (reaction time) did not show significant difference among the three drug treatments (Figure 7, bottom). As for the word fluency and two-back tests, both accuracy and reaction time measures showed no significant differences among the three drug treatments.

3.4 | Subjective sedation assessment

A significant increase in subjective sleepiness (SSS) from the near baseline score (30 and 60 min postadministration) was observed with both the placebo and diphenhydramine treatments (Figure 8, top). There were no significant differences in the intensity of subjective sleepiness between the placebo and diphenhydramine treatments (Figure 8, top), although the diphenhydramine treatment manifested a trend for increased sleepiness compared with the placebo. It seemed that the intensity of sleepiness peaked at approximately 120 to 150 min after oral administration. Another index of subjective sleepiness (LARS) showed a similar tendency with no significant difference among the three drug treatments (Figure 8, middle). It seemed that the intensity of sleepiness peaked at around 120 min after oral administration. A significant increase in subjective sleepiness (LARS) from the near baseline score (0, 30, and 60 min postadministration) was observed with diphenhydramine (Figure 8, middle).

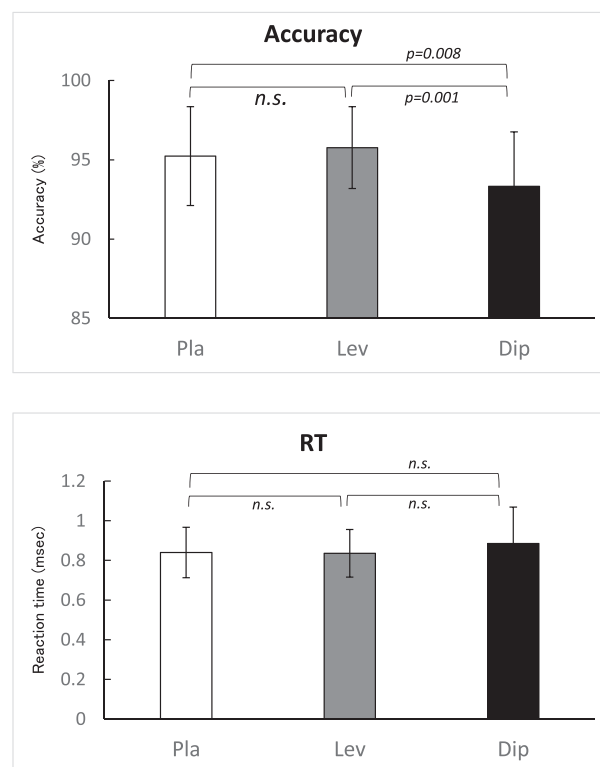


FIGURE 7 Results of the Stroop test. Accuracy values are presented as percent (top) and reaction time (RT) values are presented as milliseconds (bottom). Standard deviation is shown by error bars. Pla, placebo; Lev, levocetirizine; Dip, diphenhydramine; n.s., not significant

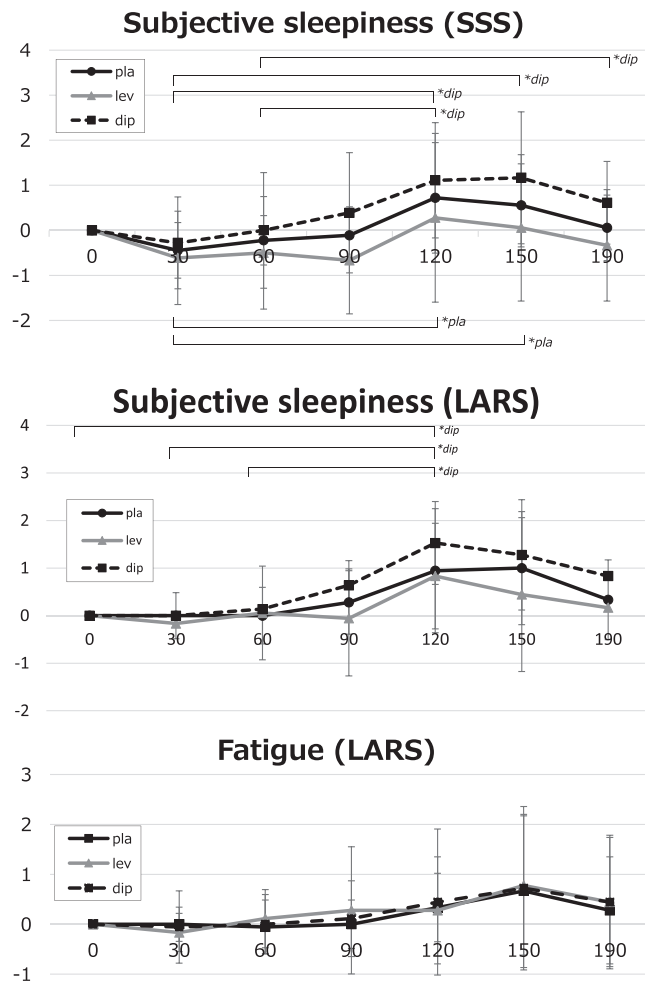


FIGURE 8 Results of subjective sleepiness and fatigue. Values are mean scores, and standard deviation is illustrated by error bars. * $p < .05$, ** $p < .001$ for the post hoc Wilcoxon signed rank test. Pla, placebo; Lev, levocetirizine; Dip, diphenhydramine

Subjective feelings of fatigue also showed a similar trend with no significant difference (Figure 8, bottom). In addition, the intensity of fatigue peaked at approximately 150 min after oral administration (Figure 8, bottom).

3.5 | Adverse events

There were no reports of specific spontaneous adverse events in the present study.

4 | DISCUSSION

As far as we know, this is the first human FDG-PET study of antihistamine treatment. In principle, increased metabolism can be interpreted as increased energy demand/consumption in the regional brain tissue. In the present study, SPM8 results (Figure 3, Table 1) revealed that regional energy consumption was more prominent and more extensive with antihistamine treatments than with placebo in the following order: diphenhydramine > levocetirizine > placebo. ROI analysis (Figure 4) revealed that the regional energy consumption during the task phase (PET2') tended to be significantly higher after treatments

with placebo, levocetirizine, and diphenhydramine than in the resting control data (PET1), suggesting the possibility of increased energy demands for executing cognitive tasks after drug treatment. Additional FDG-PET findings suggested that, after antihistamine treatment, subject's specific brain regions increased energy consumption to achieve similar outputs to those after placebo treatment. Notably, during the word fluency task, the Δ SUV values were significantly higher in the left hemisphere than in the right hemisphere. This would be reasonable because the motor language region (Broca's area) is located in the left hemisphere, suggesting that this specific brain region was sufficiently stimulated by the word fluency task in the present study. Energy consumption in the right hemisphere might be reduced to save energy. It is also interesting that Δ SUV in BA9 and BA10 showed a trend for increased energy consumption after antihistamine treatment than after placebo. In particular, Δ SUV values in BA9 were significantly higher after diphenhydramine treatment, whereas those of levocetirizine treatment seemed to be in an intermediate position (Figure 4). These data may additionally suggest that brain activation in the left BA44/BA45 (Broca's area) after antihistamine treatment was not sufficient to achieve the same performance outputs in cognitive tasks as after placebo. This possibly leads to a recruitment of surrounding prefrontal regions such as BA9 and BA10 after antihistamine treatment (Figure 3). Thus, FDG-PET seems to be useful to monitor changes in regional energy demand/consumption after antihistamine treatment.

The present results can be compared with those of previous perfusion studies using H_2O PET. Okamura and colleagues were the first to demonstrate regional blood flow changes in humans after oral administration of *d*-chlorpheniramine. This study showed regions of both significantly increased and decreased rCBF changes during a visual discrimination task with an ultrashort exposure duration (5 ms). Major significant activation was observed in the anterior cingulate gyrus, left insular cortex, and right inferior frontal gyrus (Okamura et al., 2000). The activation in the cingulate gyrus suggested that the ultrashort visual task required high concentration and attention in the study subjects. Regions of decreased perfusion (deactivation) were also observed in the left temporal and frontal cortices, suggesting that these regions are not directly involved in the information processing (Okamura et al., 2000). Another study by Mochizuki and colleagues demonstrated that administration of *d*-chlorpheniramine impaired performance in visuomotor spatial discrimination tasks. With the placebo treatment, an increased activity (activation) was observed in the cingulate cortex (BA24) and in the right parietal cortex (BA40), which might be associated with attention and visuomotor spatial cognition, respectively. After the administration of *d*-chlorpheniramine, the activation in BA40 was suppressed while that in BA24 was augmented. Suppression of BA40 activation was associated with impaired visuomotor spatial cognition due to sedative effects, whereas augmentation of BA24 activation was associated with compensation (Mochizuki et al., 2002). Another car-driving study by Tashiro and colleagues also found suppressed activation in the parietal, temporal, and occipital cortices, but augmented activation in the frontal region. It is speculated that some regions can be suppressed by a sedative antihistamine whereas other regions may be activated to compensate for functional deficits (Tashiro, Sakurada, et al., 2008). Thus, comparable brain responses

were observed in H₂O and FDG-PET studies, although the timescales were very different between FDG-PET and H₂O PET (H₂O PET data can fluctuate minute by minute, whereas FDG-PET data represent accumulations over 30 min).

In addition, hemodynamic responses after antihistamine treatment have also been studied using NIRS. In a study by Tsujii et al. (2007), an increased activation was observed in the prefrontal region during working memory and selective attention tasks in healthy adults administered placebo treatment. Such activation was suppressed by ketotifen (sedative antihistamine) but was not suppressed by epinastine (a mildly sedative antihistamine). Together with their studies in preschool children (Tsujii et al., 2009; Tsujii, Yamamoto, Ohira, Takahashi, & Watanabe, 2010), NIRS revealed that sedative and nonsedative antihistamines exert differential effects on brain hemodynamic response in healthy volunteers. In all of these NIRS studies, only reduced hemodynamic responses were observed, and no augmented hemodynamic responses were reported.

The present study is also the first one that conducted both FDG-PET and NIRS. In the present study, hemodynamic responses during the word fluency task seemed to be suppressed by antihistamine treatment compared with placebo (Figure 6), as previously demonstrated by Tsujii et al. (2007, 2009, 2010). Hemodynamic responses tended to be more suppressed after antihistamine treatment than after placebo treatment in the order placebo > levocetirizine > diphenhydramine (Figure 6), and less extensive areas showed activation after diphenhydramine treatment compared with those after placebo treatment (Figure 5), which is an inverse of the FDG-PET results. These results seem to be contradictory based on the “coupling” theory (linear correlation between the regional energy consumption and perfusion), where a slight increase in the consumption of oxygen and glucose due to regional brain activation is followed by a rapid and considerable surge in oxygen and glucose concentrations due to rapid capillary dilations in the activated brain regions. Thus, in principle, brain activation should be accompanied by a marked increase in oxy-Hb concentration. Antihistamines might possibly suppress the permeability of brain capillaries, dulling the prompt hemodynamic responses (Abbott, 2000; Sharma & Dey, 1986, 1987). However, such suppression might complicate continuous hemodynamic responses (up to 30 min, as in the present study).

Regarding the performance measures in the present study, an “accuracy” measure in the Stroop test was significantly impaired after the diphenhydramine treatment compared with the placebo treatment ($p = .008$; Figure 7, top). This accuracy measure in the Stroop test was also significantly impaired with diphenhydramine treatment compared with levocetirizine treatment ($p = .001$; Figure 7, top), suggesting that levocetirizine is distinguishable from diphenhydramine in terms of cognitive performance impairment. It is interesting to mention that, after diphenhydramine treatment, prefrontal energy consumption was significantly increased but performance was significantly impaired, whereas the prefrontal energy consumption was relatively increased and the performance was not impaired after levocetirizine treatment.

As for subjective sleepiness, a significant increase in both SSS and LARS from baseline was observed with both diphenhydramine and placebo treatments (Figure 8). Accordingly, the differences between these

drugs were not statistically significant, although diphenhydramine showed a trend for a higher subjective sleepiness than placebo (Figure 8). The reason for these nonsignificant findings might be attributable to the study environment, with the study subjects spending the FDG uptake period (30 min) in a dark and quiet study chamber that would even induce natural sleepiness in those administered the placebo treatment. Similar results were observed in previous studies of car driving (Tashiro, Sakurada, et al., 2008). Previous NIRS studies combined with cognitive tests failed to detect interdrug differences in subjective sleepiness (Tsujii et al., 2007, 2009, 2010). Thus, it is not uncommon for performance to be impaired in the absence of subjective sleepiness. Therefore, such a situation is consistent with the statement in CONGA that “qualification of new-generation antihistamines should not be based on subjective evaluations alone” (Holgate et al., 2003). In addition, the feeling of fatigue appeared to be more intense with diphenhydramine treatment than with placebo, but the difference was not significant (Figure 8).

On the basis of all of these findings, we would like to propose the following hypotheses:

1. Sedative antihistamines greatly impair neural transmission in the histaminergic nervous system, whereas nonsedative antihistamines may slightly impair neural transmission in this system. Energy demands during cognitive tasks are increased with both treatments. Slight sedative effects due to nonsedative antihistamines can be overcome by increased brain metabolic activity, whereas sedation and performance impairments due to sedative antihistamines cannot be reversed even with the increased brain metabolic activity.
2. Vascular permeability of brain capillaries may be suppressed to some extent with both treatments. Particularly under the condition of long-term cognitive load ranging from 0.5 to 1 hr, the contrast between nonsedative and sedative antihistamines will be more apparent. Finally, the oxy-Hb level will be lower under antihistamine treatments than under placebo conditions, leading to a transient break in the coupling between metabolism and perfusion.

To test and confirm the above hypotheses, various studies will be needed, including not only additional clinical studies but also basic studies of the effects of antihistamines on brain capillary permeability (Abbott, 2000; Sharma & Dey, 1986, 1987) and energy metabolism that assess the interactions of neurons and astrocytes (Magistretti & Pellerin, 1996, 1999; Mann, Pearce, Dunn, & Shakir, 2000; Pellerin et al., 2007; Zimmer et al., 2017).

4.1 | Limitations of the present study

In the present study, only one measure of cognitive tests showed a significant difference between the different drug treatments. Such a situation may not be as rare as indicated in CONGA; due to insufficient sensitivity, only some testing batteries demonstrated significant impairments (Holgate et al., 2003). In general, the difficulty of the present cognitive tasks used was not sufficiently high for the young university students recruited for the present study. For instance, three- or

four-back tasks might have more effectively contrasted the effects of the nonsedative and sedative antihistamines.

In the present FDG-PET measurements, pharmacological effects due to antihistamines and physiological effects due to cognitive tasks were mixed. Further work is required to determine the pharmacological effects of antihistamines in the resting brain.

Finally, we expected the complementary use of PET and NIRS, but we experienced some technical problems. One potential problem is that NIRS may sometimes require quite a long time (more than 60 s) to recover to the baseline state if the first activation is very strong, although 30–40 s seemed to be sufficient in many previous studies and in our pilot studies. Accordingly, we only analyzed Task1 data in the present NIRS study. Additional software and analytical methods need to be developed.

Through a direct comparison of PET and NIRS data, we recognized the poorer sensitivity of NIRS and lower signal-to-noise ratio of NIRS compared with PET data. We also hope that additional technical advancements reduce noise in NIRS data and achieve higher signal-to-noise ratios.

5 | CONCLUSION

In the present study, we confirmed the usefulness of the FDG double-injection protocol for the clinical evaluation of antihistamines in healthy volunteers. We also demonstrated that FDG-PET is sufficiently sensitive to evaluate differences in the sedative properties of different antihistamine treatments. In terms of energy (glucose) consumption, some prefrontal regions were activated more strongly and more extensively by the sedative antihistamine, probably in order to achieve maximal performance outputs under the pharmacologically impaired conditions. In contrast, in terms of blood supply, some prefrontal regions were activated less strongly and less extensively by the sedative antihistamine. Thus, physiological coupling between metabolism and perfusion in the healthy human brain may not be maintained under the pharmacological influence of sedative antihistamines. This uncoupling may be caused by a combination of increased energy demands in the prefrontal regions and suppression of vascular permeability in brain capillaries after antihistamine treatment. Further research is needed to elucidate this mechanism. In addition, the present results showed that acute oral administration of levocetirizine 5 mg did not impair performance in the Stroop test in healthy Japanese volunteers, unlike diphenhydramine 50 mg.

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CONFLICTS OF INTEREST

M. Tashiro declares potential conflicts of interest regarding the present study because this study was supported by a collaboration research grant from GlaxoSmithKline (to M. Tashiro). K. Yanai, H. Watabe, and K. Hiraoka declare potential conflicts of interest as major collaborators in the present study.

ORCID

Manabu Tashiro  <http://orcid.org/0000-0002-8860-6917>

REFERENCES

- Abbott, N. J. (2000). Inflammatory mediators and modulation of blood-brain barrier permeability. *Cellular and Molecular Neurobiology*, *20*(2), 131–147.
- Casale, T. B., Blaiss, M. S., Gelfand, E., Gilmore, T., Harvey, P. D., Hindmarch, I., ... Wong, D. F. (2003). First do no harm: Managing antihistamine impairment in patients with allergic rhinitis. *The Journal of Allergy and Clinical Immunology*, *111*(5), S835–S842.
- Church, M. K., & Maurer, M. (2012). H1-antihistamines and urticaria: How can we predict the best drug for our patient? *Clinical and Experimental Allergy*, *42*, 1423–1429.
- Church, M. K., Maurer, M., Simons, F. E., Bindslev-Jensen, C., van Cauwenberge, P., Bousquet, J., ... Zuberbier, T. (2010). Risk of first-generation H1-antihistamines: A GA²LEN position paper. *Allergy*, *65*, 459–466.
- Clough, G. F., Boutsiouki, P., & Church, M. K. (2001). Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin. *Allergy*, *56*(10), 985–988.
- Dan, H., Dan, I., Sano, T., Kyutoku, Y., Oguro, K., Yokota, H., ... Watanabe, E. (2013). Language-specific cortical activation patterns for verbal fluency tasks in Japanese as assessed by multichannel functional near-infrared spectroscopy. *Brain and Language*, *126*(2), 208–216.
- Duan, X., Tashiro, M., Wu, D., Yambe, T., Wang, Q., Sasaki, T., ... Itoh, M. (2007). Autonomic nervous function and localization of cerebral activity during lavender aromatic immersion. *Technology and Health Care: Official Journal of the European Society for Engineering and Medicine*, *15*(2), 69–78.
- Friston, K. J., Ashburner, J., Frith, C. D., Poline, J. B., Heather, J. D., & Frackowiak, R. S. (1995). Spatial registration and normalization of images. *Human Brain Mapping*, *3*(3), 165–189.
- Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. (1991). Comparing functional (PET) images: The assessment of significant change. *Journal of Cerebral Blood Flow and Metabolism*, *11*(4), 690–699.
- Friston, K. J., Worsley, K. J., Frackowiak, R. S., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping*, *1*(3), 210–220.
- Gandon, J. M., & Allain, H. (2002). Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. *British Journal of Clinical Pharmacology*, *54*(1), 51–58.
- Gillard, M., Van Der Perren, C., Moguevsky, N., Massingham, R., & Chatelain, P. (2002). Binding characteristics of cetirizine and levocetirizine to human H(1) histamine receptors: Contribution of Lys(191) and Thr(194). *Molecular Pharmacology*, *61*(2), 391–399.
- Haas, H., & Panula, P. (2003). The role of histamine and the tuberomammillary nucleus in the nervous system. *Nature Reviews. Neuroscience*, *4*(2), 121–130.

- Hindmarch, I. (1975). A 1,4-benzodiazepine, temazepam (K 3917), its effect on some psychological parameters of sleep and behaviour. *Arzneimittel-Forschung/Drug Research*, 25(11), 1836–1839.
- Hindmarch, I., Johnson, S., Meadows, R., Kirkpatrick, T., & Shamsi, Z. (2001). The acute and sub-chronic effects of levocetirizine, cetirizine, loratadine, promethazine and placebo on cognitive function, psychomotor performance, and wheal and flare. *Current Medical Research and Opinion*, 17(4), 241–255.
- Hindmarch, I., Shamsi, Z., Stanley, N., & Fairweather, D. B. (1999). A double-blind, placebo-controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function. *British Journal of Clinical Pharmacology*, 48(2), 200–206.
- Hiraoka, K., Tashiro, M., Grobosch, T., Maurer, M., Oda, K., Toyohara, J., ... Yanai, K. (2015). Brain histamine H₁ receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine. *Expert Opinion on Drug Safety*, 14(2), 199–196.
- Hock, C., Villringer, K., Müller-Spahn, F., Wenzel, R., Heekeren, H., Schuh-Hofer, S., ... Villringer, A. (1997). Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS)—Correlation with simultaneous rCBF-PET measurements. *Brain Research*, 755(2), 293–303.
- Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., & Dement, W. C. (1973). Quantification of sleepiness: A new approach. *Psychophysiology*, 10(4), 431–436.
- Holgate, S. T., Canonica, G. W., Simons, F. E., Tagliabata, M., Tharp, M., Timmerman, H., ... Yanai, K. (2003). Consensus Group on New-Generation Antihistamines (CONGA): Present status and recommendations. *Clinical and Experimental Allergy*, 33(9), 1305–1324.
- Inami, A., Matsuda, R., Grobosch, T., Komamura, H., Takeda, K., Yamada, Y., ... Tashiro, M. (2016). A simulated car-driving study on the effects of acute administration of levocetirizine, fexofenadine, and diphenhydramine in healthy Japanese volunteers. *Human Psychopharmacology*, 31(3), 167–177.
- Inami, A., Ogura, T., Watanuki, S., Masud, M. M., Shibuya, K., Miyake, M., ... Tashiro, M. (2017). Glucose metabolic changes in the brain and muscles of patients with nonspecific neck pain treated by spinal manipulation therapy: A [(18)F]FDG PET study. *Evidence-based Complementary and Alternative Medicine*. <https://doi.org/10.1155/2017/4345703>
- Kohmura, K., Iwamoto, K., Aleksic, B., Sasada, K., Kawano, N., Katayama, H., ... Ozaki, N. (2013). Effects of sedative antidepressants on prefrontal cortex activity during verbal fluency task in healthy subjects: A near-infrared spectroscopy study. *Psychopharmacology*, 226(1), 75–81.
- Kreplin, U., & Fairclough, S. H. (2013). Activation of the rostromedial prefrontal cortex during the experience of positive emotion in the context of esthetic experience. An fNIRS study. *Frontiers in Human Neuroscience*, 7, 879.
- Magistretti, P. J., & Pellerin, L. (1996). Cellular mechanisms of brain energy metabolism. Relevance to functional brain imaging and to neurodegenerative disorders. *Annals of the New York Academy of Sciences*, 777, 380–387.
- Magistretti, P. J., & Pellerin, L. (1999). Astrocytes couple synaptic activity to glucose utilization in the brain. *News in Physiological Sciences*, 177–182.
- Mann, R. D., Pearce, G. L., Dunn, N., & Shakir, S. (2000). Sedation with 'non-sedating' antihistamines: Four prescription-event studies in general practice. *BMJ*, 320, 1184–1187.
- Mochizuki, H., Tashiro, M., Tagawa, M., Kano, M., Itoh, M., Okamura, N., ... Yanai, K. (2002). The effects of a sedative antihistamine, *d*-chlorpheniramine, on visuomotor spatial discrimination and regional brain activity as measured by positron emission tomography (PET). *Human Psychopharmacology*, 17(8), 413–418.
- Molchan, S. E., Matochik, J. A., Zemetkin, A. J., Szymanski, H. V., Cantillon, M., Cohen, R. M., ... Sunderland, T. (1994). A double FDG/PET study of the effects of scopolamine in older adults. *Neuropsychopharmacology*, 10(3), 191–198.
- Murase, K., Kuwabara, H., Yasuhara, Y., Evans, A. C., & Gjedde, A. (1996). Mapping of change in cerebral glucose utilization using fluorine-18 fluorodeoxyglucose double injection and the constrained weighted-integration method. *IEEE Transactions on Medical Imaging*, 15(6), 824–835.
- Nishizawa, S., Kuwabara, H., Ueno, M., Shimono, T., Toyoda, H., & Konishi, J. (2001). Double-injection FDG method to measure cerebral glucose metabolism twice in a single procedure. *Annals of Nuclear Medicine*, 15(3), 203–207.
- Okamoto, M., Tsuzuki, D., Clowney, L., Dan, H., Singh, A. K., & Dan, I. (2009). Structural atlas-based spatial registration for functional near-infrared spectroscopy enabling inter-study data integration. *Clinical Neurophysiology*, 120(7), 1320–1328.
- Okamura, N., Yanai, K., Higuchi, M., Sakai, J., Iwata, R., Ido, T., ... Itoh, M. (2000). Functional neuroimaging of cognition impaired by a classical antihistamine, *d*-chlorpheniramine. *British Journal of Pharmacology*, 129(1), 115–123.
- Pellerin, L., Bouzier-Sore, A. K., Aubert, A., Serres, S., Merle, M., Costalat, R., & Magistretti, P. J. (2007). Activity-dependent regulation of energy metabolism by astrocytes: An update. *Glia*, 55, 1251–1262.
- Poulsen, P. H., Smith, D. F., Ostergaard, L., Danielsen, E. H., Gee, A., Hansen, S. B., ... Gjedde, A. (1997). In vivo estimation of cerebral blood flow, oxygen consumption and glucose metabolism in the pig by [¹⁵O]water injection, [¹⁵O]oxygen inhalation and dual injections of [¹⁸F] fluorodeoxyglucose. *Journal of Neuroscience Methods*, 77(2), 199–209.
- Ridout, F., & Hindmarch, I. (2003). The effects of acute doses of fexofenadine, promethazine, and placebo on cognitive and psychomotor function in healthy Japanese volunteers. *Annals of Allergy, Asthma & Immunology*, 90(4), 404–410.
- Ridout, F., Shamsi, Z., Meadows, R., Johnson, S., & Hindmarch, I. (2003). A single-center, randomized, double-blind, placebo-controlled, crossover investigation of the effects of fexofenadine hydrochloride 180 mg alone and with alcohol, with hydroxyzine hydrochloride 50 mg as a positive internal control, on aspects of cognitive and psychomotor function related to driving a car. *Clinical Therapeutics*, 25(5), 1518–1538.
- Sharma, H. S., & Dey, P. K. (1986). Influence of long-term immobilization stress on regional blood-brain barrier permeability, cerebral blood flow and 5-HT level in conscious normotensive young rats. *Journal of the Neurological Sciences*, 72(1), 61–76.
- Sharma, H. S., & Dey, P. K. (1987). Influence of long-term acute heat exposure on regional blood-brain barrier permeability, cerebral blood flow and 5-HT level in conscious normotensive young rats. *Brain Research*, 424(1), 153–162.
- Sherwood, N., & Hindmarch, I. (1993). The reliability, validity and pharmacosensitivity of four psychomotor tests. In: Hindmarch I and Stonier P (eds). *Human psychopharmacology: Measures and methods*, Volume 4. Wiley, Chichester, UK, 67–91.
- Singh, A. K., Okamoto, M., Dan, H., Jurcak, V., & Dan, I. (2005). Spatial registration of multichannel multi-subject fNIRS data to MNI space without MRI. *NeuroImage*, 27(4), 842–851.
- Sugawara, A., Masud, M. M., Yokoyama, A., Mizutani, W., Watanuki, S., Yanai, K., ... Tashiro, M. (2012). Effects of presence of a familiar pet dog on regional cerebral activity in healthy volunteers: A positron emission tomography study. *Anthrozoös*, 25(1), 25–34.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. Stuttgart, Germany: Georg Thieme Verlag.
- Tashiro, M., Duan, X., Kato, M., Miyake, M., Watanuki, S., Ishikawa, Y., ... Yanai, K. (2008). Brain histamine H₁ receptor occupancy of orally administered antihistamines, bepotastine and diphenhydramine, measured by PET with ¹¹C-doxepin. *British Journal of Clinical Pharmacology*, 65(6), 811–821.
- Tashiro, M., Horikawa, E., Mochizuki, H., Sakurada, Y., Kato, M., Inokuchi, T., ... Yanai, K. (2005). Effects of fexofenadine and hydroxyzine on brake reaction time during car-driving with cellular phone use. *Human Psychopharmacology*, 20(7), 501–509.

- Tashiro, M., Itoh, M., Fujimoto, T., Fujiwara, T., Ota, H., Kubota, K., ... Sasaki, H. (2001). ^{18}F -FDG PET mapping of regional brain activity in runners. *The Journal of Sports Medicine and Physical Fitness*, 41(1), 11–17.
- Tashiro, M., Itoh, M., Fujimoto, T., Masud, M. M., Watanuki, S., & Yanai, K. (2008). Application of positron emission tomography to neuroimaging in sports sciences. *Methods*, 45(4), 300–306.
- Tashiro, M., Mochizuki, H., Iwabuchi, K., Sakurada, Y., Itoh, M., Watanabe, T., & Yanai, K. (2002). Roles of histamine in regulation of arousal and cognition: Functional neuroimaging of histamine H_1 receptors in human brain. *Life Sciences*, 72(4–5), 409–414.
- Tashiro, M., Sakurada, Y., Mochizuki, H., Horikawa, E., Maruyama, M., Okamura, N., ... Yanai, K. (2008). Effects of a sedative antihistamine, D-chlorpheniramine, on regional cerebral perfusion and performance during simulated car driving. *Human Psychopharmacology*, 23(2), 139–150.
- Theunissen, E. L., Vermeeren, A., van Oers, A. C., van Maris, I., & Ramaekers, J. G. (2004). A dose-ranging study of the effects of mequitazine on actual driving, memory and psychomotor performance as compared to dexchlorpheniramine, cetirizine and placebo. *Clinical and Experimental Allergy*, 34(2), 250–258.
- Tsujii, T., Masuda, S., Yamamoto, E., Ohira, T., Akiyama, T., Takahashi, T., & Watanabe, S. (2009). Effects of sedative and nonsedative antihistamines on prefrontal activity during verbal fluency task in young children: A near-infrared spectroscopy (NIRS) study. *Psychopharmacology*, 207(1), 127–132.
- Tsujii, T., Yamamoto, E., Ohira, T., Saito, N., & Watanabe, S. (2007). Effects of sedative and non-sedative H_1 antagonists on cognitive tasks: Behavioral and near-infrared spectroscopy (NIRS) examinations. *Psychopharmacology*, 194(1), 83–91.
- Tsujii, T., Yamamoto, E., Ohira, T., Takahashi, T., & Watanabe, S. (2010). Antihistamine effects on prefrontal cortex activity during working memory process in preschool children: A near-infrared spectroscopy (NIRS) study. *Neuroscience Research*, 67(1), 80–85.
- Tsuzuki, D., Jurcak, V., Singh, A. K., Okamoto, M., Watanabe, E., & Dan, I. (2007). Virtual spatial registration of stand-alone fNIRS data to MNI space. *NeuroImage*, 34(4), 1506–1518.
- Verster, J. C., de Weert, A. M., Bijtjes, S. I., Aarab, M., van Oosterwijck, A. W., Eijken, E. J., ... Volkerts, E. R. (2003). Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: A randomized, double-blind, placebo-controlled trial. *Psychopharmacology*, 169(1), 84–90.
- Verster, J. C., Volkerts, E. R., van Oosterwijck, A. W., Aarab, M., Bijtjes, S. I., De Weert, A. M., ... Verbaten, M. N. (2003). Acute and subchronic effects of levocetirizine and diphenhydramine on memory functioning, psychomotor performance, and mood. *The Journal of Allergy and Clinical Immunology*, 111(3), 623–627.
- Villringer, K., Minoshima, S., Hock, C., Obrig, H., Ziegler, S., Dirnagl, U., ... Villringer, A. (1997). Assessment of local brain activation. A simultaneous PET and near-infrared spectroscopy study. *Advances in Experimental Medicine and Biology*, 413, 149–153.
- Wang, D. Y., Hanotte, F., De Vos, C., & Clement, P. (2001). Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. *Allergy*, 56(4), 339–343.
- Ye, J. C., Tak, S., Jang, K. E., Jung, J., & Jang, J. (2009). NIRS-SPM: Statistical parametric mapping for near-infrared spectroscopy. *NeuroImage*, 44(2), 428–447.
- Zimmer, E. R., Parent, M. J., Souza, D. G., Leuzy, A., Lecrux, C., Kim, H. I., & Rosa-Neto, P. (2017). [(18)F]FDG PET signal is driven by astroglial glutamate transport. *Nature Neuroscience*, 20(3), 393–395.

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