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Acta Neurol Scand 2002: 106: 24–29
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ACTA NEUROLOGICA
SCANDINAVICA
ISSN 0001-6314

The differences of clinical parameters between small multiple ischemic lesions and single lesion detected by diffusion-weighted MRI

Takahashi K, Kobayashi S, Matui R, Yamaguchi S, Yamashita K. The differences of clinical parameters between small multiple ischemic lesions and single lesion detected by diffusion-weighted MRI.
Acta Neurol Scand 2002: 106: 24–29. © Blackwell Munksgaard 2002.

Objectives – The cause of small infarction is mainly considered to be intracranial small-vessel disease. However, it is difficult to explain the mechanism of multiple, acute infarctions by small-vessel disease. We examined the differences of clinical parameters between patients with multiple small lesions and single lesion detected by Diffusion-weighted MRI (DWI). *Material and methods* – We reviewed the clinical records of 86 consecutive stroke patients with lacunar size ischemic lesions on DWI during the acute stage (within 72 h of onset). The subjects were 55 males and 31 females (mean age 72.4 ± 9.9 years). Small multiple acute ischemic lesions were defined using the following criteria 1): the lesions were detectable by DWI 2), the diameter of each lesion on DWI was less than 1.5 cm, and 3) more than one vascular territory was involved. Included in the analysis were age, sex, lipoprotein (a) levels, hematocrit, atrial fibrillation (Af), stenosis of middle cerebral artery (MCA), internal carotid artery (ICA) or basilar artery stenosis detected by magnetic resonance angiography (MRA), National Institute of Health Stroke Scale (NIHSS) at admission, and a history of hypertension, diabetes mellitus, hyperlipidemia, and smoking. *Results* – Twenty-one (24.4%) out of 86 patients with small acute infarctions had multiple acute ischemic lesions. Multiple logistic regression analysis showed that Af and stenosis of ICA or basilar artery were significantly more prevalent in patients with multiple lesions than single lesions. *Conclusion* – Multiple, small lesions visible in DWI are likely to be caused by emboli from heart or atheroma of the large vessels than single small lesion.

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Key words: diffusion-weighted MRI; small; multiple; cerebral infarction; embolism; atrial fibrillation; artery-to-artery embolism

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Accepted for publication December 20, 2001

Diffusion-weighted MRI (DWI) is a sensitive technique for detecting early changes after cerebral infarction (1). Previous ischemic lesions are common among stroke patients, and it is possible to differentiate between acute and chronic ischemic lesions, because ischemic lesions detected by DWI are diminished and nearly undetectable in the very late stages of lacunar size lesions (2).

The cause of small cerebral infarction is generally regarded to be intracranial small-vessel diseases. However, there are few reports on the association between multiple small lesions (the diameter of each lesion on DWI was less than 1.5 cm) detected by DWI and clinical parameters (3). We analyzed the differences of clinical parameters between the patients with small, multiple, acute ischemic lesions and single lesion, and discussed the mechanism of small, multiple acute ischemic stroke.

Subjects and methods

Patient recruitment

We retrospectively reviewed the clinical records of 86 consecutive patients with small ischemic stroke (the diameter of each lesion on DWI was less than 1.5 cm) who were admitted to our department between April 1999 and August 2001, and who underwent both DWI and magnetic resonance angiography (MRA) during the acute stage (within 72 h of stroke, most within 24 h). All patients presented with clinical events. We excluded patients whose strokes occurred during admission for other diseases, such as thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, vasculitis and polycythemia. The study population consisted of 55 males and 31 females, aged 31–90 years (mean age 72.4 ± 9.9 years).

Clinical evaluation

On admission, all patients underwent investigations that included hematocrit, HbA1c, blood glucose level, fasting total cholesterol, lipoprotein (a) [Lp(a)], electorocardiogram (ECG), MRA, DWI and National Institutes of Health Stroke Scale (NIHSS) (4) at admission. In selected patients, transthoracic or transesophageal echocardiography (TEE) was performed.

Neuroimaging

All studies were performed on a conventional MRI, MRA, and DWI 1.5-T system (GE, Signa Horizon Cvi 1.5T) with echo-planar imaging capability. The conventional MRI consisted of transverse T2-weighted sequences [repetition time (TR) 5000 ms; echo time (TE) 96 ms; 1 excitation] with 6-mm slices. DWI was obtained in the transverse plane with a single-shot, echo-planar, spin-echo pulse sequence with TR of 5000 ms, a TE of 96 ms, 1 excitation, and *b*-values of 1000 s/mm^2. MRA was obtained with three-dimensional time-of-flight (3D TOF). The MRA parameters were TR 33.3 ms, TE 3.2 ms, and 1 excitation. The slice thickness was 1.4 mm.

Definition

Hypertension was defined as either a systolic pressure >140 mmHg or a diastolic pressure of 90 mmHg or greater on two separate occasions. We took the blood pressure measurements 10 days or more after the onset of a stroke. Patients receiving antihypertensive treatment were also classified as having hypertension. Hyperlipidemia was defined as total cholesterol level >220 mg/dl. Patients receiving antihyperlipidemic drugs were also classified as having hyperlipidemia. Patients who had a blood glucose level of >200 mg/dl, an HbA1c level >6.2%, or who were receiving treatment for diabetes mellitus were defined as having diabetes mellitus. Patients who showed signs of atrial fibrillation (Af) on ECG were defined as having Af. We assessed the middle cerebral artery (MCA), internal carotid artery (ICA) or basilar artery stenosis using the scale of Uehara et al. (5). Stenosis (including occlusion) of the MCA, ICA or basilar artery was defined as more than 50% reduction of the signal column, signal discontinuity or signal loss on MRA.

Small multiple, acute ischemic lesions were defined by the following criteria: 1) the lesions were detected by DWI, 2) the diameter of one lesion on DWI was less than 1.5 cm, and 3) more than one vascular territory was involved. The vascular territories in the anterior circulation were the anterior cerebral artery (ACA), the MCA, the superior division of the MCA, inferior division of the MCA, the perforating branch of the MCA, the anterior choroidal artery, and the watershed of ICA. In the posterior circulation, the vascular territories were the posterior cerebral artery (PCA), the superior cerebellar artery, the anterior inferior cerebellar artery, the posterior inferior cerebellar artery, and the brainstem. Patients who had small, multiple ischemic lesions on DWI were assigned to group I, and those with only one lesion on DWI were assigned to group II.

Statistics

Continuous data are expressed as the mean ± SD. The mean values in the two groups were compared using the unpaired Student's *t*-test. The Fisher's exact test was used to analyze discrete variables and to determine univariate correlations between patients with multiple and single ischemic lesions on DWI. We also performed logistic regression analysis to estimate the independent effects of the predictive variables on occurrence of the small, multiple, acute ischemic lesions. All statistical analyses were carried out using StatView software release 5.0. Differences with a P-value of <0.05 were considered significant.

Results

Twenty-one (24.4%) out of 86 patients had multiple acute ischemic lesions. The univariate correlations between small, multiple ischemic lesions and clinical parameters are shown in Table 1. The Af and stenosis or occlusion of the ICA or basilar artery was significantly more prevalent in Group I than in Group II ($P < 0.05$). Multiple logistic

Table 1 Univariate correlations between multiple small iscehemic lesions and clinical parameters

	Small ischemic lesions on DWI		
	Multiple (group I) (n = 21)	Single (group II) (n = 65)	P-value
Af*	8 (38.1%)	7 (10.8%)	0.0078
Stenosis or occlusion of ICA or basilar artery*	7 (33.3%)	5 (7.7%)	0.0073
Diabetes mellitus	9 (42.9%)	20 (30.8%)	0.4261
Male	17 (80.1%)	38 (58.5%)	0.0723
Age (old)	75.0 ± 8.7	71.6 ± 10.1	0.1684
Hypertension	16 (76.2%)	44 (67.7%)	0.5885
Hyperlipidemia	5 (23.8%)	22 (33.8%)	0.4329
Lp(a) (mg/dl)	32.7 ± 28.5	28.6 ± 22.8	0.4941
Smoking	10 (47.6%)	22 (33.8%)	0.3035
Hematocrit (%)	38.8 ± 3.7	39.8 ± 5.2	0.4201
NIHSS at admission	7.0 ± 7.9	4.8 ± 4.1	0.0865
MCA stenosis	1 (4.8%)	6 (9.2%)	> 0.9999

Af: atrial fibrillation, ICA: internal carotid artery, LP(a): lipoprotein (a); MCA; middle cerebral artery.
NIHSS: National Institutes of Health Stroke Scale.
* Fisher's exact test; significant difference (P < 0.05).

Table 2 Multiple logistic regression analysis of the relation between multiple small ischemic lesions and clinical parameters

	Range	P-value
Af*	Absent (0), present (1)	0.0029
Stenosis or occlusion of ICA or basilar artery*	Absent (0), present (1)	0.0012
Diabetes mellitus	Absent (0), present (1)	0.2564
Age	31–90 years	0.4203
Sex	Female (0), male (1)	0.1688
Hypertension	Absent (0), present (1)	0.1830
Hyperlipidemia	Absent (0), present (1)	0.7192
Lp (a)	2.0–99.4 mg/dl	0.8262
Smoking	Never (0), former and current (1)	0.1875

* P < 0.05.

regression analysis also showed that Af and stenosis or occlusion of the ICA or basilar artery was predictors of small, acute, multiple ischemic strokes (Table 2).

Table 3 shows the number and locations of lesions on DWI, and the background of patients in group I. Aortic arch atheroma was detected by TEE in three patients with small acute multiple lesions, and one of them had an aortic aneurysm (case 11). Fig. 1a–c shows an example of the small, multiple lesions on DWI and the results of TEE in case 4.

Discussion

With the development of DWI, it became possible to detect very small ischemic lesions during the acute phase (1). Geijer et al. reported that small lesion detect by DWI disappear within 1 year from onset (2). It is uncertain when more than two small lesions are detected by DWI, whether these lesions always occur simultaneously. However, multiple lesions on DWI occur in a close period. Some patients with small infarction have more than two acute lesions on DWI in different vascular territories. Here, we discuss multiple small infarctions that include lacunar infarctions, cortical infarctions, brain stem infarction, and cerebellar infarctions.

As the cause of small infarction is often thought to be atherosclerosis or lipohyalinosis of small intracranial vessels, and because outcomes in most patients with small ischemic lesions or small vessel disease are generally good (6), further examination of these patients may not be needed. If small, multiple, acute ischemic lesions are also caused by emboli, further examinations should be performed to detect the source of the emboli to aid in secondary prevention. Some reports have shown a relationship between multiple, acute, ischemic lesions on DWI, and emboli (3, 7–9). Roh et al. (8). reported that acute, multiple brain infarctions visible on DWI within 4 days of onset, which is the case in about 30% of all patients with acute cerebral infarction, are caused by emboli. However, these patients did not only have small infarctions. They analyzed the association between the locations of multiple lesions and the mechanism of cerebral infarction, and reported that cardio embolism was the most frequent cause of strokes in patients with multiple lesions in both the anterior and posterior circulation (8). Baird et al. (7) also reported that multiple lesions visible in DWI within 72 h of onset were seen in 17% of the acute ischemic stroke patients, and that these lesions were associated with embolic stroke. Koennecke et al. (9) reported that 32 of 62 patients showed a scattered lesion pattern, and potential arterial or cardiac embolic sources were detected in 81.3% of the patients with scattered lesions.

To our knowledge, there are few reports on multiple small ischemic lesions detected by DWI. Ay et al. described multiple ischemic lesions in patients with lacunar syndrome (3). They reported that 10 of 62 patients (16%) had multiple lesions within 3 days of onset. They found no significant differences between patients with single infarction and those with multiple infarctions on DWI in terms of age, sex, presence of individual risk factors, mean number of risk factors, mean time to MRI, clinical syndrome, mode of onset, and number of etiologic investigations. However, patients with subsidiary infarctions more frequently had an underlying embolic source than patients with a single lesion. Our results are slightly

Table 3 Location and etiology of multiple small lesions detected on DWI

Case	Age (years)	Sex	Location	No. of lesion	Af	Echocardiography	MRA findings
1	62	M	L.CR, L.WS	2	No	Normal	Normal
2	90	F	L.pons, L.TH	2	Yes	Not done	Normal
3	76	M	R.TH, R.MCA	2	Yes	Normal	Normal
4	72	M	R.MCA, R.Cer, R.PCA	4	No	Atheroma of aorta*	Normal
5	75	F	L.Cer, R.pons, R.PCA	3	No	Normal*	BA severe stenosis
6	86	M	L.pons, R.TH	2	Yes	Not done	Normal
7	64	M	Bil. anterior circulation	4	No	Not done	L.ICA occlusion
8	72	M	R.MCA	2	No	Not done	R.ICA occlusion
9	84	M	R.MCA, R.TH	2	Yes	AR	Normal
10	81	M	L.MCA, R.TH, L.WS	4	No	Atheroma of aorta*	Normal
11	77	M	Bil. anterior and posterior circulation	<10	No	Not done†	Normal
12	83	M	R.CR, R.MCA, R.WS	3	Yes	MR	R.MCA severe stenosis
13	82	M	Bil.TH, R. midbrain, L. Cer	4	No	Atheroma of aorta*	Normal
14	59	M	L.CR, R.ACA, R.MCA	3	No	Not done	Normal
15	84	M	Bil Cer, L. PCA	3	No	Normal	BA severe stenosis
16	82	M	L. WS, L. hypocumpus, L. MCA	3	Yes	Normal	Normal
17	64	F	R. MCA	2	Yes	Sluggish echo of left atrium*	L.ICA occlusion
18	76	M	L.WS, L.MCA, L ACA	4	No	Normal	L.ICA stenosis
19	67	M	Bil.TH, R.midbrain	3	No	Mild MR	Normal
20	76	M	L.ACA, L.Cer.	2	No	Normal	Normal
21	63	F	L.MCA, L.WS	2	Yes	Plaque of aorta	Normal

L: left, R. right, Bil: bilateral, Af: atrial fibrillation, AR: aortic regurgitation, MR: mitral regurgitation, ICA: internal carotid artery, BA: basilar artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, ACA: anterior cerebral artery. CR: corona radiata, TH: thalamus, WS: watershed, Cer: cerebellum.
* Transesophageal echocardiography was performed.
† This patient died 7 days after admission. Autopsy revealed aortic aneurysm and dissection.

different from Ay et al. with respect to the rate of multiple lesions on DWI, and the association between multiple lesions on DWI and risk factors. In our study, the rate of small multiple acute lesions was 24.4%, and Af and stenosis or occlusion of ICA or basilar artery were independently more prevalent in multiple small lesions on DWI. We believe that this is because of the differences in selection and age of patients between our study and that of Ay et al. Their subjects had lacunar syndrome, and included those without lesions on DWI. Most had small lesions in the territory of the penetrating artery or the brain stem. Our subjects were selected based on DWI findings upon admission. All had acute lacunar infarctions or lacunar-sized cortical infarctions visible by DWI. It is reported that left cardiac thrombi and Af were more frequently present in patients with pial artery infarction than in patients with lacunar infarction (10). The subjects of Ay et al. (mean age, 65 ± 15) were also younger than our subjects. It is well known that the prevalence of Af increases with age (11, 12) and the age has a strong association with atherosclerotic lesions (5, 13). For this reason, we think that the frequency of Af and atherosclerosis of major vessels in our subjects was higher than in the subjects of Ay et al. In our study, Af and atherosclerosis of large vessels (the ICA and basilar artery) were associated with multiple small lesions on DWI. We believe that these findings indicate that small multiple lesions on DWI are caused by embolism as a result of Af or artery-to-artery embolism.

In this study, three of 21 patients with multiple ischemic lesions also had aortic arch atheroma (cases 4, 10, and 13), and one of them had an aortic aneurysm (case 11). Recurrent strokes occurred within 4 months of the first stroke in three of these four patients. Many reports have suggested that the presence of thoracic aortic atheroma (by TEE) is a risk factor for stroke or a potential source of emboli (14–17). Kazui et al. report that the presence of aortic arch atheroma is an independent risk factor for lacunar stroke (18). However, because they did not use DWI to diagnose lacunar infarction, their subjects might include patients with multiple, small lesions that would have been visible on DWI. We predict that the frequency of aortic atheroma in patients with multiple, acute small lesions may be higher than in patients with a single lesion. Unfortunately we did not perform TEE on all of subjects in our study therefore we were unable to determine the association between aortic atheroma and small multiple ischemic lesions on DWI.

In the Japanese population, age, and hypertension have a positive association with lacunar and atherothrombotic infarction, respectively (19). They also pointed out that glucose intolerance was an especially high risk for lacunar infarction.

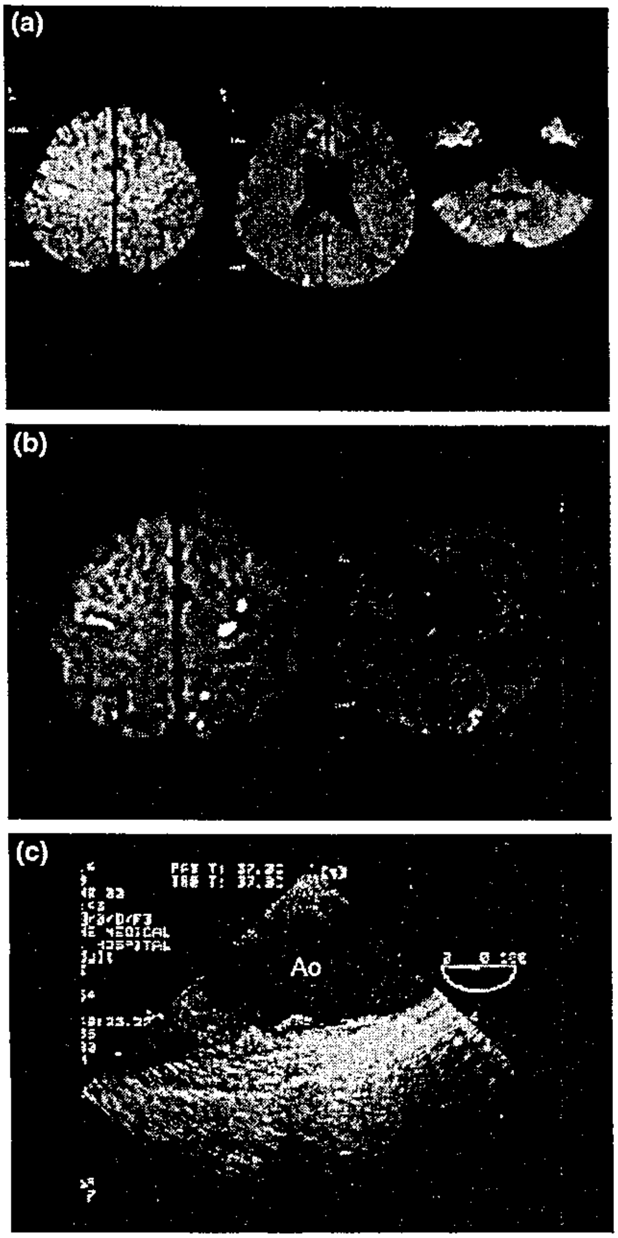

Figure 1. (a) The DWI of case 4. A 70-year-old man experienced paresis of left hand and was admitted to our hospital. DWI revealed small, high-intensity lesions in the right cortical branch of MCA and PCA territories and the right cerebellum. (b) DWI of case 4. Four months after initial admission, case 4 was readmitted to our hospital because of numbness in the left hand. DWI revealed multiple, small lesions in the anterior and posterior circulation territories bilaterally. (c) TEE in this case showed atheroma (*) of ascending aorta. Ao: aorta.

It is also well known that diabetes mellitus is associated with atherosclerosis of large vessels such as the thoracic aorta (20) or the carotid artery (21–23). The frequency of hypertension and diabetes mellitus is high in both groups I and II in our study. We consider that this is the reason that the frequency of diabetes mellitus and hypertension were not significantly different between two groups.

It is also reported that hyperlipidemia is a risk factor for atherosclerosis of large vessels such as carotid artery (23–25) or thoracic aorta (20). Thus, we had predicted that the prevalence of hyperlipidemia of group I would be higher than group II, however, there was no difference between the two groups. We consider that this might be the result of two reasons. First, total cholesterol level in patients with hyperlipidemia ($n = 27$) was not so high in our study. Mean value of their total cholesterol was 229.6 ± 43.9 mg/dl. Secondly, some of patients with hyperlipidemia in our study had been treated by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Recently it has been reported that statins may prevent atherothrombotic events not only because of cholesterol reduction, but also non-sterol effects on endothelial, macrophage, platelet, and smooth muscle (26).

In conclusion, multiple, small lesions visible in DWI are more likely to be caused by emboli from heart or atheroma of the large vessels. We must carefully consider therapeutic strategies and examinations in such patients.

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Electroencephalographic Activity in a Flanker Interference Task Using Japanese Orthography

Shuhei Yamaguchi[1], Genya Toyoda[1], Jiang Xu[1], Shotai Kobayashi[1], and Avishai Henik[2]

Abstract

■ The neural activities for color word interference effects were investigated using event-related brain potentials (ERPs) recorded in a flanker-type interference task. Kanji words (Japanese morphograms) and kana words (Japanese phonograms) were used as the flanker stimuli to obtain insights about hemispheric specialization for processing two types of Japanese orthographies. Interference effects in reaction time were larger when kanji words were presented in the left visual field and when kana words were in the right visual field. ERPs were modulated by the incongruent flankers, which generated a negative ERP component with the different onset and offset depending on flanker attributes. Consistent with the behavioral data, the interference-related negativity was observed for kanji words presented in the left visual field and for kana words in the right visual field. The negativity distributed maximally over the fronto-central site. The early part of the negativity distributed strongly over the frontal midline area, whereas it extended bilaterally over the frontal area in the late phase. The present results support the view of preferential processing of kanji in the right hemisphere and that of kana in the left hemisphere. The temporal profile of scalp topographies for the interference-related neural activity suggests that the medial and dorsolateral prefrontal regions may be involved in maintaining attentional set and conflict resolution. ■

INTRODUCTION

Attention plays a crucial role in coherent, organized behavior of organisms destined with limited capacity for information processing. The Stroop task is now frequently used as an index of attentional deficits, and serves as a neuropsychological measure for investigating the integrity of the neural network for attention (MacLeod, 1991; Stroop, 1935). Subjects are required to concentrate on the color of the printed words, while ignoring the word meaning. If subjects have a problem in the capacity to selectively attend to specific stimuli (color), the distracting information (word) may interfere with the processing of relevant information, resulting in larger interference effects. There have been long arguments regarding neural mechanisms of interference effects. These include the stage of information processing responsible for the interference of conflicting information and its neuroanatomical basis (MacLeod & MacDonald, 2000).

Functional neuroimaging techniques have explored the neural correlates of the Stroop interference effect (Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000; Taylor, Kornblum, Minoshima, Oliver, & Koeppe, 1994; Pardo, Pardo, Janer, & Raichle, 1990). Interference conditions yield consistent activation of the anterior cingulate cortex (ACC), suggesting its critical contribution to cognitive processes in the Stroop task (Bush, Luu, & Posner, 2000; Carter et al., 2000; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). Other brain regions including inferior and middle prefrontal cortex, orbital frontal cortex, superior and inferior parietal lobule, and insular cortex were also activated in the Stroop task (Peterson et al., 1999; Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997; Carter, Mintun, & Cohen, 1995; Bench et al., 1993). Among these structures, considerable attention has been given to the interaction between the ACC and dorsolateral prefrontal cortex (DLPFC) (MacDonald, Cohen, Stenger, & Carter, 2000). Differential time courses of fMRI signal changes in the two regions suggest their distinct roles during the Stroop task (Leung et al., 2000).

Because of the slowness of hemodynamic response, PET and early fMRI techniques have limited inferences about cognitive processes unfolding in the subsecond range. Event-related evoked brain potentials (ERPs) provide enhanced temporal resolution of brain activity. Whereas early ERP studies focused on the processing stage responsible for Stroop interference (Duncan-Johnson & Kopell, 1981), recent studies have attempted to identify neural correlates for interference effects in conjunction with the time course of brain activity using scalp topography and source analyses (Khateb, Michel,

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a. Kanji

赤 (=red) 緑 (=green)

b. Kana

あか (=red) みどり (=green)

Figure 1. Actual letter forms of kanji and kana words used in the experiment.

Pegna, Landis, & Annoni, 2000; Liotti, Woldorff, Perez, & Mayberg, 2000; West & Alain, 1999). In the present ERP study, we attempted to confirm the contribution of multiple frontal areas in a Stroop-type interference task and to clarify the temporal relationship among their neural activities.

Another aim of the study was to investigate hemispheric specialization for Japanese language processing. The Japanese language system has two distinct orthographies, kanji and kana. Kanji characters are graphic symbols for lexical morphemes and kana characters are phonetic symbols for syllables (see Figure 1). Clinical findings and experimental studies have suggested that these characters are processed differently in the two hemispheres. The left hemisphere is involved in phoneme-dependent characters such as kana characters, whereas kanji processing is more dependent on the right hemisphere (Nakagawa, 1994; Sasanuma, 1977). There have been few studies in which brain activity was measured directly on reading of kanji and kana characters. A flanker type of interference task is a suitable method for examining hemispheric specialization of the processing of interfering language stimuli (Weekes & Zaidel, 1996). The present study used a color patch as a target in the center of the screen and a color word as a flanker in either visual field (Henik, Ro, Merrill, Rafal, & Safadi, 1999). This paradigm enabled us to examine interactions between and within stimulus attributes (i.e., word and color) as well as hemispheric specialization of word processing.

RESULTS

Behavioral Data

Table 1 shows mean reaction times (RTs) for all experimental conditions including experimental block (kanji and kana), flanker side (left and right), word congruency (congruent and incongruent), and color congruency (congruent and incongruent). There were two significant main effects: for word congruency, $F(1,9) = 6.73$, $p < .05$, and for color congruency, $F(1,9) = 9.32$, $p < .02$. RTs were significantly slower for incongruent flankers than for congruent flankers in both word and color attributes. The interaction between word and color congruency was not significant ($p > .3$), suggesting these two flanker congruencies affected independently to RTs. The three-way interaction of Experimental block × Word congruency × Color congruency was also not significant ($p > .9$). RTs were marginally faster in kana block compared to kanji block, $F(1,9) = 5.11$, $p = .0501$, but the congruency effects for both word and color attributes were similar between kanji and kana blocks (interaction of Experimental block × Word congruency, $p > .9$; interaction of Experimental block × Color congruency, $p > .7$).

The important finding is a significant three-way interaction of Experimental block × Word congruency × Visual field, $F(1,9) = 14.3$, $p < .005$. This effect was based on the fact that the congruency effects by kanji and kana words were dependent on the side of visual field in which each type of words was presented. Further analysis demonstrated that the congruency effect was significantly larger when kanji words were presented in the left visual field compared to when they were shown in the right visual field [interaction of Visual field × Word congruency in kanji block; $F(1,9) = 12.1, p < .01$], whereas the word congruency effect was larger when kana words were presented in the right visual field

Table 1. Mean RTs (*SE*) (in msec) to a Central Patch as a Function of Experimental Block, Side of Visual Field, and Congruencies of Word and Color Attributes

	Kanji				*Kana*			
	Right Visual Field		*Left Visual Field*		*Right Visual Field*		*Left Visual Field*	
	Word Congruency		*Word Congruency*		*Word Congruency*		*Word Congruency*	
Color Congruency	*Congruent*	*Incongruent*	*Congruent*	*Incongruent*	*Congruent*	*Incongruent*	*Congruent*	*Incongruent*
Congruent	426 (15)	432 (14)	425 (16)	428 (19)	409 (14)	420 (17)	408 (15)	406 (16)
Incongruent	434 (17)	434 (14)	431 (16)	456 (14)	413 (13)	429 (13)	416 (14)	420 (12)

compared to when they appeared in the left visual field [interaction of Visual field × Word congruency in kana block; $F(1,9) = 5.14$, $p < .05$]. The color congruency effect was also dependent on the side of visual field [interaction of Visual field × Color congruency; $F(1,9) = 5.35$, $p < .05$]. The color effect was significantly larger when flankers were presented in the left visual field compared to in the right visual field. The three-way interaction of Experimental block × Visual field × Color congruency was not significant ($p > .2$), indicating that the left visual field dominancy of the color congruency effect was similar for kanji and kana blocks. In sum, the left visual field predominance was observed for both kanji word and color interference and the right visual field was predominant for kana word interference.

Electrophysiological Data

Figure 2 shows the grand average ERPs at the Fz, Cz, and Pz electrode sites for congruent and incongruent flankers. The data are presented separately according to flanker attribute (i.e., kanji word, kana word, and color), but the data from each visual field presentation of the flanker stimuli are collapsed in Figure 2. Regarding the color attribute, we collapsed ERPs in kanji and kana blocks, because no difference was observed in the ERPs to the color attribute between two blocks. The behavioral data also demonstrated no interaction of Experimental block × Color congruency effect. As seen in Figure 2, the two waveforms for congruent and incongruent flanker conditions were comparable until ~300 msec after stimulus onset. After 300 msec, the ERP for the incongruent condition diverged negatively relative to the ERP for the congruent condition although the onset of divergence was dependent to the flanker attribute. This negative shift by the incongruent flankers seems to result from overlapping of a negative potential associated with inhibitory mechanisms for suppressing incongruent information derived from flanker stimuli.

To clarify this wave shift, the ERP for the congruent condition was subtracted from that for the incongruent condition for each flanker type. This procedure yielded a negative component maximally along the midline electrodes. Figure 3 shows difference ERPs for each flanker type presented at the right or left visual field. The onset latency of the negativity for kanji word interference was 400 msec and it continued until 480 msec. For the kana word condition, the negativity started 360 msec and lasted up to 440 msec in the right flanker condition. Finally, the onset of the negativity related to color interference was 300 msec and continued until 380 msec in the left flanker condition. Thus, the duration of the negativity are similar (i.e., 80 msec) for all types of flanker interference, but its onset and offset latencies were different. The negativity was generated earliest for the color condition, then for the kana word condition, and latest for the kanji word condition.

The mean amplitudes were subjected to a repeated measure ANOVA. The main effect of congruency was significant, $F(1,9) = 52.8$, $p < .0001$, but the interaction of Congruency × Flanker attribute was not significant ($p > .7$), indicating no difference in the congruency effect among the three flanker attributes. The critical finding was a significant three-way interaction of Congruency × Flanker attribute × Flanker side, $F(2,18) = 4.71$, $\varepsilon = .90$, $p < .05$. This interaction indicates that the

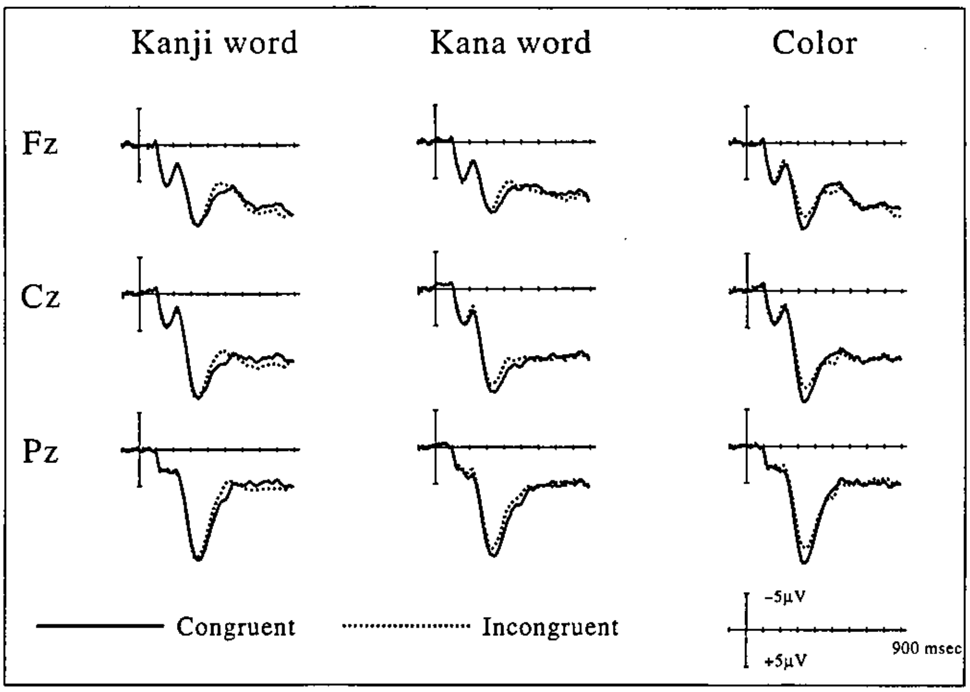


Figure 2. Grand averaged ERPs elicited by kanji word, kana word, and color attributes at the Fz, Cz, and Pz sites. The waveforms are presented separately for congruent and incongruent conditions but collapsed for the stimuli in the left and right visual fields.

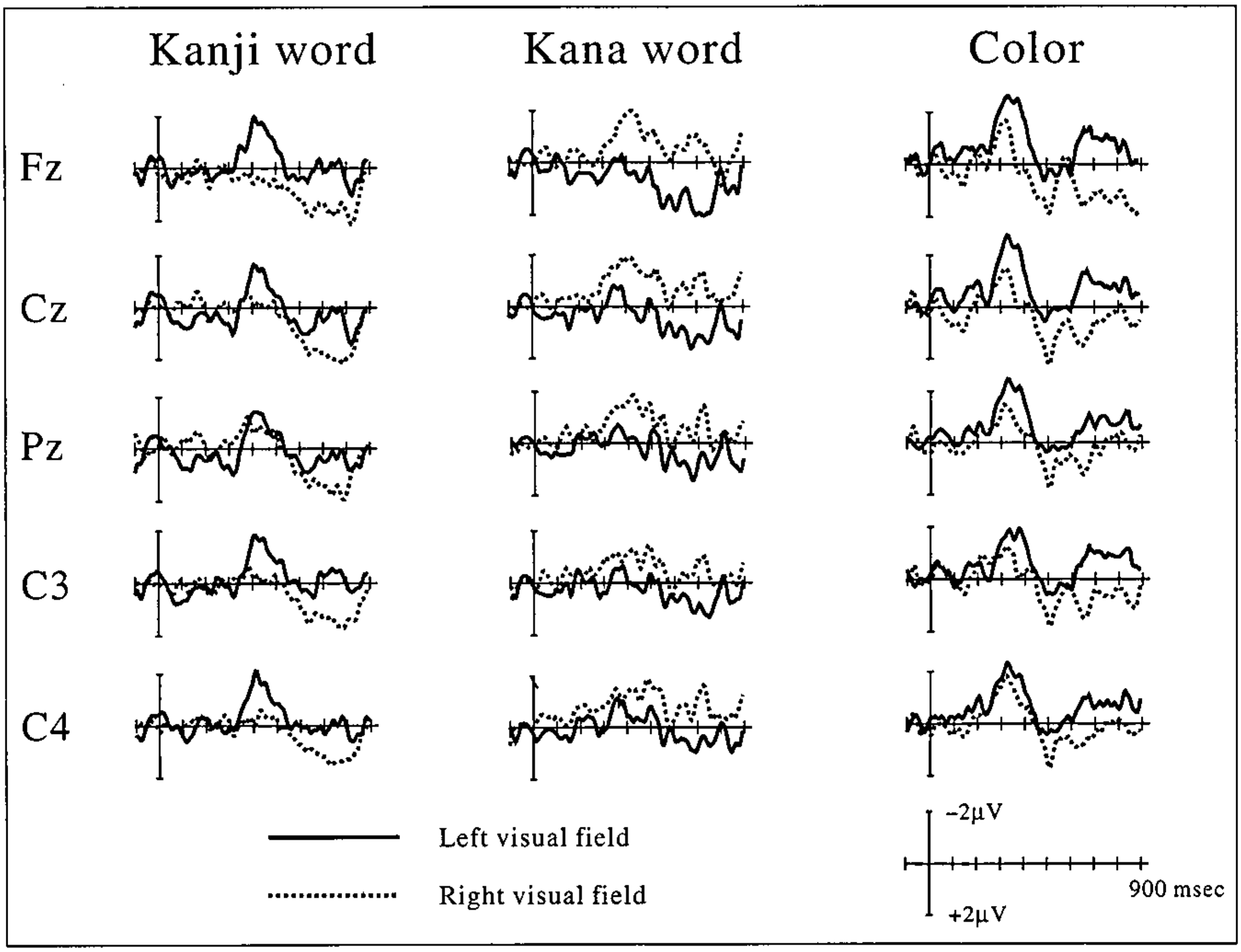


Figure 3. Grand averaged difference ERPs (incongruent condition − congruent condition) elicited by kanji word, kana word, and color attributes. The data are presented separately for the stimuli in the left and right visual fields.

interference effect (incongruent − congruent) of each flanker attribute was different depending on the side of flanker presentation. Further analysis demonstrated that the interference effect for kanji word was marginally larger when the flanker was presented in the left visual field compared to when it appeared in the right visual field [interaction of Congruency × Flanker side; $F(1,9) = 5.07$, $p = .051$]. The effect size was 1.3 μV for the left presentation [main congruency effect; $F(1,9) = 14.3$, $p < .005$] and 0.3 μV for the right presentation (main congruency effect; $p > .4$). On the other hand, the interference effect by incongruent kana word was significantly larger when they were presented in the right visual field compared to in the left visual field, $F(1,9) = 9.70$,

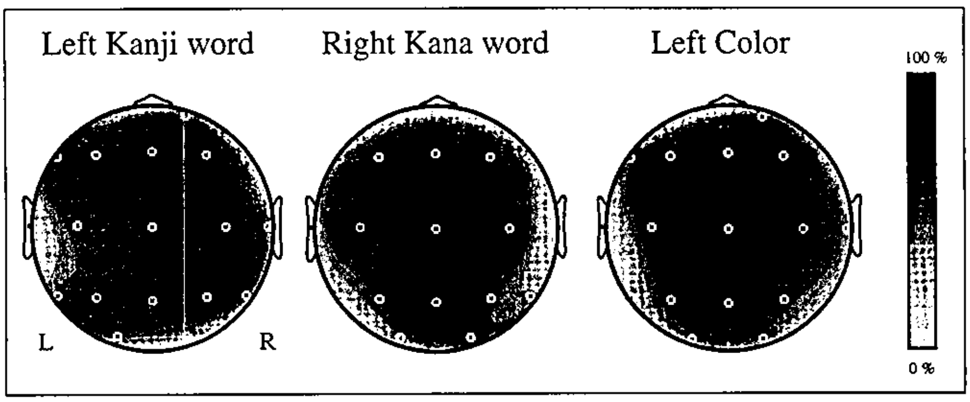
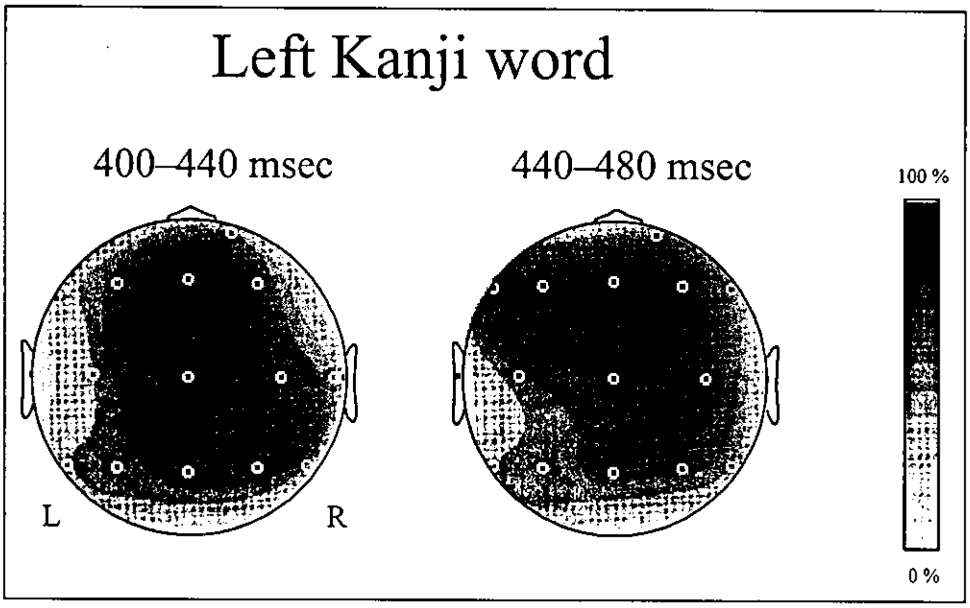


Figure 4. Scalp topographic maps of difference ERPs (incongruent condition − congruent condition) elicited by left kanji word, right kana word, and left color attributes. The ERP data were normalized within each condition and each subject. L = left; R = right.

Figure 5. Scalp topographic maps of difference ERPs (incongruent condition − congruent condition) elicited by left kanji word at the early (400–440 msec) and late (440–480 msec) latency ranges. L = left; R = right.



$p < .02$. The effect size was 1.1 μV for the right presentation [main congruency effect; $F(1,9) = 36.5, p < .001$] and 0.4 μV for the left presentation (main congruency effect; $p > .1$). Regarding the color interference effect, a significant congruency effect was observed for the left flanker condition, $F(1,9) = 9.53, p < .02$, but not for the right flanker condition ($p > .1$). The interaction of Congruency × Flanker side was not significant ($p > .2$) for the color attribute.

Then we analyzed scalp topographies of interference effects in the ERPs in relation to the flanker attribute and the side of visual field. Because the significant interference effects were observed in three flanker conditions, that is, left kanji word condition, right kana word condition, and left color condition, mean amplitudes in the three conditions were subjected to the topographical analysis. We conducted a repeated measure ANOVA using congruency, flanker condition, and electrode site as factors after normalization of mean amplitudes within each subject and each flanker condition (McCarthy & Wood, 1985). There was a significant main effect of electrode site, $F(18,162) = 12.8$, $\varepsilon = .16, p < .0001$. This effect was due to the maximal distribution of the ERPs along the midline electrode sites for all conditions. Importantly, the interaction of Congruency × Electrode site was also significant, $F(18,162) = 4.66$, $\varepsilon = .18$, $p < .01$. As seen in Figure 4, this effect was due to the fact that the congruency effect (incongruent − congruent) was most evident over the fronto-central site. There was no significant interaction of Congruency × Flanker condition × Electrode site ($p > .6$), suggesting that the ERP congruency effect in the three flanker conditions showed similar scalp distributions (Figure 4).

Furthermore, we analyzed temporal changes of the interference-related ERP modulations. For this purpose, we measured mean amplitudes separately in the first and second half of the time window in which significant interference effects were observed for each flanker condition. A repeated measure ANOVA was performed after the normalization of the mean amplitudes using the following factors: timing (early and late time window), congruency, flanker condition (left kanji word, right kana word, and left color), and electrode site. In addition to a main electrode effect, $F(18,144) = 11.7$, $\varepsilon = .15, p < .0001$, there was a significant interaction of Timing × congruency × Electrode site, $F(18,144) = 3.77$, $\varepsilon = .14, p < .05$. This interaction indicates differences in the scalp topography of interference-related ERPs modulations between the early and late phases of the measurement window. As seen in Figure 5, the topographical difference resulted mainly from distinct ERP distributions over the frontal area. In the early phase, the difference wave (incongruent − congruent) distributed strongly over the frontal midline area, whereas it extended bilaterally over the frontal area in the late phase. This temporal change in the topography was commonly observed in other two flanker conditions, and there was no statistical significance in the interaction of Timing × Congruency × Flanker condition × Electrode ($p > .2$).

DISCUSSION

Hemispheric Difference in Kanji and Kana Processing

One of the aims of the present study was to examine hemispheric differences in kanji and kana words processing. The interference effect was larger in the left flanker condition (processing in the right hemisphere) for kanji words and in the right flanker condition (processing in the left hemisphere) for kana words. The ERP recordings demonstrated that kanji word interference generated larger negativity for the left presentation whereas kana word interference generated larger negativity for the right presentation. Thus, the ERP data confirmed differential processing of kanji and kana words between the two hemispheres. These results are consistent with previous reports regarding hemispheric specialization for kanji and kana processing using behavioral and blood flow indices. In tachistoscopic experiments (Sasanuma, Itoh, Mori, & Kobayashi, 1977), kana was significantly better recognized when it was presented to the right visual field than to the left visual field, whereas kanji was recognized better in the left visual field presentation. Dyer (1973) examined hemispheric dominance of English words in a Stroop paradigm using English color words and color patches, which were presented in each visual field. The mutual interference was greatest when the color names were presented to the right visual field and the color patches to the left. This suggests that English words are predominantly processed in the left hemisphere, while colors are processed in the right hemisphere. Because both English and kana consist of phonetic orthographies, it is reasonable to suppose that they are processed in a same manner. Actually, Hatta (1981) compared Stroop effects between kanji and kana words presented in each visual field, and documented the specialization of the right hemisphere for kanji processing. A cerebral blood flow study (Sakurai et al., 2000) suggested that distinct posterior brain regions in the left hemisphere were involved in reading of kanji and kana words. In addition, the temporal–parietal junction of the right hemisphere was more active for reading of kanji compared to reading of kana, whereas the left homologous region was equally activated in reading of kanji and kana words.

The hemispheric difference between kanji and kana processing may be explained by the notion of hemispheric difference in global and local processing (Yamaguchi, Yamagata, & Kobayashi, 2000; Ivry & Robertson, 1998; Fink et al., 1996). Nakagawa's study (1994) suggested that the hemispheric advantage depends on whether the stimulus word consists of one or two characters. When kanji words consisted of more than two letters, the left hemisphere is dominant for their processing, which was contrasted to right hemispheric dominance in the case of reading one-letter kanji. In the present experiment, kanji words consisted of just one character, which was suitable for holistic processing in the right hemisphere. On the other hand, kana words consisted of two or three characters, and local processing in the left hemisphere may be necessary. The current behavioral and electrophysiological data are providing strong evidence for hemispheric specialization in kanji and kana processing.

Processing Stage for the Interference Effect

The current study provided further insights regarding the processing stage at which the interference effect is produced. If interference occurs in an early stage of information processing, kanji words are predicted to show larger interference effects than kana words, because color and kanji word are processed in the same hemisphere. However, the present RT and electrophysiological data demonstrated comparable interference effects for kanji and kana words, suggesting that the interference effect is independent of early perceptual processes. The current study does not employ a conventional Stroop task, but rather a flanker interference task. We must consider spatial filtering in this type of task. Drysdale, Fulham, and Finlay (1998) reported interference effects on the N2 component (200- to 316-msec latency range), but not on earlier components generated by unattended stimuli in a bilateral stimulus task. They claimed that filtering at the early processing stage by spatial attention is not exclusive, but some of unattended information can "break through" the early filtering even when two stimulus locations are separated by 11.5°. The current study showed that the onset latency of the interference-related negativity was in a P300 latency range (300–400 msec), and this finding seems to fit well with the notion of the late occurrence of interference effects. Duncan-Johnson and Kopell (1981) examined electrophysiological indices for Stroop interference effects. They found no difference in P300 latency between congruent and incongruent stimuli and concluded that interference effects occurred after the P300. Ilan and Polich (1999) also reported the discrepancy between RT and P300 latency and argued that interference occurred after the stimulus evaluation. The data from the present topographical analysis also supported the late selection theory. If the interference occurs at the perceptual stage, substantial hemispheric differences in the topography of the negativity are predicted because the interference effects depends on visual fields of flanker presentation. The comparable distributions of field potentials independent of stimulus attributes suggest that interference effects occur in a late stage of information processing. Thus, both the RT and ERP data support the late selection hypothesis for the Stroop interference effect.

Neural Mechanism of Interference Effect

The topographical analysis demonstrated a frontocentral distribution of the interference-related negativity. This topographical finding is consistent with previous ERP studies (West & Alain, 1999; Rebai, Bernard, & Lannou, 1997). The distribution was similar for the three types of flanker attributes: left kanji word, right kana word, and left color. The stronger distribution along the frontal midline area suggests that the negativity reflects neural activities from the prefrontal midline structure such as the ACC. There have been longstanding discussions regarding the critical neural structures for interference effects in the Stroop paradigm, but the ACC activation in this paradigm was a common finding in almost all PET and fMRI studies. It has been proposed that the ACC participates in motor control by facilitating the execution of appropriate responses and suppressing the execution of inappropriate ones (Paus, Petrides, Evans, & Meyer, 1993). Neuropsychological and electrophysiological studies have provided evidence of the involvement of the ACC in response selection (Turken & Swick, 1999) and response monitoring (Gehring & Knight, 2000). The contribution of the ACC to the interference-related negativity was also presumed in the electrophysiological studies using dipole analysis (Liotti et al., 2000). Furthermore, the interference-related negativity also extended laterally over the frontal site. This suggests that the negativity may be contributed from the DLPFC in some degree. The DLPFC has also been implicated in attentional control mechanisms in human behaviors. Behavioral data demonstrated that patients with lateral prefrontal lobe lesions made more errors or larger interference effects than normal controls in the Stroop task (Kingma, Heij, Fasotti, & Eling, 1996; Vendrell et al., 1995; Perret, 1974). Recent fMRI studies also reveal contributions of a distributed neural network including the DLPFC to the Stroop interference (Leung et al., 2000; Peterson et al., 1999).

The time course of brain activation is also an important issue for interference-related process. Leung et al. (2000) delineated the time course of activation in several brain structures during the standard Stroop task using an event-related fMRI technique. According to their findings, the ACC activation had an earlier onset compared to the activation of the inferior and middle frontal gyri, and the prefrontal activation lasted longer than that of the ACC in turn. The present ERP study demonstrated temporal and spatial dynamics of brain activation. The topographical changes of the interference-related negativity suggest that neural activities in the medial frontal and dorsolateral prefrontal regions contribute to the earlier part and later part of the negativity, respectively. The different time course of activation suggests functional segregation of the medial frontal and dorsolateral prefrontal regions, and their associated activation indicates functional interactions between them. An event-related fMRI study in a modified Stroop task also suggested functional segregation between these two structures (MacDonald et al., 2000) and provided a working model according to which the ACC monitors competition between conflicting information during task performance and drives the executive control system in DLPFC for increasing selective attention and suppressing task-irrelevant information. Further ERP studies combined with imaging studies may help to delineate the functional integration of frontal neural structures for the executive control system.

METHODS

Subjects

Ten normal right-handed male volunteers were recruited from the university community. All participants were native Japanese. They ranged from 32 to 48 years of age (mean 36.8 years) and all had normal or corrected-to-normal visual acuity. All signed consent forms before the experiment. None had any history of neurological disorders or head injury.

Stimuli and Task

Subjects were seated in a comfortable chair with a neck support in an electrically shielded, sound-attenuated room with dimmed lights. All stimuli were presented on a 20-in. cathode ray tube (CRT) with black screen color, 60 cm in front of the subject's eyes. Each stimulus was composed of a red or green square in the center of the CRT and a flanker word to the left or the right of the square. The flanker was the word "red" or the word "green" colored in red or green, using either kanji or kana characters. Kanji and kana were used in a separate experimental block. Thus, regarding the two flanker dimensions (i.e., word and color), the flanker could be congruent (e.g., central square red and flanker word "red" or flanker color red) or incongruent (e.g., central square red and flanker word "green" or flanker color green). In addition to the two-flanker dimensions, the visual field of flanker presentation was manipulated orthogonally so that there were eight flanker conditions (2 word levels × 2 color levels × 2 visual fields) for each block, and each condition occurred with equal probability.

All subjects participated in two experimental blocks, one was a kanji block and the other was a kana block. Half of the subjects started with the kanji block first; the other half with the kana block. On half of the trials in each block, the central square was red, and on the other half, it was green. Each of the eight flanker conditions was repeated 40 times. Thus, each experimental block contained 320 trials (2 central square colors × 8 flanker conditions × 20 repetitions). The practice block contained 32 trials (four trials from each of the eight flanker conditions).

The size of the central square patch was 1.5° on a side. The closest edge of the flanker word was 2.0° from the CRT center. Both kanji words, "red" and "green," were made of one letter (see Figure 1a) with the visual angle of 1.5° × 1.5°. The word "red" in kana consisted of two letters and "green" of three letters (see Figure 1b), which were displayed in a vertical arrangement with a visual angle of 2.0° × 1.0° for "red" and 3.0° × 1.0° for "green."

Each trial started with the presentation of a fixation cross in the center of the CRT. After 800-msec display of the fixation, a square patch and a flanker word appeared simultaneously for 500 msec. The interval between offset of the square with the flanker and onset of the next fixation was 1400 msec. Subjects were instructed to respond to the color of the central square patch, as fast as possible, by pressing one of two buttons of a corresponding color on a game pad, one button in each hand. The designation of colors to buttons was counterbalanced across subjects.

Electroencephalographic (EEG) Recording

EEGs were recorded using Ag/AgCl electrodes at 19 scalp sites (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). Vertical and horizontal eye movements were monitored by electrodes, placed below and lateral to the left eye. All electrodes were referenced to linked ear lobes. Electrode impedance was kept below 5 kΩ. The EEG was amplified (band pass 0.05–100 Hz), digitized (250 Hz/channel), and stored on a computer hard disk for off-line analysis. EEGs were averaged over 1024 msec and time-locked to the square patch and flanker stimuli, including 100 msec of prestimulus baseline. In order to examine congruency effects separately for word and color attributes, averaging was performed separately for word and color congruencies in each experimental block. Thus, the trials to congruent and incongruent word flankers were separately averaged irrespective of color congruency, and vice versa. This procedure was justified by the behavioral data indicating independence of word and color congruency effects on RTs. The data to red and green square patches were collapsed because of irrelevance of patch colors to interference effects. Grand averaged ERPs were also generated across 10 subjects for each flanker condition. Individual trials with excessive muscle activity (greater than 100 μV peak-to-peak amplitude) or eye movement (greater than 100 μV peak-to-peak amplitude) were excluded from the averages. Only the ERP data from correctly performed trials were included (i.e., RTs between 150 and 900 msec after the onset of the square and flanker).

Statistical Analysis

Eight flanker conditions (2 word levels × 2 color levels × 2 visual fields) and two experimental blocks (kanji and kana blocks) were orthogonally manipulated within subjects in the present experiment. Then, behavioral data were subjected to a repeated measure ANOVA using word congruency (congruent and incongruent), color congruency (congruent and incongruent), visual field (right and left), and type of orthography (kanji and kana) as factors.

Eight distinct ERP waveforms were generated as a function of flanker condition (i.e., congruent word, incongruent word, congruent color, and incongruent color for each side) in each experimental block. Interference effects in ERPs were estimated by comparing ERPs to incongruent stimuli with those to congruent stimuli. To determine the onset and offset of interference effects on ERPs, paired t tests were performed consecutively on mean amplitudes of congruent and incongruent ERPs in 20-msec time window from 200 to 600 msec at the Fz site, where maximal interference effects were observed for all flanker categories. That time window was applied to all electrode sites for measuring mean amplitudes. The mean amplitude during the time window showing interference effects was evaluated statistically by a repeated measure ANOVA with the following sources of variance: congruency (congruent and incongruent), flanker attribute (kanji word, kana word, and color), flanker side (right and left), and electrode site (19 locations). The actual time windows used for the ANOVA were 400–480 msec for the kanji word interference effect, 360–440 msec for the kana interference effect, and 300–380 msec for the color interference effect. To obtain information about cortical distributions of ERP changes related to interference effects, topographic maps of the ERPs over the scalp were calculated using spherical spline functions (Perrin, Pernier, Bertrand, & Echallier, 1989). A level of $p < .05$ was accepted as statistically significant and significance levels were adjusted with the Greenhouse–Geisser correction when appropriate. The original degree of freedom and its epsilon value (ε) were reported.

Acknowledgments

We thank Robert T. Knight for comments on the manuscript. This work was supported by grants from the Japanese Ministry of Education, Science, Sports, and Culture (11670626) and Medical Research Grants of Shimane Institute of Health Science to S. Y. and JSPS fellowship to A. H.

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＜合同シンポジウム1＞

4. 全国脳卒中データバンク構築に向けて

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Key words：急性期脳卒中データバンク，コンピューター化データベース，JSSRS，脳卒中スケール
（脳卒中 24：255―259，2002）

はじめに

近年の技術進歩は国際社会のグローバル化を促進し，臨床試験についても国際的ハーモナイゼーションの必要性が強調されている．欧米ではすでに多くの大規模臨床試験が行われ，これらの結果すなわちエビデンスに基づいた治療ガイドラインが次々と発表され，EBMが促進されている．一方，我が国ではEBMの根拠となるエビデンスも殆どない現状である．最近になり，厚生労働省の指導により，ようやく各学会で治療ガイドライン作成が始まり，今年度中には脳血管障害分野も出揃う予定である．しかし，日本人におけるエビデンスがないために，欧米の指標に経験的根拠による修正を加えて作成される可能性が強い．最初はこれでもよいとしても，ガイドラインとして発表した以上，内容を検証し，必要に応じ改訂していく必要がある．そのためには継続的に脳卒中急性期症例を蓄積し，治療効果を確認していく全国的なデータバンク構築すなわちインフラ整備がまず必要である．

脳卒中データバンクの意義

Henriques[1]は脳卒中の臨床症候群と機序の多様化により，脳卒中データバンクが脳卒中に関する臨床情報を更新していくための最適の道具として重要であると述べている．米国のNINDS Stroke Data BankのSacco[2]は，脳卒中データバンクの利点として，1）介入試験と異なり，治療効果に対する答えは出せないが，臨床試験のデザインや実施に際して重要な情報を提供する．2）データバンクの情報解析により，治療や結果として起こるイベントの頻度，対象症例数の算出に関する仮説を立てることが可能である．3）臨床試験に必要なプロトコルの項目を選定し，選択基準や除外基準を決定するのに役立つという3点を強調している．実際に米国のNINDS Stroke Data Bankではこのような目的で多くの解析を行ってきており，脳卒中スケールの評価にも役立てている．しかし，残念ながらNINDS Stroke Data Bankはすでに活動を停止したということである．これに対し，スイスのローザンヌ地区脳卒中データバンク[3]は10数年に渡ってその地区で発症した殆どの脳卒中患者を病院ベースで登録を継続しデータを出し続けている．これはBogousslavskyが創設以来自分でずっと担当しているためである．彼らの最近の報告として，脳卒中患者3,901名におけるASOによる間歇性跛行219名の検討がある[3]．Moulinら[4]はBesancon stroke registryにおけるCTやMRIの画像診断を入院後2回以上行った1,776例の急性期脳梗塞の解析で，発症3時間以内入院例は28.3%，6時間以内は48.4%としている．これは山口ら[5]による厚生省研究班による16,000例の解析結果や筆者ら[6]の脳卒中急性期患者データベースによる38%，50%よりもやや低い．このように標準化されたデータは病院間のみならず，脳卒中の実態に関する国際比較に用いることが可能であり，臨床試験とくに欧米で開発された薬剤のbridging試験の際に試験デザインを検討するために有用な情報を提供する．

我が国における脳卒中データバンクの構築経過

筆者ら[7]は1999年から脳卒中急性期患者データベース構築研究（Japan Standard Stroke Registry Study：JSSRS）を開始した．当初18の脳卒中治療基幹施設で仕様を検討し，試行を繰り返して2000年度にほぼ内容項目を固定し，2001年にversion 3.0を完成し，現在北

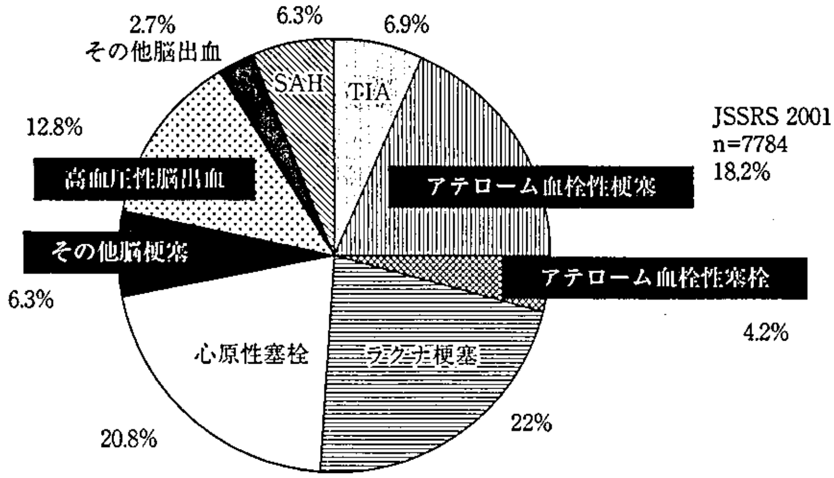

図1　厚生科学研究事業（JSSRS 2001）で集積した脳卒中の病型別頻度

海道から沖縄まで約50施設で連続症例の登録を行っている．脳卒中重症度評価は日本脳卒中学会で作成した定量的脳卒中スケール（Japan Stroke Scale:JSS）と国際的に最もよく使用されているNIH Stroke Scale（NIHSS）を採用した．また，評価の手間を省くため，JSS-NIHSS combined scaleの入力画面を作成し，ベッドサイドで評価したものをコンピューター上で入力するとJSSとNIHSSに変換されて表示されるようにした．これにより複雑なJSSの計算が瞬時に可能となった．必須項目としての脳卒中スケールの入力率は82%と，確定診断入力率97%に比して低いが内容から考えると比較的良好である．スケールが命であると協調しているので現在はさらに入力率が向上していると思われる．診断分類はNINDS-IIIを用いている．また，画像診断の入力は膨大な項目数となるのでまず，大まかな分類を選択入力し，ページを変えてMRI画像所見や血管撮影所見が表示されたビジュアルな画面で部位をチエックすることで詳細入力が出来るようにしている．予後は国際的に最もよく使用されているmodified-Rankin Scaleを用いているがGlasgow Outcome ScaleやBarthel indexも入力出来るような長期予後追跡入力画面も作成してある．いずれのスケールも内容を一覧できる頁が設けてあるので評価内容を確認するのも容易である．本データベースは各病院のデータベースとして機能し，定期的に患者個人情報を自動的に消去した電子データを事務局に送り集積する．現在，JSSRSのホームページを作成中であり，完成後はこのホームページを通じて研究者は自動的に暗号化されたデータをインターネット経由で簡単に事務局に送ることが出来るようになる．いずれはこのように自動的に集計されたデータをある程度自動解析できるようなシステムにしたいと考えているが，入力ミスや個人が追加した病名などのデータチエックは専門家でないと出来ないのが難点である．

我が国の急性期脳卒中患者の実態

2001年度までに集積した約8,000例のデータ解析による脳卒中病型別頻度では急性期脳卒中救急診療の拠点病院が多いためか，ラクナ梗塞よりもアテローム血栓性梗塞がやや多い結果となっている（図1）．アテローム血栓性梗塞には頸動脈や大動脈弓のアテローム潰瘍などからの塞栓すなわちartery to artery embolismも含まれる．この診断は頸部エコー検査や経食道心臓超音波検査まで行わないと困難な場合が多い．したがって，この集計で4%にアテローム血栓性塞栓症が認められたことは，本研究参加施設の診断精度の高さを示している．大動脈アテローム由来の塞栓症を頸動脈アテローム由来の塞栓と分けてその他脳梗塞に分類している施設もあるので，実際にはもっと頻度が高い可能性がある．年齢別頻度の中央値は約70歳であった．急性期脳梗塞における発症から来院までの時間の分布をみると3時間以内が38%，6時間以内でほぼ半数を占めていた．慶應大学救急部のrt-PA適応例数の推測[8]では，全国で年間約1万例としているが，筆者らの調査では，rt-PAが認可された場合にはもっと増加する可能性を示している．図2は急性期脳卒中患者の入院時脳卒中スケールとその変化をJSSとNIHSSの相関図としてみたものである．JSSの3つに分かれた

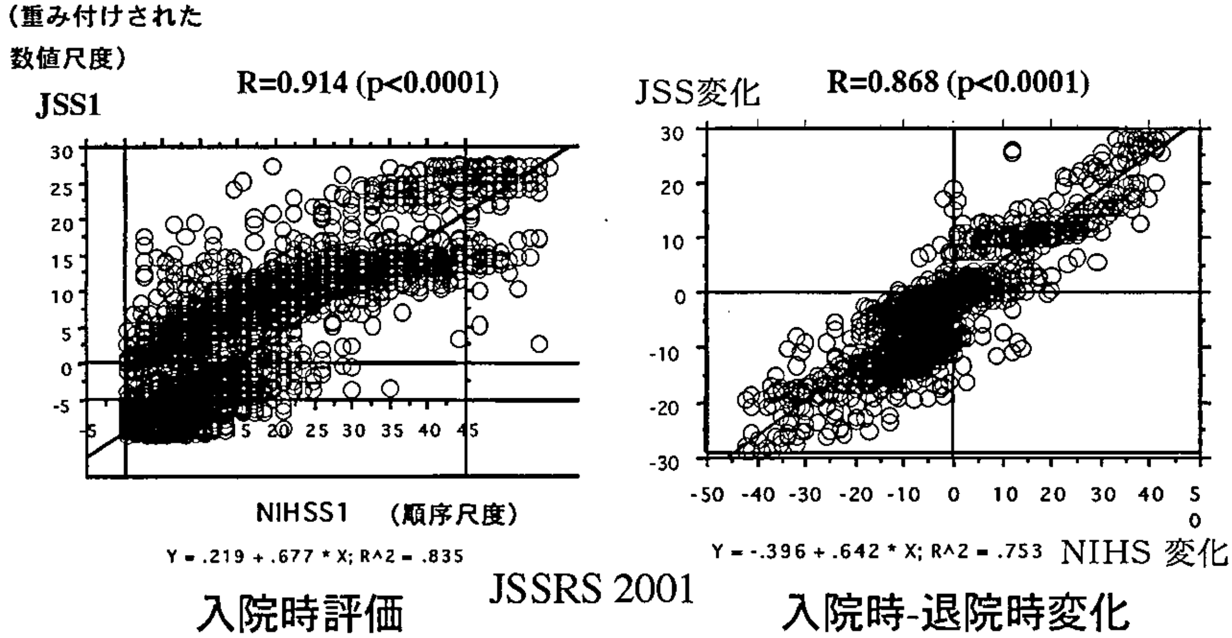

図2　急性期脳卒中患者の入院時脳卒中スケールとその変化を JSS と NIHSS の相関図としてみたもの．JSS の3つに分かれた範囲内に NIHSS のかなり広い範囲が含まれることを示している．変化に関しての相関は良好である．

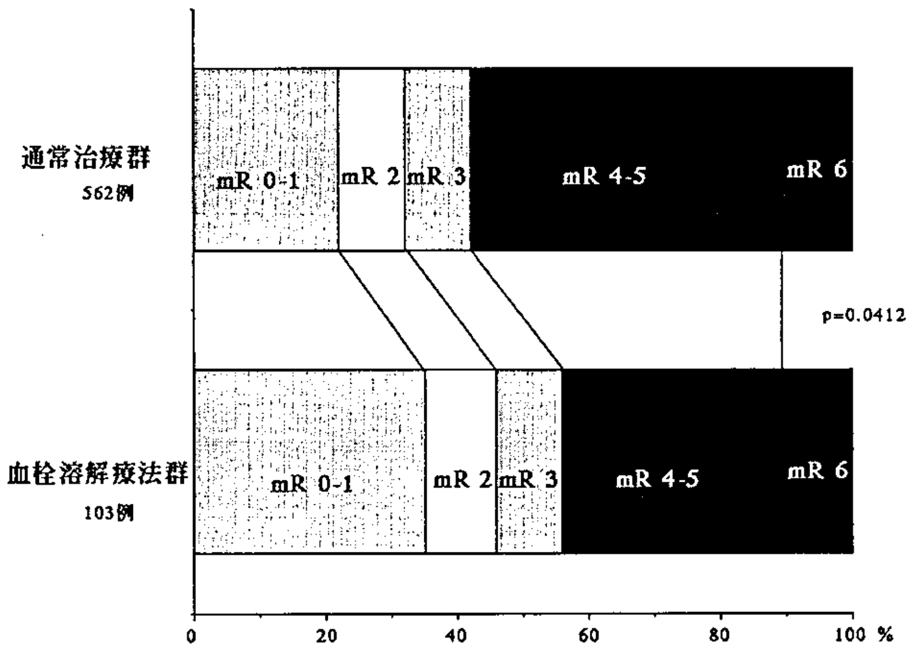

図3　脳梗塞急性期患者（発症3時間以内で入院時重症度 NIHSS 6-29 の症例）における血栓溶解療法（tPA 静注・動注，UK 動注・大量静注）の効果を通常治療群と比較したもの．血栓溶解療法群で有意に退院時予後の改善が認められた．

範囲内に NIHSS のかなり広い範囲が含まれることを示している．JSS は意識レベルに大きなウエイトを置いているので，この3群は恐らく意識レベルの JCS の3段階と一致するものと思われる．スコアの変化に

表1 発症3時間以内入院脳梗塞で入院時NIHSS 6-29の症例における，血栓溶解療法の有無による背景因子，脳卒中スケール，Rankinスコア等の比較（JSSRS 2001）．血栓溶解療法群では入院時重症度が高いが改善幅が大きく，Rankinによる予後も有意に良好である．また，NIHSSよりJSSがより鋭敏に変化を捉えていることが分かる．

	血栓溶解療法群	血栓溶解療法なし群	p値
症例数	106	583	
年齢	70±10	74±11	p=0.0007
発症入院時間	1.2±0.8	1.4±0.9	p=0.0178
入院時JSS	13.4±5.1	11.5±6.0	p=0.0027
退院時JSS	16.5±6.6	14.4±6.7	p=0.0033
入院時NIHSS	7.7±9.7	8.6±9.1	N.S.
退院時NIHSS	11.7±14	11.7±12.6	N.S.
JSS変化	−5.7±9.1	−2.9±7.9	p=0.0014
NIHSS変化	−4.7±13.7	−2.6±10.7	p=0.0797
m-Rankin scale	2.9±2.1	3.4±1.8	p=0.0117

関しての相関は良好である．危険因子の中で注目されたのは心房細動の頻度の高さであった．脳梗塞患者における心房細動の年代別頻度は50才未満では6.6%であったが，60代で12.4%，70代で20.8%，80才以上では35%と加齢と共に直線的に増加していた．この大半が非弁膜症性心房細動である．高齢者の脳塞栓が増加し予後不良者が多くなっていることと裏付ける成績である．この結果をさらに同じデータベースで共同研究を行っている中国の瀋陽脳科病院における2,000例のデータと比較すると，中国では心房細動が日本の7分の1以下と極めて少なく，その結果として脳塞栓も脳卒中全体のわずか0.6%と非常に少ない．我が国での高齢化がいかに進んでいるかを示すものであると思われる．

発症3時間以内の入院時重症度NIHSS 6-29の脳梗塞681例の予後について検討するとRankinスコアが3以上の予後不良例が65.6%を占めている．そこで，脳梗塞急性期患者（発症3時間以内で入院時重症度NIHSS 6-29)における血栓溶解療法(tPA静注・動注，UK動注・大量静注）の効果を通常治療群と比較してみた（図3）．その結果，血栓溶解療法群で有意にRankinスコアでみた予後が改善していた．さらに発症3時間以内入院脳梗塞で入院時NIHSS 6-29の症例における，血栓溶解療法の有無による背景因子，脳卒中スケール，Rankinスコア等の比較を行った．血栓溶解療法群では入院時重症度が高いが改善幅が大きく，Rankinによる予後も有意に良好であった．また，NIHSSよりJSSがより鋭敏に変化を捉えていることが示された(表1)．この結果は日本脳卒中学会Stroke scale委員会で作成した重み付けされたJSSが血栓溶解療法対象例のように中等症患者の場合には重症度変化をみるのに適していることを示すものである．

おわりに

本システムは全国調査研究用のデータバンクとしてだけでなく，急性期脳卒中を扱う中核病院の臨床データベースとして継続的に機能するものであり，各施設において自らの脳卒中診療内容の正確な把握，全国標準の集計が容易となり，今後の医療情報開示，インフォームドコンセント推進に必要な資料作成に大きな威力を発揮すると思われる．また，脳卒中急性期治療薬についての独自の調査を短期間に行うことが可能となる．今後はEBMのためのデータバンクとして今年中に法人化される予定の日本脳卒中協会のデータバンク部門として継続させて行くことが正式に決定され，参加施設も増加している．

なお，本データバンク研究に参加希望者は下記まで連絡をして頂きたい(skdr3nai@shimane-med.ac.jp)．

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