tion to the contralateral MTL. These quite different conditions under different seizure frequencies in contralateral %Pi produced significant correlation with seizure frequency.

The NAA/(Cho + Cr) ratio in the ipsilateral MTL has the largest correlation coefficient with seizure frequency among the four spectroscopy data sets, suggesting that the NAA/(Cho + Cr) ratio in the ipsilateral MTL is the best index for showing TLE severity. The lateralization of the TLE focus is of major importance, especially for presurgical decisions for intractable TLE. In the present study, the lateralization of TLE in the low seizure-frequency group (< 1/month) was detected more clearly using ^{31}P MRS, while ^{1}H MRS showed highly significant lateralization detectability in the high seizure-frequency (> 1/month) group. Two cases with disagreement between the ^{1}H MRS results and clinical data were in the low seizure-frequency group, but four cases with disagreement between the ^{31}P MRS results and clinical data were in the high seizure-frequency group. In total, ^{1}H MRS seems more useful for clinical application.

Although only four patients showed atrophies, the MTL atrophies detected by MRI were located on the ipsilateral side to the focus, and all of the four had smaller NAA/(Cho + Cr) ratios in ipsilateral MTL than in contralateral MTL. Some investigations have reported that morphological MRI study of TLE patients is very useful for evaluating the severity and laterality of TLE.[20,21] The reason for the low atrophy detectability by MRI in the present study may lie in the fact that we did not use a pulse sequence with specificity for evaluating MTL atrophy.

In conclusion, we performed ^{1}H and ^{31}P MRS for detecting the lateralization of the TLE focus. There was no significant correlation between NAA/(Cho + Cr) and %Pi. The values of NAA/(Cho + Cr) in ^{1}H MRS showed significant differences between ipsilateral and contralateral MTL of TLE patients. The decrease in ipsilateral NAA/(Cho + Cr) had the largest correlation coefficient with seizure frequency. These results suggest that ^{1}H MRS provides more important information than ^{31}P MRS concerning neuronal dysfunction in MTL of TLE patients.

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An earlier component of face perception detected by seeing-as-face task

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To investigate the time sequence of the neural processes underlying face perception, magnetoencephalography was performed using a seeing-as-face task, in which visual inputs were identical across two conditions, but subject perceptions differed: one being a non-specific pattern of geographical shapes, the other being a percept of a face. Subtraction between the two conditions revealed a response occurring 120 ms after stimulus onset in right occipital, ~50 ms earlier than previously reported response at a latency of 170 ms at the right fusiform gyrus. As our novel task completely excluded differences in low-level properties of visual stimuli between control and face conditions, these two responses were considered specific to face perception. The result supported the two-stage theory of face processing. *NeuroReport* 15:225–229 © 2004 Lippincott Williams & Wilkins.

Key words: Face perception; Magnetoencephalography (MEG); M100; M170; Seeing-as-face

INTRODUCTION

The mechanisms of face recognition represent one of the most interesting topics in the field of cognitive neuroscience. Neuroimaging studies using PET or fMRI, and event related potentials (ERP) have consistently shown that faces elicit specific brain responses from relatively well-defined areas in the ventral occipitotemporal cortex, known as the fusiform face area (FFA) [1–5]. The time sequence of cognitive and neural processes underlying this ability has been studied extensively over the past few years, and converging evidence from ERP and MEG suggests that an essential stage in the cerebral processing of faces occurs in the FFA 170 ms after stimulus onset [6]. In a recent MEG study, Liu *et al.* demonstrated that an earlier M100 component, observed at a latency of around 105 ms, is associated with the detection of face category [7], and this result awaits further replication studies.

Another focus for studies of face recognition has been the extent to which facial configuration alone, in the absence of appropriate facial features, can elicit face-specific neurophysiological responses, such as FFA activation in fMRI or PET studies, or M170 response in MEG studies. In other words, the question is whether these responses are specific to human faces or generalized to other face-like stimuli. Studies using schematic faces have shown that a basic facial configuration is sufficient to activate the FFA [8]. A similar trend has been observed in MEG studies. A schematically drawn human face (such as a smiley face) is sufficient to elicit the face-specific N170 at the scalp, in addition to the intracranially recorded analogue, N200 [4,9]. These data suggest that the face-specific structural-encoding mechanism can adapt itself to process novel stimuli if they convey physiognomic information as a face. These results have been further extended to studies in which induction of a face context triggers face-specific activity in ERP during processing of stimuli not normally perceived as face components [10]. Similar findings have been reported from PET studies, in which visual stimuli did or did not activate face-specific areas in the FFA, depending on whether the subject was trained to detect a face in a visually masked display [11]. These results imply that even simple geographical shapes can elicit face-specific neurophysiological responses if, and only if, the subject perceives the pattern as a face. Given these recent findings on schematic faces, the present MEG study tried to investigate stages of processing in face perception in humans. Our novel seeing-as-face task paradigm MEG experiment allowed comparison of the processing of identical visual inputs assigned different task-related status. A critical point of this task paradigm was that the same visual inputs were used across two conditions, one being a non-specific pattern of geographical shapes, the other being a percept of face, thus specifically addressing what brain areas are activated when faces are perceived.

MATERIALS AND METHODS

Subjects: A total of 11 normal subjects (four males, seven females) were studied, ranging in age from 22 to 43 years

old (mean 26.5 years). All subjects displayed normal or corrected visual acuity, and all were right-handed (according to the Edinburgh Scale [12]). Subjects were fully informed of the MEG recording and written informed consent was obtained from each subject prior to the experiment, which was approved by the Ethics Committee at Tokyo Dental College in accordance with the Declaration of Helsinki.

MEG recording: MEG was measured using a 306-channel whole-scalp neuromagnetometer (Vectorview, Neuromag, Helsinki, Finland). The system was equipped with two orthogonal planar gradiometers and one magnetometer at each of the 102 measurement locations (arranged in a helmet-shaped array). Subjects were seated in a reclined chair inside a magnetically shielded room. Subjects were looking straight ahead, and instructed to fixate on a point to the front and keep their eyes open while stimuli were presented. The exact position of the head with respect to sensors was determined by measuring magnetic signals produced by currents led into four indicator coils that were placed at known sites on the scalp. Location of the coils with respect to cranial landmarks were determined using a 3D digitizer (Isotrak, Polhemus, Colchester, Vermont) to allow alignment of the MEG and MRI coordinate systems. Head MRIs were obtained using a 1.5 T Siemens Symphony system (Erlangen, Germany). MEG responses were recorded using a 0.1–200 Hz bandpass filter, and digitized at a sampling rate of 997 Hz. The analysis period of 400 ms included a pre-stimulus DC baseline of 100 ms. Epochs in which signals exceeding 1500 fT/cm were excluded from averaging, and an additional set of data was collected.

Stimuli and device: Stimuli were schematic black-and-white patterns, comprising four ovals and four rectangles (Fig. 1). Stimuli were projected onto a screen in front of the subject. Distance between the eyes of the subject and the stimuli was 160 cm. Each stimulus was 40 cm wide and 30 cm high, with a resolution of 640 × 480 pixels. Stimuli were edited using Photoshop software (Adobe Systems, San Jose, California) on a personal computer, and presented under software control (LabVIEW, National Instruments, Austin, Texas). Each stimulus was presented for 500 ms, with an interstimulus interval of 3000 ms. MEG data for each subject were obtained from two blocks; each comprised 200 successive images. Magnetic signals with 200 trials in each session were averaged with trigger pulses that were generated at the onset of stimulus presentation.

Subjects performed a 1-back repetition detection task in which they were required to press a button whenever they saw two identical patterns in a row. At the first block, subjects were instructed to only look at rectangles, which were arranged to form an abstract pattern (non-face condition). After the first block, subjects were reassured that each pattern was perceived just as an abstract image. At the second block, subjects were instructed to look at ovals only, and told they were arranged to form a face pattern and the task was to detect whether two successive faces were identical or not (face condition). The two conditions actually utilized visually identical inputs, with only subject perceptions (task-related behavior) differing. Magnetic signals were averaged using time-locked trigger pulses generated with a photo sensor in front of the projector. The sensor

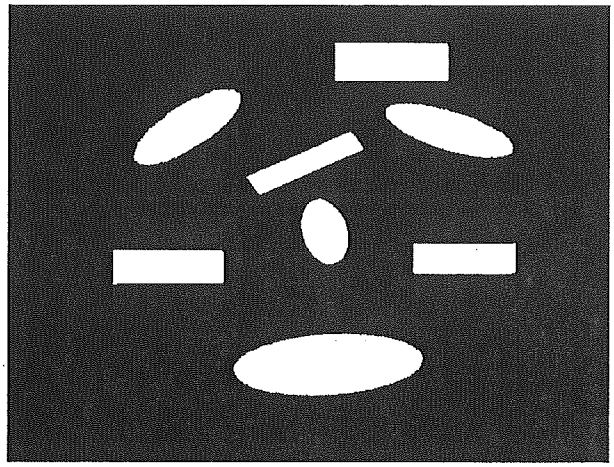

Fig. 1. An example of stimulus. Four ovals were arranged to form a face, whereas four rectangles yielded abstract patterns. In the experiment, no subjects noticed that the ovals were arranged to form a face before instruction.

detected changes in luminance elicited by a small square projected beside the stimuli, which appeared at the stimulus onset. Subjects could not see the small square giving rise to the trigger onset. Subjects were instructed to see the center of each stimulus without blinking the eyes during presentation. Stimuli under each condition were delivered in pseudorandom order, with identical order between the two conditions. A total of 50 different prepared images were presented four times each, and visual evoked magnetic fields from 200 trials under each condition were off-line averaged.

Data analysis: Averaged responses measured at each condition, non-face and face, were digitally low-pass filtered at 140 Hz. Mean amplitude from −100 ms to 0 ms before stimulus onset served as a baseline at each channel. Each evoked response was averaged separately off-line for each subject. Cerebral sources of responses were modeled as equivalent current dipoles (ECDs). Each ECD was estimated using a spherical head model [13], which was fitted to the inner curvature of the skull using MR images from individual subjects. The ECDs that best described the most predominant source were first determined by a least-squares search at response peaks, based on data from 114-306 channels, and ECDs with adequate correlation were analyzed and overlapped on individual MRIs. Finally, all channels were taken into account, analysis was extended to the whole time window, and all ECDs were included simultaneously in a time-varying multi-dipole model [13,14]. Subtraction of averaged responses between these two conditions was then taken by calculating differences at each digitized point. In estimating subtraction waveforms, mean amplitude from −100 ms to 0 ms was also used as a baseline. In order to investigate spatial distribution, we used the signals from the 204 planar gradiometers, which reflected local cerebral activities under each channel. A pair of gradiometer at 102 points measured the two orthogonal derivatives of radial magnetic field. To further analyze magnetic signals, local root-mean-square (RMS) amplitude (i.e. square root of the sum of squared fT/cm values) was calculated for each subject and each condition [15]. In this

study, local RMS amplitudes, summed over the two gradiometers, were computed to measure field strength at each latency around bilateral frontal, temporal, parietal and occipital regions. Each of the eight regions included 24 channels. Statistical analysis was performed using ANOVA with Bonferroni-Dunn's correction for multiple comparisons, and $p < 0.0001$ was considered significant.

RESULTS

Waveforms: In all subjects, four major components were identified within the time window of 0–300 ms in the waveforms measured at each condition. Peak latencies occurred at ~90 ms, 120 ms, 170 ms and 220 ms after stimulus onset. Figure 2 shows the grand average waveforms measured at these two conditions, and subtraction from representative subject 1: panels (a) and (b) depict 204-channel grand average waveforms measured through face and non-face conditions, respectively. Subtracting waveforms were obtained by subtracting each point of the response measured through the non-face condition from that through face condition in every channel separately, which showed three components in all subjects. Statistical analysis, which compared the amplitudes of RMS from the latency of 0 ms to 300 ms every 10 ms, revealed significant differences at latencies of 120 ms, 170 ms and 220 ms between amplitudes (face minus non-face) and baseline condition ($p < 0.0001$). When grand averages of the eight regions (right and left frontal, temporal, parietal, and occipital) were compared, bilateral occipital regions displayed greater contributions to the response at the latency of 120 ms than any other regions judging from fullview window. Also, statistical analysis using RMS revealed that the amplitudes of right and left occipital regions were significantly larger than other areas ($p < 0.0001$). Figure 2c,d shows subtraction waveforms between face and non-face conditions provided by calculating differences at each latency. The most notable finding was the enhanced components at latencies of 120 ms (107–131 ms) and 170 ms (164–198 ms) after stimulus onset in subtracted waveforms. The amplitude of the right occipital area was larger than that of the left ($p = 0.0128$; Fig. 2d).

RMS: Figure 3 shows RMS from the 24 channels of the occipital region in Subject 1. Red and blue lines denote face and non-face conditions in the right occipital region, respectively. Signals observed under the face condition were larger at most latencies than signals under non-face conditions. The most prominent finding was dissociation of amplitudes in RMS around the latency of 120 ms between these two conditions, causing the peak around this latency seen from subtraction waveforms (black line). Subtractions between the two conditions are shown as black and yellow lines, for the right and left occipital channels (24 each), respectively. Signals at the latencies of 120 ms and 170 ms were more marked in the right occipital channels. These tendencies were recognized in all 11 subjects, suggesting that neural activation should be evoked by this experiment in this order of latencies (three additional subjects performed a reverse version of the seeing-as-face task, in which rectangles were arranged to form a face and ovals were arranged to form abstract images. Under these conditions, results were essentially the same as for the standard test).

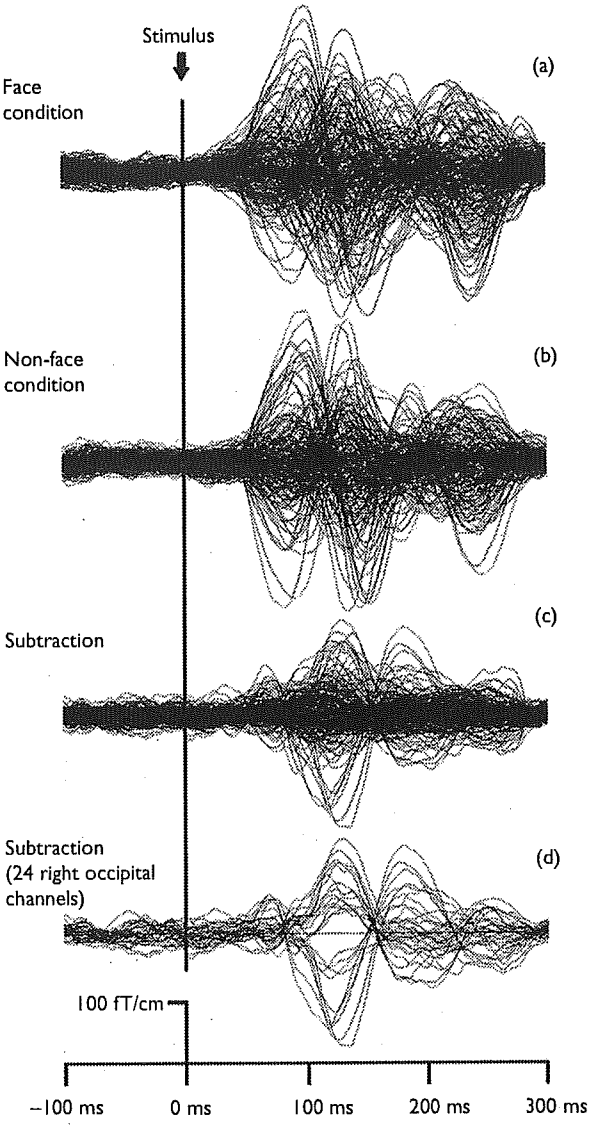

Fig. 2. MEG waveforms of a representative subject (Subject 1 in Table 1). (**a–c**) Superimposed waveforms from 204 channels; (**d**) was extracted from the 24 right occipital channels. (a) Face condition. (b) non-face condition. (c,d) Subtraction between face and non-face conditions. Before subtraction (a,b) four major components were identified, at 90 ms, 120 ms, 170 ms and 220 ms after stimulus onset. After subtraction (c,d) two components (120 ms and 170 ms after stimulus onset) were revealed as face-specific responses. The x-axis is the time (latency) described as ms and the y-axis represent the amplitudes described as fT/cm across panels.

Table 1 shows peak latencies and amplitudes for responses at latencies of 120 ms and 170 ms across all subjects, by calculating results from 24-channel RMS of the right occipital region from subtraction. All subjects displayed three or four peaks in subtracted RMSs, and mean latencies of response around 120 ms and 170 ms were 119.2 ± 6.8 ms (range 107–131 ms) and 176.6 ± 10.0 (range 158–198 ms), respectively.

Source modeling: ECDs were estimated from averaged data measured under each condition. At latencies of 158–198 ms, ECD was estimated only from averaged data

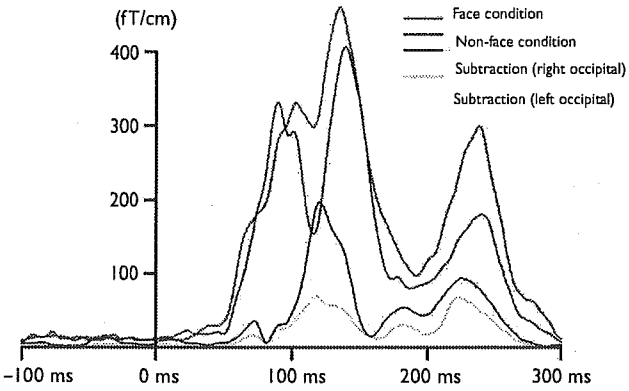

Fig. 3. RMS from 24 channels from a representative subject (Subject I in Table I). Red and Blue lines represent face and non-face conditions, with the black line representing subtraction between the two conditions in the right occipital region. Subtraction between the two conditions for the left occipital region is indicated as the yellow line. Note that M100 in subtraction is prominent in the right occipital region, but not in the left occipital region. The x-axis is time (latency; ms) and the y-axis represents the amplitudes of 24 channels' RMS described (fT/cm).

Table I. Peak latencies and amplitudes for M100 and M170 across 11 subjects, after calculating from 24-channel RMS of the right occipital region from subtraction (corresponding to black line in Fig. 3).

Subject No.	M100		M170	
	Latency (ms)	Peak amplitude (fT/cm)	Latency (ms)	Peak amplitude (fT/cm)
1	124	202	182	76
2	116	115	164	88
3	131	96	185	79
4	122	98	182	96
5	125	81	174	120
6	112	183	171	102
7	107	136	179	109
8	114	157	158	104
9	115	142	175	135
10	116	234	198	170
11	128	105	175	82
mean	119.1	140.8	176.6	105.5
s.d.	7.4	48.8	10.7	27.9

measured in face condition at the occipito-temporal region. By the integration to MRI data where available, the source location was along the posterior ventral surface of temporal lobe, which corresponded to fusiform gyrus. Nine subjects exhibited bilateral magnetic fields and two subjects exhibited unilateral magnetic fields representative of cortical activation at these latencies, as determined from MEG contour maps. In contrast, no significant responses were observed from averaged data in non-face acquisition, indicating that estimated ECDs were specific to seeing-as-face manipulation.

DISCUSSION

In the present study, two MEG components were clearly identified, at latencies of ~120 ms and ~170 ms. Response at the latency of ~170 ms was consistent with previously reported components in many studies, which were 140–170 ms in latency (M170) and generated in the inferior occipito-temporal cortex. The component at ~120 ms was observed predominantly in the right occipital region, ~50 ms earlier than the component of face identification, and was suggestive of the M100 component corresponding to the stage of face categorization in the previous report by Liu *et al.* [7].

Experiments investigating the mechanisms involved in visual processing often fail to separate low-level encoding mechanisms from higher-level, behaviorally relevant mechanisms. As for studies of face recognition, neural responses elicited by face stimuli have been compared with responses to control stimuli such as other objects, complex abstract patterns, or scrambled faces [1–6]. These tasks have inherently shared the same drawbacks, i.e., responses could simply reflect differences in the low-level properties of visual stimuli: differences that are difficult to investigate systematically. In particular, early visual evoked responses have been shown to be very sensitive to changes in low-level physical features. That might be, at least partially, the reason most previous reports have not found any face selectivity at early latencies (< 150 ms) except for a few studies in which this problem was carefully treated [7,16,17]. Our novel seeing-as-face task was developed to tackle this problem. As the same visual inputs were used across all conditions, our findings specifically address the components elicited when faces are perceived. The M170 component in the fusiform gyri and the M100 in the right occipital cortex were therefore as a result of identical visual inputs eliciting the visual percept of a face.

Our result was in agreement with the report by Liu *et al.*, in that two components were significant in the stage of human face perception. An earlier response at a latency of 120 ms was clearly observed in addition to M170, and corresponds to the M100 component noted by Liu *et al.* [7]. Our observation supports their argument that the M100 reflects the percept of the subject, not simply the low-level properties of the stimulus, since M100 response was only observed when a stimulus was perceived as a face, rather than as an abstract. Liu *et al.* further demonstrated the M100 as unrelated to face recognition (identification) and suggested that the later M170 component reflects identity of the face. As our schematic faces were defined by the arrangement of nonfacial features comprising simple geometric shapes, no identification process existed in the task paradigm. Accordingly, in contrast with the argument put forward by Liu *et al.*, our results imply that the M170 reflects the structural encoding of faces, and concurs with other previously published evidence. Several authors have found that the M170 was unaffected by face familiarity, and suggested an association with pre-categorial structural encoding of faces, rather than with later processes involved in face recognition or identification [18–20]. An explanation of those conflicting reports would be that M170, but not M100, is associated with the processes by which identification begins, but not identification *per se*, which of course awaits future studies. Our study represents a first tentative step in the identification of the stages of processing involved in face perception, using a novel task paradigm. The results demonstrated that simple geographic patterns elicited M100 and M170 responses if, and only if, those stimuli were perceived as a face by the subject. These results provide useful insights, but also clearly identify the limitations of our study. Firstly, the fact that subjects were instructed to see

the stimuli as a face obviously implies that the results simply reflect the attentional condition of subjects. Although the two conditions were identical with regard to visual input and task (1-back repetition detection task), face condition may have created additional visual demands, potentially affecting subject attention. Secondly, our experimental tasks involved reconstruction of face representations from fragmentary evidence. The results might thus be explained by the more general process of coherent synthesis of a percept (not specifically face) from insufficiently specified inputs, which may be a necessary process in high-level perception. Unfortunately, we cannot exclude these two possibilities. However, the fact that our results are essentially consistent with previous reports of face recognition, i.e., latency and generation sites of the two components, suggests that the two components observed are specific for faces, not for general processes such as attention or reconstruction. Of course, this requires further investigation and our present study, although novel as far as the task paradigm goes, should be interpreted as complementing and extending previous studies. In summary, we observed two MEG components, M100 and M170, in the processing stages of face perception. The nature of our task paradigm, i.e., identical stimuli identical across two conditions, strongly supports the notion that the observed responses are face-specific. In addition, we have provided evidence that task paradigms such as the seeing-as-face task are able to identify neural activity that is inextricably involved in face perception. This implies that the same approach, where comparison is made between neural activations in response to identical inputs under different perceptions, may be extended to other classes of objects. Unfortunately, we cannot run experiments comparable to those reported herein on other stimulus categories, as we have not found MEG markers selective for other categories. When these markers are found in future, some of the limitations inherent in the present study will be resolved and moreover, the task paradigm can be applied to object recognition in a more general sense. Furthermore, this paradigm might also prove useful not only for MEG, but also for the fMRI and PET techniques, which are susceptible to changes in low-level physical features in visual stimuli.

CONCLUSION

Face perception processing occurs as early as ~100 ms (M100) after stimulus presentation, as revealed by the seeing-as-face task. M170, indicated as a face-related response in many prior papers, was also detected in the present study. The nature of our task, i.e. identical visual inputs with different subjective perceptions, strongly suggests that M100 and M170 are specific to face perception. Similar tasks may prove useful in future studies of visual recognition.

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Magnetic brain activity elicited by visually presented symbols and Japanese characters

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A standard model of word reading postulates that the posterior inferior temporal cortex is involved in the processing of written words. This processing probably occurs within 200 ms after stimulus presentation. In order to characterize this process more precisely, we conducted a MEG study during a reading task in nine right-handed normal Japanese subjects. The subjects were required to respond to a word pertaining to the human body so that all stimuli would be subject to the same semantic processing. The trials for non-target conditions, such as kanji words, meaningful kana words, kana pseudowords and symbols were analysed to avoid possible P300 effect. The magnetic response peak of around 200 ms for symbols was smaller than any of the other three letter conditions. This result may suggest that M200 reflects the word-specific process such as visual word form recognition. *NeuroReport* 15:771–775 © 2004 Lippincott Williams & Wilkins.

Key words: Kanji; Kana; Language; M200; MEG; Semantic processing; Symbol; Visual word form recognition

INTRODUCTION

The ability to read words is one of our most important skills. Some lesion studies have revealed the importance of the posterior inferior temporal cortex (PITC) for processing visually presented words and letters [1]. The crucial role of PITC in word recognition has been further supported by studies using PET [2] and fMRI [3]. Further evidence for word-specific processing in PITC has been obtained from electric stimulation studies [4]. These imaging modalities have recently become widely favored, and they are also being used for detailed localization of the parts of the human brain activated during such a process. However, neither PET nor fMRI technique has the temporal resolution necessary to uncover the time course of events within the neuronal networks, since they measure the changes triggered in blood flow.

In order to answer questions about the dynamics of brain activity related to reading, the use of electrophysiological methods such as EEG and MEG, which provide high temporal resolution in the range of milliseconds, is highly appropriate. Nobre [5] performed intracranial recordings in the inferior temporal sulcus/fusiform gyrus and observed that letter string-specific activation peaked 150–200 ms after stimulus onset, followed 200 ms later by semantically sensitive activation in the medial temporal areas. Reading printed words may target the posterior fusiform and lingual gyri for visual processing in a proposed word recognition model [6]. In recent studies using MEG, the magnetic response peak at about 200 ms (M200 component) to the visual presentation of words has been found in PITC [7,8]. The M200 (M180 in [8]) component of the evoked magnetic field was larger for the processing of words and false font stimuli compared with nonverbal stimuli. In a PET study [2], although the areas in the left medial extrastriate visual cortex were activated by visually presented pseudowords that obey English spelling rules as well as by actual words, these areas were not activated by nonpronounceable strings of letters or letter-like forms. Considering first the differences between pseudowords and nonsense letter strings, a string of letters that follows the spelling rules of English could be seen as a legitimate visual word form. Secondly, a difference could also be due to the pronounceability of particular letter strings. Pseudowords and real words are pronounceable presentations, whereas false fonts and illegitimate strings of letters are not. A third possible explanation for the reduced activity of the PIT areas to nonpronounceable stimuli is that there will be no subsequent semantic processing. If the third hypothesis is true, M200 will depend on semantic processing. In other words, semantic processing will be included in the component of M200. The absence of activation in PITC for nonpronounceable strings of letters or letter-like forms [2] might be explained in terms of the lack of semantic processing. It is still not known whether lexical-semantic processing already begins in the latency range of the M200 component. To explore this issue further, we designed a MEG experiment to compare the PIT activities after the visual presentations of symbols, which have no visual word form or

pronounceability but have semantics, kanji words and kana words that are both pronounceable and have meanings, and kana pseudowords that can be pronounced but have no meaning. It was of great interest to us whether there would be any difference in M200 between symbols and words, and between pseudowords and real words. Modern Japanese sentences are written in kanji (morphograms) and kana (syllabograms) combinations without spaces between words. Kanji were brought from ancient China and each kanji has semantic value as well as phonetic, whereas kana were constructed later as simplifications of kanji but represent only Japanese short syllables (mora). Kanji are used for writing most nouns, stem of verbs, adverbs and adjectives. In contrast, kana are usually used to write inflectional endings, conjunctions, particles, foreign words and onomatopoeic expressions. There are about 2000 kanji characters and 71 kana characters in daily use. This mixed usage of kanji and kana in the Japanese writing system has brought a unique pathological condition in brain lesion patients showing severe kana alexia with relatively well-preserved kanji reading [9]. However, a MEG study reported that there was no difference between kanji and kana processing [7]. The main goal of the present study was to investigate whether symbols would elicit the M200 component in a similar way as words. The second aim was to clarify the difference in processing between real words and pseudowords and between kanji and kana. If the M200 component reflects a part of the semantic processing, it would emerge for symbols like for actual word and pseudoword stimuli. However, if the M200 component reflects some processing stage specific to language between the morphological and semantic processing such as the visual word form recognition, the M200 component to symbols would be less than that to character stimuli.

MATERIALS AND METHODS

Subjects: Nine healthy native Japanese-speaking subjects (three females and six males), aged between 20 and 52 (mean 29.2±8.4 years), participated in the current experiment. They were all right-handed as confirmed by a modified version of the Edinburgh Inventory [10], and had normal, or corrected-to-normal, vision. The protocol had been approved by the Ethical Committee of the Graduate School of Tokyo Medical and Dental University. Informed consent was obtained from all participants after the nature and possible risks of the experiment were explained.

Stimuli: Four non-target and two target conditions were used (Table 1). Non-target conditions consisted of kanji words, meaningful kana words, kana pseudowords and symbols (136 stimuli or 23% expectations for each kind); target conditions, which pertained to the human body, comprised kanji words and meaningful kana words (24 times or 4% for each kind). A white semilucent screen was placed at a distance about 30 cm from the eyes and each stimulus was presented in the center of the screen with a visual angle delimited to about 2° vertically and either 2 or 4° horizontally under the control of a computer (Valustar, NEC, Japan). The stimuli were black on a white background. The kanji and meaningful kana word lists consisted of the same words, although they appeared in different character types, and the numbers of letters also differed due to the nature of the different character types. The symbols were recruited from the symbol and wingdings font of Microsoft Word. The experiment consisted of six sessions, with each session comprising five blocks of trials. For each block, six types of stimuli

Table 1. Examples of kanji words (one character), kana words (two characters), kana pseudowords (two characters) and symbols.

Stimuli		Examples				592 (100%)
Kanji words	Nontarget	皿 (dish)	土 (soil)	服 (clothes)	北 (north)	136 (23%)
Kana words		さら (dish)	つち (soil)	ふく (clothes)	きた (north)	136 (23%)
Kana pseudowords		れは (meaningless)	せあ (meaningless)	のゆ (meaningless)	つあ (meaningless)	136 (23%)
Symbols		(floppy disk)	(air plane)	(bomb)	(sandglass)	136 (23%)
Human body kanji words	Target	足 (foot)	首 (neck)	肩 (shoulder)	胸 (chest)	24 (4%)
Human body kana words		あし (foot)	くび (neck)	かた (shoulder)	むね (chest)	24 (4%)

Target stimuli are shown in the lower portion. The trials of these stimuli were excluded from the analysis.

were arranged in a pseudo-randomized order for 1.2 s per word or symbol, but no more than 3 stimuli in the same condition appeared consecutively. The intertrial interval varied randomly from 0.3 to 0.5 s. Ten-second intervals were inserted after each block of 20 stimuli, and blinking and swallowing, prohibited during the block of stimuli to minimize artifacts, were permitted during these intervals.

Procedure: The subjects were required to lie on a bed in a dimly lit, sound-attenuated, magnetically shielded room. They were asked in advance to click the castanets whenever a word pertaining to the human body was presented. By this task, all stimuli would be processed semantically while the vigilance of the subjects was monitored.

Recordings of event-related magnetic fields (ERFs) were carried out in the using a Magnes 2500, 148-channel, whole-head system manufactured by Biomagnetic Technologies (San Diego, CA, USA) with a band pass of 0.1–400 Hz and digitized at a rate of 1024 Hz for 1000 ms including a 100 ms pre-stimulus baseline before stimulus presentation. Epochs containing a magnetic field in which the difference between maximum and minimum potentials > 4000 fT were deemed to have artifacts and were excluded from averaging. The averaged waveforms were digitally filtered using a lowpass filter of 30 Hz. The ERF waveforms elicited by the target stimuli are likely to be superimposed by large P300. Target stimuli would also be affected by motion preparation components. To avoid this, we excluded the target stimuli from the following analysis. The number of responses included in the averaging was ≥ 74 for each type of presentation and for each subject. The root mean square (RMS), i.e., the sum of the square root of all 148 sensor amplitudes mean averaged over the following time window for the components, were used to evaluate the magnitude of the magnetic field obtained. The average RMS for a 150–250 ms period was adopted as the magnitude of M200. The point during a 150–400 ms period showing the maximum RMS was adopted as the M200 peak, and the time from the stimulus onset to that point as the M200 latency. If the maximum was reached at 150 or 400 ms, the point with the highest amplitude nearest the 200 ms point was adopted as the M200 peak. For each condition, a single signal source was estimated from the 38-channel data for the posterior half of each hemisphere. Source analyses based on a single equivalent current dipole modeling (ECD) were estimated using 38 sensors in the temporo-parieto-occipital regions on each hemisphere. Only data meeting the following five criteria were accepted: (1) a correlation between the theoretical fields generated by the model and the observed fields > 0.90; (2) a goodness-of-fit (a parameter used to determine how well the observed measurements and the resulting dipole fit agree with the model) > 90%; (3) a 95% confidence volume for the location of the dipole $< 2.14\,cm^3$ (corresponding to the volume of an 8 mm radius globe); (4) ECDs located on the cortex in MR images; (5) temporal stability of ECDs for > 10 ms associated with the preceding four criteria. Criterion (4) was checked by visual inspection. Statistical analyses were carried out using repeated measure ANOVA. The Greenhouse-Geisser correction procedure was used where appropriate.

RESULTS

Behavioral data: Response accuracy (mean ± s.d.) in the kanji and kana conditions during recordings was 95.0 ± 4.6 and 95.8 ± 5.5%, respectively. Accuracy of all the subjects was > 83% in each of the conditions, allowing all of them to enter the succeeding analysis.

Event-related fields: Figure 1 shows grand-averaged MEG waveforms for the four non-target conditions. Under each of the four conditions, visual inspection revealed three components: M150 peaking at 150 ms, M200 at 200 ms and M400 at 400 ms after stimulus onset. For the amplitude of M200, the symbol condition showed a smaller amplitude than the kanji word, kana word and kana pseudoword conditions. Figure 2 presents the grand-averaged RMS of 9 subjects for the magnetically evoked fields of all 148 channels. No difference among the four conditions was found for the amplitude or latency of M150. However, RMS waveforms began to differ between experimental conditions about 170 ms after the stimulus onset. The waveforms for the symbol condition appeared to begin later and persist longer. ANOVAs revealed significant main effects of stimulus condition for the M200 amplitude ($F(3,24)=4.42$, $\epsilon=0.596$, $p < 0.05$) and latency ($F(3,24)=2.73$, $\epsilon=0.728$, $p < 0.01$) in the left hemisphere, indicating that M200 was reduced and delayed for symbols compared to any of the other conditions. M200 did not differ between kanji words and kana words on both hemispheres. Localization of M200 showed inter-individual variability, due mainly to differences in cortical anatomy, and therefore different distributions of neural activity in MEG sensors. The sources of M200, which showed satisfactory dipole solutions on the left hemisphere, were localized in the vicinity of the fusiform gyrus (6 of 9 subjects for kanji words, 5 for kana words, 5 for kana pseudowords and 4 for symbols), inferior temporal gyrus (1 for kanji words, 2 for kana words, 1 for kana pseudowords and 1 for symbols), angular gyrus (1 for kana words and 2 for kana pseudowords) and lingual gyrus (1 for kanji words and 1 for symbols). Figure 3 shows an example of the determination of the source of the M200 electrical currents, located in the vicinity of the fusiform gyrus. The location did not differ significantly between any two of the four conditions.

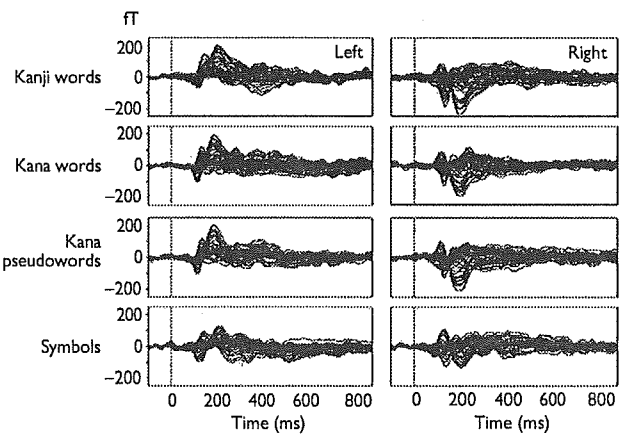

Fig. 1. Grand-averaged (n=9) event-related field (ERF) waveforms elicited by four non-target conditions (kanji words, kana words, kana pseudowords and symbols) during the semantic task recorded from 38 sensors in the temporo-parieto-occipital regions on each hemisphere. Three magnetic components can be detected (M150, M200 and M400).

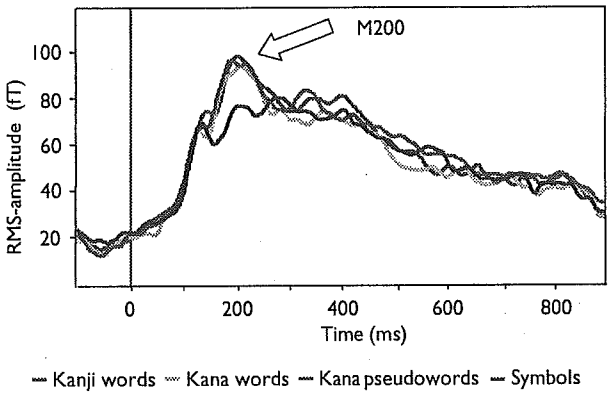

Fig. 2. Grand-averaged root mean square (RMS) waveforms recorded from the whole head are shown separately for the kanji word condition (red), kana word condition (yellow), kana pseudoword condition (green) and symbol (blue) condition. The M200 component in the symbol condition is smaller and later than in the other three conditions.

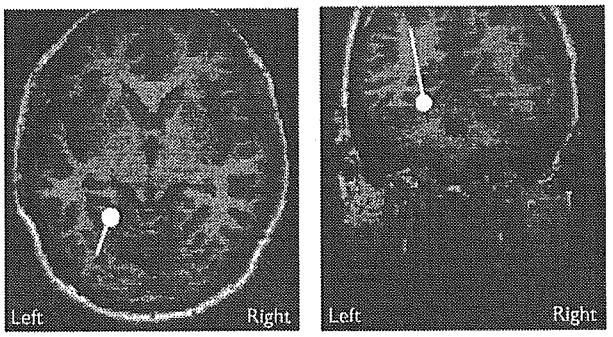

Fig. 3. White circle with a bar indicates one representative equivalent current dipole (ECD) source estimated during the M200 time window in the kanji word condition from one subject superimposed onto horizontal and coronal MRI scans. There was no difference among the four conditions.

DISCUSSION

The present experiment assessed the response of PITC during semantic judgment of kanji words, kana words, kana pseudowords and symbols, and compared the magnitude of activations between words and symbols. The MEG data revealed that M200 for symbols was smaller than for any other condition. One possible explanation is that the processing of words may activate the neural substrates that subserve visual word form recognition. Consistent with this perspective, the present study revealed greater activation in PIT during the processing of real words and pseudowords relative to symbols. An alternative explanation would be that at least a part of M200 is involved in phonological processing and that, in the case of symbols, little phonological processing occurs. However, recent studies using fMRI [11,12] have revealed that the left inferior prefrontal cortex plays a critical role in phonological processing, inconsistent with lesion deficit studies with neurological patients [13]. Therefore the plausibility of the second interpretation seems very slight. The third explanation that no semantic processing following early visual processing can result in the absence of M200 must be abandoned, because symbols have meaning and are subject to semantic processing in spite of the fact that they cannot be pronounced.

In the current study there was no effect of lexicality on M200 localized in PITC. This result is in line with studies using fMRI [14] and PET [2] that failed to find reliable activation differences between actual words and pronounceable nonwords in these areas. However, a PET study of word-naming [15] demonstrated less activation for real words than pseudowords. In contrast, a recent study using event-related fMRI of lexical decision [16] reported the reverse result, namely, stronger activation for real words than pseudowords was obtained in bilateral occipito-temporal brain areas. PET and fMRI studies have produced conflicting findings probably as a result of design and task differences. Brain activations in a block design may have been influenced by strategic effects on task performance like a stereotypic response, whereas they were elicited by individual events in an event-related design. When subjects were required to articulate the stimuli, different (although likely overlapping) and more extensive populations of neurons would be engaged compared to a lexical decision task. In contrast to PET and fMRI studies, the fact that there is no difference in the component peaking around 200 ms between actual words and pseudoword was consistently shown in a cortical surface ERP study [5] and MEG studies (1 M in [17]). Based on the present result, it seems that pseudowords may be processed in a similar way to real words in the vicinity of PITC when participants are not required to give any overt response and when an event-related design is used.

The results that the M200 responses for kanji and kana were similar in shape and consequently the locations of ECDs to kanji and kana did not differ are in accord with the previous findings [7], suggesting that kanji and kana may be processed similarly. In our previous MEG study [18] the source of M200 was localized in the vicinity of the fusiform gyrus for both kanji and kana nouns, although the amplitude of the component for kanji was larger than that for kana nouns. Coupled with the lesion study [19] indicating that there was no neuroanatomical relationship between impairments of certain high cortical functions, such as the reading of morphograms and syllabogarms, and lesion sites, our results provide converging evidence that kanji words and kana words may be processed in the same anatomical regions. Koyama [7] interpreted the kanji-kana dissociation in reading as reflecting the greater graphic complexity of some kanji. A limitation of this study that should be noted was the use of the ECD modeling. The fundamental principle of localizing the putative source depends on the basic assumption that it is reasonable to consider a single discrete source for the phenomena in question that can be appropriately mathematically modeled [20]. Many early (latency up to ~100 ms poststimulus) fields such as sensory evoked fields have a high goodness of fit to a single ECD model. When such sources are mapped onto the corresponding MRI, the locations are found to fall within the appropriate sensory cortex. This model provides validity to the source localization of such phenomena. This is less likely to be true for later (longer latency) evoked fields components that likely involve widely distributed cognitive processing that cannot be reasonably modeled with a single or simple set of sources. M200 response most probably represents the summed activity from multiple intracranial generators. Although most of the localizations during M200 period were estimated in the vicinity of the

PITC, a few subjects showed activations in the angular gyrus. We previously reported that the ECDs for the particles (Joshi in Japanese), which are always written in kana, were mainly located in the supramarginal and angular gyri, while those for nouns (both in kanji and kana) tended to be located in the posterior-inferior-temporal areas [18]. It remains unclear whether spatially distinct sources may reflect a different aspect of the encoding process that leads to word recognition.

CONCLUSION

The present study demonstrated that M200 for symbols was smaller than any other letter condition, but there were no differences between actual words and pseudowords or between kanji and kana. These results provide evidence that M200 may reflect the prelexical process such as visual word form recognition.

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—Photogravure—

Pharmacological Modulations on the Human Cognitive Processes: An fMRI Study

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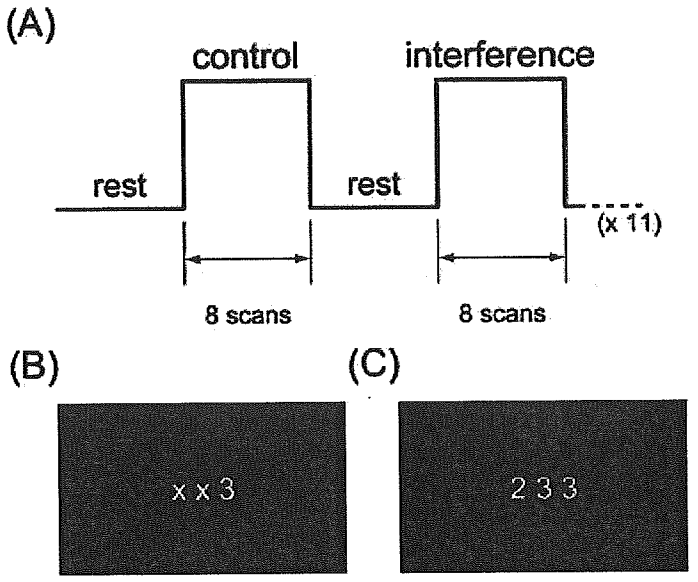

Fig. 1

Investigating modulatory effects of psychopharmacological agents in the human brain allows for not only functional characterization of particular neurotransmitter systems in the human cognition, but better understanding of pathophysiology and treatment of neuropsychiatric disorders[1]. Here we conducted a functional magnetic resonance imaging (fMRI) study to map effects of a dopamine D_2 antagonist (sultopride) on a decision-making process. In a single scanning session, ten male, right-handed, healthy subjects performed a Stroop-like cognitive interference task[2] (**Fig. 1**). In the absence of dopaminergic manipulations, comparison of blood oxygenation level dependent (BOLD) signals during the interference condition against those during the control condition revealed a widely distributed network implicated in the decision-making process with cognitive interference (**Fig. 2A**). Upon the administration of the D_2 antagonist, however, many of these regions exhibited decreased activities, and the effects were found to be most prominent in regions around the cerebellum, the thalamus, the anterior cingulate cortex, and the motor areas (**Fig. 2B**). Subsequent studies should address the role of individual components in the observed brain circuits, as well as what the decrements of activations mean in the neurophysiological context.

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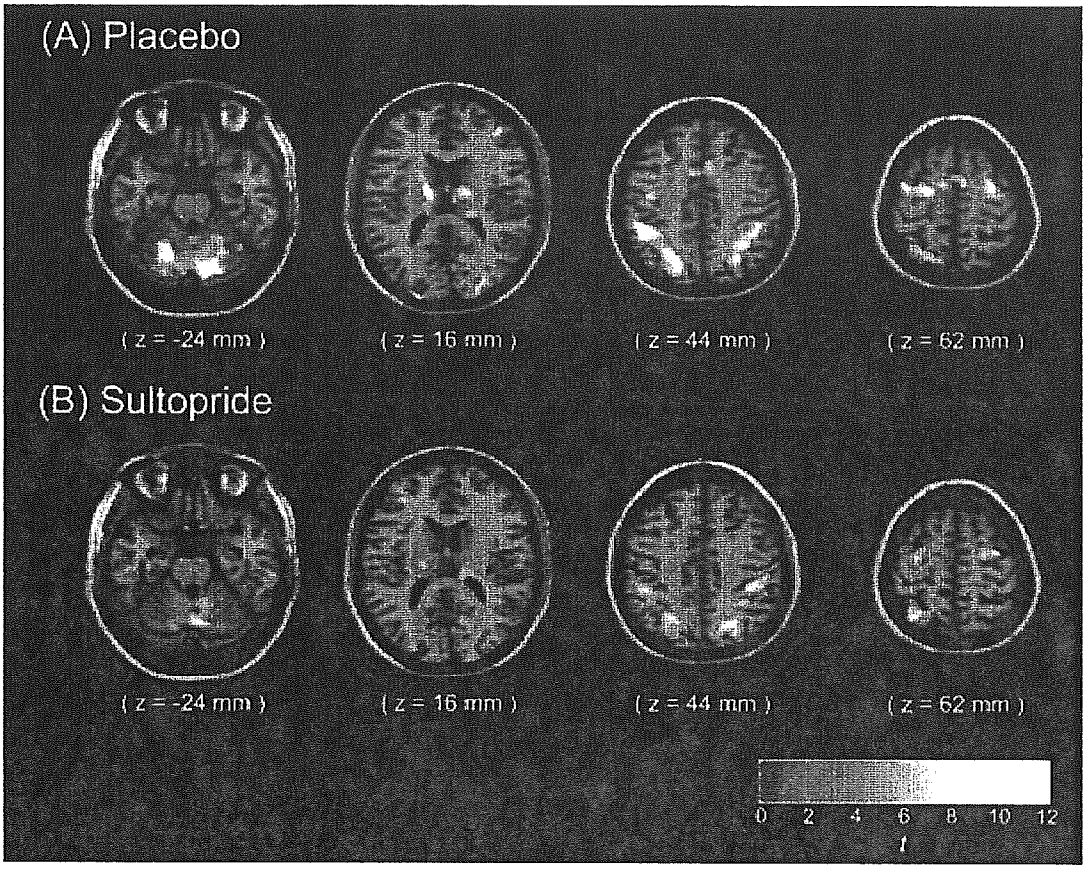

Fig. 2

Fig. 1 (A) Schematic diagram illustrating the cognitive interference task employed. A single scanning session consisted of blocks (containing eight scans) of control and interference trials interspaced by resting periods. During the trials, subjects are instructed to report by button press the identity of the number that differs from the other two. (B)-(C) Examples of the trials. During the control trials, the distractors were the letter 'x', whereas during the interference trials, the distractors were other numbers, thereby imposing higher cognitive demands.

Fig. 2 Activated regions during the interference trials in contrast to the control trials (A) with no dopaminergic manipulations and (B) under the administration of a D_2 antagonist (sultopride). The results are based on a group analysis with statistical parametric mapping (SPM) software[3] and with a statistical threshold of $P<0.001$ (uncorrected).

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ACTA PSYCHIATRICA SCANDINAVICA

Eleven-year clinical outcome of schizophrenia in Bali

Kurihara T, Kato M, Reverger R, Tirta IGR. Eleven-year clinical outcome of schizophrenia in Bali.
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Objective: To contrast the short-term and long-term outcome of schizophrenia in Bali.
Method: The clinical outcomes of 46 schizophrenic patients (DSM-IV-TR) consecutively admitted to Bangli Mental Hospital were evaluated by Positive and Negative Syndrome Scale (PANSS) and Eguma's Social Adjustment Scale (ESAS) at a 11-year follow-up, which was subsequent to a 5-year follow-up.
Results: Neither the PANSS score nor the ESAS score were significantly different, and there was a significant correlation between the two follow-up data. Subjects categorized into either the best or worst outcome group at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up more often than those who were categorized into the medium outcome groups at the 5-year follow-up.
Conclusion: The 5-year outcome of schizophrenia strongly predicted the 11-year outcome, especially for subjects who had gone into either a remissive or severe deterioration state within 5 years.

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Key words: schizophrenia; follow-up studies; outcome assessment; developing countries

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Significant outcomes

- The result indicating that 43.5% of patients had achieved either remission or partial remission at 11-year follow-up raised questions about the established, pessimistic view towards the chronicity of schizophrenia.
- Medium-term (5 year) outcome of schizophrenia strongly predicted long-term (11-year) outcome in Bali where only a minority of patients receive maintenance treatment.
- If an intervention strategy combining relevant maintenance medication with social support is conducted successfully in the future, the overall outcome of schizophrenia in Bali may improve over the longer term.

Limitations

- The relatively small sample size.
- The hospital-based sample may be a major source of bias.
- The investigation of predictors of outcome may be hindered by the limited number of outcome variables or by the lack of some important clinical data at inclusion.

Introduction

Outcome studies of schizophrenia are important given that diagnostic concepts are based in part on assumptions about outcome, and baseline data in this area are essential for psychiatrists for their clinical practice (1). Moreover, such studies could be useful for the evaluation of treatment effects with different modes of treatment, and they have the potential to improve clinical subtyping of patients

with schizophrenia. Dementia praecox was initially regarded as an illness leading to an inevitable non-remitting endstate over time; however, subsequent outcome studies have revealed a different and more optimistic pattern of courses for schizophrenia. Davidson and McGlashan (2) reviewed follow-up studies of schizophrenia, and found that although a broad heterogeneity exists in long-term outcome, 21–57% of subjects achieve a good outcome, ranging from mild impairment to recovery. Furthermore, it was demonstrated that the medium- to long-term course of schizophrenic patients shows a high degree of stability, suggesting that the illness tends to reach a plateau of psychopathology early in the course (1, 3–6). Jeste et al. (7) also stated that the course of schizophrenia in late life appears stable. However, it remains unclear whether this outcome stability is also observed in developing countries where only a minority of patients undergoes regular maintenance treatment.

Longitudinal follow-up studies from Asian countries reported a good outcome of schizophrenia in Hong Kong (8), Singapore (6, 9), and India (10). The predictor of a good outcome was a shorter length of illness before admission in both studies in Singapore. The International Pilot Study on Schizophrenia (11, 12) and the subsequent Determinants of Outcomes of Severe Mental Disorder (13) by the World Health Organization indicated that the course and outcome of schizophrenia was more favorable in developing than in developed countries. However, as Singapore and Hong Kong should not be categorized as developing but rather developed countries, Lee et al. (8) concluded that the concept of developing or a developed country as a predictor of the long-term outcome of schizophrenia is not applicable, at least to the two sites in Asia. They also stated that traditional Asian family-based cultures may contribute to the good outcome of schizophrenia. In contrast, Ran et al. (14) demonstrated that the clinical outcome of schizophrenia in a rural Chinese community was poor, especially for patients who had never received antipsychotic drug treatment because of either financial problems or a lack of relative's knowledge of schizophrenia. Even today, there is a dearth of long-term outcome studies on schizophrenia in Asia (9); thus, more research findings are needed from other Asian countries to allow for discussion on the outcome of schizophrenia in this area.

Aims of the study

The aim of the study is to investigate the long-term (11-year) outcome of schizophrenia in Bali, and to contrast the outcome with that of short-term follow-up (5-year). We hypothesized that the 11-year outcome would be worse than the 5-year outcome, because only a minority of patients receive maintenance treatment in this developing country setting.

Material and methods

Study area

Bali is located in South-east Asia and is one of more than 10 000 islands that make up Indonesia. It is famous as a tourist resort and for its unique Hindu-based culture. There are 3 048 317 people living in Bali (2001; at the 11-year follow-up) and the island is almost entirely ethnically and culturally homogeneous. The industry is now in the developing stages. The basic unit of society is a community referred to as 'banjar', which consists of several hundred households. Both the religious ceremonial aspect and social activity of the 'banjar' is recognized as essential in Bali. Bali had 260 psychiatric beds at the 11-year follow-up, of which 225 were at the Bangli Mental Hospital, the primary mental health facility on the island, with a further 25 at a private mental hospital and 10 at a general hospital. The number of psychiatric beds on the island at the 11-year follow-up was almost the same as that at the 5-year follow-up when there were 270 psychiatric beds with 225 at Bangli Mental Hospital, 25 at a private hospital, and 20 at a general hospital. The only difference between the two points was that there were 10 fewer beds at the general hospital.

Subjects and criteria

Details were described in our previous 5-year follow-up study (15). In brief, the subjects were 59 consecutive patients who had been hospitalized at the Bangli Mental Hospital in Bali (Indonesia) with no prior psychiatric treatment between January 1990 and April 1991 and whose diagnosis met PPDGJ-II Criteria (16) for schizophrenia. The subjects represent nearly all schizophrenic patients who were seeking psychiatric admission at that time, given that the hospital accounts for approximately 87% of the psychiatric beds in Bali. The screening criteria of PPDGJ-II for schizophrenia are identical to those of DSM-III (17). No subjects had comorbidity of either organic mental disorders or psychoactive substance-abuse disorders. At the previous 5-year follow-up, of the 59 subjects, 51 (86.4%) could be followed up. In the present

study, at the 11-year follow-up, 46 (78.0%) could be followed up. All 46 subjects were re-diagnosed as having schizophrenia according to DSM-IV-TR criteria (18). Five dropped out because of death due to a physical disease.

Follow-up interview

The clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (19, 20). The validity and reliability of the Indonesian version has been established (21). We used Eguma's Social Adjustment Scale (ESAS) (22, 23 and see Appendix) for the assessment of social adjustment. After those assessments, the rater asked the subjects about their medication status. All of the subject's evaluations were based not only on their clinical interview but also on information from family members. The rater was blind to the clinical assessment at the 5-year follow-up. Inter-rater reliability between the rater in the present study and the rater at the 5-year follow-up was established, giving a reliability of 0.83 with the PANSS according to analysis of variance (ANOVA) interclass correlation coefficient (ICC) (24) and a reliability of 0.82 with the ESAS according to the ICC (25). In addition to these main outcome indexes, we also investigated the readmission rate, duration of readmission, work status, and marital status to demonstrate the overall outcome of the subjects. Information regarding medication status and readmission sometimes did not coincide completely among informants, and thus information was derived not only from interviews but was also corroborated by medical records. One characteristic of the study is that the medication status of the subjects between the two points is clearly shown, and most subjects had been either non-medicated or on irregular medication due to the developing country setting. The study was approved by the Indonesian Institute of Science, and all subjects gave written informed consent to participate in the study.

Statistical analysis

To compare the overall clinical outcome between the 5-year follow-up and 11-year follow-up, we developed a point scoring system from 1 to 5 to quantify the range from (A) Self-supportive to (E) Hospitalized on the ESAS. Two-tailed *t*-test and Pearson's correlation were used for the comparison of the PANSS score and the ESAS score between the two points of follow-up. For a detailed comparison, we divided subjects into good (subjects with a score in the bottom 33rd percentile/cutoff score 53), moderate (subjects with a score in the 33rd to 67th percentile/cutoff score 95), and poor (subjects with a score in the top 33rd percentile/score with 96 or over) outcome categories according to the PANSS assessment at the 5-year follow-up. When we divided subjects into the three groups at the 11-year follow-up, the above-mentioned cutoff score was used. Chi-squared test was used for the comparison of the PANSS groups and the ESAS categories between the two follow-up points.

A multiple regression analysis was conducted to investigate the predictors of outcome. Either the PANSS scores or the ESAS scores at the 11-year follow-up were used as the dependent variable, with age at onset, age at inclusion, sex, educational period, number of family members, and duration of untreated psychosis (DUP) as independent variables.

Moreover, Kruskal–Wallis test was employed to investigate the difference between either the PANSS scores or the ESAS scores at the 11-year follow-up among subjects with regular medication, irregular/brief medication, and non-medication.

Results

Sample description

Of the 46 subjects, 27 were males and 19 were females. Subjects had a mean age of 26.7 years (SD 7.83) at the first entry, mean educational period of 6.3 years (SD 3.48), mean age at onset of 24.3 years (SD 6.94), mean length of first hospitalization of 35.0 days (SD 28.8), DUP of 27.9 months (SD52.50), and mean number of family members of 5.0 (SD 2.30). No subjects lived alone.

Overall outcome at 11-year follow-up

The mean positive, negative, general psychopathology, and total scores on the PANSS of 46 subjects at the 11-year follow-up were 17.91 (SD 9.87), 20.11 (SD 11.31), 36.48 (SD 13.93), and 74.50 (SD 33.61), respectively. Of 46 subjects, 11 (23.9%) were in remission and nine (19.6%) were in partial remission defined by DSM-IV-TR. Eighteen subjects (39.1%) were classified on the ESAS as 'self-supportive', six (13.0%) as 'semi-self-supportive', seven (15.2%) as 'socially adjusted to family or community', 15 (32.6%) as 'maladjusted', while none were classified as 'hospitalized'. Seven-

teen subjects (37.0%) worked full-time, 10 subjects worked part-time (21.7%), and 19 subjects (41.3%) did not work at all. Of 46 subjects, 28 (60.9%) had been re-hospitalized after inclusion in the study, and the mean length of readmission was 63.8 days (SD 104.8). No subjects were hospitalized at follow-up. Twenty-nine (63.0%) had been married, and of those, one was divorced and one was widowed.

Relationship between sociodemographic data and outcome

Age at onset, age at inclusion, sex, educational period, number of family members, and DUP did not predict the clinical outcome at the 11-year follow-up as measured by the PANSS or the ESAS.

Relationship between medication status and outcome

Between the 5- and 11-year follow-ups, seven (15.2%) had been on regular medication, 16 (34.8%) had been on medication at irregular intervals or at some point during the period, while 23 (50.0%) had never undergone medical treatment during the period. Eight subjects (17.4%) were on medication at the 11-year follow-up interview. Both the subjects in the regular medication group and those in the irregular/brief medication group tended to have higher scores both on the PANSS and ESAS than did subjects in the no-medication group; however, this difference did not reach the level of statistical significance (Table 1).

Relationship between 5-year and 11-year clinical outcome

The PANSS score was not significantly different between the 5- and 11-year follow-up [74.37 (SD 32.17) vs. 74.50 (SD 33.61)], and it was significantly correlated between the two points of follow-up ($r = 0.870$; $P < 0.0001$). Moreover, the ESAS score was not significantly different between the 5- and 11-year follow-up [2.26 (SD 1.10) vs. 2.44 (SD 1.33)], and it was significantly correlated between the two points of follow-up ($r = 0.755$; $P < 0.0001$). As to the PANSS for three groups, both those in the good outcome group and those in the poor outcome group at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up more commonly than did those who were categorized into moderate outcome groups ($P < 0.05$) (Table 2). As for ESAS, both those in the best category 'self-supportive' and those in the worst category 'maladjusted' at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up than did those who were categorized into either 'semi-self-supportive' or 'socially adjusted to family or community' ($P < 0.001$) (Table 3).

Discussion

Stability of long-term outcome of schizophrenia

In the present study, the 5-year outcome of schizophrenia strongly predicted the 11-year outcome. Thus, the result failed to support our original hypothesis that the 11-year outcome would be worse than the 5-year outcome in Bali where only a minority of the patients receives maintenance treatment. The percentages of subjects who were on regular medication during the two follow-up points and that of those who were on medication at the time of 11-year follow-up were only 15% and 17%, respectively. Nevertheless, the present results replicated other outcome studies carried out in developed countries demonstrating that the medium- to long-term course of schizophrenic patients was stable and revealed neither marked deterioration nor significant improvement, suggesting that the illness tends to reach a plateau of psychopathology early in the course (1, 3–6). Of these studies, the percentage of subjects on medication at follow-up was 59% (1) and 76% (4), respectively, and the percentage of subjects who underwent treatment at follow-up was 60% (5) and 52% (6), respectively. Why is the long-term outcome of schizophrenia stable not only in the developed countries but also in this non-industrialized society where only a minority of the patients received regular maintenance medication? We hypothesize that there may be therapeutic

Table 1. Medication status and clinical outcome at 11-year follow-up

			Symptom status		
	PANSS score (SD)	ESAS score (SD)	Remission (%)	Partial remission (%)	Symptomatic (%)
Regular medication group ($n = 7$)	79.00 (30.87)	2.57 (1.27)	1 (14.3)	2 (28.6)	4 (57.1)
Irregular/brief medication group ($n = 16$)	85.63 (33.08)	2.88 (1.20)	1 (6.3)	4 (25.0)	11 (68.8)
No medication group ($n = 23$)	65.39 (33.49)	2.09 (1.38)	9 (39.1)	3 (13.0)	11 (47.8)

Kruskal–Wallis test was used for comparison of either the PANSS score or the ESAS score among the three groups. No significant differences were found.

Table 2. PANSS groups at two points of follow-up

	11-year follow-up			Category change	
	Good (%)	Moderate (%)	Poor (%)	Same (%)	Changed (%)
5-year follow-up					
Good	15 (88.2)	2 (11.8)	0 (0)	15 (88.2)	2 (11.8)
Moderate	3 (18.8)	8 (50.0)	5 (31.3)	8 (50.0)	8 (50.0)
Poor	1 (7.7)	1 (7.7)	11(84.6)	11 (84.6)	2 (15.4)

Chi-squared test was used for the category change among the three groups between the two points. Significant difference was found ($P < 0.05$).

factors associated with stable long-term outcome of schizophrenia besides maintenance psychiatric medication. In Bali, sociocultural factors such as a supportive and favorable emotional environment for schizophrenic patients [both among family members (26) and the general public (27)], a working environment that facilitates the schizophrenic patients to work at jobs suited to their decreased ability, and traditional healing frequently used by the patients might be therapeutic. Although we could not prove this hypothesis directly from our data in this study, it is plausible that these community-based support systems prevent further deterioration of the course of the illness.

Prospect of the outcome of schizophrenia in longer term

Detailed analysis in the present study showed that subjects categorized either into best or worst outcome groups at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up than those who were categorized into medium outcome groups at the 5-year follow-up. The result suggests that the progression, either amelioration or deterioration, in psychopathology and social functioning of schizophrenic patients stabilizes within 5 years, especially for those who either recovered to a remissive state or progressed to a severe deterioration state. Patients with relatively moderate symptoms tend to fluctuate in their outcome still at the 11-year follow-up. Ogawa et al. (23) followed up 140 schizophrenic patients over a period of 21–27 years and found that fluctuating courses of social functioning in the early stage of the illness showed differentiation on the whole to two directions in the later stage, namely to either a 'stable self-supportive' state or a 'chronic institutionalized' state. Whether the subjects in the present study in this developing country setting will reveal such a bipolarization over a longer term needs to be investigated in the future.

Transcultural comparison with other Asian countries

Factors that make it difficult to compare the present study findings with those of other outcome studies may include differences in the diagnostic criteria, duration of follow-up, sample size, and the terms of 'good' outcome. However, it is worthwhile to try to make such a transcultural comparison with neighboring countries in Asia. Kua et al. (6) followed up schizophrenic patients for 20 years in Singapore, and revealed that the percentage of patients categorized into either good or fair outcome based on aggregation of work and treatment status was 65%. Lee et al (8) followed up first-onset schizophrenic patients for 15 years in Hong Kong, and found that 53% of the subjects were recovered according to Bleuler's Severity Scale, while 21% of the subjects were rated as having a good psychosocial adjustment according to the Global Assessment of Functioning Disability ratings. Moreover, Thara (10) demonstrated that 59% of the schizophrenic patients were asymptomatic at the syndromal level on the Present State Examination (9th edn) at 20-year follow up in their Madras Longitudinal Study in India. All three of the above studies concluded that the outcome of schizophrenia was better than that in Western developed countries. In the present study, if we define good outcome as either remission or partial remission defined by DSM-IV-TR, 43.5% of the subjects in the present study fell into

Table 3. ESAS categories at two points of follow-up

	11-year follow-up				Category change	
	(A) Self-supportive (%)	(B) Semi-self-supportive (%)	(C) Socially adjusted to family or community (%)	(D) Maladjusted (%)	Same (%)	Changed (%)
5-year follow-up						
(A) Self-supportive	13 (81.3)	2 (12.5)	1 (6.3)	0 (0)	13 (81.3)	3 (18.8)
(B) Semi-self-supportive	3 (33.3)	2 (22.2)	3 (33.3)	1 (11.1)	2 (22.2)	7 (77.8)
(C) Socially adjusted to family or community	2 (14.3)	2 (14.3)	3 (21.4)	7 (50.0)	3 (21.4)	11 (78.6)
(D) Maladjusted	0 (0)	0 (0)	0 (0)	7 (100)	7 (100)	0 (0)

Chi-squared test was used for the category change among the four groups between the two points. Significant difference was found ($P < 0.001$).

the category. Moreover, in terms of social adjustment, 39.1% of the subjects were classified as 'self-supportive' on the ESAS. Thus, the outcome of schizophrenia in Bali was slightly worse than that of other Asian countries, given that the rate of good outcome observed was lower.

The percentage of hospitalized subjects at follow-up was 6.9% in Singapore (6), 9% in Hong Kong (8), and 3.3% in India (10), whereas no subjects were hospitalized at follow-up in this study. These small numbers of hospitalized patients in these Asian countries may reflect the high levels of family involvement in patient's care, which prevent long-term confinement in institutions (28). All subjects in this study lived with their family, and the percentage of single subjects was 41%, which was lower than that in Singapore (80%) (6) and in India (60%) (10).

Predictor of the outcome

No sociodemographic predictors of outcome were found in this study. Clinical factors, including modality of treatment, mode of delivery, and comorbidity of either organic mental disorders or psychoactive substance abuse disorders, did not differ among the subjects. The supportive and favorable attitude toward schizophrenic patients observed among the family members (26) and general residents (27) in Bali may have contributed to overall outcome. However, it is impossible to determine from the present data whether these factors are a predictor of outcome, because all subjects seemed to be blessed with the good emotional environment uniformly.

Maintenance medication and outcome

The clinical outcome revealed by the PANSS and ESAS of non-treated subjects tended to be better than that of medicated subjects, although the tendency was not statistically significant. As the efficacy of antipsychotics is well established (14, 29), it is not plausible that the lack of maintenance medication positively affected the long-term outcome of schizophrenia. The results reflect the finding that most patients in remission withdrew from maintenance treatment in this developing country setting.

However, it should also be noted that roughly half of non-medicated subjects were symptomatic. Furthermore, 69% of the subjects in the irregular/brief medication group were also symptomatic. The inadequate level of treatment offered to these patients might relate to the finding that the overall outcome of schizophrenia in Bali is somewhat worse than that of other Asian countries. An appropriate therapeutic intervention for these patients is essential. If an intervention strategy combining relevant maintenance medication with social support is conducted successfully in the future, the overall outcome of schizophrenia in Bali may improve over the longer term.

Limitations

The present study has several limitations. First, the small number of subjects made it rather difficult to interpret the results. Secondly, the outcome variables were limited. Thirdly, our hospital-based sampling method may have missed a significant number of schizophrenic patients who remained untreated in the community. Finally, clinical data at inclusion (e.g. mode of onset, premorbid function, either PANSS or ESAS assessment), which can be used as predictors of outcome, was lacking.

In conclusion, the 5-year outcome of schizophrenia in Bali strongly predicted the 11-year outcome, especially for subjects who had gone into either a remissive or severe deterioration state within 5 years. Previous studies performed in developed countries demonstrated that the medium- and long-term course of schizophrenic patients shows a high degree of stability, suggesting that the illness tends to reach a plateau of psychopathology early in the course. The present study replicated these finding in a developing country where only a minority of subjects underwent maintenance treatment.

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