Magnetic brain activity elicited by visually presented symbols and Japanese characters

Yasuhiro Shirahama,[1,4,CA] Katsuya Ohta,[2] Atsuko Takashima,[1] Eisuke Matsushima[2] and Yoshiro Okubo[3]

[1]Section of Psychiatry and Behavioral Science; [2]Section of Liaison Psychiatry and Palliative Medicine, Graduate School of Tokyo Medical and Dental University, I-5-45 Yushima, Bunkyo-ku, Tokyo II3-85I9; [3]Department of Neuropsychiatry, Nippon Medical School, Japan; [4]Sangenjaya Hospital, I-2I-5 Sangenjaya, Setagaya-ku, Tokyo I54-0024, Japan

[CA]Corresponding Author and Address: sanjyaik@livedoor.com

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 I5:77I–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 I. 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.

—160—

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 cm³ (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.
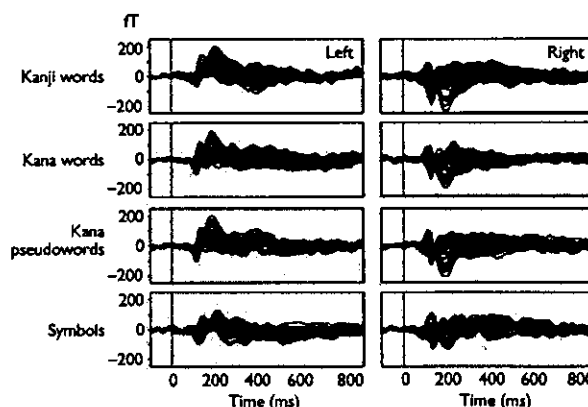

Fig. I. Grand-averaged (n=9) event-related field (ERF) waveforms elicited by four non-target conditions (kanji words, kana words, kana pseudowords and symbols) during the semantic task recorded from 38 sensors in the temporo-parieto-occipital regions on each hemisphere. Three magnetic components can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

– 161 –

— Kanji words — Kana words — Kana pseudowords — Symbols
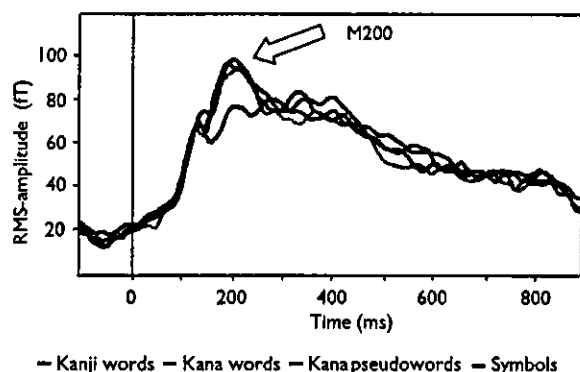
Fig. 2. Grand-averaged root mean square (RMS) waveforms recorded from the whole head are shown separately for the kanji word condition (red), kana word condition (yellow), kana pseudoword condition (green) and symbol (blue) condition. The M200 component in the symbol condition is smaller and later than in the other three conditions.
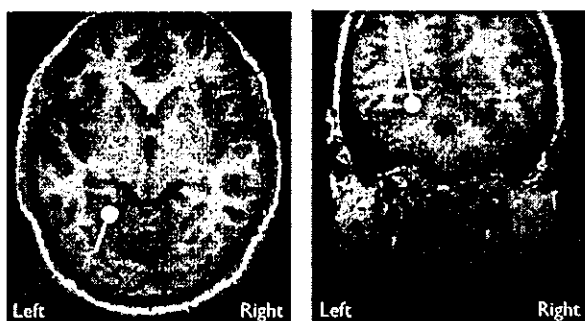
Fig. 3. White circle with a bar indicates one representative equivalent current dipole (ECD) source estimated during the M200 time window in the kanji word condition from one subject superimposed onto horizontal and coronal MRI scans. There was no difference among the four conditions.

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 syllabograms, 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

— 162 —

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.

REFERENCES

1. Henderson VW. Anatomy of posterior pathways in reading: a reassessment. *Brain Lang* 29, 119–133 (1986).
2. Petersen SE, Fox PT, Snyder AZ and Raichle ME. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science* 249, 1041–1044 (1990).
3. Puce A, Allison T, Asgari M, Gore JC and McCarthy G. Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. *J Neurosci* 15, 5205–5215 (1996).
4. Usui K, Ikeda A, Takayama M, Matsuhashi M, Yamamoto J, Takeshi S *et al.* Conversion of semantic information into phonological representation: a function in the left posterior basal temporal area. *Brain* 126, 632–641 (2003).
5. Nobre AC, Allison T and McCarthy G. Word recognition in the human inferior temporal lobe. *Nature* 372, 260–263 (1994).
6. Price CJ. The anatomy of language: contributions from functional neuroimaging. *J Anat* 197, 335–359 (2000).
7. Koyama S, Kakigi R, Hoshiyama M and Kitamura Y. Reading of Japanese Kanji (morphograms) and Kana (syllabograms): a magnetoencephalographic study. *Neurophychologia* 36, 83–98 (1998).
8. Eulitz C, Eulitz H, Maess B, Cohen R, Pantev C and Elbert T. Magnetic brain activity evoked and induced by visually presented words and nonverbal stimuli. *Psychophysiology* 37, 447–455 (2000).
9. Yamadori A. Ideogram reading in alexia. *Brain* 98, 231–238 (1975).
10. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113 (1971).
11. Clark D and Wagner AD. Assembling and encoding word representations: fMRI subsequent memory effects implicate a role for phonological control. *Neuropsychologia* 41, 304–317 (2003).
12. Kuo KJ, Yeh TC, Lee CY, Wu YT, Chou CC, Ho LT *et al.* Frequency effects of Chinese character processing in the brain: an event-related fMRI study. *Neuroimage* 18, 720–730 (2003).
13. Iwata M. Kanji versus Kana: neuropsychological correlates of the Japanese writing system. *Trends Neurosci* 7, 290–293 (1984).
14. Tagamets MA, Novick JM, Chalmers ML and Friedman RB. A parametric approach to orthographic processing in the brain: an fMRI study. *J Cogn Neurosci* 12, 281–297 (2000).
15. Sakurai Y, Momose T, Iwata M, Sudo Y, Ohtomo K and Kanazawa I. Different cortical activity in reading of Kanji words, Kana words and Kana nonwords. *Cogn Brain Res* 9, 111–115 (2000).
16. Fiebach CJ, Friederici AD, Müller K and Cramon YV. fMRI evidence for dual routes to the mental lexicon in visual word recognition. *J Cogn Neurosci* 14, 11–23 (2002).
17. Sekiguchi T, Koyama S and Kakigi R. The effect of stimulus repetition on cortical magnetic responses evoked by words and nonwords. *Neuroimage* 14, 118–128 (2001).
18. Takashima A, Ohta K, Shirahama Y, Matsushima E, Horiguchi T and Nishikawa T. Difference of semantic processing and character types in silent reading of words. A study using MEG. In: Hirata K, Koga Y, Nagata K and Yamazaki K (eds). Recent Advances in Human Brain Mapping. Amsterdam; Elsevier Science; 2002, pp. 513–517.
19. Sugishita M, Otomo K, Kabe S and Yunoki K. A critical appraisal of neuropsychological correlates of Japanese ideogram (kanji) and phonogram (kana) reading. *Brain* 115, 1563–1585 (1992).
20. Reite M, Teale P and Rojas DC. Magnetoencephalography: applications in psychiatry. *Biol Psychiatry* 45, 1553–1563 (1999).

−163−

統合失調症の情動認知障害の認知神経科学
—— 久留米大学における取り組みを中心に ——

前 田 久 雄　　　森 田 喜一郎

特集：生物学的精神医学研究の現状と展望（2）

統合失調症の情動認知障害の認知神経科学
—— 久留米大学における取り組みを中心に ——

前 田 久 雄[1,2]　　森 田 喜一郎[1,2]

1. はじめに

　統合失調症にみられる情動障害としては，すでに発病脆弱性として存在するものと発病後に新たに生じる症状としての二つの側面がある。前者の1例としては，Ciompi L (1989)[1]が，脆弱性の本質は，情動や認知がからんだ複雑な状況に適切に対処する能力の障害とストレスに対する感受性の亢進であると想定したものがある。後者は，古くは Bleuler E (1908) が統合失調症の基本症状の一つとして情動障害（平板化）を挙げて以来，陰性症状として臨床家に広く認知されているところである。さらには，典型的には関係妄想や肉親否認妄想などを想定して妄想知覚の生成過程を分析したり，自明性の喪失の背景となっているものを吟味すると，これらの現象の背後に，他者の感情や情動を正しく認知できていないことが大きな要因として存在することが容易に想定できる（例えば Phillips & David)[29]。

　情動を感覚・神経情報の入力・出力という視点でとらえると，環境刺激－知覚－評価－情動－行動の選択－行動という一連の心理過程からなっている[12]。人が社会生活を送る上で最も重要な機能は適切な対人関係を築き維持することであるが，その基盤となるものが他者の表情や言葉から，そこに表出されている感情や情動を読み取る能力である。人の感情のうち，恐怖，驚き，怒り，悲しみ，不快，喜びなど動因としてのエネルギーの強いものを情動と呼ぶ[15]。

　人の表情写真や表情画から，そこに表出されている感情や情動を読み取り命名する機能を表情認知という（詳細は総説参照)[13][14]。統合失調症では顔貌認知にはほとんど障害は認められないものの表情認知が障害されているとする報告が数多くみられる[13][14]。

　この障害は急性期に顕著にみられ症状寛解とともに軽快する状態依存的 (state dependent) な変動を示す[2][4]一方，統合失調気質や統合失調型人格障害でも認められ素因依存的 (trait depen-

Cognitive neuroscience of impairments of affect recognition in schizophrenia -a review with emphasis on studies in the Department of Neuropsychiatry, Kurume University School of Medicine-

1)久留米大学医学部精神神経科〔〒830-0011 久留米市旭町67〕Hisao Maeda, Kiichiro Morita：Department of Neuropsychiatry, Kurume University School of Medicine. 67, Asahimachi, Kurume 830-0011, Japan

2)久留米大学高次脳疾患研究所　Cognitive and Molecular Research Institute of Brain diseases, Kurume University
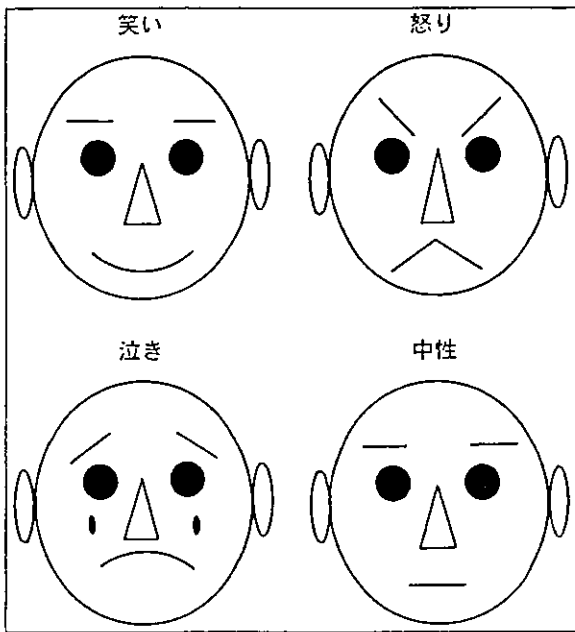
【前田久雄　E-mail：maehisa@med.kurume-u.ac.jp】

図1 聴覚P300記録に際し注視するよう求められた表情画[18]

dent）な所見でもあるとする報告もある[19][20]。病型では妄想型より非妄想型で障害が大きい[7][10]。恐怖や怒りなどの陰性感情と喜びの陽性感情との比較では一定の結果は得られていない。

　これらの表情認知に関する知見は神経心理学検査で見いだされたものであり，その障害の本態を脳の機能と関連づけ生物学的に解明しようとしたものではない。さらに，表情認知に付随してどのような感情や情動が被験者に生じたかという観点にも欠けている。我々の研究室で行っている研究は，表情認知に際しての事象関連電位や探索眼球運動などの精神生理学的指標やSPECT，fMRIなどの脳機能画像を捉えることで，統合失調症にみられる情動認知障害の本態を明らかにしようとするものである。

2．事象関連電位
(Event-related potentials, ERPs)

　ERPsは，oddball課題などを課したときに現れる脳波で，通常，課題となる刺激をトリガーとして平均加算する方法が行われる。課題刺激の感覚モダリティにより聴覚ERPs，視覚ERPsなどと呼ばれる。各波形は入力情報の処理過程を反映するとされており[6]，なかでも後期陽性成分の

一つであるP300は，刺激の探知や認知・評価[6][31]，あるいは認知文脈の更新[3]に関連した電位であるとされている。さらにP300振幅は分配された注意資源量を反映するとされるが[30]，刺激の出現頻度，課題の難易度，課題遂行に伴う報酬の大きさ，動機付けの程度，覚醒度や注意水準，期待度なども影響することが知られており，その本態は一義的ではない。情動も影響するという報告もあり[9]，我々はこの現象を確認するとともに情動認知の研究に応用している。繰り返し測定すると慣れも生じる[17]。一方，P300潜時は，注意資源の分配速度[30]や刺激の評価に要する時間[6]を反映するとされる。しかし，P300の発生源は明らかでなく多発生源説が有力である。統合失調症ではP300振幅の低下がtrait markerであるとされるが，開眼して記録した聴覚P300振幅は急性期からの回復とともに増大しstate markerとしての性質ももっている[16]。

　被験者が表情画（図1）を注視した条件のもとで聴覚ERPsを記録すると，P300に対する表情の影響をみることができる[18][21][22]。健常者では，すべての記録部位で表情間に有意差がみられ，「泣き」表情注視時のP300振幅は「中性」表情注視時の振幅とほとんど差がみられないのに対して，「怒り」さらには「笑い」表情注視時には前2者と比較して振幅が有意に低下していた（図2，A）。潜時は「泣き」で最長，「中性」で最短と，P300振幅の表情間の差を潜時の違いに帰することはできなかった。表情の識別率にも表情間に差は認められなかった。これらのことは，それぞれの表情によって被験者に誘起された情動の違いによってP300振幅に対する影響も異なっており，「笑い」によって引き起こされる情動（おそらく喜び）のP300振幅を低下させる力が最も大きいことを示している。

　ところが統合失調症者（服薬中）では，表情によるこのようなP300振幅への影響の相違はみられなかった（図2，B）。亜型別に検討してみると，妄想型（n＝6）では健常者と同じく「笑い」でP300振幅が最も小さかったが，非妄想型（n＝9）では「泣き」で最小と健常者とは逆であった。表情の識別率には，健常者，両亜型間に
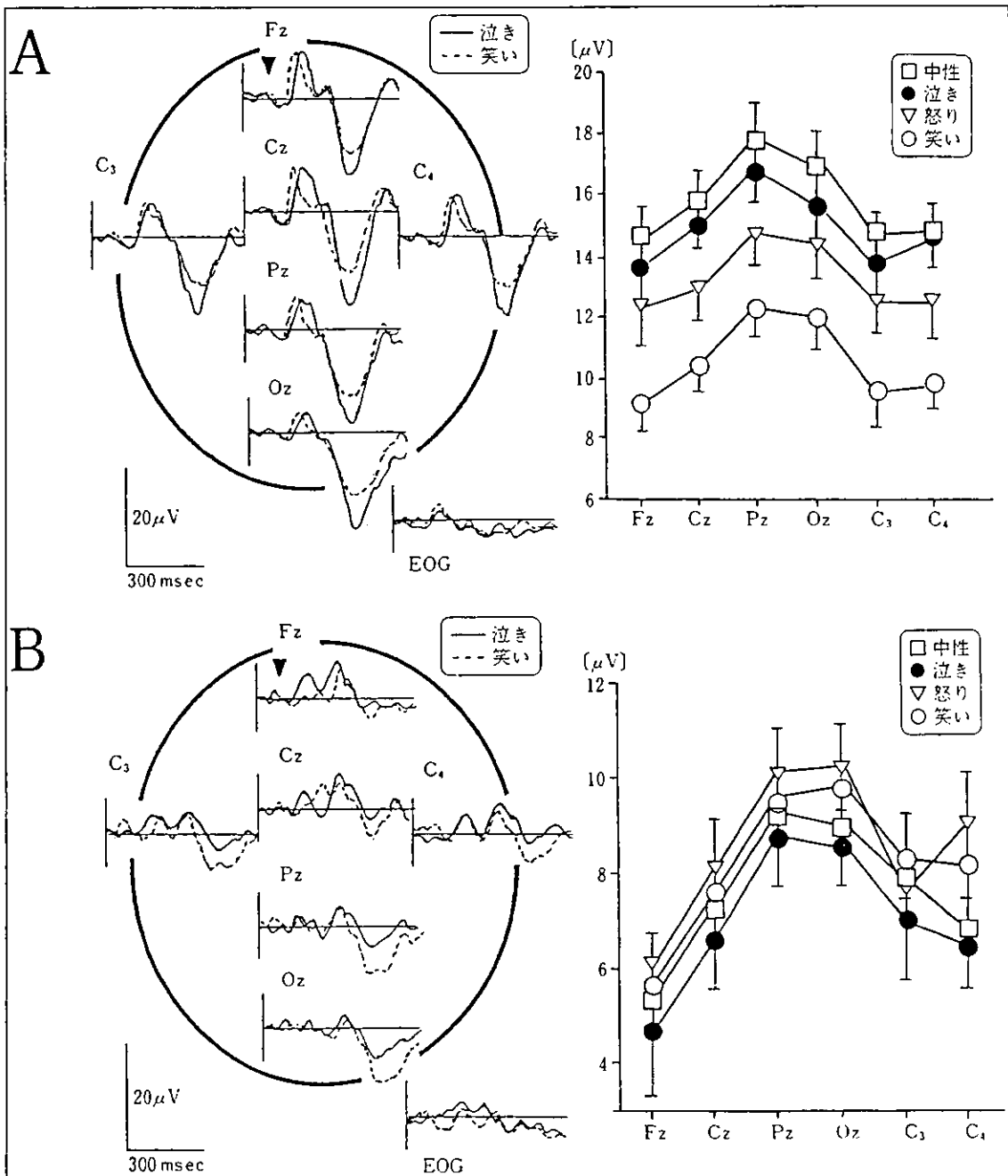
図 2　聴覚 P 300 振幅に対する注視表情画の影響[18]
　　　A：健常者（n＝20）　B：統合失調症者（n＝15）。左図はそれぞれの典型例の事象関連電位。右図
は記録部位ごとの P 300 振幅の平均値と標準誤差。

有意差を認めなかった。このことは，「笑い」表情によって誘起される情動が統合失調症，なかでも非妄想型では健常者と異なっており，P 300 振幅を低下させる機能をもたず，むしろ P 300 振幅を増大させる傾向をもっていることを示している。これらに所見は統合失調症の急性期症状の回復とともに改善した[37]。

表情画や表情写真を刺激とした視覚 P 300 を記録することで，P 300 に対する表情の影響をより直接的に解析することができる[26][36]。未服薬の統合失調症者 26 名と健常対照者 26 名を対象として，乳児の表情写真を課題刺激とした視覚 P 300 を記録した[26]。図 3 に示したように，健常者では聴覚 P 300 の場合と同様な表情間差がみられ，
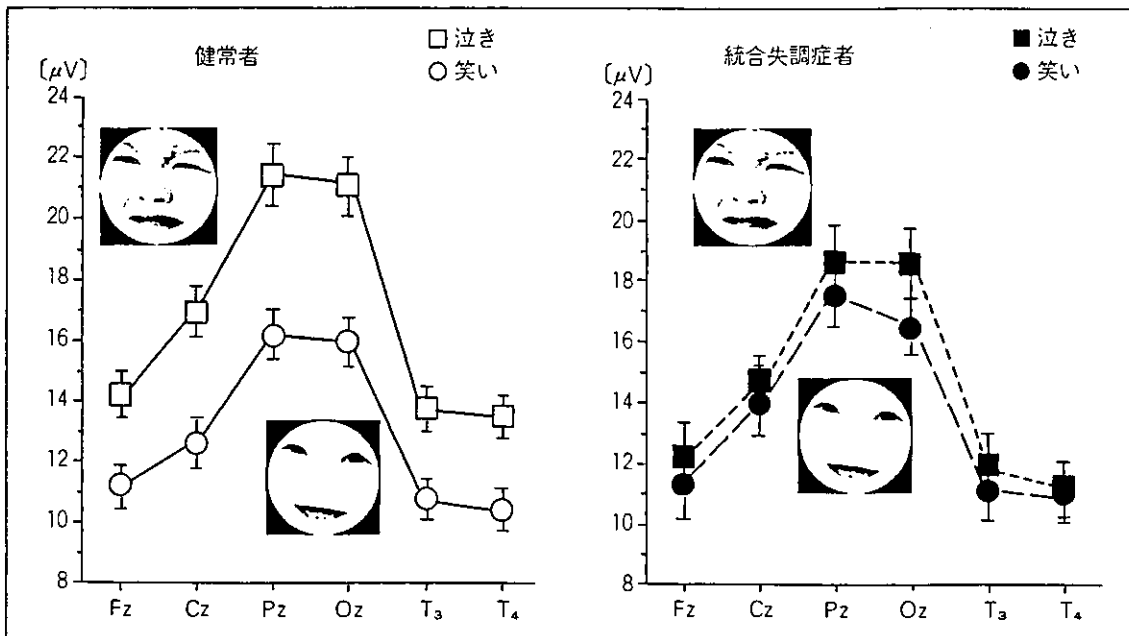
図3　乳児の表情写真を刺激図とした視覚 P 300 振幅[26]
　　左図：健常者（n＝26），右図：未服薬の統合失調症者（n＝26）。健常者では表情間に有意差（P
　＜0.0001）がみられたが，統合失調症者では有意差は見られなかった。

「笑い」による P 300 振幅の方が「泣き」による
ものよりも有意に低下していた（図3，左）。統
合失調症者では両表情間に差はみられなかった
（図3，右）。このことは，統合失調症者で聴覚お
よび視覚 P 300 振幅に対し，表情による影響がみ
られないということが服薬によるものではないこ
とを示すとともに，先に述べた統合失調症にみら
れた所見の解釈の正さを支持している。さらに，
聴覚 P 300 振幅の場合と同様な亜型による相違も
認められること，抗精神病薬による治療によって
表情間の P 300 振幅の差が健常者にみられる所見
に近づくことも確認している。

　これらの一連の研究から示唆されることは，統
合失調症者は表情そのものの識別は正しくできる
ものの，表情によって引き起こされる情動の様相
が健常者とは異なっており，特に，「笑い」表情
によって喚起される情動が健常者とは際立って異
質で P 300 振幅を低下させず，むしろ増大させる
傾向さえ持っていることである。「笑い」が他者
に喜びを伝えなごみをもたらす機能が統合失調症
者には作動せず，場合によっては逆の効果を生む
かのようである。このような特徴は非妄想型の急
性期に最も顕著であり，治療による病状の回復と

ともに改善する傾向をもっている。今後はさらに
完全寛解群，高リスク群，他の精神神経疾患など
との比較検討を行う予定である。

3．探索眼球運動
(Exploratory eye movements)

　探索眼球運動を用いた研究は小島らによって始
められた[8]。まず，被験者に S 字図を観察させ，
その後，図の一部を改変した図を探索させる課題
を課した際の眼球運動の軌跡が定量的に分析され
た。その結果，統合失調症者では停留時間の延長
や総移動距離の短縮などが認められ trait
marker であるとされた。我々の研究室では，S
字図の代わりに表情図や表情写真を用い，探索眼
球運動に及ぼす表情の影響や統合失調症にみられ
る特徴などの研究を行っている。詳細な測定方法
は他書[25][32]を参照していただきたい。

　探索眼球運動のもつ精神生理・神経心理学的な
意味であるが，後で描画することを指示されて提
示図を眺める場合（自由探索）は，主に，受動的
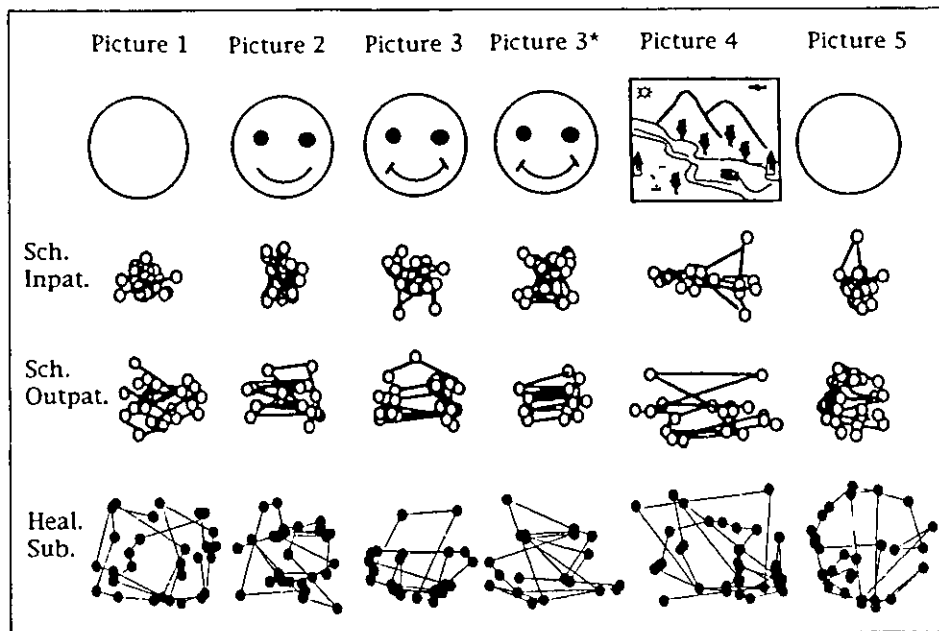な視覚認知（入力過程）に際しての眼球運動の軌
跡が描出される。一方，直前に提示された図との
違いがあるかどうかを求められる確認探索課題が

図4　提示された表情画に対する探索眼球運動[32]

まず最初に，「風景画以外のすべての図は検査終了後に描いてもらいます」との
指示を与えた後，約 30 秒の間隔をおいて Picture 1 から順番に 15 秒間づつ提示さ
れた。Picture 3*の前には，「前の図と違うところはないか，よく確認してくださ
い」と指示した。入院中の統合失調症者（Sch. Inpat. n＝30），外来通院中の統合
失調症者（Sch. Outpat. n＝30），健常者（Heal. Sub. n＝30）から記録されたが，
図示されているのはそれぞれの典型例。小さな丸は注視点が 0.2 秒以上停留した点
を示す。

課せられた場合（確認探索）には，異同の探索と
いう作動記憶を要する実行機能である問題解決行
動としての側面（出力過程）を併せ持つことにな
る。

　図 4 は表情画を 15 秒間提示したときの眼球運
動の様子である[32]。各グループ，各図ごとに平均
値を算出すると，Picture 4 を除きすべての図で，
健常者に較べ入院中の統合失調症者の平均停留時
間は長く，停留点総数は減少，総移動距離は延長
していた。Picture 4 では停留点総数だけで有意
差がみられなかった。外来通院中の統合失調症者
の値はすべて両グループの中間に位置していた
が，平均停留時間と総移動距離ではすべての図で
健常者との間に有意差を認めた。これらの結果は
小島らの報告[8]を支持している。注目すべきは，
表情画のうち前図との相違の有無を求めた
Picture 3*で（確認探索），健常者では他の表情
画と比較し，平均停留時間は短く，停留点総数は
多く，総移動距離は長くなっていたが，統合失調

症者ではこのような差は認められなかった。この
ことは，統合失調症者では異同の探索という実行
機能に障害がみられることを示している。

　乳児の表情写真を用いて探索眼球運動に対する
表情の影響を調べてみると，健常者では自由探索
条件下では影響はみられなかったが，確認探索条
件下では「泣き」と較べ「笑い」で有意に停留点
総数が増加し，総移動距離が延長した[25]。統合失
調症者では，いずれの条件下でも表情の違いによ
る差を認めなかった。このことは，入力過程に付
随する単純な探索眼球運動よりも実行機能として
の側面を併せ持つ探索眼球運動の方が情動の影響
を受けやすいこと，および統合失調症者ではこの
影響もみられないことを示している。しかし，自
由探索条件下の探索眼球運動も，内的に個々人の
「楽しかった体験」あるいは「悲しかった」体験
を想起させると，前者では停留点総数が増加し総
移動距離は延長するが，健常者と較べ統合失調症
者ではその程度が小さく変動しにくい[24][34]。

これらの結果は，探索眼球運動の各指標が統合失調症者の視覚認知特性を示すだけでなく，実行機能の障害や情動反応性の異常を示す指標となりうることを示唆している。さらに，統合失調症の臨床経過の指標にもなりうることも判っている[23)28)35)]。

4．脳機能画像
(Functional neuroimaging)

SPECT，PET，fMRI などの脳機能画像の進歩により，人の情動の脳内機序に関する研究も可能になってきた。しかし，それぞれの方法に固有な空間分解能や時間分解能の限界から，まだ再現性の高い知見は少ないのが現状である[27)]。

その中で，喜び，悲しみ，あるいは不快感を引き起こす映像を見ている際の局所脳血流量 (rCBF) を PET を用いて測定した Lane らの結果は興味深い[9)]。それによると，情動の種類に関係なく後頭・頭頂・側頭葉，側頭葉前部，扁桃核・海馬，視床下部，中脳中心灰白質などが両側性に賦活されている。これは，筆者が動物実験の結果に基づいて提唱した情動回路の入力系および脳幹情動系が描出されているとみなすことも可能である[11)]。一方，4 T の fMRI を用いて喜び，悲しみ，怒り，恐怖，不快を表した表情写真を提示した際の脳内の賦活をみた Gur らの研究[5)]でも，健常者では，顔貌認知に関与するとされる紡錘回に加えて，後頭葉，前頭葉下部，扁桃核・海馬が賦活されている。しかし，統合失調症者では，表情は正しく識別できているのに脳内の賦活された部位は極めて少なかったことも報告しており，Phillips ら[29)]や Takahashi ら[33)]の報告と共通している。

我々も，予備的ではあるが，SPECT で，健常者では「泣き」と「笑い」の表情間に側頭葉下部，前頭葉眼窩面，帯状回（いずれも両側）の賦活に差がみられるのに対して，統合失調症者ではそれがみられないことを観察している。fMRIでは，健常者では「泣き」と「笑い」で扁桃核・海馬領域の賦活の様相が異なることや，統合失調症者では，この領域の賦活が健常者とは逆になる所見も得ている。今後さらに，方法論的な検討を加

え，情動の中枢機構や統合失調症者にみられる情動認知障害の本態の解明を目指したい。

5．おわりに

最初にも述べたように，情動の研究には，情動の形成やそれを動因とした行動に至る過程，すなわち感覚・神経情報の入・出力過程，さらには情動の種類にわけて解析する必要がある。その観点に立つと，ERPs と自由探索条件下の探索眼球運動は入力過程の，確認探索条件下の探索眼球運動は出力過程にも関連した研究手法であり，脳機能画像は両過程および個別情動の中枢を脳の構造と関連づけて三次元的，可視的に解明できる手法である。

これまで紹介してきた ERPs や探索眼球運動の結果から，統合失調症にみられる情動認知障害の本態の一端として，統合失調症者は表情の識別はほぼ正しくできるものの，表情，中でも「笑い」に対する本人の情動反応の様相がかなり健常者とは異質があることが判明した。これはSPECT や fMRI を用いた脳機能画像でも裏付けされた。今後さらにこの領域の研究が進展し，統合失調症の治療に貢献できる日がくることを期待したい。

文 献

1) Ciompi L(1989) The dynamics of complex biological psychosocial systems-four fundamental psychobiological mediators in the long-term evolution of schizophrenia. Br J Psychiatry 155 (Suppl 5)：15-21.
2) Cutting J(1981) Judgement of emotional expression in schizophrenia. Br J Psychiatry 139：1-6.
3) Donchin E, Coles MGH(1988) Is the P 300 component a manifestation of context updating? Behav Brain Sci 11：357-374.
4) Gessler S, Cutting J, Frith CD, et al (1989) ：Schizophrenic inability to judge facial emotions. A controlled study. Br J Clin Psychol 28：19-29.

5) Gur RE, McGrath C, Chan RM, et al (2002) : An fMRI study of facial emotion processing in patients with schizophrenia. Am J Psychiatry 159 : 1992-1999.

6) Hillyard SA, Kutas M(1983) Electro-physiology of cognitive processing. Ann Rev Psychol 34 : 33-61.

7) Kline JS, Smith JE, Ellis HC(1992) Par-anoid and nonparanoid schizophrenic process-ing of facially displayed affect. J Psychiat Res 26 : 169-182.

8) Kojima T, Matsushima E, Nakajima K, et al (1990) Eye movements in acute, chronic and remitted schizophrenics. Biol Psychiatry 27 : 975-989.

9) Lane RD, Reiman EM, Ahern GL, et al(1997) Neuroanatomical correlates of happiness, sad-ness, and disgust. Am J Psychiatry 154 : 926-933.

10) Lewis SF, Garver DL(1995) Treatment and diagnostic subtype in facial recognition in schizophrenia. J Psychiat Res 29 : 5-11.

11) Maeda H, Maki S, Morimoto H(1990) A proposed emotional circuit for defensive attack behavior. In Iwai E, Mishkin M, eds. Vision, Memory, and Temporal Lobe. New York, Elsevier-USA, 169-173.

12) 前田久雄(1993) 情動と情報処理. 臨床精神医学 22 : 1261-1267.

13) 前田久雄(1997) 顔貌・表情認知の情報処理過程I 脳波と筋電図 25 : 362-368.

14) 前田久雄(1997) 顔貌・表情認知の情報処理過程II 脳波と筋電図 25 : 447-454.

15) 前田久雄(1998) 情動とは. 臨床精神医学 27 : 5-10.

16) Maeda H, Morita K, Kawamura N, et al (1996) Amplitude and area of the auditory P 300 with eyes open reflect remission of schizophrenia. Biol Psychiatry 39 : 743-746.

17) Maeda H, Morita K, Nakamura J, et al (1995) Reliability of the task-related compo-nent (P 3 b) of P 3 event-related potentials. Psychiat Clin Neurosci 49 : 281-286.

18) 前田久雄, 森田喜一郎, 山口浩(1999) 聴覚 P 300 成分に対する表情認知の影響. 健常者と分裂病者の比較. 臨床脳波 41 : 565-570.

19) Mikhailova ES, Vladimirova TV, Iznak AF, et al(1996) Abnormal recognition of facial expression of emotions in depressed patients with major depression disorder and schizotypal personality disorder. Biol Psychiatry 40 : 697-705.

20) Morrison RL, Bellack AS, Mueser KT(1988) Deficits in facial-affect recognition and schizo-phrenia. Schizophr Bull 14 : 67-83.

21) 森田喜一郎, 森田恵史, 山口 浩, 他(2000) 健常者の聴覚事象関連電位に対する表情認知の影響. 臨床脳波 42 : 7-11.

22) Morita Y, Morita K, Yamamoto M, et al (2001) Effects of facial affect recognition on the auditory P 300 in healthy subjects. Neurosci Res 41 : 89-95.

23) 森田喜一郎, 龍 博昭, 森田恵史, 他(2001) 老年期分裂病者の探索眼球運動における特徴-晩期寛解について-. 臨床脳波 43 : 171-176.

24) 森田喜一郎, 小路純央, 山本寛子, 他(2002) 精神分裂病周辺障害者の探索眼球運動の特徴-精神分裂病者, 健常者との比較検討-. 臨床脳波 44 : 439-446.

25) 森田喜一郎, 富田 克, 上野雄文, 他(2002) 精神分裂病者と健常者の探索眼球運動-赤ちゃんの表情の影響-. 臨床脳波 44 : 154-159.

26) 森田喜一郎, 早稲田芳史, 富田 克, 他(2003) 未服薬統合失調症者と健常者の視覚誘発事象関連電位 (P 300 成分)-情動の影響をふまえて-. 臨床脳波 45 : 76-82.

27) Murphy FC, Nimmo-Smith I, Lawrence AD (2003) Functional neuroanatomy of emo-tions : a meta-analysis. Cogn Affect Behav Neurosci 3 : 207-233.

28) Nakayama H, Morita K, Mori K, et al(2003) Improvement of exploratory eye movements in schizophrenic patients during recovery period. Psychiat Clin Neurosci 57 : 169-176.

29) Phillips ML, David AS(1995) Facial proces-sing in schizophrenia and delusional misidentification : cognitive neuropsychiatric approaches. Schizophr Res 17 : 109-114.

30) Polich J(1991) P 300 in clinical applica-tion ; meaning, method, and measurement. Am J EEG Technol 31 : 201-231.

31) Pritchard WS(1981) Psychophysiology of P 300. Psychol Bull 89 : 506-540.

32) Ryu H, Morita K, Shoji Y, et al(2001) Abnormal exploratory eye movements in schizophrenic patients vs healthy subjects. Acta Neurol Scand 104 : 369-376.

33) Takahashi H, Koeda M, Oda T, et al(2004) An fMRI study of differential neural response to affective pictures in schizophrenia. Neuro-Image 22 : 1247-1254.

34) 上野雄文, 森田喜一郎, 早稲田芳史, 他(2002) 精神分裂病者の探索眼球運動における情動の影響：健常者との比較検討. 臨床神経生理学 30 : 60-66.

35) Yamaguchi H, Morita K, Ryu H, et al(1999) Improvement of eye movement of schizo-phrenic patients associated with day hospital treatment. J Brain Sci 25 : 153-163.

36) Yamamoto M, Morita K, Tomita Y, et al (2000) Effect of facial affect stimuli on audi-tory and visual P 300 in healthy subjects. Kur-ume Med J 47 : 285-290.

37) Yamamoto M, Morita K, Waseda Y, et al (2001) Changes in auditory P 300 with clinical remission in schizophrenia : Effects of facial -affect stimuli. Psychiat Clin Neurosci 55 : 347-353.

Regular Article

Recognition of facial expression and visual P300 in schizophrenic patients: Differences between paranoid type patients and non-paranoid patients

TAKEFUMI UENO, MD,[1] KIICHIRO MORITA, MD,[2] YOSHIHISA SHOJI, MD,[1] MASASHI YAMAMOTO, MD,[1] HIROKO YAMAMOTO, MD AND HISAO MAEDA, MD[1]

[1]*Department of Psychiatry and* [2]*Cognitive and Molecular Research Institute, Kurume University School of Medicine, Kurume, Japan*

Abstract

This study compared the effects of facial affective stimuli on visual event-related potentials (ERP) in schizophrenic patients and healthy subjects using photographs of babies depicting sadness (crying face), neutrality (neutral face), and pleasure (smiling face). Visual ERP were recorded using an oddball paradigm in 32 schizophrenic patients (16 paranoid type and 16 non-paranoid patients) and 32 age-matched healthy subjects. The P300 amplitude, latency, and the subject's reaction time were recorded. The P300 amplitude when viewing a photograph of a smiling baby was the smallest registered of three photographs for healthy subjects and paranoid type patients with successively greater amplitudes for neutrality and sadness. However, the P300 amplitude was the smallest while viewing crying photographs and was the largest while viewing a smiling photograph for non-paranoid patients. These results suggest that the P300 amplitude is influenced by viewing emotionally moving facial expressions and that the effect is different for different subtypes of schizophrenia. These differences may reflect differences in information processing resulted from emotional influences caused by visual-affective stimuli.

Key words   event-related potentials, facial affect recognition, P300, schizophrenia, subtype.

INTRODUCTION

Event-related potentials (ERP) have been used as a tool to investigate biological correlates of information processing in the human central nervous system.[1-3] So far, few studies on the effect of emotion have been reported, and little is known about the effect of facial affect on ERP in healthy subjects.[4-6] Yee *et al.* reported that the magnitude of P300 amplitudes is greater in response to unpleasant pictures than to pleasant ones, and suggested that the difference may reflect the emotional intensity of stimuli rather than valence.[5] Using a visual oddball paradigm, Lang *et al.* also reported that the P300 amplitude increases particularly in response to angry expressions.[6] These authors suggest that subjects are more engaged by an angry expression than by a happy one, or that the angry face evokes greater emotional intensity than the happy face. The hypothesis was predicated on the theory that subjects' cognitive engagement would vary depending on the emotional content of the attended stimulus, and that this variation would be discernible in some aspect of the P300 component.

Schizophrenic patients have been shown to manifest a significant deficit in the ability to correctly identify the emotions associated with facial expressions.[7-10] Such patients have a distinctive deficit in emotional appropriateness, and an impaired ability to correctly identify facial affect might contribute to this deficit. Interestingly, Kline *et al.* examined the relationship between diagnostic subtypes and facial affect recogni-

tion and found that patients with paranoid schizophrenia are more able to recognize facial expressions than non-paranoid patients.[10] It has also been demonstrated that patients with paranoid type schizophrenia may be more adept at facial recognition than non-paranoid patients.[11] However, no study has looked at the effects of facial affect recognition on ERP in subtypes of schizophrenic patients. The visual P300 provides objective data that can be used to identify subtypes of schizophrenia. Thus, the patterns of effects of facial affect may help us improve our understanding of the mechanism of schizophrenia, especially the difference between subtypes. The present study was conducted to determine how facial affect expression influences visual ERP in schizophrenic patients and to identify what differences, if any, exist between paranoid type and non-paranoid patients compared with healthy subjects. We recorded visually evoked ERP while subjects viewed three different photographs of babies showing different facial affects.

METHODS AND MATERIALS

Subjects

Subjects included 32 healthy volunteers (16 men and 16 women) ranging in age from 21 to 38 years (mean, 26.0 ± 3.8 SD) and 32 patients with schizophrenia (16 paranoid type and 16 non-paranoid patients) diagnosed according to the 4th edition of the Diagnostic and Statistical Manual by two psychiatrists. Patients were aged 16–34 years (26.5 ± 4.7, overall; 27.8 ± 3.5, paranoid type [eight men, eight women]; and 24.5 ± 6.0, non-paranoid patients [10 men, six women; disorganized type, 10; catatonic type, 2; undifferentiated type, 4]). There were no significant differences in ages among the three groups (healthy subjects, paranoid type patients, non-paranoid patients). All patients were receiving psychiatric medication. No patients or healthy subjects had visual disabilities and all recognized the present photographs. Time of onset, the duration of illness, the duration of hospitalization, and time of admission are shown in Table 1. The ethics committee of Kurume University approved the present study. Written informed consent was obtained from all subjects prior to their inclusion in the study.

Electroencephalogram recording

ERP were recorded from Ag/AgCl electrodes at the Fz, Cz, Pz, Oz, T_3 and T_4 positions according to the International 10–20 System with reference electrodes connected to the mastoids. A forehead electrode served as the ground. Electrodes were affixed above and lateral to the left eye to monitor horizontal and

Table 1. Summarized time of onset, duration of illness, time of admission, and duration of hospitalization. Significant differences between paranoid type patients and non-paranoid patients are seen in the time of onset

	Non-paranoid patients	Paranoid type patients	
Onset (years)	16.8 ± 1.9	26.7 ± 4.6	$P < 0.001$
Duration of illness (years)	6.2 ± 5.9	2.1 ± 1.6	$P < 0.05$
Duration of admission (years)	0.81 ± 0.72	0.37 ± 0.52	ns
Times of admission (times)	1.7 ± 1.1	0.82 ± 0.80	$P < 0.05$
Ages of recording (years)	24.5 ± 6.0	27.8 ± 3.5	$P < 0.05$
Duration of education (years)	10.3 ± 2.0	13.0 ± 1.7	$P < 0.01$
Positive symptom scores	26.6 ± 3.8	24.0 ± 3.7	ns
Negative symptom scores	23.5 ± 3.7	20.1 ± 3.7	$P < 0.05$
Dose of medicine (mg/day)	334.2 ± 173.6	360.6 ± 154.1	ns

vertical eye movements. All impedance was kept below 5 KΩ and the band pass filter was 1–100 Hz. Probability of the presentation of target stimuli was 20% (baby facial photographs: smiling, crying and neutrality) and the probability was 80% for non-target stimuli (flowers), which did not include facial expression. Stimulus duration was 250 ms. Photographs were presented in a random sequence at a mean rate of 0.7 Hz. Emotions depicted included pleasure (smiling), sadness (crying) and no emotion (neutrality), each type of photograph presented in an equal probability. Each subject sat in a sound attenuated, electrically shielded room and was asked to relax with eyes open. All subjects were asked to gaze at the baby's face on a TV monitor positioned 0.5 m away (Visual angle: ±5° horizontally, ±3° vertically). All participants were asked to count and push a button with their dominant hand in response to target stimuli. Subjects were requested to refrain from blinking during the test. Sampling was initiated 100 ms prior to the stimulus onset and continued for 1 s. An averaged waveform was obtained from 20 artifact-free individual target stimuli for each type of picture for each block.[2,12,13] Trials that exceed ±50µV were automati-

cally rejected from the averaging process. The averaged value prior to the stimulus (100 ms) was used as a baseline. Three blocks (smiling and flower, crying and flower, neutrality and flower) presented to each subject constituted for one session. The order of presentation was the smiling or crying photograph at first block, the neutral photograph at second block, and the crying or smiling photograph at third block. The smiling and the crying photographs were counterbalanced. The averaged waveform taken from three target photographs (smiling, neutrality and crying) were evaluated as data. The P300 latency was estimated from the latency of the largest positive peak within the time range of 250 and 600 ms. The P300 amplitude was calculated from the baseline to the peak of the positive waveform within a time window of 250–600 ms. The N200 amplitude was calculated from the baseline to the peak of the negative wave form between N100 and P300 wave forms. All waveform were constructed after smoothing treatment (Nihonkoden).

Protocol for recording event-related potentials and evaluating facial expression

Sessions included the presentation of the three photographs (smiling, crying and neutrality) during a double-task performance to sustain attention and arousal levels (counting and pressing a button upon seeing the target photographs). After completing a session, subjects were asked to look closely at each of the three photographs (smiling, crying and neutrality) to evaluate the affective facial expression. All healthy subjects and patients responded correctly for the two photographs: the smiling photograph caused a pleasurable feeling and the crying photograph caused a sad feeling. In total, 25% of healthy subjects and 16% of patients felt pleasure when viewing the neutral photograph and others felt no emotion. There were no significant differences in recognizing facial expressions between paranoid type patients and non-paranoid patients.

Clinical evaluation and medication

The clinical state of all patients was assessed using the Positive and Negative Symptom Scale[14] administered by two psychiatrists within a week from the P300 recording. Higher scores of the Positive and Negative Symptom Scale from two psychiatrists were taken into the present analysis as data. All patients were treated with neuroleptics, the mean daily dose (mg/day) of chlorpromazine equivalent being 360 ± 154.1 for paranoid type patients and 334 ± 173.6 for non-paranoid patients. There were no significant differences in neu-

roleptic dosages between paranoid type patients and non-paranoid patients.

Statistical analysis

ERP data were examined using two-way repeated measures ANOVA to evaluate epsilon factors and revised using G-G corrections whenever the epsilon level exceeded 1.0. Three-way ANOVA (groups × emotions × electrodes) was performed to assess the main group effect. Next, two-way ANOVA (emotion × electrodes) was evaluated in each group (paranoid type, non-paranoid patients, and healthy subjects). Furthermore, two-way ANOVA (order × electrodes) was evaluated in each group (paranoid type, non-paranoid patients, and healthy subjects) to evaluate the order effect. Fisher's protected least significant differences, determined as post-hoc, was used to test for significant differences between the three pictures. A probability lower than 5% was considered to indicate statistical significance. Correlation between P300 measurements and symptom scores was expressed as Pearson's product-moment correlation coefficient (r). Bracelet's t-test was used to evaluate statistical significance. Values are presented as the mean ± standard deviation (SD) in the text.

RESULTS

P300 peak amplitude

A group main effect was seen using the three-way ANOVA (group × photograph × electrode; for group, F $[2, 1116] = 132.9$, $P < 0.0001$). The P300 peak amplitude of healthy subjects was significantly larger than those in the other groups (Fig. 1). The order of amplitude was: healthy subjects > paranoid type patients > non-paranoid patients. A significant interaction was noted between group × photograph and group × electrode. In healthy subjects, the amplitude while viewing the photograph of the crying face was the largest and the amplitude obtained while viewing the photograph of the smiling face was the smallest (F $[2576] = 51.4$, $P < 0.0001$). The order of amplitude levels for healthy subjects was crying face > neutrality > smiling face (Fig. 2). The amplitudes were similar for the three photographs among all schizophrenic patients. However, patients with paranoid type had the largest amplitude while viewing the photograph of the crying face and smallest while viewing the photograph of the smiling face (F $[2270] = 3.9$, $P < 0.05$). Thus, the order of amplitude (crying face > neutrality > smiling face) was the same as for healthy subjects (Fig. 3). However, in non-paranoid patients, the amplitude while viewing the photograph of the crying face was
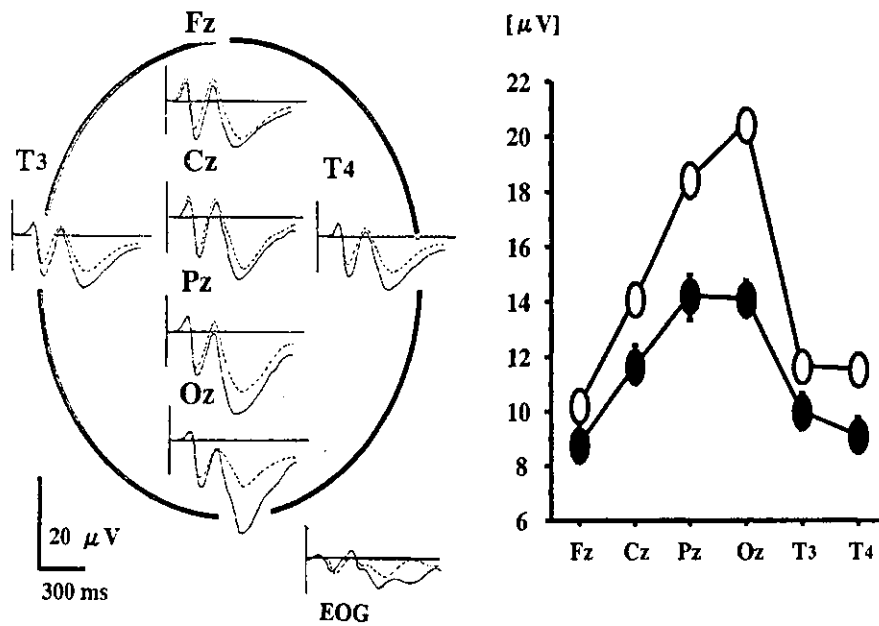
Figure 1. Event-related potentials in schizophrenic patients and healthy controls. Left, Grand-averaged waveforms in normal subjects (solid lines) and schizophrenic patients (dotted lines). Right, Mean amplitude of P300 in normal subjects (O) and schizophrenic patients (●). Bars indicate standard errors.
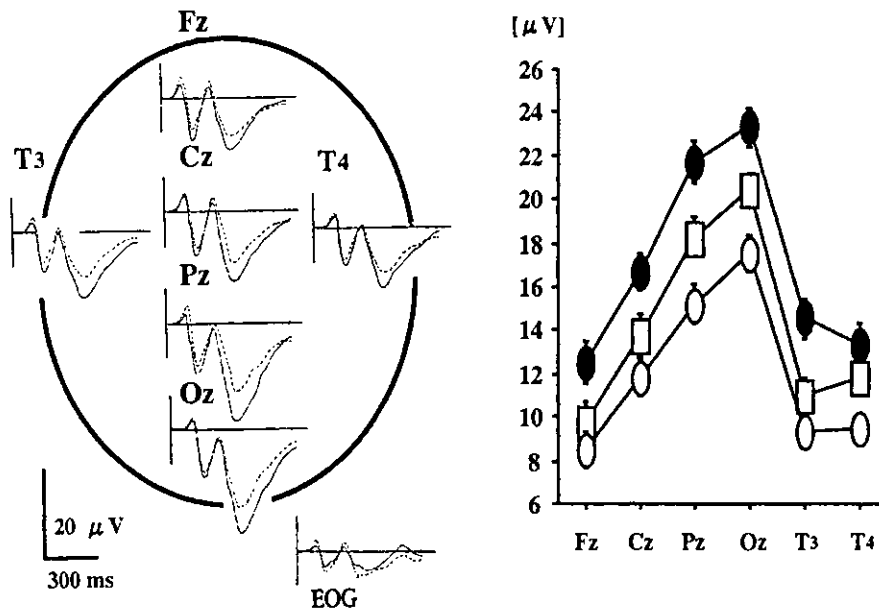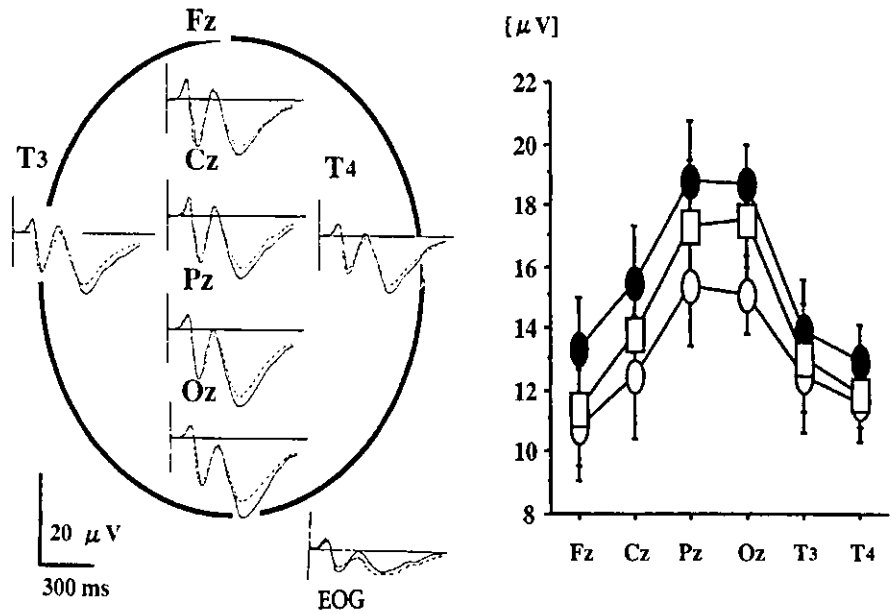

Figure 2. Effects of facial-affect stimuli on visual P300 amplitude in healthy subjects. Left, Grand-averaged waveforms when viewing crying baby photograph (solid lines) and when viewing crying baby photograph (dotted lines). Right, Mean amplitude of P300 amplitude when viewing crying baby photograph (●), when viewing neutral baby photograph (□), and when viewing smiling baby photograph (O). Bars indicate standard errors.

smallest and the amplitude obtained while viewing the photograph of the smiling face was largest (F [2270] = 6.8, $P < 0.01$). The order of the amplitude levels was, thus, reversed as compared with the other two groups (Fig. 4).There was no significant difference in the order effect on the P300 amplitude in each group. The amplitude at the first block (smiling plus crying photographs) was not significantly different from those at the second (neutral photograph) and the third (smiling plus crying photographs) blocks in the three groups.
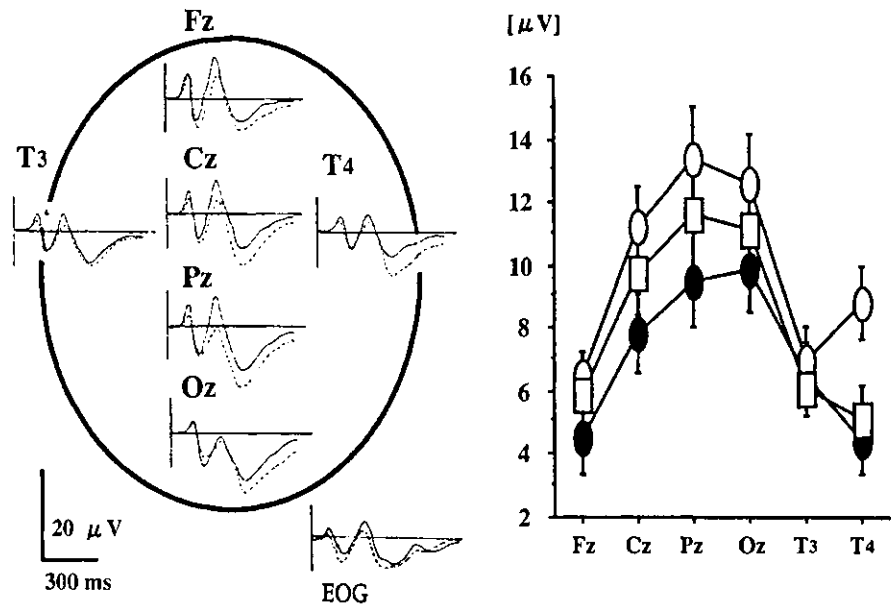
P300 latency

The P300 latency in healthy subjects was significantly shorter than that in schizophrenic patients overall (F [1,1116] = 6.7, $P < 0.05$). A group main effect was seen using three-way ANOVA (for group, F [2,1116] = 18.1, $P < 0.0001$). The P300 latency in healthy subjects was not significantly different from that in paranoid type patients but was significantly shorter than that in non-paranoid patients ($P < 0.0001$). The P300 latency in paranoid type patients was also significantly shorter

Figure 3. Effects of facial-affect stimuli on P300 amplitude in paranoid type patients. Left, Grand-averaged waveforms when viewing crying baby photograph (solid lines) and when viewing crying baby photograph (dotted lines). Right, Mean amplitude of P300 amplitude when viewing crying baby photograph (●), when viewing neutral baby photograph (□), and when viewing smiling baby photograph (○). Bars indicate standard errors.

Figure 4. Effects of facial-affect stimuli on P300 amplitude in non-paranoid patients. Left, Grand-averaged waveforms when viewing crying baby photograph (solid lines) and when viewing crying baby photograph (dotted lines). Right, Mean amplitude of P300 amplitude when viewing crying baby photograph (●), when viewing neutral baby photograph (□), and when viewing smiling baby photograph (○). Bars indicate standard errors.

than that in non-paranoid patients ($P < 0.0001$). The latency was similar for the three photographs in the three groups.No significant difference was observed in the order effect on the P300 latency in each group. The latency at the first block (smiling plus crying photographs) was not significantly different from those at the second (neutral photograph) and the third (smiling plus crying photographs) blocks in the three groups.

N200 amplitude

A group main effect was seen using three-way ANOVA (group × photograph × electrode; for group, F [2,1116] = 45.1, $P < 0.0001$). The N200 peak amplitude

of healthy subjects was significantly smaller than those in non-paranoid patients but significantly larger than those in paranoid type patients. A significant interaction was noted between group × photograph. In both healthy subjects and paranoid type patients, there were no significant differences observed among the three facial stimuli. However, non-paranoid patients had the largest amplitude while viewing the photograph of the crying face and the smallest while viewing the photograph of the smiling face (F [2270] = 11.9, $P < 0.0001$).There was no significant difference in the order effect on the N200 amplitude in each group. The amplitude at the first block (smiling plus crying photographs) was not significantly different from those at the

Table 2. The relationship between negative symptom scores and P300 amplitude for each affective stimulus in paranoid type patients (upper) and in non-paranoid patients (lower).

	Fz	Cz	Pz	Oz	T3	T4
Paranoid type patients						
Sadness	−0.71**	−0.73**	−0.57**	−0.60**	−0.46*	−0.27
Neutrality	−0.54**	−0.62**	−0.51*	−0.41	−0.36	−0.38
Pleasure	−0.68**	−0.65**	−0.53*	−0.45*	−0.44	−0.46*
Non-paranoid patients						
Sadness	−0.43	−0.45*	−0.41	−0.53*	−0.51*	−0.40
Neutrality	−0.52*	−0.44	−0.51*	−0.55**	−0.58**	−0.38
Pleasure	−0.38	−0.33	−0.35	−0.43	−0.42	−0.26

$*P < 0.05; **P < 0.01.$

second (neutral photograph) and the third (smiling plus crying photographs) blocks in the three groups.

Accuracy of counting and button pressing

Both counting and button pressing accuracy exceeded 80% for all subjects for each photograph. In healthy subjects, both counting and button pressing accuracy did not differ between the three emotional stimuli (counting, 97.6 ± 3.4%; button, 98.7 ± 2.1%). Both counting and button pressing accuracies in healthy subjects were higher than both of those in two groups of schizophrenic patients. The two groups of schizophrenic patients had similar button pressing accuracies during exposure to the three photographs (95.6 ± 5.3% for paranoid type patients, 95.0 ± 4.5% for non-paranoid patients). However, counting accuracies in paranoid type patients tended to be higher than that in non-paranoid patients (P = 0.055; 95.1 ± 6.0% for paranoid type patients, 93.0 ± 7.0% for non-paranoid patients).

Reaction time

Differences in reaction time were obtained using two-way ANOVA (photograph × group, F [2,172] = 4.5; P < 0.05). Reaction time in non-paranoid patients was significantly slower than that in healthy subjects and in paranoid type patients. There was no difference in reaction time between healthy subjects and paranoid type patients. Reaction times for each photograph were similar in the three groups.

Symptom scores and medications

The positive symptom scores were 24.0 ± 3.7 for paranoid type patients and 26.6 ± 3.8 for non-paranoid patients. The negative symptom scores were 20.1 ± 3.7 for paranoid type patients and 23.5 ± 3.7 for non-paranoid patients. The positive scores of non-paranoid

patients were not significantly different from those of paranoid type patients. However, the negative scores of non-paranoid patients were significantly higher than those of paranoid type patients (F [1,26] = 5.65, p < 0.05). The P300 amplitude correlated negatively with the negative symptom scores (crying, r = −0.57, P < 0.001; neutral, r = −0.51, P < 0.001; smiling, r = −0.39, P < 0.01) (Table 2). However, neither the positive symptom score nor the dose of medication correlated with the P300 amplitude in each affective stimulus.

DISCUSSION

The present findings show that the visual P300 amplitude is affected by exposure to affectivity-charged photographs. Polich suggested that the P300 might be a good indicator for determining the effect of attention resource diversion both in healthy subjects and patients with mental disorders.[2] In the present study, the amplitude of the P300 was largest when sadness (crying face) was evoked and smallest when happiness (smiling face) was evoked in healthy subjects. All subjects reported that the crying photograph made them feel uncomfortable while the smiling photograph evoked comfortable feelings. Assuming that the magnitude of the P300 amplitude reflects the emotional impact of seeing the facial expression, attention resources devoted to evoking the visual P300 appear to be diverted by exposure to external stimuli. The P300 amplitude to the angry and happy faces may depend on allocation of attention. It has been reported that the angry expression may elicit more focused attention, and possibly more arousal, from subjects than happy expression,[6] thus, the attention resources diversion theory can explain the present findings in healthy subjects.

Another explanation is that an unpleasant face or picture induced greater emotional intensity than a pleasant face or picture in studies using a visual oddball