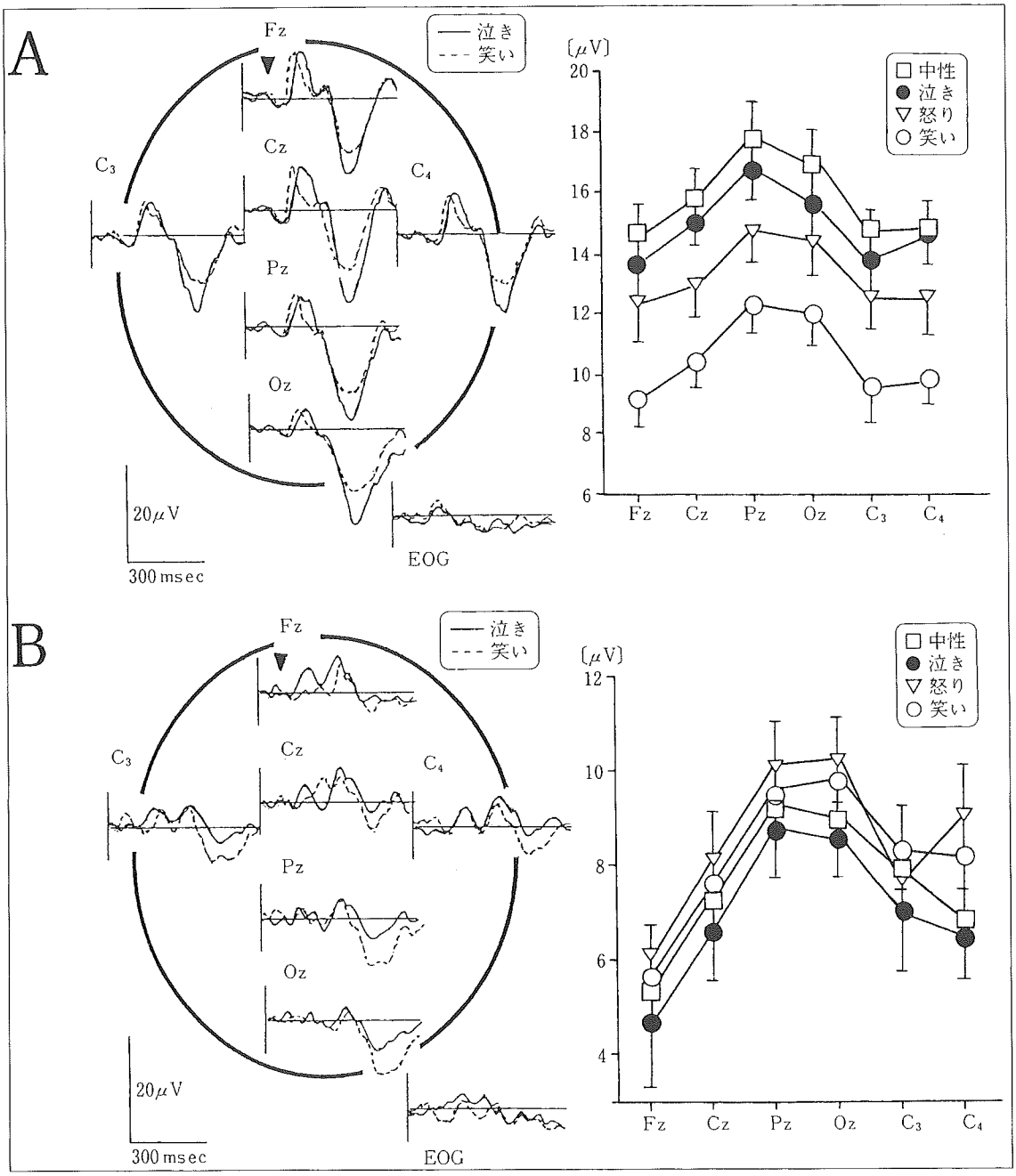

図2　聴覚P300振幅に対する注視表情画の影響[18]

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P300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，P300振幅を低下させる機能をもたず，むしろP300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P300を記録することで，P300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P300を記録した[26]。図3に示したように，健常者では聴覚P300の場合と同様な表情間差がみられ，

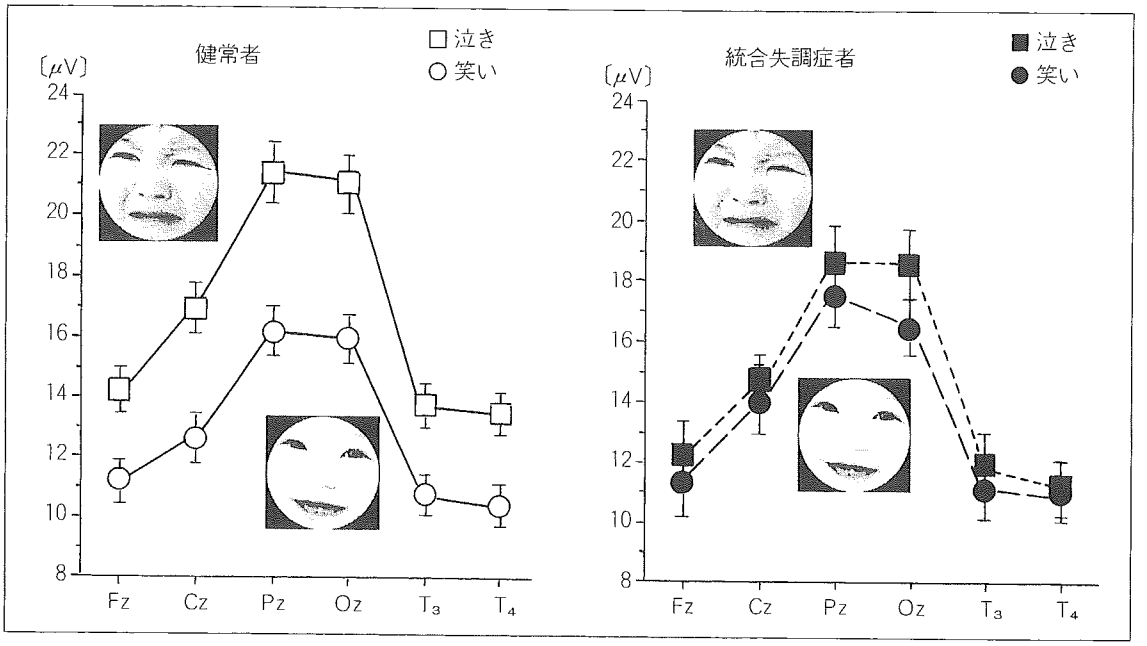

図3 乳児の表情写真を刺激図とした視覚P300振幅[26]
左図：健常者（n＝26），右図：未服薬の統合失調症者（n＝26）。健常者では表情間に有意差（P〈0.0001）がみられたが，統合失調症者では有意差は見られなかった。

「笑い」によるP300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P300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P300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P300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P300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

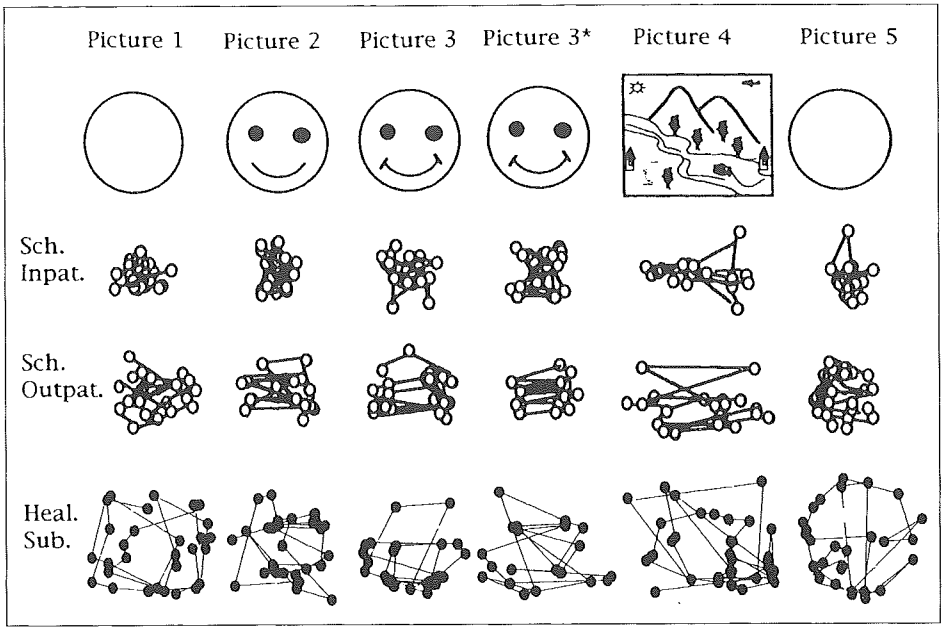

図4　提示された表情画に対する探索眼球運動[32]

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，4T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。

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Regular Article

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

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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-

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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.

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

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 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 neuroleptic 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

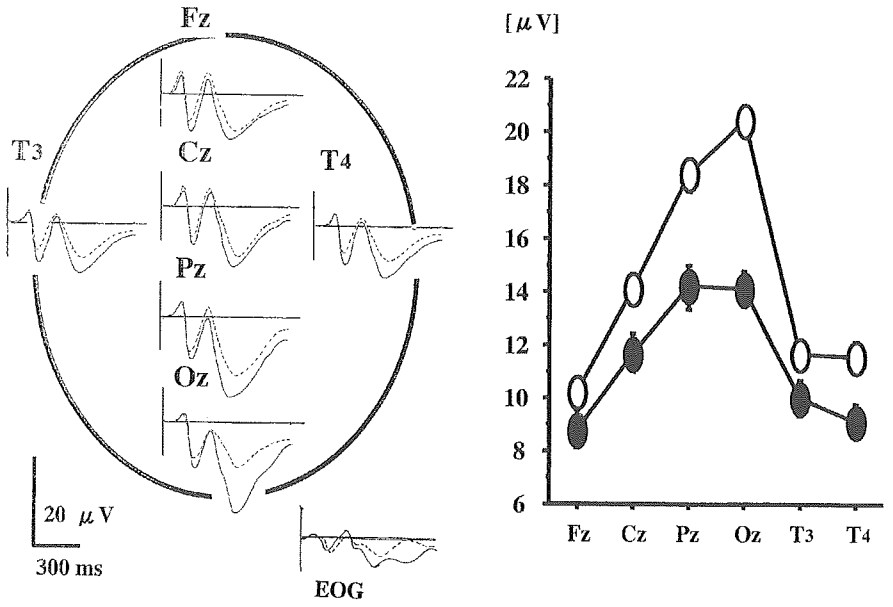

Figure 1. Event-related potentials in schizophrenic patients and healthy controls. Left, Grand-averaged waveforms in normal subjects (solid lines) and schizophrenic patients (dotted lines). Right, Mean amplitude of P300 in normal subjects (○) and schizophrenic patients (●). Bars indicate standard errors.

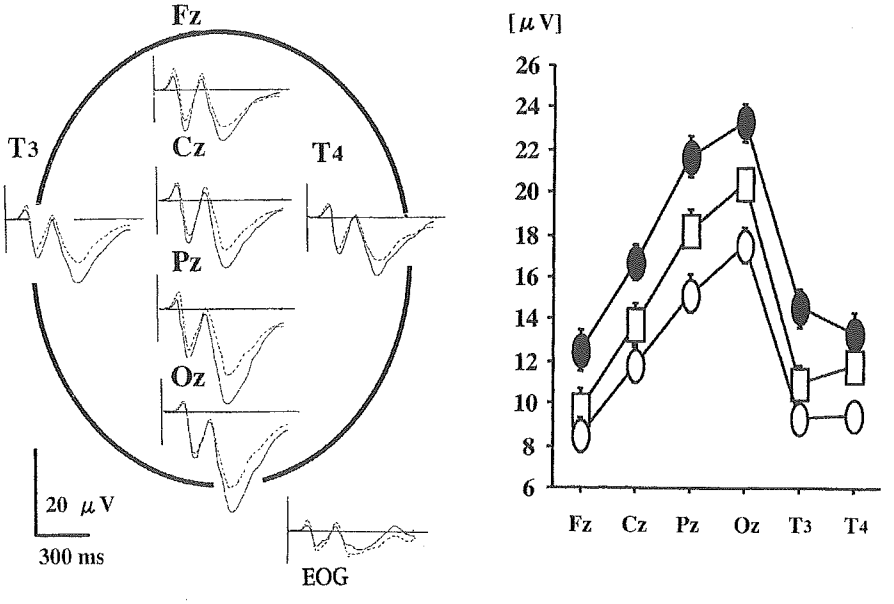

Figure 2. Effects of facial-affect stimuli on visual P300 amplitude in healthy subjects. Left, Grand-averaged waveforms when viewing crying baby photograph (solid lines) and when viewing crying baby photograph (dotted lines). Right, Mean amplitude of P300 amplitude when viewing crying baby photograph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

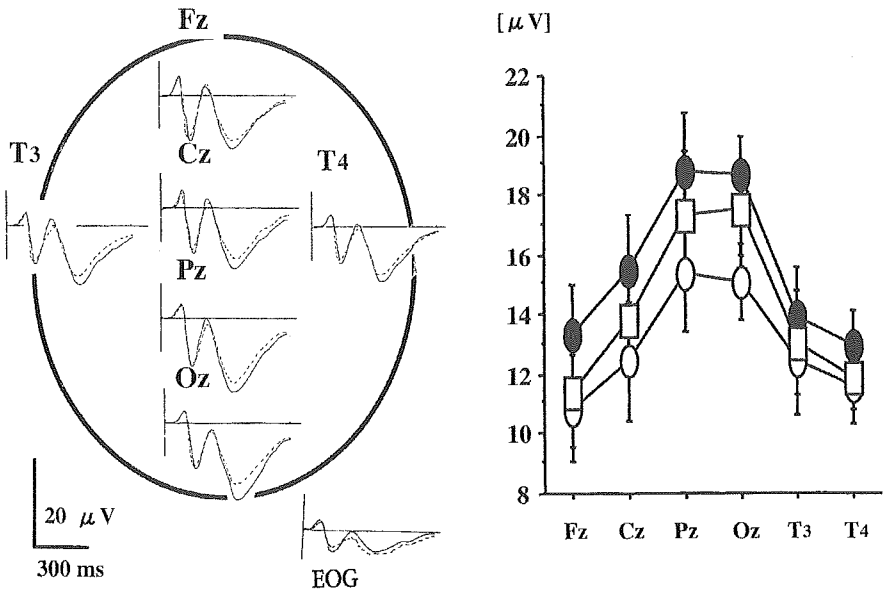

Figure 3. Effects of facial-affect stimuli on P300 amplitude in paranoid type patients. Left, Grand-averaged waveforms when viewing crying baby photograph (solid lines) and when viewing crying baby photograph (dotted lines). Right, Mean amplitude of P300 amplitude when viewing crying baby photograph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

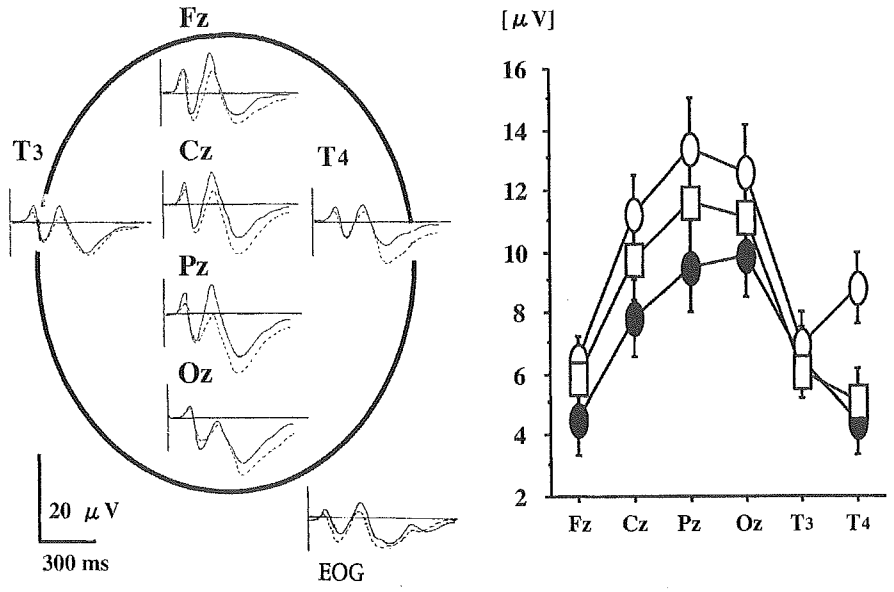

Figure 4. Effects of facial-affect stimuli on P300 amplitude in non-paranoid patients. Left, Grand-averaged waveforms when viewing crying baby photograph (solid lines) and when viewing crying baby photograph (dotted lines). Right, Mean amplitude of P300 amplitude when viewing crying baby photograph (●),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

paradigm in healthy subjects.[5,6] The authors suggest that subjects found the unpleasant face or pictures more intense than the pleasant ones. If these findings are valid, the visual P300 amplitude should increase when the subject views an unpleasant photograph, such as one expressing sadness, because a strong emotional response is evoked.

Schizophrenic patients have been reported to have a deficit in their ability to recognize the affect associated with a facial expression.[7–9] This disability may disturb interpersonal relationships because normal cues are not responded to according to standard social conventions. Recently, An *et al.* reported that P300 amplitude generated by negative emotional stimulus were significantly larger than those of positive stimuli in healthy subjects, however, in schizophrenic patients, P300 amplitudes generated by negative emotional stimulus were significantly smaller than those of positive stimuli in patients with schizophrenia.[15] The authors concluded that schizophrenic patients might have a negative emotion specific deficit at the level of the voluntary affective encoding stage. Our findings are generally in accordance with theirs, however, results indicated that the findings might vary between subtypes. We hypothesize that the emotional arousal of individual patients induced by visual facial affect stimulus may have caused the differences in emotional effects between the two groups of patients rather than simply due to the difference of facial affect recognition. However, the difference in facial recognition may not be denied totally as has been reported before, because this study presented such simple emotional photographs in relation to previous studies.[11]

It has been reported that latency is not affected by different emotional stimuli in healthy subjects,[6] suggesting that the stimulus evaluation time is independent on the subject's emotional state. In the present study, the P300 latency was also the same in all three groups. The pattern implies that different mechanisms affect the amplitude and latency of the P300 during recognition of the emotional content of facial expression as reported before.[6]

The N200 reflects the discrimination of stimuli and the latency became larger according to the difficulty of task discrimination.[16] The N200 amplitude reduction in schizophrenic patients has been reported previously.[17,18] Hrayasu *et al.*, reported that the N200 reduction was not observed in neuroleptic-naïve schizophrenia and the authors suggest that an overlap between N200 and P300 components may account for the absence of an N200 amplitude effect.[19] It has been reported that the N200 amplitude and latency were affected by facial perception.[20] In the present study, the N200 amplitude was largest in non-paranoid patients especially when viewing crying photographs. The difference between paranoid type patients and non-paranoid patients may be a result of the difference in N200 amplitude. The large N200 amplitude could reduce the P300 amplitude in non-paranoid patients. In paranoid type patients, the N200 amplitude was smaller than those in healthy subjects as reported before.[17,18] However, in non-paranoid patients, the N200 amplitude was larger than those in the other two groups. It should be considered that the P300 differences might account for the differences of the N200 amplitude as reported before.[19] Further study is needed to clarify the N200 components in detail.

It has been reported that the reaction time to unpleasant stimuli is faster than to pleasant stimuli.[1] However, we failed to identify differences in reaction time or the accuracy of button pressing between either of the stimulus types upon presentation of the target stimulus. Thus, the effects of facial-affect stimuli on the P300 may be due to direct effects on attention resources allocated through emotional processing.

The negative correlation between both P300 amplitude and the negative symptom score suggests that these measures are somehow associated with symptoms in schizophrenia. In the present study, the correlation coefficient was the largest for sadness (crying face) in both subtypes of schizophrenia, suggesting that the deficit in recognizing unpleasant emotions is reflected in the ERP. We feel that the level of facial affection evoked by stimuli is related to negative symptoms, as reported previously.[13]

Finally, there are differences between paranoid type and non-paranoid schizophrenic patients in fundamental cognitive processing. The manner of P300 values (amplitude, latency) caused by facial affective stimulus of paranoid type schizophrenic patients was similar to those of healthy subjects, indicating that the recognition process reflected by P300 values is better preserved in the paranoid type of schizophrenia than other subtypes. The onset of non-paranoid patients was faster than that of paranoid patients in the present study. Olichney reported that the early onset schizophrenia had significantly smaller auditory P300 amplitude than the late onset schizophrenia and healthy subjects.[21] Furthermore, the paranoid type patients were more accurate than non-paranoid schizophrenia patients with expressions of emotion and the non-paranoid patients had more severe emotional recognition deficits than the paranoid type patients.[22] We suggest again that the emotional arousal level induced by facial-affect stimuli, especially negative emotion, may vary depending on the subtype of schizophrenia. There was no difference of facial performance among three facial stimuli because differences in the present

facial stimuli were so easy to discern. However, there was a possibility that the high degree of affection evoked by facial stimuli may cause a reduction in more complex facial recognition. The failure to accurately read non-verbal emotional cues may contribute to inappropriate social responses, as well as decreasing the patient's sense of social efficacy.[23,24] Improvements to schizophrenics' social skills should perhaps focus more on training in emotion perception.

Future studies

All patients were taking neuroleptic medication so potentially confounding effects of medication cannot be discounted. The present results analyzed were of ERP only. Other measures, such as skin conductance, heart rate, and reaction time are needed to monitor the emotional responses.

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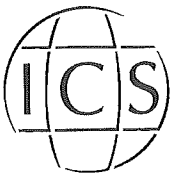

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The improvement of cognitive function reflected by event-related potentials in drug-naive schizophrenia with atypical antipsycotics

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Abstract. Atypical antipsychotic medications are a novel medicine recently discovered and developed for clinical use. In the present study, we investigated the effects of atypical antipsychotic medications on the event-related potentials, especially (ERPs), P300 component, in 30 drug-naive schizophrenic patients. We used positive and negative syndrome scores to assess the symptoms. ERPs were recorded with a visual oddball paradigm. Subjects were asked to count and push a button in response to the targets (crying or smiling baby photographs). ERPs were recorded before the treatment (S1), after 3 months (S2), and 12 months (S3). Before taking medicine, there were no significant differences in the P300 amplitude in response to neither the crying nor the smiling photographs. Both the P300 amplitude and area were significantly larger in S2 and S3 than those in S1. The P300 latency became significantly longer at S3 than S1. A significant negative correlation was obtained between the P300 amplitude and the negative syndrome scores. Atypical antipsychotic medications may be a useful medicine for recovery of cognitive function reflected by the P300 in schizophrenic patients.

Keywords: Event-related potentials; P300; Atypical antipsychotic drugs; Facial affection; Drug-naive schizophrenia

1. Introduction

Recently developed atypical antipsychotic medications are reported to be effective against not only positive schizophrenic symptoms but also negative symptoms, and to

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have fewer extra-pyramidal symptoms and other side effects than conventional agents in patients with schizophrenia.

Event-related potentials (ERPs) have been used as a biologic marker of information processing by the human brain. A later ERP component designated P300 is thought to reflect cognitive processes and attentional resource allocation when working memory is engaged [7]. P300 amplitude reduction is one of the most consistent biologic observations in schizophrenic patients, as both a trait marker and a state marker [1,2,6,8]. However, a few reports have described the effects of atypical antipsychotic medications on cognitive function as reflected by ERPs [3,4]. Long-term detailed studies of the effects of atypical antipsychotic medications on the cognitive function are needed to better understand the underlying core impairment of schizophrenia. We longitudinally investigated the effects of three atypical antipsychotic medications (perospirone, risperidone, olanzapine) on the P300 component in schizophrenic patients for 1 year from the drug-naive phase to the recovery phase. We also considered the effects of the three drugs on facial affective recognition, and how this recognition affected the ERP parameters.

2. Subjects and methods

2.1. Subjects

Patients N=30 were divided into two groups: Paranoid type (N=20) and Un-paranoid (N=10) according to DSMIV, by two psychiatrists participated in this study. All patients did not take any medicine at the session first.

2.2. Method

ERPs were obtained with a visual oddball task at Fz, Cz, Pz, Oz, T3, T4 electrodes. A crying baby or a smiling baby photograph were the target stimuli (probability: 20%) while a neutral baby photograph was the non-target stimuli (probability: 80%). All subjects were asked to push a button as soon as the photographs appeared, and mental count to target stimuli (double tasks). P300 amplitude and latency were measured for further analysis.

2.3. Clinical evaluation

The clinical state of all patients was assessed by two psychiatrists using the positive and negative syndrome scale (PANSS) within a week after ERPs recording.

2.4. Drugs

Three kinds of atypical antipsychotic medications, perospirone (12–32 mg/day), risperidone (3–20 mg/day), and olanzapine (5–20 mg/day) were used. Each patient took one kind of atypical antipsychotic medications in the present study.

2.5. Measurement

ERPs were recorded at session 1 (S1: drug naïve state, pre-treatment), session 2 (S2: after about 3 months medication: 3.3±1.3 months), and session 3 (S3: after 12 months medication: 11.9±2.0 months).

3. Statistical analyses

Three-way ANOVA (condition: patient or control×facial affection: crying or smiling baby×recording sites), and two-way ANOVA in each group were calculated. Fisher PLSD was used as a post hoc test to estimate the significance (<5%). Pearson's product–moment correlation coefficient was also used. The Ethics Committee of Kurume University approved the present study. Written informed consent was obtained from all subjects prior to study.

4. Results

The P300 amplitude at S1 was significantly smaller than that at S2 ($p<0.0001$) and S3 ($p<0.0001$) (Fig. 1) both when viewing a smiling baby and viewing a crying baby. The P300 amplitude when viewing a smiling baby was not significantly different from that when viewing a crying baby at S1, but the P300 amplitude when viewing crying baby was significantly larger than that when viewing smiling baby at S2 ($F=12.5$, $p<0.001$) and S3 ($F=16.3$, $p<0.0001$).

The P300 latency at S3 was significantly longer than that at S1 ($p<0.01$) and S2 ($p<0.05$). There was no significant difference of the P300 latency between when viewing crying baby and viewing smiling baby at S1 and S2, however, the P300 latency when viewing crying baby was significantly shorter than that when viewing smiling baby at S3 ($F=22.4$, $p<0.0001$).

A significant negative correlation was found between the P300 amplitude and the negative syndrome scores ($r=-0.53$, $p<0.001$) at Pz recordings site. The P300 amplitude was not significantly correlated with the positive syndrome scores at Pz recordings site.

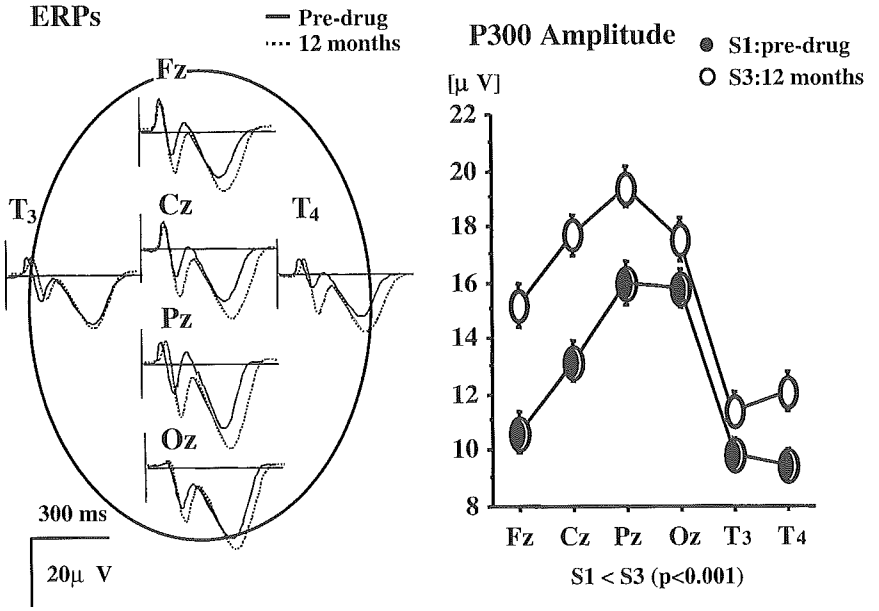

Fig. 1. Left: grand-averaged waveforms in patients with schizophrenia before (solid lines) and after (dotted lines) the treatment. Right: mean amplitude of P300 in patients before (○) and after treatment (●). Bars indicate standard errors (S.E.).

5. Discussion

The results strongly suggested that the atypical antipsychotic medications were an effective medicine against both negative symptoms and positive symptoms in schizophrenic patients, and improved their cognitive dysfunction. Indeed, it was previously reported that atypical antipsychotic medications increased acetylcholine release at the prefrontal cortex and the hippocampus of rats. Acetylcholine has been thought to increase cognitive functions such as memory. Thus, this is possibly how cognitive function is improved in schizophrenic patients. Furthermore, the emotional brain function reflected by the facial affective stimuli [5] may recover after atypical antipsychotic medication treatment as to the same measure of healthy subjects. Atypical antipsychotic drugs treatment could improve not only the symptoms of patients but also improvement in social, occupational, and inter-personal functions based on the recovery of cognitive functions, especially those associated with emotional processes. Finally, the present study indicated that ERPs can be a useful neurophysiologic diagnostic tool.

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陽性・陰性感情負荷が探索眼球運動に及ぼす影響

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THE EFFECT OF POSITIVE AND NEGATIVE EMOTION ON THE EXPLORATORY EYE MOVEMENTS

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本研究では，健常者79名（男性：42名，女性：37名）を対象に，陽性・陰性感情のイメージ想起と表情写真および音声負荷によって引き起こされた情動が，視覚的認知機能を反映する客観的指標とされる探索眼球運動に及ぼす影響を検討した．なお，解析要素として，平均移動距離，総移動距離，平均停留時間，停留点総数を用いた．その結果，注視点の平均移動距離および総移動距離は，陰性感情を負荷することによって有意に短縮したが，再び陽性感情を負荷することによって，陰性感情負荷前と同じレベルまで回復した．また，注視点の平均停留時間は，陰性感情を負荷することによって有意に延長し，再び陽性感情を負荷することによって，陰性感情負荷前と同じレベルまで回復した．さらに，注視点の停留点総数は，陰性感情を負荷することによって有意に減少し，再び陽性感情を負荷することによって陰性感情負荷前と同じレベルまで回復した．再現性の検討は，検査法の妥当性および臨床応用するにあたり重要な問題であるため，20名の被験者に対して，1カ月の期間をおき，再現性を検討した．その結果，施行1と施行2の間に，全ての解析要素で有意な差は認められず，施行間に正の相関が認められ，本検査の再現性が得られた．これらの結果から，感情負荷時の探索眼球運動は，情動を反映する精神生理学的指標になりえると示唆された．

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はじめに

日常生活において，視覚的情報は我々の行動を決定していく上で大変重要なものである．特に，対人場面において，「瞳は，心の窓」と言われる様に，見る働きは社会生活を営んでいく上で，重要な役割を担っている．我々は他人の表情やまなざし，態度を見ることによって，その人の気持ちや考えていることを察し，その場に適した行動をとっている．また，臨床場面においても，我々は，患者の表情やまなざし，態度からその人の現在の病態を，経験的に推測している．これまで，目の動き，つまり眼球運動については，動く指標を追跡することや，絵や図形を見ている時の自由な注視点の動きについて研究されており[1)2)]，特に探索眼球運動は人における視覚的認知機能を反映する客観的指標であるとされている[3)-7)]．

感情は，人の行動および対人関係において大変重要なものである．感情状態は，接近行動や回避行動などのように，外界への関わりを促進したり，抑制したりする．特に強い悲しみや苦しみなどの陰性感情を伴う状況は阻害的に働くことが多く，さらに，その行動は冷静な判断や思考を妨げ，非論理的な思考を導き，不合理な行動を引き起こす[8)]．しかしながら，感情状態と認知機能を反映

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