Neuroscience 131 (2005) 523–534

THE AMYGDALA OF PATIENTS WITH PARKINSON'S DISEASE IS SILENT IN RESPONSE TO FEARFUL FACIAL EXPRESSIONS

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Abstract—We previously found that patients with Parkinson's disease (PD) were impaired with respect to recognition of fear and disgust in facial expressions. To investigate the neural mechanisms that underlie this impairment, we recorded visual event-related potentials (ERPs) in response to the viewing of fearful facial expressions. Ten normal elderly volunteers and nine patients with PD were studied. Fearful, surprised, and neutral facial expressions were presented randomly for 500 ms each, with a probability of 0.1, 0.1, and 0.8, respectively. The locations of the components of the ERPs were analyzed using a scalp–skull–brain/dipole tracing method. The ERPs elicited in response to the facial stimuli consisted of a negative peak (N1), two positive peaks, and a subsequent slow negative shift. For N1, the equivalent current dipoles were concentrated in the fusiform gyrus, right superior temporal gyrus, parahippocampal gyrus, cingulate cortex, and cerebellum, in normal subjects. In response to the fearful stimulus, dipoles were also generated from the amygdala in seven out of 10 normal subjects. In contrast, in patients with PD, N1 was centered bilaterally in the angular gyrus and supramarginal gyrus, and there was no neuronal activity in the amygdala. After N1, dipoles moved toward the frontal region in normal subjects, whereas they remained in the parietal lobes in patients with PD. These results suggest that neither the amygdala nor the temporal visual-associated cortices are involved in responding to fearful expressions in patients with PD. Corticostriatal connections may be variably affected by a lack of dopamine or by pathological changes in the amygdala. Thus, somatosensory recruitment may overcome the mild cognitive emotional deficits that are present in patients with PD owing to a dysfunction of the amygdala.

Key words: event-related potentials, face recognition, amygdala, dipole tracing method, Parkinson's disease.

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Abbreviations: ANOVA, analysis of variance; DT, dipole tracing; ECD, equivalent current dipole; EEG, electroencephalogram; ERP, event-related potential; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PD, Parkinson's disease; PET, positron emission tomography; RT, reaction time; SSB, scalp-skull-brain; STAI, state trait anxiety inventory; 3-D, three-dimensional.

In social interactions, comprehension of the emotional states of others is essential for understanding behavior and avoiding unnecessary conflict. Facial expressions are central to communicating emotion, and interpreting facial expression is crucial for effective social interaction. In primates, including humans, the amygdala is important for the expression of appropriate social behavior and particularly for interpreting non-verbal communication such as facial expression.

Several recent neuropsychological studies have reported deficits that affect the recognition of specific emotions. Patients with selective lesions of the amygdala (Adolphs et al., 1994, 1995, 1999a) show severely impaired recognition of facial expressions of fear. People with Huntington's disease (Sprengelmeyer et al., 1996) are particularly poor at recognizing facial expressions of disgust. In the case of Parkinson's disease (PD), the findings are less clear. While some studies have reported that patients with PD exhibit deficits in comparing emotional facial expressions (Jacobs et al., 1995), others have found no impairment of emotion recognition (Adolphs et al., 1998). In a previous study, we found that patients with PD showed deficits in recognizing fear and disgust in photographs and video recordings of facial expressions, but recognition of emotion in written verbal stimuli was apparently normal in the same patients (Kan et al., 2002). This observation was supported by Sprengelmeyer et al. (2003), who reported that medicated and unmedicated patients with PD exhibited impaired recognition of facial expressions. Functional neuroimaging has revealed that both the amygdala and striatum or insula are involved in processing expressions of fear and disgust (Morris et al., 1996; Phillips et al., 1997; Krolak-Salmon et al., 2003). As there is evidence that the amygdala and striatum do not function normally in patients with PD (Mattila et al., 1999; Ouchi et al., 1999), it is possible that the disturbance of emotional recognition in patients with PD can be attributed to pathological changes in these regions of the brain.

In this study, we hypothesized that dysfunction of the amygdala in patients with PD changes the neural substrates that are normally used to recognize emotion. To investigate the neural mechanisms that are involved in recognizing facial expressions in patients with PD, we recorded visual event-related potentials (ERPs) related to the recognition of fearful expressions, and determined the location of the equivalent current dipoles (ECDs). We estimated the location of the source of the ECDs by means of the scalp–skull–brain/dipole tracing (SSB/DT) method. The SSB/DT method can approximate the distribution of surface potentials of human electroencephalograms

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doi:10.1016/j.neuroscience.2004.09.054

(EEGs) to the position and vector dipole moment of an ECD, estimated by minimizing the mean squared error of the dipole potentials that are recorded from the surface electrodes (He et al., 1987; Nishijo et al., 1994, 1996; Hayashi et al., 1995; Homma et al., 1994). The SSB/DT method has been used to reliably evaluate neural activity in deep locations, such as the limbic system (Masaoka and Homma, 2000; Masaoka et al., 2003).

EXPERIMENTAL PROCEDURES

Subjects

Ten elderly healthy normal volunteers (range of age: 49–71 years; median: 63.5; all male) and nine patients with PD (range of age: 51–79 years; median: 72; seven males, two females) participated in the study. All patients were treated with medications that are appropriate for patients with PD. The severity of parkinsonian symptoms in all cases was equivalent to 2 or 3 on the Hoehn–Yahr scale (Hoehn and Yahr, 1967). As anxiety causes activation of the amygdala (Masaoka and Homma, 2000), the state of anxiety of each patient was measured before each experiment using Spielberger's state trait anxiety inventory (STAI; Spielberger, 1983). STAI consists of two anxiety scales, state anxiety, and trait anxiety. Informed consent was obtained from each participant, and the experimental procedures were approved by the Ethics Committee of Showa University School of Medicine.

Experimental paradigm

We used a three-stimulus oddball paradigm. Facial expressions were performed by professional male and female actors, and were the same as those that were used in our previous study (Kan et al., 2002). We used three different facial expressions, namely, fearful, surprised, and neutral (see below). The fearful face was defined as the target stimulus, the surprised face as a rare non-target, and the neutral face as a frequent non-target.

Experimental setup

Digitized color photographs of faces edited to a height of 10 cm and a width of 13 cm were displayed on a 15-inch TFT-LCD monitor that was placed at a distance of approximately 80 cm in front of the eyes of the subject. Fearful, surprised, and neutral facial expressions were presented for 500 ms, with a probability of 0.1, 0.1, and 0.8 in random order, respectively, at intervals of 1500 ms. The order of stimulus presentation was controlled by a personal computer (Compaq Presario Desktops; Hewlett-Packard Development Company, L.P., CA, USA). Subjects were instructed to keep their eyes open and to fix their gaze on the monitor screen. Each subject was asked to press a button with his or her right index finger as soon as a target stimulus appeared on the monitor. Each subject completed four to six experimental sessions, each of which consisted of the presentation of 150 stimuli. Three random sequences were used to create the order of stimulus presentation within each session.

Data acquisition

EEGs were recorded using 19 Ag/AgCl electrodes that were fixed to the scalp according to the International 10/20 system, and a reference electrode was attached to the right earlobe. Electrode impedances were held below 5 kΩ throughout the recording. Potentials were amplified and bandpass-filtered (0.53–120.00 Hz) by the EEG recorder (EEG-1100; Nihon Kohden Corporation, Tokyo, Japan), and data were stored on an EEG analyzer (DAE-2100; Nihon Kohden Corporation). The data were sampled at 2-ms intervals (sampling rate, 500 Hz) and thereafter were stored on magnetic optical disks for off-line analysis.

To construct an SSB/DT model of the head on which the ECD data could be overlaid, we obtained T1-weighted magnetic resonance imaging (MRI) recordings using a 1.5 Tesla system (MAGNETOM Impact Expert; Siemens-Asahi Medical Technologies, Tokyo, Japan) in the DICOM3 format from each subject, and then reconstructed wire-frame models for the shape of the scalp, skull, and brain of each subject.

Data analysis

For the off-line analysis of data, waveforms were averaged after rejecting the trials containing signals that were compromised by blinking or excessive eye movement ($>$50 μV). We also excluded trials in which the subject failed to perform the task correctly. The remaining trials that were contaminated with other artifacts, such as slow potential shifts caused by sweating, were carefully eliminated from the final average. The time window for averaging was from 100 ms before to 900 ms after the presentation of each visual stimulus. Reaction time (RT) was defined as the interval between the presentation of the target stimulus and the pressing of the response button by the subject. Consequently, there were three averaged waveforms for each subject corresponding to the three stimuli (target, frequent non-target, rare non-target).

The zero baseline for measuring the ERPs was obtained by averaging the amplitudes of the first 100 ms of the whole analysis window for each channel. As will be described in the Results, three peaks (two positive and one negative) were identified in the ERPs. The peak latency and amplitude of each wave were measured in the average waveform for each stimulus. Average peak amplitudes during the 50-ms period on either side of the peak (for example, from 350 to 450 ms for P400) were calculated with respect to the pre-stimulus baseline for each stimulus for each subject. The data were analyzed using a three-way analysis of variance (ANOVA) with repeated measures [group (normal or patients: between-subjects factor)$\times$stimulus (target, frequent non-target or rare non-target: within-subjects factors)$\times$electrode (within-subjects factors)]. Similarly, a separate ANOVA was conducted for the six temporal electrodes (P3, T5, O1 vs. P4, T6, O2). Statistical significance was set at $P<0.05$.

To determine the location of the stereotaxic coordinates of the current source generators of the ERPs, ERP data were analyzed according to the methods of Masaoka and Homma (2000) and Masaoka et al. (2003) with a Brain Space Navigator (BS-navi; Japan Graphics, Tokyo, Japan), using the realistic three-layer head model (SSB) for each subject, and assuming standard conductivity (0.33 S/m for skin and brain, 0.0041 S/m for bone). Using a boundary element method, the SSB/DT can calculate potential distributions generated by one or two assumed dipoles on the surface of the head. The actual potential distributions recorded from the 19 scalp electrodes (Vobs) were compared with the calculated potential distribution (Vcal) for one or two ECDs and the locations and vector moments of one or two dipoles were changed within the three-dimensional (3-D) head model until the squared difference between the Vobs and the Vcal was minimal (one-dipole estimation or two dipole estimation, respectively). We chose the two dipole estimation in this study. We evaluated only dipoles for which root-mean-square quality of fit (dipolarity) exceeded 98%, because only dipolarity values greater than 98% indicate agreement between the estimated dipoles and the observed potential (Homma et al., 1994).

Differences in the percentage of incorrect responses, RT, and the anxiety score between patients with PD and normal subjects were analyzed using the Mann-Whitney U statistic. χ^2 Tests with Yates' adjustment were used to compare the appearance of dipoles between normal subjects and patients with PD. In all cases, $P<0.05$ was considered statistically significant.

Table 1. Task performance by normal subjects and patients with Parkinson's disease

	Age (y.o.)	Sex	RT (seconds)	Correct response (%)	Rejection ratio* (%)		
					Frequent non-target	Rare target	Rare non-target
Normal subjects (N = 10)							
No. 1	55	M	0.539	99.6	3.2	1.9	1.9
No. 2	53	M	0.727	99.8	27.4	1.6	8.3
No. 3	49	M	0.584	99.6	48.4	3.2	16.7
No. 4	67	M	0.730	98.0	37.5	11.4	28.8
No. 5	63	M	0.626	97.6	38.0	12.0	28.6
No. 6	61	M	0.691	99.7	1.6	2.0	3.2
No. 7	71	M	0.830	98.3	45.1	10.1	17.9
No. 8	64	M	0.789	95.9	29.0	7.3	13.2
No. 9	66	M	0.594	98.0	17.7	13.4	20.5
No. 10	64	M	0.671	98.2	24.3	6.7	7.1
Mean			0.68±0.09	98.5±1.24			
Patients of Parkinson disease (N=9)							
No. 1	51	M	0.900	99.7	15.7	2.6	7.4
No. 2	77	M	0.966	98.8	24.1	29.1	8.2
No. 3	76	F	0.937	99.0	22.5	21.8	23.6
No. 4	68	F	0.707	97.8	21.6	13.7	14.7
No. 5	72	M	0.576	99.6	12.3	6.2	3.5
No. 6	60	M	0.532	98.9	18.3	4.2	24.4
No. 7	70	M	0.772	99.3	10.9	6.4	4.4
No. 8	79	M	0.663	99.0	23.0	15.9	5.3
No. 9	73	M	0.576	98.0	27.0	8.9	10.2
Mean			0.74±0.17	98.9±0.65			

* The number of trials excluded from the final average divided by the total number of frequent non-target stimulus=neutral face, rare target=fearful face, rare non-target=surprised face. M, male; F, female.

RESULTS

Task performance

The normal subjects responded correctly to 98.5±1.24% of the stimuli, whereas the patients with PD responded to 98.9±0.65%. As is evident from the percentage of correct responses and RTs (Table 1), normal subjects and patients with PD performed the task equally well (Mann-Whitney U test, $P>0.05$). The mean STAI scores for anxiety were 40.2±5.9 in normal subjects and 42.3±11.2 in patients with PD. The mean scores for state anxiety were 40.9±8.6 in normal subjects and 37.6±8.4 in patients with PD. There were no significant differences between the anxiety scores of patients with PD and those of normal subjects.

ERPs

Typical ERPs for one normal subject and one patient with PD for the three stimuli [target (fearful face), rare non-target (surprised face), and frequent non-target (neutral face)] are shown in Figs. 1 and 2, respectively. Three components of the ERPs elicited by each stimulus were identified, namely, a negative peak (N1), two positive peaks (P1 and P2), and a slow negative shift. The latency and amplitude of P1 and N1 appeared to be similar, regardless of the stimuli. The general morphology of the waveform was similar in normal subjects and patients with PD. N1 and P1 were present predominantly at occipito-temporal sites on the scalp (O1, O2, T5, and T6). The topographical map of the N1 peak in Figs. 3A and 4A (the same as those shown in Figs. 1A and 2A) also indicated occipitotemporal negativity (Figs. 3B and 4B). The mean latency of these components (measured at O1) is presented in Table 2. The latency of N1 was within a range of 250–550 ms, although the range varied among different subjects. Consequently, we estimated the location of the ECDs for each component of the waveform for each subject, rather than using an overall averaged waveform of all subjects.

The mean amplitudes of P1, N1, and P2 were analyzed separately using three-way ANOVA (group×stimulus×electrode). The main effects were not significant in the components of P1 or N1. There was a significant interaction of group×stimulus in both P1 and N1 [P1, $F(2,54)=3.918$, $P<0.05$; N1, $F(2,54)=6.606$, $P<0.01$], which indicated a stimulus-specific amplitude increase in patients with PD. P2 was maximal at O1. The mean value of the average amplitude of P2 measured at O1 was 2.2±2.5 μV (target), 1.9±1.8 μV (frequent non-target), and 3.7±2.2 μV (rare non-target) in normal subjects, whereas it was 6.7±4.3, 7.2±4.7, and 6.5±4.0 μV, respectively, in patients with PD. There was a significant main effect of group [$F(1,72)=12.802$, $P<0.05$]. The amplitudes of the P2 voltages in patients with PD were larger than in the normal subjects. There was neither a significant main effect nor a significant interaction among group, stim-

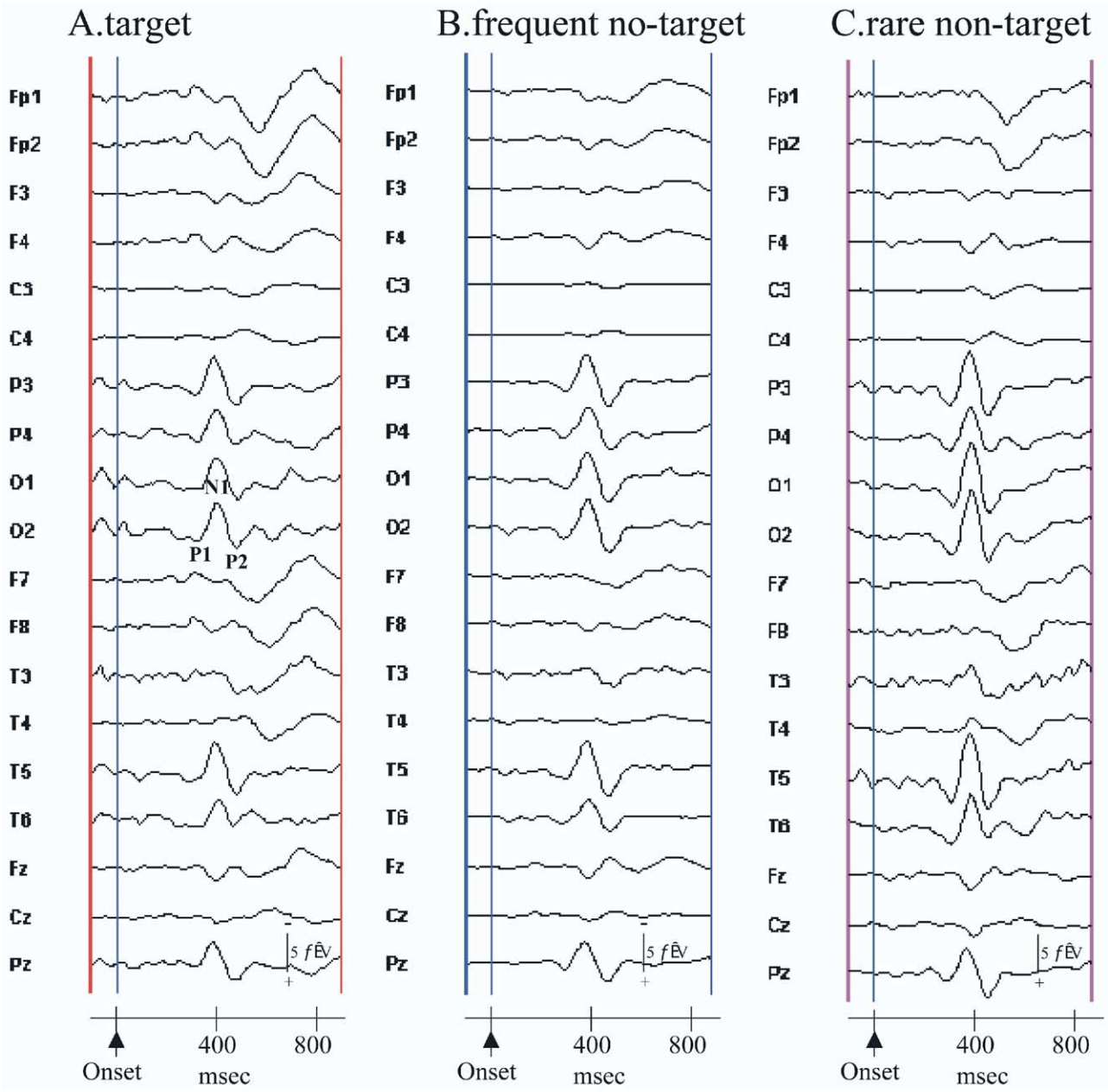

Fig. 1. Examples of ERPs recorded from a normal subject (No. 2). Abbreviations on the left indicate the position on the scalp of each recording electrode. The ERP had three components: a negative peak (N1), two positive peaks (P1 and P2), and a subsequent negative shift. (A) Target (fearful face); (B) frequent non-target (neutral face); (C) rare non-target (surprised face). The latency and amplitude of P1 and N1 were similar for the different facial emotions.

ulus, and electrode in the separate ANOVA for the six temporal electrodes (P3, T5, O1 vs. P4, T6, O2). No significant laterality of the mean amplitude was present in either group.

Source generators of ERPs

We failed to find any significant ECDs for P1 in any of the subjects. The ECDs that were estimated for N1 in response to the fearful facial expression were generated from the bilateral amygdala (total of nine dipoles in seven out of 10 normal persons), but there were no such dipoles in the amygdala in nine patients with PD (Fig. 5; Table 3). In a χ^2 test comparing zero out of nine persons and seven out of 10 persons, this finding was statistically significant ($\chi^2=9.98$, $df=1$, $P<0.01$). One dipole was also generated from the right amygdala in response to a surprised facial expression in both the normal and PD groups, which was not statistically significant ($\chi^2=0.01$).

Except for those in the amygdala, the ECDs that were estimated for N1 in response to target stimuli were distributed mainly within the left fusiform gyrus, right inferior temporal gyrus, bilateral superior temporal

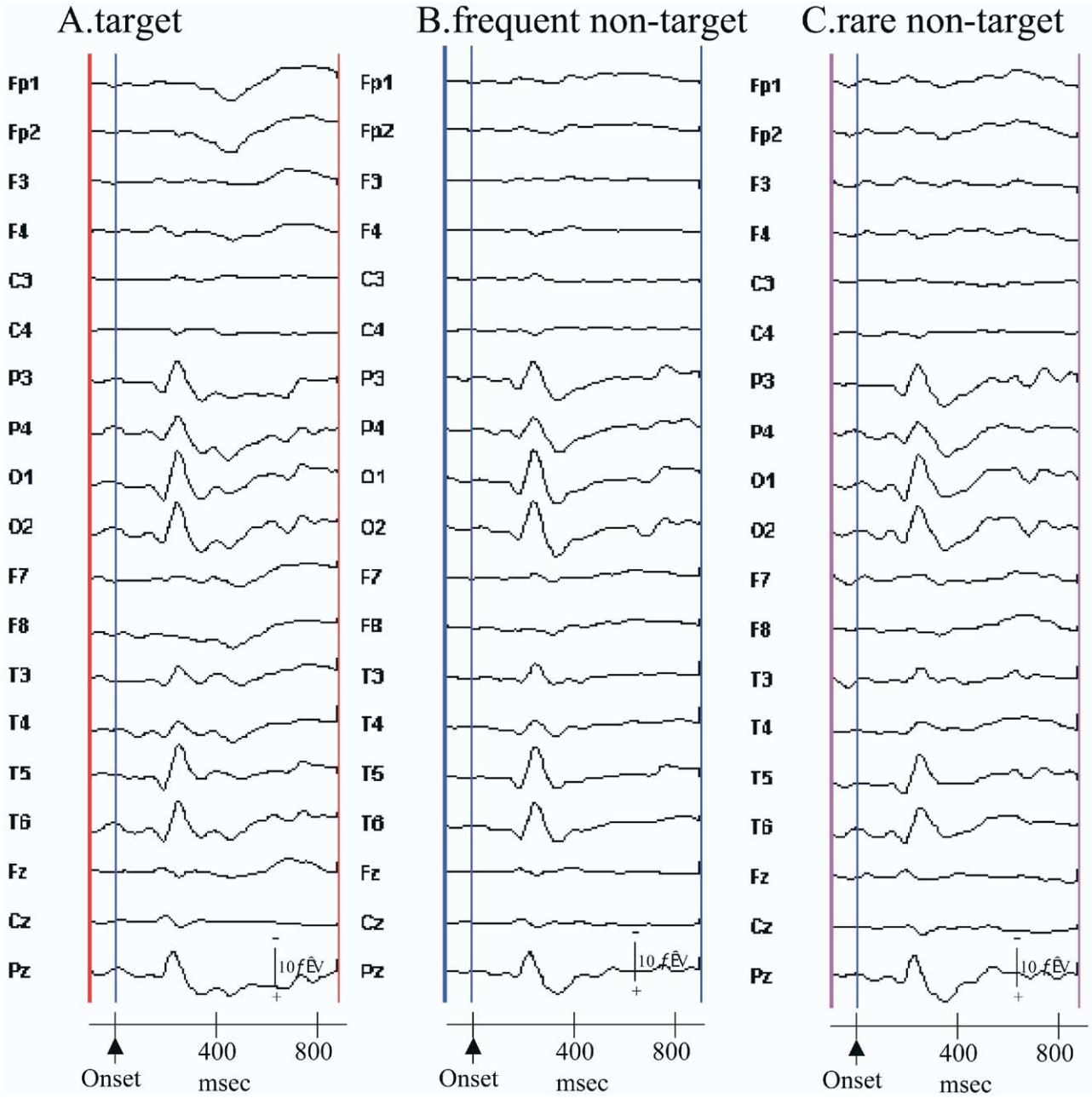

Fig. 2. Examples of ERPs recorded from a patient with PD (No. 5). (A) Target (fearful face); (B) frequent non-target (neutral face); (C) rare non-target (surprised face). The general morphology of the waveform was similar, whereas the peak amplitude was larger than in the normal subject (see Fig. 1).

gyrus, and cerebellum, in normal subjects. In response to non-target stimuli (both neutral and surprised facial expressions), the ECD were also distributed in the bilateral fusiform gyrus, parahippocampal gyrus, cingulate cortex, retrosplenial cortex, and right precuneus, as well as in the right inferior temporal gyrus and bilateral superior temporal gyrus. In patients with PD, the ECDs distributed in regions similar to those of normal subjects were less abundant, and most of the dipoles were located in the parietooccipital cortex, particularly in the supramarginal and angular gyrus.

In normal subjects, the ECDs that were estimated for P2 in response to fearful facial expressions were diversified in the right inferior temporal gyrus, bilateral angular gyrus, left orbitofrontal gyrus, right middle frontal gyrus, and left retrosplenial cortex (Fig. 6, Table 4). The ECDs for P2 in response to non-target stimuli were distributed more widely than those in response to the target stimulus, being located in the bilateral inferior temporal gyrus, left superior temporal gyrus, parahippocampal gyrus, right superior lobule, right precuneus, left orbitofrontal gyrus, and left middle frontal gyrus. In contrast, in patients with PD, the dipoles

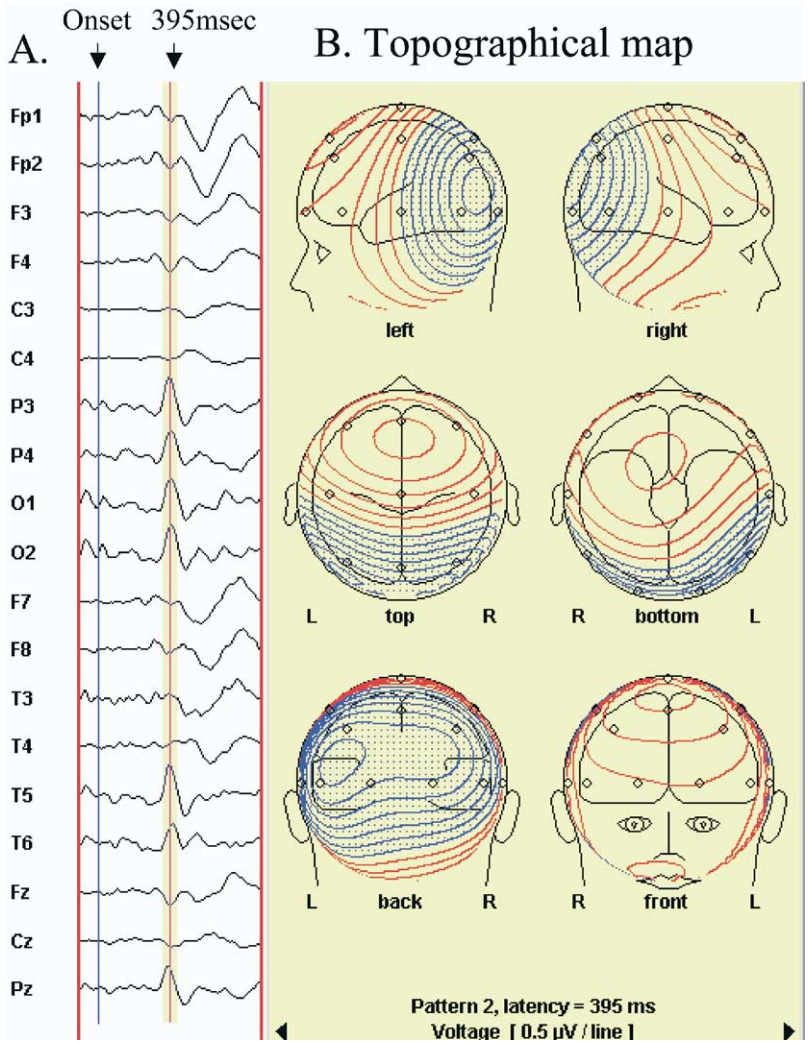

Fig. 3. Examples of topographical maps at component N1 of the ERPs in response to the target stimulus recorded from the same normal subject shown in Fig. 1A. (A) ERPs. The peak latency of N1 was 395 ms after visual presentation of the target stimulus. (B) 3-D topographical maps at the peak of the N1 displayed in Fig. 3A. Negativity was located in the occipitotemporal region.

for P2 were concentrated around the bilateral intraparietal sulci, and were found in the cingulate cortex, retrosplenial cortex, and thalamus (Fig. 6B).

In normal subjects, the ECDs for N1 were mainly concentrated in the bilateral temporal lobes, and then migrated toward the frontal region. In contrast, in patients with PD, the ECDs for N1 were centered in the bilateral parietal lobes and subsequently migrated upward.

DISCUSSION

The most important observation in this study was that the ERPs elicited in response to fearful facial expressions were generated within the parietal somatosensory cortex in patients with PD, whereas the equivalent ECDs in normal subjects were located in the amygdala and visual temporal cortex. These findings support our hypothesis that dysfunction of the amygdala in patients with PD causes a change in the neural substrates that are normally used to recognize emotion.

Application of DT to ERPs

ERPs are one of several physiological measures of activity in the CNS that can be used in cognitive studies. The application of DT to scalp-recorded EEG data can provide temporal resolution of neural activity in milliseconds, resulting in improved spatial resolution for non-invasive studies of the *in vivo* functioning of the human brain. Several DT methods have been used to determine the topographical location of neural activity, including brain electric source analysis (Scherg and Picton, 1991; Scherg, 1992), low resolution brain electromagnetic topography (Pascual-Marqui et al., 1994, 1999), and SSB/DT modeling (He et al., 1987; Nishijo et al., 1994, 1996; Hayashi et al., 1995; Homma et al., 1994). In the SSB/DT method that we developed, the head model consists of three compartments of uniform conductance that correspond to the scalp, skull, and brain. The accuracy of the calculations involved in the application of these models depends primarily on the ratios of the conductivities of the three com-

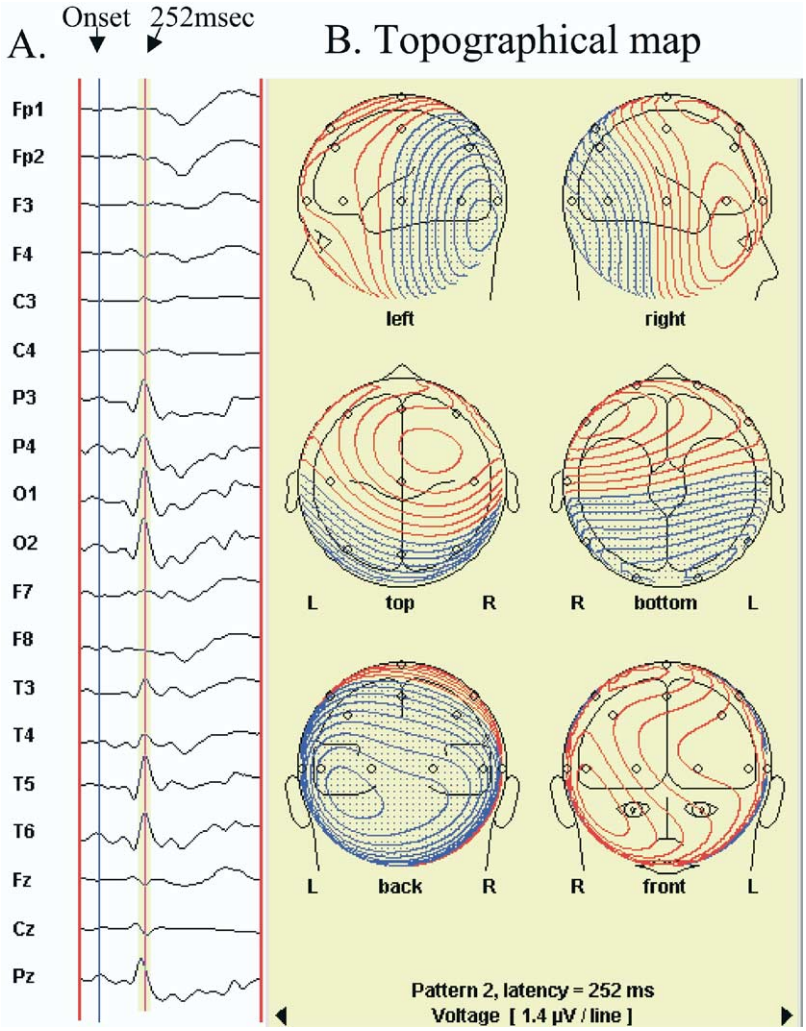

Fig. 4. Examples of topographical maps at component N1 of the ERPs in response to the target stimulus recorded from the same patient with PD shown in Fig. 2A. (A) ERPs. Peak latency of the N1 was 252 ms after visual presentation of the target stimulus. (B) 3-D topographical maps at the peak of N1 displayed in Fig. 4A.

partments that correspond to the scalp, skull, and brain (Homma et al., 1994, 1995). It has been reported that the absolute mean deviation of actual dipoles (generated artificially at known coordinates in the monkey brain) from estimated dipoles (calculated from the surface potential distributions) was within 3.0–9.0 mm (Nishijo et al., 1994). We found previously that the location of the dipoles estimated by SSB/DT corresponded to the location of intracerebral depth electrodes, which were able to record epileptic spikes simultaneously (Homma et al., 2001). While no detailed comparative study has been made of the aforementioned SSB/DT methods techniques, our technique has been shown to be useful in the investigation of activity in the amygdala and other areas of the limbic system (Masaoka and Homma, 2000; Masaoka et al., 2003).

Comparison of components N1 and N170

Studies of ERPs recorded from the scalp (Bentin et al., 1996; Eimer, 2000a,b) or by means of magnetoencephalography (MEG; Watanabe et al., 1999; Halgren et al., 2000; Liu et al., 2000) have identified a posteriolateral negative peak at a latency of approximately 170 ms, which has been termed N170. N170 was reportedly elicited by facial stimuli, but not by other (control) stimuli, and was generated within the fusiform gyrus. This observation was consistent with the results of a functional MRI (fMRI) study carried out by Kanwisher et al. (1997). The latencies of face-specific potentials in EEGs recorded from the scalp were prolonged in comparison to simultaneous MEG recordings (Watanabe et al., 1999). A face-sensitive, surface-negative potential that peaked approximately 200 ms after the presentation of the stimulus was also recorded from the bilateral fusiform and inferior temporal gyri in a study of intracranial ERPs, in medicated epileptic patients (Allison et al., 1999). However, N170 is apparently not affected by the familiarity of the face or repeated exposure to the stimulus, which suggests that N170 is associated with the precategorical structural encoding of faces, rather

Table 2. Peak latencies of waveform and reaction time[a]

	Stimulation	P1 (ms)	N1 (ms)	P2 (ms)	RT (seconds)
Normal subjects					
No. 1	N	204	251	460	
	F	197	243	460	0.54
	S	203	243	460	
No. 3	N	213	278	360	
	F	200	278	356	0.58
	S	227	282	369	
No. 9	N	199	278	396	
	F	201	270	388	0.59
	S	201	271	410	
No. 5	N	226	278	412	
	F	213	282	478	0.63
	S	213	282	482	
No. 10	N	282	370	510	
	F	282	385	504	0.67
	S	282	378	504	
No. 6	N	300	395	482	
	F	326	404	482	0.69
	S	321	404	478	
No. 2	N	456	512	599	
	F	460	521	582	0.72
	S	456	521	582	
No. 4	N	469	521	595	
	F	469	530	604	0.73
	S	473	530	599	
No. 8	N	482	538	617	
	F	473	530	638	0.79
	S	482	543	617	
No. 7	N	465	547	630	
	F	473	543	656	0.83
	S	472	551	664	
PD patients					
No. 6	N	221	274	365	
	F	217	278	478	0.53
	S	226	291	473	
No. 5	N	191	247	330	
	F	195	252	352	0.58
	S	191	217	360	
No. 9	N	188	221	330	
	F	191	227	330	0.58
	S	191	224	321	
No. 8	N	334	399	508	
	F	302	384	530	0.66
	S	280	367	530	
No. 4	N	204	247	321	
	F	204	252	330	0.70
	S	191	243	326	
No. 7	N	326	395	569	
	F	333	395	578	0.77
	S	326	404	560	
No. 1	N	321	417	508	
	F	313	399	525	0.90
	S	330	417	517	
No. 3	N	326	412	582	
	F	360	404	582	0.93
	S	330	430	473	
No. 2	N	447	512	595	
	F	452	512	578	0.97
	S	456	512	573	

[a] F, fear; N, neutral; S, surprise.

than with the subsequent processes involved in face recognition or identification (Eimer, 2000a). Several studies have addressed the differences between the cerebral mechanisms that subserve facial identification and those that are involved in recognizing facial emotion using ERP recordings (Münte et al., 1998; Bobes et al., 2000; Campanella et al., 2002; Eimer and Holmes, 2002), positron emission tomography (PET), and fMRI (Sergent et al., 1994; Puce et al., 1995; Phillips et al., 1998; Narumoto et al., 2001). In this study, we identified three components of the ERPs evoked in the emotion-recognition task, namely, a negative wave (N1), two positive waves (P1 and P2), and a subsequent negative shift. These potentials were distributed bilaterally within the occipitotemporal region of the scalp. The ECDs estimated for N1 in normal subjects were located in the fusiform gyrus, parahippocampal gyrus, inferior and superior temporal gyri, and amygdala. We suspect that the N1 component of ERPs, as described in this study, is a wave that is distinct from N170 and may include responses to other visual or emotional processes.

The latency of N1 recorded from O1 was within the range 250–550 ms, although there were large interindividual differences in this range. In a previous study, the components of emotion-modulated ERPs were observed in the range 250–600 ms (Münte et al., 1998) and individual differences in latency were greater than the latency of N170 reported by Watanabe et al. (1999). The extremely strong correlation between RT and N1 latency might be attributable to some unidentified problem within the stimulus delivery system, in that most of the variations in both parameters were due to variations between the supposed and actual stimulus presentation time. However, this does not explain why latencies were consistently much shorter in some subjects than in others. Another explanation for the differences among individuals with respect to the N1 latency is age. Age-related slowing of access to domain-specific memory representations and response decisions has been noted in previous studies (Pfütze et al., 2002; Takakura et al., 2003). Finally, prolongation of the RT and the N1 latency may reflect impairment of visual acuity or attention, which is more prominent in elderly people; elderly individuals, of course, were participants in this study.

The source generators of ECDs

In patients with PD, the locations of the ECDs for N1 differed markedly from those in normal subjects. Specifically, in patients with PD, the dipoles were concentrated bilaterally in the parietal cortex along the intraparietal sulcus, including the supramarginal gyrus, angular gyrus, and superior parietal lobule; there was no involvement of the amygdala in any of the PD patients in response to fearful facial expressions. As high levels of anxiety produce activation in the amygdala (Masaoka and Homma, 2000), it is possible that, in our study, the observed differences in activation of the amygdala in normal subjects and in patients with PD were owing to differences in the degree of anxiety in each group. However, this is unlikely to be the case, because the anxiety scores were not significantly different in normal subjects, as compared with PD patients.

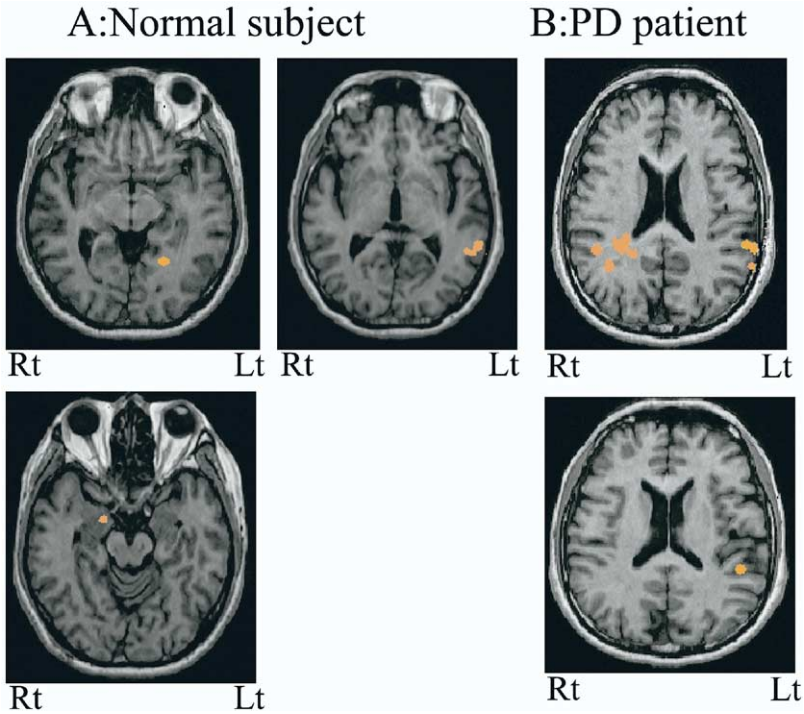

Fig. 5. Location of dipoles estimated for component N1 on images acquired by MRI. Dipoles were superimposed stereotaxically on each subject's MRI scan. (A) Normal subject (No. 6, 350–450 ms after the onset of a stimulus). (B) PD patient (No. 2, 460–560 ms after the onset of a stimulus). Note that the estimated dipoles were located in the left parahippocampal gyrus, right amygdala, and left superior temporal gyrus in the normal subject, whereas the same dipoles were located in the bilateral supramarginal and angular gyrus in the patient with PD.

The results suggest that a dysfunction of amygdala is present in PD, which is consistent with previous studies (Mattila et al., 1999; Ouchi et al., 1999).

Our results also raise the question of why the area along the intraparietal sulcus was activated during emotional cognition in patients with PD. It is well known that the parietal lobe is involved in receiving visual information; a ventral stream of projections to the inferotemporal cortex plays a major role in the perceptual identification of objects, while a dorsal stream that leads into the posterior parietal region mediates the required sensorimotor transformations for visually guided actions (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992). However, this model does not explain emotional cognition. The superior temporal sulcus region has reciprocal connections with the amygdala, which, in turn, is reciprocally connected to orbitofrontal cortex (Amaral et al., 1992). This three-part system has been proposed as the basis of social cognition (Adolphs, 1999b). Supramarginal lesions in the right hemisphere have led to deficits in recognizing, labeling, and building conceptual knowledge about facial expressions (Adolphs et al., 2000). Temporal and limbic-related cortices are involved in retrieving emotional information, whereas somatosensory-related cortices permit the recalling of knowledge about emotion (Adolphs et al., 2003). Our results suggest that the parietal somatosensory cortex is

Table 3. Location and number of the ECDs for N1[a]

	Temporal lobe												Parietal lobe						Others					
	Fusi		ITG		MTG		STG		ParaHC		A		SMG		AG		Precune		Cinglate		Retro		Cbll	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Non-target stimuli (neutral and surprised face)																								
Normal	12	10	0	5	0	3	4	14	10	10	0	1	0	0	3	1	2	10	6	2	4	2	11	15
PD	5	10	9	4	3	11	11	12	4	21	0	1	15	24	21	5	2	5	3	9	4	4	22	23
Target stimulus (fearful face)																								
Normal	9	0	0	4	0	3	2	5	0	3	4	5	0	0	0	1	0	4	1	1	0	3	7	5
PD	6	4	7	8	8	7	1	2	4	3	0	0	9	3	19	15	1	5	1	1	6	1	6	5

L=left, R=right

[a] A, amygdala; AG, angular gyrus; Cbll, cerebellum; Fusi, fusiform gyrus; HC, parahippocampal; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; precune, precuneus; retro, retrosplenial cortex; SMG, supramarginal gyrus, STG, superior temporal gyrus; T, thalamus.

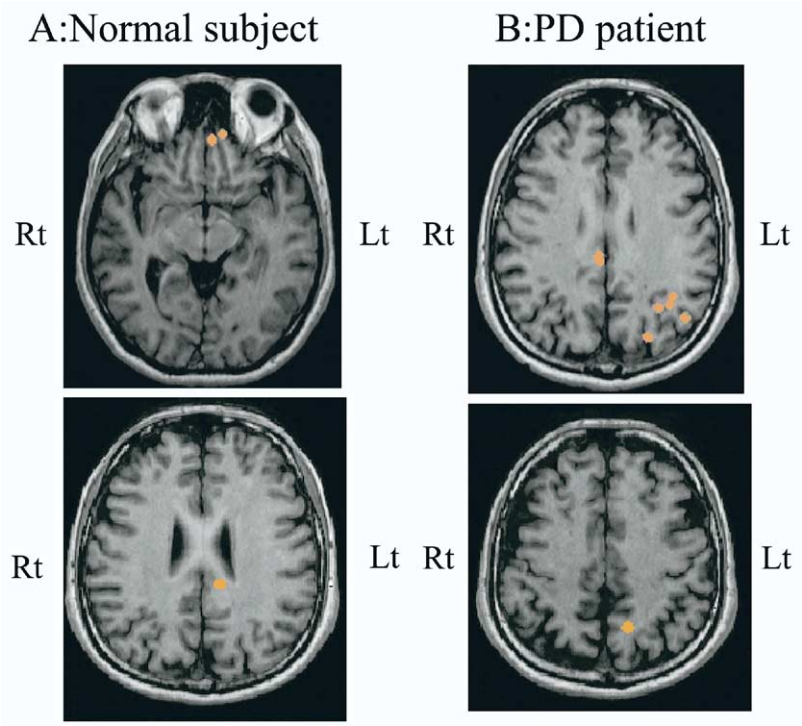

Fig. 6. Location of dipoles estimated for component P2 and the subsequent negative shift in the ERP on images acquired by MRI. Dipoles were superimposed stereotaxically on each subject's MRI scan. (A) Normal subject (No. 4, 550–650 ms after the onset of a stimulus). (B) PD patient (No. 5, 300–400 ms after the onset of a stimulus). Note that estimated dipoles were located in the left straight and orbital gyrus, cingulate cortex in the normal subject, whereas the same dipoles were concentrated around the intraparietal sulcus and were also observed within the cingulate cortex and superior parietal lobule in the patient with PD.

preferentially recruited for emotional recognition in patients with PD, because both the amygdala and orbitofrontal cortex show relatively less response to facial expressions than is the case in normal subjects. Mild deficits in recognition of fear and disgust in facial expressions, due to dysfunction of the amygdala in patients with PD, may be overcome by enhanced recruitment of the parietal cortex.

In this study, the value obtained by subtracting the latency of N1 from RT was significantly greater in patients with PD than in normal subjects. In addition to slowing of movement, slowing of cognitive processing—which is not restricted to the motor domain—can occur in PD (Sawamoto et al., 2002). We suspect that the relatively longer RT of patients with PD after recognition of a fearful facial expression includes a change in emotional cognition. In such patients, the ECDs calculated from P2 and the subsequent negative shift were generated in the parietal cortex along the intraparietal sulci, cingulate cortex, and retrosplenial cortex; the same dipoles in normal subjects migrated from the temporal and parietal lobes to the frontal lobe. Perception of static facial expressions—as compared with dynamic emotional perception—activated a motor,

Table 4. Location and number of the ECDs for P2 and the following negativity[a]

	Temporal lobe						Parietal lobe										Frontal lobe						Others							
	ITG		STG		ParaHC		SMG		AG		SPL		PoG		Precune		OrG		IFG		MFG		Cinglate		Retro		T		Cbll	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Non-target stimuli (neutral and surprised face)																														
Normal	7	8	4	1	7	9	0	0	2	2	2	8	2	2	0	4	8	0	3	1	10	1	7	2	3	6	2	0	4	2
PD	8	3	1	3	5	13	6	15	31	27	7	10	6	1	4	2	3	4	2	1	6	0	3	5	7	4	6	5	5	15
Target stimulus (fearful face)																														
Normal	0	3	1	0	0	1	0	0	2	3	2	1	0	0	0	0	4	0	1	0	1	3	1	0	2	0	0	0	0	2
PD	1	1	2	0	4	0	1	6	5	6	2	2	0	0	3	3	0	1	0	1	0	0	3	6	3	8	1	3	2	11

L=left, R=right

[a] AG, angular gyrus; Cbll, cerebellum; IFG, inferior frontal gyrus; ITG, inferior temproral gyrus; MFG, middle frontal gyrus; OrG, orbitofrontal gyrus; paraHC, parahippocampal gyrus; PoG, postcentral gyrus; precune, precuneus; retro, retrosplenial cortex; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; T, thalamus.

prefrontal, and parietal cortical network, which is involved in motor imagery (Kilts et al., 2003). The migration of the ECDs also raises the possibility that different mental strategies are involved in emotional processing in normal subjects and in patients with PD. Patients with mild symptoms of PD have been reported to perform cognitive tasks as accurately as normal subjects, although the pattern of activation (as measured by PET) in normal subjects differed from that of patients with PD (Owen and Doyon, 1999; Dagher et al., 2001). Similarly, corticostriatal connections may be variably affected by a lack of dopamine or by pathological changes in the amygdala during the recognition of facial expressions in patients with PD.

CONCLUSIONS

This study revealed that normal subjects and patients with PD use different neural substrates to recognize emotion in facial expressions. The ECDs for component N1 of the ERPs evoked by fearful facial expressions were located in the parietal-associated cortex, in patients with PD. In normal subjects, the dipoles for the same stimulus were generated in the fusiform gyrus, amygdala, parahippocampal gyrus, and superior temporal gyrus, and then moved to the left orbitofrontal gyrus and middle frontal gyrus. The mild deficits in the recognition of fear in facial expressions exhibited by patients with PD may be attributable to visual information, related to facial emotion being analyzed, using neural pathways that differ from those subserving this function in normal subjects.

Acknowledgments—We are grateful to Dr. T. Nagamine (Human Brain Research Center, Kyoto University Graduate School of Medicine) for technical advice, and to Prof. Y. Okamoto (Chiba Institute of Technology), Dr. M. Inoue (Department of Neurology, Showa University School of Medicine), and Prof. Y. Iwamura (Kawasaki University of Medical Welfare) for useful criticism of an earlier version of this manuscript.

This study was supported in part by a Showa University Grant-in-Aid for Innovative Collaborative Research Projects, a Special Research Grant-in-Aid for Development of Characteristic Education from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, and a Grant-in-Aid for Scientific Research on Priority Areas (c) from the Japanese Ministry of Education, Culture, Sports, Science and Technology (No.15590910).

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(Accepted 20 September 2004)
(Available online 22 January 2005)