of patients was significantly lower than that of controls (37.1±20.4 and 52.2±25.3 ng/ml in patients and controls, respectively; P=0.00003; Fig. 1A). The mean serum EGF level was also significantly lower in patients than in controls (395.5±231.7 vs. 560.7±357.1 pg/ml; P=0.002; Fig. 1B).

The relation between serum NF levels and age was examined. The age of both patient and control groups ranged from 21 to 59 years. As shown in Fig. 1C (BDNF), Fig. 1D (EGF) and Table 4, there were no significant correlations between serum NF levels and age in either group.

Because both BDNF and EGF were measured simultaneously within the same individuals, the correlation between serum BDNF and EGF was examined in each group. In the controls, a negative correlation between BDNF and EGF levels was found (r=−0.387, P=0.0002; Fig. 2A). In contrast, there was no significant correlation between the serum BDNF and EGF levels in the patients (P=0.161, Fig. 2B).

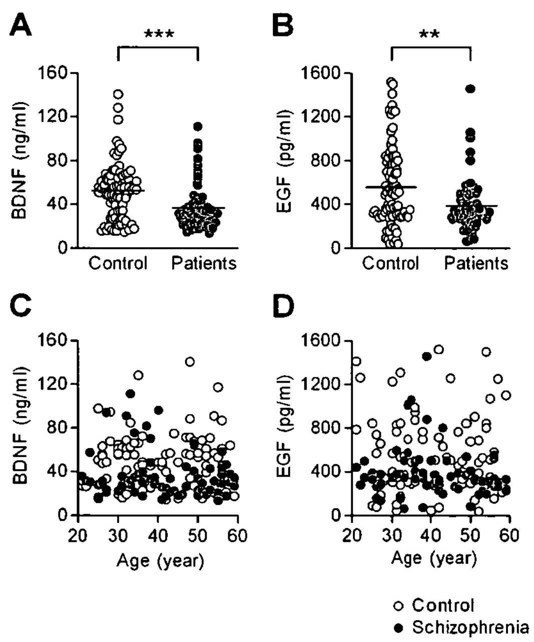

Fig. 1. Serum levels of (A) BDNF and (B) EGF measured by two-site enzyme immunoassay in normal controls (N=87) and patients with chronic schizophrenia (N=74). Compared with controls, patients exhibited lower serum levels of both neurotrophic factors (BDNF, ***P<0.001; EGF, **P<0.01). Horizontal lines indicate the mean levels. Distributions of serum (C) BDNF and (D) EGF levels in controls (open circles) and patients (filled circles) with age. No significant correlation was observed between NF levels and age (21–59 years) in the two groups. BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor.

Table 4
Correlations between levels of neurotrophic factors and clinical parameters in patients with schizophrenia

Clinical parameters		N	BDNF		EGF	
			r	P	r	P
Age		74	−0.031	0.795	−0.227	0.053
Age at onset		74	0.303	0.009	0.052	0.644
Duration of illness		74	−0.196	0.098	−0.281	0.016
CPZ-EQ (mg/day)		74	0.051	0.520	0.079	0.327
BMI (kg/m^2)		44	0.171	0.267	−0.088	0.569
GAF		33	0.024	0.843	−0.076	0.727
BPRS	Total	33	−0.099	0.588	0.349	0.046
	Positive	33	−0.189	0.303	0.347	0.047
	Negative	33	0.102	0.558	0.127	0.468

CPZ-EQ, Chlorpromazine Equivalents; BMI, Body Mass Index; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale.

Since the distribution of BDNF in the control group appeared bimodal as shown in Fig. 2A, we examined whether the low-BDNF group (40 ng/ml of BDNF as a tentative threshold for the dichotomy; N=26) and high-BDNF group (N=61) differed in their biological parameters. Statistical analyses revealed that there were no significant differences in their BMI (P=0.627), age (P=0.959), sex ratio (P=0.654), and smoking habit (P=0.464).

3.2. Correlation of serum BDNF and EGF levels with clinical parameters

Overall, clinical parameters did not exhibit robust correlations with the BDNF and EGF levels (P>0.05/10 [=0.005], corrected for multiple comparisons in Table 4 and Fig. 2B), although age at onset was marginally correlated with the BDNF level (r=0.303, P=0.009). We also analyzed the effects of BMI and smoking habit on NF levels. There were no significant correlations between serum NF levels and BMI in patients (P=0.267 for BDNF, P=0.569 for EGF, N=44) or in controls (P=0.687 for BDNF, P=0.697 for EGF, N=34). In addition, NF levels were not significantly different between the presence (N=11 for patients, N=16 for controls) and absence (N=12 for patients, N=18 for controls) of smoking habit in patients (P=0.735 for BDNF, P=0.132 for EGF) and in controls (P=0.569 for BDNF, P=0.593 for EGF).

3.3. Type of antipsychotic drugs and neurotrophic factor levels

Thirteen patients had been taking one or more typical antipsychotic drugs, while thirty-one other patients had been taking only atypical antipsychotic drugs. We found

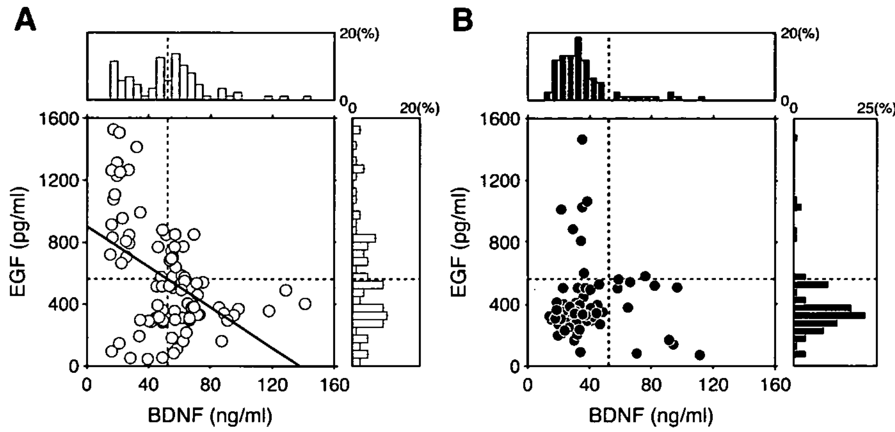

Fig. 2. Relation between the serum levels of BDNF and EGF measured simultaneously in (A) normal controls and (B) chronic schizophrenia patients. For controls, serum levels of the two neurotrophic factors were negatively correlated as shown by the line ($r=-0.387$, $P=0.0002$). The histograms above and on the right of the main plots show the fractions of subjects that fall into particular intervals of serum BDNF (in steps of 5 ng/ml) and EGF (in steps of 50 pg/ml) levels, respectively. In both histograms, dotted lines represent the mean levels of BDNF (52.2 ng/ml) and EGF (560.7 pg/ml) of normal controls, respectively. BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor.

that the levels of both BDNF and EGF did not differ between the patients taking typical and atypical antipsychotic drugs ($P>0.05$, Fig. 3A and B). In addition, there was no significant correlation between

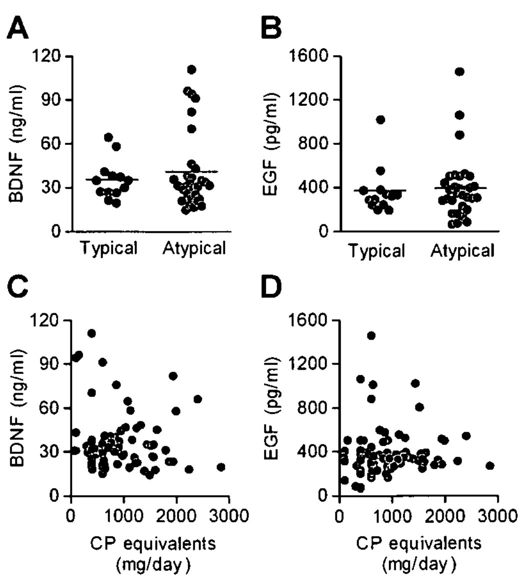

Fig. 3. Effects of antipsychotic drugs on serum (A) BDNF and (B) EGF levels. For both neurotrophic factors, no significant differences were seen between patients taking typical ($N=13$) and atypical ($N=31$) antipsychotic drugs. Horizontal lines indicate the mean levels. Antipsychotic dosages in chlorpromazine equivalents were correlated neither (C) with serum BDNF nor (D) with EGF levels ($N=74$). BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor; CP, chlorpromazine.

the chlorpromazine equivalents of medication and serum NF levels (Fig. 3C and D; Table 4).

We also analyzed the effects of anticholinergic drugs on the NF levels. Thirty-five patients had been taking anticholinergic drugs including biperiden and trihexyphenidyl in combination with antipsychotic drugs. NF levels were not significantly different between the patients with (BDNF, 37.9±20.1 ng/ml; EGF, 395.8±225.0 pg/ml; $N=35$) and without (BDNF, 36.3±20.9 ng/ml; EGF, 395.3±240.5 pg/ml; $N=39$) anticholinergic drugs ($P=0.626$ for BDNF, $P=0.475$ for EGF).

4. Discussion

4.1. Lower serum BDNF and EGF levels in schizophrenia

As summarized in Tables 1 and 2, previous studies have mostly reported low serum BDNF levels (Grillo et al., 2007; Pirildar et al., 2004; Tan et al., 2005; Toyooka et al., 2002; Zhang et al., 2007), while changes in the serum EGF level have remained a matter of controversy (Futamura et al., 2002; Hashimoto et al., 2005). In the present study, at least, it was clearly shown that most of the chronic schizophrenia patients had lower serum levels of EGF as well as BDNF. Mean serum BDNF values were 37.1 and 52.2 ng/ml in patients and controls, respectively, in the present study. These values were higher than those in several other reports, but, as can be seen in Table 1, BDNF levels varied considerably among the studies reported. Such differences may be due to the antibodies used against neurotrophic factors, the methods of measurement, and the sampling conditions. Actually, the

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values in the present study fell into a range similar of values to those in the reports adopting similar methods (Toyooka et al., 2002). In addition, this decrease in NFs was observed in patients regardless of age, ranging from the early 20s to the late 50s. This observation was consistent with previous reports showing no correlation between age and serum BDNF levels (Grillo et al., 2007; Huang and Lee, 2006; Toyooka et al., 2002), lending credence to the hypothesis that schizophrenia is the behavioral outcome of aberration in the neurodevelopmental processes.

In the present work, the simultaneous measurement of NFs revealed a significant negative correlation between serum BDNF and EGF levels in controls (Fig. 2A), whereas there was no correlation between the two NF levels in patients (Fig. 2B), possibly reflecting their low levels of both BDNF and EGF. The fact that no control subjects showed high serum levels of both BDNF and EGF is of particular interest. Neurite outgrowth from EGF-responsive stem cell-derived neurons can be enhanced by treatment with BDNF (Shetty and Turner, 1999), while BDNF reportedly induced the down-regulation of EGF receptors (Huang et al., 1988). In addition, the co-application of transforming growth factor-alpha, a member of the EGF family, with BDNF blocked the BDNF-triggered up-regulation of AMPA receptor expression and currents (Namba et al., 2006). Thus, complementary roles of both factors may underlie the normal development of the nervous system. In other words, chronic schizophrenia may represent a state deficient in NF-regulated neural functions, leading eventually to various mental malfunctions.

The origins of serum BDNF and EGF are not yet completely understood. EGF reportedly enters the brain through the blood-brain barrier (BBB) in mouse (Pan and Kastin, 1999). BDNF is reported to be transported across the BBB in normal mouse (Pan et al., 1998) and rats with cerebral ischemia (Schäbitz et al., 2000), while another report has argued that the transport of BDNF is negligible (Sakane and Pardridge, 1997). EGF and BDNF are produced in various peripheral tissues (Plata-Salamán, 1991; Radka et al., 1996), in addition to the central nervous system as described above. Nevertheless, the serum levels of NFs can be used as clinical markers, since they show different distributions between patients and controls, as shown in previous studies as well as in the present study.

4.2. Clinical parameters and neurotrophic factors

We failed to find any clinical parameters that demonstrated robust correlation with the two NF levels. As shown in Tables 1 and 2, previous reports also examined the correlation between clinical parameters and NF levels: the BDNF level was correlated with the negative symptom subscore of the Positive and Negative Syndrome Scale (Tan et al., 2005); the serum EGF level was significantly correlated with the BPRS score (Hashimoto et al., 2005). Although the reasons for the discrepancy between the previous and present results are unclear, differences in demographic characteristics of the patients (such as age at onset, illness duration, sample size, distribution of BPRS score, and dosage of antipsychotic drugs) might provide at least a partial explanation.

Other factors than psychiatric parameters have been reported to affect serum BDNF levels. BMI (Suwa et al., 2006) and age (Ziegenhorn et al., 2007) showed positive and negative correlation with BDNF levels, respectively. Patients with atopic dermatitis have higher levels of serum BDNF in association with the severity of symptoms (Raap et al., 2005; Namura et al., 2007), while smokers have lower values as compared with non-smokers (Kim et al., 2007). We could not completely rule out the possibility that these factors affected the values in the present study, since data could not be obtained from all participants. However, the limited data suggested that neither BMI nor smoking habit affected neurotrophic levels in patients or controls.

4.3. Types of antipsychotic drugs and serum neurotrophic factor levels

In the present study, the NF levels were not correlated with any types or dosages of medications. Although Grillo et al. (2007) found a significant correlation between the BDNF level and clozapine dosage, other investigators found no significant correlation between BDNF (Hori et al., 2007; Shimizu et al., 2003; Tan et al., 2005; Toyooka et al., 2002; Zhang et al., 2007) or EGF level (Futamura et al., 2002) and antipsychotic dosages. In addition, treatment with olanzapine for 8 weeks (Hori et al., 2007) or antipsychotic drugs (risperidone for most patients) for 6 weeks (Pirildar et al., 2004) did not alter BDNF levels in blood. It was recently suggested that the effects of atypical and typical antipsychotic drugs on the BDNF level were different. In animal experiments, haloperidol, a typical antipsychotic drug, decreased the BDNF expression in the hippocampus, whereas atypical antipsychotics did not affect or even up-regulated this expression (Bai et al., 2003; Chlan-Fourney et al., 2002; Parikh et al., 2004). In addition, atypical antipsychotics, but not haloperidol, stimulated neurogenesis in the subventricular zone of the rat brain (Wakade et al., 2002). Clinically, chronic treatment with haloperidol, but not olanzapine, was associated with a significant reduction in gray matter volume in schizophrenia patients with first-

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episode psychosis (Lieberman et al., 2005). However, the present study failed to show that the type of drug affects either the BDNF or the EGF serum level. This observation might indicate a limitation concerning the measurement of serum NFs for predicting their function in the brain. Nevertheless, the serum levels of NFs could be used as clinical markers from the viewpoint that they are independent of the type of medication used.

In conclusion, we showed herein that patients with chronic schizophrenia have lower serum levels of both BDNF and EGF across all ages, possibly reflecting pervasive abnormal signaling of NFs underlying the pathophysiology of schizophrenia. A future study should investigate NFs of patients with schizophrenia before pharmacological intervention or those undergoing the first-episode of the disease, thereby addressing whether this overall reduction in NFs is a common characteristic in the symptomatology of schizophrenia.

Role of funding source

Funding for this study was provided by a Grant-in-Aid for Science Research (C) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan, to H. S. (No. 1659028), a Grant-in-Aid for Encouragement of Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS) to N. Y. (No. 18790852) and to Y. I. (No. 17790821). MEXT and JSPS had no further role in the study design, collection, analysis and interpretation of data, writing of the report, and the decision to submit the paper for publication.

Contributors

Y.I. measured the concentrations of BDNF and EGF proteins, analyzed the data and wrote the manuscript. N.Y. undertook the statistical analyses of whole data including neurotrophic factor levels and demographical data, and wrote the manuscript. M.N. developed the two-site enzyme immunoassay for BDNF and EGF and measured the concentrations of BDNF and EGF proteins. I.I, T.T and T.Y recruited the subjects for this project and collected blood samples. Y.O and H.S designed and supervised the whole study and wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgments

We are grateful to all the subjects who participated in the study. We also thank the staff of Asai hospital for their assistance in collecting the demographic data.

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Please cite this article as: Ikeda, Y., et al., Low serum levels of brain-derived neurotrophic factor and epidermal growth factor in patients with chronic schizophrenia, Schizophr. Res. (2008), doi:10.1016/j.schres.2008.01.017

Cerebral Cortex Advance Access published January 17, 2008

Cerebral Cortex
doi:10.1093/cercor/bhm214

Neural Correlates of Human Virtue Judgment

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Neuroimaging studies have demonstrated that the brain regions implicated in moral cognition. However, those studies have focused exclusively on violation of social norms and negative moral emotions, and very little effort has been expended on the investigation of positive reactions to moral excellence. It remains unclear whether the brain regions implicated in moral cognition have specific roles in processing moral violation or, more generally, process human morality per se. Using functional magnetic resonance imaging, brain activations during evaluation of moral beauty and depravity were investigated. Praiseworthiness for moral beauty was associated with activation in the orbitofrontal cortex, whereas blameworthiness for moral depravity was related to the posterior superior temporal sulcus. Humans might have developed different neurocognitive systems for evaluating blameworthiness and praiseworthiness. The central process of moral beauty evaluation might be related to that of aesthetic evaluation. Our finding might contribute to a better understanding of human morality.

Keywords: blameworthiness, moral, orbitofrontal cortex, praiseworthiness, superior temporal sulcus, virtue

Introduction

The emerging field of cognitive neuroscience is providing new insights into the neural basis of moral cognition and behaviors. As David Hume (1978) and Adam Smith (1976) already noted in the 18th century, some contemporary philosophers have emphasized the importance of emotion and intuition in moral judgment, although moral reasoning could contribute to moral judgment (Haidt 2001; Greene and Haidt 2002). Supporting this view, recent neuroimaging studies and brain lesion studies have demonstrated that emotion-related brain regions such as the posterior superior temporal sulcus (pSTS), medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), and amygdala play important roles in moral judgment (Damasio 2000; Greene and Haidt 2002; Takahashi et al. 2004; Moll et al. 2005). Previous psychological as well as neuroimaging studies mainly focused on violation of social norms and negative moral emotions such as guilt or embarrassment (Greene and Haidt 2002; Haidt 2003a, 2003b; Takahashi et al. 2004; Moll et al. 2005; Mobbs et al. 2007). Morals are standards or principles of right or wrong behaviors and the goodness or badness of human character. It remains unclear whether the brain regions implicated in moral cognition are specialized in processing immorality, that is, negative deviance from social norms or, more generally, processing deviance from social standards regardless of whether the stimuli positively or negatively deviate from them. There has been very little study on positive moral emotions or psychological responses to moral beauty, but with the advent of the positive psychology movement (Seligman and Csikszentmihalyi 2000), researchers have started to focus on positive moral emotions. Many people experience spontaneous pleasure when they can help others without any expectation of reward. Neuroimaging studies suggest that cooperative behaviors might be psychologically rewarding (Rilling et al. 2002; de Quervain et al. 2004; Moll et al. 2006). It is also human nature that we are easily and strongly moved by people who are cooperating with others. Haidt (2003a, 2003b) started to call an emotion elicited by others' act of virtue or moral beauty as "elevation." When people observe others' virtuous, commendable acts, they feel warm, pleasant, and "tingling" feelings and are motivated to help others and to become better people themselves. Hume (1978) wrote that "a generous and noble character never fails to charm and delight us" and Smith (1976) noted that "man desires, not only praise, but praiseworthiness." We also could have an aesthetic feeling in human virtuous acts and be often attracted by the beauty itself (Haidt 2003a). However, there are very few studies to have concentrated on this aspect of moral beauty. According to Haidt (2003a), we cannot have a full understanding of human morality until we can explain why and how people are so powerfully affected by the sight of a stranger helping another stranger.

For the evolution and persistence of cooperation, it is necessary for humans to detect cheaters and cooperators. Otherwise, selfish strategies will eliminate cooperative strategies (Axelrod and Hamilton 1981; Cosmides and Tooby 1992). Cosmides and Tooby (1992) argued that humans have evolved neurocognitive systems that specialize in detecting "cheating," violation of social contracts, and that produce a feeling that those who violate social norms should be blamed and punished. In fact, functional magnetic resonance imaging (fMRI) studies reported activation in brain regions such as pSTS and MPFC during detection of violation of social contracts (Canessa et al. 2005; Fiddick et al. 2005). On the other hand, it is also argued that humans have evolved a neurocognitive system that skillfully assesses the cooperativeness of others (Price 2006), and empirical evidence suggests that people will cooperate with those whom they have observed cooperating with others (Wedekind and Milinski 2000; Milinski et al. 2002). However, there is as yet no documented study regarding the investigation of the neural correlates during the observance of praiseworthy, virtuous acts of others.

In this study, we investigated the brain activation associated with the judgment of moral beauty, virtue, comparing it with that of moral depravity, vice. We hypothesized that the judgment of moral beauty and depravity would show different brain activation patterns. Specifically, moral depravity would be linked to brain regions, such as pSTS and MPFC, and moral beauty would recruit the brain regions implicated in positive emotions, such as OFC.

Materials and Methods

Participants

Fifteen healthy volunteers (mean age 20.1 years, standard deviation [SD] = 0.8) participated in this study. All subjects were Japanese and right-handed. The participants were free of any criteria for neuropsychiatric disorders based on unstructured psychiatric screening interviews. None of the participants were taking alcohol at the time nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. All participants underwent an MRI to rule out cerebral anatomic abnormalities. After complete explanation of the study, written informed consent was obtained from all participants and the study was approved by the Institutional Ethics Committee.

Materials

Three types of short sentences were provided (neutral, moral beauty, and moral depravity). Each sentence was written in Japanese and in the 3rd person. Sentences of moral depravity were expressing moral violation, and those of moral beauty were expressing acts like charity, self-sacrifice, altruism, humanitarianism, and so on. Neutral sentences were expected to express no prominent emotional content. In order to validate our expected results, we conducted an initial survey. We prepared 30-35 sentences for each of 3 conditions (neutral, moral beauty, and moral depravity). Forty-two other healthy volunteers (21 males and 21 females, mean age 22.5 years, SD = 3.3) than the subjects participating in this fMRI study were screened. Using 7-point Likert scales, they read and rated each sentence in terms of morality/immorality (−3 = extremely immoral, 0 = neither moral nor immoral, and 3 = extremely moral) and praiseworthiness/blameworthiness (−3 = extremely blameworthy, 0 = neither praiseworthy nor blameworthy, and 3 = extremely praiseworthy). Based on the initial survey, we selected 18 sentences for each of the 3 conditions. These sentences are shown in Supplementary Table S1. The sentences were projected via a computer and a telephoto lens onto a screen mounted on a head coil. The subjects were instructed to read the sentences silently and were told to imagine the events described in the sentences. They were also told that they should rate the sentences according to how moral/immoral or praiseworthy/blameworthy the events were. After reading each sentence, the subjects were instructed to press a selection button with the right index finger, indicating that they had read and understood it. The experimental design consisted of 6 blocks for each of the 3 conditions (neutral, moral beauty, and moral depravity) interleaved with 20-s rest periods. We used a block design rather than an event-related design as it is difficult to obtain sufficient understandable stimuli, that is, depictions of moral beauty and depravity are difficult to parse rapidly (Luo et al. 2006). The order of presentation for the 3 conditions was randomized. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In each 24-s block, 3 different sentences of the same condition were presented for 8 s each. Using 7-point Likert scales, the participants rated each sentence in terms of morality/immorality and praiseworthiness/blameworthiness after the scans.

Image Acquisition

Images were acquired with a 1.5 Tesla Signa system (General Electric, Milwaukee, WI). Functional images of 203 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; time echo [TE], 50 ms; time repetition [TR], 4 s; matrix, 64 × 64; and field of view, 24 × 24 cm). High-resolution, T1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices, 3-dimensional Spoiled-Grass sequence, slice thickness 1.5 mm; TE, 9 ms; TR, 22 ms; flip angle, 30°; matrix, 256 × 192; and field of view, 25 × 25 cm).

Analysis of Functional Imaging Data

Data analysis was performed with statistical parametric mapping software package (SPM02) (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (Mathworks, Natick, MA). All volumes were realigned to the 1st volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute template. After normalization, all scans had a resolution of 2 × 2 × 2 mm^3. Functional images were spatially smoothed with a 3-dimensional isotropic Gaussian kernel (full width at half maximum of 8 mm). Low frequency noise was removed by applying a high-pass filter (cutoff period = 192 s) to the fMRI time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convolved with a hemodynamic response function. Statistical parametric maps for each contrast of the t-statistic were calculated on a voxel-by-voxel basis.

To assess the specific condition effect, we used the contrasts of the moral beauty minus neutral (MB − N) and moral depravity minus neutral (MD − N). A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. This procedure provides a better generalization for the population from which data are obtained. The contrast images were obtained from single-subject analysis and entered into the group analysis. A 1-sample t-test was applied to determine group activation for each effect. We used SPM's small volume correction to correct for multiple testing in regions about which we had a priori hypothesis. These a priori volumes of interest (VOIs) included the pSTS, MPFC, and OFC. VOIs for pSTS (angular gyrus), MPFC (superior and medial frontal gyrus), and OFC (inferior frontal gyrus) were defined by standardized VOI templates implemented in brain atlas software (Maldjian et al. 2003). Significant activations surviving this correction at $P < 0.05$ are reported. We describe activations outside regions of interest surviving a threshold of $P < 0.001$, uncorrected, with an extent threshold of 10 contiguous voxels. To assess common activation in MB − N and MD conditions, we conducted a conjunction analysis of MB − N and MD − N contrasts at the 2nd level.

We conducted regression analysis to demonstrate a more direct link between regional brain activities with the subjective judgments of praiseworthiness and blameworthiness. Using the mean of the ratings of praiseworthiness and blameworthiness for each subject as the covariate, regression analysis with the contrasts (MB − N and MD − N) and the covariate was performed at the 2nd level. The masks of MB − N and MD − N contrasts from the 1-sample t-test ($P < 0.001$) were applied to confine the regions where significant activations were observed. Using the effect sizes, representing the percent signal change, of the contrasts (MB − N and MD − N) at the peak coordinates uncovered by regression analysis, we plotted the fMRI signal changes and ratings of praiseworthiness and blameworthiness.

Results

Initial Survey

As we predicted, neutral sentences were judged neither moral/praiseworthy nor immoral/blameworthy. The averages of the ratings of morality/immorality and praiseworthiness/blameworthiness for neutral sentences were 0.0 (SD = 0.1) and 0.0 (SD = 0.1), respectively. The average of ratings of morality and praiseworthiness for 18 sentences of moral beauty were 2.3 (SD = 0.8) and 1.8 (SD = 0.9), respectively. The average of ratings of immorality and blameworthiness for 18 sentences of moral depravity were -2.4 (SD = 0.7) and -2.1 (SD = 0.8), respectively.

Self-Rating

The self-rating results of the subjects participating in the fMRI study were comparable to the results obtained in the initial survey. The averages of the ratings of morality/immorality and praiseworthiness/blameworthiness for neutral sentences were 0.1 (SD = 0.2) and 0.0 (SD = 0.1), those of morality and praiseworthiness for sentences of moral beauty were 2.5 (SD = 0.3) and 2.1 (SD = 0.5), and those of immorality and blameworthiness for sentences of moral depravity were -2.4 (SD = 0.3) and -2.1 (SD = 0.4), respectively. Self-ratings of immorality were correlated with blameworthiness ($r = 0.58$, $P = 0.025$), and those of morality were correlated with praiseworthiness ($r = 0.68$, $P = 0.005$).

fMRI Result

The MB-N condition produced activations in the left OFC, left dorsal lateral prefrontal cortex (DLPFC), left supplementary motor area (SMA), left temporal pole, and visual cortex, (Table 1 and Fig. 1*A*). The MD - N condition produced activations in the left pSTS and MPFC (Table 1 and Fig. 1*B*). The activations in a priori regions (pSTS, MPFC, and OFC) survived a threshold of $P < 0.05$ corrected for multiple comparisons across a small VOI. A conjunction analysis of MB - N and MD - N contrast revealed no significant activations.

Regression analysis revealed positive linear correlations between self-rating of praiseworthiness and the degree of activation in the left OFC ($x = -38$, $y = 28$, and $z = -20$) in MB - N contrast (Figs 2*A* and 3*A*). There were correlations between self-rating of blameworthiness and the degree of activation in the left pSTS ($x = -54$, $y = -66$, and $z = 28$) in MD - N contrast (Figs 2*B* and 3*B*). Theses correlations in a priori regions (pSTSC and OFC) survived a threshold of $P < 0.05$ corrected for multiple comparisons across a small VOI.

Table 1
Brain activations in moral beauty condition and moral depravity condition relative to neutral condition

Brain region	L/R	Coordinates			Z-score
		x	y	z	
Moral beauty-neutral					
Visual cortex	L/R	14	−90	−8	4.59
OFC*	L	−40	32	−20	3.39
Temporal pole	L	−50	18	−24	3.51
SMA	L	−48	0	48	3.52
DLPFC	L	−52	26	14	3.30
Moral depravity-neutral					
MPFC*	L/R	6	58	14	4.35
pSTS*	L	−54	−64	30	3.40

Note: Coordinates and Z-score refer to the peak of each brain region. L, left; R, right. All values, $P < 0.001$, uncorrected. *$P < 0.05$, corrected for multiple comparisons across a small VOI.

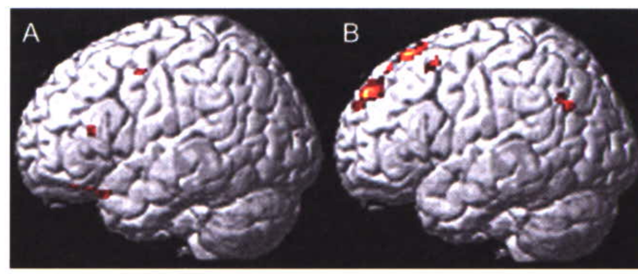

Figure 1. Images showing brain activations in response to (*A*) MB − N condition and (*B*) MD − N condition. (*A*) Significant activation in OFC is shown. (*B*) Significant activations in MPFC and pSTS are shown.

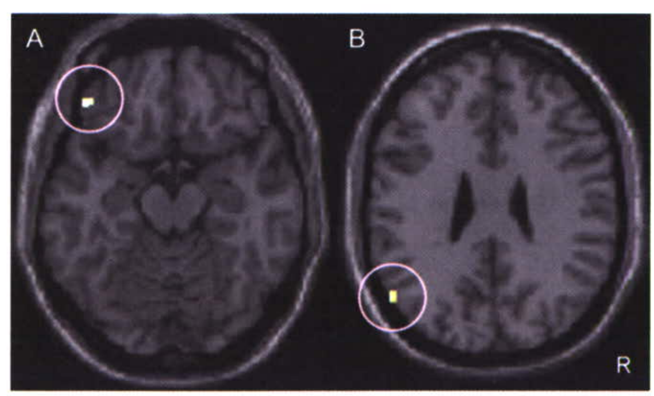

Figure 2. Correlations between self-ratings of (*A*) praiseworthiness (*B*) blameworthiness and brain activations. (*A*) Correlation between self-rating of praiseworthiness and degree of activation in left OFC in MB − N contrast. (*B*) Correlations between self-rating of blameworthiness and degree of activation in pSTS in MD − N contrast. Within the images, R indicates right. Numbers at bottom indicate coordinates of Montreal Neurological Institute brain.

Discussion

This study has demonstrated that the brain activations during evaluation of positive deviance from the moral standard, moral beauty, showed different patterns from those of negative deviance, moral depravity. In line with previous reports, moral depravity conditions relative to neutral condition produced greater activity in the left pSTS and MPFC, the components of neural substrates that have been suggested to be involved in human moral cognition (Takahashi et al. 2004; Moll et al. 2005). A novel finding in this study was that moral beauty conditions relative to neutral condition produced greater activity in the left frontal regions, such as OFC, DLPFC, and SMA. This means that the regions suggested to play important roles in moral cognition are more specialized in processing moral violation and do not cover human morality per se.

Although self-ratings of immorality were correlated with blameworthiness and those of morality were correlated with praiseworthiness, empirical evidence suggests that blameworthiness for immoral acts and praiseworthiness for commendable or cooperative acts were not symmetrical. In other words, blameworthiness for impulsive immoral acts without deliberate intention was discounted compared with deliberate immoral acts, whereas praiseworthiness for commendable acts was not discounted regardless of whether the positive acts were impulsive or deliberate (Pizarro et al. 2003). This is also common in legal culpability. This means that people tend to link blameworthiness to intention and the process of wrongdoing, whereas they tend to link praiseworthiness to outcomes of positive acts regardless of deliberate intention or not.

Figure 3. Regression lines of correlations between (*A*) praiseworthiness (*B*) blameworthiness and degree of brain activation. (*A*) There were correlations ($r = 0.82$, degrees of freedom [df] = 13, $P < 0.001$) between self-rating of praiseworthiness and degree of activation in OFC. (*B*) There were positive linear correlations ($r = -0.83$, df = 13, $P < 0.001$) between self-rating of blameworthiness and degree of activation in pSTS.

Moral depravity produced activation in the pSTS and MPFC, and the degree of pSTS activation was correlated with blameworthiness. Originally, STS was known to be activated by biological motions such as movement of eyes, mouth, hands, and body (Allison et al. 2000), and it has been suggested to have a more general function in social cognition such as detecting behavioral information that signals the intention of others (Gallagher and Frith 2003) and behavior of agents (Frith U and Frith CD 2003). MPFC appears to be responsible for inferring the cause of others' behavior, attribution. Previous studies have shown activation in the MPFC during judgments made on the basis of attributional information (Amodio and Frith 2006). It is suggested that, for the evolution and persistence of cooperation, humans have evolved neurocognitive systems that specialize in the detection of cheating and that motivate people to blame and punish those who violate social norms (Cosmides and Tooby 1992). Supporting this view, recent fMRI studies reported activation in brain regions such as the pSTS and MPFC during detection of the violation of social contracts (Canessa et al. 2005; Fiddick et al. 2005). Considering the functions of pSTS and MPFC, these regions might process intention of wrongdoings and, consequently, blameworthiness might be associated with the activation in pSTS.

The lack of activation in the pSTS and MPFC in response to moral beauty supports psychological studies in which people do not put a premium on the deliberate intention of commendable acts. Instead, correlation between the subjective ratings of praiseworthiness and the degrees of activation in the left OFC suggests that they regard positive outcome itself rather than intention of the act to be a main factor for praiseworthiness because the OFC is known to be involved in processing reward (Rolls 2006) and positive stimuli such as pictures (Northoff et al. 2000), taste (Small et al. 2003), and music (Blood and Zatorre 2001). It is also reported that the OFC was associated with maternal love (Bartels and Zeki 2004; Nitschke et al. 2004). The association between OFC activation and self-rating of praiseworthiness could be regarded as corresponding to Smith's phrase "The love of praiseworthiness" (Smith 1976).

Previous functional imaging studies have investigated the neural correlates processing facial beauty (Aharon et al. 2001; O'Doherty et al. 2003) or aesthetic beauty such as shapes or arts (Kawabata and Zeki 2004; Vartanian and Goel 2004; Jacobsen et al. 2006), and activation of reward-related subcortical and limbic areas including the OFC was reported. The connection between aesthetic judgment and moral feeling has long been emphasized in aesthetic theory (Kant 1952). Our finding could be interpreted in the context of aesthetic theory, that is, the neurocognitive system processing moral beauty might be related to that of aesthetic beauty.

We observed activation in other prefrontal areas in the left hemisphere, such as DLPFC and SMA, although activation in these unpredicted areas needs to be interpreted with caution. It is still unclear whether there is a hemispheric specialization in the processing of moral cognition, but it is suggested that frontal regions in the left hemisphere are associated with approach behavior, whereas frontal areas in the right hemisphere are associated with avoidance (Davidson 1992). Previous studies reported activation in the motor area in response to positive stimuli such as paintings, music, money, humor, and concepts (Blood and Zatorre 2001; Elliott et al. 2003; Mobbs et al. 2003; Kawabata and Zeki 2004; Cunningham et al. 2005). Although the exact role of the motor area in such tasks is not well known, it is suggested that the positive stimuli might mobilize the motor system to take some action toward them.

Although domain-specific emotional response is suggested to play a central role in moral judgments, domain-neutral reasoning could play certain roles as well (Haidt 2001; Greene and Haidt 2002). In a predictable situation, context-independent knowledge of event is processed automatically and routinely. This domain-specific process is suggested to be mediated in the medial and ventral prefrontal cortex. On the other hand, in a less predictable situation, context-dependent knowledge of event is processed with the operation of domain-neutral reasoning, which is suggested to be mediated in the DLPFC (Greene and Haidt 2002; Moll et al. 2005). It is also widely argued that emotions evolved to promote quick and automatic reaction in life-threatening situations (Fredrickson 1998). Although these models have been well fitted for negative emotions, quick and decisive actions are not typically required in a situation that gives rise to positive emotions. Instead, a wider range of thoughts or actions is required in situations where positive emotions occur (Fredrickson 1998). The DLPFC was reported to be recruited during evaluation of natural or artistic aesthetic stimuli (Cela-Conde et al. 2004). Although the exact role of the DLPFC in aesthetic evaluation remains unclear, our results suggested that context-dependent knowledge contributes to the evaluation of moral beauty.

In conclusion, evaluation of moral excellence and moral violation might be processed differently in the human brain. However, any generalization of our findings needs to be approached with caution as the social background of the participants, such as culture, generation, religion, and education, could affect the results. Still, our results suggest that humans might have developed different neurocognitive systems for evaluating blameworthiness (cheaters) and praiseworthiness (cooperators). Our finding might contribute to a better understanding of the neural basis of human morality.

Supplementary Matrial

Supplementary table S1 can be found at: http://www.cercor.oxfordjournals.org/.

Funding

Molecular Imaging Program on "Research Base for PET Diagnosis" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government, a Grant-in-Aid for Scientific Research from the MEXT (15390438); a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health from the Japanese Ministry of Health, Labor and Welfare (H19-KOKORO-004).

Notes

Conflict of Interest: None declared.

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Cerebral Cortex April 2008;18:898-903
doi:10.1093/cercor/bhm120
Advance Access publication July 17, 2007

Brain Activations during Judgments of Positive Self-conscious Emotion and Positive Basic Emotion: Pride and Joy

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We aimed to investigate the neural correlates associated with judgments of a positive self-conscious emotion, pride, and elucidate the difference between pride and a basic positive emotion, joy, at the neural basis level using functional magnetic resonance imaging. Study of the neural basis associated with pride might contribute to a better understanding of the pride-related behaviors observed in neuropsychiatric disorders. Sixteen healthy volunteers were studied. The participants read sentences expressing joy or pride contents during the scans. Pride conditions activated the right posterior superior temporal sulcus and left temporal pole, the regions implicated in the neural substrate of social cognition or theory of mind. However, against our prediction, we did not find brain activation in the medial prefrontal cortex, a region responsible for inferring others' intention or self-reflection. Joy condition produced activations in the ventral striatum and insula/operculum, the key nodes of processing of hedonic or appetitive stimuli. Our results support the idea that pride is a self-conscious emotion, requiring the ability to detect the intention of others. At the same time, judgment of pride might require less self-reflection compared with those of negative self-conscious emotions such as guilt or embarrassment.

Keywords: medial prefrontal cortex, positive emotions, pride, superior temporal sulcus, theory of mind, ventral striatum

Introduction

Although there have been numerous neuroimaging studies on basic emotions (fear, disgust, happiness, and sadness) that have led to a better understanding of the neuroanatomical correlates of emotions (Lane et al. 1997; Phan et al. 2002), only a few studies on complex social emotions such as guilt, embarrassment, and jealousy have been reported (Shin et al. 2000; Berthoz et al. 2002; Takahashi et al. 2004, 2006).

We previously examined brain activation associated with negative self-conscious emotions, guilt, and embarrassment (Takahashi et al. 2004). Self-conscious emotions are founded in social relationship and arise from concerns about others' evaluations of self (Eisenberg 2000; Tangney and Dearing 2002; Haidt 2003; Kalat and Shiota 2006). In other words, one needs the ability to represent the mental states of others, that is, theory of mind (ToM), to recognize self-conscious emotions. Negative evaluation of self or the behavior of self is fundamental to guilt and embarrassment, whereas positive evaluation of self leads to the emotion of pride. Negative self-conscious emotions promote moral behavior and interpersonal etiquette (Eisenberg 2000; Haidt 2003). Impairment of processing these emotions could lead to amoral, socially inappropriate behaviors observed in neuropsychiatric disorders (Beer et al. 2003; Miller et al. 2003; Sturm et al. 2006).

Supporting the notion that self-conscious emotions involve inferences about others' evaluation of self (Leary 2007), judgment of guilt and embarrassment produced activations in the medial prefrontal cortex (MPFC), posterior superior temporal sulcus (pSTS), and temporal poles (Takahashi et al. 2004; Kalat and Shiota 2006), the regions implicated in ToM, social cognition (Adolphs 2001; Calarge et al. 2003; Frith U and Frith CD 2003; Gallagher and Frith 2003), and moral judgment (Greene and Haidt 2002; Moll et al. 2005).

In contrast, a positive self-conscious emotion, pride has been largely unstudied by researchers. Pride refers to self-esteem, joy, or pleasure derived from achievements. It arises when people believe that they are responsible for desired outcomes (Leary 2007). As a self-conscious emotion, pride also drives people to behave in moral, socially appropriate ways (Tracy and Robins 2004a). Specifically, the "achievement-oriented" form of pride promotes prosocial behaviors, such as caregiving and achievement (Tracy and Robins 2004b). However, the hubristic form of pride could be maladaptive, and impairment of processing pride could be related to some psychiatric disorders. Narcissistic personality disorder is characterized by a grandiose sense of self-importance and lack of empathy (American Psychiatric Association 1994). It was reported that empathy and ToM rely on common networks, the MPFC, pSTS, and temporal poles (Vollm et al. 2006). Therefore, the hubristic form of pride could be regarded as a dysfunction of ToM. Affective disorder could also be linked to impairment of the processing of pride. Manic state is a condition with inflated self-esteem, whereas depressive episode could be a condition with low self-esteem (American Psychiatric Association 1994). Studying the neural substrates associated with pride should add to the understanding of the neural basis of these neuropsychiatric disorders.

We aimed to measure brain activations associated with the judgment of pride by showing scenarios, comparing them with brain activations associated with the primary positive emotion, joy, using functional magnetic resonance imaging (fMRI). We hypothesized that joy and pride conditions would show different brain activation patterns, and specifically, that joy condition would activate brain regions involved in hedonic processing, for example, the ventral striatum (Mobbs et al. 2003, 2005; Britton et al. 2006), whereas pride condition would activate the brain regions involved in social cognition (Adolphs 2001) or ToM (Calarge et al. 2003; Frith U and Frith CD 2003; Gallagher and Frith 2003), for example, MPFC, pSTS, and temporal poles.

Materials and Methods

Participants

Sixteen healthy right-handed Japanese university students (8 men, mean age 21.5 years, standard deviation [SD] = 2.2; 8 women, mean age 21.3 years, SD = 1.3) were studied. Their mean educational achievement level was 14.4 years (SD = 1.3). They did not meet any criteria for psychiatric disorders. None of the controls were taking alcohol or medication at the time nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. All subjects underwent an MRI to rule out cerebral anatomic abnormalities. After complete explanation of the study, written informed consent was obtained from all subjects, and the study was approved by the Ethics Committee.

Materials

Three types of short sentences were provided (neutral, joy, and pride). Each sentence was written in Japanese and in the first person, past tense. Each sentence was expected to express joy, pride, or no prominent emotional content. We used joyful scenarios depicting hedonic, appetitive, and survival events like eating, reproduction, and economic behaviors because these stimuli are thought to be directly related to "basic" positive emotional processing. For most of the pride sentences, we used scenarios in which the protagonist was a winner of a prize or competition as a result of achievement. In order to validate our expected results, we conducted an initial survey. Other university students (20 men and 20 women, mean age 22.5 years, SD = 3.3) than the subjects participating in this fMRI study were screened. We prepared 28-32 sentences for each of 3 conditions (neutral, joy, and pride). The described situations were rated according to how joyful or proud they were using a 7-point analog scale (0 = none, 6 = extremely intense). Based on the initial survey, we selected 18 sentences for each of the 3 conditions. The selected joy sentences were judged to express joy. The mean rating of joy was 4.3 (SD = 0.5). The selected pride sentences were judged to express pride. The mean rating of pride was 4.5 (SD = 0.3). The neutral sentences were judged to express virtually no joy or pride. The mean ratings of joy and pride for neutral sentences were 0.7 (SD = 0.3) and 0.4 (SD = 0.2), respectively. Examples of the sentences are shown in Table 1. The sentences were projected via a computer and a telephoto lens onto a screen mounted on a head coil. The subjects were instructed to read the sentences silently and were told to imagine that the scenario protagonist was himself/herself. They were also told that they should rate the sentences according to how joyful or pride instilling the situations were. After reading each sentence, the subjects were instructed to press a selection button with the right index finger, indicating that they had read and understood it. The experimental design consisted of 6 blocks for each of the 3 conditions (neutral, joy, and pride) interleaved with 20-s rest periods. The order of presentation for the 3 conditions was randomized. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In each 24-s block, 3 different sentences of the same emotional class were presented for 8 s each. After the scan, the subjects read the sentences presented during the scan, and they were asked to rate the sentences according to how they would feel if the scenario protagonist were himself/herself. The participants rated the intensity of joy, pride, and other emotions (anger, sadness, fear, disgust, and shame) for each sentence using a 7-point analog scale.

Table 1
Examples of sentences

Neutral	I took a class at the college. I had breakfast. I watched the Olympics on TV. I recorded a baseball game on video tape. I prepared for an examination. I went to school yesterday. I watched sports news on TV. I bought a medicine for cold.
Joy	I won a lottery. I won at gambling at a casino. I ate my favorite cake. I had a date with my girl/boy friend. I had a delicious dinner. I received a Christmas present. I went to Hawaii with my friends. I was gifted with a bouquet on my birthday.
Pride	I was awarded a prize for my novel. I won the championship in a golf tournament. I got a perfect score in mathematics. I graduated at the head of my class. I won the first prize in a piano contest. I graduated from the most prestigious university. I obtained a scholarship. I won a prize at a scientific meeting.

Images Acquisition

Images were acquired with a 1.5-Tesla Signa system (General Electric, Milwaukee, WI). Functional images of 203 volumes were acquired with T_2^*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; time echo [TE], 50 ms; time repetition [TR], 4 s; matrix, 64 × 64; field of view, 24 × 24 cm). High-resolution, T_1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices, 3-dimensional [3D] spoiled Grass sequence, slice thickness 1.5 mm, TE, 9 ms; TR, 22 ms; flip angle, 30°; matrix, 256 × 192; field of view, 25 × 25 cm).

Analysis of Functional Imaging Data

Data analysis was performed with statistical parametric mapping software package (SPM02) (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (Mathworks, Natick, MA). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute template. After normalization, all scans had a resolution of 2 × 2 × 2 mm^3. Functional images were spatially smoothed with a 3D isotropic Gaussian kernel (full width at half maximum of 8 mm). Low-frequency noise was removed by applying a high-pass filter (cutoff period = 192 s) to the fMRI time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convoluted with a hemodynamic response function. Statistical parametric maps for each contrast of the t-statistic were calculated on a voxel-by-voxel basis.

To assess the specific condition effect, we used the contrasts of joy minus neutral (J-N), pride minus neutral (P-N), and pride minus joy (P-J). A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. This procedure provides a better generalization for the population from which data are obtained. The contrast images were obtained from single-subject analysis and entered into the group analysis. A one-sample t-test was applied to determine group activation for each effect. To assess common activation in P-N and J-N conditions, we conducted a conjunction analysis of P-N and J-N contrasts at the second level. A statistical threshold of $P < 0.05$ corrected for multiple comparisons across the whole-brain was used, except for a priori hypothesized regions, which were thresholded at $P < 0.0005$ uncorrected (only clusters involving 10 or more contiguous voxels are reported). These a priori regions of interest included the ToM-related regions (MPFC, pSTS, and temporal poles), reward/food-related regions (striatum, insula, and orbitofrontal cortex), and emotion-related limbic regions (amygdalohippocampal regions and anterior cingulate cortex). We conducted regression analyses to demonstrate a more direct link between regional brain activities with the subjective judgments of joy and pride. Using the mean of the ratings of joy and pride for each subject as the covariate, regression analyses with the contrasts (J-N and P-N) and the covariate were done at the second level (height threshold at $P <$ 0.001, uncorrected, and extent threshold of 5 voxels). The masks of J-N and P-N contrasts from one-sample t-test ($P < 0.001$) were applied to confine the regions where significant activations were observed. Using the effect sizes, representing the percent signal changes, of the contrasts (J-N and P-N) at the peak coordinates uncovered in the regression analyses, we plotted the fMRI signal changes and ratings of joy and pride.

Results

Self-rating

The neutral sentences were judged as carrying no prominent emotions. The mean ratings of joy and pride for neutral sentences were, respectively, 0.7 (SD = 0.7) and 0.4 (SD = 0.4), for joy sentences 4.9 (SD = 0.7) and 1.1 (SD = 1.1), and for pride 4.1 (SD = 0.9) and 4.9 (SD = 0.6). Ratings of other emotions (anger, sadness, fear, disgust, and shame) were virtually zero. Although pride sentences were judged as containing joy, their mean ratings of pride were significantly greater than those of joy ($t = 2.9$, degrees of freedom [df] = 30, $P = 0.007$). The mean ratings of joy were significantly greater for joy sentences than for pride sentences ($t = 2.9$, df = 30, $P = 0.007$).

fMRI Result

Pride condition relative to neutral condition (P–N) produced greater activations in the right pSTS, left temporal pole (Table 2 and Fig. 1*A*). We did not find significant activation in the MPFC. Joy condition relative to neutral condition (J-N) produced greater activations in the ventral striatum including the nucleus accumbens, anterior cingulate cortex, hippocampal regions, and insula/operculum (Table 2 and Fig. 1*B*). P–J condition produced greater activations in the right pSTS ($x = 42$, $y = -66$, $z = 22$; $t = 7.39$; 92 voxels). A conjunction analysis of P–N and J–N contrasts revealed no significant activations.

Regression analyses revealed positive linear correlations between the self-rating of pride and the degree of activation in the pSTS (middle temporal gyrus, $x = 44$, $y = -66$, $z = 20$; $t = 5.25$; 14 voxels) (Figs 2*A* and 3*A*). There were positive linear correlations between the self-rating of joy and the degree of activation in the ventral striatum (nucleus accumbens, $x = -12$, $y = 2$, $z = -6$; $t = 6.26$; 6 voxels) (Figs 2*B* and 3*B*).

Discussion

This study demonstrated that the brain activations during judgments of the positive self-conscious emotion, pride, showed different patterns from those of the basic positive emotion, joy. Pride conditions relative to neutral condition produced greater activity in the right pSTS and left temporal pole, the components of neural substrates of social cognition or ToM (Allison et al. 2000; Adolphs 2001; Frith U and Frith CD 2003; Gallagher and Frith 2003; Moll et al. 2005). In contrast, joy conditions relative to neutral condition produced greater activity in the key nodes of processing hedonic and appetitive stimuli, the ventral striatum including the nucleus accumbens (Breiter and Rosen 1999; Salamone et al. 2003; Cardinal and Everitt 2004) and insula/operculum (Britton et al. 2006; Porubska et al. 2006; Rolls 2006). In addition, regression analyses showed that the subjective ratings of pride and joy correlated with the degrees of activation in the pSTS and ventral striatum, respectively.

Pride, by definition, is subsumed by basic emotion, joy (Tracy and Robins 2004a). In fact, our behavioral rating results showed that ratings of joy for pride sentences were high, although they were lower for pride sentences than for joy sentences. Therefore, it was expected that activations in the regions related to basic emotions, for example, the ventral striatum, might be observed. However, significant activation in such regions was not found, and the conjunction analysis of P–N and J–N did not find common activation in these regions, suggesting that joy derived from pride scenarios was not high enough to activate these regions. We used joyful scenarios containing hedonic and appetitive events that usually motivate biological behaviors like eating, reproduction, and economic behaviors. The mesolimbic dopamine system from the ventral tegmental area to the nucleus accumbens mediates the motivation to obtain reward. In other words, dopamine systems are more necessary for "wanting" incentives than for "liking" them (Berridge and Robinson 1998). Motivational processes are important for positive emotions such as happiness and joy (Lyubomirsky 2001). In an fMRI environment, it is difficult to induce liking, but participants might have felt "wanting" for reward such as money or food, leading to activation in the ventral striatum (Breiter and Rosen 1999; Salamone et al. 2003; Cardinal and Everitt 2004). In contrast, although pride sentences were articulated as joyful, their lack of hedonic contents might account for the lack of activation in such regions.

Table 2
Brain activations in pride condition and joy condition relative to neutral condition

Brain regions	L/R	Coordinates			*t*-score
		x	*y*	*z*	
Pride–neutral					
pSTS	R	42	−66	20	4.30
Temporal poles	L	−50	20	−24	4.62
Joy–neutral					
Ventral striatum	R	4	4	−6	4.5
Anterior cingulate cortex	L	−6	38	12	4.6
Hippocampal regions	L/R	−32	−16	−18	4.94
Insula/operculum	L/R	40	−28	18	5.39

Note: L, left; R, right. Coordinates and *t*-score refer to the peak of each brain region.

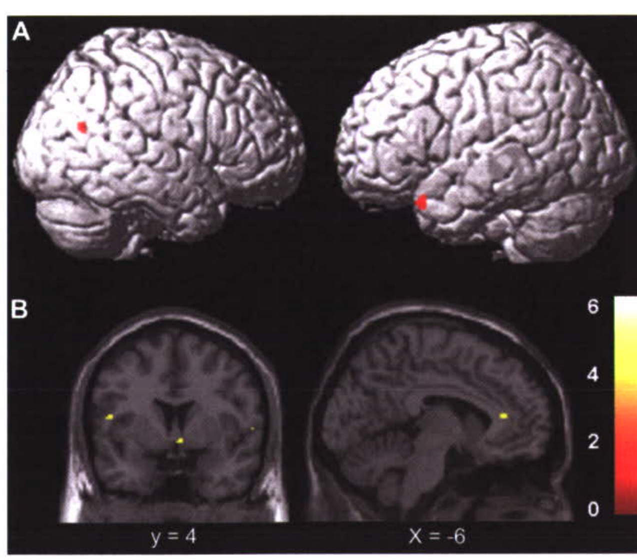

Figure 1. Images showing brain activation in joy and pride conditions relative to neutral condition. (*A*) Pride minus neutral. Activated regions were in the right posterior STS and left temporal pole. (*B*) Joy minus neutral. Activations in the ventral striatum, insula/operculum, and anterior cingulate were shown. Significant differences were recognized at a height threshold ($t > 4.07$; $P < 0.0005$, uncorrected) and extent threshold (10 voxels).

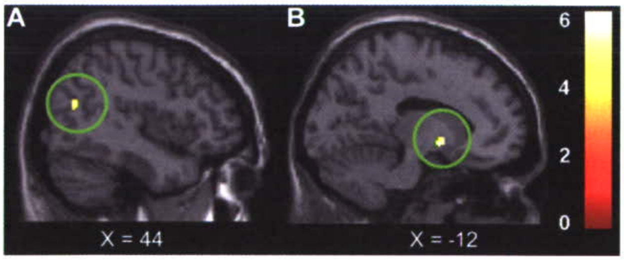

Figure 2. Correlation between brain activation and the self-ratings of pride and joy, with height threshold ($P < 0.001$) and extent threshold (5 voxels). (*A*) There was positive linear correlations between self-rating of pride and the degree of activation in the pSTS. (*B*) There was positive linear correlations between self-rating of joy and the degree of activation in the ventral striatum. The bar shows the range of the *t*-score. Within the image, L indicates left. Numbers in the bottom low indicate the *z*-coordinates of the Montreal Neurological Institute brain.

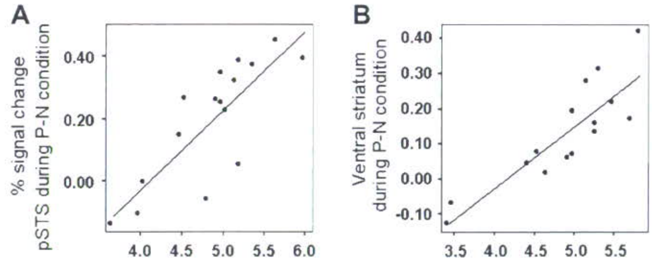

Figure 3. Plots and regression lines of correlations between self-ratings and the degree of activation in the brain regions. (*A*) Positive correlations ($r = 0.81$, df = 14, $P < 0.001$) between self-rating of pride and the degree of activation in the pSTS. (*B*) Positive linear correlations ($r = 0.86$, df = 14, $P < 0.001$) between self-rating of joy and the degree of activation in the ventral striatum.

Furthermore, as discussed below, unfamiliarity with some events depicted in pride scenarios might attenuate wanting for such events.

Our previous study has shown activation in the 3 key regions of ToM, the MPFC, pSTS, and temporal poles (Frith U and Frith CD 2003; Gallagher and Frith 2003) during the evaluative process of negative self-conscious emotions such as guilt and embarrassment (Takahashi et al. 2004). In addition, a recent clinical study reported that patients with frontotemporal lobar degeneration had impaired processing of negative self-conscious emotions (Sturm et al. 2006). Therefore, we expected that a positive self-conscious emotion would also recruit these regions. Although activations in the pSTS and temporal poles by pride scenarios were in agreement with our prediction, in disagreement was the lack of significant activation in the MPFC.

Although the precise roles of these 3 regions remain unclear, it was suggested that the pSTS and temporal poles are more concerned with the nature of socially relevant stimuli (Gallagher and Frith 2003; Decety and Grezes 2006). In other words, these regions are involved mainly in the early stage of social cognition, initial appraisal of socially relevant stimuli that support ToM ability, but not in ToM reasoning per se (Frith U and Frith CD 2003; Gallagher and Frith 2003).

Originally, the STS was known to be activated by biological motions such as movement of eyes, mouth, hands, and body (Allison et al. 2000), and it has been suggested to have a more general function in social cognition such as detecting explicit behavioral information that signals the intention of others (Gallagher and Frith 2003) and behavior of agents (Frith U and Frith CD 2003). The higher order association cortices including the pSTS mature in the last stage of brain development (Gogtay et al. 2004), and this might be associated with the fact that, like all self-conscious emotions, pride emerges later in the course of development than basic emotions like fear and joy (Tracy and Robins 2007). In addition, impairments in recognizing self-conscious emotions have been reported in children with autism (Capps et al. 1992; Kasari et al. 1993), in which STS abnormalities are highly implicated (Zilbovicius et al. 2006).

Bilateral temporal poles with greater effect on the left side have also been consistently recruited during ToM task (Calarge et al. 2003; Frith U and Frith CD 2003; Gallagher and Frith 2003). Although the left temporal pole contributes to the composition of sentence meaning (Vandenberghe et al. 2002), the temporal pole activation in P–N condition cannot simply be attributed to the use of sentences because neutral stimuli also require sentence comprehension. The temporal poles are generally engaged in retrieving episodic memories such as emotional and autobiographical memory (Fink et al. 1996; Dolan et al. 2000; Sugiura et al. 2006). In ToM task, the retrieval of episodic memories enables us to understand and simulate the mental state of others (Gallagher and Frith 2003). This role of memory process in understanding others' mental state might result in activation in the temporal pole in the P–N condition. Additionally, a recent study has suggested that this region is involved in storage and recall of contextual information (Mobbs et al. 2006). Because the subjects might not have direct experience of all the pride scenarios, the activation in the temporal pole may suggest that the subjects were reminded of contextual information of themselves or others (e.g., famous person) associated with pride scenarios (Mobbs et al. 2006; Sugiura et al. 2006).

The MPFC appears to be responsible for ToM reasoning or mentalizing, the ability to represent others' perspective (Frith U and Frith CD 2003; Gallagher and Frith 2003; Amodio and Frith 2006). This ability allows us to infer the cause of others' behavior, attribution. Previous studies have shown activation in the MPFC during judgments made on the basis of attributional information (Amodio and Frith 2006), and it is suggested that the MPFC is activated when cues that have been processed in an early stage of social cognition are used in a particular way, that is, to infer the intention (Gallagher and Frith 2003; Ochsner 2004) and emotional state (Aichhorn et al. 2006) of others. The lack of activation in the MPFC might stem from pride scenarios such as used in the present study. Most pride scenarios described situations in which the protagonist was a winner of a prize or competition as a result of achievement. Winning a prize or competition, by definition, is a symbol that inevitably indicates others' positive evaluations or judgments for one's own achievement. Therefore, in order to detect how one is evaluated by others in these situations, one might have less necessity to "infer" the mental state of others by using cues that have been processed in the early stage of social cognition. Another explanation for the lack of significant activation in the MPFC during judgments of pride might be possible. The argument regarding the role of the MPFC in ToM is mainly based on classical, explicit ToM tasks that usually used false belief stories (Frith U and Frith CD 2003; Gallagher and Frith 2003), whereas our task was an implicit ToM task in which the subjects were not explicitly instructed to represent the mental state of others, and the pSTS rather than MPFC plays a more central role (Saxe and Kanwisher 2003). A body of psychological studies has demonstrated that people have self-positivity biases, tendencies to have a positive attitude toward self. People tend to accept responsibility for desired outcomes but to attribute negative events to external causes (Greenwald and Banaji 1995; Leary 2007). Self-positivity biases are known to operate implicitly and automatically without conscious reflection (Greenwald and Banaji 1995; Leary 2007). The MPFC is a key node of a neural system subserving explicit reflection of self (Johnson et al. 2002). Therefore, the subjects might have judged some scenarios as pride ones without elaborate self-reflection.

This study has some limitations. First, as mentioned above, a complex self-conscious emotion could be accompanied by basic emotion. Although we understand that it is not feasible to assess a "pure" form of emotion, the results of regression analysis tell us that brain activations during pride condition could not simply be accounted for by the accompanying emotion. Second, self-conscious emotions depend on society and culture (Haidt 2003). The social background of participants, such as generation, religion, and education, could be confounding factors. For example, there are some empirical studies to support the traditional view that Japanese culture is collectivistic, putting a premium on social harmony, whereas Northern American culture is individualistic, highlighting personal achievement (Kitayama et al. 2006). At the same time, individualism is increasing in contemporary Japanese society especially among the young generation (Cusick 2007). Therefore, examining the effect of generations on self-conscious emotions would be an interesting future theme, and any generalization of our findings needs to be approached with caution. Finally, self-conscious emotions are more difficult to elicit in an MRI environment than basic emotions (Tracy and Robins 2004a). For this reason, we used an emotion judgment task, not an emotion induction task. To complement fMRI studies, lesion studies that can assess real-life human social behavior are recommended.

In conclusion, we investigated the neural substrates of judgments of a positive self-conscious emotion and demonstrated a difference from those of a basic positive emotion at a neural basis level. Supporting the concept that pride could be regarded as a member of the self-conscious emotions family, judgments of pride produced activation in the components of neural substrates implicated in social cognition or ToM. At the same time, judgment of pride might require less self-reflection compared with those of negative self-conscious emotions such as guilt or embarrassment. We expect our findings regarding joy and pride to have broad implications for the neural basis of some neuropsychiatric disorders such as depression or schizophrenia characterized by anhedonia and narcissistic personality or affective disorder, characterized by inappropriate pride, respectively.

Funding

Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government; the MEXT (15390438); the Japanese Ministry of Health, Labor and Welfare Health (Labor Sciences Research Grant H15-KOKORO-003).

Notes

Conflict of Interest: None declared.

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【特別企画】早期治療をめざす

早期治療とは何か

―精神医学・医療のニューフロンティア―

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はじめに

最近、精神科関係の雑誌や書籍に、早期介入や早期診断、早期治療、early intervention という言葉を見かけるようになった。厚生労働省は、予防によって医療費の減少をめざすことを最重点施策にしており、メタボリックシンドロームなる言葉も、成人病のリスクに警鐘をならし、成人病患者を減らすことを視野に入れたものである。精神疾患の早期介入も、その一環ではないかと受け取られる向きもあるかもしれないが、残念ながらその施策の中で生まれたものではなく、輸入ものである。筆者らは、早期介入という直訳は正確に意図するところを伝えておらず、早期相談・支援・治療が本来の趣旨を表現していると考えて使用している。しかし、輸入概念であるといっても、地球規模で考えれば、時代の流れは共通する認識と実践を惹起しているのかもしれない。

疾患はその始まりの早期に気づかれ、処置されることがよいに決まっている。当たり前のことがなぜ今話題になり、ニューフロンティアなどとも言われるのか。ここに至るには長い道のりがあった。一九世紀末に医学的疾患であると提唱された主な精神疾患、統合失調症や双極性障害（躁うつ病）が、疾患として受け入れられ、身体の臓器に（この場合脳に）基盤をもつものであることが概略是認されるのに一世紀近くかかったのである。つい三十数年前には、統合失調症は「家族の共謀の産物、虚構である」とする著名な論客もいたくらいである。

しかしその後三〇年あまりの間に、精神疾患の治療は早期相談・支援・治療の時代になった。おそらくまだわが国の精神医学・精神科医療のこの動向は、固有の事情によって、おおいに未消化のままのはずである。統合失調症の病前機能、リスクファクター、脆弱性、環境的・遺伝的成因、予防を主な関心としてきた筆者にとっても、事態は追いついていけない速さで進んだ。一九九六年六月の第一回早期精神病国際会議（メルボルン）に参加した小椋力琉球大学教授（当時）と筆者は、前年から準備していた日本精神障害予防研究会を三ヵ月早く発足させ、毎年研究会を開催したが、オーストラリアや英国、スカンジナビア諸国のように早期治療を普及させえなかった。

精神疾患の早期相談・支援・治療に取り組んだ国では、相談者の増加、入院の減少、医療費の減少にとどまらず、自殺者の減少などの医療本来の目的の改善という結果が報告され始めている。並行して、そのような医療の方法の医学的根拠を解明する研究も進められた。それが、

発症早期からの縦断的脳画像や遺伝子多型や発現、あるいはリスクファクターとしての大麻使用などの研究であったため、統合失調症の新しい側面の病態が解明された。

　このようにして、早期介入の医療は医学研究の新しい焦点をも掘り起こしながら、驀進している。もし、入院減少や経費の縮減のみではなく、人生への疾患の悪影響を軽減することが可能であるならば、わが国に適した方法での適用を考える価値がある。

　しかし、わが国の医療制度や医療費の問題は楽観を許さない段階まできている。今までと同じシステムを維持するなら、早晩、〝医療サービスの縮小は必至〟という見通しが濃厚である。その意味でも、医療費を増やさなくとも精神科医療の質を改善できる方途に、われわれ専門家はチャレンジしなければならない。早期からの相談・支援・治療は精神科医療にそのような可能性をもたらす一つの方法であると思う。

早期治療に至った経緯

　クレペリンによる統合失調症の初期の概念である「早発性痴呆」は、慢性進行性経過を重要な診断基準とするものであったため、早期の診断や治療は視野に入りにくかったと思われる。進行性経過を十分確認した後の治療であったから、治療の重点は、疾患過程が進行した慢性期患者の機能回復の試みとなった。作業療法、最近では生活機能訓練、あるいは保護工場というアイデアになりがちであったであろう。あるいは、そのような疾患過程にある患者の体験を理解しようとする試みや、そのような患者とともに生活する空間の提供、コロニーや生活の場のよりよいあり方としての治療共同体であった。最近ではデイケアや宿泊施設である。疾患過程の発現自体を防止する考えや試みの出現は、他の疾患に比べて非常に遅れた。

　もちろん統合失調症の発症初期の記述に焦点をおくコンラッド[1]やわが国では中安[2]の「初期分裂病（統合失調症）」の考究があったが、医療システム化を促進するような治療論としての発展はなかった。初期統合失調症論は、あくまでも統合失調症の初期の精神病理を記述しようとするところにモチベーションがあったといえる。

　一次予防を展望した統合失調症の病前適応や発症リスクファクター研究は、胎生期や周産期、あるいは新生児期・幼児期の重要な要因を発見・解明したが、それに比べて発症に近接する病態解明や治療論の開発は遅れた。

　クロウ（Crow）らはノースウィック・パーク（Northwick Park）病院の初回エピソード統合失調症の連続臨床研究の第二報[3]で、無作為割り付け二重盲検比較試験によって、実薬が偽薬よりも有意に再発が少ないことを示すとともに、発症から薬物治療開始までの期間（精神病未治療期間 duration of untreated psychosis：DUP）一年未満は、一年以上よりも、治療開始から再発までの期間が有意に長い（生存率が高い）ことを示した。

　筆者らはすぐにデイケアの六二例を調査し、初発後五年以内の再発を指標に、一年以内の早期に抗精神病薬治療を開始した者は、再発が有意に少ない（フィッシャーの直接確率 x^2 値＝五・七六九七七、p＝〇・〇一六三、片側検定）ことを明らかにした[4]。

　国際的にも次々とDUPが短いと予後がよいことが確認された。この動向は、オーストラリアや英国、スカンジナビア諸国では早期治療の取り組みとなって現れた。米国では、治療よりも病態研究に重点がおかれ、薬物治療や疾患経過の影響のない初回エピソード統合失調症を対象とする病態研究が推奨された。一九八八年の統合失調症国家計画では、統合失調症初回エピソード患者を重視することが強調された[5]。残念ながらわが国では、両方ともに特別強調されなかった。

　とりわけパトリック・マクゴーリ[6]を中心とするメルボルン大学精神科グループは、DUPの予後予測性があることを重視して、ビクトリア州政府の支援も得て精神病早期予防・介入セン

ター（ＥＰＰＩＣ）を設置、早期受診を大々的に訴え、早期受診者を実際に増やした。その結果、統合失調症患者の入院治療は減り、医療費も減少した。これを契機に州政府の支援はいっそう拡大した。統合失調症初回エピソード以前の前駆期からの働きかけがより有効である可能性を想定し、病気の心配を含む相談を受けるＰＡＣＥクリニックを設け、思春期や青年期の人々を対象に、インターネットやリーフレット、パンフレット等で情報を普及させ、相談や支援、一部に治療を始めた。

ここで、今までの統合失調症の早期でも初回統合失調症でもなく、初回精神病あるいは早期精神病を対象にするというパラダイム転換が行われた。つまり、精神病症状を目安にして疾病早期の対象を発見するが、それらの人々は精神疾患に発展しない人々も含み、また、精神疾患に発展したとしても統合失調症とは限らない。一過性に終わる精神病（急性一過性精神病など）、妄想性障害、精神病症状を伴う気分障害（うつ病、双極性障害）、さらに大麻や薬物・アルコール起因性の精神病、ＰＴＳＤによるものも含まれていることがある。

つまり、疾患または一過性の精神病症状を目安にして、その精神疾患または精神病への発展を防止しようとする実践的な取り組みなのである。ここには、疾患の診断や疾患への発展、何が疾患と関連する症状かなどにこだわる従来の視点ではなく、精神病症状を早期に軽減し、あわよくば精神疾患への発展を防止したいという精神保健と精神医学の原点的実践的な視点がある。

英国のブレア政権がいち早く国家医療政策に導入したことによって、精神疾患の早期介入は、研究や試行段階を飛び越えて医療・保健施策の課題ともなった。

早期治療とは

つまり、統合失調症の転帰を改善したいという願いは、ＤＵＰの発見、その短縮の試みから始まって、統合失調症初回エピソード、そして統合失調症とは診断できない段階である早期精神病エピソード（後ろ向きに考えた統合失調症前駆期と重なる場合もある）へと発展したのである。

そして現在最も注目されているのは、ニュージーランド出生コホート研究で明らかにされた思春期早期の精神病症状様体験（psychotic like experiences：ＰＬＥｓ）である。一一歳児童の十数％が体験していると報告される精神病症状の意味は何であろうか？　ＰＬＥｓを強く体験した児童は、二六歳時には、その九〇％が社会生活不適応、七〇％が何らかの精神病症状を有しており、二五％は統合失調症様障害に罹患していた。九〇％以上の子どもの一五年後の精神保健不良を予測するという重要な目安であることが、ＰＬＥｓの何よりの意義であろう。しかもそれが発達のまだ遅くない時期であり、その体験だけでなく、身体、心理、家族、友人、学校、社会とさまざまな働きかけの領域が考えうるのである。

ほんとうに一一歳という思春期早期に精神病症状が体験されているのであろうか？　ニュージーランドの一地方（Dunedin）のみの現象ではないか、という当然の疑問が生じる。

西田と筆者は、二〇〇六年七月に三重県のある市の五〇〇〇人以上の中学生の協力を得て無記名アンケート調査を実施した（学校関係者は一切回答内容を見ることができない方法で行った）。その結果、一五％の子どもがＰＬＥｓをたしかに体験したと報告した。一二歳の子どもも一三％であった。したがってそれよりも若年に体験が存在する可能性が高い。また、そのような子どもたちは、やせるための意図的嘔吐、厭世気分・希死念慮、いじめ、同居の大人からの暴力、飲酒などときわめて高い相関を示した。

オランダでも、同じく質問紙法で一四歳児一九％と報告されている[7]（英国で九〜一二歳児を対象にローレンスら[8]が質問紙で調査したが、五九％が何らかのＰＬＥｓを体験したと報告した