and collected data would be invalid, thus subjects would have to mark correct answers more than 90% in each block. To manipulate controllability, feedback was correctly given to subjects in the HC blocks. On the other hand, during the LC blocks, bogus feedback was given irrespective of subjects' real performance. Standard of bogus feedback was independently set for each subject in the following manner: mean rate of correct responses in blocks of the HC condition was determined for each subject. In the following LC blocks, feedback indicating a correct answer was randomly given at a rate below 15% of the mean rate of correct responses by the subject in the HC blocks. For example, if a subject performed the task with a rate of 90% accuracy in the HC blocks, feedback indicating a correct answer was delivered at a rate of 75%, randomly in the LC blocks.

Procedures

Subjects were instructed to eat a light breakfast on the morning of the experiment, and caffeine-containing beverages were not allowed. Subjects suffering from an infectious illness within 2 weeks of the experiment were rescheduled. All subjects had 8 PET scans of 60 s each, and at 13-min intervals.

Subjects performed 8 blocks of the mental arithmetic task using HC and LC conditions as described above. Just before and immediately at the end of each block, subjects were asked to rate the strength of experienced stress on a 10-point scale (1: not at all; 10: extremely stressful). In addition, to evaluate subjective sense of control over the task, subjects were asked to rate how much (as a percentage) of their correct answers could be attributed to their own ability and effort but not to incidental factors (0–100%) at the end of each block. Just before the start of each block, and just after the end of each block, blood samples were taken from each subject using a heparinized cannula inserted in the right forearm vein to measure endocrine and immune indices. Cardiovascular indices were continuously recorded throughout experimental sessions. At the end of each experimental session, subjects were fully debriefed about purpose and manipulation of the experiment, and were thanked. All subjects were paid 15,000 yens for participation.

Measurement of physiological data

Cardiovascular indices

Cardiodynamic activity was recorded using electrocardiography (ECG) and non-invasive finger blood pressure (FINAP) measurements. To determine heart rate (HR), ECG was recorded using a MP 100 system (BIOPAC Systems, Inc.). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded using the finger cuff of a Portapres Model 2 (TNO Biomedical Instrumentation Inc.) attached to the third finger of the non-dominant arm of each subject. Analyses of ECGs and FINAP waveforms were performed using the software AcqKnowledge for the MP 100 system. Mean values of HR, SBP, and DBP were determined for 2 min just before the task as baseline, and during 2 min of the task in each block.

Neuroendocrine indices

Blood was collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes to measure epinephrine, norepinephrine, and ACTH. Tubes were kept on ice, centrifuged for 10 min, and plasma was removed and frozen at −80 °C until analysis. Concentrations of plasma epinephrine and norepinephrine were determined by high performance liquid chromatography. The intra-assay coefficient of variation was less than 5%, and inter-assay variations were less than 6% for measurements of epinephrine and norepinephrine. ACTH was assayed in triplicates using an immunoradiometric assay (Mitsubishi Chemical, Inc.). The intra-assay coefficient of variation was less than 6%, and inter-assay variations were less than 7% for measurements of ACTH.

Immune indices

Blood samples for immunological determinations were collected in heparinized tubes. The number of total lymphocytes per sample was determined using a standard means. Percentages of lymphocyte subsets were determined by flow cytometry (FACS Calibur, Becton-Dickinson). A whole-blood lysis method was used to stain cells with the following pairs of Fluorescein isothiocyanate/Phycoerythrin-conjugated monoclonal antibodies (DAKO, Inc.). Isotype-matched antibodies were mouse IgG1, CD3+/CD4+helper T cells, CD3+/CD8+cytotoxic T cells, CD3−/CD19+B cells, and CD3−/CD16+/CD56+NK cells.

Neuroimaging by PET

Image acquisition

During each block, distribution of regional cerebral blood flow (rCBF) was measured with a General Electric ADVANCE NXi PET scanner operated in a high-sensitivity three-dimensional mode. A venous catheter for administering the tracer was inserted in an antecubital fossa vein in the left forearm. After the subject's head was positioned in the inflatable plastic head-holder that prevented possible head movements, a 10-min transmission scan using a rotating ^{68}germanium pin source was completed. In each block, following a 370-MBq bolus injection of $H_2^{15}O$ over 30 s, scanning was started and continued for 60 s. Initiation of bolus injection was time-locked to the start of presentation of the stimulus, and presentation of the stimulus lasted until 30 s after termination of scanning. The integrated radioactivity accumulated during 60 s of scanning was used as the index of rCBF. Eight scans were acquired per subject, and interval between successive scans was 15 min in order to allow for radioactive levels to return to baseline level. A Hanning filter was used to reconstruct images into 35 planes with 4.5-mm thickness and a resolution of 2 mm × 2 mm (full width half maximum).

Image processing and analysis

SPM 99 (Friston et al., 1995) implemented in Matlab (version 5.3, Mathworks, Sherborn, Massachusetts) was used for spatial pre-processing and statistical analyses. Images were initially realigned using sinc-interpolation to remove artifacts before being transformed into a standard stereotactic space. Images were corrected for whole brain global blood flow by proportional scaling, and smoothed using a Gaussian kernel to a final in-plane resolution of 10 mm at full width at half maximum.

Differences within conditions (HC vs. LC) were the primary focus of this study, and subtraction analyses of images (HC (1–3 blocks) minus LC (6–8 blocks), and LC minus HC) were conducted to reveal significant increases of rCBF. Effects at each voxel were estimated using a general linear model. Voxel values for each contrast yielded a statistical parametric map of the t statistic (SPM t) and were subsequently transformed to a unit normal distribution (SPM Z). Peak voxel-value significance thresholds were set at $p<0.001$ (uncorrected), and cluster significance thresholds were set at 20 voxels.

Furthermore, to examine functional associations between brain activity reflected by increase of rCBF and peripheral cardiovascular, endocrine, and immune activities, a correlation map was composed for each condition to identify brain regions that were activated in synchrony with each physiological index. Changes in values of HR, SBP, and DBP were computed by subtracting means of values at baseline from means of values during the mental arithmetic task. Changes in values of epinephrine, norepinephrine, ACTH, and percentages of lymphocyte subsets were calculated by subtracting values before each block from values after each block. We conducted correlation analyses using such change values of physiological indices. Additionally, to examine psychological effects on brain activity accompanying appraisal processes, we conducted similar correlation analyses between rCBF and self-report data of sense of control and change values of subjective stress from before each block to after each block. These correlation analyses were conducted between the rCBF increase and each physiological and psychological index in the whole brain in the HC (1–3 blocks) and LC (6–8 blocks) conditions across subjects, separately. For the correlation analyses, statistical threshold was set at $p<0.001$ (uncorrected) for height, and clusters larger than 20 contiguous voxels were reported. Those relatively conserved thresholds were determined considering inflation of type I error rates in many comparisons, correlation analyses in the present study, and expansion of cluster sizes of activated voxels by image smoothing. The above thresholds would keep the probability of a false positive to a minimum according to analytical conditions used in the present study (Forman et al., 1995).

Results

Self-report and behavioral data

For each subject, means of sense of control and subjective stress were calculated using rating scores in HC (1–3) blocks, middle (4 and 5) blocks, and LC (6–8) blocks, in the "early low controllability" and the "late low controllability" groups (Table 1). Both groups commonly conducted the HC task in HC blocks, and conducted the LC task in LC blocks. The "early low controllability" group conducted the LC task whereas the "late low controllability" group conducted the HC task in the middle blocks. A two-way mixed (Group (early low controllability vs. late low controllability) × Block (HC, middle, LC)) analysis of variance (ANOVA) revealed a significant interaction between Group and Block for sense of control ($F(2, 18)=6.28$, $p<0.01$). Additional analyses using LSD tests ($p<0.05$) indicated that subjects in both groups had a lower sense of control in the LC blocks than in the HC blocks, and subjects in the "early low controllability group" reported lower sense of control than subjects in the "late low controllability" group in the middle blocks. No significant effects ($F<1.46$) were observed for change values of subjective stress. These results suggested that we could successfully manipulate controllability of an acute stressor, independently from subjective severity of stress.

Table 1
Means and standard deviations for self-report and behavioral parameters

	Block	Early low controllability	Late low controllability
Sense of control	HC	84.39 (7.82)	79.00 (9.01)
	Middle	76.67 (13.20)	86.00 (11.26)
	LC	80.83 (7.05)	75.33 (10.23)
Subjective stress	HC	2.78 (9.41)	3.87 (3.54)
	Middle	7.33 (7.29)	0.50 (6.22)
	LC	7.61 (6.40)	5.67 (8.29)
Accuracy of task (%)	HC	93.29 (2.72)	91.45 (3.32)
	Middle	88.68 (5.81)	93.59 (4.19)
	LC	82.22 (12.04)	86.79 (9.27)

HC, high controllability; LC, low controllability.

Mean rates of correct responses in the mental arithmetic task during the HC, middle, and LC blocks were calculated (Table 1). Although bogus feedback was provided in the LC condition, net performance of the task for each subject was evaluated. A main effect of Block was significant ($F(2, 18)=3.91$, $p<0.05$), indicating that subjects' performance was poorer in LC blocks than in HC blocks. Additionally, LSD tests ($p<0.05$) revealed that task accuracy was reduced in the "early low controllability" group whereas accuracy was maintained in the "late low controllability" group in the middle blocks. These results suggested that experimental manipulation of uncontrollability of the task interfered with performance of subjects, and these effects could not be attributed solely to effects of the order of tasks.

Physiological data

For each subject, means of physiological (cardiovascular, neuroendocrine, and immune) data at each observation point were calculated for HC, middle, and LC blocks. A three-way mixed ANOVA (Group (early low controllability vs. late low controllability) × Block (HC, middle, LC) × Period (baseline vs. task)) was conducted for each parameter. Means, standard deviations, and all significant effects in ANOVAs are summarized in Table 2.

For cardiovascular indices, significant interactions between Block and Period were observed in HR, SBP, and DBP ($F(2, 18)=16.97, p<0.001$; $F(2, 18)=7.08, p<0.01$; $F(2, 18)=6.51, p<0.01$, respectively). Additional analyses using LSD tests ($p<0.05$) revealed that such cardiovascular activities were significantly enhanced during the task compared to baseline activity in each condition of blocks (HC, middle, LC). However, degree of enhancement was more prominent in HC blocks than in LC blocks. A significant interaction between Group, Block, and Period was found for HR ($F(2, 18)=3.93, p<0.05$), suggesting that degree of increase in HR was larger in the "late low controllability" group than in the "early low controllability" group in the middle blocks. Thus, at least for HR, observed effects of controllability of tasks (HC vs. LC) on cardiovascular activity did not result from order of tasks and from habituation to the stressor. For neuroendocrine indices, concentrations of epinephrine, norepinephrine, and ACTH significantly or statistically marginally increased after the task compared to baseline ($F(1, 9)=10.08$, $p<0.05$; $F(1, 9)=3.58$, $p<0.10$; $F(1, 9)=4.77$, $p<0.10$, respectively). Furthermore, a significant interaction between Block and Period was observed for epinephrine ($F(2, 18)=5.69, p<0.05$), suggesting that increment in epinephrine level was more salient following the HC blocks than following the LC blocks. Although an interaction between Group, Block, and Period for epinephrine level was statistically marginal ($F(2, 18)=2.64$, $p<0.10$), LSD tests ($p<0.05$) showed that an increase in epinephrine concentration after the task from baseline in the middle blocks was significant in the "late low controll-

Table 2
Means and standard deviations of cardiovascular, neuroendocrine, and immune parameters

		Block	Early low controllability		Late low controllability	
			Baseline	Task	Baseline	Task
Cardiovascular	HR (bpm)	HC	68.70 (8.02)	89.96 (18.49)	74.67 (11.18)	102.13 (14.85)
		Middle	65.46 (5.64)	83.13 (11.47)	76.56 (10.12)	93.50 (14.57)
		LC	68.88 (8.57)	84.41 (12.66)	76.23 (8.07)	91.02 (11.22)
	SBP (mmHg)	HC	120.48 (19.70)	136.10 (21.61)	138.53 (28.20)	153.21 (27.53)
		Middle	117.84 (18.82)	130.10 (24.41)	136.56 (25.70)	149.71 (24.47)
		LC	124.44 (22.57)	134.99 (22.82)	141.16 (19.92)	148.91 (22.64)
	DBP (mmHg)	HC	63.15 (12.32)	73.99 (18.49)	69.07 (12.32)	77.70 (9.98)
		Middle	60.05 (17.61)	69.96 (17.41)	67.31 (11.75)	76.08 (9.46)
		LC	64.03 (20.42)	71.71 (19.39)	70.72 (7.93)	75.30 (7.45)
Neuroendocrine	ACTH (pg/ml)	HC	26.94 (8.43)	30.78 (14.42)	25.13 (8.28)	26.80 (8.87)
		Middle	22.42 (6.03)	23.67 (8.41)	20.70 (4.83)	20.10 (4.57)
		LC	23.94 (7.52)	26.44 (7.11)	19.27 (4.23)	21.27 (5.07)
	E (pg/ml)	HC	38.33 (17.35)	47.78 (32.23)	34.67 (4.47)	66.67 (31.00)
		Middle	36.67 (10.80)	41.67 (21.60)	36.00 (5.48)	52.00 (20.49)
		LC	35.56 (12.05)	40.00 (16.87)	41.33 (11.93)	58.67 (25.88)
	NE (pg/ml)	HC	187.22 (26.11)	206.11 (44.84)	260.67 (75.48)	256.67 (71.38)
		Middle	174.17 (41.40)	196.67 (32.20)	235.00 (73.06)	248.00 (76.04)
		LC	169.44 (33.96)	197.78 (38.80)	250.00 (80.52)	250.67 (59.32)
Immune	NK cells (%)	HC	18.63 (10.33)	21.23 (9.09)	16.04 (3.55)	20.40 (5.77)
		Middle	14.30 (6.18)	17.45 (8.57)	13.18 (1.98)	14.33 (2.97)
		LC	16.68 (4.28)	18.23 (7.82)	12.76 (3.59)	15.34 (4.00)
	Helper T cells (%)	HC	34.27 (6.47)	33.31 (5.48)	44.71 (5.37)	42.09 (4.46)
		Middle	37.77 (5.37)	36.46 (5.20)	47.46 (5.69)	47.31 (4.87)
		LC	37.70 (4.45)	36.38 (5.48)	48.31 (7.08)	46.94 (8.04)
	Cytotoxic T cells (%)	HC	31.56 (8.67)	30.70 (8.84)	23.63 (9.56)	23.02 (9.90)
		Middle	32.90 (8.37)	31.58 (8.10)	25.71 (8.04)	24.14 (9.43)
		LC	31.63 (8.30)	30.82 (8.42)	25.18 (9.08)	24.92 (9.13)
	B cells (%)	HC	14.47 (5.96)	15.00 (5.12)	14.47 (5.96)	15.00 (5.12)
		Middle	16.60 (4.13)	16.18 (4.13)	16.60 (4.13)	16.18 (4.13)
		LC	14.39 (2.58)	14.00 (2.82)	16.33 (3.65)	1572 (3.49)

HC, high controllability; LC, low controllability; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACTH, adrenocorticotropic hormone; E, epinephrine; NE, norepinephrine; NK, natural killer cells.

ability” group but not in the “early low controllability” group. Thus, effects of controllability of the stressor on changes in epinephrine level seemed beyond the simple order effects of tasks or habituation. For immune indices, main effects of Period were significant in NK cells, helper T cells, and cytotoxic T cells ($F(1, 9)=27.94$, $p<0.001$; $F(1, 9)=8.46$, $p<0.05$; $F(1, 9)=6.52$, $p<0.05$, respectively), indicating that the acute stressor increased the proportion of NK cells, but decreased proportions of helper T cells and cytotoxic T cells. Furthermore, main effects of Block were also significant in NK cells and helper T cells ($F(2, 18)=8.93$, $p<0.01$; $F(2, 18)=19.94$, $p<0.001$, respectively), indicating that increase in numbers of NK cells and decrease in numbers of helper T cells were more salient in the HC blocks than in the LC blocks.

Cardiovascular–neuroendocrine–immune pathways

Theoretically, variations of immune functions in acute stress situations are mediated by autonomic and neuroendocrine activities. To elucidate such pathways, we conducted regression analyses using a change scoring system (task—baseline) of each immune parameter as a dependent variable, and change score systems of cardiovascular (HR, SBP, and DBP) and neuroendocrine (epinephrine, norepinephrine, and ACTH) parameters as dependent variables in HC and LC blocks, separately. Results showed that epinephrine significantly predicted increase in NK cells, and decreases in helper T cells and cytotoxic T cells in the LC blocks; whereas no parameters accounted for variations of immune functions in the HC blocks (Table 3). Thus, autonomic activity (secretion of epinephrine) might directly regulate redistribution of lymphocytes when the subjects are

Table 3
Regression analyses for immune parameters

	HC				LC			
	NK	hT	cT	B	NK	hT	cT	B
HR	0.17	−0.19	0.65	0.55	0.11	−0.01	0.45	0.23
SBP	−0.46	0.21	−0.53	0.52	−0.20	−0.05	0.09	−0.70
DBP	0.33	−0.17	0.62	−0.73	0.05	0.19	−0.51	0.14
E	0.40	**−0.87**	−0.56	−0.31	**0.90**	**−0.77**	**−0.84**	−0.45
NE	−0.02	0.10	−0.04	0.24	0.25	−0.37	0.11	0.16

HC, high controllability; LC, low controllability; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACTH, adrenocorticotropic hormone; E, epinephrine; NE, norepinephrine; NK, natural killer cells; hT, helper T cells; cT, cytotoxic T cells; B, B cells.
Values represent beta coefficients, and bold values represent statistically significant results ($p<0.05$).

faced with reappraisal of stressor controllability, but autonomic, neuroendocrine, and immune systems might be activated relatively independently when the stress situation is evaluated as controllable.

PET data: subtraction analyses

Results of subtraction analyses are summarized in Table 4. Subtraction of HC minus LC blocks revealed a significant increase in rCBF in the middle temporal (BA 22, $x=56$, $y=-42$, $z=-14$) and fusiform (BA 20, $x=-54$, $y=-36$, $z=-22$) gyri in the temporal lobe, the middle occipital gyrus (BA 19, $x=-50$, $y=-58$, $z=-10$) and the cuneus (BA 18, $x=-2$, $y=-82$, $z=16$) in the occipital lobe, and the bilateral cerebellum ($x=-26$, $y=-64$, $z=-46$; $x=32$, $y=-54$, $z=-44$) (Fig. 1a). No increase in rCBF was observed in the PFC. The reversed pattern of subtraction (LC–HC) revealed a significant increase in rCBF in a wider range of loci including the medial and right lateral OFC (BA 10, coordinates of peak, $x=32$, $y=54$, $z=-2$). Furthermore, increased rCBF was observed in the dorsal ACC (BA 32, $x=-6$, $y=24$, $z=42$) expanding to the adjacent MPFC, the right lateral PFC (LPFC; $x=20$, $y=44$, $z=26$; BA 8, $x=46$, $y=24$, $z=42$), and the thalamus ($x=14$, $y=2$, $z=12$) (Fig. 1b). Additional activation was found in several loci in the PFC and temporal areas (Table 4).

In addition to self-report, behavioral, and physiological data, means of rCBF at each peak activation location observed for comparisons of HC minus LC and LC minus HC were determined for HC, middle, and LC blocks. A two-way mixed ANOVA (Group (early low controllability vs. late low controllability) × Block (HC, middle, LC)) was conducted for rCBF at each location. No rCBF in activated sites observed from subtraction of HC minus LC showed a significant interaction between Group and Block, suggesting that activations in temporal and occipital cortices, and the cerebellum observed in the HC blocks were independent of the manipulation of uncontrollability, and changes in rCBF in those sites were probably attributed to habituation (Fig. 2a). On the other hand, rCBF in the OFC, loci in the LPFC, and ACC observed by comparing LC minus HC values showed a significant or marginal interaction between Group and Block ($F(2, 18)=4.26, 5.54, 2.55, 4.27$; $p<0.05, 0.05, 0.10, 0.05$, respectively; Fig. 2b). These results clearly indicated that activation in PFC areas observed in LC minus HC blocks were caused by manipulation of uncontrollability.

PET data: correlation analyses

High controllability

Since we were interested in functional association between brain regions including the PFC, limbic, and midbrain areas, and peripheral physiological responses, we limited ourselves to report significant correlations in such regions. We revealed that changes in HR positively correlated with rCBF in the midbrain ($x=-2$, $y=-34$, $z=-18$, $Z=4.68$) and changes in SBP correlated with rCBF in the pons ($x=6$, $y=-14$, $z=-24$, $Z=3.75$) (Fig. 4a) in the HC blocks. For immune parameters, increase in numbers of NK cells positively correlated with rCBF in the right hippocampus ($x=30$, $y=-10$, $z=-14$, $Z=3.49$) (Fig. 5a) and the pons ($x=8$, $y=-40$, $z=-34$, $Z=3.13$). Analyses using other physiological and psychological (sense of control and subjective stress) parameters showed no significant correlations with rCBF.

Low controllability

Overall, larger ranges showed significant correlations with cardiovascular, neuroendocrine, and immune parameters in the LC blocks than in the HC blocks. Changes in HR showed a positive correlation with increases in rCBF in several loci in the MPFC (BA 8, $x=-6$, $y=24$, $z=42$, $Z=5.53$; BA 10, $x=-2$, $y=64$, $z=12$, $Z=4.68$; BA 9, $x=-16$, $y=46$, $z=30$, $Z=4.36$), an anterior lateral part of the right OFC (BA 11; $x=26$, $y=58$, $z=-22$, $Z=4.37$) (Fig. 3b), and the thalamus ($x=4$, $y=-6$, $z=4$, $Z=3.95$) in the LC blocks. Changes in SBP significantly correlated with increases in rCBF in an anterior part of the ACC (BA 32, $x=-6$, $y=40$, $z=31$, $Z=4.10$), the

Table 4
Significant increases in rCBF between High controllability and Low controllability blocks

Salience	Region	Side	BA	x	y	z	Z score
a. HC–LC							
	Middle temporal gyrus	R	22	56	−42	−14	4.32
	Middle occipital gyrus	L	19	−50	−58	−10	4.09
	Cerebellum	L		−26	−64	−46	3.88
	Cuneus	L	18	−2	−82	16	3.88
	Fusiform gyrus	L	20	−54	−36	−22	3.58
	Cerebellum	R		32	−54	−44	3.51
b. LC–HC							
	Orbitofrontal cortex	R	10	32	54	−2	5.32
	Anterior cingulate cortex	L	32	−6	38	42	4.78
	Medial prefrontal cortex	R	8	16	32	42	4.61
	Lateral prefrontal cortex	R	8	20	44	26	4.47
	Lateral prefrontal cortex	R	8	46	24	42	4.39
	Superior temporal gyrus	L	40	−56	−60	28	4.37
	Lateral prefrontal cortex	L	10	−32	54	6	4.31
	Anterior cingulate cortex	R	32	14	30	28	4.00
	Thalamus	R		14	2	12	3.97

Coordinates are in MNI space (SPM99). HC, high controllability; LC, low controllability; R, right; L, left; BA, Brodmann's area; *x*, *y*, *z*, three-dimensional coordinates used to determine a voxel referring to medial–lateral (*x*: positive=right), anterior–posterior (*y*: positive=anterior), and superior–inferior (*z*: positive=superior) positions; rCBF, regional cerebral blood flow.

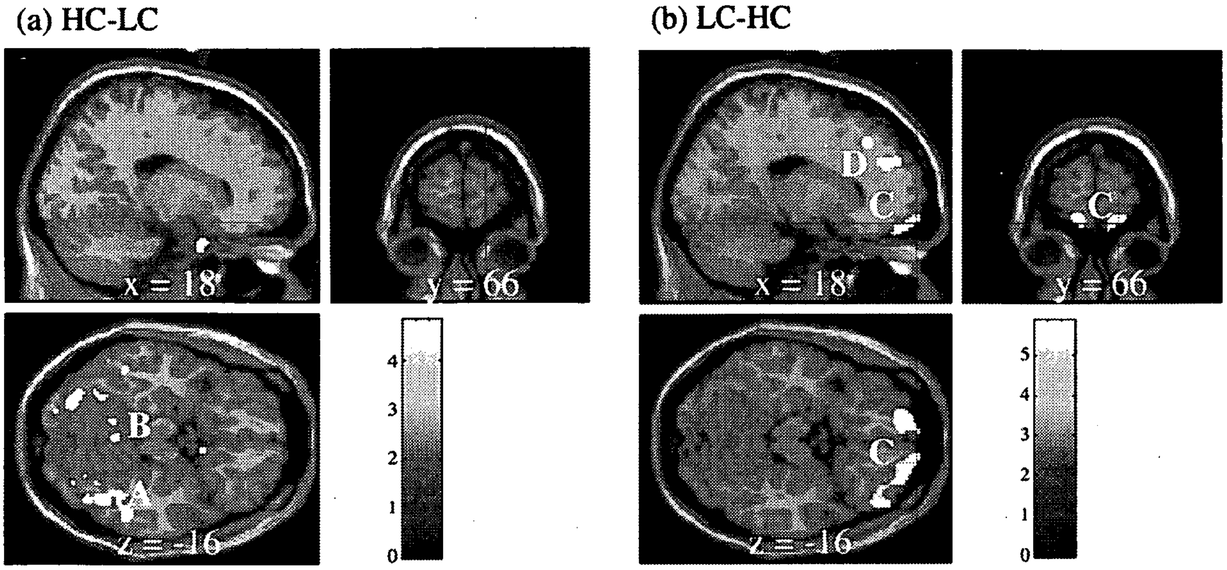


Fig. 1. (a) Statistical parametric map (SPM99) showing significant increases of regional cerebral blood flow (rCBF) in the High controllability blocks minus the Low controllability blocks. (b) Statistical parametric map (SPM99) showing significant increases of rCBF in the Low controllability blocks minus the High controllability blocks. An uncorrected p value of 0.001 was used as threshold for each subtraction analysis. HC, high controllability; LC, low controllability; A, visual areas; B, cerebellum; C, orbitofrontal cortex; D, medial prefrontal cortex.

right lateral OFC (BA 47, $x=40$, $y=40$, $z=-2$, $Z=3.87$) (Fig. 4b), and the pulvinar ($x=22$, $y=-30$, $z=10$, $Z=4.14$). Scatter plotting showed strength of these correlations between brain activity and cardiovascular parameters (Figs. 3 and 4).

For immune parameters, increase in proportion of NK cells correlated with increase in rCBF in the medial OFC (BA 11; $x=-12$, $y=30$, $z=-28$, $Z=4.33$), the bilateral OFC (BA 47, $x=34$, $y=36$, $z=-24$, $Z=3.90$; BA 47; $x=-34$, $y=22$, $z=-18$, $Z=3.09$) (Fig. 5b). Additionally, correlations were observed in several loci in the anterior MPFC (BA 10, $x=24$, $y=62$, $z=10$, $Z=3.96$; BA 10, $x=-8$, $y=50$, $z=10$, $Z=3.84$; BA 10, $x=-26$, $y=56$, $z=14$, $Z=3.63$), the left insula ($x=-38$, $y=-14$, $z=14$, $Z=3.99$), and the left hippocampus ($x=-30$, $y=-32$, $z=-8$, $Z=3.86$). Decrease in proportion of helper T cells correlated with decrease in rCBF in the medial OFC (BA 11, $x=18$, $y=16$, $z=-18$, $Z=3.61$), and the right insula ($x=48$, $y=16$, $z=-10$, $Z=3.49$) (Fig. 6b). Correlations were found also in the MPFC (BA8, $x=16$, $y=52$, $z=40$, $Z=4.39$). Scatter plotting indicated that correlations between brain activity and immune parameters were not necessarily clear and linear (Figs. 5 and 6), though statistically significant. These results suggested that associations between brain and immune activities should not be direct but indirect (see Discussion).

No endocrine parameters showed significant correlations with rCBF at the rigorous threshold ($p<0.001$). However, considering the limited imaging spatial resolution using PET, and the above reported results of regression analyses showing influences of epinephrine on NK cells and helper T cells, we conducted correlation analyses for endocrine parameters using a more liberal threshold ($p<0.005$) to explore possible functional associations between the brain and endocrine activities. As a result, changes in epinephrine concentration positively correlated with rCBF in foci in the OFC (BA 47, coordinates of peak, $x=42$, $y=44$, $z=-6$, $Z=2.91$), foci in the MPFC (BA9, $x=-16$, $y=52$, $z=30$, $Z=4.06$; BA 10, $x=14$, $y=56$, $z=10$, $Z=3.47$), the midbrain ($x=6$, $y=-32$, $z=-18$, $Z=3.70$), and the parahippocampal gyrus ($x=34$, $y=-18$, $z=-18$, $Z=2.97$) in the LC blocks (Fig. 7), but not in the HC blocks. Scatter plotting is not shown because this correlation analysis is just exploratory and preliminary. Psychological (sense of control and subjective stress) parameters showed no significant correlations with rCBF.

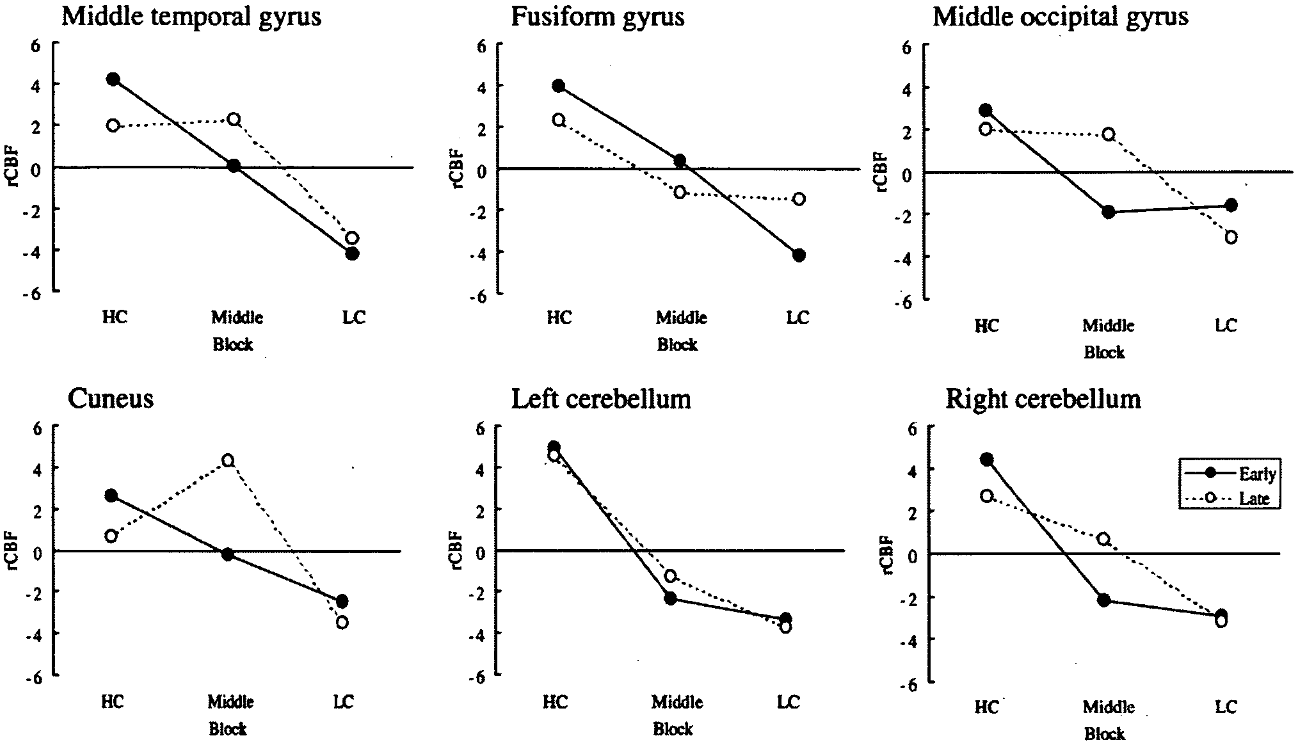
Some activation showing correlations between brain and physiological activity expanded to out of brain areas (Figs. 3–7). Relatively long time of experimental session (approximately 2 h) might cause such motion artifacts. However, it was confirmed that each peak of activation was in brain areas, thus the above results about correlations should be interpretable.

Discussion

Functional association between brain and cardiovascular, neuroendocrine, and immune responses accompanying appraisal of stressor controllability

The major finding in this study was that the neural network within the OFC, MPFC, ACC, and LPFC was activated when subjects had to update appraisal of stressor controllability. Furthermore, the present study indicated that PFC regions including the OFC and MPFC were commonly associated with peripheral immune responses, i.e., redistribution of lymphocytes, and with cardiovascular and neuroendocrine activities which probably mediated changes in immune functions, accompanying appraisal of stressor controllability. The PFC does not directly regulate peripheral immune cells but does so indirectly via autonomic and neuroendocrine pathways. Specifically, The OFC and MPFC might firstly affect activities of nuclei in stress-related brain structures such as the thalamus, hypothalamus, and midbrain through direct neural projections, and secondly such centers of autonomic and endocrine systems might affect immune functions through modulation of cardiovascular parameters, and secretion of catecholamines and acetylcholine (Maier and Watkins, 1998; Tracey, 2002). Observed activations of the thalamus, pulvinar, and midbrain correlating with HR, SBP, and epinephrine, respectively, might indicate involvement

(a) Changes of rCBF in activated areas in HC-LC



(b) Changes of rCBF in activated areas in LC-HC

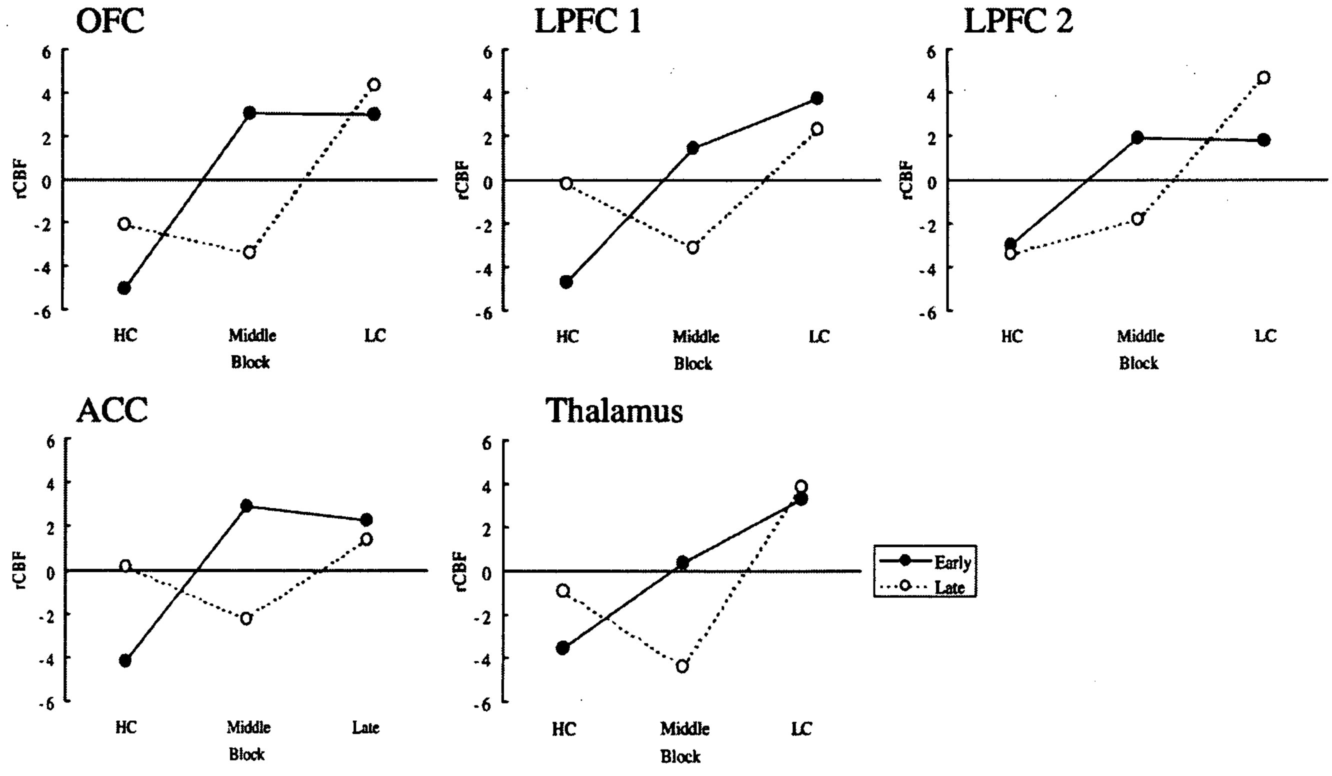
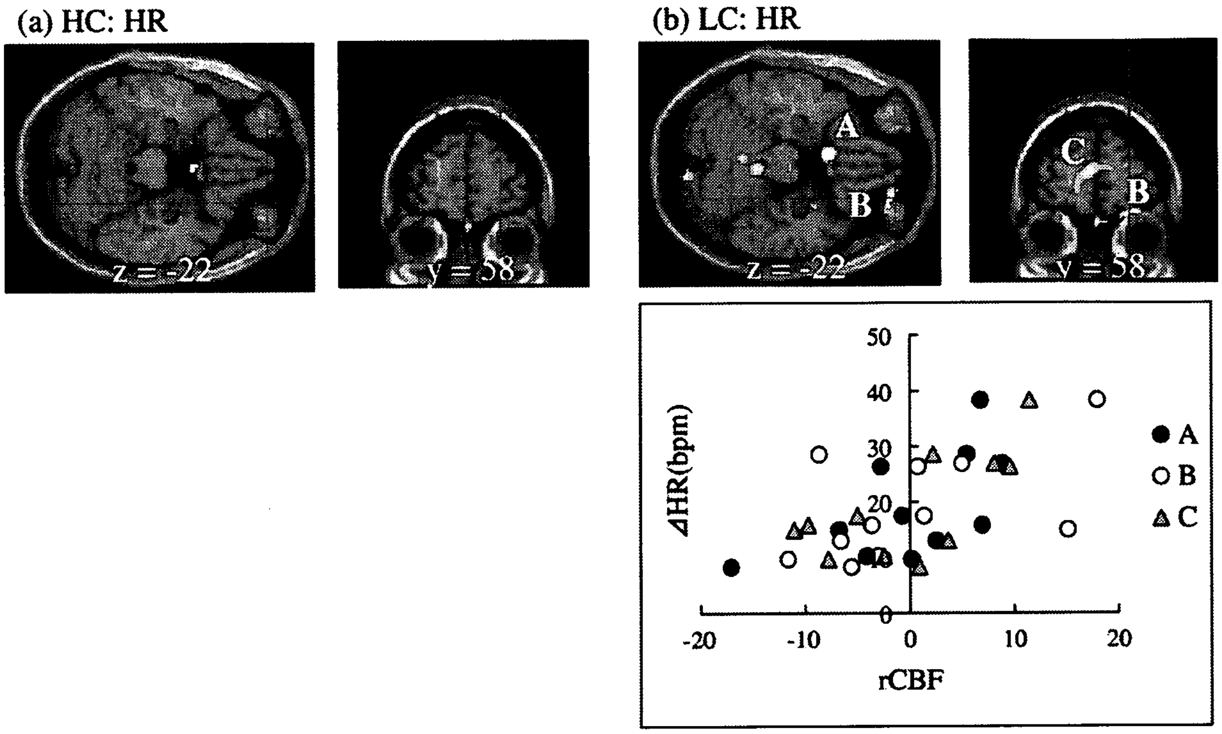


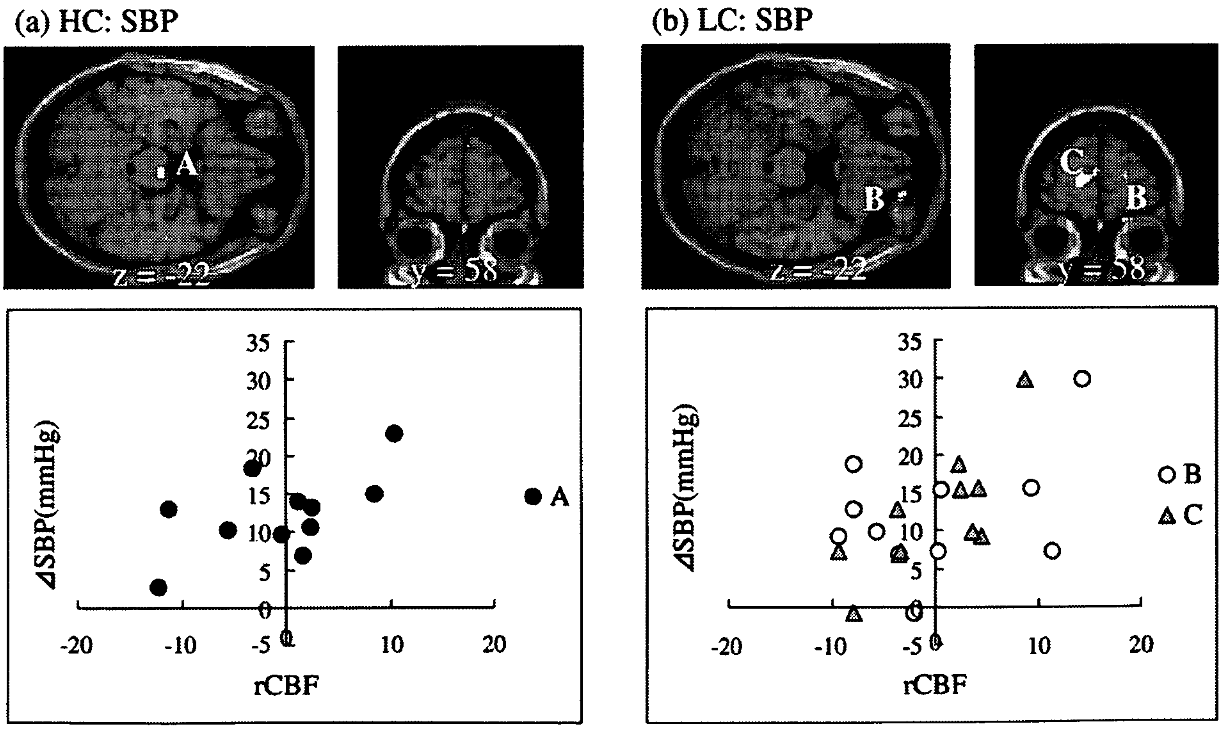
Fig. 2. (a) Changes of regional cerebral blood flow (rCBF) in activated brain areas across HC, middle, and LC blocks in "early low controllability" group and "late low controllability" group in subtraction of HC minus LC. (b) Changes of rCBF in activated brain areas across HC, middle, and LC blocks in "early low controllability" group and "late low controllability" group in subtraction of LC minus HC. HC, high controllability; LC, low controllability.



(a) HC: HR

(b) LC: HR

Fig. 3. Results of correlation analyses in High controllability (a) and Low controllability (b) blocks showing significant positive correlations between heart rate and regional cerebral blood flow (rCBF). An uncorrected p value of 0.001 was used as threshold. HC, high controllability; LC, low controllability; A, medial orbitofrontal cortex; B, lateral orbitofrontal cortex, C, medial prefrontal cortex.



(a) HC: SBP

(b) LC: SBP

Fig. 4. Results of correlation analyses in High controllability (a) and Low controllability (b) blocks showing significant positive correlations between systolic blood pressure and regional cerebral blood flow (rCBF). An uncorrected p value of 0.001 was used as threshold. HC, high controllability; LC, low controllability; A, Pons; B, medial orbitofrontal cortex; C, medial prefrontal cortex.

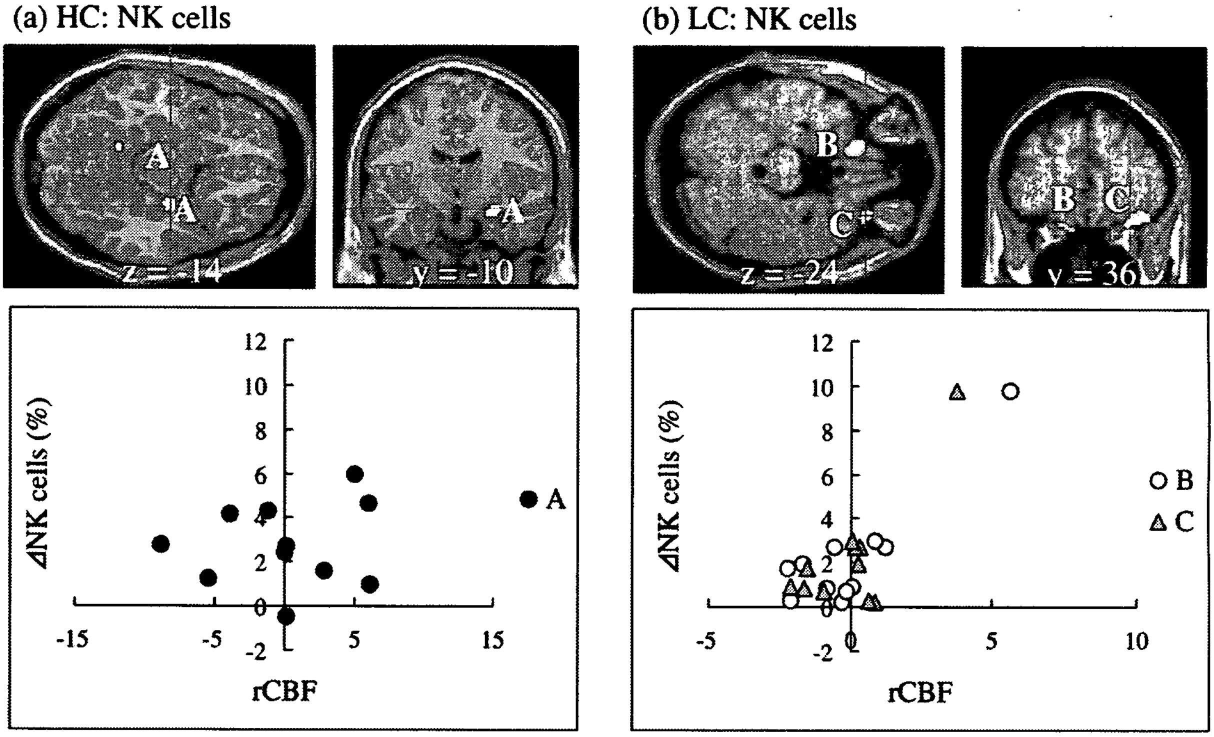


Fig. 5. Results of correlation analyses in High controllability (a) and Low controllability (b) blocks showing significant positive correlations between proportions of natural killer cells and regional cerebral blood flow (rCBF). An uncorrected p value of 0.001 was used as threshold. HC, high controllability; LC, low controllability; A, hippocampus; B, C, lateral orbitofrontal cortex.

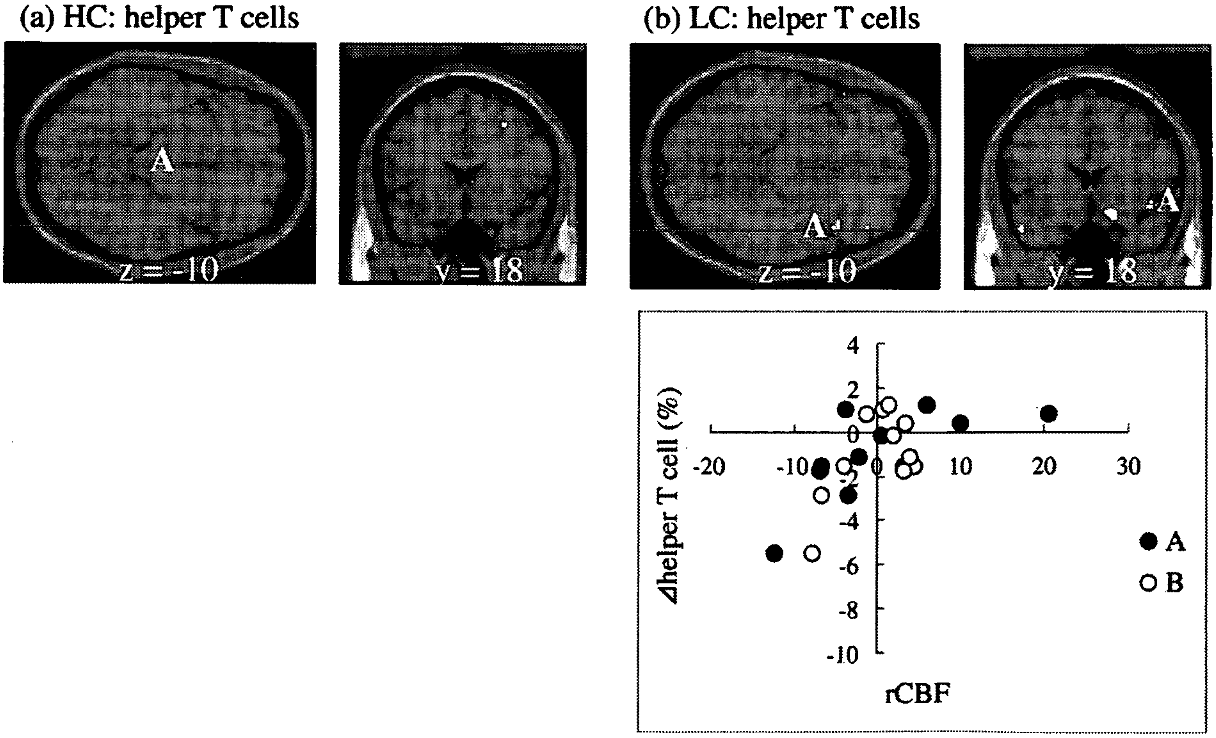


Fig. 6. Results of correlation analyses in High controllability (a) and Low controllability (b) blocks showing significant positive correlations between proportions of helper T cells, and regional cerebral blood flow (rCBF). An uncorrected p value of 0.001 was used as threshold. HC, high controllability; LC, low controllability; A, insula; B, medial orbitofrontal cortex.

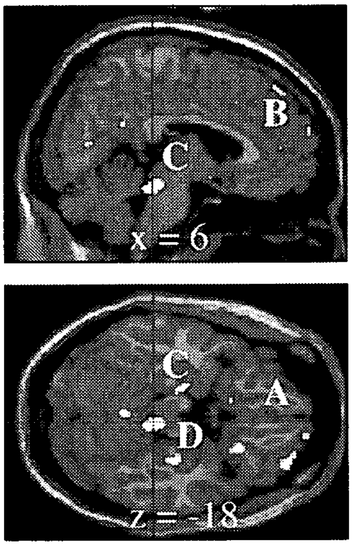


Fig. 7. Results of correlation analyses in Low controllability blocks showing a significant positive correlation between concentration of blood epinephrine and regional cerebral blood flow (rCBF). An uncorrected p value of 0.005 was used as threshold. A, orbitofrontal cortex; B, medial prefrontal cortex; C, midbrain; D, parahippocampal gyrus.

of parts of such neural routes. Significant but non-linear correlations between rCBF and immune parameters shown in scatter plotting (Figs. 5 and 6) suggested such indirect association of brain activity and peripheral immune functions.

Another possibility for the association of PFC activation and immune parameters is the afferent feedback from peripheral immune activity to the brain. Increase in number of NK cells during acute stress tasks leads to enhancement of activation of the inflammatory transcription factor NF-kappaB (Richlin et al., 2004) and should result in enhanced production of inflammatory cytokines such as IL-1β and tumor necrosis factor (Lisowska and Witkowski, 2003; Liang et al., 2004). Those cytokines can result in changes in visceral or interoceptive senses in local sites, and information about these changes can be conveyed to the brain via vagal pathways, and is finally projected to the insula and OFC (Craig, 2003; Critchley, 2005). In addition, information on cytokines themselves can be carried via the sensory vagus to the hypothalamus and the dorsal vagal complex in the midbrain (Hosoi et al., 2000; Tracey, 2002). The observed correlations between activation in the insula and OFC and changes of NK and helper T cells might, at least partly, reflect such an immune function as the "sixth sense" (Blalock, 1984, 1994). Thus, the present results suggested that bi-directional functional association between the brain and peripheral immune functions might become dominant when a stressor is less controllable, and thus, when more efficient coping is needed for the challenging environment.

Although the order of conditions of high and low controllability was not counterbalanced, the design of this study allowed us to confirm that neither effects of the order of conditions nor effects of habituation and adaptation to the stress situation completely explained changes in brain activation and physiological responses. Changes in subjects' ratings on sense of control, behavioral accuracy in the mental arithmetic task, HR, epinephrine, and rCBF in loci in the PFC corresponded to timing of initiation of manipulation of low controllability. Furthermore, because subjects' ratings of intensity of stress were not significantly different between the HC and LC blocks, the results described above can not be attributed to accumulated stress or increased fatigue which the subjects might have felt as the stress task progressed. Thus, these results showed that experimental manipulation of stressor controllability was valid, and we suppose that subjects adapted to the mental arithmetic task in the HC blocks at once, and later had to make reappraisal of controllability of the task after introduction of manipulation of low controllability in the following LC blocks.

Functional associations between discrete regions in the PFC and peripheral physiological responses in stress situations have been reported in earlier human neuroimaging studies. Wang et al. (2005) indicated that rCBF in the right OFC and dorsal ACC measured by perfusion functional magnetic resonance imaging (fMRI) showed positive correlations with perceived stress during a mental arithmetic task. Locations of peaks in those activated areas are very close to those observed in subtraction of LC minus HC in the present study. Since Wang et al. (2005) did not manipulate stressor controllability, subjects' ratings of perceived stress in their study might have reflected primary appraisal of impact of the stressor (Lazarus and Folkman, 1984), but not secondary appraisal of controllability or possibility of coping with the stressor. However, consistent activations in the OFC and ACC in their study and ours suggested that those regions of the PFC were involved in appraisal processes of stressors. Furthermore, in Wang et al.'s study (2005), activations in the right OFC and dorsal ACC positively commonly correlated with changes in HR and cortisol level as a result of the task. Critchley et al. (2000a) also revealed that rCBF measured by PET in the right anterior lateral OFC and dorsal ACC correlated with cardiovascular activities reflected by HR and blood pressure changes during stress tasks including mental arithmetics. Another study by the same group (Critchley et al., 2000b) showed that activations in the right OFC and anterior MPFC measured by fMRI were associated with sympathetic arousal indexed by skin conductance responses (SCR) during a gambling task. Although influences of appraisal of stressor controllability have not been examined in previous studies, locations of PFC sites where activation was observed substantially overlap with brain regions showing positive correlations with autonomic and even immune activities (e.g., HR, SBP, epinephrine, and NK cells) observed in the LC blocks in the present study. Taken together, our present results confirmed previous findings on functional associations between brain, cardiovascular, and neuroendocrine activities in acute stress situations, and further expanded these findings by showing that common brain regions could regulate functions including peripheral immune functions. It should be noted that the OFC and anterior insula are important centers both for efferent modulation over peripheral visceral and somatic responses and for afferent feedback projection from the body (Craig, 2003; Critchley, 2005). Thus, brain activity observed in the present study might reflect both of such processes. Unfortunately, limited temporal resolution of PET imaging prevented from dissociation of brain activity for efferent and afferent processes. As Critchley et al. (2000b) dissociated neural activity related to generation and afferent representation of SCR, event-related fMRI might be helpful to test this issue further.

Anatomical evidence indicates that the OFC, MPFC, and ACC may be the appropriate brain regions for a highly complex processing for adaptation (Kringelbach and Rolls, 2004; Kringelbach, 2005). The OFC, especially its posterior parts receives inputs from all sensory modalities including visceral afferents, and thus is supposed to integrate sensory information, and to evaluate values of reward and punishment (Kringelbach et al., 2003; De Araujo et al., 2003; O'Doherty et al., 2001). Medial parts of the OFC, MPFC, and ACC have extensive outputs to other brain regions which drive emotional and stress responses such as the hypothalamus, periaqueductal gray, amygdala, and thalamus (Bandler et al., 2000; Price, 2005). Some theorists have proposed that these PFC areas can work as a functional unit called the orbital and medial prefrontal network (Price, 1999, 2005; Öngür and Price, 2000). Although this neural network has originally been considered to serve as a sensory-visceromotor link for consummatory behaviors, we speculate that it might also work to establish a representation of stress situations, and to modulate both behavioral and physiological responses on the basis of evaluation of stressor controllability. This speculation is supported by a recent animal study clarifying that the MPFC in rats plays a critical role in mechanisms by which stressor controllability affects not only behavioral but also serotonergic activity in the dorsal raphe (Amat et al., 2005). Previous neuroimaging studies showed that the lateral OFC (lateral part of BA 10 and BA 47) was often co-activated with the ACC and adjacent MPFC, especially when subjects were delivered with a kind of punishment, leading to a change in ongoing behavior (Petrovic et al., 2002; Kringelbach and Rolls, 2003; Walton et al., 2004). This pattern of prefrontal activation was consistent with our results in the LC blocks. This might indicate that increases in errors (bogus feedback), perceived uncontrollability, and reduced performance experienced in the LC blocks were detected as punishers for the subjects, who attempted to improve their performance. Common patterns of brain activation observed in correlation analyses with cardiovascular, neuroendocrine, and immune parameters in the present study might further imply that the orbital and medial prefrontal networks can change not only behaviors, but also can affect physiological responses to adapt to various stressful environments, and further can monitor inner physiological responses via afferent feedback signals from the body.

Interestingly, in spite of common correlations between activation in the OFC and MPFC and peripheral physiological responses in the LC blocks, self-report data of controllability and subjective stress showed no significant correlation in those regions. This result also suggested that observed correlations between brain activation and the body accompanying stressor appraisal in this study might not mean conscious modulation of bodily responses by higher order cortical brain regions but reflect complex and possibly bi-directional functional associations between the brain and body described above. Recently, we tested this issue in a stochastic learning task where cardiovascular, neuroendocrine, and immune responses and self-report of controllability could be continuously recorded, with a rigorous between-subject yoked paradigm (Kimura et al., 2007). In physiological data, low controllability was involved in a consistent pattern as the present study, i.e. downward regulation of physiological responses. However, though subjective rating of controllability was finally dissociated between a high controllability group and a low controllability group, we found no significant correlation between subjective controllability and physiological responses. The adaptation processes dependent on controllability appraisal can work, at least partly, automatically and unconsciously via the bi-directional brain and body systems.

Contrary to the less controllable situation, prefrontal activation and its association with physiological parameters were not shown in the highly controllable situation. Instead, visual and motor areas in temporal and occipital lobes and the cerebellum were activated there. Those patterns of brain activation have been observed in previous neuroimaging studies using mental arithmetic tasks (Critchley et al., 2000a; Dehaene et al., 2004; Dedovic et al., 2005; Rivera et al., 2005). One should note that activation in those areas showed a decrease in the latter blocks, irrespective of manipulation of uncontrollability. This might reflect decreased levels of brain activity leading to saving of cognitive resource, accompanying adaptation or proficiency to tasks. Furthermore, in the highly controllable situation, the pattern of peripheral physiological responses might be driven mainly by subcortical regions but not by higher order PFC regions in the brain. The observed association between activation in the midbrain and pons and HR and SBP in the HC blocks in the present study might reflect such processes.

Modulation of redistribution of lymphocytes in acute stress and possible mediating mechanisms

Rates of circulating blood lymphocytes do not usually exceed 5% of the whole population of lymphocytes in the body (Shepard, 2003). However, even small fluctuations in numbers of specific subtypes of lymphocytes can have large effects on biological defenses of the body against infection, and in maintenance of homeostasis (Engler et al., 2004). The present study showed that acute stress responses in peripheral immune functions and possibly mediating cardiovascular, and neuroendocrine activities were neither rigid nor stereotyped, but were regulated flexibly and dynamically on the basis of evaluation of current environmental factors such as stressor controllability. Specifically, we clarified that physiological stress responses were strengthened when a stressor was well controlled, whereas at least portions of those responses (i.e. HR, epinephrine, NK cells and helper T cells) were, to some degree, attenuated or regulated downward when the stressor was less controllable and reappraisal of the stressor was required. Although down-regulation of physiological responses can be done either by reduction of sympathetic activity, enhancement of vagal activity, or both, the vagus nerve systems might play a critical role in such flexible regulation (Thayer and Brosschot, 2005). Several lines of evidence support this argument. Firstly, due to differences in temporal kinetics of neuroeffectors, sympathetic effects are relatively slow compared to vagal effects (Saul et al., 1990), thus the latter ones should be more suitable for fast and delicate regulation. Secondly, sympathoexcitatory subcortical neural circuits are under tonic inhibitory control by the prefrontal cortex (Thayer and Friedman, 2002; Amat et al., 2005). Thus, it has been argued that increased prefrontal activity was associated with more efficient inhibitory control of autonomic, endocrine, and immune activities (Thayer and Lane, 2000; Davidson, 2000; Lane et al., 2001), on the other hand, reduced prefrontal activity was associated with insufficient control and sometimes led to mental and physical pathological states (Friedman and Thayer, 1998; Thayer et al., 1996, 1998; Cohen et al., 1999). Our study showed that the combination of increased involvement of the PFC and attenuated elicitation of physiological responses in the less controllable situation agreed with this argument. Probably, such phenomena might represent the processing of search mechanisms for appropriate strategies for coping, and for the prevention of energy expenditure by cutting off provided energy to ongoing behaviors and physiological responses which have become inappropriate. Since much energy is necessary for cascades of immune responses, down-regulation of elicitation of immune responses might be more appropriate in a stressful but uncertain situation. For adaptation to constantly changing environmental demands, patterns of organized variability, rather than static levels are required in the central brain and peripheral physiological systems (Thayer and Brosschot, 2005). Unfortunately, technical difficulties prevented us to directly measure parameters indexing vagal activity such as blood concentration of acetylcholine. Future studies are required to elucidate these mechanisms in more details.

We observed enhanced activation of the PFC; attenuation of immune, cardiovascular, and neuroendocrine stress responses; and a positive correlation between PFC activation and the physiological responses in the less controllable situation. One might wonder that this is a triadic contradiction. If prefrontal activation is associated only with enhancement of vagal activity, and if vagal activity results in attenuation of physiological responses, then not a positive but negative correlation should be observed between prefrontal activity and physiological responses. However, to interpret this ostensible contradiction, we should quote the concept of central autonomic network (CAN) proposed by Benarroch (1993, 1997). Anatomically, the CAN is composed of both prefrontal and limbic structures: the ACC, OFC, insula, ventromedial PFC, amygdala, hypothalamus, periaquaductal gray, and nuclei in the midbrain. Observed PFC regions in correlation analyses of cardiovascular, neuroendocrine, and immune parameters in the present study corresponded to PFC regions in the CAN. These components are thought to be reciprocally interconnected, and output of the CAN is directly linked both to sympathetic and parasympathetic influences on peripheral organs including the immune system. Thus, the CAN is not a linear but rather a complex system including many positive and negative feedback loops governing both sympathetic and parasympathetic outputs. In such a system, to concretely predict final results of activity of the system is difficult. Indeed, prefrontal activation might induce enhancement of sympathetic activity in one situation, and might induce enhancement of vagal activity in another situation. A PET study inevitably has limitations to elucidate the causality and dynamic properties of highly complicated neural systems. Nonetheless, the present study clarified that PFC regions could indeed regulate physiological systems including the immune system although either sympathetic or vagal influences existed in an acute stress situation.

Limitations of the present study

Several limitations existed in the present study. Firstly, it is arguable whether manipulation of false feedback about performance adopted in the present study is indeed the psychological equivalent of low controllability. Conceptual validity of the present findings should be further tested using various other tasks and experimental manipulation of controllability. Secondly, since there are large individual differences in any physiological responses, the small sample size in this study might be problematic. For example, although subjects were randomly assigned to the "early low controllability" group and the "late low controllability" group, values of some physiological parameters at baseline differed between the groups (Table 2). Statistically, these incidental individual differences did not affect interactions of experimental manipulations. However, generalization of the present findings must be further tested using larger samples. Thirdly, the experimental paradigm adopted in the present study and PET scanning required relatively longer time compared to other imaging techniques such as fMRI. Probably that should cause noise in images by motion artifacts. Finally, any neuroimaging studies including PET studies are substantially correlational, and they have little power to elucidate causality of factors. Thus, it is desirable that association between prefrontal activity and physiological responses in acute stress, and its modulation on the basis of appraisal of the stressor indicated in the present study should be further examined using other methodologies such as animal studies and lesion studies in humans.

Nevertheless, despite the abovementioned limitations, the present study demonstrated that the prefrontal neural network including the OFC, LPFC, MPFC, ACC, and insula played a critical role in appraisal of stressors, and in tuning of cardiovascular, neuroendocrine, and immune responses for adaptation to complex and varying environments.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research of the Japan Society for the Promotion of Science (No. 16330136) and by a Health and Labour Sciences Research Grant on Research on Occupational Safety and Health from Japan Ministry of Health, Labour, and Welfare (No. H17-RODO-5). Portions of the present study were presented at the 10th Annual Meeting of the Organization for Human Brain Mapping (Budapest, Hungary, June 2004) and at the Annual Meeting of Society for Psychophysiological Research (Santa Fe, October 2004).

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産業ストレス研究(Job Stress Res.)，15，00-00(2008)

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原著

新指針に基づいた事業場におけるメンタルヘルス対策の状況，および改正労働安全衛生法に基づいた長時間労働者への医師面接の実施状況

――事業場規模別による比較検討――

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Current Status of Worksite Mental Health Care and Doctors' Interviews of Workers with Long Working Hours Based on The New Occupational Mental Health Guidelines and The Revised Industrial Safety and Health Law in Japan: A Comparison by Worksite Size

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Abstract The Revised Industrial Safety and Health Law went in to effect in April 2006, meanwhile new guidelines for mental health care were published. The situation is however unclear about both the current status of mental health care in the workplace and the implementation of necessary doctor-worker interviews in accordance with the new law and its guidelines. In November 2006, a questionnaire was mailed to randomly selected personnel／labor staff at 500 workplaces (with 1,000 plus employees) and 1,000 workplaces (with 50-999 employees) with a response rate of 18.0% (31 and 239 respectively). Among workplaces with 1,000 plus employees, the implementation proportions for establishing a mental health plan were 61%, education／training 97%, improvement of work environment 48%, establishment of a consultation system ~~93~~ 94%, and return-to-work support at 77%; among workplaces with 50-999 employees, these proportions were 19%, ~~60~~ 61%, 17%, 58%, and 31%. The implementation proportion of doctor-worker interviews was 90% among 1,000 plus employee workplaces and 52% among 50-999 employee workplaces. The implementation proportions of mental health care activities were found greater than that of a previous survey done in 2002. However,

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the gap in the proportions between workplaces with 1,000 plus and 50-999 employees still appears wide. Despite doctor-worker interviews having now become mandatory, the implementation proportion within workplaces of 50-999 employees was still found to be low.

Key words: doctor's interview (医師面接), mental health care (メンタルヘルス対策), occupational mental health (産業精神保健), overwork (過重労働)

抄録邦訳

平成18年4月に改正労働安全衛生法が施行され，それに伴い，職場のメンタルヘルスの新指針が公表されたが，新指針，改正法に基づいた，事業場におけるメンタルヘルス対策，医師面接の実施状況は明らかになっていない。平成18年11月に全国の企業の本社事業場データベースより従業員数1,000名以上の事業場500社，従業員数50～999名の事業場1,000社をランダム抽出し，これらの事業場の人事労務担当者に調査票を郵送した。それぞれ31社，239社（全体の回答率は18.0%）から回答が得られた。従業員数1,000名以上の事業場では，「心の健康づくり計画」を作成している割合は61%，教育研修の実施率は97%，職場環境改善の実施率は48%，相談体制を確立している割合は 94 ~~93~~%，職場復帰支援体制を確立している割合は77%であり，従業員数50～999名の事業場では，それぞれ19%，~~60~~%， 61 17%，58%，31%であった。医師面接については，従業員数1,000名以上の事業場の実施率は90%，従業員数50～999名の事業場の実施率は52%であった。事業場におけるメンタルヘルス対策の実施率は，平成14年に実施された先行調査の結果に比べ上昇していたが，事業場規模間でその実施率の差が大きかった。医師面接においては，面接が義務化されたにもかかわらず，従業員数50～999名の事業場における医師面接の実施率は低かった。

1．はじめに

長時間労働，過重な業務量や責任，持続的な緊張下での作業などの過重労働およびその他の様々な職業性ストレス要因により，心身の健康障害を生じる労働者が増加しており，精神障害・自殺および脳・心臓疾患による業務上疾病申請・認定件数も増加の傾向にある。平成17年10月には労働安全衛生法が改正され，一定の条件を満たした長時間労働者に対して医師による面接を実施することが義務化され，平成18年4月から施行された。また，改正労働安全衛生法施行に伴い，平成18年3月には，厚生労働省から職場のメンタルヘルスの新指針「労働者の心の健康保持増進のための指針」[1]が公表された。職場のメンタルヘルスの新指針では，平成12年に公表された旧指針「事業場における労働者の心の健康づくりのための指針」[2]よりも法的位置づけがより明確になり，4つのケアなどの旧指針の内容を踏まえながら，衛生委員会等での調査審議，メンタルヘルス対策を積極的に推進する旨の表明，心の健康づくり計画の実施状況の評価及び計画の見直し，個人情報への配慮などの新しい事項が盛り込まれている。

指針に従った対策の実施状況については，平成14年に全国の事業場（労災保険対象事業場リスト）から無作為に抽出した事業場を対象に，旧指針公表直後のメンタルヘルス対策の実態調査（回答率31.5%）[3]が行われている。この調査[3]では，4割の事業場が心の健康づくりに積極的になっている一方，「心の健康づくり計画」の策定，教育研修，相談，職場環境等の改善などの実施率はいずれも1～3割程度であり，メンタルヘルス対策に関心を持ちながらも，具体的な役割分担や計画の策定には至っていない事業場が多いという現状が明らかになっている。また，平成17年に実施された丹下らの調査[4]では，調査対象事業場に偏りがある点，および回答率が低い点に注意が必要であるものの，5～8割の事業場で何らかの形でメンタルヘルス対策の具体的取り組みが実施されていた。社会経済生産性本部の全国の上場企業を対象に実施されたアンケート調査[5]では，従業員の健康づくり施策全体の中でメンタルヘルスに関する対策に力を入れる企業の割合は平成14年の33%から平成18年には59%に倍増したと報告されている。~~近年事業~~場におけるメンタルヘルス対策の実施率は ここ数年で 急激に改善していると推測される。しかし，新指針では，「心の健康づくり計画」の策定にあたっての衛生委員会等の活用や計画の評価を行うこと，さらに個人情報の保護への配慮を重要視し，また効果的

なメンタルヘルス対策の進め方として，①教育・研修および情報提供，②職場環境等の評価と改善，③メンタルヘルス不調者への相談対応，④職場復帰の支援を挙げている。新指針公表後のこれらメンタルヘルス対策の個別の要素の実施状況は不明である。

また，過重労働者に対する医師面接では，過重労働対策等のための面接指導マニュアル・テキスト作成委員会によって「長時間労働者への面接指導マニュアル（医師用）」[6]が作成されており，面接指導の基本的な流れとして，①事業場および労働者から情報を収集し，②疲労，ストレス，うつ病の可能性のある場合にはより詳細な面接調査を実施し，③診察・検査，医学的な判断を行って評価・判定を下す。これに基づいて，④労働者に対する保健指導および⑤事業者への事後措置の意見を述べる，と要約されている。改正法施行前の平成17年労働安全衛生基本調査[7]では，長時間労働を行った労働者に対して医師面接を実施した事業場の割合は従業員数50～999名の事業場で2～6割，従業員数1,000名以上の事業場で9割以上であり，従業員数が多くなるほど，医師面接の実施率が高いと報告されているが，改正法施行後の実施率は明らかにされていない。また，医師面接実施時の問題点や困難についても明確にされていない。

本研究では職場のメンタルヘルス新指針公表・改正労働安全衛生法施行後~~6~~9ヵ月（平成18年12月～平成19年1月）の時点での事業場のメンタルヘルス対策の状況，および過重労働者への医師面接の実施状況を把握するために，事業場を対象とした調査を実施した。

2．方　法

2.1 調査対象

本調査では，専属産業医の選任が必要な従業員数1,000名以上の事業場およびそれ未満で産業医の選任が必要でかつ過重労働者への医師面接が義務づけられている従業員数50～999名の事業場に注目した。企業データベースを持つ会社に，本社従業員数50名以上の企業1,500社のランダム抽出を依頼した。従業員数1,000名以上の本社事業場では総数1,556社から500社をランダム抽出し，従業員数50～999名の本社事業場では24,747社から1,000社をランダム抽出した。平成18年11月中旬に，抽出された企業の本社事業場にアンケートを送付し，人事労務担当者に回答を依頼した。平成19年1月末までに返信があった有効回答数は270社（18%）であり，これらを分析対象とした（従業員数1,000名以上は31社，従業員数50～999名は239社）。回答が得られた事業場の業種は製造業（56.7%），卸売・小売業（12.6%），建設業（8.1%），サービス業（7.4%）などであった。また，事業場の地域分布は北海道が1.9%，東北が5.9%，関東が41.1%，北陸・甲信越が6.7%，東海が15.2%，近畿が12.6%，中国・四国が8.9%，九州・沖縄が7.8%であった。

2.2 調査手続き

回答者自身，および勤務する事業場について，以下の内容を含む質問紙調査を実施した。

2.2-1 職場のメンタルヘルスの新指針に関する質問

(a) 平成18年3月に「労働者の心の健康の保持増進のための指針」が公表されたことを知っているかどうか
(b) 衛生委員会等における「心の健康づくり計画」の立案・策定
(c) 「心の健康づくり計画」に盛り込まれている具体的内容（「心の健康づくり計画」を策定している事業場のみを対象に質問）
(d) 「心の健康づくり計画」が策定されない理由（「心の健康づくり計画」を策定していない事業場のみを対象に質問）
(e) メンタルヘルス教育の実施状況
(f) ストレス要因の把握と，それに対する改善策の実施
(g) 相談体制の確立
(h) 職場復帰体制の確立
(i) 健康情報の取り扱いに関する取り決めおよび，それを周知させるための教育の実施

2.2-2 過重労働者に対する医師面接に関する質問

(a) 平成18年4月から労働安全衛生法における過重労働者に対する医師面接の義務化が開始されたことを知っているかどうか
(b) 過重労働者に対する医師面接を実施しているかどうか
(c) 医師面接の実施対象者の選定法（時間外労働時間の基準，希望者か全員か）
(d) 医師面接の実施体制
(e) 医師面接で使用しているツール
(f) 医師面接での実施上の困難

(c)　　(b)

~~[illegible]~~〜(f)は~~[illegible]~~で「医師面接を実施している」と回答した事業場のみを対象に質問した。

医師面接の実施対象者選定の際の時間基準については，厚生労働省令では100時間以上の超過勤務者が医師面接の義務対象となるが，これ以外にも事業場で独自の基準を設けて医師面接を実施することが努力義務として記載されているため，これを数値で報告してもらい，その分布を見ることとした。

以上の項目から，事業場における「心の健康づくり計画」の策定率，メンタルヘルス教育の実施率，相談体制や職場復帰体制の確立の割合，過重労働者に対する医師面接の実施率などを，先行の調査報告[3]に合わせて，従業員数1,000名以上と従業員数50〜999名の2群に分けて算出した。なお本調査ではこれ以外に事業場規模に関する質問を行っていないため，さらに詳細な事業場規模別の比較はできていない。解析にはSAS ver 9.1を用い，フィッシャーの正確確率検定によって事業場規模による差の検定を行った。また，有意確率は両側5％とした。

3. 結　果

回答事業場の基本属性を表1に示す。従業員数1,000名以上の事業場は従業員数50〜999名の事業場に比べ，常勤の医療従事者や専属・嘱託の臨床心理士，メンタルヘルス担当者を雇用している割合が有意に高かった。

全表の％についている
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表1．対象事業場の基本属性

		事業場従業員数		事業場規模による差
		50-999名 N＝239 ~~(%)~~	1,000名以上 N＝31 ~~(%)~~	p
業種	鉱業	0.8	0.0	<.05
	建設業	9.2	0.0	
	製造業	55.6	64.5	
	電気・ガス水道	1.3	3.2	
	運輸	2.5	0.0	
	通信	0.4	3.2	
	卸売・小売	13.4	6.5	
	金融・保険	2.9	3.2	
	不動産業	0.0	3.2	
	サービス業	7.5	6.5	
	医療・福祉	0.0	3.2	
	その他	6.3	6.5	
所在地	北海道	1.7	3.2	n.s.
	東北	6.3	3.2	
	関東	39.7	51.6	
	北陸・甲信越	7.1	3.2	
	東海	15.9	9.7	
	近畿	13.0	9.7	
	中国・四国	8.8	9.7	
	九州・沖縄	7.5	9.7	
産業保健スタッフの有無(複数回答可)	非常勤看護師・保健師	8.1	29.0	<.01
	常勤看護師・保健師	22.9	80.6	<.01
	非常勤産業医	75.4	58.1	n.s.
	常勤産業医	7.3	67.7	<.01
	嘱託・専属の精神科医・心療内科医	10.6	54.8	<.01
	嘱託･専属のカウンセラー･臨床心理士	11.9	32.3	<.01
	THP心理相談担当者	6.8	45.2	<.01
	産業カウンセラーの有資格者	12.0	63.3	<.01
	その他のメンタルヘルス専門職	5.5	16.7	<.05

※事業場従業員数は本社の従業員数（パート等の非常勤を含む）を表す。

3.1　新指針に基づくメンタルヘルス対策について

3.1-1　メンタルヘルスの新指針の公表の既知率

従業員数1,000名以上の事業場では，全ての事業場の人事労務担当者が新指針の公表を知っていたのに対し，従業員数50～999名の事業場で新指針の公表を知っていたのは70.0%であった。

3.1-2　「心の健康づくり計画」の立案・策定

従業員数1,000名以上の事業場では，6割強が労使で協議し，産業医の助言を得ながら「心の健康づくり計画」を策定しているのに対し，従業員数50～999名の事業場で「心の健康づくり計画」を策定しているのは2割弱であり，3割弱は衛生委員会でメンタルヘルス対策に関する審議が実施されていなかった（表2-Ⅰ）。

3.1-3　「心の健康づくり計画」に盛り込まれている内容

新指針では「心の健康づくり計画」に盛り込むべき内容として6つ（「その他」を含めると7つ）の事項を挙げているが，「心の健康づくり計画の実施状況の評価及び計画の見直しに関すること」を除く5つの事項は，従業員数1,000名以上の事業場の7～8割，従業員数50～999名の事業場の5～7割が盛り込んでいた。一方，「心の健康づくり計画の実施状況の評価及び計画の見直しに関すること」を盛り込んでいる事業場の割合

表2.「心の健康づくり計画」の立案・策定，盛り込まれている内容，策定されない理由

	事業場従業員数		p
	50-999名 (%)	1,000名以上 (%)	
Ⅰ.「心の健康づくり計画」の立案・策定について	N＝232	N＝31	
1．労使で協議し，産業医の助言を得ながら「心の健康づくり計画」を策定している	18.5	61.3	
2．衛生委員会等でメンタルヘルス対策に関する問題点は挙げられているが，計画の立案・策定は行われていない	54.7	32.3	~~<.01~~ <.01 1行下に移動して下さい．
3．衛生委員会等でメンタルヘルス対策に関する審議が行われていない	26.7	6.5	
Ⅱ.「心の健康づくり計画」に盛り込まれている内容（複数回答可。Ⅰで1．と回答した事業場を対象）	N＝42	N＝19	
1．事業者がメンタルヘルス対策を積極的に推進する旨の表明に関すること	66.7	78.9	n.s.
2．事業場における心の健康づくり体制の整備に関すること	64.3	78.9	n.s.
3．事業場における問題点の把握及びメンタルヘルス対策の実施に関すること	64.3	73.7	n.s.
4．メンタルヘルス対策を行うために必要な人材の確保及び事業場外資源の活用に関すること	54.8	78.9	n.s.
5．労働者の健康情報の保護に関すること	50.0	73.7	n.s.
6．心の健康づくり計画の実施状況の評価及び計画の見直しに関すること	33.3	47.4	n.s.
7．その他労働者の心の健康づくりに必要な措置に関すること	4.8	15.8	n.s.
Ⅲ.「心の健康づくり計画」が策定されない理由（複数回答可。Ⅰで2．又は3．と回答した事業場を対象）	N＝185	N＝12	
1．策定が面倒だから	3.2	0.0	n.s.
2．策定にはお金がかかるから	3.8	0.0	n.s.
3．策定する適当な人材がいないから	28.1	33.3	n.s.
~~4.~~ 具体的に何をすれば良いか分からないから 一文字左にずらして，文頭を揃えて下さい	56.8	8.3	<.01
5．策定しても効果があるかどうか分からないから	18.3	8.3	n.s.
6．以前から具体的施策をしており，総論という形での文書化が後回しになっているから	19.4	50.0	<.05
7．策定する必要性を感じないから	10.2	0.0	n.s.
8．その他	9.7	25.0	n.s.

※欠損値：50-999名でⅠが7社，Ⅱが1社，Ⅲが4社。

は，従業員数1,000名以上の事業場で5割弱，従業員数50～999名の事業場で3割強であった（表2-II）。

3.1-4 「心の健康づくり計画」が策定されない理由

「心の健康づくり計画」を策定していない理由は，事業場の規模によって異なっていた。従業員数1,000名以上の事業場では「以前から具体的施策をしており，総論という形での文書化が後回しになっているから」と答えた割合が最も高かったのに対し，従業員数50～999名の事業場では「具体的に何をすれば良いか分からないから」と答えた割合が最も高かった。また，事業場の規模に関係なく，「策定する適当な人材がいないから」と答えた割合が2番目に高かった（表2-III）。

3.1-5 メンタルヘルス教育の実施

従業員数1,000名以上の事業場では，8割以上の事業場で管理監督者教育が実施され，5割以上の事業場でセルフケア教育および事業場内産業保健スタッフ等への教育が実施されていたのに対し，従業員数50～999名の事業場では，4割弱の事業場がメンタルヘルス教育を実施していなかった（表3-I）。

3.1-6 ストレス要因の把握と改善策の実施

従業員数1,000名以上の事業場では，7割5分の事業場でストレス要因の把握が行われており，そのうちの6割5分（全体の5割弱）がストレス要因に対する改善策を実施していた。一方，従業員数50～999名の事業場では，改善策の実施まで行っている事業場は2割にも満たず，5割以上の事業場がストレス要因の把握を行っていなかった（表3-II）。

3.1-7 相談体制の確立

相談体制については事業場規模に関係なく，最も多かったのが事業場内産業保健スタッフによる相談体制

表3．メンタルヘルス教育の実施，ストレス要因の把握と改善，相談体制，職場復帰体制，健康情報の取り決めと教育

	事業場従業員数		p
	50-999名 （%）	1,000名以上 （%）	
I．メンタルヘルス教育の実施（4．以外，複数回答可）	N＝233	N＝31	
1．セルフケア教育を実施している	28.3	54.8	<.01
2．~~ラインケア~~管理監督者教育を実施している	40.3	83.9	<.01
3．事業場内産業保健スタッフへの教育を実施している	18.0	51.6	<.01
4．メンタルヘルス教育~~は行っていない~~を実施していない	39.5	3.2	<.01
II．ストレス要因の把握，改善策の実施	N＝232	N＝31	
1．ストレス要因を把握し，それに対する改善策を実施している	16.8	48.4	
2．ストレス要因は把握しているが，それに対する改善策は実施していない	30.6	25.8	<.01
3．ストレス要因を把握していない	52.6	25.8	
III．相談体制の確立（4．以外，複数回答可）	N＝236	N＝31	
1．管理監督者による相談を確立している	22.0	41.9	<.05
2．事業場内産保スタッフによる相談を確立している	28.8	80.6	<.01
3．事業場外資源による相談を確立している	28.4	54.8	<.01
4．相談体制を確立していない	42.4	6.5	<.01
IV．職場復帰体制の確立	N＝235	N＝31	
何らかの形で職復帰体制を確立している	31.1	77.4	<.01
V．健康情報に関する取り決めと，その教育	N＝237	N＝31	
1．健康情報の取り扱いに関する取り決めを行っており，健康情報を慎重に取り扱う方法についての教育を行っている	47.3	77.4	
2．健康情報の取り扱いに関する取り決めは行っているが，健康情報を慎重に取り扱う方法についての教育は行っていない	28.2	22.6	~~<.01~~ <.01 半行下に移動して下さい．
3．健康情報の取り扱いに関する取り決め~~は~~を行っていない	24.5	0.0	

※欠損値：50-999名でIが6社，IIが7社，IIIが3社，IVが4社，Vが2社。

で，次いで事業場外資源による相談体制，管理監督者による相談体制であった。但し，事業場規模の間で実施率に有意な差が見られ，従業員数50～999名の事業場では4割の事業場が相談体制を確立していなかった（表3-III）。

3.1-8　職場復帰体制の確立

従業員数1,000名以上の事業場では8割弱の事業場が何らかの形で職場復帰体制を確立していたのに対し，従業員数50～999名の事業場で職場復帰体制を確立していたのは3割程度であり，有意な差が見られた（表3-IV）。

3.1-9　健康情報の取り扱いに関する取り決めと，その教育

従業員数1,000名以上の事業場では，全ての事業場で健康情報の取り扱いに関する取り決めが行われており，そのうち8割弱が健康情報の取り扱いを周知させるための教育を実施していた。一方，従業員数50～999名の事業場で健康情報の取り扱いに関する取り決めを行っているのは7割5分であり，そのうち6割強（全体の半数弱）が教育を実施していた（表3-V）。

3.2　過重労働者に対する医師面接について

3.2-1　過重労働者への医師面接義務化の既知率と医師面接の実施率

従業員数1,000名以上の事業場では，全ての事業場が医師面接の義務化を知っており，ほとんどの事業場が医師面接を実施していたのに対し，従業員数50～999名の事業場では2割強の事業場が医師面接の義務化を知らず，約半数の事業場が医師面接を実施していなかった（表4）。

3.2-2　医師面接の実施対象者の選定法

医師面接の実施に関する時間外労働の基準は多いものから，月80時間以上，月100時間以上，月45時間以上であった（表5-I）。また医師面接は「時間外労働基準を満たした者全員に実施している」と答えた事業場が約半数であり，「時間外労働基準を満たし，本人が希望する者」，「時間外労働が著しく多い者は全員，その他の者は希望者のみ」，「その他，独自の方法で実施」と答えた事業場はそれぞれ15%程度であった（表5-II）。

3.2-3　医師面接の実施体制　(表6-I)

面接を行う医師は，ほぼ全ての事業場で産業医であったが，一部の事業場では，産業医以外の医療機関の医師が実施していた。また，面接は医師のみによって実施されることが多かったが，従業員数1,000名以上の事業場では，3割の事業場で産業看護職がまず面接し，産業医につなぐ形態をとっていた~~（表6-I，II）~~。

3.2-4　医師面接で使用しているツール　(表6-II)

医師面接で最もよく使用されているツールは，産業医学振興財団から提供されている面接指導医師用チェックリスト[8]であり，4割の事業場で使用されていた。次いで疲労蓄積度自己診断チェックリスト[9]が3割程度の事業場で使用されていた（表6-III）。

3.2-5　医師面接の実施状況

従業員数50-999名の事業場では，毎月平均して12.0名（標準偏差21.3名）が面接対象となり，5.2名（標準偏差7.3名）を面接していた（N＝102：無回答22社を除く平均）。従業員数1,000名以上の事業場では，毎月平均して50.0名（標準偏差102.2名）が面接対象となり，18.8名（標準偏差23.4名）を面接していた（N＝23：無回答5社を除く平均）。

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3.2-6　医師面接での実施上の困難

医師面接での実施上の困難として多く挙げられたものは，医師・産業医の面接時間がとれない（従業員数50～999名で22%，従業員数1,000名以上で36%），面接後の事後措置の進め方が分からない（同18%，4%），医師面接を希望する従業員がいない（同20%，11%），医師面接後の内容が事業場にフィードバックされない（同16%，21%）であった。自由記述では，医師面接の技術，スケジュール調整の困難さ，受診者が少ないこと，事後措置が困難な点が挙げられていた。

「1000名以上で……
50～999名で……」
の順に入れかえて下さい

入れかえ

入れかえ

入れかえ

表4．労働安全衛生法（安衛法）改正を知っている事業場，長時間労働者への医師面接の実施率

	事業場従業員数		
	N=239 50-999名 ~~(~~%~~)~~	N=31 1,000名以上 ~~(~~%~~)~~	P
安衛法改正を知っている	78.7	100.0	<.01
長時間労働者への医師面接を実施している	52.3	90.3	<.01

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表1と同様に，事業場規模と% の間に
総数(N)を追加して下さい．