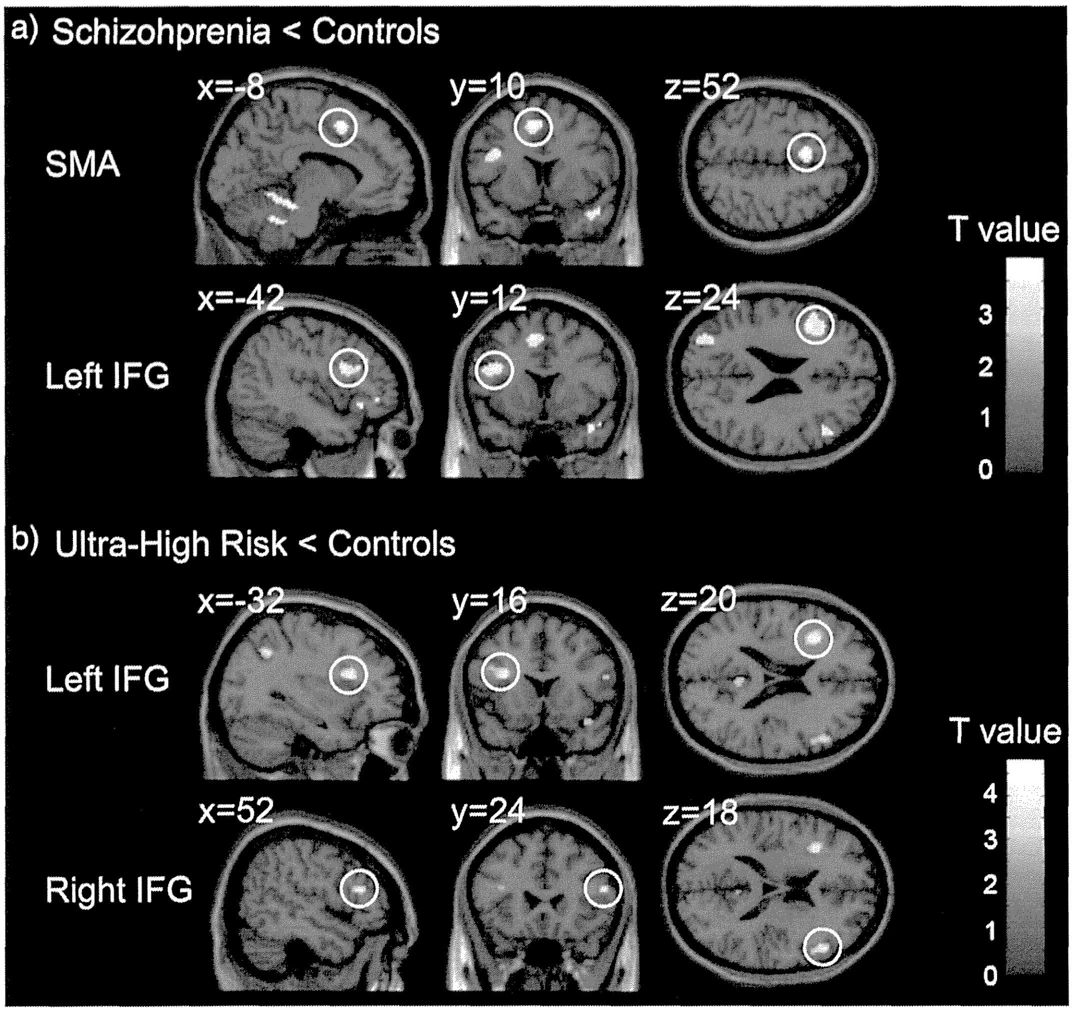

Fig. 2. fMRI results of the non-word compared with word contrast between-group analyses. Significant differences in activity in the between-group analyses of increased responses to non-words compared with words across 20 controls, 20 participants with schizophrenia, and 11 ultra-high risk subjects. For presentation purposes, maps thresholded at uncorrected $p = 0.01$ and a cluster size of 10 voxels are displayed. The color scale refers to t values. (a) Brain regions in which activity was decreased in patients with schizophrenia compared with controls. The supplementary motor area (SMA) centered at coordinates (−8, 10, 52) (top), and the left inferior frontal gyrus (IFG) centered at coordinates (−42, 12, 24) (bottom). (b) Brain regions in which activity was decreased in the ultra-high risk subjects compared with controls. The right IFG centered at coordinates (−32, 16, 20) (top), and the left IFG centered at coordinates (52, 24, 18) (bottom).

Table 2
Between-group analyses of lexicality effects.

Locations	BA	Peak coordinate			Z score	Cluster size (mm^3) ($p < 0.01$, uncorrected)	Uncorrected p
		x	y	z			
Non-words > words							
Controls (n = 20) > schizophrenia (n = 20)							
Left SMA	6/8	−8	10	52	3.55	156	0.0002
Left IFG, pars triangularis	45	−42	12	24	3.19	314	0.0007
Schizophrenia > controls							
No suprathreshold peak							
Controls (n = 20) > UHR (n = 11)							
Left IFG	44/45	−32	16	20	3.55	228	0.0002
Right IFG, pars triangularis	45	52	24	18	3.11	82	0.0009
UHR > controls							
No suprathreshold peak							
Words > Non-words							
No suprathreshold peak							

Abbreviations in this and following tables: BA: approximate Brodmann's area, SMA: supplementary motor area, IFG: inferior frontal gyrus, UHR: participants with ultra-high risk. Threshold for statistical significance was set at uncorrected $p < 0.001$ if the peak coordinates were approximately in ROIs with a cluster size threshold of 10 voxels in uncorrected $p < 0.01$ statistical maps, while the false discovery rate $p < 0.05$ was adapted for peaks in other regions. The coordinates were identified and labeled using the WFU PickAtlas and AAL atlas (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003, 2004).

Table 3
Summary of signal intensity and LIs in functional ROIs.

	Subjects with schizophrenia (n = 20)		Subjects with UHR (n = 11)		Control subjects (n = 20)		Effect size	*df*	F or *t* value	p Value
	Mean	S.D.	Mean	S.D.	Mean	S.D.				
Sphere at (−42, 12, 24)										
Left	1.50	1.73			3.22	2.24	−0.61	38	2.7	0.010
Right	0.83	1.34			1.51	1.46	−0.34	38	1.5	0.13
LI	0.256	0.622			0.425	0.343	−0.24	38	1.1	0.29
Sphere at (−32, 16, 20)										
Left			−0.11	1.84	0.74	1.11	−0.40	1, 28	6.8	0.014
Right			−0.14	2.32	0.29	0.88	−0.06	1, 28	1.0	0.32
LI			0.006	0.626	0.253	0.632	−0.28	1, 28	5.7	0.024
Sphere at (52, 24, 18)										
Left			1.90	4.45	3.59	2.42	−0.33	1, 28	3.3	0.080
Right			0.43	3.27	2.21	1.76	−0.48	1, 28	0.9	0.35
LI			0.347	0.451	0.229	0.412	0.19	1, 28	3.3	0.079

Abbreviations: LI, laterality index; UHR, ultra-high risk.

transition to psychosis. The present study adds to previous literature a finding of aberrant functional activity in the IFG related to phonological word processing in patients with schizophrenia and clinical high-risk individuals.

Leftward lateralization in the non-word compared with word activity contrast was reduced in the UHR group compared with the control group, but not in the schizophrenia group in the current study. The difference between the clinical groups may be the result of a unilateral decrease in left IFG activity in the UHR group (effect size $d = -0.40$ for the left side and $d = -0.06$ for the right), and the relatively bilateral decrease in the schizophrenia group ($d = -0.61$ for the left and $d = -0.34$ for the right) (see Table 3). A previous lexical decision fMRI study reported that the loss of lateralization in genetic high-risk individuals was attributable to reduced left hemisphere activity, while in the schizophrenia group, it was due to increased right side activity (Li et al., 2007a). These results are consistent with the current study in the UHR group, but not consistent regarding the schizophrenia group. This discrepancy could be caused by the heterogeneity of study participants including left handedness and high average age in the previous study. It could also be the result of a difference in the task designs. The event-related design of the current fMRI task made it possible to show the difference in the lateralization of activity during the processing of non-words compared with words, while the previous block-design fMRI study examined activity during lexical decision task block compared with rest condition. It has been suggested that brain hemispheric lateralization and progressive specialization, which relate to the innovation of language, have a genetic basis and schizophrenia is a manifestation of genetic diversity in the evolution of the language capacity characteristic of humans (Crow, 1995, 1996, 1997, 1998). The previous lexical decision fMRI study by Li et al. and the current result may suggest the genetic basis of psychosis (Crow, 2004).

There are several methodological considerations and limitations of the present study. First, antipsychotic medications may have had some effect on fMRI signal intensities, although previous studies of unmedicated genetic high-risk individuals also reported reduced left hemisphere activity and loss of leftward lateralization in IFG (Li et al., 2007a,b). Although eight individuals of the current UHR group were antipsychotic naïve, the small sample size of the UHR group may make it difficult to come to a definitive conclusion on the issue. Second, the lack of a first episode schizophrenia group makes the current results difficult to interpret during the course of illness. Furthermore, the cross-sectional design supports descriptive rather than causal interpretation regarding issue on illness stage progression.

Overall, we found reductions in IFG activity in clinical high-risk individuals and patients with schizophrenia in the lexical decision fMRI task, but a decrease in leftward lateralization was revealed only in the high-risk group. The reduced inferior frontal activity in the clinical group was considered to be involved in the dysfunctional phonological processing. These findings are also potentially related to pathophysiological changes during the course of schizophrenia, and add to the understanding of the nature of language processing disturbances in the illness.

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Contributors

H. Yamasue and R. Hashimoto designed the fMRI task and study protocol. S. Koike and K. Kasai designed and managed the recruitment and clinical evaluation of the clinical participants of the study. H. Yamasue, T. Natsubori, H. Inoue, Y. Takano, and N. Iwashiro collected the MRI and clinical data. H. Yamasue and T. Natsubori managed the literature searches and analyses and wrote the manuscript. W. Gonoi, H. Sasaki, H. Takao, and O. Abe managed the MRI protocol and data collection. R. Hashimoto and N. Yahata contributed to analysis and interpretation of data. All authors contributed to and approved the final manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest in relation to this study.

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Original Research Article

Correlation between both Morphologic and Functional Changes and Anxiety in Alzheimer's Disease

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Key Words
Alzheimer's disease · Neuropsychiatric symptoms · Behavioral and psychological symptoms of dementia · Anxiety · Neuroimaging

Abstract
Introduction: Although anxiety symptoms are often observed in Alzheimer's disease (AD), little attention has been paid to this symptom compared with other neuropsychiatric symptoms. ***Methods:*** Twenty-six patients with mild AD underwent both magnetic resonance imaging and single photon emission tomography with technetium-99m ethyl cysteinate dimer. Neuropsychiatric symptoms were evaluated using the Behavioral Pathology in Alzheimer's Disease Scale (Behave-AD). We investigated the relationship between anxiety and neuroimaging using Statistical Parametric Mapping 8 software. ***Results:*** The Behave-AD anxiety score was correlated with hyperperfusion in the bilateral anterior cingulate cortices and a reduction in the gray matter volume in the right precuneus and inferior parietal lobule. ***Conclusion:*** Our results suggest that anxiety in AD could overlap with the neural correlates of anxiety disorders, and that the specific degeneration associated with AD might be associated with anxiety.

Introduction

Although the core symptoms of Alzheimer's disease (AD) are memory impairment and deficits in other cognitive domains [1], neuropsychiatric symptoms are commonly observed at some time during the clinical course. These symptoms are referred to as behavioral and

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psychological symptoms of dementia and range from psychotic manifestations to mood alterations linked to various symptoms with motor manifestations and sleep or appetite problems [2, 3]. Anxiety is seen in 25–75% of the patients with AD [2–7] and often overlaps with agitation, depression, and psychosis [8–10]. Especially anxiety in mild AD can overlap with depression [11]. Furthermore, anxiety is known to be associated with a deterioration in the patient's quality of life, nighttime behavioral disturbances, and caregiver's burden [12–15]. Therefore, the assessment of anxiety in AD is important. However, anxiety in AD has not attracted as much attention as other behavioral and psychological symptoms of dementia in previous studies [16].

Previous studies investigating anxiety in AD have reported that anxious mood was the most common symptom among the various symptoms of anxiety [5, 17]. Some studies have also reported that 5–15% of the subjects met the diagnostic criteria for generalized anxiety disorder (GAD) [5, 18]. Calleo et al. [19] reported that 43% of the patients with AD and anxiety who had a Neuropsychiatric Inventory score for anxiety of more than 4 points met the criteria for GAD. Some reports indicated that treatments for anxiety disorder, including short-acting benzodiazepine or cognitive behavioral therapy, were also effective for the treatment of anxiety in AD [20–22]. However, a consensus on how to define anxiety in dementia, including AD, has not yet been achieved [16]. Previous reports suggest that anxiety in AD might have a mechanism similar to that of anxiety disorders such as GAD.

From a neuroimaging point of view, only a few studies have investigated the association between anxiety in patients with AD and structural or metabolic changes in the brain [23–25]. Hashimoto et al. [23] reported that anxiety might be associated with hypometabolism in the bilateral medial temporal lobes. On the other hand, Poulin et al. [24] reported that the Neuropsychiatric Inventory anxiety score might be associated with a relatively preserved amygdala volume, which is a component of the fear circuitry. Other neuroimaging studies of anxiety disorders have reported functional abnormalities in key components of the fear circuitry, including the amygdala and some areas of the prefrontal cortex, especially the anterior cingulate cortex (ACC) [26]. Although these reports suggest that the neurobasis of anxiety in AD might be similar to that of anxiety disorders, the results do not coincide fully. Moreover, the modality of these studies was limited to either magnetic resonance imaging (MRI) or ^{18}F-FDG-PET alone. Some reports have pointed out a discrepancy between the patterns of structural and metabolic brain alterations in AD [27, 28]. Therefore, in this study, we used both single photon emission tomography (SPECT) imaging with technetium-99m ethyl cysteinate dimer, which provides functional images of the brain, and a brain MRI scan, which provides structural images of the brain simultaneously in the same subjects. We then investigated how anxiety in AD is related to the structure and function of the brain.

Materials and Methods

Subjects

Twenty-six consecutive Japanese subjects who had been referred to the Jikei University Hospital outpatient clinic were enrolled in this study. All patients were diagnosed as having probable AD based on the National Institute of Neurology and Communicative Disorder and Stroke/Alzheimer's disease and Related Disorder Association (NINCDS/ADRDA) criteria [29]. All diagnoses were made after evaluations of the patients' past medical history, physical or neurological examinations, routine blood tests, MRI, and SPECT. All patients were assessed using a comprehensive neuropsychological test battery, including a Mini-Mental State Examination (MMSE; 0–30 points) [30], a Frontal Assessment Battery (0–15 points) [31], and the Clinical Dementia Rating Scale sum of boxes (0–18 points). Furthermore, neuropsychiatric symptoms, including anxiety, were assessed based on information obtained from a structured interview with each patient's caregiver, and the anxiety was rated using the anxiety subscale of the Behavioral Pathology in

Alzheimer's Disease Scale (Behave-AD; total score, 0–75 points; anxiety score, 0–12 points) [32]. Patients were excluded if a history of other neurological disease, brain injury, substance abuse, major depressive or psychotic disorder, epilepsy, delirium, metabolic disorder, or treatment with acetylcholine esterase inhibitor were noted. The present retrospective study was approved by the Ethics Committee of the Jikei University School of Medicine.

Assessment of Anxiety/Phobia in Patients with AD

We assessed the anxiety of the patients using the Behave-AD. Four items of the Behave-AD were used for the assessment: (1) anxiety regarding upcoming events, (2) other anxieties, (3) fear of being left alone, and (4) other phobias. The severity of each of these items was evaluated on a scale of 0, 1, 2, or 3 points.

Brain MRI Procedure

Twenty-three subjects underwent a brain MRI examination using a 1.5T MRI system (MAGNETOM Avanto; Siemens Medical Systems, Erlangen, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence at 544/2.2/1 (TR/TE/excitation) produced a gapless series of continuous, thin sagittal sections, using the following parameters: flip angle, 15 degrees; matrix, 256 × 256; field of view, 23 × 23 cm; section thickness, 1.00 mm.

Preprocessing of MRI Data (Voxel-Based Morphometry, VBM)

Data were processed using Statistical Parametric Mapping 8 (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) software running on MATLAB 8.0 (MathWorks, Natick, Mass., USA). The gray matter (GM) was segmented using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) with default parameters. The preprocessing can be summarized as follows: all MR images were bias-corrected, and the tissues were classified within a unified model. DARTEL was used to register the images. Subsequently, normalized GM-segmented images were smoothed with a Gaussian kernel with an 8-mm full-width-at-half-maximum.

Brain SPECT Procedure

Twenty-six subjects underwent cerebral blood flow measurements while lying down in a supine position with eyes closed in a quiet room. Each subject was injected intravenously with 600 MBq of technetium-99m ethyl cysteinate dimer. Twenty minutes later, brain SPECT was performed using the step-and-shoot method: 50 s per angle and 72 angles for a total of 22 min. The matrix size was 128 × 128, and the location window was 140 keV, at 20%. For prefilter and absorption correction, a ramp filter (order, 8.0; cutoff, 0.27) was used. The image voxel size was 3.2 mm. The SPECT system used was a three-detector gamma camera (PRISM-IRIX; Shimadzu Medical Co., Kyoto, Japan) with a low-energy high-resolution collimator. The SPECT images were prepared using attenuation correction according to Chang's method.

Preprocessing of SPECT Data

SPECT data were also processed using SPM8. Each SPECT image was normalized to the ^{99m}Tc-ECD template in the Montreal Neurological Institute space using linear proportions and a nonlinear sampling algorithm. The normalized SPECT images were thereafter smoothed using a 12-mm full-width-at-half-maximum kernel.

Statistical Analysis

Demographic data were analyzed using SPSS 20.0 J for Windows (SPSS Japan Inc., Tokyo, Japan). Correlations between the Behave-AD anxiety item score and clinical variables were examined using the Spearman rank correlation coefficient.

The imaging data were analyzed using SPM8, which utilizes the general linear model. We used the multiple regression model of SPM8 and explored the regional volume/regional cerebral blood flow, which is correlated with the Behave-AD anxiety score. The Behave-AD affective score and the MMSE were treated as confounding covariates. We first set the threshold as $p < 0.001$ without correction for multiple comparisons to prevent type II errors. The extent threshold was set at 100 voxels. Once the group difference was found, a post hoc analysis was performed to investigate regional changes using small-volume correction (SVC) with WFU PickAtlas software. Significance levels were set at a family-wise error-corrected p level of <0.05. We determined the Montreal Neurological Institute coordinates to identify the anatomical region of the clusters.

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Table 1. Demographic and clinical characteristics of the AD patients (n = 26)

	Mean	SD	Behave-AD items	Mean	SD
Female gender	20 (77%)		Behave-AD total score	5.47	5.77
Age, years	74.95	7.29	Paranoid and delusional ideation	0.89	1.93
Duration, months	27	16.9	Hallucination	0.09	0.75
Education, years	12.42	2.87	Activity disturbances	0.81	1.32
CDR-SB	4.53	3.19	Aggressiveness	0.7	1.4
MMSE	23	5.23	Diurnal rhythm disturbances	0.33	0.86
FAB	12.79	3.33	Affective disturbance	0.81	1.27
			Anxieties and phobias	1.2	1.07

CDR-SB = Clinical Dementia Rating scale sum of boxes; FAB = frontal assessment battery.

Table 2. Clinical characteristics of anxiety in AD patients

Four items of the Behave-AD	Mean ± SD
Anxiety regarding upcoming events	0.73±0.67
Anxiety (other)	0.73±0.60
Fear of being left alone	0.15±0.37
Phobias (other)	0

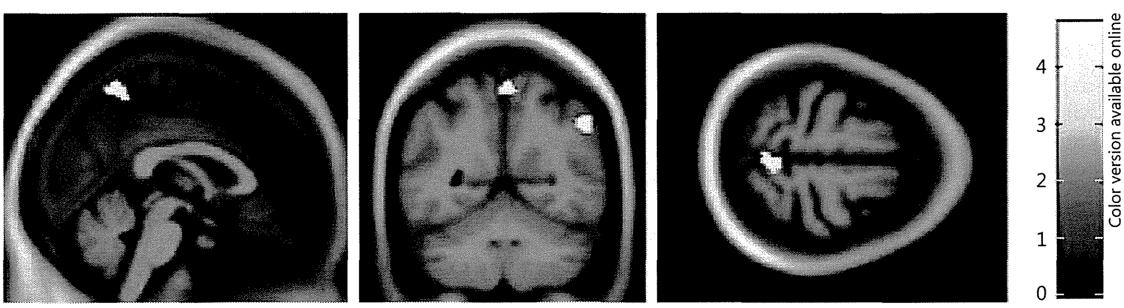

Fig. 1. Regions with a significant negative correlation between the Behave-AD anxiety item score and the GM volume ($p < 0.05$ with SVC). VBM showed a negative correlation between the Behave-AD anxiety score and the GM volume in the right Pcs and the IPL. A significant positive correlation was not seen between the GM volume and the Behave-AD anxiety item score.

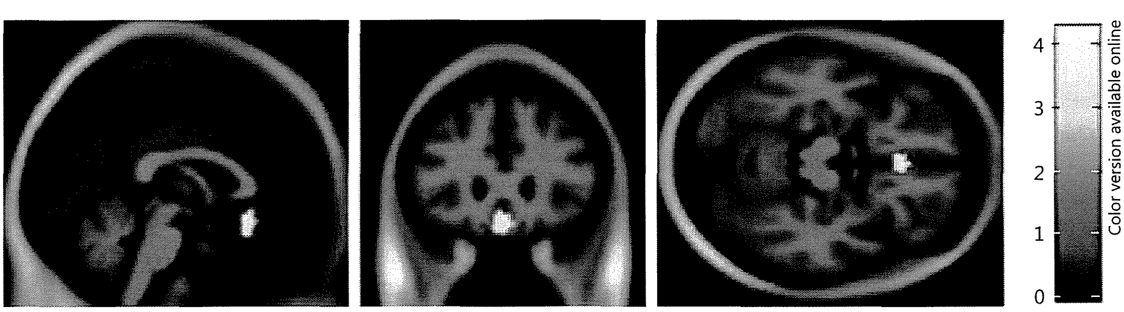

Fig. 2. Regions with a significant positive correlation between the Behave-AD anxiety item score and the rCBF ($p < 0.05$ with SVC). A significant positive correlation between the Behave-AD anxiety score and the rCBF was found in the bilateral ACCs. A significant negative correlation was not observed between the rCBF and the Behave-AD anxiety item score.

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Table 3. Location, cluster size, and voxel peaks of brain regions with a significant correlation between the Behave-AD anxiety item score and a decreased GM volume

Region	Coordinates, mm			Peak t	Cluster size	SVC, family-wise error-corrected p
	x	y	z			
Pcs	1.5	–55.5	61.5	4.82	338	0.026
Right IPL	51	–55.5	39	4.68	243	0.018

Table 4. Location, cluster size, and voxel peaks of brain regions with a significant correlation between the Behave-AD anxiety item score and an increased rCBF

Region	Coordinates, mm			Peak t	Cluster size	SVC, family-wise error-corrected p
	x	y	z			
Bilateral ACCs	0	26	–16	4.31	111	0.015

Results

Patient Characteristics

Table 1 shows the demographic and clinical characteristics of the AD patients. The mean MMSE score was 23.0 ± 5.23, and most of the patients were considered to have mild-stage AD. The range of Behave-AD anxiety scores in the entire sample was from 0 to 4 points (0 points, n = 4; 1 point, n = 9; 2 points, n = 8; 3 points, n = 3; 4 points, n = 2); table 2 shows the mean and SD of each of the four items. Furthermore, the Behave-AD anxiety score was correlated with the Behave-AD total score (r = 0.550, p value = 0.004) and the affective score (r = 0.528, p value = 0.006).

VBM Results

We found a significant negative correlation between the Behave-AD anxiety score and the GM volume in the right precuneus (Pcs) and inferior parietal lobule (IPL) (fig. 1; table 3). We did not find any significant positive correlation between the GM volume and the Behave-AD anxiety item score.

SPECT Results

Regarding the SPECT data, we found a significant positive correlation between the Behave-AD anxiety score and the rCBF in the bilateral ACC (fig. 2; table 4). We did not find any significant negative correlation between the rCBF and the Behave-AD anxiety item score.

Discussion

We investigated the relationships between morphological or functional imaging and symptomatic anxiety in patients with AD. The demographic data revealed that anxiety is correlated with affective symptoms, while imaging data revealed that anxiety is correlated with atrophy of the right Pcs and IPL and hyperperfusion of the bilateral ACC.

Anxiety has been reported in 25–75% of the patients with AD [2–7]. Especially an anxious mood is more common than other symptoms such as fearfulness [5, 17]. Anxiety in AD was

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reported to often overlap with agitation, depression, and psychosis [8–10]. Especially in mild AD, anxiety can overlap with depression [5, 11]. The present demographic data showed that the anxiety score of the Behave-AD was higher than the phobia score. In addition, anxiety was significantly correlated with serious affective symptoms. Thus, the present demographics results were consistent with those of previous studies.

From a neuroimaging viewpoint, the present neuroimaging data showed that the Behave-AD anxiety score was significantly correlated with hyperperfusion in the bilateral ACC and with atrophy in the right Pcs and IPL. Regarding the functional imaging results, the ACC is a component of the fear neurocircuitry, and various studies have shown that the ACC is involved in anxiety disorders [26]. Although most of these previous studies were functional MRI studies, they showed that the ACC was activated in response to fear stimuli. Besides fear stimuli, several studies have reported an increased baseline brain function of the ACC in patients with anxiety disorder [33, 34]. The ACC might regulate the activation of other components, including the amygdala, and hyperactivation of the ACC in anxiety disorder might serve as a compensatory mechanism [35, 36]. On the other hand, only a few neuroimaging studies have examined anxiety in AD. However, these results were not consistent, and Hashimoto et al. [23] reported that anxiety in AD was associated with hypometabolism of the medial temporal lobe, which is a component of the fear neurocircuitry. Our functional imaging results also suggested that anxiety in AD might involve the fear circuitry, and the neurobasis of anxiety in AD might be similar to that of anxiety disorders.

Regarding the morphological imaging results, several reports have suggested that the Pcs and IPL could be related to anxiety. The GM volume of the right Pcs was decreased in patients with panic disorder [37]. Patients with generalized social phobia showed a reduced neural activation related to implicit learning in the left IPL [38]. Both the Pcs and the IPL were associated with the overgeneralization of conditioned fear, which is an important conditioning correlate of anxiety [39]. In addition, both structures are known to be associated with the degeneration of AD [40, 41]. Furthermore, accumulation of amyloid and tau in the posterior cingulate located near the Pcs is correlated with anxiety in mild cognitive impairment [42]. Our morphological imaging results suggested that the neurobasis of anxiety in AD might be associated with the specific degeneration that is characteristic of AD, and not just a change in the fear circuitry.

Our study has several limitations. First, the sample size was limited. Second, we did not consider psychosocial factors. Orrell et al. [43] reported that anxiety in dementia was associated with a greater dependency, problems in the patient-caregiver relationship, and stressful life events. The patient-caregiver relationship, in particular, might influence the Behave-AD score. Third, we did not use instruments exclusively designed for the assessment of anxiety in dementia, such as the Rating Anxiety in Dementia scale [44]. Since the Behave-AD is a general-purpose neuropsychiatric instrument, anxiety might not have been adequately assessed. Fourth, the anxiety score of the Behave-AD may not be normally distributed, and our neuroimaging results should be interpreted carefully.

Despite these limitations, our study revealed that the neural correlates of anxiety in AD might be similar to those of anxiety disorder. These findings suggest that treatments for anxiety disorder, such as cognitive behavioral therapy, might also be effective for treating anxiety in AD. Our results also raise the question of whether anxiety might be associated with the specific degeneration that is characteristic of AD and not just be a simple change in the fear circuitry. Further research with a larger number of subjects and precise assessments of anxiety symptoms and psychosocial factors is needed to answer this question.

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Regular Article

Network analysis for motives in suicide cases: A cross-sectional study

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Aim: Suicide victims have various distresses or motives. There are few studies on how these motives toward suicide relate with each other. We used network analyses to extract the structures of correlations among the motives for suicide.

Methods: We obtained datasets of suicide victims from 2007–2009 in Japan in cooperation with Ibaraki Prefectural Police Headquarters. The data were analyzed by network centrality measures and a structural analysis by block modeling.

Results: Among the motives, depression and physical illness showed relatively high scores of 'degree centrality', whereas depression and unemployment showed relatively high scores of 'betweenness centrality'. Structural analysis by block modeling resulted in eight blocks. The most important block comprised eight motives, including conflict between parent and child, marital conflict, economic hardship, and overloaded with debt.

Conclusion: Depression and physical illness were important and priority areas for completed suicides, although these two motives had different influences on suicide behaviors. Furthermore, structural analysis revealed the important role of a block, including some familial and financial motives, which induced hopelessness. Our results suggest that it might be useful to consider the common ways in which motivations for suicide are tied together when suicide intervention is launched from a social model point of view.

Key words: completed suicide, hopelessness, motive, network analysis, police statistics.

SUICIDE VICTIMS ARE subject to various stress factors, in addition to other motivations for ending their lives. The latter include problems related to family, health, finances, work or school, and romance. Most of these problems are psychosocial in nature and they can be intricately intertwined, thereby leading a person to attempt suicide.

To generate more effective prevention strategies, it is very important to understand not only mental disorders but also hierarchies and correlations among complex psychosocial risk factors, including distress and motives in cases of completed suicide. However, it is unclear how different motives for suicide are inter-connected and which combination of motives is the most important and prevalent in individuals who commit suicide. In most of the research in Japan,[1–8] motives have simply been aggregated separately for each suicide case, and potential correlations among various suicide cases have not been studied.

In Japan, two large statistical datasets concerning suicide are widely available; one is a statistical report by the national police agency and the other is a report by the Japanese Ministry of Health and Labor. The police statistics count the number of suicide victims in each region under the jurisdiction of the local police station. The police have investigated personal characteristics and background factors of each case. Results of this investigation include various motives

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for each suicide; these are then compared to a previously compiled list of suicide motives. From this the investigation identifies up to three possible motives for a given suicide, based upon evidence, such as suicide notes or other documentation.[9] If these combinations of motives from different suicide cases are not simply aggregated but analyzed as a network, we could reveal the hierarchies and correlations of the motives for suicide.

Network analysis has recently been developed in order to clarify complex correlations among multiple factors.[10–13] Using this analysis technique, we can uncover the structure of correlations involved in multiple events like suicides.[14] This type of network analysis has been successfully applied to medical research,[11–13] but to date its application in social medicine has been limited.

Therefore, to clarify the correlations among the motives, we investigated networks of multiple motives for individual suicide victims, based on data obtained from police statistics. We extracted the structure of correlations among motives for suicide by using network analyses.

METHODS

Subjects

We obtained detailed datasets of completed suicide in cooperation with Ibaraki prefectural police headquarters as well as with permission from the Ibaraki prefectural government. Suicide rates in the prefecture are 25 per 100 000 persons yearly, which is the average rate in Japan. The number of suicide victims from 2007–2009 was 2293 in the prefecture. We used the dataset of all 2293 suicide cases. The sample was composed of 1691 (73.7%) male cases and 602 (26.3%) female cases, with an age range of 12–98 years and a mean of 52.3 years with an SD of 18.5 years (mean = 51.3, SD = 17.8 years for male cases; mean = 55.1, SD = 20.3 years for female cases).

From an ethical perspective, the data were provided to us after unlinkable anonymizing, which meets the exception condition of 'Ethical Guidelines for Epidemiological Research' of Japan;[15] thus, no individual could be identified. The guideline states that epidemiological surveys of subjects whose identities are both anonymous and unlinkable do not have to be approved by an ethics committee. Therefore we did not apply for approval of the ethics committee about this study.

Procedure

Motives for suicide were classified into eight major categories by the format of police statistics: (i) family problems; (ii) health problems (physical and mental); (iii) economic and livelihood problems; (iv) work-related problems; (v) romantic problems; (vi) school-related problems; (vii) others; and (viii) unknown. These eight major categories of motives are presented in bold font in Table 1. Each major category is subdivided into 53 minor categories. Up to three minor motivation categories were recorded for each case of suicide. We extracted all motives for the suicides from the datasets.

In network analysis, structures in which some elements are linked to others can be considered to be networks. When a network is presented graphically, network nodes are connected by edges.[16] In this study, a node corresponds to a single motive and edges correspond to suicide victims having multiple motives. When a suicide victim had a pair of motives, we considered that these two motives were linked, or tied to each other. Structures in which certain motives are linked to other motives are considered to be a network.

To apply network analysis, we changed the style of datasets from a case-by-variable matrix to an adjacency matrix, in which each motive was listed both in both rows and columns.[14] We entered the adjacency matrix into the UCINET v6 program (Analytic Technologies, Lexington, KY, USA) for descriptive analysis.[17]

Statistical analysis

The number of motives in each minor category was summarized separately according to sex (male, female) and age (under 39, 40–64, and over 65). A χ^2-test was used for statistical analyses to detect differences in sex and age, with a statistical significance level fixed at $P < 0.05$. The Bonferroni correction was used for post-hoc multiple comparisons to control for type I error rate.

In network descriptive analysis, we performed the following analyses.

(A) Calculated centrality measures for each motive as a node.
(B) Performed a structural analysis by block modeling.

Table 1. Distributions of subjects among motives and centralities

	Number of subjects (%)						Centralities ($n = 451$)	
		Sex		Generation				
Categories	Total	Male	Female	Adolescents	Adults	Elderly	Degree	Betweenness
Family problems	**235 (8.3)**							
Conflict between parent and child	28 (1)	19 (0.9)	9 (1.2)	6 (0.7)	12 (0.9)	10 (1.5)	0.269	0.021
Marital conflict	51 (1.8)	39 (1.9)	12 (1.7)	19 (2.3)	27 (2.1)	5 (0.7)	0.385	0.021
Conflict between other family members	21 (0.7)	15 (0.7)	6 (0.8)	5 (0.6)	9 (0.7)	7 (1)	0.269	0.015
Death of family member	29 (1)	23 (1.1)	6 (0.8)	3 (0.4)	12 (0.9)	14 (2.1)	0.212	0.002
Hopeless situation for the family	55 (1.9)	37 (1.8)	18 (2.5)	6 (0.7)	24 (1.8)	25 (3.7)	0.346	0.014
Severe verbal reprimand	4 (0.1)	3 (0.1)	1 (0.1)	4 (0.5)	0 (0)	0 (0)	0.019	0
Stress of raising children	7 (0.2)	2 (0.1)	5 (0.7)	4 (0.5)	2 (0.2)	1 (0.1)	0.096	0
Physical and/or verbal abuse	1 (0)	1 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0.058	0
Exhaustion from caring for infirm family	13 (0.5)	5 (0.2)	8 (1.1)	0 (0)	9 (0.7)	4 (0.6)	0.135	0
Other family problems	26 (0.9)	15 (0.7)	11 (1.5)	10 (1.2)	7 (0.5)	9 (1.3)	0.212	0.011
Health problems (physical & mental)	**971 (34.4)**							
Physical illness	346 (12.3)	228 (10.9)	118 (16.4*)	23 (2.8)	136 (10.4)	186 (27.8)*	0.519	0.048
Depression	402 (14.2)	230 (10.9)	172 (23.9)*	141 (17)	184 (14.1)	77 (11.5)	0.731	0.217
Schizophrenia	87 (3.1)	52 (2.5)	35 (4.9)	46 (5.5)*	30 (2.3)	11 (1.6)	0.269	0.01
Alcoholism	17 (0.6)	17 (0.8)	0 (0)	5 (0.6)	10 (0.8)	2 (0.3)	0.25	0.004
Drug abuse	4 (0.1)	2 (0.1)	2 (0.3)	2 (0.2)	2 (0.2)	0 (0)	0.077	0
Other mental illness	74 (2.6)	42 (2)	32 (4.4)	25 (3)	29 (2.2)	20 (3)	0.404	0.071
Physical disability	28 (1)	19 (0.9)	9 (1.2)	5 (0.6)	11 (0.8)	12 (1.8)	0.231	0.004
Other health problems	13 (0.5)	10 (0.5)	3 (0.4)	5 (0.6)	5 (0.4)	3 (0.4)	0.135	0.016
Economic and livelihood problems	**454 (16.1)**							
Bankruptcy/business failure	5 (0.2)	5 (0.2)	0 (0)	1 (0.1)	3 (0.2)	1 (0.1)	0.058	0
Business struggling	74 (2.6)	72 (3.4)*	2 (0.3)	12 (1.4)	55 (4.2)*	7 (1)	0.423	0.024
Unemployment	52 (1.8)	50 (2.4)*	2 (0.3)	24 (2.9)	27 (2.1)	1 (0.1)	0.462	0.073
Unable to find employment	17 (0.6)	17 (0.8)	0 (0)	10 (1.2)	7 (0.5)	0 (0)	0.173	0.006
Economic hardships	76 (2.7)	61 (2.9)	15 (2.1)	16 (1.9)	42 (3.2)	18 (2.7)	0.5	0.065
Overloaded with debt*	98 (3.5)	93 (4.4)*	5 (0.7)	29 (3.5)	64 (4.9)*	5 (0.7)	0.385	0.017
Assumption of excessive debt	4 (0.1)	4 (0.2)	0 (0)	0 (0)	4 (0.3)	0 (0)	0.077	0
Debt (other)	91 (3.2)	88 (4.2)*	3 (0.4)	24 (2.9)	57 (4.4)	10 (1.5)	0.385	0.015
Harassment by debt-collectors	8 (0.3)	8 (0.4)	0 (0)	2 (0.2)	4 (0.3)	2 (0.3)	0.115	0
Suicide for death benefit	9 (0.3)	9 (0.4)	0 (0)	2 (0.2)	7 (0.5)	0 (0)	0.173	0.008
Other financial problems	20 (0.7)	17 (0.8)	3 (0.4)	3 (0.4)	13 (1)	4 (0.6)	0.192	0.002
Work-related problems	**129 (4.6)**							
Failure at work	19 (0.7)	19 (0.9)	0 (0)	4 (0.5)	13 (1)	2 (0.3)	0.154	0
Inter-personal relations at work	23 (0.8)	20 (1)	3 (0.4)	14 (1.7)	9 (0.7)	0 (0)	0.212	0.007
Trouble adjusting to changing work environment	18 (0.6)	16 (0.8)	2 (0.3)	9 (1.1)	9 (0.7)	0 (0)	0.192	0.002
Work-related fatigue	47 (1.7)	42 (2)	5 (0.7)	19 (2.3)	28 (2.2)	0 (0)	0.308	0.015
Other work problems	22 (0.8)	20 (1)	2 (0.3)	10 (1.2)	11 (0.8)	1 (0.1)	0.25	0.016
Romantic problems	**63 (2.2)**							
Marital problems	4 (0.1)	3 (0.1)	1 (0.1)	4 (0.5)	0 (0)	0 (0)	0.058	0
Heartbreak	23 (0.8)	18 (0.9)	5 (0.7)	19 (2.3)*	4 (0.3)	0 (0)	0.212	0.003
Extra-marital affair	4 (0.1)	3 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)	0 (0)	0.115	0
Conflict in relationship	29 (1)	19 (0.9)	10 (1.4)	24 (2.9)*	4 (0.3)	1 (0.1)	0.308	0.008
Other romantic problems	3 (0.1)	2 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	0 (0)	0.038	0
School-related problems	**24 (0.9)**							
Entrance examination problems	2 (0.1)	1 (0)	1 (0.1)	2 (0.2)	0 (0)	0 (0)	0.077	0
Problems related to academic future	8 (0.3)	8 (0.4)	0 (0)	8 (1)*	0 (0)	0 (0)	0.058	0
Disappointment with grades	2 (0.1)	2 (0.1)	0 (0)	2 (0.2)	0 (0)	0 (0)	0.077	0
Inter-personal relations with teachers	1 (0)	1 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0.019	0
Bullying	1 (0)	1 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0.038	0
Conflict with friends at school	3 (0.1)	1 (0)	2 (0.3)	3 (0.4)	0 (0)	0 (0)	0.077	0.007
Other school problem	7 (0.2)	5 (0.2)	2 (0.3)	7 (0.8)	0 (0)	0 (0)	0.135	0.017
Others	**85 (3)**							
Public disclosure of crime	9 (0.3)	8 (0.4)	1 (0.1)	5 (0.6)	3 (0.2)	1 (0.1)	0.096	0.001
Crime victim	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0	0
Copycat suicide	5 (0.2)	4 (0.2)	1 (0.1)	0 (0)	3 (0.2)	2 (0.3)	0.115	0
Loneliness	28 (1)	23 (1.1)	5 (0.7)	7 (0.8)	10 (0.8)	11 (1.6)	0.404	0.061
Neighborhood problems	2 (0.1)	1 (0)	1 (0.1)	0 (0)	1 (0.1)	1 (0.1)	0.038	0
Other	41 (1.5)	37 (1.8)	4 (0.6)	16 (1.9)	17 (1.3)	8 (1.2)	0.288	0.055
Unknown	**861 (30.5)**							
Unknown	861 (30.5)	664 (31.6)	197 (27.3)	239 (28.8)	395 (30.3)	207 (31)	0.019	0
Total	2822	2101	721	831	1302	668		

Significant difference between the sexes and among generations. *$P < 0.05$ after Bonferroni's correction.

Centrality measures are indices for assessing and comparing the importance of each node.[18] We calculated two basic centrality measures, 'degree centrality' and 'betweenness centrality'. Degree centrality evaluates the number of edges (suicide victims) that connect to a node (motive). A node that has many edges and is connected with a number of other nodes is evaluated as having a high level of degree centrality. Betweenness centrality detects nodes that are located between other nodes and that act as connectors between nodes.

A block modeling is the structural analytic method for network to simplify representation of a multi-relational network that captures some of the general features of a network's structure. It also classifies nodes as 'blocks' through their structural equivalence in the network and it determines the structure of inter-block or intra-block relations. Nodes in the same block are regarded as structurally equivalent, and they generally have competitive roles.[19] To perform block modeling, we used the Convergence of Iterated Correlations (CONCOR) algorithm. The CONCOR is an algorithm partitioning nodes into blocks in terms of structural equivalence. CONCOR splits the initial data into several blocks according to depth of split parameter.

'Density' is defined as the total of all the ties in a network divided by the number of possible ties. Density is one of the most common measures used in network analysis. We can measure the density within a block, or the density between a pair of blocks. If the density of a block were higher than the density of other blocks, then this high-density block would include highly related nodes. Moreover, if the density between a pair of blocks is higher than the average density of the whole network, then the correlation between these two blocks might be highly significant. We call density in each block the intra-block density, and density between blocks the inter-block density. We calculated densities by blocks to summarize inter- and intra-block network. The average density for the entire networks was regarded as the cut-off value for significance of inter- and intra-block densities.

RESULTS

Data demographic and distributions

A total of 2822 motives were extracted from 2293 cases. The motives for 861 cases (37.5%) were unknown. Concerning the number of motivating factors cited in these cases, 981 (42.8%) had one motive, 373 (16.3%) had two, and 78 (3.4%) had three. Among these, 451 cases (19.7%) in which there had been multiple motives for suicide were used in the network analysis. The 451 cases with multiple motives included 345 (76.5%) male cases and 106 (23.5%) female cases, with an age range of 13–93 years and a mean of 50.0 years with a standard deviation (SD) of 16.5 years (mean = 49.3, SD = 15.4 years for male cases; mean = 52.3, SD = 19.5 years for female cases).

Details of the data demographics appear in Table 1. Among eight major categories of motives, most suicide victims suffered from health problems (971 cases), followed by economic and livelihood problems (454 cases). With regard to minor categories, depression was the largest, followed by physical illness. Regarding sex, female cases demonstrated significantly higher rates of physical illness as well as higher rates of depression than male cases. On the other hand, female cases demonstrated lower rates of business struggling, unemployment, overloaded with debt, and debt (other) than male cases. With respect to age, relative to the preceding two groups, adolescent and young adults (under 39 years) showed significantly higher rates of schizophrenia, heartbreak, conflicts in relationships, and problems related to academic future. Adults aged 40–64 years presented significantly higher rates of business struggling and overloaded with debt than other groups. The elderly (over 64 years old) demonstrated significantly higher rates of stress from physical illness than other groups.

Network analysis for motives

Figure 1 is a whole network comprising all motives. As shown in figure, physical illness and depression were the most important motives; these were centrally located, large in size, and strongly inter-connected. Family problems and economic and livelihood problems were identified around these two large motives. We therefore constructed descriptive analyses to explore more details of the network as follows.

(A) Centrality measures

Table 1 shows distributions of centralities for each motive. Degree centrality measuring revealed that the depression (degree centrality scores [DC] = 0.73),

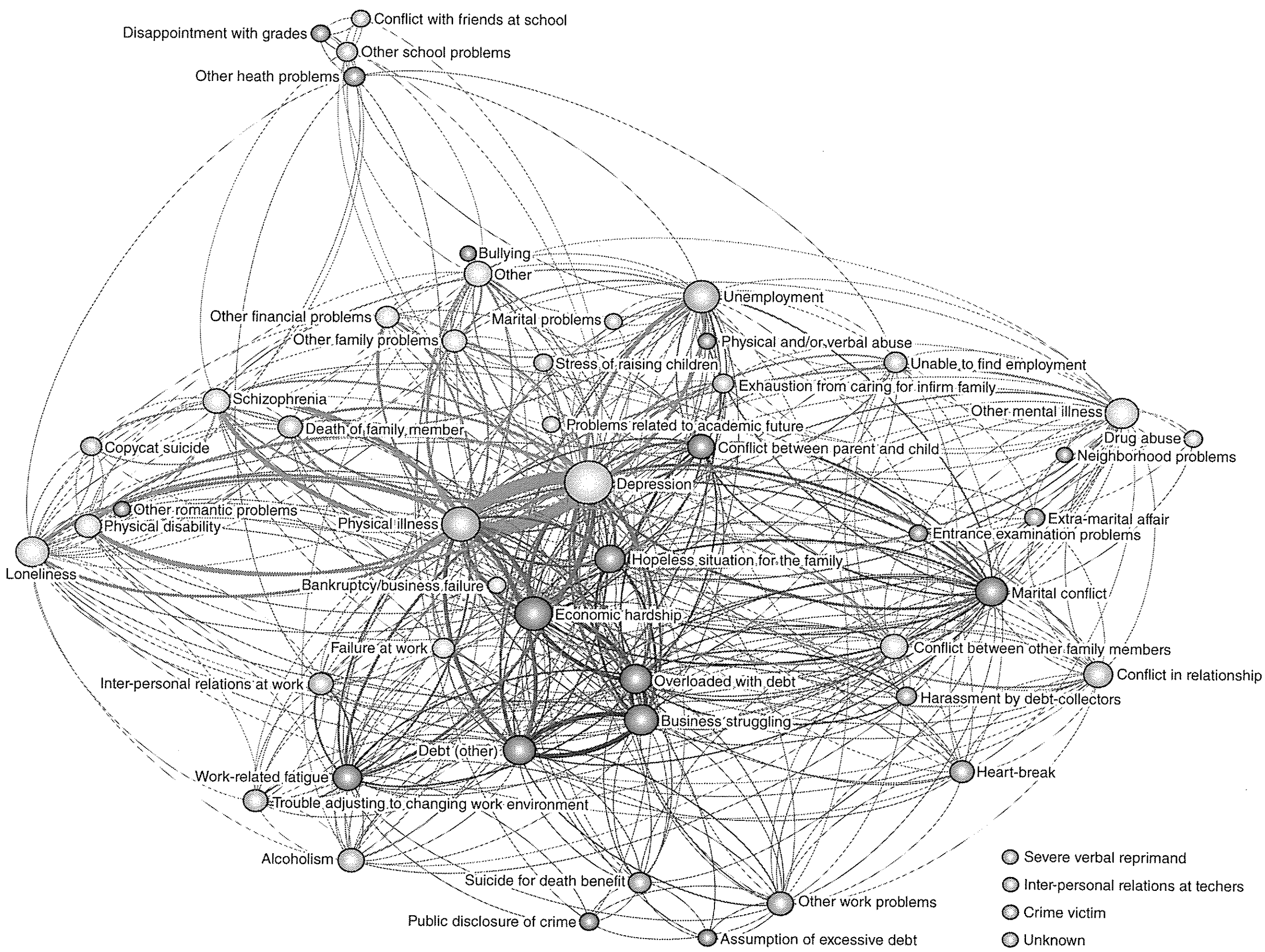

Figure 1. Whole network of motives of suicides. This figure depicts an entire network of the motives of 451 suicides visualized by the Gephi program. Each node represents a simple motive as shown by the labels. Each tie (edge) means that if one suicide victim had two motives, the correlation between them is indicated. Thus, each tie represents correlations between motives. Identical colors for both nodes and ties indicate the same blocks of motives. Widths of ties are determined by number of correlations between two motives. The size of each node is determined by degree centrality. Locations of each node are determined by weight of ties.

the physical illness (DC = 0.52), and economic hardships (DC = 0.50) were the top three motives and they were highly connected with other nodes. Betweenness centrality measures revealed that depression (betweenness centrality scores; BC = 0.22), unemployment (BC = 0.07), and economic hardship (BC = 0.07) comprised the top three motives that mediated between nodes.

(B) Block modeling by CONCOR

Setting the depth of splits to 3 led to the most meaningful results in relation to interpretation of networks. The CONCOR method divided all motives into eight blocks as shown in Figure 2. Blocks were named and ranked according to the order of structural equivalence. Block 1 consisted of eight minor categories of motives. Block 2 consisted of 11 minor categories of motives, and was the second largest. Block 3 consisted of 16 minor categories of motives, and had the largest number of minor categories among all the blocks. Block 4 consisted of five motives. Block 5 consisted of four motives. Blocks 6, 7 and 8 all had three motives. On closer examination of the details of intra-blocks, conflict between parent and child, hopeless situation

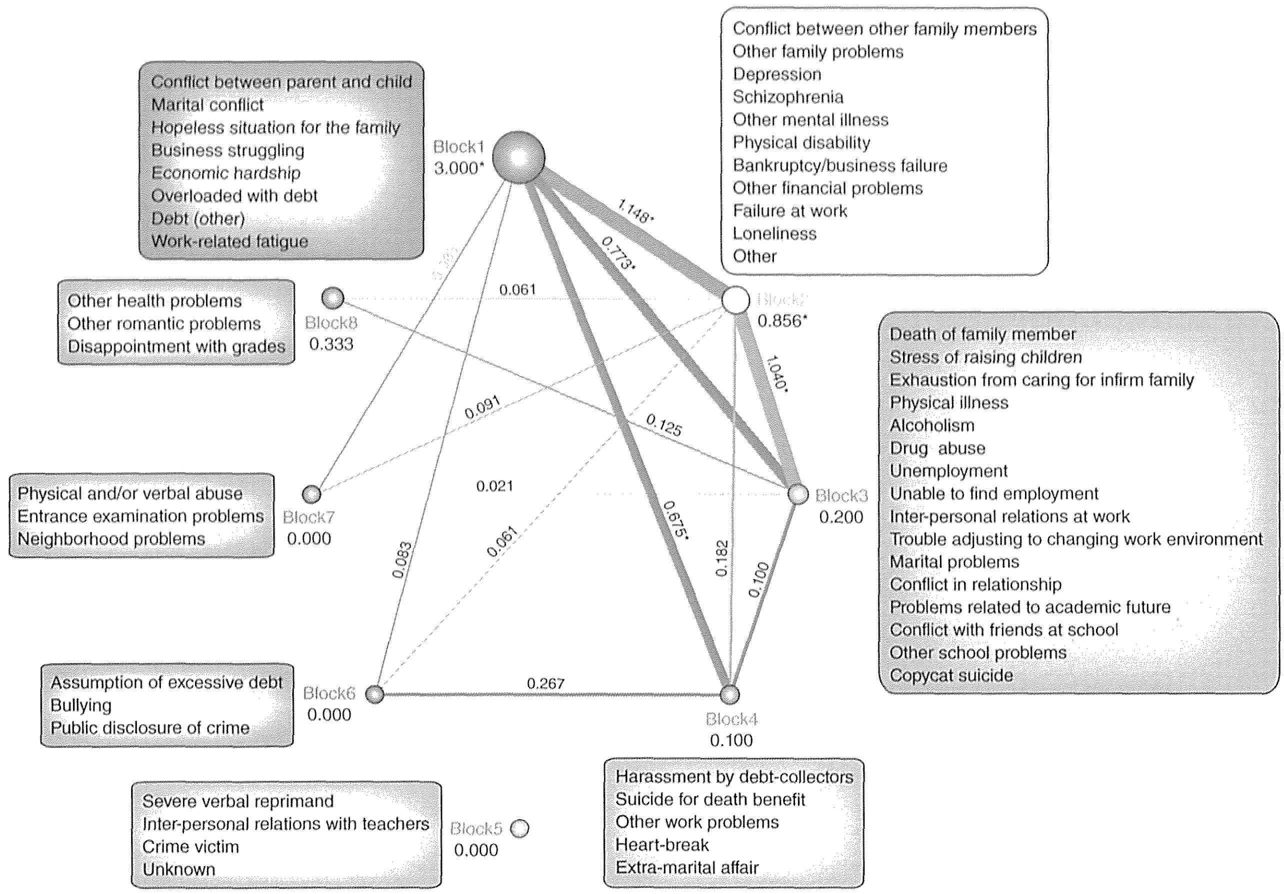

Figure 2. Inter-block network about motives of suicides. This network indicates the inter-block networks; blocks represent as full circular nodes, with node size representing the number of intra-block density. The width of each tie reflects the mean of sums of edges between blocks. The numbers under the label of each node refer to the density of each block. The number above the edges represents the density of inter-block network. Labels of motives located on square background indicate the member of motives in each block. Numbers with an asterisk are greater than cut-off score.

for the family, business struggling, etc. had a similar structure in Block 1. In Block 2, the most important motive was depression. Depression, schizophrenia, physical disability, etc. had a similar structure. In Block 3, the most important motive was physical illnesses. Physical illness, unemployment, alcoholism, etc. were related in a similar structure.

Figure 2 presents inter-, and intra-block network structures and numbers of density. An average of the whole network density of 0.44 was used as cut-off density value for density by blocks. As shown in Figure 2, the density in Block 1 was 3.00, which was the highest among intra-block densities. The density in Block 2 was 0.85, which was the second highest among intra-block densities. The density in Blocks 3, 4, 5, 6 7, and 8 were lower than cut-off value. The inter-block density between Block 1 and Block 2 was 1.15, which was the highest among inter-block densities. The inter-block density between Blocks 2 and 3 was 1.04, which was the second highest among inter-block density. The inter-block density between Blocks 1 and 3 was 0.77, and the density between Blocks 1 and 4 was 0.68. These were greater than cut-off value. Thus, it was regarded that Block 1 was a centered network of motives, and Blocks 1, 2, and 3 were core components of suicides motives.

DISCUSSION

In this study, we clarified the role and correlations of motives that drive individuals to suicide. First, the importance of depression and physical illness as critical motivating factors is underscored by centrality measures. On the other hand, the block modeling revealed that the role of depression and the role of physical illness are different, and that elements of family problems and economic problems have special roles in the process of suicide.

To our knowledge, this is the first study of network analyses that has explored correlations among motives for suicide. Although the simple aggregation of information from suicide cases has been reported in other studies,[1,2,4,5] the present network analysis revealed the structure of suicide motive networks and the specific role of several motives that were not previously detected by the earlier studies. Predisposing factors, environment, and life events are background factors in a suicide, and the complex interaction of these factors creates a risk of suicide. Previous studies evaluated the diagnosis of mental disorders and psychological proneness separately as risk factors of suicide.[20–22] The strength of this study is that it offers a comprehensive coverage of both background and risk factors related to suicide; furthermore, it ranks these factors as well as their functional correlations.

Among the motives for suicide, depression and physical illness emerge as especially important targets for suicide prevention. Block modeling classified the depression into Block 2 and the distress of physical illness into Block 3, which suggests that the role of depression is different from that of physical illness. These findings were consistent with previous reports.[21,23]

The correlations between each block have been perceived to have a hierarchical interpretation as they involve both core and peripheral components.[24] In our study, it is also revealed that Block 1, which involves conflict between parent and child, hopeless situation for the family, and business struggling, has the highest intra-block density and has the most number of inter-block ties. Thus, the motives in Block 1 might have more important roles than motives in other blocks. Nevertheless, these motives are not frequent in the demographical data. How do we think about the role of Block 1? Not all suicide attempts occur during a depressive episode[25] and several psychosocial risk factors have been studied to predict suicide other than depression, including hopelessness, psychache, impulsivity, and negative life event.[26–28] Beck and colleagues[29] defined hopelessness as negative future expectancies, speculated that the central factor of suicidality is the emergence of hopelessness and believed that affective symptoms were secondary.[30] From a sociocultural viewpoint, the Asian view of the self is more dependent on the correlations with others than Western countries and this is likely to affect future expectations.[31] In this respect, acute life stresses evoked by family conflicts, job and financial security issues can be considered as a negative relationship with others. These acute life stresses play more important roles for suicide in Asia than in Western countries.[32] Therefore, we speculate that Block 1 is the group of acute stresses consisting of negative future expectations, or hopelessness, through the view of the self, which is dependent on others. As the motives of Block 1 have a link to hopelessness, those motives might strongly reinforce the process of committing suicide according to Beck's theory.

This study has several limitations. First, the data were collected by police officers who assessed the motives that were clearly indicated as causes of each suicide, such as documentation in a suicide note. This might overestimate unknown motives when compared to the methods employed in a psychological autopsy. Among patients who had admitted attempting suicide in a Chinese geriatric psychiatry unit, the average number of suicide motives was 2.2 per person;[33] however, in this study, the average of motives, excluding unknown motives, was 1.37 per person. In addition to unknown motives, there may be multiple motives for a person who commits suicide. Second, in this analysis, each edge of intermotives was a suicide victim. Therefore, two motives tied by one edge had a direct relation mediated by a suicide victim. However, three motives tied by two edges might not have direct relations. For example, when there are three nodes A, B, and C, and edges are between A and B and between B and C, we need to interpret carefully whether A and C have a correlation intermediated by B.

In spite of these limitations, our study indicates that physical and mental illness are central in the network of suicide, and also that 'hopelessness' plays an important role in suicide. To prevent suicide, we have to improve the psychoeducation and community care for acute family and financial problems evoking hopelessness, as well as mental health strategies, especially for depression. Further research investigating correlations of motives using a psychological autopsy with larger populations and various regions will be needed to extract the generalized networks of suicidal motives.

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