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Research Article

A Reduced Gray Matter As A Predisposed Risk Factor For The Delirium After Cardiac Operations

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Abstract

Objectives

Delirium is a common neurobehavioral disturbance in older patients after surgery. A decrease in the volume of the cortical gray matter (GM) could be a risk factor for the postoperative delirium and may be a predictive clue for the incidence.

Methods

The patients with the age range from 58 to 87 underwent an elective cardiac operation during two periods, i.e., between August 2005 and August 2006 (study 1) as well as between July 2016 and December 2018 (study 2). The total subjects included in the two studies were study 1 (84) and 2 (91) for a total of 175. Before the surgery, an MRI study was conducted. The MRI data were processed to calculate the absolute volumes of the pre-defined region of interest using Statistical Parametrical Mapping 8. The delirium was diagnosed according to the DSM-IV criteria.

Results

Thirty-two of the 175 patients (18.3%) developed delirium. Based on a comparison to the age-controlled non-delirium patients, a statistically significant reduction in the GM volume of the delirium patients was observed in the widespread cerebral cortices as well as in the cerebellum. The decreased volume of the temporal lobe generated a cut-off value for the incidence of delirium with a moderate value (0.810) of area under the curve.

Conclusions

The atrophic change in the GM can be associated with the vulnerability to delirium after cardiac surgery. The MRI measurement before surgery may provide a useful value for the prediction of a postoperative syndrome.

Key words: Delirium; Cardiac Surgery; Brain MRI; Predisposing Factors; Atlas-Based; Elderly Patient; Cerebral Cortex; Atrophy

Introduction

Delirium is a neurobehavioral syndrome characterized by the several functional deficits, i.e., attention, cognition, emotion, circadian rhythm and psychomotor functioning [1,2]. The phenomenology of the syndrome can be attributed to the transient disruption of normal neuronal activity, and the pathophysiology may be associated with changes in the neurotransmitter and dysfunctions of the neural networks [3-6]. The etiology of delirium is a multifactorial complex caused by predisposing and precipitating risk factors [1, 2, 5 ~ 11]. The former factor includes advanced age, cognitive impairments, sensory impairments and coexisting medical disease. Medical procedures, such as surgery and medication, as well as worsening of their physiological conditions are contained in the latter factor. The sum of the two factors may define the risk of developing delirium.

Cardiac surgery in elderly people results in delirium in about 11.4 % to 30.7 % of patients based on recent studies [12 ~ 18]. Circumstantial evidence suggests that the elderly people have a decreased reserve capacity to respond to noxious precipitating insults such as surgery. Delirium in elderly patients after a surgical procedure is clinically critical, because it has an association with worse outcomes [1, 7, 19, 20], e.g., longer hospital stays, higher rates of mortality, and longer-term decline in their functional and cognitive status. However, the main medical procedure to delirium, such as prevention and treatment, still remains a significant problem in the hospital [7~9, 21 ~ 23]. Consequently, clinical and biological information of an individual patient to appropriately predict the incidence of delirium is necessary to develop a preventive measure including pharmacological and non-pharmacological methods, being required for the investigation of preventive procedures for delirium to obtain an accurate effect of the intervention.

An increased risk of developing into delirium after the operation may be associated with the changes in the brain MRI characteristics of neurovascular and neurodegenerative changes [25]. While the association of the atrophic brain change and the delirium was not consistently observed in a few studies [26 ~ 28], we have recently demonstrated an association between the smaller pre-operative cortical brain volume, i.e., the temporal and limbic lobes, and the delirium after a cardiac operation by an in vivo volumetric MRI study [29]. The brain structural alteration can be involved in the vulnerability to the post-operative delirium [24, 25]. In addition, the atlas-based methods used in the study lead to a calculation of a cut-off value of the brain volume to discriminate between the delirium and non-delirium groups, showing a moderate value (>0.8) to predict postoperative delirium [29].

In the present study, we carried out another investigation of the same protocol used in our previous study [29], and analyzed the combined data including the previous experiment to obtain an expanded evaluation of the volumetric change in a larger sample of patients.

Materials and Methods

This study consisted of two investigations, i.e., study-1 and study-2 (Table 1). We have already described study-1 concerning the subjects, pre-operative evaluations and peri-and post-operative evaluations in a previous paper [29]. Study-2 was also carried out using the same experimental protocol as the former one.

Subjects

All the subjects of the combined study who underwent scheduled cardiac operations in the Department of Cardiothoracic Surgery, Tokyo Medical and Dental University, University Hospital Faculty of Medicine (Tokyo, Japan) were more than 57 years old, because the youngest age of the delirium patients in study-1 was 58 years old [29, 30]. The patients of study-1 and study-2 underwent surgery between August 2005 and August 2006 and between July 2016 and November 2018, respectively. Patients who were admitted for an emergency operation during this period were excluded from the present study. Approval was obtained from the Ethics Committee of the Tokyo Medical Dental University and all patients gave written informed consent.

Pre-operative evaluations

The pre-operative evaluation included medical history, body mass index, impairments in their physical condition, handicaps, alcohol consumption, smoking habits and the Mini-Mental State Examination (MMSE) [31] (Table 1). Neither alcoholism (alcohol abuse and/or alcohol dependence) nor dementia was diagnosed by the preoperative assessment in the subjects of the present study [1]. There was no patient who had a depressive syndrome checked by a pre-operative interview [1, 18].

A few days before the operations, the subjects of study-1 underwent an MRI study using a 1.5-tesla General Electric Signa (General Electric, Milwaukee, WI, USA) with a standard head coil. One hundred twenty-four sections of a T1-weighted 3-dimensional fast spoiled-gradient recalled sequence were obtained in an axial orientation as 1.5-mm thick sections (repetition time [TR] = 17 ms; echo time [TE] = 3 ms; flip angle = 20 °; field of view [FOV] = 22 cm; number of excitations = 1; pixel matrix = 256 x 256). In study-2, the patients underwent an MRI study using a 3-T MRI system (Trillium Ovale; Hitachi Healthcare, Tokyo, Japan) with a head coil. One hundred sixty-seven sections of a T1-weighted 3-dimensional fast spin-echo sequence were obtained in a sagittal orientation as 1-mm thick sections (repetition time [TR] = 450 ms; echo time [TE] = 6.2 ms; field of view [FOV] = 256 x 256 mm; number of excitations = 1; pixel matrix = 288 x 256).

Peri-and post-operative evaluations

The operating procedure, operation time, anesthetic time, use of extracorporeal circulation, amount of blood loss and blood transfusion requirement during the surgery were obtained from the flow chart (Table 1). The post-operative medical factors for the intensive care and any cardiopulmonary complications were also included in the analyses for the risk factors of delirium (Table 1). The administration of dexmedeto midine (α_2-adrenergic agonist) [23,24] was included in the evaluations of study-2, while no subjects in study-1 received the drug during the peri- or post-operative periods.

Table 1: Comparisons of pre-, peri- and post-operative variables between the delirium group and the non-delirium group (univariate analysis)

	Study 1		Study 2		Total (Study 1 + Study 2)	
Varialble	Delirium group (n = 19)	Nondelirium group (n = 65)	Delirium group (n = 13)	Nondelirium group (n = 78)	Delirium group (n = 32)	Nondelirium group (n = 143)
Pre-operative data						
Age	73.1 ± 6.4*	69.4 ± 6.5	77.7 ± 6.2**	70.7 ± 6.6	75.0 ± 6.6 ***	70.1 ± 6.6
Sex (male)	13 (68.4%)	39 (60.0%)	12 (92.3%)	52 (66.7%)	25 (78.1%)	91 (63.6%)
Handedness (r/l)	14/5	62/3	12/1	73/5	26/6 *	135/8
Body mass index	21.6 ± 3.0*	23.6 ± 3.0	22.9 ± 3.1	24.2 ± 2.9	22.6 ± 3.2	23.2 ± 3.1
Hypertension	18 (94.7%)	51 (78.5%)	9 (69.2%)	50 (64.1%)	27 (84.4)	101 (70.6%)
Diabetes mellitus	6 (31.6%)	27 (41.5%)	6 (46.1%)	20 (25.6%)	12 (37.5%)	47 (32.9%)
Hemodialysis	5 (26.3%)*	3 (4.6%)	1 (7.7%)	5 (6.4%)	6 (18.8%)*	8 (5.6%)
Hypercholesteremia	6 (31.6%)	32 (49.2%)	3 (23.1%)	28 (35.9%)	9 (28.1%)	60 (42.0%)
Cerebral vascular disease	2 (10.5%)	13 (20.0%)	2 (15.3%)	9 (11.5%)	4 (12.5%)	22 (15.4%)
History of smoking	9 (47.3%)	33 (508%)	9 (69.2%)	44 (56.4%)	18 (56.3%)	77 (53.8%)
Daily alcohol use	9 (50%)	20 (30.8%)	7 (53.8%)*	18 (23.0%)	16 (50.0%)*	38 (26.6%)
Visual disturbance	1 (5.3%)	5 (7.7%)	0 (0.0%)	1 (1.3%)	1 (3.1%)	6 (4.2%)
Auditory disturbance	2 (10.5%)	2 (3.1%)	0 (0.0%)	2 (2.6%)	2 (6.3%)	4 (2.8%)
History of cancer	3 (16.7%)	8 (12.3%)	1 (7.7%)	12 (15.4%)	4 (12.5%)	20 (14.0%)
History of delirium	3 (15.8%)	0 (0.0%)*	0 (0.0%)	6 (7.7%)	3 (9.4%)	6 (4.25)
Mini-mental state examination	26.3 ± 3.4	26.7 ± 2.7	26.8 ± 2.9*	28.3 ± 2.0	26.5 ± 3.2*	27.7 ± 2.5
Peri-operative data						
Operation time （min）	404.7 ± 89.2	399.7 ± 109.3	527.6 ± 189.7	495.7 ± 177.7	454.6 ± 149.4	452.1 ±157.5
Anesthetic time (min)	510.9 ± 92.8	506.1 ± 111.4	692.0 ± 200.3	627.3 ± 188.0	584.5± 169.4	572.2 ± 168.6
Extracorporeal circulation (on)	10 (52.6%)	40 (61.5%)	7 (53.8%)	37 (47.4%)	17 (53.1%)	77 (53.8)
Blood loss (ml)	797.7 ± 559.4	1119.1 ± 1142.5	2380.8 ± 1709.0	2444.5 ± 1865.9	1439.7 ± 1392.1	1847.1 ± 1709.5
Blood transfusion	12 (66.7%)	32 (49.2%)	12 (92.3%)	72 (92.3%)	24 (75.0%)	104 (72.7%)
Type of operation						
CABG	7	31	2	14	9	45
VS	5	18	4	25	9	43
CABG + VS	3	5	0	4	3	9
TAA	3	7	3	26	6	33
TAA + VS	1	2	3	5	4	7
The others	0	2	1	4	1	6
Post-operative data						
Incubation period (days)	1.5 ± 1.6	1.5 ± 2.0	2.55 ± 3.75	0.76 ± 1.0	1.9± 2.7	1.1 ± 1.6
Intensive care unit stay (days)	4.2 ± 2.1	5.3 ± 10.0	7.9 ± 5.8*	3.8 ± 2.2	5.7 ± 4.4	4.5 ± 2.7
Cardiopulmonary complication	11 (61.2%)	44 (67.7%)	6 (46.1%)	28 (35.9%)	17 (53.1%)	72 (50.3)

Continuous variables are expressed as mean ± SD, and categorical data are expressed by the number of patients. The two-tailed Student's t- test or Welch's t-test was used for the continuous variables. The comparison of proportions was analyzed by the Chi square tests. If the expected cell frequencies were < 5, we used Fisher‘s exact test for the analysis. History of smoking; more than 100 (cigarette/day x year) CABG; Coronary artery bypass graft: VS; Valve surgery: TAA; Thoracic aortic aneurysm.
* p<0.05、** p<0.01, *** p<0.001 Delirium group vs each counterpart.

After the operation, all the patients were daily assessed not only by the medical staff of the Department of Thoracic Cardiovascular Surgery, but also by well-trained psychiatrists (co-authors (AS, HM and TT) until discharged. The presence of delirium was determined by the psychiatrists according to the DSM-IV-TR criteria for delirium [32]. The severity of delirium was evaluated using the severity items of the Delirium Rating Scale-Revised-98 (DRS-R-98) [33].

MRI data processing

The MRI data were processed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm) in which we applied the VBM8 toolbox which is an extension of the unified segmentation model consisting of a spatial normalization, bias field correction, and tissue segmentation [34]. Registration to the stereotactic space of the Montreal Neurological Institute (MNI) consisted of a linear affine transformation and nonlinear deformation using high-dimensional Diffeomorphic Anatomical Registration through Exponential Lie Algebra (DARTEL) normalization [35].

Six parameters of the segmentation process, i.e., 'Bias regularization', 'Bias FWHM', 'Warping regularization', 'Sampling distance', 'Use-SANLM de-noising filter', and 'MRF weighting' were carried out with the default settings of VBM8, whereas the 'Modulated normalized' in the 'Writing options' was set to 'affine + non-linear (SPM8 default)' to obtain the absolute volume. The voxel size of the preprocessed image was 1.5 x 1.5 x 1.5 mm.

After the preprocessing by the VBM8 tool of the SPM8 software, the absolute GM volume of the region of interest was evaluated using the whole brain mask generated by WFU PickAtlas ver. 2.5.5 [36] in SPM8. The evaluated volume was expressed as the fraction (%) of the total intracranial volume, i.e., the sum of the total volumes of the gray matter (GM), white matter (WM) and CSF space.

Statistical analysis

We compared the pre-, peri- and post-operative factors between the delirium group and the non-delirium group. The continuous variables are expressed as the mean ± SD, and the categorical data are expressed as proportions. The two-tailed Student *t* test or the Welch's t-test was used for the continuous variables. The comparison of the proportions was analyzed by the Chi square tests. If the expected cell frequencies were < 5, we used Fisher's exact test for the analysis. The variables with a p value < 0.05 were entered into a backward stepwise logistic regression analysis requiring a p value less than 0.05 to remain. In addition, a comparison between the two groups of the brain volumes was carried out using ANCOVA with the type of MRI appliance as well as other appropriate valuables as a covariate. For adjustment of the multiple comparisons, the statistical significance level was set at a P value of < 0.05 by the Bonferroni correction. A correlation with age was analyzed by the Pearson test. All the statistical analyses were carried out using the Statistical Package for the Social Sciences, version 17.0 (SPSS, Inc., Chicago, IL, USA). In addition, a receiver operating characteristic (ROC) analysis was performed to evaluate the accuracy to predict the post-operative delirium using MedCalc (Version 17.9.7; MedCalc Software, Ostend, Belgium).

Results

General

The patients underwent six types of cardiac surgeries (number of patients) that included coronary artery bypass graft (CABG) surgery (54), valve (VS) surgery (52), CABG and VS surgery (12), thoracic aortic aneurysm (TSA) surgery (39), TAS and VS surgery (11) and others (7) (Table 2). The cardiac surgery using extracorporeal circulation was carried out on 77 patients (53.8 %).

Thirty-two of the 175 patients (18.3 %) developed delirium after the cardiac surgery. The incidence ratio of delirium for each study was 22.9 % (study 1) and 14.3 % (study 2). The youngest age of the delirium patients in study-2 was 66 years old, while the age was 58 in study 1. The mean ± SD of the severity score of DRS-R-98 was 20.9 ± 6.9.

Peri- and post-operative variables

In the pre-operative data of the total study (study1 plus study-2), there was a statistically significant difference (p < 0.05) between the delirium group and the non-delirium group in age, handedness, hemodialysis, alcohol daily use and MMSE (Table 1). No difference between the two groups was found in the examined peri- and post-operative data (Table 1). The frequency of the administration of dexmedetomidine in the delirium group (12 patients (92.3%)) was similar to that of the non-delirium group (56 patients (70.0%)) in study-2, while there was no administration of the drug in study 1. The multivariate logistic regression analysis, in which the significant variables based on the univariate comparison test were entered, revealed that advanced age and daily alcohol consumption were important risk factors of post-operative delirium (Table 2).

MRI study

The comparisons of the absolute total intracranial volume and the fractions of the GM, WM and CSF space between the delirium group (n = 32) and non-delirium group (n = 143) are shown in (Table 3). The ANCOVA analysis using the type of MRI, the age of the patients and the daily alcohol use as a covariate revealed a statistically significant change in the GM ($F = 21.086$, $df = 1, 170$, $p < 0.05$ after adjustment) and WM ($F = 5.881$, $df = 1, 170$, $p < 0.05$ after adjustment) of the delirium group.

Table 4 shows the results of the GM of the whole brain divided into eight areas. The GM fraction of the delirium group was significantly decreased in four brain areas, i.e., the frontal lobe ($F = 11.889$, $df = 1, 170$), temporal lobe ($F = 27.840$, $df = 1, 170$), parietal lobe ($F = 11.885$, $df = 1, 170$), limbic lobe ($F = 24.484$, $df = 1, 170$) and cerebellum ($F = 12.476$, $df = 1, 170$), after an adjustment by the Bonferroni correction for the multiple comparison within the components.

An ROC curve analysis was carried out on the GM volume data in the brain area in which there was a statistically significant difference between the two groups to evaluate the accuracy to predict delirium after the operation (Table 5). The AUC value of the temporal lobe (0.810) was relatively higher than those of the other brain areas (Figure 1A). The positive predictive and negative predictive values of the temporal lobe was 37.9 % and 93.6 %, respectively, whereas the highest of each predictive value was observed in the frontal lobe (58.3%) and in the limbic lobe (95.6%).

(Figure 1B) shows scatter plots of the brain volume and age in the temporal lobe, showing the optimal cut-off levels calculated by the ROC curve analysis. A statistically significant correlation between the brain volume and age was found in all the subjects ($r = -0.481$, $df = 1,173$, $p < 0.001$).

Discussion

The present study demonstrated that the pre-evaluated brain GM volume of the patients developed into the post-operative delirium was significantly decreased compared to that of the age-controlled nondelirium patients. The reduction in the fraction of the GM volume in the delirium patients was more widespread than found in the previous study (29), i.e., the cerebral cortices including the frontal and parietal lobes and the cerebellum, as the sample size of the present study was increased by integration with the new experiment of study 2. Thus, it is likely that the morphological change in the brain was associated with the incidence of the postoperative delirium in the non-demented elderly patients.

The recent studies also suggested an increased risk of delirium after the operation was related to the changes in the brain MRI characteristics of neurovascular as well as of neurodegenerative alterations [5. 24 ~ 30, 37]. The alterations in the neural substrate in the white matter and gray matter may be linked to the vulnerability of the postsurgical delirium. The present study provided further information about the association between the decline in the GM volume and the sensitive response to the surgical procedures in the elderly. In addition, the measurement of the absolute brain GM volume by the Atlas-based method subsequently produced a cut-off value to predict the occurrence of delirium with a moderate accuracy. The high-risk patients that developed delirium could be discriminated by the level of the GM of the brain region, such as the temporal lobe with a positive predictive and negative predictive values, 37.9 % and 93.6 %, respectively. The division between the high and low-risk patients before the elective surgery is critical information for medical care including the prevention procedure and an early detection of the onset of delirium. Moreover, the separation between them may be required for the investigations of the pharmacological and non-pharmacological procedures in order to make an accurate evaluation of the preventing effect.

The pathophysiology of delirium is considered to be the widespread disturbance of higher cortical functions [3, 5] as well as a changed functional connectivity among the neural networks [4], manifesting the main features regarding consciousness and attention. The brain atrophic change in the non-demented elderly patients observed in the present study was possibly involved in the transient dysfunction for the integration and processing of sensory information and motor responses caused by the stressful procedures during the peri- and post-operations [3]. The decline in the GM volume with a certain variation is observed as a normal part of healthy aging in the elderly (see Figure 1B) [38, 39], which probably includes an age-related decrease in several brain structural networks such as the temporal lobe-related one [23]. Advanced age was one of the important risk factors for the delirium after the cardiac surgery [1, 2, 7 ~ 11, 13, 15,16,18,19]. Thus, the structural alteration in the non-demented elderly patients could be one of the important components associated with the vulnerability to the post-operative delirium.

In the recent studies after the cardiac operation, the rates of the incidence of developing delirium varied from 11.4 ~ 30.7 % (12 ~ 18). The rates of the incidence also showed a variation from 22.6 (study 1) to 14.3 % (study 2) in the present study. In addition, there was a subtle Statistically discrepancy between both studies regarding the pre-operative variables with a statistically significant difference based on the univariate comparison test, i.e., body mass index, hemodialysis, daily alcohol use, history of delirium and MMSE. The multivariate logistic regression analysis of the combined patients demonstrated that daily alcohol consumption and advanced age were important risk factors of post-operative delirium, in which the significant variables based on the univariate comparison test. No patients in the present study have a history of alcohol abuse that can be a risk factor of the post-operative delirium [1, 2, 11]. As the patients with a daily habit of alcohol consumption did not have any history developed to the level of misuse, it is unlikely that the post-operative delirium in the patients was attributed to the withdrawal from an excessive intake of alcohol. However, the daily alcohol use was consequently taken into as one of the covariates for the statistical analysis of the MRI data.

All the MRI data of the patients were spatially normalized to the standard brain by a component of the VBM method, and predefined ROI labeling of software was applied to calculate the absolute brain volume of a specific brain area. The large variations in the brain structure of older people with an age-related neurodegenerative process [37, 38] might lead to a restriction in achieving the normalization across subjects. In spite of the difference in the subjects as well as of the MRI measurements between studies 1 and 2, the fractions of the total intracranial volume in the ROI, such as the temporal lobe, were distributed without any clear difference between the two studies (see Figure 1B). An ROC curve analysis using the data of the fractions generated a similar cut-off value for the discrimination between the delirium and non-delirium groups in the examined brain areas (data not shown).

In conclusion, the present study on the cardiac operation provided information that the atrophic brain change in the elderly people without dementia may be associated with the development. The cut-off value of the brain volume subsequently generated by the methodological procedure of the present study would be useful to predict the high and low-risk patients to develop post-operative delirium before the surgery. The discrimination of the patients is relevant to the understanding and investigating strategies to prevent patients from the delirium. However, further studies using a larger group of subjects after cardiac operation as well as after non-cardiac operations are required to generalize the results of the present study, because the number of patients in the present study was still limited.

Table 2: Predictive factors of delirium after cardiac surgery resulting from the multivariate logistic regression analysis

Variable	Odds Ratio	95% Confidence interval	p value
Age (per year)	1.140	1.062 - 1.224	0.000
Daily alcohol use	3.744	1.538 - 9.115	0.004

Variables with significantly different changes between the delirium group and the non-delirium group ($p < 0.05$), i.e., age, handedness, hemodialysis, daily alcohol use and MMSE, were entered into a backward stepwise logistic regression analysis requiring a p value less than 0.05 to remain (Wald Chi- square test, df=1).

Table 3: Comparison of the total intracranial volume and the components between the delirium group and the nondelirium group.

	Delirium (n=32)	Non-delirium (n=143)	F value of ANCOVA (p value)
Total intracranial volume (ml)	1371 ± 28	1324 ± 13	2.198 (0.140)
Gray matter (%)	34.6± 0.46	37.0 ± 0.21	21.086 (0.000)*
White matter (%)	42.0 ± 0.53	40.6 ± 0.24	5.881 0.016)*
CSF space (%)	23.4 ± 0.48	22.4 ± 0.19	3.975 (0.048)

Data are expressed as mean ± SD. The volume of each component, i.e., gray matter, white matter and CSF space, is expressed as a fraction (%) of the total intracranial volume. The comparison was analyzed by ANCOVA with the age and daily alcohol use of the patients as well as the type of MRI appliance as covariates. * The statistical significance level was set at a P value of < 0.0167 adjusted by the Bonferroni correction for the multiple comparison within the components.

Table 4: Comparison of the entire brain areas between the delirium group and the nondelirium group.

Brain Areas	Delirium group (n = 32) (95% CI)	Non-delirium group (n = 143) (95% CI)	F value of ANCOVA (p value)
Frontal lobe	9.023± 0.132 (8.763 - 9.283)	9.515 ± 0.060 (9.396 - 9.636)	11.188 (0.001)*
Temporal lobe	5.501 ± 0.092 (5.319 - 5.685)	6.045 ± 0.042 (5.962 - 6.128)	27.840 (0.000) *
Parietal lobe	4.278 ± 0.072 (4.135 - 4.421)	4.557 ± 0.033 (4.492 - 4.622)	11.885 (0.001)*
Occipital lobe	3.248 ± 0.056 (3.137 - 3.360)	3.354 ± 0.026 (3.303 - 3.404)	2.793 (0.097)
Limbic lobe	3.526 ± 0.050 (3.427 - 3.625)	3.803± 0.023 (3.758 - 3.848)	24.484 (0.000) *
Sub-lobal area	2.887 ± 0.063 (2.758 - 3.008)	3.016 ± 0.029 (2.959 - 3.073)	3.563 (0.061)
Cerebellum	4.160 ± 0.106 (3.952 - 4.369)	4.570 ± 0.048 (4.482 - 4.6724)	12.476 (0.001) *
Brainstem	0.275 ± 0.006 (0.262 - 0.287)	0.284 ± 0.003 (0.278 - 0.290)	1.654 (0.200)

Data are expressed as mean ± SD. The volume of each brain area is expressed as a fraction (%) of the total intracranial volume. The comparison between the groups and the estimation of 95 % confidence interval were analyzed by ANCOVA with the age and sex of the patients as well as the type of MRI appliance as covariates. * The statistical significance level was set at a P value of < 0.00625 adjusted by the Bonferroni correction for the multiple comparison within the components. CI: confidence interval.

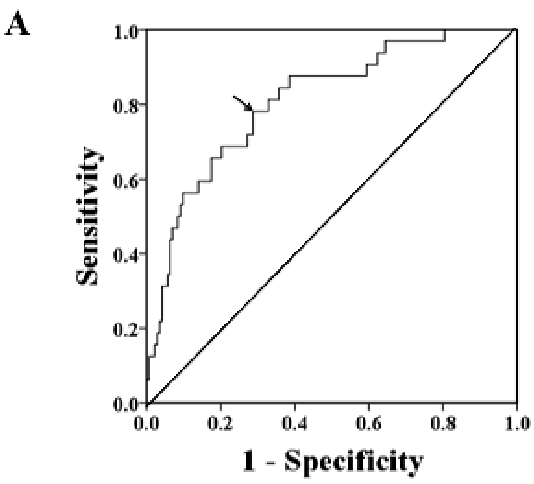
Table 5: Data of ROC curve analysis in the brain areas for prediction of delirium after the cardiac operation.

Brain area	AUC (95% CI)	Optimal cut-off value of brain volume (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Frontal lobe	0.674 * (0.599 - 0.742)	8.409	43.8	93	58.3	88.1
Temporal lobe	0.810 ** (0.744 - 0.865)	5.778	78.1	71.3	37.9	93.6
Parietal lobe	0.741 ** (0.670 - 0.805)	4.301	62.5	79	40.0	90.4
Limbic lobe	0.729 ** (0.657 - 0.794)	3.885	90.6	45.5	27.1	95.6
Cerebellum	0.743 ** (0.671 - 0.806)	4.206	71.9	75.5	39.7	92.3

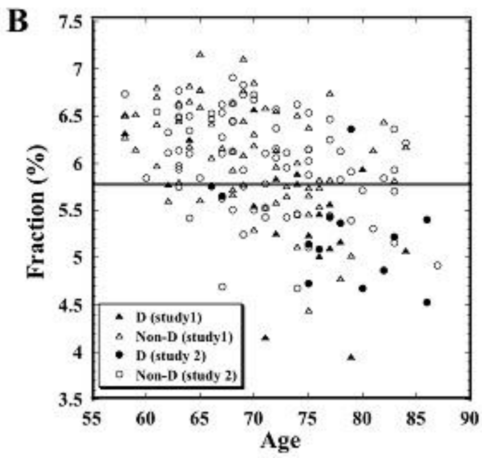
After the analysis of the ROC curve, the optimal cut-off value of the brain volume for adequate sensitivity and specificity was evaluated based on the Youden index. ROC; receiver operating characterisitic: AUC; area under the curve: CI; confidence interval.
* p < 0.01, ** P < 0.0001.

Figure 1. Results of the gray matter (GM) volume of the temporal lobe.

(A) ROC curve to predict delirium after a cardiac operation. After calculation of the AUC (0.810), the optimal cutoff point was evaluated by the Youden index. The arrows indicate the optimal cutoff points of the temporal lobe (see Tables 4&5).



(B) A scatter plot of the GM volume with age. The volume of the brain area is expressed as a fraction (%) of the total intracranial volume. The solid line indicates the optimal cut-off value of the brain volume based on the ROC curve analysis (5.778%). The dotted line shows a linear regression analysis between the age (x) and value of fraction (y) of the brain region of the total patients including studies 1 and 2 ($y = -0.0429 \times x + 8.993$, $r = -0.481$, df = 1,173, $p < 0.001$). Filled triangles (▲); the delirium patients in study 1, open triangles (△); the non-delirium patients in study 1, filled circles (●); the delirium patients in study 2, open circles (○); the non-delirium patients in study 2.



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References

1. Inouye SK, Westendrop RGJ, Saczynski JS(2014) Delirium in elderly people. Lancet; 383(9920): 911-922.
2. Marcantonio ER.(2017) Delirium in Hospitalized Older Adults. N Engl J Med; 377:1456-1466.
3. Maldonado JR.(2018) Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. Int J Geriatr Psychiatry; 33(11): 1428-1457.
4. Young JWS.(2017) The network model of delirium. Med Hypotheses; 104: 80-85.
5. Rengel KF, Pandharipande PP, Hughes CG.(2018) Postoperative delirium. Presse Med ; 47(4 Pt 2): e53-e64.
6. van Montfort SJT, van Dellen E, Stam CJ, et al. (2019): Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis. Neuroimage Clin; 23: 101809.

7. Rudolph JL, Marcantonio ER.(2011) Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg; 112(5): 1202-1211.
8. Trabold B, Metterlein T.(2014) Postoperative delirium: risk factors, prevention, and treatment. J Cardiothorac Vasc Anesth; 28(5): 1352-1360.
9. Hollinger A, Siegemund M, Goettel N, et al. (2015): Postoperative Delirium in Cardiac Surgery: An Unavoidable Menace? J Cardiothorac Vasc Anesth; 29(6): 1677-1687.
10. Gosselt AN, Slooter AJ, Boere PR, et al.(2015): Risk factors for delirium after on-pump cardiac surgery: a systematic review. Crit Care; 19: 346.
11. Raats JW, Steunenberg SL, de Lange DC, et al.(2016): Risk factors of post-operative delirium after elective vascular surgery in the elderly: A systematic review. Int J Surg; 35: 1-6.
12. Mufti HN, Hirsch GM(2017) Perioperative prediction of agitated (hyperactive) delirium after cardiac surgery in adults - The development of a practical scorecard. J Crit Care; 42: 192-199.
13. Ogawa M, Izawa KP, Satomi-Kobayashi S, et al.(2017): Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery. PLoS One: 29; 12(12): e0190359.
14. Kotfis K, Szylińska A, Listewnik M, et al.(2018): Early delirium after cardiac surgery: an analysis of incidence and risk factors in elderly (≥65 years) and very elderly (≥80 years) patients. Clin Interv Aging. 30; 13: 1061-1070.
15. Jarvela K, Porkkala H, Karlsson S, et al.(2018): Postoperative Delirium in Cardiac Surgery Patients. J Cardiothorac Vasc Anesth; 32: 1597-1602.
16. Sanson G, Khlopenyuk Y, Milocco S, et al.(2018): Delirium after cardiac surgery. Incidence, phenotypes, predisposing and precipitating risk factors, and effects. Heart Lung; 47(4): 408-417.
17. Jones D, Matalanis G, Mårtensson J, et al.(2019): Predictors and Outcomes of Cardiac Surgery-Associated Delirium. A Single Centre Retrospective Cohort Study. Heart Lung Circ; 28(3): 455-463.
18. Oldham MA, Hawkins KA, Lin IH, et al.(2019): Depression Predicts Delirium After Coronary Artery Bypass Graft Surgery Independent of Cognitive Impairment and Cerebrovascular Disease: An Analysis of the Neuropsychiatric Outcomes After Heart Surgery Study. Am J Geriatr Psychiatry; 27(5): 476-486.
19. Saczynski JS, Marcantonio ER, Quach L, et al.(2012): Cognitive trajectories after postoperative delirium. N Engl J Med; 367: 30-39.
20. Koster S, Hensens AG, Schuurmans MJ, et al.(2012): Consequences of delirium after cardiac operations. Ann Thorac Surg; 93(3): 705-711.
21. Oh ES, Fong TG, Hshieh TT et al.(2017): Delirium in Older Persons: Advances in Diagnosis and Treatment. JAMA; 318(12): 1161-1174.
22. Ibrahim K, McCarthy CP, McCarthy KJ, et al.(2018): Delirium in the Cardiac Intensive Care Unit. J Am Heart Assoc; 16:7(4). e008568.
23. Liu Y, Li XJ, Liang Y, Kang Y.(2019) Pharmacological Prevention of Postoperative Delirium: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Evid Based Complement Alternat Med; 9607129.
24. Kant IMJ, de Bresser J, van Montfort SJT, et al.(2017): MRI Markers of Neurodegenerative and Neurovascular Changes in Relation to Postoperative Delirium and Postoperative Cognitive Decline. Am J Geriatr Psychiatry; 25(10): 1048-1061.
25. Nitchingham A, Kumar V, Shenkin S, et al.(2018): A systematic review of neuroimaging in delirium: predictors, correlates and consequences. Int JGeriatr Psychiatry; 33(11): 1458-1478.
26. Root JC, Pryor KO, Downey R, et al.(2013): Association of pre-operative brain pathology with post-operative

delirium in a cohort of non-small cell lung cancer patients undergoing surgical resection. Psychooncology; 22(9): 2087-2094.

27. Cavallari M, Hshieh TT, Guttmann CR, et al.(2015): Brain atrophy and white-matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons withoutdementia. Neurobiol Aging; 36(6):2122-2129.
28. Brown CH 4th, Faigle R, Klinker L, et al.(2015): The Association of Brain MRI Characteristics and Postoperative Delirium in Cardiac Surgery Patients. Clin Ther ; 37(12): 2686-2699.
29. Shioiri A, Kurumaji A, Takeuchi T, et al.(2016): A Decrease in the Volume of Gray Matter as a Risk Factor for Postoperative Delirium Revealed by an Atlas-based Method. Am J Geriatr Psychiatry; 24(7): 528-536.
30. Shioiri A, Kurumaji A, Takeuchi T, et al.(2010): White matter abnormalities as a risk factor for postoperative delirium revealed by diffusion tensor imaging. Am J Geriatr Psychiatry; 18(8): 743-53.
31. Folstein MF, Folstein SE, McHugh PR.(1975) “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res; 12(3): 189-98.
32. American Psychiatric Association. Diagnostic and statistical manual, 4th Edn, text revision. Wasington, DC: American Psychiatric Association, 2000.
33. Trzepacz PT, Mittal D, Torres R, et al.(2001): Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognition test for delirium. J Neuropsychiatry Clin Neurosci; 13(2): 229-242.
34. Ashburner J, Friston KJ .(2005) Unified segmentation. Neuroimage; 26(3): 839–851.
35. Ashburner J.(2007) A fast diffeomorphic image registration algorithm. Neuroimage; 38(1): 95-113.
36. Maldjian JA, Laurienti PJ, Kraft RA et al.(2003), An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fmri data sets. NeuroImage; 19(3): 1233–1239.
37. Cavallari M, Dai W, Guttmann CR, et al.(2016): Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. Brain; 139(Pt 4): 1282-1294.
38. Fotenos AF, Snyder AZ, Girton LE, et al.(2005): Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. Neurology; 64(6): 1032-1039.
39. Pfefferbaum A, Rohlfing T, Rosenbloom MJ, et al.(2013): Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. Neuroimage; 65: 176-193.