Chapter 20
Brain Development and Aging Using Large Brain MRI Database

Yasuyuki Taki

Abstract Now we confront a super aging society in Japan. In the situation, it is important to preserve our cognitive function for entire life by preventing us from pathological brain aging. To perform the aim, we have built a large brain magnetic resonance imaging (MRI) database from around 3,000 subjects aged from 5 to 80 in order to reveal how brain develops and ages. We have also collected several cognitive functions, lifestyle such as eating and sleeping habits, and genetic data. Using the database, we have revealed normal brain development and aging and also have revealed what factors affect brain development and aging. For example, sleep duration is significantly associated with the gray matter volume of the bilateral hippocampi. In addition, there were significant negative correlation between alcohol drinking and gray matter volume of the frontoparietal region and body mass index and gray matter volume of the hippocampus in cross-sectional analysis. In addition, having intellectual curiosity showed significant negative correlation with regional gray matter volume decline rate in the temporoparietal region. These findings help understanding the mechanism of brain development and aging as well as performing differential diagnosis or diagnosis at an early stage of several diseases/disorders such as autism and Alzheimer's disease.

Y. Taki (✉)
Department of Nuclear Medicine & Radiology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-cho, Aoba-ku, 980-8575 Sendai, Japan

Division of Medical Neuroimage Analysis, Department of Community Medical Supports, Tohoku Medical Megabank Organization, Tohoku University, 4-1 Seiryo-cho, Aoba-ku, 980-8575 Sendai, Japan

Division of Developmental Cognitive Neuroscience, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-cho, Aoba-ku, 980-8575 Sendai, Japan
e-mail: ytaki@idac.tohoku.ac.jp

20.1 Introduction

Now we confront a super aging society in Japan. In the situation, it is important to preserve our cognitive function for entire life by preventing us from pathological brain aging. Recently, the importance of human neuroimaging database was recognized greatly. The normal brain structure and function database can be used as the references not only for neuroimaging study for humans but also for early diagnosis and computer-aided automated diagnosis of the brain diseases. The most remarkable recently developed method for brain image analysis is voxel-based morphometry (VBM). It includes anatomical standardization of the brain to a standard brain, brain tissue segmentation and finally voxel-based statistical analysis based on general linear model. This technique enables us to extract brain regions which show correlations between tissue volume and variables, such as age, sex, and other subject's characteristics. We can analyze not only age-related normal changes but also diseased brain, such as dementia and schizophrenia. It has been believed that functional imaging precede structural imaging to detect early pathological findings of the diseases. However, recent development of high-resolution structural imaging and sophisticated analytical technique enable us to detect the brain disease at very early stage. Now we have collected over 3,000 brain MRI of healthy Japanese aged from 5 to 80 and constructed an MRI database together with their characteristics such as age, sex, lifestyle information, blood pressure, present and past disease history, and cognitive functions. This is a largest brain MRI database in Japan and one of the largest one in the world.

20.2 Imaging Studies of Brain Development

20.2.1 Correlation Between Gray Matter Density-Adjusted Brain Perfusion and Age Using Brain MR Images of 202 Healthy Children

In understanding brain aging, the knowledge of brain maturation is very important, for the relationship between brain maturation and brain aging is regarding as a "mirror pattern." In detail, brain regions that mature earlier such as occipital regions are robust in brain aging, whereas brain regions that mature rather late such as prefrontal regions are vulnerable for aging. Brain development continues through childhood and adolescence. Recently, it has been revealed that human brain development is a structurally and functionally nonlinear process. However, despite this growing wealth of knowledge about maturational changes in brain structure in children, the trajectory of brain perfusion with age in healthy children is not yet well documented.
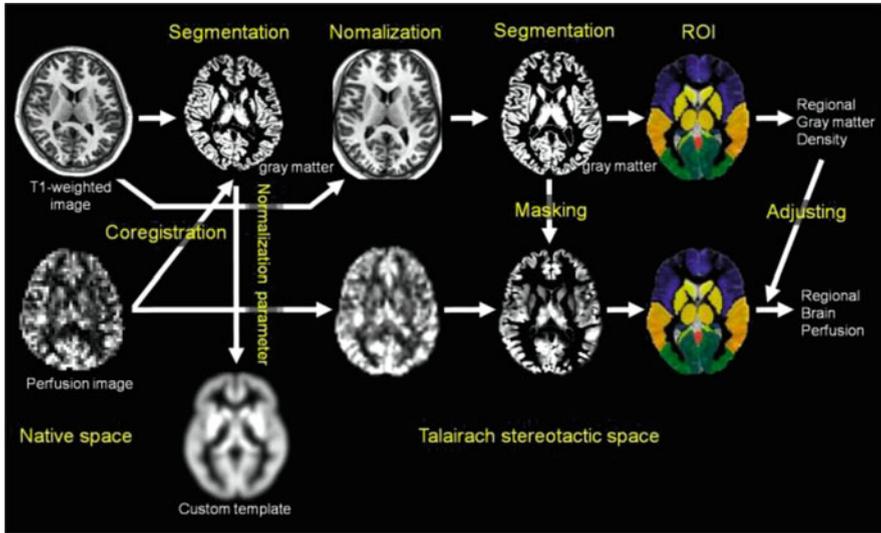
Fig. 20.1 Schematic of the image analysis

Recently, arterial spin-labeling (ASL) perfusion magnetic resonance imaging (MRI) has been developed for evaluating brain perfusion. We examined the correlation between brain perfusion and age using pulsed ASL MRI in a large number of healthy children.

We collected data on brain structural and ASL perfusion MRI in 202 healthy children aged 5–18 years. Structural MRI data were segmented and normalized, applying a voxel-based morphometric analysis. Perfusion MRI was normalized using the normalization parameter of the corresponding structural MRI. We calculated brain perfusion with an adjustment for gray matter density (BP-GMD) by dividing normalized ASL MRI by normalized gray matter segments in 22 regions. Next, we analyzed the correlation between BP-GMD and age in each region by estimating linear, quadratic, and cubic polynomial functions, using the Akaike information criterion (Fig. 20.1).

As a result, the correlation between BP-GMD and age showed an inverted U shape followed by a U-shaped trajectory in most regions [1–3]. In addition, age at which BP-GMD was highest was different among the lobes and gray matter regions, and the BP-GMD association with age increased from the occipital to the frontal lobe via the temporal and parietal lobes.

In the frontal lobe, all gray matter regions showed an inverted U-shaped trajectory for the correlation between BP-GMD and age, and the best fit was a negative quadratic or positive cubic polynomial function. The estimated age at which BP-GMD was highest was earlier in the precentral gyrus, cingulate gyrus, and anterior cingulate cortex than in the superior, middle, and inferior frontal gyri (Fig. 20.2).
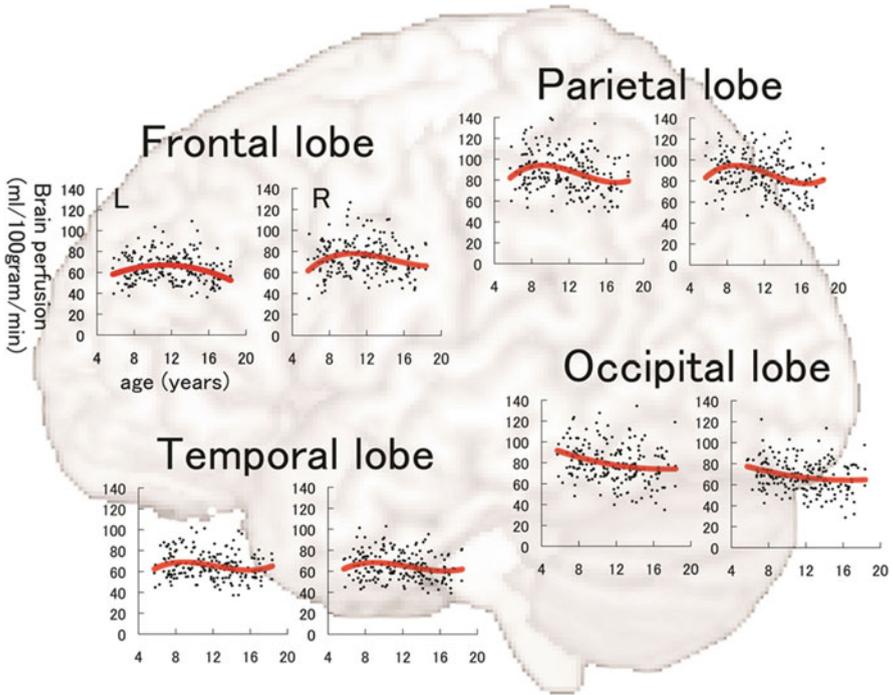
Fig. 20.2 Correlation between brain perfusion, adjusted for gray matter density, and age in the frontal lobe, parietal lobe, occipital lobe, and temporal lobe in each hemisphere

We demonstrated a correlation between BP-GMD and age using ASL brain perfusion MRI in a large number of healthy children over a wide age range. As a result, the trajectory of the correlation between BP-GMD and age showed an inverted U-shaped second-order polynomial function in most regions in the frontal lobe, a third-order polynomial function in the parietal and temporal lobes, and a U-shaped second-order and negative linear correlation in the occipital lobe. Our results indicate that higher-order association cortices mature after the lower-order cortices in terms of brain perfusion. As a result, the trajectory of the correlation between BP-GMD and age showed an inverted U shape followed by a U-shaped trajectory in most regions. In addition, the age at which BP-GMD was highest was different among the lobes and gray matter regions, showing a progression from the occipital lobe to the frontal lobe, via the temporal and parietal lobes. Our results indicate that higher-order association cortices mature after the lower-order cortices mature. This may help not only clarify the mechanisms of normal brain maturation from the viewpoint of brain perfusion but also distinguish normal from developmental disorders that show abnormal brain perfusion patterns.

20.2.2 Correlation Between Sleep Duration and Gray Matter Volume Using Brain MR Images of 290 Healthy Children

Sleep is essential for living beings, and sleep loss has been shown to affect hippocampal structure and function in rats by inhibiting cell proliferation and neurogenesis in this region of the brain. We aimed to analyze the correlation between sleep duration and the hippocampal volume using brain magnetic resonance images of 290 healthy children aged 5–18 years. We examined the volume of gray matter, white matter, and the cerebrospinal fluid (CSF) space in the brain using a fully automated and established neuroimaging technique, voxel-based morphometry, which enabled global analysis of brain structure without bias toward any specific brain region while permitting the identification of potential differences or abnormalities in brain structures. We found that the regional gray matter volume of the bilateral hippocampal body was significantly positively correlated with sleep duration during weekdays after adjusting for age, sex, and intracranial volume [4]. Our results indicated that sleep duration affects the hippocampal regional gray matter volume of healthy children. These findings advance our understanding of the importance of sleep habits in the daily lives of healthy children.

20.3 Imaging Studies of Brain Aging

20.3.1 Correlation Between Baseline Regional Gray Matter Volume and Global Gray Matter Volume Decline Rate

Evaluating whole-brain or global gray matter volume decline rate is important in distinguishing neurodegenerative diseases from normal aging and in anticipating cognitive decline over a given period in non-demented subjects. Whether a significant negative correlation exists between baseline regional gray matter volume of several regions and global gray matter volume decline in the subsequent time period in healthy subjects has not yet been clarified. Therefore, we analyzed the correlation between baseline regional gray matter volumes and the rate of global gray matter volume decline in the period following baseline using magnetic resonance images of the brains of 381 healthy subjects by applying a longitudinal design over 6 years using voxel-based morphometry.

All subjects were Japanese individuals recruited from our previous brain-imaging project. We selected participants who had lived in Sendai City at the time of the previous study, whose collected data had no missing values and who had no serious medical problems from an initial 1604 eligible persons. All participants were screened with a mail-in health questionnaire and underwent telephone and personal interviews. Persons who reported a history of any malignant tumor,

head trauma with loss of consciousness for >5 min, cerebrovascular disease, epilepsy, any psychiatric disease, or claustrophobia were excluded from the study. All subjects were screened for dementia using the Mini-Mental State Examination (MMSE). An experienced neuroradiologist examined the MR scans for any tumors and cerebrovascular disease. The final sample consisted of 381 participants (40.1 % of the eligible cohort: 158 men, 223 women). All images were collected using the same 0.5 T MR scanner, including baseline images using MP-RAGE pulse sequences. After the image acquisition, all MR images were analyzed using statistical parametric mapping 2 in Matlab. We calculated gray matter volume and white matter volume using fully automated techniques. To normalize the head size of each subject, we defined the gray matter ratio (GMR) as the percentage of gray matter volume divided by the intracranial volume. Next, to reveal the annualized rate of change in GMR with age, we determined the annual percentage change in GMR (APC_{GMR}) for each subject. We determined regional gray matter volume using voxel-based morphometry. To investigate the correlation between baseline regional gray matter volume and APC_{GMR}, we performed a multiple regression analysis with age, gender, intracranial volume, and APC_{GMR} as independent valuables and baseline regional gray matter volume as a dependent valuable. We used the random field theory method to correct for the Familywise Error Rate (FWE); any resulting P-value less than 0.05 was considered significant. Next, we tested whether the gray matter regional volume that showed the significant negative correlation with APC_{GMR} at baseline could predict whether the APC_{GMR} was above or below the APC_{GMR} mean by applying a standard (not stepwise) linear discriminant analysis in SPSS11.5. For the discriminant analysis, we used the mean gray matter volume over a cluster in each region, and the regional gray matter volume as defined by multiple regression analysis. We set the significance level at $P < 0.05$.

As a result, the gray matter regions showing significant negative correlation with APC_{GMR} adjusted for age, gender, and intracranial volume are shown in Fig. 20.1. Baseline regional gray matter volumes of the right PCC/precuneus and the left hippocampus showed significant negative correlations with APC_{GMR} after adjusting for age, gender, and intracranial volume (right PCC/precuneus, $t = 5.42$, $P = 0.020$; left hippocampus, $t = 5.29$, $P = 0.035$) [1]. Therefore, we used the gray matter regions of the right PCC/precuneus and the left hippocampus in the next discriminant analysis. Baseline regional gray matter volume of both the right PCC/precuneus and the left hippocampus significantly distinguished whether APC_{GMR} was above or below the APC_{GMR} mean. The F-value, p-value, and discriminant function coefficient were 13.51, <0.001, and 0.833 in the right PCC/precuneus and 5.71, 0.017, and 0.350 in the left hippocampus, respectively. Overall, 58.4 % of the APC_{GMR} (55.8 % of APC_{GMR} below the mean of APC_{GMR} and 60.9 % of APC_{GMR} above the mean of APC_{GMR}) was correctly distinguished using the discriminant function (Fig. 20.3).

This study provides the first longitudinal findings showing that baseline regional gray matter volumes in the right PCC/precuneus and the left hippocampus show a significant negative correlation with the rate of global gray matter volume decline

Fig. 20.3 Gray matter regions showing significant negative correlations with annual percent change of the gray matter ratio (APC$_{GMR}$) adjusted for age, gender, and intracranial volume
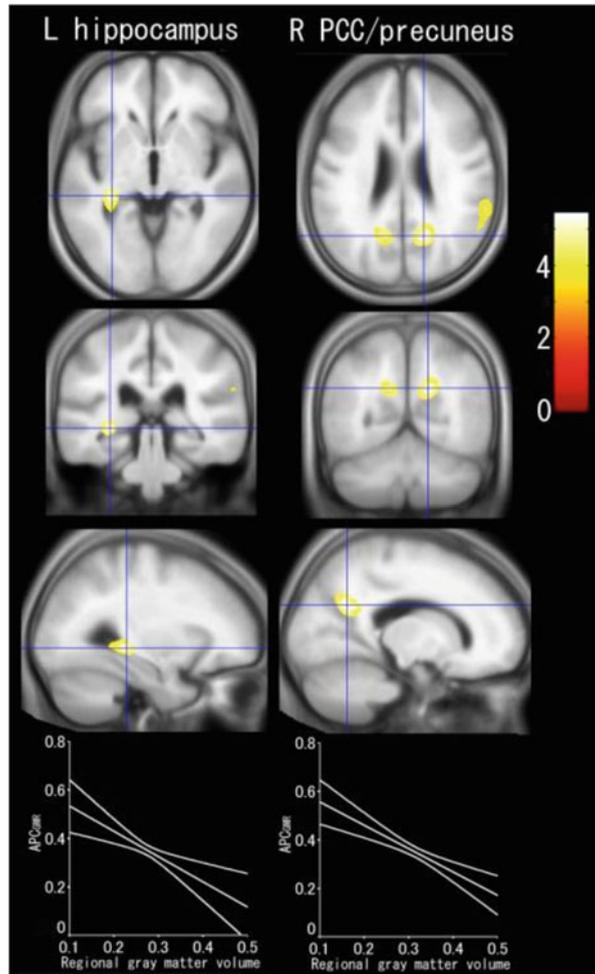
in the following period, as represented by APC$_{GMR}$, adjusting for age, gender, and intracranial volume. In addition, baseline regional gray matter volumes of both the right PCC/precuneus and the left hippocampus significantly distinguished whether the APC$_{GMR}$ was above or below the APC$_{GMR}$ mean. These results indicate that subjects who had smaller baseline regional gray matter volumes in those regions showed higher rate of global gray matter volume decline in the following period.

In summary, using a longitudinal design over 6 years in 381 community-dwelling healthy individuals, we examined the correlation between baseline regional gray matter volume and the rate of global gray matter volume decline in the following period. We found a significant negative correlation between APC$_{GMR}$ and the baseline regional gray matter volumes of the right PCC/precunei and the left hippocampus after adjusting for age and gender. In addition, baseline regional gray

matter volume of both the right PCC/precuneus and the left hippocampus significantly distinguished whether the APC_{GMR} was above or below the APC_{GMR} mean. Our results suggest that baseline regional gray matter volume predicts the rate of global gray matter volume decline in the following period in healthy subjects. Our study may contribute to distinguishing neurodegenerative diseases from normal aging and to predicting cognitive decline.

20.3.2   Correlation Between Degree of White Matter Hyperintensities and Global Gray Matter Volume Decline Rate

Whether the degree of white matter hyperintensities (WMHs) shows a significant correlation with the rate of global gray matter volume decline over a period following initial baseline measurement remains unclear. The purpose of the present study was to reveal the relationship between the degree of WMHs at baseline and the rate of global gray matter volume decline by applying a longitudinal design. Using a 6-year longitudinal design and magnetic resonance images of the brains of 160 healthy individuals aged over 50 years and living in the community, we analyzed the correlation between degree of WMHs using Fazekas scaling at baseline and rate of global gray matter volume decline 6 years later. To obtain the rate of global gray matter volume decline, we calculated global gray matter volume and intracranial volume at baseline and at follow-up using a fully automated method. As a result, the annual percentage change in the gray matter ratio (GMR, APC_{GMR}), in which GMR represents the percentage of gray matter volume in the intracranial volume, showed a significant positive correlation with the degree of deep WMHs and periventricular WMHs at baseline, after adjusting for age, gender, present history of hypertension, and diabetes mellitus [2].

The degree of WMHs, both DWMH and PVWMH, at baseline showed a significant positive correlation with the rate of global gray matter volume decline, represented by APC_{GMR}, adjusting for age, gender, and present history of hypertension and diabetes mellitus in healthy subjects using longitudinal analysis. To our knowledge, we are the first to show the correlation between the degree of WMHs at baseline and the rate of subsequent global gray matter volume decline in healthy elderly individuals. Our result is partially consistent with recent studies that showed a significant positive correlation between the degree or load of WMHs and decreases in gray matter volume in healthy elderly people, although those studies were conducted using cross-sectional design. However, another recent study using longitudinal analysis has shown that WMH is not a predictor of brain atrophy rate in elderly subjects. The inconsistency between the findings of the recent study and the present study may have arisen from differences in the volume that was measured. In the present study, we focused on the rate of decline of gray matter volume, not whole-brain volume, because gray matter volume is significantly correlated with

several cognitive functions. Our results suggest that the rate of global gray matter volume decline could be predicted using the degree of WMHs at baseline, evaluated by simple visual scaling.

In summary, using a longitudinal design over 6 years in 160 community-dwelling healthy individuals, the degree of WMHs was measured at baseline, and the rate of global gray matter volume decline was obtained. As a result, APC_{GMR} showed a significant positive correlation with the degree of deep WMHs and periventricular WMHs at baseline adjusting for age, gender, and present history of hypertension and diabetes mellitus. Our results suggest that degree of WMHs at baseline predicts the rate of subsequent gray matter volume decline and also suggests that simple visual scaling of WMHs could contribute to the prediction of the rate of global gray matter volume decline.

20.3.3   Risk Factors for Brain Volume Decrease

20.3.3.1   Alcohol Drinking

We also tested the correlation between gray matter ratio and lifetime alcohol intake. There was a strong negative correlation between the log-transformed lifetime alcohol intake and the gray matter ratio [5]. Figure 20.4 shows the gray matter regions that had a significant negative correlation between the lifetime alcohol intake and the regional gray matter volume. The gray matter volume of the bilateral middle frontal gyri showed a significant negative correlation with the log-transformed lifetime alcohol intake.
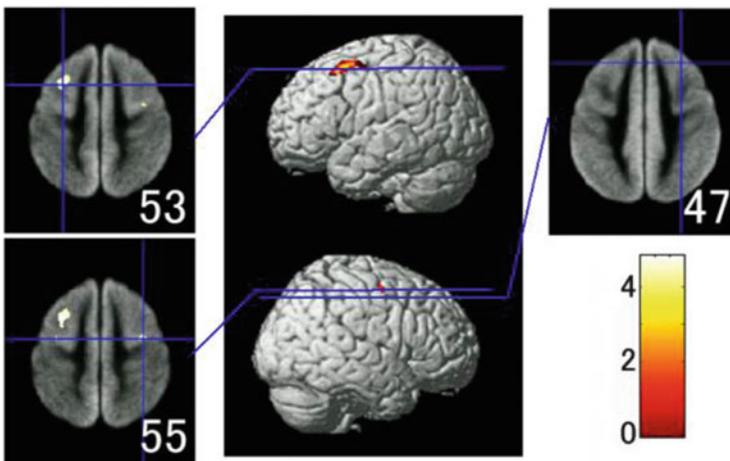
Fig. 20.4   Brain regions that showed negative correction between gray matter volume and lifetime alcohol intake
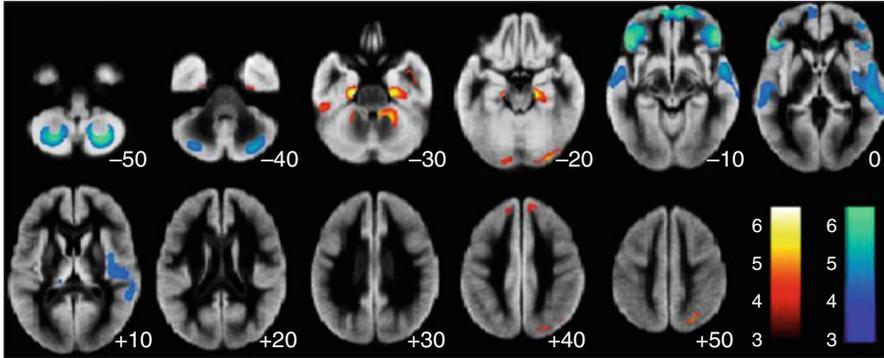
Fig. 20.5 T brain regions that showed correlations between gray matter volume and body mass index (BMI). *Red* and *blue color* indicated negative and positive correlations, respectively

20.3.3.2 Obesity

We tested correlation between gray matter ratio and obesity. As an indicator for obesity, body mass index (BMI) was used. Volumetric analysis revealed that there are significant negative correlations between BMI and the gray matter ratio, which represents the percentage of gray matter volume in the intracranial volume, in men ($p < 0.001$, adjusting for age, systolic blood pressure, and lifetime alcohol intake), whereas not in women. VBM revealed that regional gray matter volumes of the bilateral medial temporal lobe, occipital lobe, frontal lobe, and anterior lobe of the cerebellum show significant negative correlation with BMI, and those of the posterior lobe of the cerebellum, perisylvian regions of the bilateral frontal and temporal lobes, and bilateral orbitofrontal gyri show significant positive correlation with BMI in men [6] (Fig. 20.5).

20.4 Conclusion

We constructed a large-scale brain MRI database for healthy Japanese and clarified age-related volume changes of the human brain and their risk factors. Several factors such as hypertension, alcohol drinking, and obesity are related with gray matter volume reduction of several regions. In addition, we have shown that several factors such as baseline gray matter volume structure and white matter lesions predict the global gray matter volume decline rate. These results may contribute to the understanding of normal brain aging, as well as age-related brain diseases, such as dementia.

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