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The JSPN Award for Special Contributions to Psychiatric Research Lecture

Neuroimaging-based Brain-age Estimation and Exploration of Imaging Biomarkers for Epilepsy

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Abstract

Epilepsy is a common and diverse brain disorder, and the underlying mechanisms of its multiple forms and comorbidities are largely unknown. Recent advances in machine learning methods have enabled us to estimate an individual's "brain-age" based on neuroimaging, and this "neuroimaging-based brain-age estimation" is expected as a novel individual-level biomarker for neuropsychiatric disorders. The current study investigated the brain-age for different categories of epilepsy and the following clinical questions: (1) the effects of psychosis on temporal lobe epilepsy (TLE), (2) clinical differentiation for psychogenic non-epileptic seizures (PNES), and (3) clinical discrimination between juvenile myoclonic epilepsy (JME) and progressive myoclonus epilepsy (PME). First, 1196 T1-weighted MRI scans from healthy controls (HC) were used to build a brain-age prediction model by support vector regression, and this model was applied to calculate the brain-predicted age difference (brain-PAD: predicted age-chronological age) in the HC and 318 patients with epilepsy or PNES. Consequently, almost all categories of epilepsy exhibited a significant increase in brain-PAD by over 4 years. TLE with hippocampal sclerosis had a significantly higher brain-PAD than several other categories. In addition, the mean brain-PAD in TLE with inter-ictal psychosis was 10.9 years, whereas that in TLE without psychosis was 5.3 years. The effects of psychosis on the increase in brain-PAD in TLE were significant. PNES demonstrated a

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comparable mean brain-PAD with that of patients with epilepsy. PME had a higher brain-PAD than JME. This study supports a different brain aging process in epilepsy from healthy subjects, which may be associated with hippocampal sclerosis or inter-ictal psychosis. Furthermore, neuroimaging-based brain-age estimation may provide novel insight into the diverse symptoms of epilepsy. This article also discusses other potential imaging biomarkers for epilepsy.

Keywords: epilepsy, neuroimaging, magnetic resonance imaging, psychosis, machine learning

Introduction

Epilepsy is a highly prevalent neurological disorder that affects just under 1% of the population and 50 million people worldwide 13), and in addition to the presence of drug-resistant epilepsy whose seizures cannot be eliminated, it is often associated with psychiatric symptoms such as depression and psychosis, and comorbidities such as cognitive dysfunction 4). In this context, neuroimaging is expected to play a role as a biomarker to detect focal epileptogenic lesions, identify risk factors for various comorbidities, and elucidate the pathophysiology 24) (Figure 1). Neuroimaging such as magnetic resonance imaging (MRI) and positron emission tomography (PET) can be used not only to visualize focal epileptogenic lesions, but also quantitatively and minimally invasively analyze the brain structure and function using various analysis techniques. In particular, recent advances in machine-learning have been marked, and many studies are being conducted for clinical applications. Among them, a technique to estimate the "brain-age" of an individual from MRI and other sources is expected to be a new biomarker for neuropsychiatric disorders that can be applied at the individual level. The authors performed brain-age estimation in various categories of epilepsy patients and conducted several comparative studies assuming clinically applicable situations. In the following, we first explain brain-age estimation, and then introduce issues we focused on and their significance, such as differences in brain-age abnormalities and the presence of psychotic symptoms in each category of epilepsy.

I. Neuroimaging-based Brain-age

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Estimation and Neuropsychiatric Disorders

The brain changes with aging, which is known to be associated with altered brain function and sometimes neurodegenerative diseases. The aging process of the brain is biologically complex and varies markedly among individuals, and the diversity of brain-age may contribute to the diversity of individual minds and neuropsychiatric disorders. Recent developments in machine-learning and its applications have been marked, and it is now possible to predict human brain-age using structural MRI and functional brain images 6). This brain-age prediction system based on neuroimaging allows us to obtain image data from many healthy individuals and their chronological age patterns, and when we input new image data into them, we can estimate their brain-age based on the learning (Fig. 2). This system can show accuracy with a margin of error of less than five years for adults and less than one year for children and adolescents 6).

The application of such brain-age prediction systems to neuropsychiatric disorders has been spreading rapidly in recent years in order to explore the relationship between brain aging and neuropsychiatric disorders. For example, brain-age in Alzheimer's disease is said to be an 81% accurate and sensitive predictor of the transition from mild cognitive dysfunction to dementia 10). In a recent study by the authors, an increase in brain-age of about 9 years was observed in Alzheimer's disease, which was significantly higher than that in Parkinson's disease (an increase of about 2 years) 2). In schizophrenia, an increase in brain-age of 5.5 years was reported, and an increase of less than 2 years was also observed in the at risk mental state (ARMS), suggesting an acceleration of brain-age before and after the onset of schizophrenia 12). Subsequently, longitudinal imaging analysis revealed that brain aging accelerates 2.5-fold immediately after the onset of schizophrenia, and that brain-age increases but does not accelerate 5 years after illness onset 16). Furthermore, brain-age is also known to be associated with fluid intelligence, allostatic load, and mortality in the general population 7). In epilepsy, an increase in brain-age of 4.5 years was reported for drug-resistant focal epilepsy as a whole 14), but the differences by focal site, value in generalized epilepsy, and effect of psychiatric symptoms remained unknown.

II. Brain-age and Significance in Each Epilepsy Type

In our report 22), structural MRI data

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from 1,196 healthy controls were first analyzed, and from the obtained numerical values of gray and white matter volumes of each brain region, a brain-age prediction model fitting the chronological age of each individual was constructed by machine-learning using nu-support vector regression (nu-SVR). Although there is no set view on the choice of machine-learning algorithm to be used for the brain-age prediction system, nu-SVR is different from other algorithms such as epsilon-SVR in that the number of support vectors can be adjusted. We applied this brain-age prediction model to neuroimaging data from 318 patients with epilepsy (or psychogenic seizures) and calculated the brain-predicted age difference (brain-PAD: predicted age-chronological age).

The results showed that brain-age increased by approximately 5 years in each epilepsy category (Fig. 3). This was consistent with the report by Pardoe, H. R. et al. 14). In particular, temporal lobe epilepsy with hippocampal sclerosis showed a significant increase in brain-age compared with temporal lobe epilepsy without MRI findings, idiopathic generalized epilepsy, and extra-temporal lobe epilepsy. In the most severe group, epileptic encephalopathy and progressive myoclonus epilepsy, brain-age increased by more than 15 years. While the degree of increase in brain-age varied according to the type of epilepsy, the fact that the increase was generally seen in all types of epilepsy suggests that repetitive seizures due to neuronal abnormalities and overexcitation may accelerate brain aging, which is consistent with recently reported findings of progressive cortical thickness loss in focal epilepsy 9) and phosphorylated tau deposition in the pathological tissues 23). Interestingly, a significant increase in brain-age was also observed in idiopathic generalized epilepsy, in which seizures are often suppressed by drugs. This may be due to genetic predisposition, neurodevelopmental abnormalities, or epileptic activity during the inter-ictal period in idiopathic generalized epilepsy.

III. Psychotic Symptoms and Brain-age in Temporal Lobe Epilepsy

The comorbidity rate of psychotic symptoms such as hallucinations and delusions in epilepsy is 7.8-times higher than that in the general population 5), and since they are particularly common in temporal lobe epilepsy, some neurobiological pathogenic mechanism has been postulated, but no clear mechanism or biomarker has yet been identified. The authors have reported abnormalities of brain networks in temporal lobe epilepsy with psychotic symptoms 17)21), and in light of

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increased brain-age in schizophrenia 12)16), brain-age may be a new biomarker in epileptic psychosis at the individual level. In the present study, brain-age was compared in 21 patients with temporal lobe epilepsy with interictal psychosis and 206 patients with temporal lobe epilepsy without psychosis. The temporal lobe epilepsy group without psychosis showed an average increase of 5.3 years, while the group with psychosis showed a significant increase of 10.9 years ($P < 0.001$, Fig. 4). This remained significant after adjusting for the presence or absence of hippocampal sclerosis ($P = 0.005$). Therefore, this is consistent with the reported difference in brain-age between schizophrenia and healthy individuals of about 5 years, and may suggest that the mechanisms by which abnormal brain aging occurs in temporal lobe epilepsy and psychosis may be independent of each other. On the other hand, although the diagnosis of the presence or absence of psychotic symptoms or prediction of their onset in temporal lobe epilepsy using brain-age is expected in the future, the area under the curve (AUC) of the receiver operating characteristic curve (ROC) for diagnosing such symptoms in the present data was 0.694, which may still make it difficult to use as a biomarker alone.

IV. Psychogenic Non-epileptic Seizures

Psychogenic nonepileptic seizures are a group of seizure symptoms that resemble epileptic seizures but are thought to be caused by a psychogenic mechanism, and because they are not epilepsy, it is important not to erroneously treat them with antiepileptic drugs 11). On the other hand, diagnosis is often difficult, and in some cases, prolonged videoencephalography is necessary to make a definitive diagnosis, but there are only a limited number of places where this examination can be performed 11). In the present study 22), the authors compared the brain-age of patients with psychogenic non-epileptic seizures and those with epilepsy, based on the fact that it would be clinically useful if biomarkers based on MRI could be used to differentiate between the two groups. As a result, as shown in Figure 3, the brain-age of patients with psychogenic non-epileptic seizures increased to the same extent as that of patients with epilepsy, and there was no significant difference between the two groups. Although the mechanism of the seizure must be different from that of epilepsy, some brain abnormality was also thought to occur in psychogenic non-epileptic seizures. The authors also reported white matter network abnormalities in psychogenic non-epileptic seizures using diffusion tensor

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imaging 20).

V. Juvenile Myoclonic Epilepsy and Progressive Myoclonic Epilepsy

Juvenile myoclonic epilepsy comprises a group of idiopathic generalized epilepsies that mainly develop at around 15 years of age and produce myoclonic seizures, and generally, there are many cases showing a good response to drugs and the prognosis is not poor. On the other hand, progressive myoclonus epilepsy refers to a group of neurodegenerative disorders such as dentatorubral-pallidoluysian atrophy and mitochondrial disease, characterized by progressive myoclonus, intellectual regression, and cerebellar ataxia. Progressive myoclonus epilepsy is often difficult to differentiate from juvenile myoclonic epilepsy because the symptoms are similar in the early stages of the disease 1). In the present study, we compared the brain-age of the two groups of patients to explore the possibility of differentiating between them by neuroimaging biomarkers. The results showed that brain-age was markedly higher in patients with progressive myoclonus epilepsy. However, the small sample size and limited data from the early stages of the disease suggest that further validation is needed before brain-age can be used as a biomarker in practice.

VI. Limitations of the study

Limitations of the present study included: differences in the sample size of each group, lack of detailed assessment of clinical symptoms, and influence of medications. In particular, it has been reported that antipsychotic drugs further accelerate brain-age in schizophrenia 16), which may have influenced the results. The effects of antiepileptic drugs are unknown, for example, it generally takes an average of 7 years or more for a correct diagnosis of psychogenic non-epileptic seizures 15), and unnecessary antiepileptic medication during that time may have caused an increase in brain-age. In addition, since factors such as drinking, smoking, and diabetes also influence brain-age 8), taking these factors into account may further improve the accuracy of clinical application of brain-age in the future.

VII. Search for Neuroimaging Biomarkers in Epilepsy

Since seizure control is the cornerstone of epilepsy treatment, and surgical resection of focal lesions is often effective for drug-resistant epilepsy, which occurs in about 30% of patients, the most important role of neuroimaging at present is the identification of focal lesions. In this regard, various approaches have been attempted to visualize and identify focal

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lesions using new imaging and analysis methods, nuclear medicine imaging, and multimodality techniques for lesions that cannot be identified by conventional MRI sequencing, and the authors have often reported on this 3)18)19).

On the other hand, the various comorbidities of epilepsy, including cognitive dysfunction, mental and behavioral problems, and sudden death, also require advanced approaches. Despite clinically similar epilepsy onset, seizure symptoms, and antiepileptic drug treatment, these comorbidities occur in some cases and not at all in others, and elucidation of where in the brain these differences exist is expected. In particular, the relationship between epilepsy and comorbid psychiatric symptoms is considered to be bidirectional 4), and since psychiatric symptoms sometimes precede the onset of epilepsy, clarifying the mechanism of psychiatric symptoms in epilepsy will not only contribute to improving the quality of life of patients with epilepsy, but also provide more detailed knowledge of the brain pathology associated with epilepsy. Considering the contributions that have been made to neuropsychiatry, the establishment and utilization of neuroimaging as a minimally invasive and useful biomarker should be highly anticipated, and further research is warranted.

VIII. Psychiatry and Neurology

Finally, psychiatry and neurology should also be mentioned. The two have had various historical relationships, and there have been recent concerns that dementia could be classified as a neurological disorder by being dropped from psychiatric disorders in the draft ICD-11. Epilepsy is already classified as a neurological disease, and it is a field of neurology worldwide. However, what is the difference between psychiatric and neurological disorders? For example, the division of orthopedics and cardiology was determined by nature, and they involve different organs. On the other hand, the division between psychiatric disorders and many neurological disorders is artificially drawn, even though they both occur in the same organ, the brain, and the authors believe that this line is ultimately drawn for the convenience of academics. However, knowledge of neurological diseases and symptoms is also important in psychiatric clinical practice, and since neurological diseases affecting the brain can inevitably cause many psychiatric symptoms, it is thought that brain-related clinical practice can be developed more by becoming closer and communicating with each other. Japan has a unique culture in which psychiatrists have been involved in the treatment of

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epilepsy, and the Japanese Society of Psychiatry and Neurology is a valuable society that has both psychiatry and neurology in its name. As members of this society, the authors hope to continue to work to build bridges between the two.

Conclusion

In this study, we applied a neuroimaging-based brain-age prediction system for various types and comorbidities of epilepsy, and reported an increase in brain-age in each type of epilepsy and the effect of inter-ictal psychosis on brain-age. Our findings suggest an abnormal brain aging process in epilepsy, and we expect that the neuroimaging-based brain-age prediction system will be established as an imaging biomarker that is minimally invasive and applicable at the individual level, even in standard medical care.

We have no conflicts of interest to disclose in relation to this paper.

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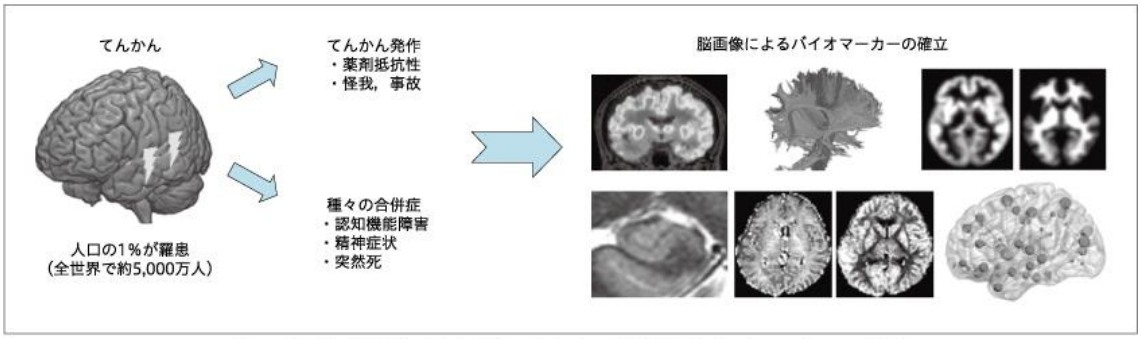

図1　発作や合併症などの多様なてんかんの病態と画像バイオマーカーへの期待

Fig. 1 Diverse pathological conditions of epilepsy, including seizures and comorbidities, and expectations regarding imaging biomarkers.

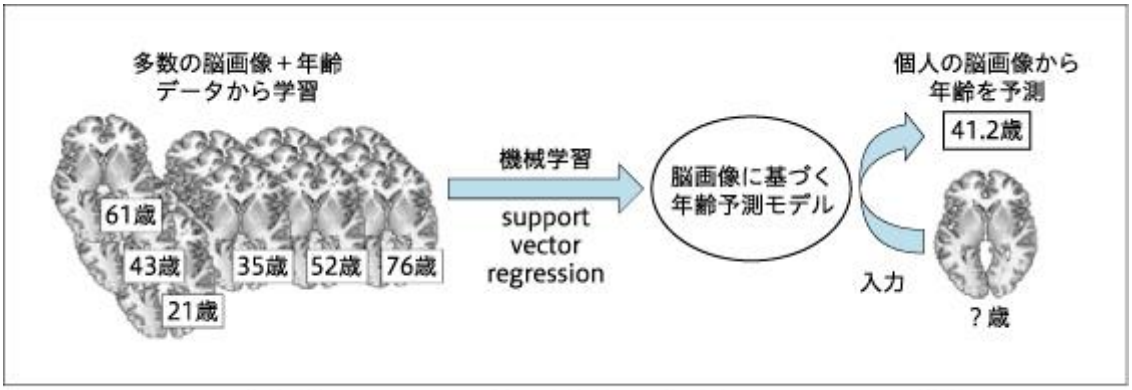

図2　機械学習による脳画像に基づく脳年齢予測システムの構築

Fig. 2 Construction of a brain-age prediction system based on neuroimaging using machine-learning.

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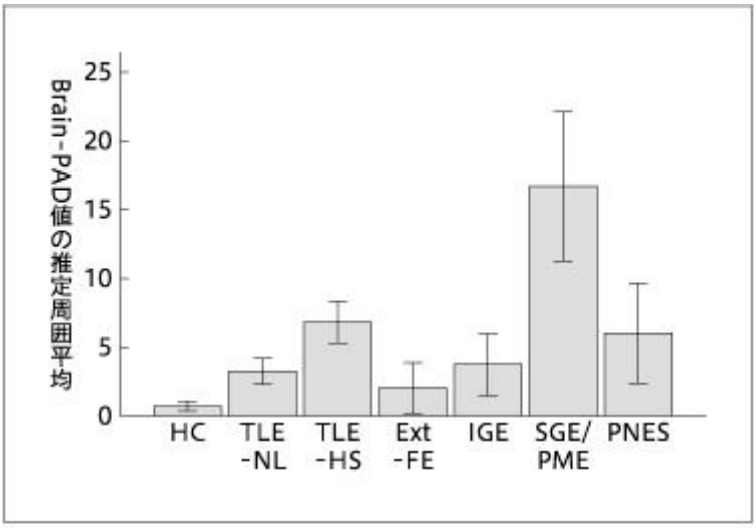

図3　各てんかん類型における脳年齢上昇

年齢・性別で補正したBrain-PAD（予測年齢－実年齢）値．エラーバーは標準誤差の2倍を示す．
HC：健常群，TLE-NL：MRI無病変の側頭葉てんかん，TLE-HS：海馬硬化を伴う側頭葉てんかん，Ext-FE：側頭葉外てんかん，IGE：特発性全般てんかん，SGE：てんかん性脳症，PME：進行性ミオクローヌスてんかん，PNES：心因性非てんかん性発作．
（文献22より一部改変）

Fig. 3 Increase in brain-age in each epilepsy type.
Brain-PAD (predicted age - chronological age) values corrected for age and sex. Error bars indicate twice the standard error.
HC: healthy subjects, TLE-NL: non-lesional temporal lobe epilepsy on MRI, TLE-HS: temporal lobe epilepsy with hippocampal sclerosis, Ext-FE: extra-temporal lobe focal epilepsy, IGE: idiopathic generalized epilepsy, SGE: symptomatic generalized epilepsy, PME: progressive myocardial epilepsy, PNES: psychogenic non-epileptic seizures.
(Partially modified from Ref. 22).

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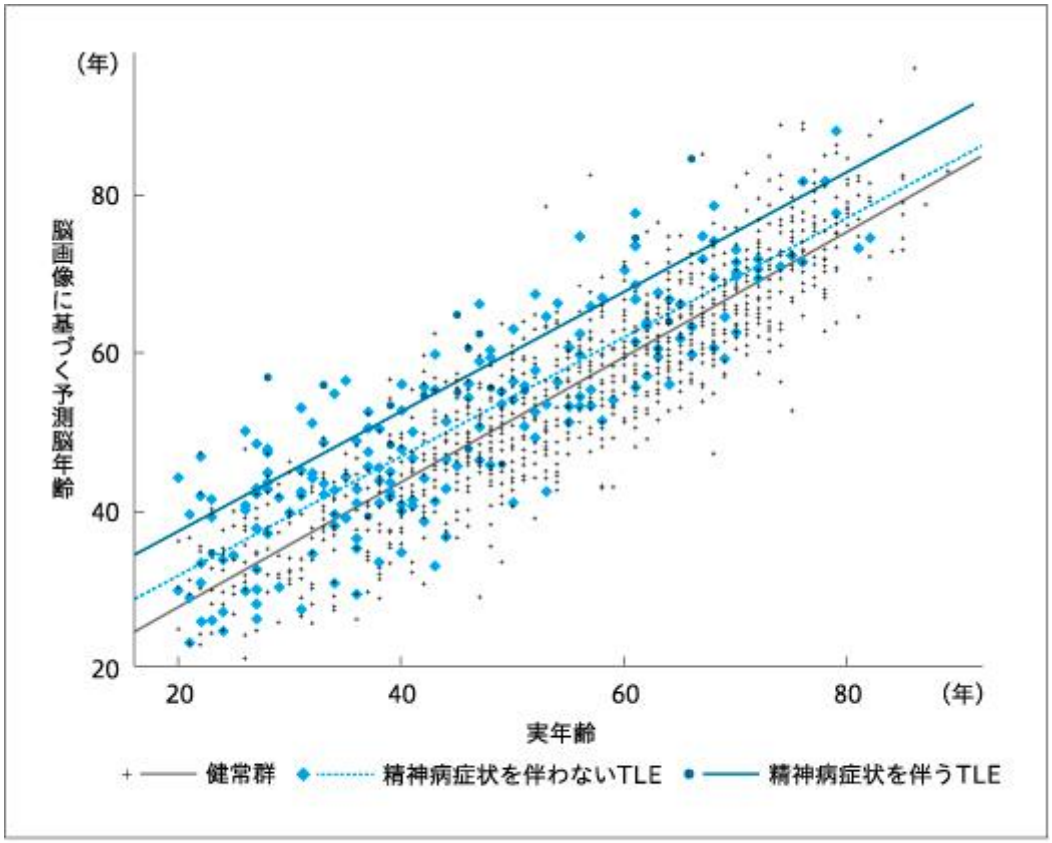

図 4　精神病症状の有無と側頭葉てんかんにおける脳年齢上昇
(文献 22 より作成)

Fig. 4 Presence of psychotic symptoms and increase in brain-age in temporal lobe epilepsy.
(Prepared from Ref. 22).

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