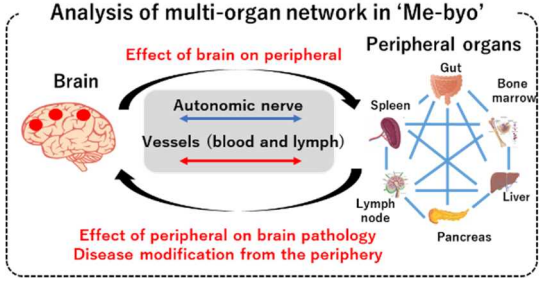
R&D item

1～4. Brain and multi-organ network in Alzheimer's disease, vascular dementia and Parkinson's disease dementia

Progress until FY2023

1. Outline of the project

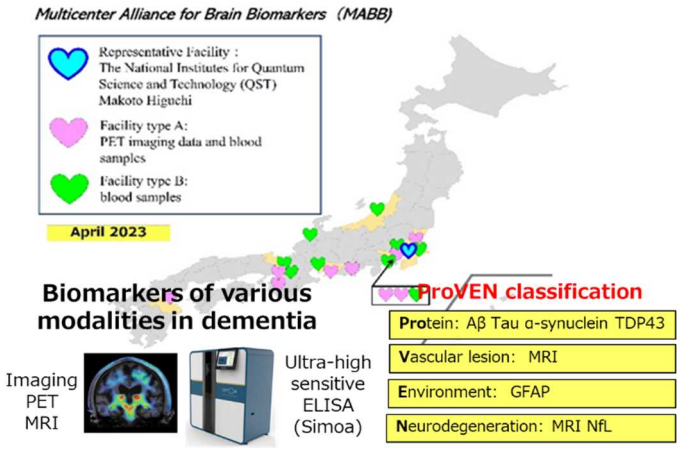
Alzheimer's disease (AD) vascular dementia, and Parkinson's disease dementia are the three major dementias. We aim to elucidate the multi-organ network in these dementias by mathematical analysis using novel mouse models and human cohorts to develop risk prediction and prevention methods. We will use a model in which the causative protein starts to accumulate in "Me-byo" state and symptoms develop later, enabling us to analyze the preclinical stages of various pathological conditions. We are also conducting human cohorts in preclinical conditions.



2. Achievement in 2023

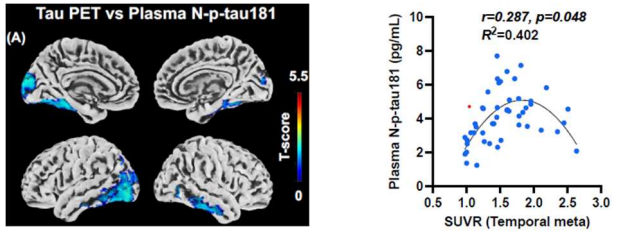
A multicenter cohort of 'Me-byo' for dementia

The MABB (multicenter alliance for brain biomarkers) 'Me-byo' cohort, in which 18 institutions are currently participating, is a multicenter alliance that promotes the development of imaging and blood biomarkers. The MABB research is characterized by the availability of secondary use of data and samples from other clinical studies, which will accelerate validation of biomarkers.

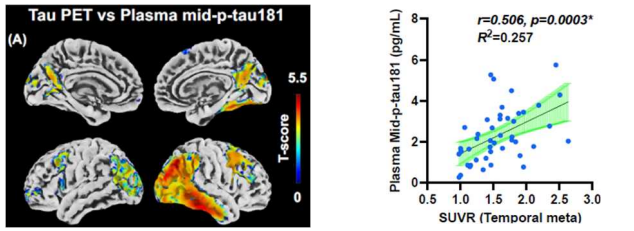


In analyzing this pre-disease cohort, our research group is focusing on the **ProVEN** classification, which is a more comprehensive categorization of dementia.

Specifically, this involves analyzing pathological proteins such as amyloid β and tau (Protein), brain inflammatory environment (Environment), vascular lesions (Vascular), and neurodegeneration (Neurodegeneration) using biomarkers in body fluids, MRI, and PET. This year, we have developed a novel highly sensitive detection system (ELISA) for phosphorylated tau (p-tau) in blood, which is one of the most important markers that accumulates in AD and is correlated with neural damage.



With conventional ELISA methods for measuring p-tau, the correlation with tau accumulation observed in PET was lost, particularly as the pathology progressed.



With the novel ELISA method for measuring p-tau, the correlation with tau accumulation observed in PET was maintained.

3. Future plans

Various types of data will be collected from original disease models and dementia "Me-byo" cohorts. Furthermore, we will identify candidate biomarkers that contribute to early diagnosis through data-driven analysis of multi-organ networks, and try to predict and prevent the development of dementia.

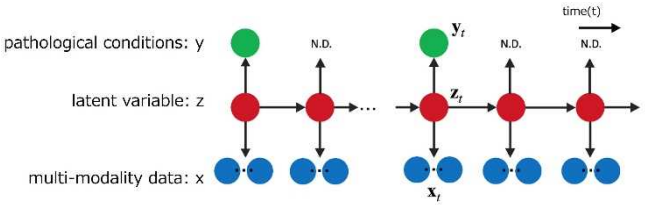
R&D item

5. Elucidation of Inter-Organ Networks in Dementias by AI and Mathematical Research

Progress until FY2023

1. Outline of the project

Our aim is to understand inter-organ networks by constructing data-driven mathematical models in animal models combined with human data. AI and machine learning techniques will be exploited to use the limited data we have collected from living organisms effectively by removing noise from the data and filling in missing values. Also, We will develop machine learning algorithms that can integrate mathematical models with human data, which enable estimation of the condition of each organ and identification of the early stages of dementia using non-invasive and cost-effective measurements in the preclinical 'ME-BYO' conditions.



$$z_{k,t+1}=F(z_{k,t})+\eta_{k,t} \quad x_{n,t}=Uz_{k,t}+u+\varepsilon_{n,t} \quad y_{k,t}=Vz_{k,t}+v+\xi_{k,t}$$

U, V: weight matrix
u, v: bias
ε_n, ξ_k, η_k: noise

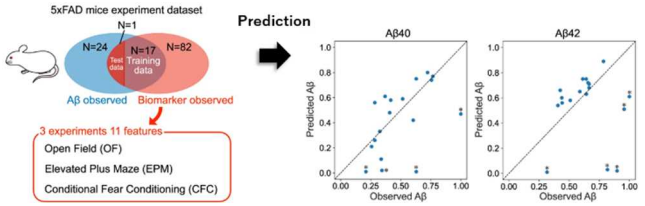
2. Achievement in 2023

Development of a Machine Learning Model to contribute to the Discovery of Early Indicators of Alzheimer's Disease

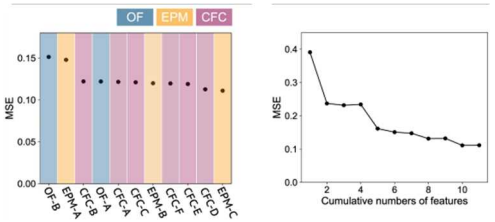
Alzheimer's disease (AD) is a disorder characterized by the progressive neuronal degeneration of the brain. Predominantly seen in the elderly, it is marked by memory decline and cognitive impairment. While the exact cause remains unclear, it is known that in the brains of Alzheimer's patients, the accumulation of a protein called amyloid-beta (Aβ) precedes neuronal degeneration. Current methods to assess the accumulation of Aβ in the brain are costly and invasive. Therefore, a simple and non-invasive biomarker that can predict the amount of Aβ accumulation, measurable from blood, urine, imaging, or other sources, would be highly useful for the early prediction of AD onset.

Typically, when using machine learning to predict Aβ accumulation from biomarkers, paired data (where both the biomarker and Aβ accumulation are observed in the same sample) is required. However, obtaining such paired data is costly and labor-intensive, which has been a barrier in biomarker discovery. In this context, a research group led by Honda Naoki and Yuichiro Yada at Hiroshima University developed a machine learning model that enables the quantitative prediction of Aβ accumulation even with limited paired data. This technological advancement is expected to facilitate the development of novel AD biomarkers based on the predictability of Aβ accumulation.

These research findings were published in the international academic journal npj Systems Biology and Applications" on November 23, 2023.



Using publicly available data where both behavioral characteristics and Aβ levels were measured, we demonstrated that the amount of Aβ in the brain can be estimated from three non-invasive behavioral analysis results.



It was suggested that it is important to use the results of multiple behavioral analyses, not just one, to predict the amount of Aβ.

3. Future plans

We will construct data-driven mathematical models for multimodal data obtained from animal models and preclinical human 'ME-BYO' cohorts to elucidate the transformation of the inter-organ network. We will also apply this to the achievement of prediction and prevention methods for dementia based on brain-organ interactions.