The Brain Bank for Aging Research

Resources consisting of consecutive autopsy cases from a general geriatric hospital
(http://www.mci.gr.jp/BrainBank)

Brain Bank

1. Paraffin blocks and glass slides
   Consecutive autopsy cases (1972.5–): 6,945 cases
   Clinical, radiological and pathological database
2. Partially frozen brain (1995.1–): 1,852 cases
   Genomic resources
3. Frozen half brains (2001.7–): 652 cases
   Resources for Neuroscience Research

Clinical Longitudinal Studies

Dementia and Parkinsonism
MCI Resource

- Neurodegenerative: 33 cases, 57%
- Vascular disease: 9 cases, 15%
- Unremarkable: 6 cases, 11%
- Metabolic: 1 case, 2%
- Cerebral contusion: 2 cases, 4%
- Hippocampal sclerosis: 2 cases, 4%
- Neurodegenerative + vascular disease: 4 cases, 7%
Dementia Resource

- Neurodegenerative, 126 cases, 56%
- Vascular, 64 cases, 28%
- Others, 12 cases, 5%
- Creutzfeldt-Jacob disease, 6 cases, 3%
- Metabolic, 5 cases, 2%
- Cerebral contusion, 4 cases, 2%
- Unremarkable, 1 case, 0%
- Vascular disease + neurodegenerative, 9 cases, 4%
Degenerative MCI Resource

- DLB + ALS: 3%
- AGD + DLB: 3%
- AGD + NFTD, 2, 6%
- AD, 6 cases, 19%
- AD + DLB: 3%
- AD + AGD, 3, 9%
- PSP, 1, 3%
- PD, 3, 9%
- NFTD, 6, 18%
- AGD, 6, 18%
Degenerative Dementia Resource

- Huntington, 1, 1%
- DLB/ PSP/ DG, 1, 1%
- DLB/ DNTC, 1, 1%
- CBD/ DG, 1, 1%
- DG/ PSP, 1, 1%
- AD/ DG, 2, 2%
- DG+ NFTD, 4, 3%
- ALS, 4, 3%
- Others, 5, 4%
- NFTD, 6, 5%
- PSP, 9, 7%
- AD+ DLB, 9, 7%
- DG, 15, 12%
- DLB, 22, 17%

AD, 44, 34%
Legal background and Philosophy

- Storage and research use of autopsy material, based on Article 18 of the Cadaver Autopsy and Preservation Act, Japan
- Informed consent at autopsy permission for registration to the brain bank
- “Donated specimens stay in public domain and should be served for promotion of public welfare”
- “TMGH and TMIG should help research for cure of age-associated cognitive and motor decline
- Brain donation from patients “Please use every part of my body to conquer the diseases that will kill me” Emeritus Professor of the University of Tokyo Yasuo Toyokura’s living will.
- To encourage young investigators for aging research
Materials and Methods

Serial autopsy cases of a dignified community-based general and emergent geriatric hospital

- ① Every autopsy, taken care by neuropathologists in order to determine how to sample nervous tissues most appropriately
- ② Making 7mm slice, taking photo and freezing with dry ice powder of the non-dominant or disease-non-affected half of the brain
- ③ To store in deep freezer
- ④ Small samples, in special fixation for immunohistochemical and ultrastructural studies
- ⑤ To fix in 20% buffered formalin for 7-13 days of the contralateral half of the brain and hold brain cutting conference every week for clinical, radiological and macroscopic correlations
- ⑥ To prepare specimens with international standard
Harvesting a brain

Attending Neuropathologists, handling every case

Sliced with 7mm-thickness, taken photos and snap frozen

Digital databased
A fresh sliced brain, frozen in a safety cabinet (P2)
A mobile freezer (A), a copper plate chilled in a deep freezer (B), aluminum foil (C)
Snap frozen with dry ice powder
Every slice, sealed with a Zip Lock and double sealed with a larger Zip Lock
Deep freezer storage rooms, capacity for 800 cases
Every day maintenance

1) Deep freezer storage rooms, in strict air conditioning, to check temperature of deep freezer at 9:00, 16:00 and 22:00

2) To connect alarm to the central surveillance system for emergency call to an on call member of BBAR

3) A back up freezer with large amount of dry ice, with 10kg dry ice space in each deep freezer

4) Emergent repair service from 9:00 to 17:00 by a sales representative of the distributor of deep freezers (Asahi Life Science)
Brain Cutting (1972.5.1-)

Clinical, radiological and macroscopic pathological correlations with Dpts. Neurol. & Pathol. TMGH
BBAR Protocol

Fresh Frozen Half

Fixed Half
Automatic Immuno-stainer

The contract with a commercial laboratory with our protocol
The same staining available everywhere in Japan
Histological Specimens

Tissue Block

Relational data base
6,945 cases
International standardization
BBAR Resource Center: Blocks and Glass slides of 6,945 cases
Staging of Neurofibrillary Tangles (Braak)

AT8 & Gallyas- Braak silver staining

Neurofibrillary changes
Staging of Senile Plaques (Braak)

Anti-Abeta immunostain and Modified Methenamine Silver Stain
### Staging of Lewy body (BBAR)

H.E. & anti-ubiquitin and phosphorylated α-synuclein antibody

<table>
<thead>
<tr>
<th>Clinical Pathology</th>
<th>Lewy subtype</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 negative</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>0.5 positive in neuropil</td>
<td>B: brain stem (A: amygdala)</td>
<td>N/A</td>
</tr>
<tr>
<td>1. Intracellular positive</td>
<td>B: brain stem (A: amygdala)</td>
<td>N/A</td>
</tr>
<tr>
<td>2. LB+ degeneration No related parkinsonism No related dementia</td>
<td>B: brain stem T: transitional</td>
<td>N/A</td>
</tr>
<tr>
<td>3. Parkinson disease No dementia</td>
<td>B: brain stem T: transitional</td>
<td>-</td>
</tr>
<tr>
<td>4. DLB/PDDT</td>
<td>T: transitional</td>
<td>+</td>
</tr>
<tr>
<td>5. DLB/PDDN</td>
<td>N: neocortical</td>
<td>+</td>
</tr>
</tbody>
</table>

Staging of Argyrophilic Grains (BBAR)

Degenerative Pathology Database

A/G CDR PMI NFT SP Grain AA LB AT UD apoE NPD
92F 3 15:35 VI C 0 3 2L 0 1 44 AD/AA

CDR (clinical dementia rating): 0-3
NFT (tangle: Braak Stage): 0-6
SP (senile plaque: Braak Stage): 0-3
Grain (argyrophilic grain, TMBB Stage): 0-3
AA (amloid angiopathy, TMBB Stage): 0-3
Lewy (Lewy body, TMBB Stage): 0-5
τ-astro (tau-immunoreactive astrocytes): 0-3
ubq (ubiquitin-immunoreactive dots): 0-3
NPD: neuropathological diagnosis
Vascular Pathology Database

Clinical Information
- Stroke event 0, 1, 2, 3
- Neuroimaging CT, MRI, SPECT, PET

Neuropathology Database
- Embolism: E, e
- Thrombosis: T, t
- Lacuna: L, l
- White matter change Specified
- Hemorrhage H, h
- Subarachnoid hemorrhage Sah

Large capital when contributing to clinical symptoms or accompanying secondary degeneration
In the parenthesis at agonal stage

Any vascular lesion is contributory to mental and motor decline in the elderly

Prospective clinical study is imperative for disclosure of a specific vascular lesion, responsible for cognitive decline
BBAR Rules

1. The application should include IRB#, funding resource and abstract

2. The application approved by the bank committee, consisting of the vice president of TMIG, the chairpersons of the Departments of Pathology and Department of Neurology, the director of BBAR, and the outside advisory board members.

3. The application approved by the IRBs of the applicant’s institute, TMIG and TMGH

4. The applicants, approved to be appointed as a visiting scholar to TMIG
Brain Bank Project

Prospective longitudinal clinical studies of dementia and parkinsonism

- Neursopsychological examination
- Voxel based morphometry with MRI
- CSF and blood biomarker
- PET: FDG, PIB, Dopamine (CFT, Raclopride) flumazenil

Based on neuropathological studies of BBAR
## CSF Biomarker

<table>
<thead>
<tr>
<th>Disease</th>
<th>$\tau$</th>
<th>$P_\tau$</th>
<th>$A_\beta$</th>
<th>HVA</th>
<th>5HIAA</th>
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<tbody>
<tr>
<td>Alzheimer disease</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>→</td>
<td>→</td>
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<tr>
<td>Parkinson disease</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Dementia with Lewy bodies</td>
<td>→</td>
<td>→</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>↓</td>
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<tr>
<td>Tangle predominant dementia</td>
<td>↗</td>
<td>↗</td>
<td>→</td>
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<td>→</td>
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<tr>
<td>Argyrophilic grain dementia</td>
<td>↗</td>
<td>↗</td>
<td>→</td>
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<td>→</td>
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<tr>
<td>Cortico-basal degeneration</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
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<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>↑</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
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</table>
## CSF: HVA, 5HIAA (ng/ml) (autopsy confirmed)

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<tr>
<th></th>
<th>n</th>
<th>HVA</th>
<th>5HIAA</th>
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<tr>
<td>AD</td>
<td>4</td>
<td>19.6 ± 6.4</td>
<td>14.1 ± 5.7</td>
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<tr>
<td>PD</td>
<td>1</td>
<td>6.3</td>
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<td>PDD/DLB</td>
<td>6</td>
<td>11.2 ± 4.8</td>
<td>7.3 ± 4.2</td>
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<td>PSP</td>
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<td>20.5 ± 11.8</td>
<td>19.2 ± 5.5</td>
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<tr>
<td>CBD</td>
<td>1</td>
<td>29.0</td>
<td>15.9</td>
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<tr>
<td>DG</td>
<td>2</td>
<td>27.2 ± 18.2</td>
<td>22.6 ± 18.2</td>
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<tr>
<td>MND</td>
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<td>30.6 ± 14.5</td>
<td>30.7 ± 16.0</td>
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<tr>
<td>SCD</td>
<td>1</td>
<td>24.7</td>
<td>14.9</td>
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<tr>
<td>Pick</td>
<td>1</td>
<td>43.5</td>
<td>17.1</td>
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<tr>
<td>Others</td>
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<td>21.0 ± 2.3</td>
<td>21.0 ± 4.8</td>
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</table>
MRI (voxel based morphometry)

70’s, F, Amnesia, MMSE 28/30

Hippocampal atrophy difficult to determine

80’s, F, Dementia, MMSE 18/30

VSRAD with atrophy of entorhinal cortex, displayed as blue
Z score 1.9 (>1.6)

Z score 2.2
Pons/ Midbrain tegmentum ratio
Amyloid Pet Image of a brain bank donor with living will
Informed Consent for Registration to the Brain Bank

Please check the approved column
☐ To register the Brain Bank for Aging Research

IRB approval is required for research use of specimens registered to the Brain Bank for Aging Research. Each research should have aim to conquer aging and dementia,

Special Consent
To examine brain: Yes, No (please circle one)
Distribution

• Paraffin and frozen sections, prepared by brain bank technicians
• Frozen specimens, prepared by a brain bank doctor with exact anatomical identification attached with a photo, prepared on a dry ice plate in a cryostat of -35°C, by autoclaved small forceps
The Minimal Requirement

#1 anterio cingulate
#2 F2
#3 Meynert
#4 Amygdala
#5 T2
#6 Basal Ganglia
#7 Anterior Hippocampus
#8 Subthalamic Nucleus
#9 Posterior Hippocampus
#10 Precentral Gyrus
#11 Supramarginal Gyrus
#12 畔溝
#13 Cerebellum with Dentate
#14 Medulla
#15 Pons (Locus coeruleus)
#16 Midbrain (substantia nigra)
#17 Spinal Cord (C8, T12, L5, S2)
<table>
<thead>
<tr>
<th></th>
<th>Body</th>
<th>Brain</th>
<th>PD (LBD)</th>
<th>PSP</th>
<th>CBD</th>
<th>MSA</th>
<th>NPH</th>
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<td>0</td>
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<tr>
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<td>(4)</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>1</td>
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<tr>
<td>Sum</td>
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Undeline: BBAR protocol, Others: minimum protocol, *partial frozen, ○: frozen half hemisphere
## PDBRN, 2006

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<tr>
<th></th>
<th>PDBRN</th>
<th>PD (LBD)</th>
<th>PSP</th>
<th>CBD</th>
<th>MSA</th>
<th>SCA2</th>
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<tr>
<td><strong>TMGH</strong></td>
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<tr>
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<tr>
<td><strong>Sum</strong></td>
<td>151</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Undeline: BBAR protocol, Others: minimum protocol, *partial frozen, ◯: frozen half hemisphere*
Brain Net Japan

The Brain Bank Committee, the Japanese Society of Neuropathology

1. To form interface with brain banks and institutional collections

2. To build up information networks for possible cowork with researchers

3. The first Brain Bank Symposium at the 2007 JSNP Annual Meeting (2007.5.30)

4. The Brain Bank Session at the 2008 JSNP Annual Meeting (2008.05.26)
Collaboration List in Japan (34)

- TMIG Proteome, Glycoprotein
- Human Tissue Pathology
- Molecular Pathology
- Molecular Biology

- Tokyo Metro. Inst. Neurology
  Epilepsy Research,
  Molecular Physiology

- Tokyo Metro. Inst. Psychiatry
- Grad. Med. Univ. Tokyo
  Neuropathology, Neurology
  Radiology, Oto-Rhino-Laryngology

- Grad. Frontier Sciences
- Grad. Pharm. Univ. Tokyo
- Grad. Med. Univ. Niigata
- Grad. General Culture, Univ. Tokyo
- Grad. Med. Tokyo Medical and Dental Univ.
  Neuropathology
  Neurology
  Pathology

- Grad. Med. Univ. Kyoto
- Grad. Med. Tohoku Univ.
- Jichi Medical School
- Biochemistry
- Dpt. Med. Tsukuba Univ.
- Neurology
- Neurology

- Developmental Medicine
- Psychiatry
- Neurology
- Neurology
- Pharmacology
- Molecular Biology
- Natl. Ctr. Long. Life
- Alzheimer Research
- Riken
- Alzheimer Research
- Osaka Bio
- Prostaglandin Research
- Mitsubishi Research Inst.
- Alzheimer Research
- Toray Medical Inst.
- Parkinson Research
The BBAR CREW

**TMIG**

**Neuropathology**
Chairman: Murayama, S
Staff: Saito, Y
Hatsuta, H
Fellow: Adachi, T
Yamadera, M
Funabe, S
Technician: Aikyo, N
Harada, M
Naoi, N
Kimura, Y

**PET Clinical Center**
Chairman: Ishii, K

**Pathology**
Chairman: Sawabe, M
Staff: Arai, T
Kasahara, I

**TMGH**

**Neurology**
Chairman: Kanemaru, K
Staff: Komiya, T
Nishina, Y
Shiina, M
Sunakawa, M
Hiroyoshi, Y
Kurashige, T
Eguchi, K

**Psychiatry**
Chairman: Furuta, K

**Radiology**
Chairman: Tokumaru, A

**Rehabilitation**
Staff: Kato, T