From specimens to Biomarkers?

Harmonization of Biobanks SOP'S in the discovery of novel candidate biomarkers for Alzheimer's disease (AD).

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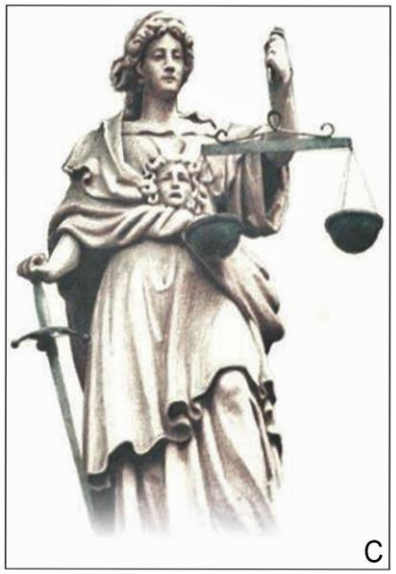
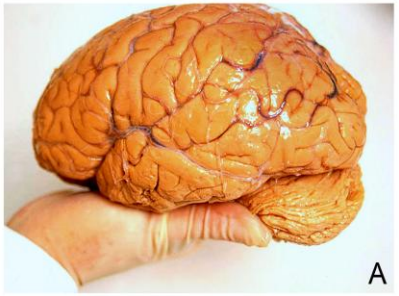
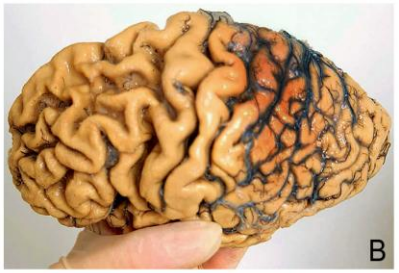
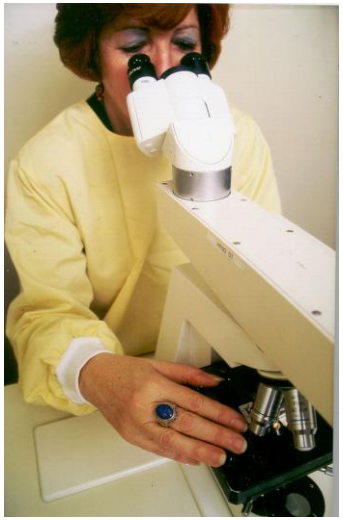
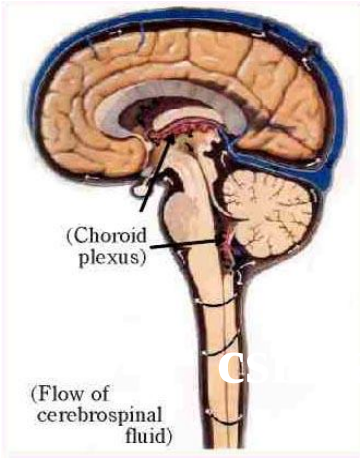
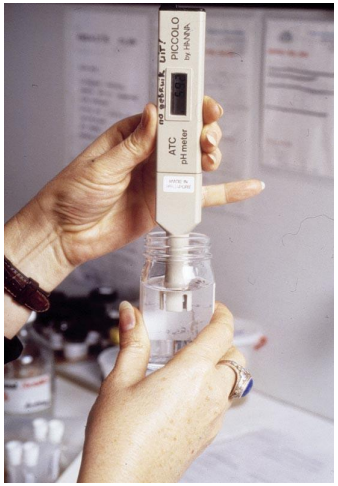












ADPD ,Barcelona 9-13 March, 2011

Brain Bank / Biobank Clinics

Human specimens supplied by Brain/Tissue/Bio (BTB) Banks are a rich source of adequately collected and preserved specimens of the human body in health and disease.

The specimens form an essential bridge between the clinics, basic science, post-mortem tissue banks and biotechnical companies which results in translational medicine and research.

It is crucial to build the bridge between population banks, clinical banks and post mortem banks to ensure the flow of clinical /genetic information available at the population banks to the post-mortem banks and create a global D-base, accessible for the international scientific community.

The bridge between banks and clinicinas will create the roadmap for understanding the pathology and identifying valid Biomarkers.

Neuroimaging

MRI measurements of atrophy
Amyloid plaque detection (PET)
Spect imaging (Dopamine system in DLB)
Cerebral blood flow (FDG)

Biological markers

Cerebrospinal fluid markers (Aβ, Tau, alfa-synuclein)
Blood (cytokines, alfa-synuclein, p53)
Plasma proteins
Urine (NTP; Alzheimr's Disease Reaction Titer)
Oxidative stress
Neurochemical markers/Olfactory biomarkers

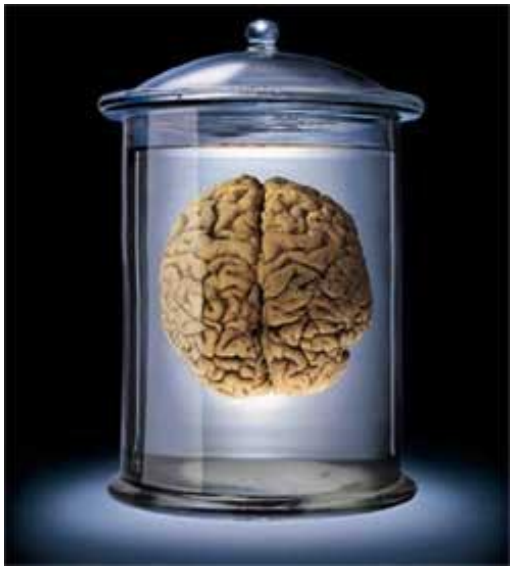
Ideal Combination

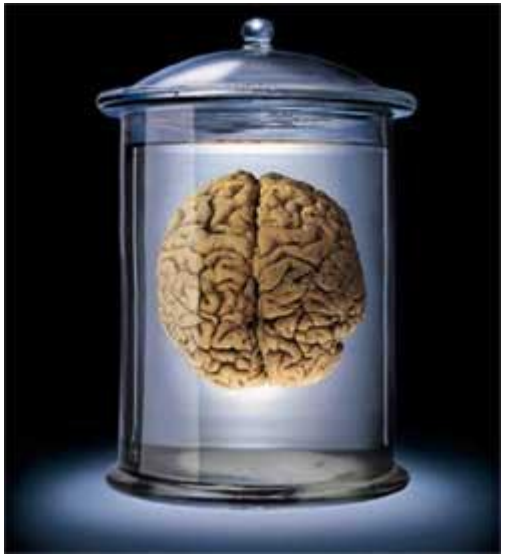
CSF Biomarkers + imaging +clinical assessment

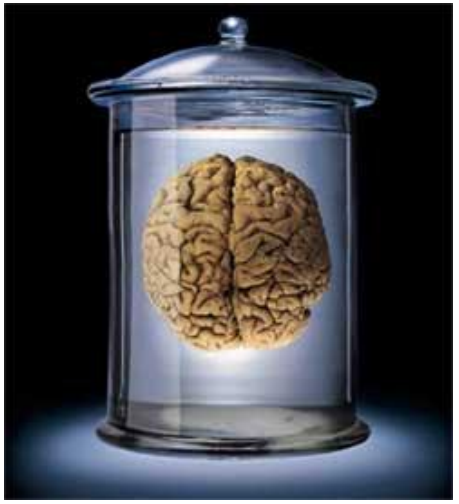
Biomarkers; what's in a name???

- A **biomarker** is a substance used as an indicator of a biologic state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention.
- **No controversy**; we need an array of biomarkers both in the living patient and at post mortem autopsy.
- Biomarkers have an important role in early diagnostics, predictive value of disease progression and in target development.

A brain bank is *not* a collection of brains in jars







A brain bank is *a* ***collaboration*** between many disciplines:

Neurology, Pathology, Radiology, Psychiatry, Ethics, Genetics

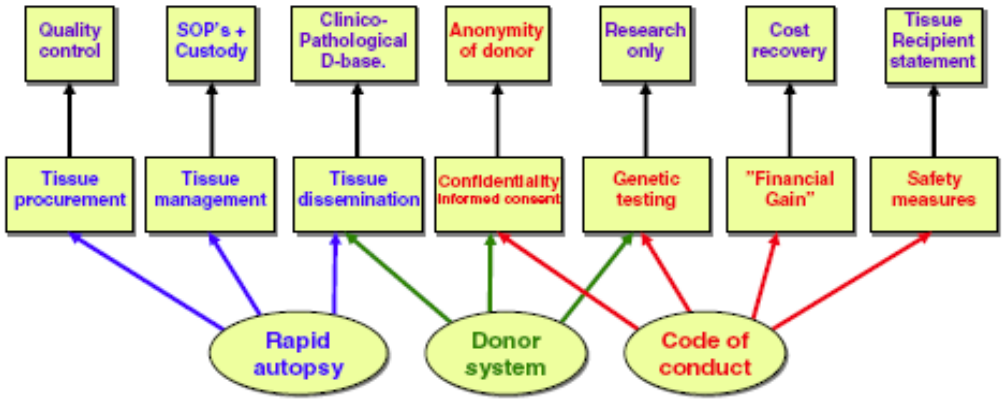


Fig. 2 *Overview of the pyramided structure of BTB-banks* The base line of the pyramided tissue banks structure consists of the donors, Code of conduct and rapid autopsies, ensuring the quality and ethics of the collected specimens. The middle row indicates the seven issues which form the Golden standard for banks collecting human specimens. The upper row illustrates the subsequent flow to regulatory and ethical guidelines for safe repositories

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Biobanks for biomarkers in neurological disorders
The Da Vinci bridge for optimal clinico-pathological connection

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ARTICLE INFO

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Keywords:
Biomarkers
BTB-banks
Dementia
Early diagnostics
CSF
Blood
Cells

ABSTRACT

The diagnosis of dementing disorders is severely hampered by the absence of reliable biomarkers that can be measured in body fluids such as blood, urine and cerebro-spinal fluid (CSF).
Searching for biomarkers is hampered by the huge variability between individuals; the use of autopsy specimens induces significant data fluctuation due to rapid post-mortem changes in the specimens.
The search for biomarkers obtained from living donors has contributed already a vast amount of data.
The role of amyloid and tau as early diagnostic markers in the pathology of dementia has been reported in differential involvement in Alzheimer's disease (AD), late onset Alzheimer disease (LOAD), Lewy Body dementia (DLBD), Vascular dementia, fronto-temporal lobar degeneration (FTLD), Mild cognitive impairment (MCI) and non neurological controls.
In the coming decennia, brain/tissue/biobanks (BTB-banks) will have a major role in identifying the relevant biomarkers and will collect, preserve and type RNA and DNA extracted from brain/tissue/body fluids in order to update the pathological hallmarks of dementing disorders.
The present paper reviews and compares the currently known/clinically applied biomarkers in dementia which can be identified and incorporated into clinical drug trials and elucidate proposed mechanisms of disease and drug action. Furthermore, the review screens a panel of biomarkers used for early and differential diagnosis and comments on the validity of these biomarkers in reflecting the typical hallmarks of neurological disorders.

BioBanks – The Da Vinci bridge in Biomarkers research

Human subjects
Health / disease

Hystology/
cytology

CSF
Urine

Whole blood
Plasma
Serum

Tissue/
Tissue arrays

Cardiac Blood
Ventricular CSF

Stored cells
Cultured cells

Biomarkers
In vivo

Biomarkers at
Autopsy

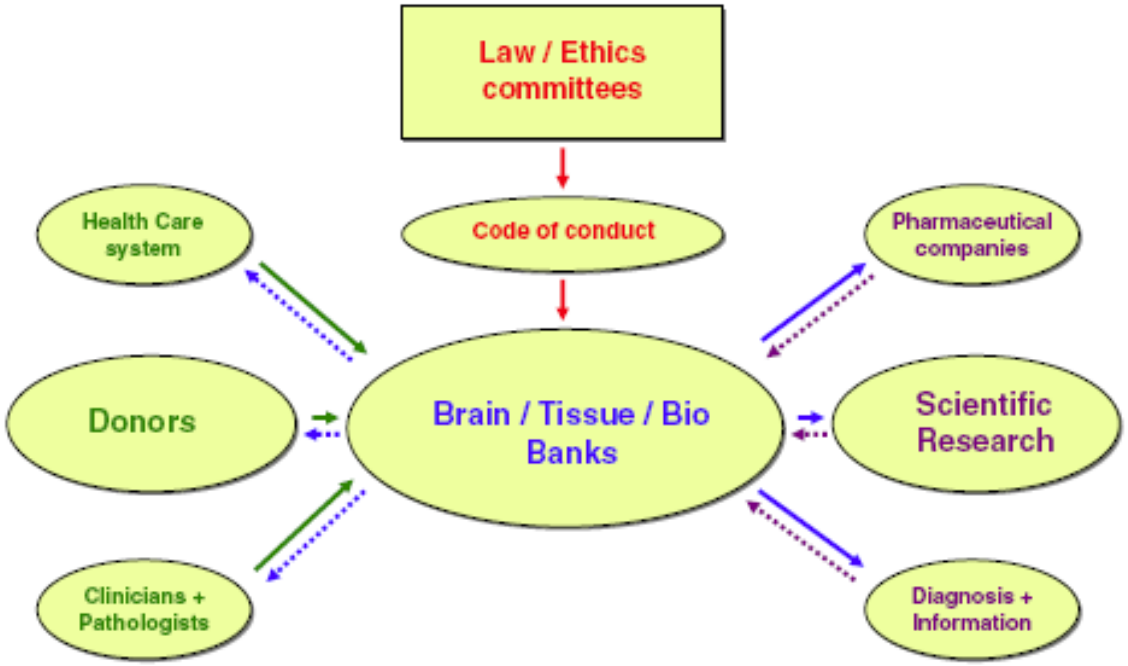


Fig. 1 *Flowchart of BTB-banks interfaces* This scheme illustrates BTB-banks as intermediaries to facilitate the availability of specimens for research. The middle line shows the three main parties who make this combination a success; the donors on the one hand, the BTB-banks and the scientific research community on the other hand. The local health care system, policy makers, clinicians, pathologists are the supporting elements and it is obvious that the main core of the banks is adherence by local legislation, ethics review committee and a solid code of conduct

Biobanking Activities

- Recruitment
- Consent
- Collection
- Transport
- Storage
- Annotation
- Aliquot and Derivative Production
- Regulatory Compliance
- Scientific Consultation
- Materials Transfer

The Science of Banking

- **Key scientific issues must be addressed**
  - What materials to collect
  - What data to collect and how to document it
  - What are the appropriate testing and processing methods
  - How do we validate processes
  - What are the appropriate quality biomarkers
  - Impact of storage on materials
- **Key International, National, Regional legislation and policy must be addressed**
  - Ethics and privacy standards
  - Materials Access and control
- **Logistical Issues**
  - Long term effort and storage
  - Complex operations involving many disciplines
  - Need for constant revisions

The Future of Biobanking

- Accelerate Research
  - Strategic planning and interaction with large scale translational research initiatives
  - Enabling, through coordination and guidance the regionally funded collection of well defined and distinctive cohorts for specific programs
  - Integration of additional existing collections and biobanks based on the rigorous quality assessment already in place for founding members
  - Facilitate access to existing materials
- Protect Research Investment
  - Facilitating access and defining equitable costing for Biobanking
  - Ongoing evaluation of biobank accessibility programs and materials
  - Ensure highest ethical, privacy and legislative compliance
- Leadership in the Research Community
  - Expanding outreach to communities of interest (scientific, public, patient and policy)
  - Further development of best practices – leading to certification

The future of molecular and translational research relies on the availability and quality of bio-specimens.

7 golden standards of Brain Banking

1. A well established local **donor system** in which consent is obtained for the use of tissues for scientific research and access to the medical records**.**
2. **Rapid autopsies** with a very short post-mortem delay and a **fresh dissection**; these are a prerequisite for an increasing range of **technical procedures and new systems such as neuronal cultures.**
3. Compatibility of **protocols for tissue procurement, management, preparation and storage** for diagnostics and scientific research.
4. A generally accepted consensus on the **clinical and neuro-pathological diagnostic criteria.**
5. **Quality control** of the dissemintaed samples (**pH/agonal state**).
6. Abiding internationally accepted guidelines for the **ethical and legal** aspects conform the local medico-legal system.
7. Monitoring proper **safety procedures**.

Nederlandse Hersenbank

Codicil nr: [200501]

Meibergdreef 33
1105 AZ Amsterdam

[C]

Name : A. Trevalyan
D. o. B. : 14/02/1937
Address : Battersea highway 2001
Postal code : 2001 AT Town : Comden

I herewith give consent for a post-mortem brain autopsy and declare that my brain may be used for scientific research in the frame work of the Brain Bank project. I also give consent for acces to my medical file and use of the information for research purposes.

Signature:

Date:

General Practitioner:
Name : Dr F. Bloggs
Tel. Nr : 020 – 123654

Next of kin:
Name : ms L. Trevalyan
Tel. Nr. : 06 – 32145678

In case of demise, please contact AS SOON AS POSSIBLE:

monday to Friday, during office hours, the Brainbank : 020 – 566 5499

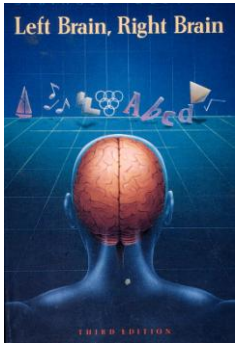
outside office hours, the VUMC emergency desk : 020 – 444 4330

Ethical/Legal code of conduct

- Written informed consent is obtained from both the donor and the next-of-kin (or designated representative in absence of family) for the following:

  - brain autopsy during which the brain tissue (and in case of separate permission the spinal cord) is removed.

  - the subsequent use of the material for scientific research.
  - the accompanying use of clinical data pertaining to the donor's medical history.
- In case of power of attorney has been given by a person, the holder of this power of attorney can sign the consent forms on behalf of the person who is incapable of giving the permission in person. The consent of the holder of the power of attorney covers the above mentioned areas.
- In case there may arise a conflict among next of kin regarding the potential donation after death, the NBB will first seek consensus. If this consensus cannot be reached, and although the NBB may legally have the right to perform the autopsy, the NBB will decline to do so.
- All tissues and remains are handled with the utmost respect.
- All tissue recipients are informed on the possible hazardous nature of the tissues and sign for handling all material with the necessary safety methods. All recipients are responsible to return unused tissues to the NBB and dispose tissue remains according to the local safety rules for disposal



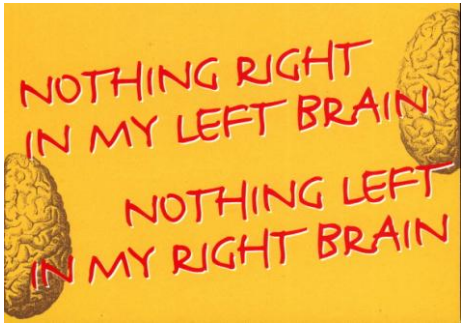
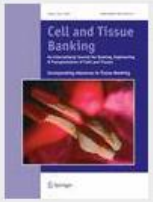


Fig. 1 Over view of the fresh and fixed dissection methods employed by the TRC

Journal Article



Standard Operating Procedures, ethical and legal regulations in BTB (Brain/Tissue/Bio) banking: what is still missing?

Journal	Cell and Tissue Banking
Publisher	Springer Netherlands
ISSN	1389-9333 (Print) 1573-6814 (Online)
Status	ONLINE FIRST
Category	Review Paper
DOI	10.1007/s10561-007-9055-y
Subject Collection	Biomedical and Life Sciences
SpringerLink Date	Tuesday, November 06, 2007

(1) Netherlands Institute for Neurosciences, Royal Dutch Academy of Science, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands

Received: 7 May 2007 **Accepted:** 2 October 2007 **Published online:** 6 November 2007

Abstract The use of human biological specimens in scientific research is the focus of current international public and professional concern and a major issue in bioethics in general. Brain/Tissue/Bio banks (BTB-banks) are a rapid developing sector; each of these banks acts locally as a steering unit for the establishment of the local Standard Operating Procedures (SOPs) and the legal regulations and ethical guidelines to be followed in the procurement and dissemination of research specimens. An appropriat Code of Conduct is crucial to a successful operation of the banks and the research application they handle. What are we still missing ? (1) Adequate funding for research BTB-banks. (2) Standard evaluation protocls for audit of BTB-bank performance. (3) Internationally accepted SOP's which will facilitate exchange and sharing of specimens and data with the scientific community. (4) Internationally accepted Code of Conduct. In the present paper we review the most pressing organizational, methodological, medico-legal and ethical issues involved in BTB-banking; funding, auditing, procurement, management/handling, dissemination and sharing of specimens, confidentiality and data protection, genetic testing, "financial gain" and safety measures. Taking into consideration the huge variety of the specimens stored in different repositories and the enormous differences in medico-legal systems and ethics regulations in different countries it is strongly recommend that the health-care systems and institutions who host BTB-Banks will put in getting adequate funding for the infrastructure and daily activities. The BTB-banks should define evaluation protocols, SOPs and their Code of Conduct. This in turn will enable the banks to share the collected specimens and data with the largest possible number of researchers and aim at a maximal scientific spin-off and advance in public health research.

Keywords Brain/Tissue/Bio banking - Code of Conduct - Donors - Ethics - Financial gain - Funding - Genetic testing - Informed consent - Safety - Sharing

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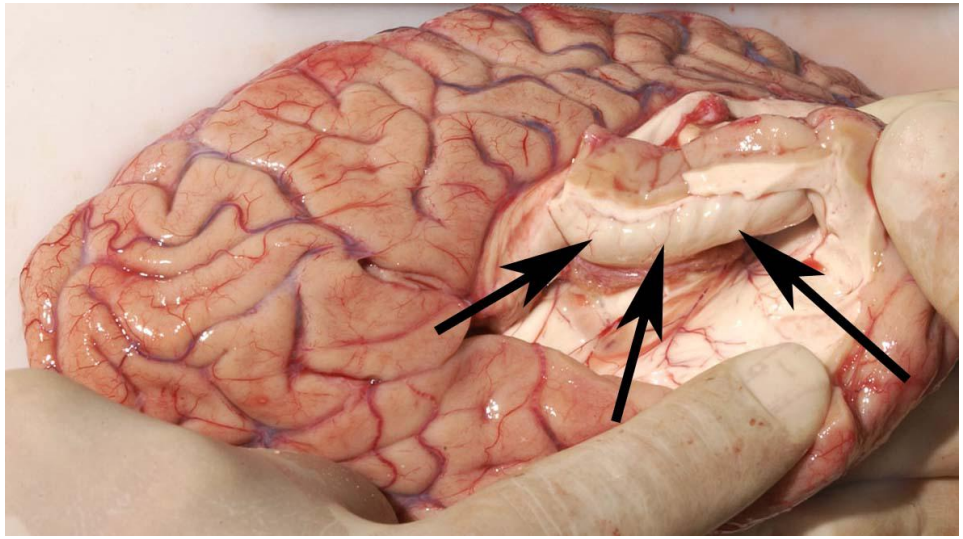


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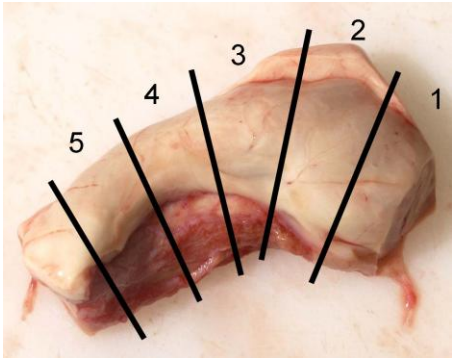
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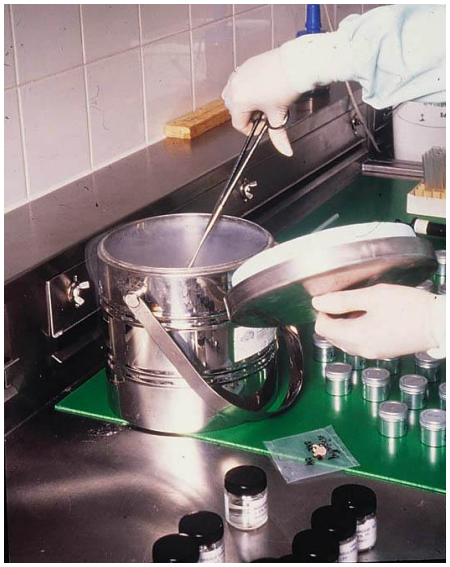
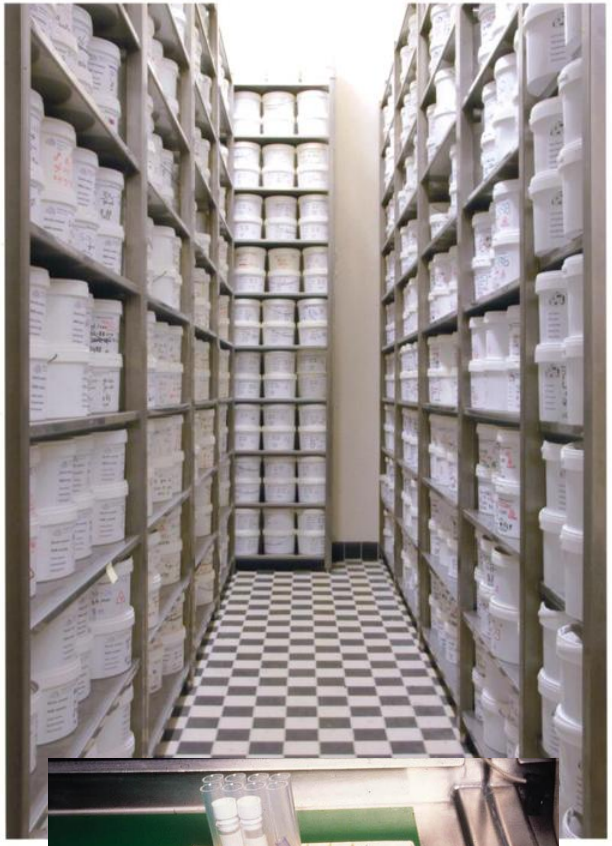
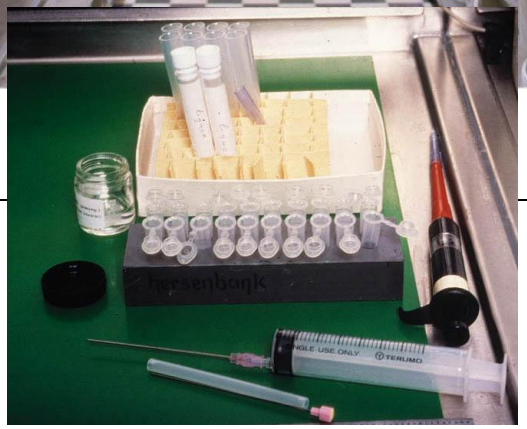


Freezing

Storage (1)

Storage (2)

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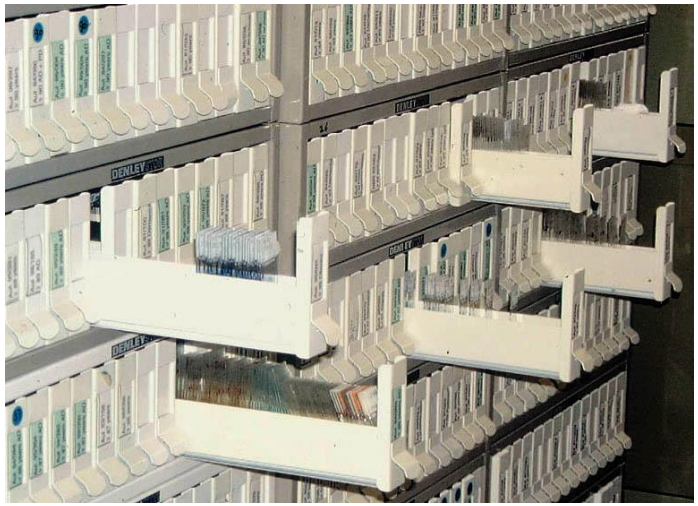
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Matching Factors in BTB banking

- **Ante-mortem:**
- **Age**
- **Gender**
- **Clinical diagnosis**
- **Agonal State**
- **Medication**
- **Circadian variation**
- **Seasonal Education**
- **variation**
- **Lateralization**
- **Family history/genetic load**
- **Education**

- **Post-mortem:**
- **Post-mortem delay**
- **Organ weight**
- **CSF / Brain pH**
- **Cause of death**
- **Clock time of death**
- **Date of death**
- **Death to refrigeration**
- **Freezing / fixation**
- **Storage time**

ELSEVIER

Molecular Brain Research 28 (1995) 311–318

MOLECULAR BRAIN RESEARCH

Research report

Tissue pH as an indicator of mRNA preservation in human post-mortem brain

Ann E. Kingsbury [a], Oliver J.F. Foster [b,*], Angus P. Nisbet [c], Nigel Cairns [d], Louise Bray [c], David J. Eve [c], Andrew J. Lees [e], C. David Marsden [b]

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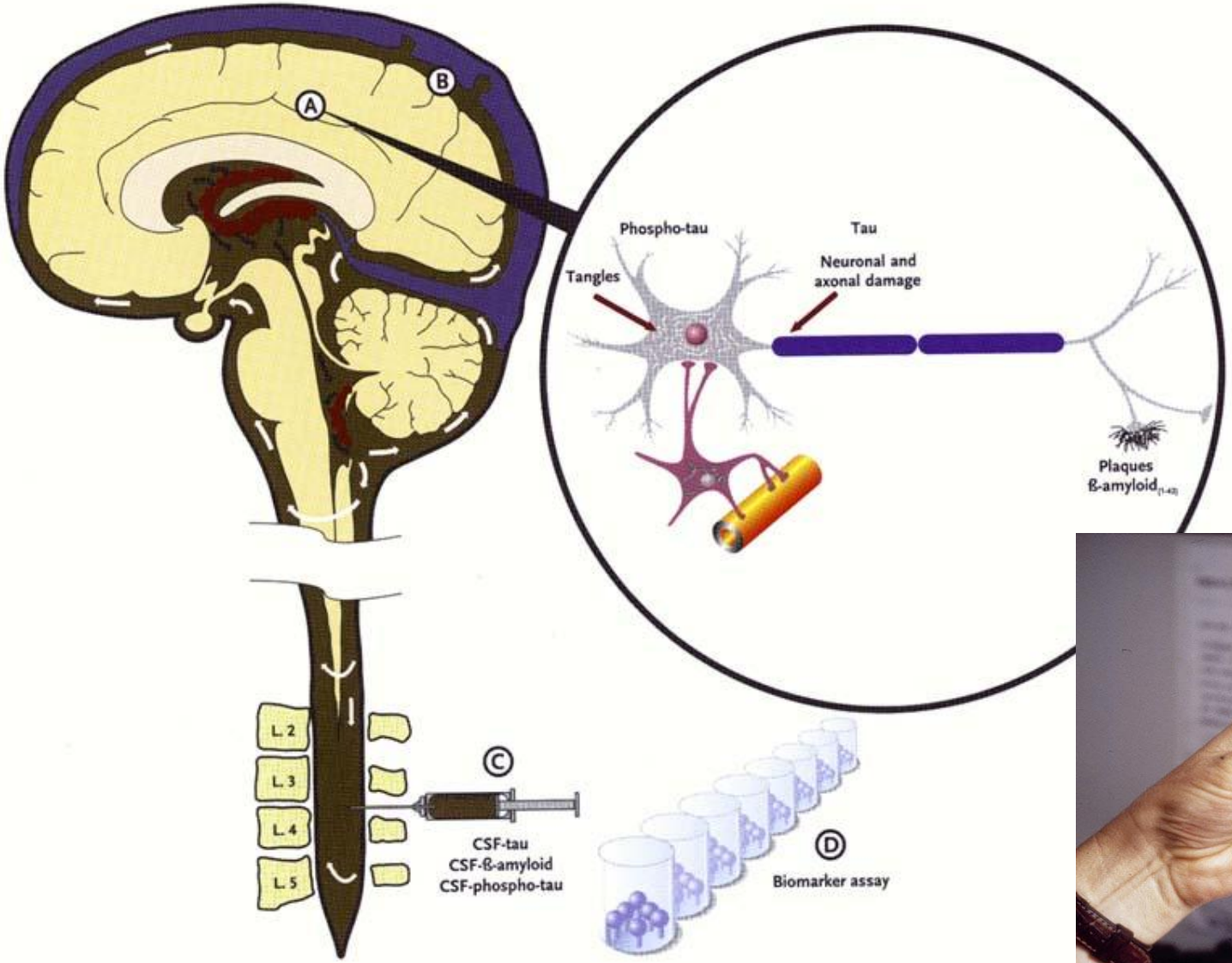
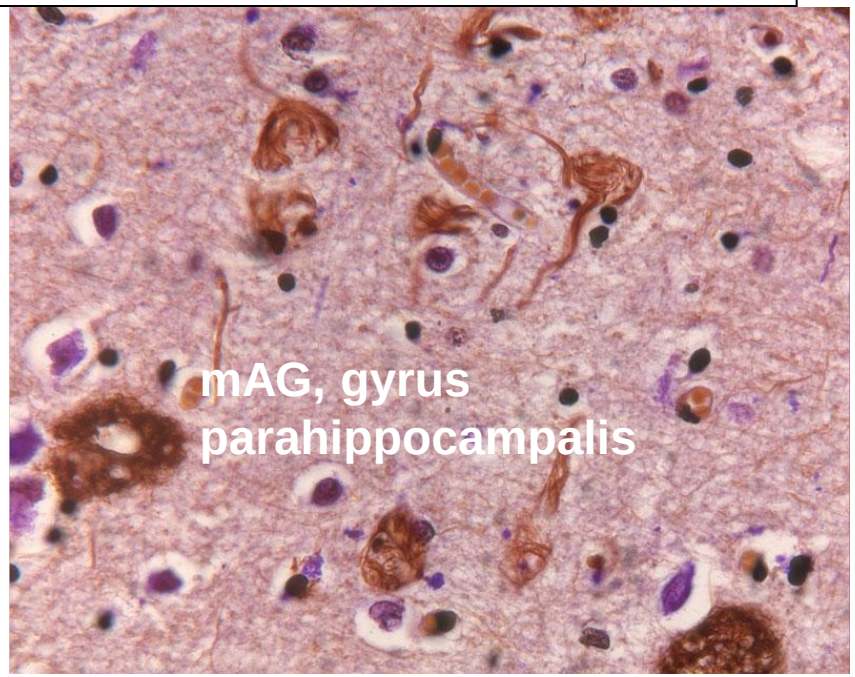
[e] *National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK*

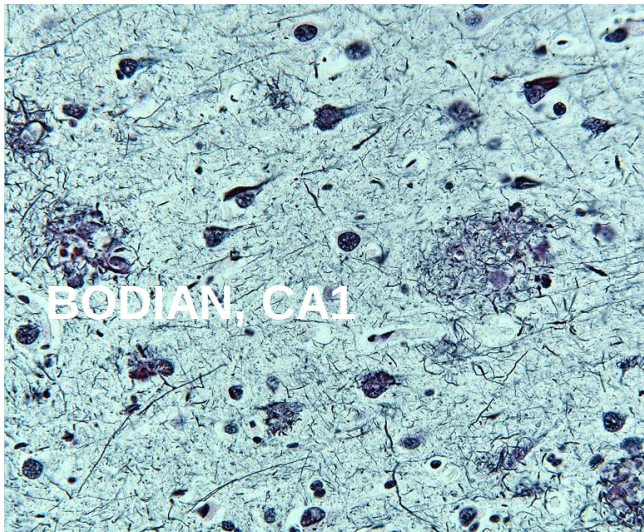
Accepted 20 September 1994


A
B
Phospho-tau
Tau
Tangles
Neuronal and
axonal damage
Plaques
ß-amyloid(1-42)
L 2
L 3
L 4
L 5
C
CSF-tau
CSF-ß-amyloid
CSF-phospho-tau
D
Biomarker assay

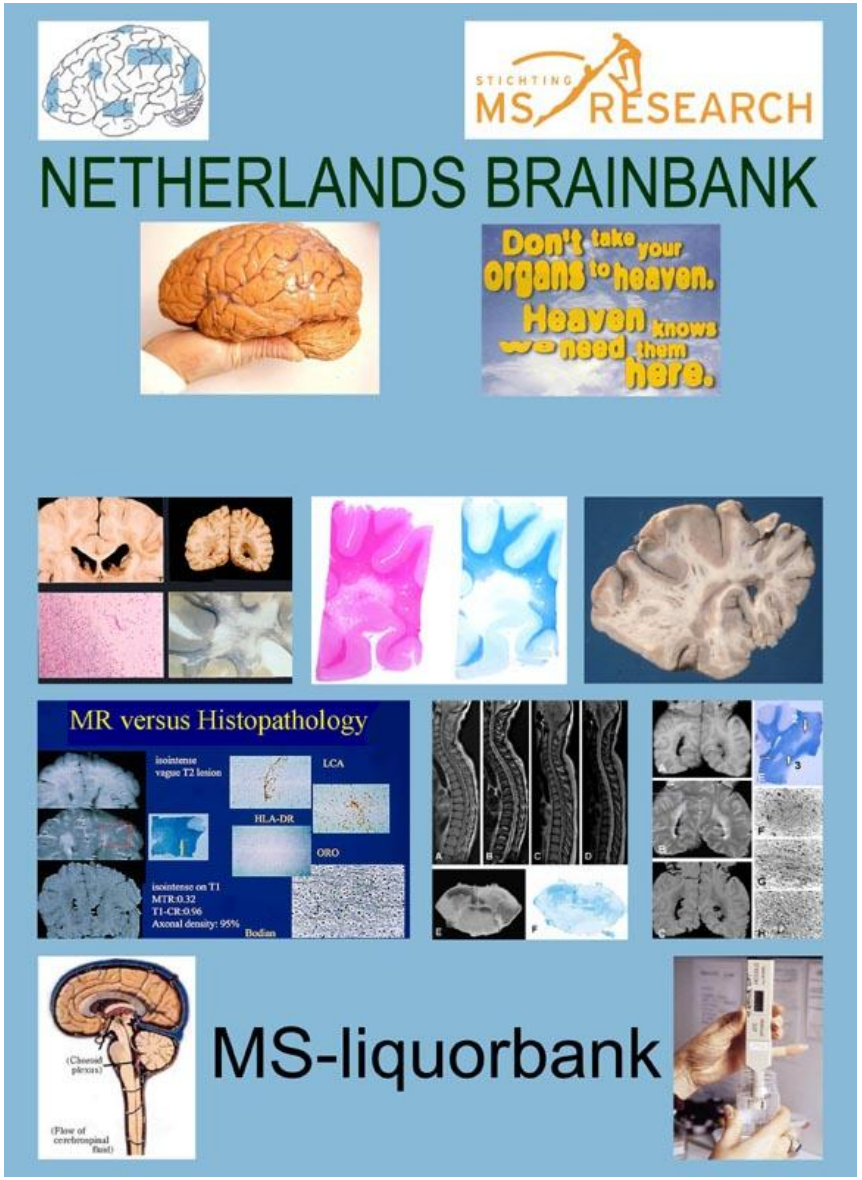

PICCOLO
by HANNA
ATC
pH meter

Neuropathological diagnosis





MRI guided pathology of Multiple Sclerosis



MS donors

Neurology – clinical diagnosis

Radiology – MRI

Neuropathology
Immunology

CSF markers for incipient Alzheimer's disease-

Lancet Neurol 2003; **2:** 605–13

CSF P-Thr181
Elevated in AD

CSF T-tau
Elevated in AD

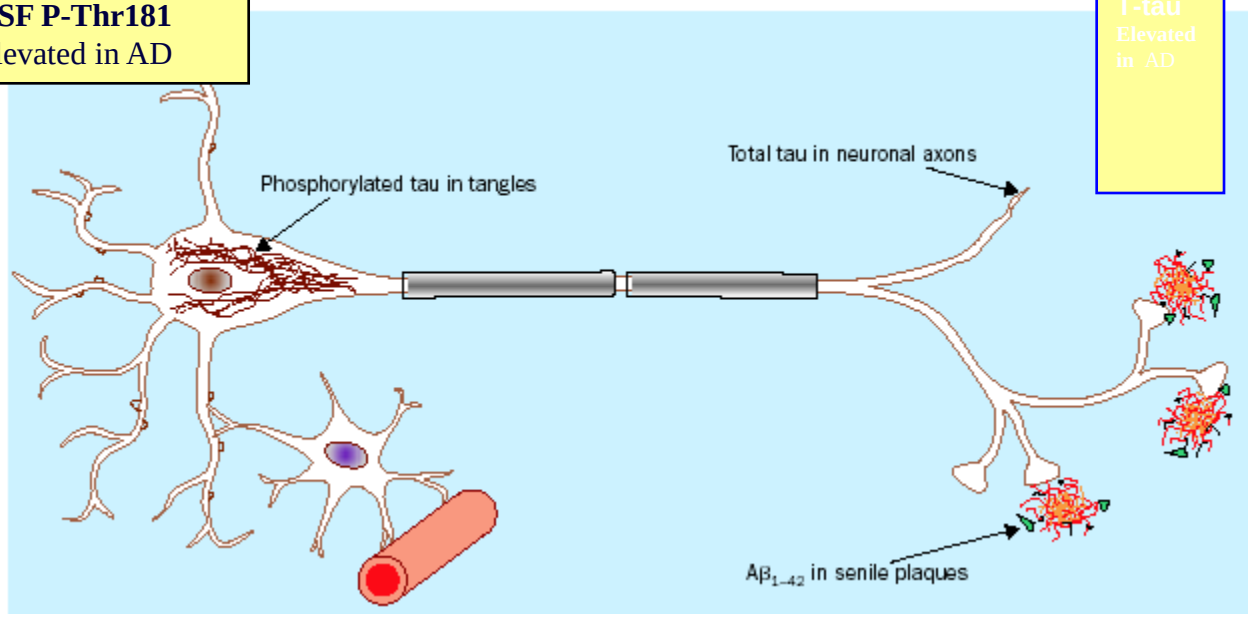


Figure 1. Schematic drawing of a neuron with an adjacent astrocyte and capillary. The central pathogenetic processes in AD and their corresponding biochemical markers are depicted. Total concentration of tau protein is a marker of neuronal and axonal degeneration, $A\beta_{1-42}$ concentration is a marker of plaque formation, and concentration of phosphorylated tau is a marker for hyperphosphorylation of tau and formation of tangles.

Maximizing the Potential of Plasma Amyloid-Beta as a Diagnostic Biomarker for Alzheimer's Disease

Esther S. Oh · Juan C. Troncoso · Stina M. Fangmark Tucker

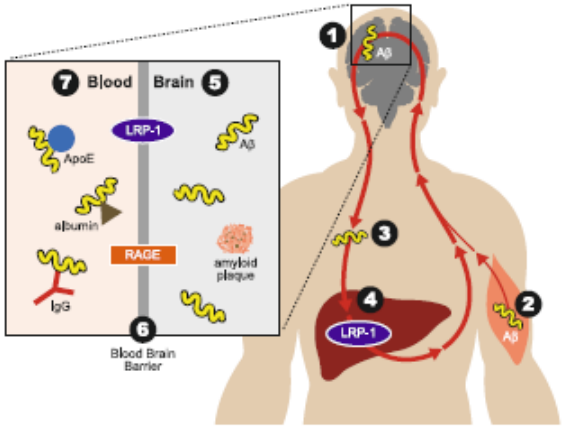


Fig. 1 Amyloid-beta (Aβ) 1-40 and 1-42 are synthesized in the brain (Laird et al. 2005) (1), as well as in the periphery (Irizarry et al. 1997; Joachim et al. 1989; Vassar et al. 1999) (2). Circulating Aβ peptides enter the blood stream (3) and are partly cleared by the LRP-1 receptors in the liver (Tamaki et al. 2006) (4). Soluble extracellular brain Aβ (5) may accumulate in the brain parenchyma as amyloid plaques. Receptor mediated movement of the soluble Aβ through the blood–brain barrier (BBB) (6) is mediated by transporters such as low-density lipoprotein receptor-related protein-1 (LRP-1) (Deane et al. 2004; Shibata et al. 2000) for efflux, and receptor for advanced glycation end products (RAGE) (Deane et al. 2003) for influx. Once in the blood, Aβ peptides are bound by numerous binding proteins such as ApoE (Tanzi et al. 2004), albumin (Biere et al. 1996), and others (7). Aβ-specific IgG is also able to bind Aβ peptide in the blood, and may induce efflux of Aβ from the brain to the blood via the "peripheral sink" mechanism (DeMattos et al. 2001)

doi:10.1093/brain/awm136 *Brain* (2007), **130**, 2320–2326

No association of CSF biomarkers with APOEε4, plaque and tangle burden in definite Alzheimer's disease

Sebastiaan Engelborghs,[1,2,6,7] Kristel Sleegers,[3,6,8] Patrick Cras,[4,6,9] Nathalie Brouwers,[3,6,8] Sally Serneels,[3,6,8] Evelyn De Leenheir,[5] Jean-Jacques Martin,[5] Eugeen Vanmechelen,[10] Christine Van Broeckhoven[3,6,8] and Peter Paul De Deyn[1,2,5,6]

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ORIGINAL PAPER

Increased TDP-43 protein in cerebrospinal fluid of patients with amyotrophic lateral sclerosis

Takashi Kasai · Takahiko Tokuda · Noriko Ishigami · Hiroshi Sasayama · Penelope Foulds · Douglas J. Mitchell · David M. A. Mann · David Allsop · Masanori Nakagawa

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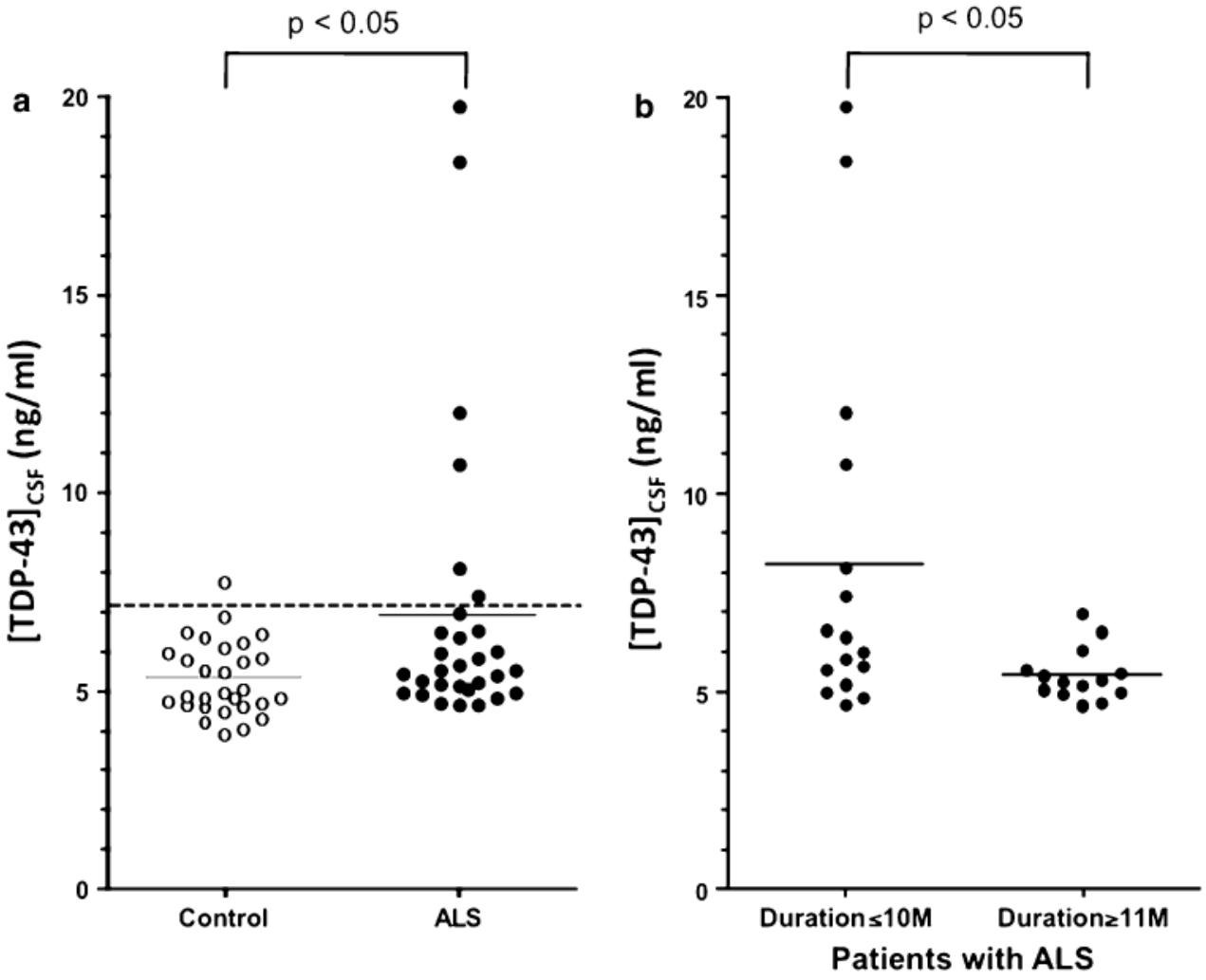

Fig. 2 **a** Plots for the concentrations of TDP-43 in CSF in the control patients ($n = 29$) and the patients with SALS ($n = 30$). The *solid line* represents the mean values of the concentrations of each group. The concentration of CSF TDP-43 in the SALS group was significantly higher than that in the age-matched control subjects ($p = 0.023$, Mann–Whitney *U* test). The *dashed line* corresponds to the 95% upper confidence level for the control group (7.18 ng/ml). **b** Plots for the concentrations of TDP-43 in CSF in the ALS patients examined within 10 months of onset (duration $\leq$ 10 M, $n = 16$) and those examined after 11 months or more of onset (duration $\geq$ 11 M, $n = 14$). The former showed significantly higher levels of CSF TDP-43 than the latter ($p = 0.028$, Mann–Whitney *U* test)

Evaluation of CSF Biomarkers as Predictors of Alzheimer's Disease: A Clinical Follow-Up Study of 4.7 Years

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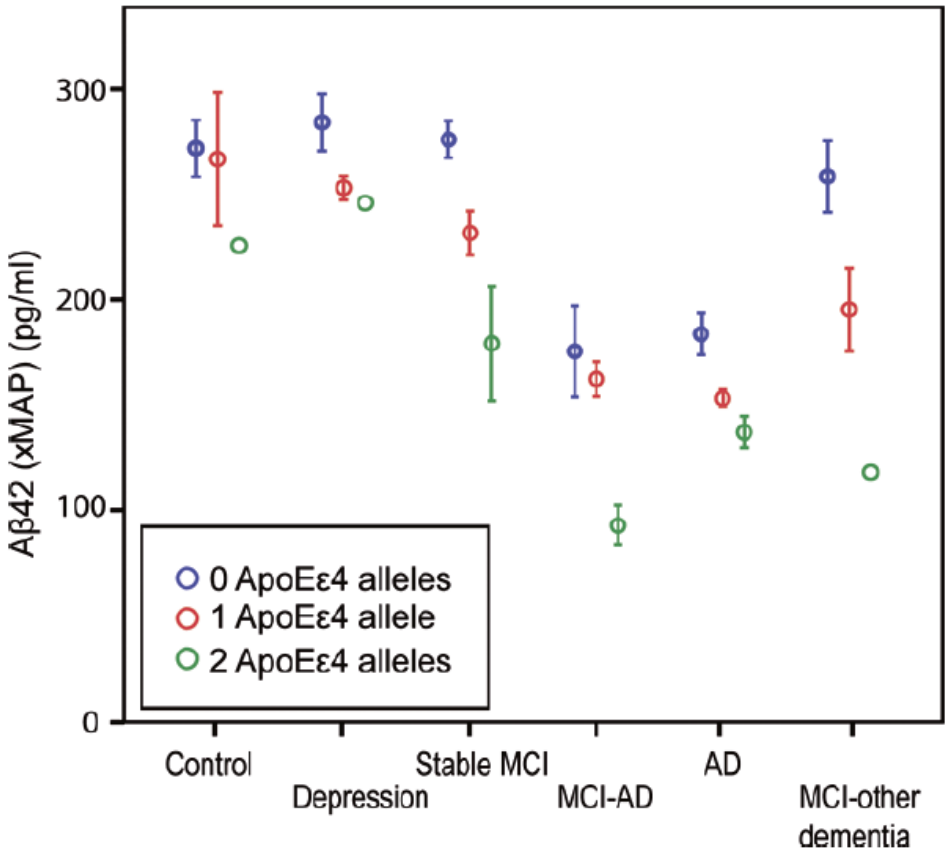

Fig. 1. Figure 1 depicts the levels of Aβ_{42} in the different diagnostic groups, stratified by the number of *APOE ε4* alleles. The levels of Aβ_{42} differed significantly between subjects with *AD* when compared to controls, cases with depression, or cases with stable MCI, respectively, even when analyzing the subgroups with zero or one *APOE ε4* alleles separately ($p<0.01$). Similarly, the levels of Aβ_{42} differed significantly between subjects with *MCI-AD* when compared to controls, cases with depression, or cases with stable MCI, respectively, even when analyzing the subgroups with zero or one *APOE ε4* alleles separately ($p<0.01$). Error bars represent SEM.

Table 1
Reported ocular changes in AD

Part of the eye	Reported ocular changes in AD	Journal (Year)	Ref.	*N* (AD,control)
Pupil	Enhanced pupil response to cholinergic drops	Science (1994)	[69]	19,32
		Neuroreport (1996)	[78]	25,24
		J Neurol Neurosurg Psych (1994)	[70]	26,23
		Neurobiol Aging (2003)	[72]	14,30
		Acta Neurol Scand (1996)	[73]	24,50
		Neuropsychobiology (1999)	[74]	29,29
		Biol Psychiatry (1997)	[75]	67,80
		Rev Neurol (1996)	[76]	10,20
		Nippon Ronen Igakkai Zasshi (1996)	[77]	53,29
Pupil	Altered pupil flash response	Aging Clin Exp Res (2007)	[100]	23,23
		Int J Psychophysiol (2000)	[101]	10,5
		Int J Psychophysiol (2003)	[91]	15,30
		J Neurol Neurosurg Psych (1997)	[102]	9,9
Lens	Aggregation of Aβ, Supra-nuclear cataract	Lancet (2003)	[106]	9,8
Retina	Narrow retinal veins and decreased venular blood flow	Invest Ophthalmol Vis Sci (2007)	[120]	9,8
Retina	Retinal Nerve Fiber Layer (RNFL) thinning	Invest Ophthalmol Vis Sci (2007)	[120]	9,8
		Neurosci Lett (2007)	[119]	26,38
Retina	RNFL abnormalities and cell loss	Acta Neurol Scand (1996)	[121]	26,23
		Archives of Ophthalmology (1991)	[122]	26,30
		Neurology (2006)	[123]	40,50
Retina	Abnormal pattern electroretinogram (PERG)	Ann Neurol (1989)	[137]	6,6
		Ann Neurol (1989)	[138]	13,30
Optic Disc	Optic disc pallor, pathologic disc cupping, and thinning of the neuro-retinal rim	Acta Neurol Scand (1996)	[121]	26,23
		Archives of Ophthalmology (1991)	[122]	30,32
		Neurology (2006)	[123]	40,50

Ocular Biomarkers for Early Detection of Alzheimer's Disease

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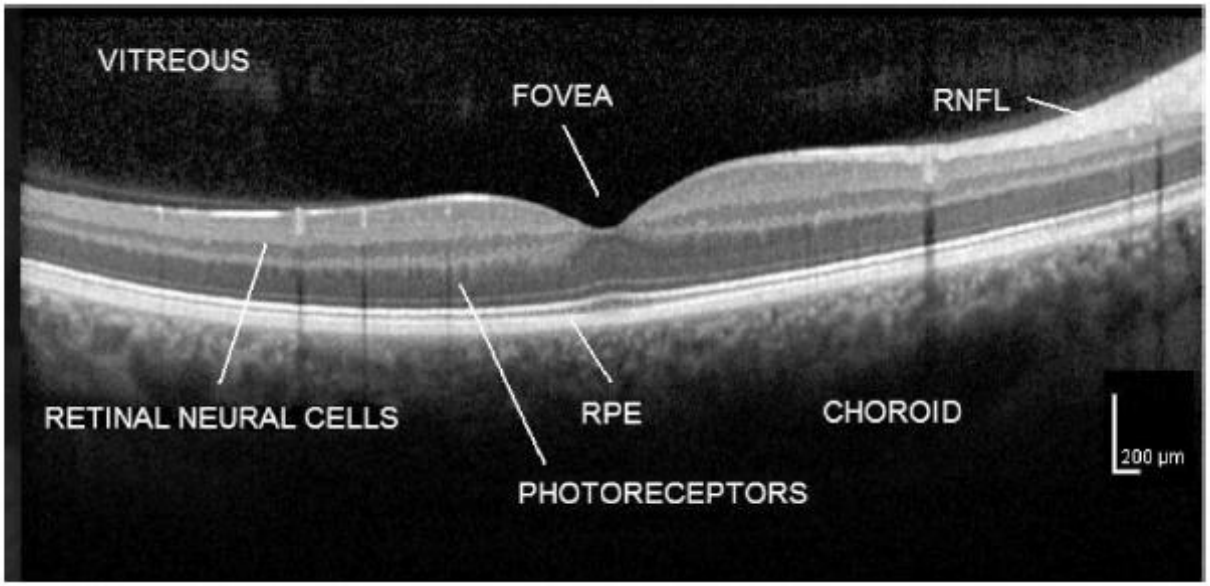
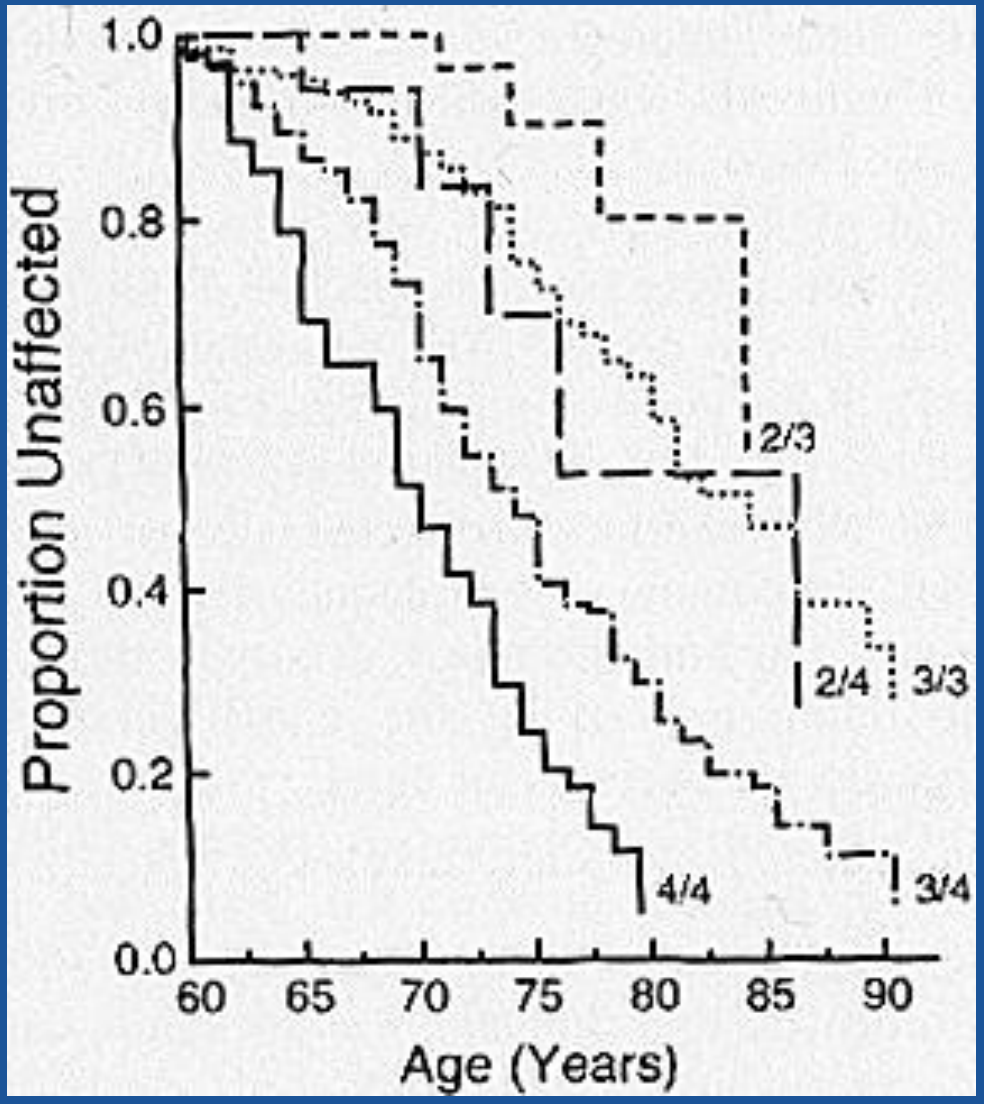


Fig. 5. OCT scan showing the retinal layers around the fovea. The layer closest to the vitreous humour is the retinal nerve fiber layer (RNFL) which contains fibers emerging from the retinal ganglion cells below. Also just beneath the RNFL is the retinal vasculature (evident from the vertical shadows cast in this OCT scan). Beneath the retinal ganglion cells are the bipolar, amacrine and horizontal cells, followed by a layer of photoreceptor cells. The photoreceptor cells are nourished by the deeper retinal pigment epithelium and a rich posterior vascular layer called the choroid. *OCT scan courtesy of Chris Barry, Lions Eye Institute, Perth, Australia.*

APOE polymorphism

CON - 31% 1 or 2 E4 alleles

AD - 64% 1 or 2 E4 alleles



Corder et al. 1994

Valid Biomarkers identified in human specimens prove that the best model for human disease is human disease

SCIENTIFIC COMMENTARY

With or without *FUS*, it is the anatomy that dictates the dementia phenotype

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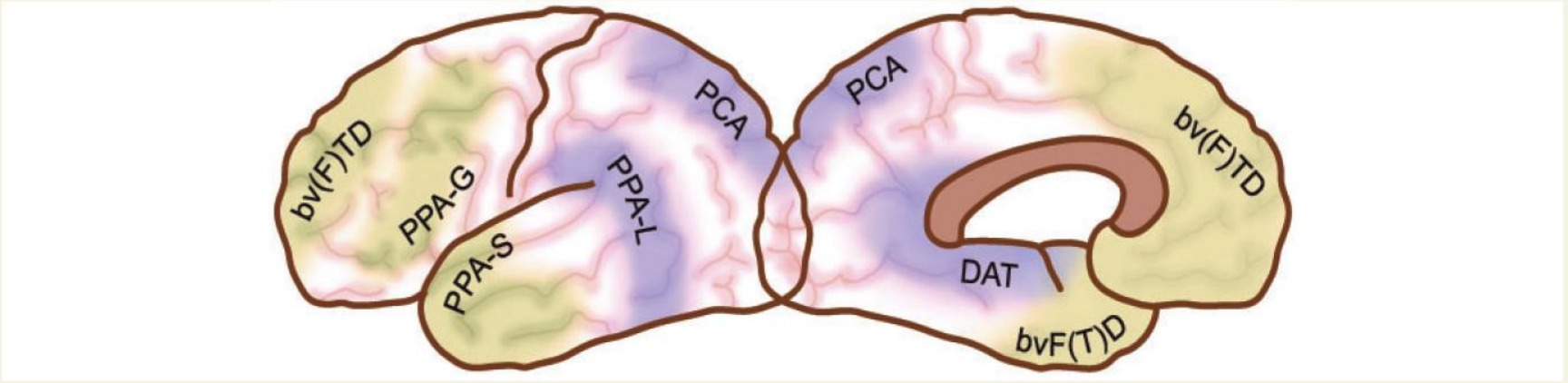

Figure 1 Diagrammatic representation of the most distinctive atrophy sites for some major dementia syndromes. In each case, total atrophy may extend beyond the shaded areas as well. The tan shading indicates syndromes caused predominantly by FTLD and the lilac shading syndromes caused predominantly by Alzheimer's disease: DAT = amnestic dementia of the Alzheimer type; PCA = posterior cortical atrophy syndrome.

Will CSF analysis become routine in people with memory complaints?

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See Articles page 619

Publication of the study by Visser and co-workers[1] in this issue of *The Lancet Neurology* highlights the fact that a substantial proportion of people who do not have a clinical diagnosis of Alzheimer's disease (AD) have CSF levels of tau and β-amyloid that suggest an underlying AD pathology. The findings are based on a prospective study involving 20 memory clinics across Europe with clinical follow-up of up to 3 years. The CSF analysis is based on a single sample time, and the CSF $A\beta_{42}$:tau ratio was appropriately selected as the most sensitive method of analysis. The abnormal CSF signature was recorded in 28 of 89 (31%) people with no cognitive complaints (controls), 31 of 60 (52%) people with cognitive complaints but no measurable impairment (subjective cognitive impairment), 56 of 71 (79%) people with memory complaints and measurable impairment but no functional decline (amnestic mild cognitive impairment), and 25 of 37 (68%) people with memory complaints and measurable impairment in features of cognition other than memory but no functional decline (non-amnestic mild cognitive impairment). These findings are in line with the proposal that has been made to diagnose AD in its pre-dementia stages,[2,3] and also adds to the knowledge about subjective cognitive impairment, which is a risk factor for AD, albeit less than is mild cognitive impairment.[4] The difference between amnestic and non-

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ORIGINAL PAPER

Sporadic amyotrophic lateral sclerosis of long duration is associated with relatively mild TDP-43 pathology

Yasushi Nishihira · Chun-Feng Tan · Yasuhiro Hoshi · Keisuke Iwanaga · Megumi Yamada · Izumi Kawachi · Mitsuhiro Tsujihata · Isao Hozumi · Takashi Morita · Osamu Onodera · Masatoyo Nishizawa · Akiyoshi Kakita · Hitoshi Takahashi

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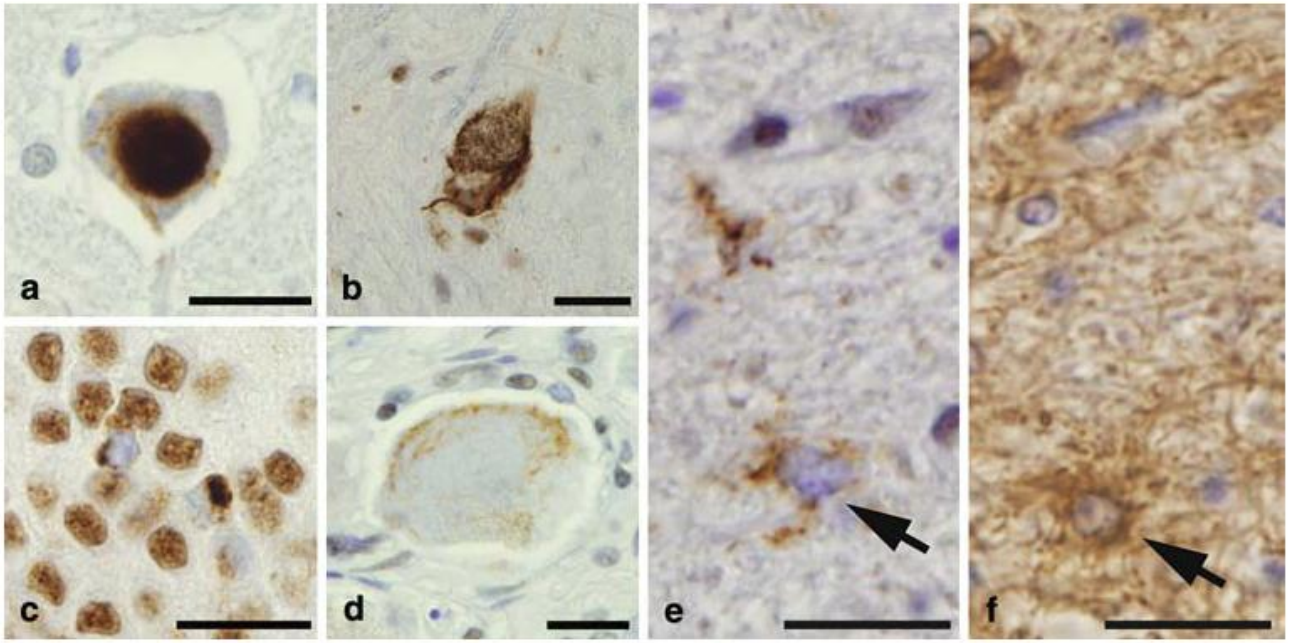

Fig. 2 TDP-43-immunoreactive (ir) neuronal cytoplasmic inclusions are evident in neurons in the hypoglossal nucleus (**a**), substantia nigra (**b**), hippocampal dentate gyrus (granule cells, **c**) and cervical dorsal root ganglion (**d**). **e**, **f** The spinal anterior horn. The section stained with the anti-TDP-43 antibody, showing a glial cell with TDP-43-ir cytoplasmic inclusions (*arrow*, **e**). The mirror section stained with the anti-glial fibrillary acidic protein (GFAP) antibody, revealing that the glial cell is an astrocyte with GFAP-ir radiating processes (*arrow*) (**f**, the original image was inverted for comparison). **a** Case 3; **b**, **c** case 6; **d** case1; **e**, **f** case 1. *Bars* **a**, **b**, **d**–**f** 20 μm, **c** 50 μm

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ORIGINAL PAPER

Increased TDP-43 protein in cerebrospinal fluid of patients with amyotrophic lateral sclerosis

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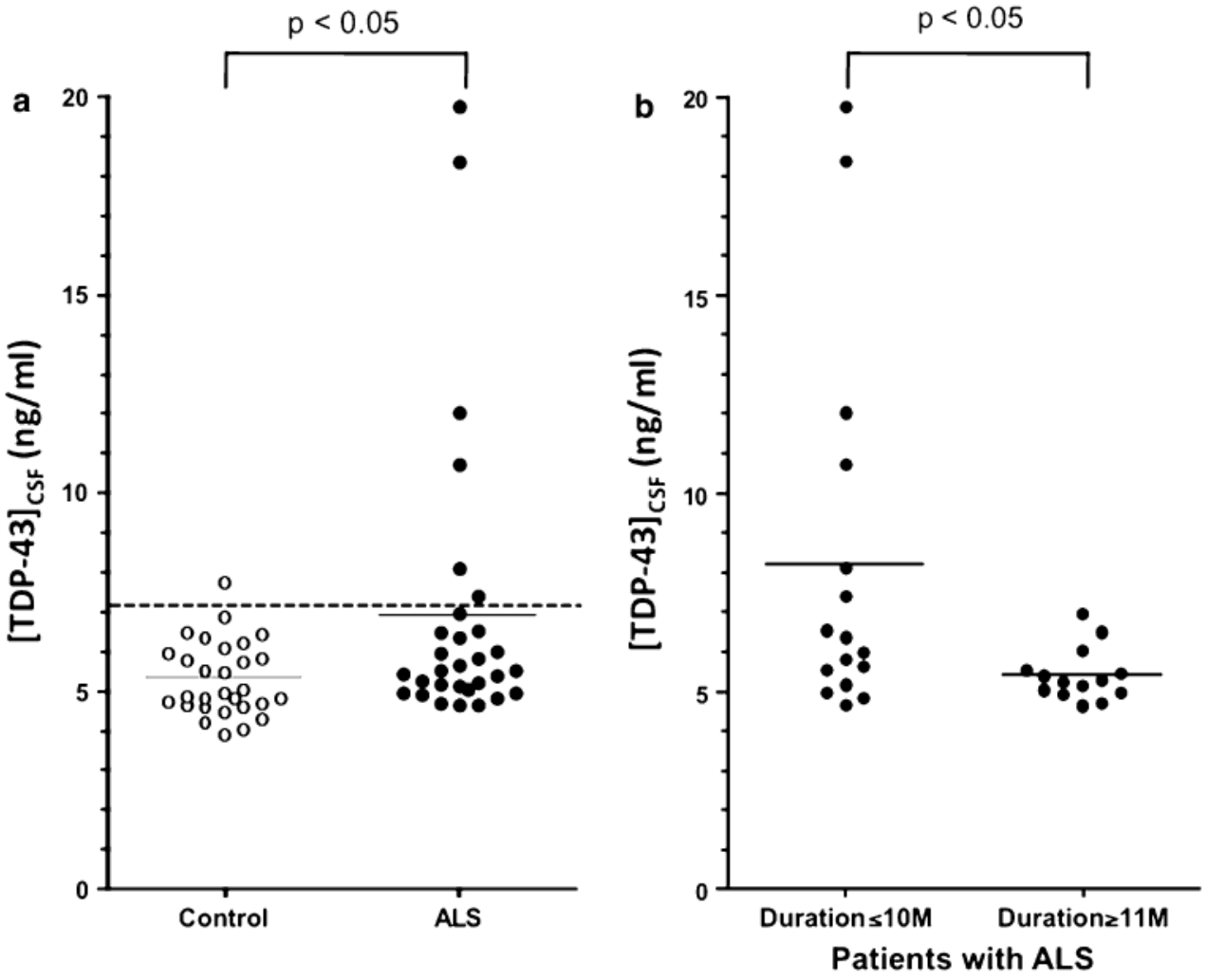

Fig. 2 **a** Plots for the concentrations of TDP-43 in CSF in the control patients ($n = 29$) and the patients with SALS ($n = 30$). The *solid line* represents the mean values of the concentrations of each group. The concentration of CSF TDP-43 in the SALS group was significantly higher than that in the age-matched control subjects ($p = 0.023$, Mann–Whitney *U* test). The *dashed line* corresponds to the 95% upper confidence level for the control group (7.18 ng/ml). **b** Plots for the concentrations of TDP-43 in CSF in the ALS patients examined within 10 months of onset (duration $\leq$ 10 M, $n = 16$) and those examined after 11 months or more of onset (duration $\geq$ 11 M, $n = 14$). The former showed significantly higher levels of CSF TDP-43 than the latter ($p = 0.028$, Mann–Whitney *U* test)

Table 2 Consensus-based recommendations for CSF withdrawal procedure

Item	Procedure	Ideal situation
1	Preferred volume	At least 12 mL; first 1–2 mL for basic CSF assessment (see issue 33); last 10 mL for biobanking
		Record volume taken and fraction used for biobanking
2	Location	Vertebral body L3–L5
3	If bloody	Do not process further
		Criteria for bloody: more than 500 red blood cells/μL
		Record number of blood cells in diagnostic samples
4	Type of needle	Atraumatic
5	Type of collection tube	Polypropylene tubes, screw cap, volume 1–2 mL
6	Time of day of withdrawal and storage	Preferably standardized within each center, allowing for intercenter differences in local logistics
		Record date and time of collection
7	Other body fluids that should be collected simultaneously	Serum
8	Other body fluids that should be collected simultaneously	Plasma: EDTA (preferred over citrate)
9	Storage temperature until freezing	Room temperature before, during, and after spinning
10	Spinning conditions	Serum: 2,000*g*, 10 min at room temperature
		CSF: 400*g*, 10 min at room temperature/2,000*g* if no cells are to be preserved
11	Time delay between withdrawal and spinning and freezing	Optimal for CSF: 1–2 h
		Optimal for serum: 30–60 min
		Thus doing both body fluids simultaneously, ideally within 1 h
		After spinning, samples must be divided into aliquots and frozen immediately for storage at −80°C
12	Type of tube for aliquots	Small polypropylene tubes (1–2 mL) with screw caps; record manufacturer
13	Aliquots	A minimum of 2 aliquots is recommended; the advised research sample volume of 10 mL should be enough for >10 aliquots
14	Volume of aliquots	Minimum 0.1 mL; depending on total volume of tube: 0.2, 0.5, and 1 mL; preferably, the tubes are filled up to 75%
15	Coding	Unique codes; freezing-proof labels; ideally barcodes to facilitate searching, to aid in blinding the analysis and to protect the privacy of patients
16	Freezing temperature	−80°C
17	Additional items on sample collection protocols that must be recorded	Location of samples
18	Additional items on sample collection protocols that must be recorded	Surveillance of freezers
19	Additional items on sample collection protocols that must be recorded	Splitting of samples over 2 or more freezers

EDTA = ethylenediaminetetraacetic acid.

Cerebrospinal fluid α-synuclein in neurodegenerative disorders—A marker of synapse loss?

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Table 1
Clinical data and cerebrospinal fluid (CSF) analysis for the diagnostic groups[a].

Groups	Cont	PD	DLB	AD
Number	55	15	15	66
Sex (% female)	54	27	40	71
Age (years)	65 (62–70)	71 (63–76)	79 (76–80)[b]	77 (73–82)[b]
MMSE	30 (29–30)	29 (27–30)	23 (19–23)[b]	20 (14–26)[b]
α-Syn (pg/mL)	395 (298–452)	417 (246–522)	334 (220–406)	296 (234–372)[b]
$A\beta_{(1-42)}$ (pg/mL)	673 (563–765)	649 (585–738)	403 (341–517)[b]	359 (313–413)[b]
T-tau (pg/mL)	307 (202–397)	294 (258–340)	379 (262–473)	702 (555–886)[b]
$P\text{-}tau_{181}$ (pg/mL)	50 (36–58)	52 (49–59)	55 (41–63)	94 (71–122)[b]

Abbreviations used: AD: Alzheimer's disease, $A\beta_{(1-42)}$: β-amyloid$_{(1-42)}$, α-syn: α-synuclein, Cont: cognitively normal control individuals, DLB: dementia with Lewy bodies, MMSE: mini-mental state examination, PD: Parkinson's disease, $P\text{-}tau_{181}$: tau phosphorylated at threonine 181, T-tau: total tau.

[a] Data are given as medians (inter-quartile range).

[b] $p < 0.001$ compared with Cont.

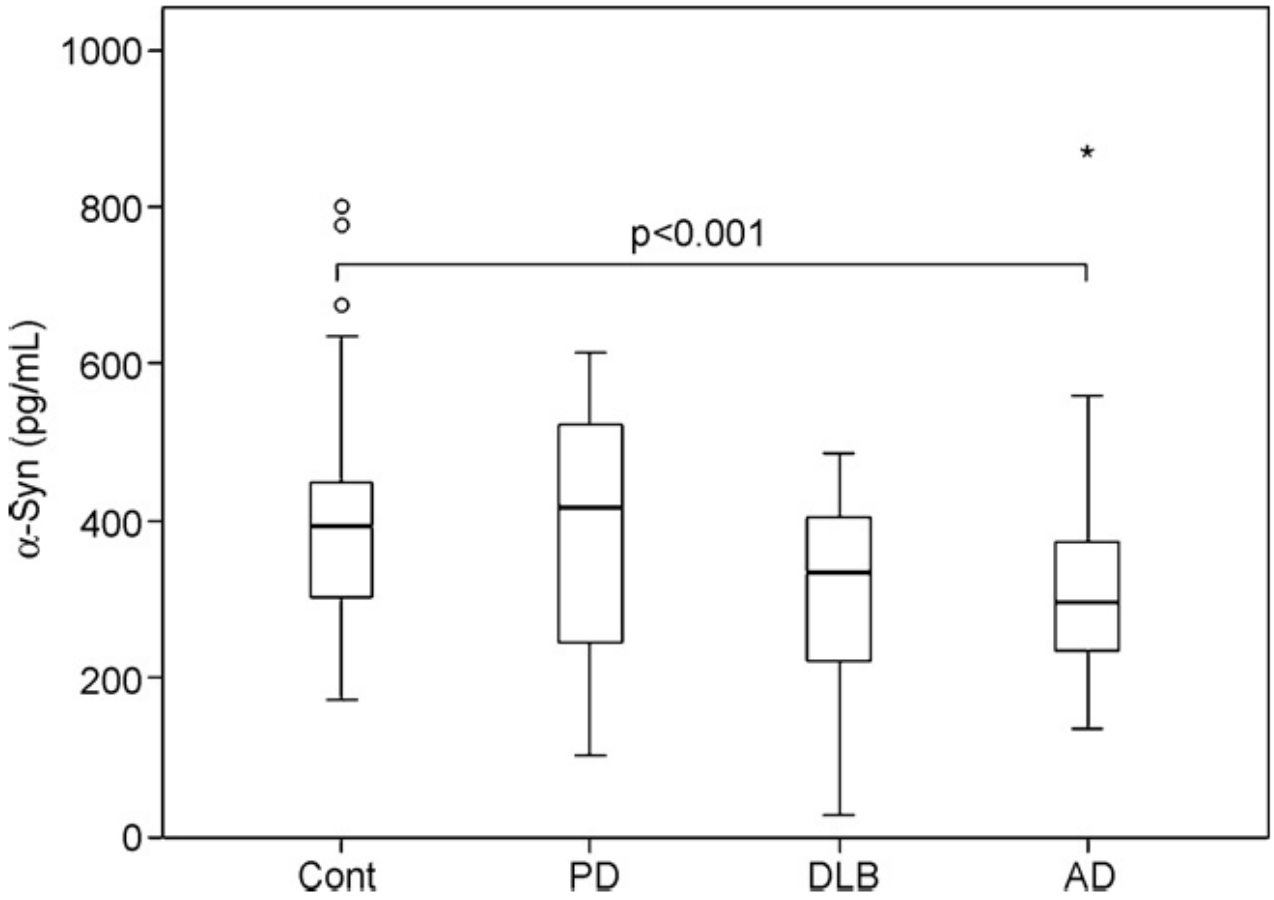

Fig. 2. α-Synuclein (α-syn) levels (pg/mL) in CSF samples from cognitively normal control individuals (Cont) ($N = 55$) and from subjects with Parkinson's disease (PD) ($N = 15$), dementia with Lewy bodies (DLB) ($N = 15$) and Alzheimer's disease (AD) ($N = 66$). The lower, upper and line through the middle of the boxes correspond to the 25th percentile, 75th percentile and median, respectively. The whiskers on the bottom extend from the 5th percentile and top 95th percentile.

Table 2
Clinical data and cerebrospinal fluid (CSF) analysis for the Alzheimer's disease (AD) patient group subdivided according to MMSE score[a].

AD group	MMSE <20	MMSE ≥20
Number	30	36
Sex (% female)	70	72
Age (years)	77 (74–82)	77 (72–82)
α-Syn (pg/mL)	264 (221–330)[b]	337 (250–399)
$A\beta_{(1\text{-}42)}$ (pg/mL)	369 (313–398)	351 (314–425)
T-tau (pg/mL)	712 (588–904)	689 (528–884)
$P\text{-}tau_{181}$ (pg/mL)	95 (76–134)	94 (68–121)

Abbreviations used: $A\beta_{(1-42)}$: β-amyloid$_{(1-42)}$, α-syn: α-synuclein, MMSE: mini-mental state examination, $P\text{-}tau_{181}$: tau phosphorylated at threonine 181, T-tau: total tau.

[a] Data are given as medians (inter-quartile range).

[b] $p = 0.02$ compared with MMSE score of 20 or higher within the AD group.

Detection of elevated levels of α-synuclein oligomers in CSF from patients with Parkinson disease

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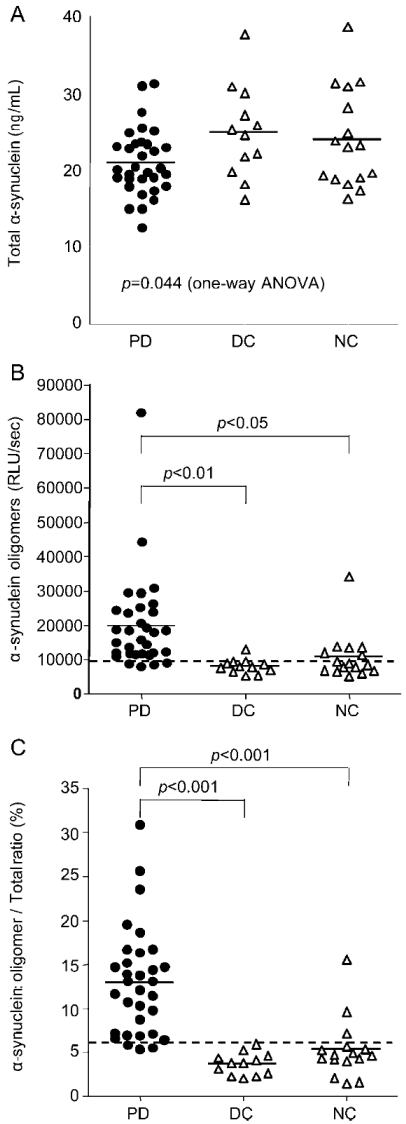
A. Tamaoka, MD, PhD
M. Nakagawa, MD, PhD
O.M.A. El-Agnaf, PhD

Figure 1 Levels of total and α-synuclein oligomers in CSF from patients with Parkinson disease (PD) and controls



Individual values of the level of total α-synuclein (A), α-synuclein oligomers (B; RLU = relative luminescence units), and the ratio of α-synuclein oligomers to total α-synuclein (C; oligomer/total ratio, %) in CSF from patients with PD (solid circles), disease controls (DC; solid triangles), and normal controls (NC; open triangles). Each bar represents the mean value. Dashed lines in (B) and (C) indicate respective cutoff values that yield the most reliable sensitivity and specificity by receiver operating characteristic curves (B: 9,950 RLU/s for the levels of CSF α-synuclein oligomers; C: 6.165% for the ratio of α-synuclein oligomers to total α-synuclein in CSF; see figure 2). ANOVA = analysis of variance.

CSF α-Synuclein Does Not Discriminate Dementia with Lewy Bodies from Alzheimer's Disease

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Abstract. In this study, we assessed whether cerebrospinal fluid (CSF) levels of the biomarker α-synuclein have a diagnostic value in differential diagnosis of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). We also analyzed associations between CSF biomarkers and cognitive performance in DLB and in AD. We included 35 DLB patients, 63 AD patients, 18 patients with Parkinson's disease (PD), and 34 patients with subjective complaints (SC). Neuropsychological performance was measured by means of the Mini-Mental Status Examination (MMSE), Visual Association Test (VAT), VAT object-naming, Trail Making Test, and category fluency. In CSF, levels of α-synuclein, amyloid-β 1-42 (Aβ_{1-42}), total tau (tau), and tau phosphorylated at threonine 181 (ptau-181) were measured. CSF α-synuclein levels did not differentiate between diagnostic groups ($p = 0.16$). Higher ptau-181 and higher tau levels differentiated AD from DLB patients ($p < 0.05$). In DLB patients, lower Aβ_{1-42} and higher total tau levels were found than in SC and PD patients ($p < 0.05$). In DLB patients, linear regression analyses of CSF biomarkers showed that lower α-synuclein was related to lower MMSE-scores (β(SE) = 6(2) and $p < 0.05$) and fluency (β (SE) = 4(2), $p < 0.05$). Ultimately, CSF α-synuclein was not a useful diagnostic biomarker to differentiate DLB and/or PD (α-synucleinopathies) from AD or SC. In DLB patients maybe lower CSF α-synuclein levels are related to worse cognitive performance.

Keywords: Alzheimer's disease, biomarkers, cerebrospinal fluid, dementia with Lewy bodies, diagnosis, α-synuclein

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer's disease (AD) [1]. In pathological studies, DLB accounts for more than 20% of dementia cases [2,3]. Clinical hallmarks are cognitive decline accompanied by parkinsonism, visual hallucinations, and fluctuating cognitive performance and consciousness [2,4]. Unfortunately, diagnostic criteria have modest sensitivity and it can be difficult to differentiate

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Table 1
Clinical data, neuropsychological test results and CSF biomarkers by diagnostic group

	SC ($n = 34$)	PD ($n = 18$)	DLB ($n = 35$)	AD ($n = 63$)
Age	67 ± 5	67 ± 8	$71 \pm 8^{a,b}$	69 ± 7
Female	16 (44%)	8 (42%)	6 (17%)^{a,d}	34 (52%)
α-Synuclein (ng/ml)	18 (14–26)	23 (18–32)	20 (15–27)	16 (13–23)
$A\beta_{1-42}$(pg/ml)	823 (661–1018)^{c,d}	875 (719–987)^{c,d}	479 (386–661)^{a,b}	484 (387–545)^{a,b}
Tau (pg/ml)	252 (208–354)^{c,d}	196 (130–268)^{c,d}	382 (265–574)^{a,b,d}	613 (416–897)^{a,b,c}
Ptau-181 (pg/ml)	48 (38–56)^{d}	49 (37–60)^{d}	53 (42–72)^{d}	82 (63–1143)^{a,b,c}
MMSE	$28 \pm 1^{c,d}$	$29 \pm 1^{c,d}$	$21 \pm 5^{a,b}$	$21 \pm 4^{a,b}$
VAT	$12 \pm 1^{c,d}$	–	7 ± 4^{a}	5 ± 4^{a}
Naming	12 ± 0^{d}	–	12 ± 1	11 ± 2^{a}
TMT-A	$41 \pm 13^{c,d}$	–	119 ± 82^{a}	103 ± 82^{a}
TMT-B	$100 \pm 41^{c,d}$	–	$416 \pm 190^{a,d}$	$240 \pm 124^{a,c}$
Fluency	$24 \pm 5^{c,d}$	-	12 ± 5^{a}	12 ± 5^{a}

Data are expressed as mean $\pm$ SD, median (I-Q range), n (%). Differences between groups were assessed with ANOVA, adjusted for age and gender. Biomarkers and TMT are presented as raw data, but statistics were performed using log-transformed data. SC: subjective complaints, PD: Parkinson's disease, DLB: Dementia with Lewy bodies, AD: Alzheimer's disease, MMSE: mini-mental state examination, VAT: Visual Association Test, Naming: VAT object naming, TMT: Trail Making Test, Fluency: Category fluency. $^{a}p < 0.05$ compared to SC. $^{b}p < 0.05$ compared to PD. $^{c}p < 0.05$ compared to DLB. $^{d}p < 0.05$ compared to AD.

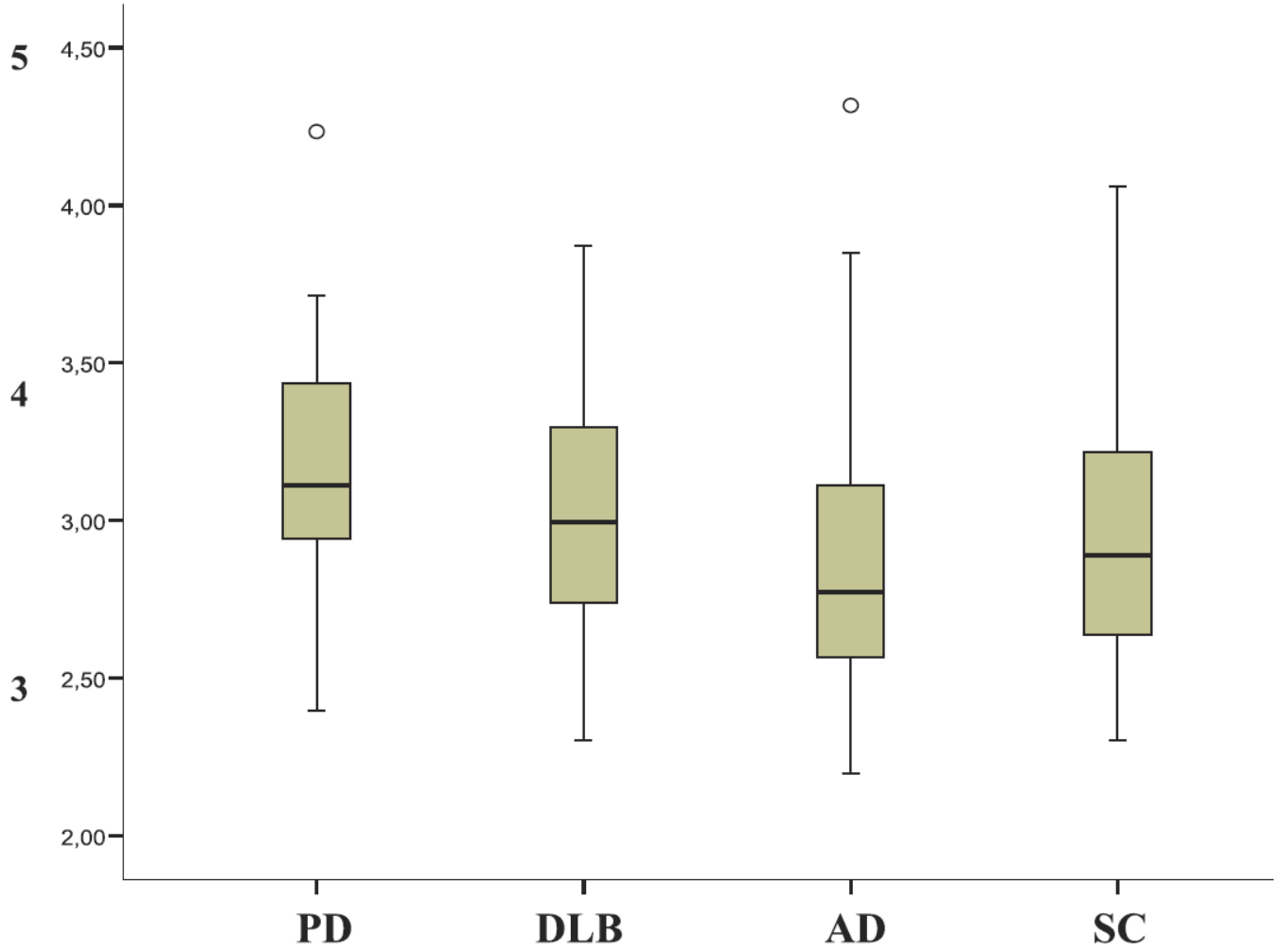

Fig. 1. Box and whisker plots of log transformed CSF α-synuclein levels (ng/ml) by diagnostic group. Patients with Parkinson's disease (PD) ($n = 18$), dementia with Lewy bodies (DLB) ($n = 35$), Alzheimer's disease (AD) ($n = 63$), and subjective complaints (SC) ($n = 34$). The line through the middle of the boxes corresponds to the median and the lower and the upper lines to the 25th and 75th percentile respectively. The whiskers extend from the 5th percentile on the bottom to the 95th percentile on top. Group comparisons were performed using analysis of variance (ANOVA), corrected for age and gender. CSF α-synuclein levels, adjusted for age and gender, were not different among the diagnostic groups ($p = 0.16$).

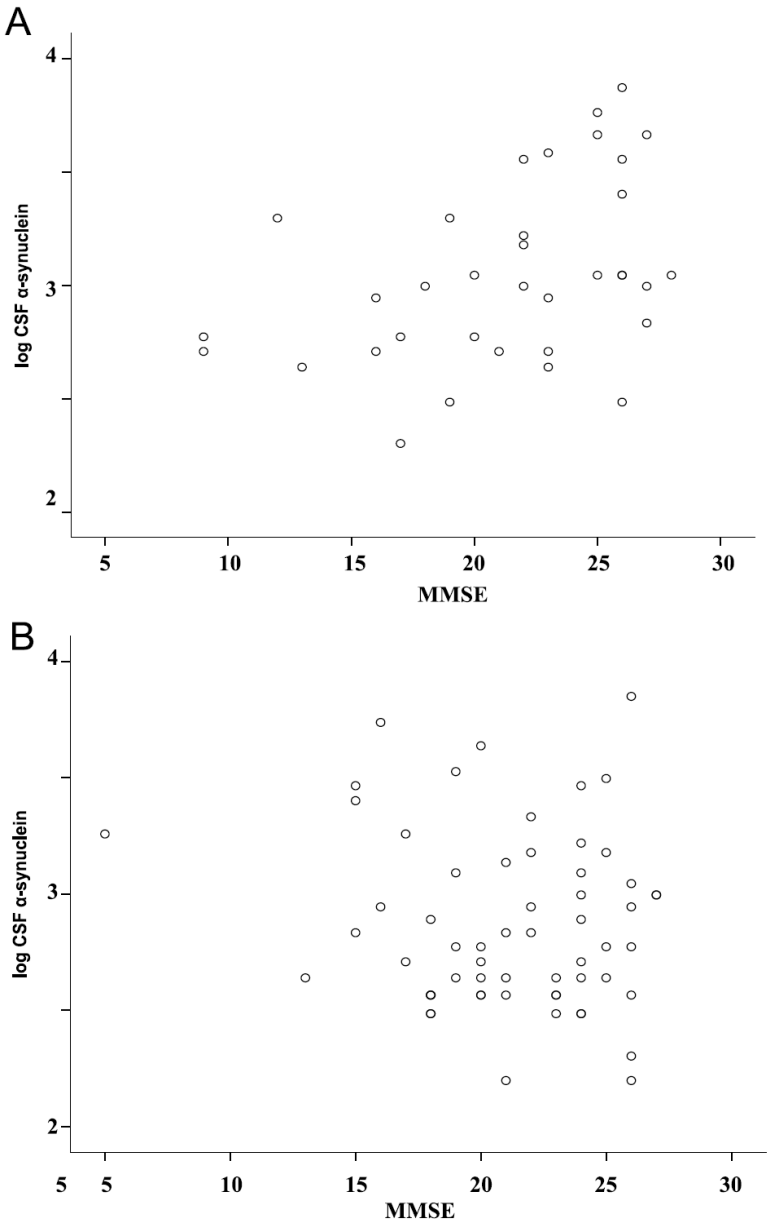

Fig. 2. A) Scatterplot of the distribution of log transformed CSF α-synuclein levels (ng/ml) and MMSE in patients with DLB. The X-axis shows the MMSE scores and the Y-axis the CSF α-synuclein levels. The MMSE and CSF α-synuclein levels have a positive association in the DLB group, as shown by linear regression analysis with age and gender as covariates ($\beta = 6(2)$, $p < 0.05$). B) Scatterplot of the distribution of log transformed CSF α-synuclein levels (ng/ml) and MMSE in patients with AD. The MMSE and CSF α-synuclein levels have no association in the AD group, as shown by linear regression analysis with age and gender as covariates ($\beta = -1(1)$, $p = 0.35$).

Early-onset versus late-onset Alzheimer's disease: the case of the missing *APOE* ε4 allele

Wiesje M van der Flier, Yolande A L Pijnenburg, Nick C Fox, Philip Scheltens

Some patients with early-onset Alzheimer's disease (AD) present with a distinct phenotype. Typically, the first and most salient characteristic of AD is episodic memory impairment. A few patients, however, present with focal cortical, non-memory symptoms, such as difficulties with language, visuospatial, or executive functions. These presentations are associated with specific patterns of atrophy and frequently with a young age at onset. Age is not, however, the only determinant of phenotype; underlying factors, especially genetic factors, seem also to affect phenotype and predispose patients to younger or older age at onset. Importantly, patients with atypical early-onset disease seldom carry the *APOE* ε4 allele, which is the most important risk factor for lowering the age of onset in patients with AD. Additionally, the *APOE* ε4 genotype seems to predispose patients to vulnerability in the medial temporal areas, which leads to memory loss. Conversely, patients negative for the *APOE* ε4 allele and with early-onset AD are more likely to be predisposed to vulnerability of cerebral networks beyond the medial temporal lobes. Other factors are probably involved in determining the pattern of atrophy, but these are currently unknown.

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	Typical AD	Atypical AD
Presenting clinical feature	Memory	Non-memory
Disease course	Less aggressive	More aggressive
Age at onset	Mean 75 years	Mean 55 years
APOE genotype	Promoted by one or two ε4 alleles	Promoted by absence of ε4 alleles
Neuropathology	Plaques and tangles	Plaques and tangles
CSF biomarker concentrations	Decreased $A\beta_{1-42}$ and increased tau and ptau	Decreased $A\beta_{1-42}$ and increased tau and ptau
PET		
FDG	Decreased temporoparietal metabolism, especially in medial temporal lobe	Decreased temporoparietal metabolism, especially in posterior cortex
^{11}C-PiB	Increased uptake	Increased uptake
Structural MRI	Hippocampal atrophy	Temporoparietal atrophy, frontoparietal atrophy, or both

The atypical phenotype of AD seems to be promoted by a younger age at onset in the absence of the *APOE* ε4 allele. Biomarker profiles suggest that both subtypes have the same pattern of senile plaques and neurofibrillary tangles, but that hypometabolism and atrophy differ, which suggests that genetic factors, environmental factors, or both, cause vulnerability in specific and distinct regions. AD=Alzheimer's disease. $A\beta_{1-42}$=amyloid β protein 42. tau=total microtubule-associated protein tau. ptau=phosphorylated microtubule-associated protein tau. FDG=^{18}F-fluorodeoxyglucose. ^{11}C-PiB=^{11}C-Pittsburgh compound B.

Table: **Clinical and biomarker characteristics of typical and atypical AD**

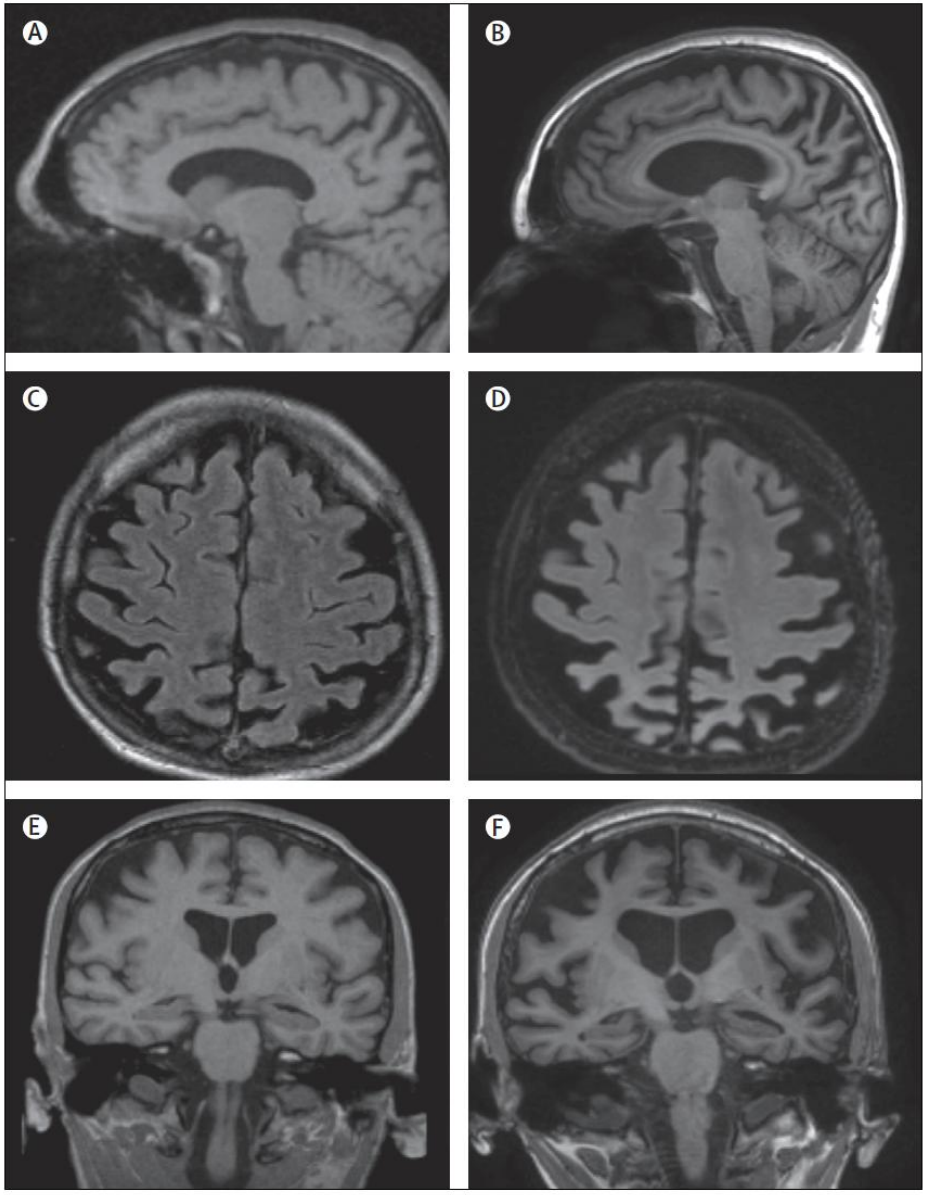

Figure 1: MRI at baseline (left column) and at 2 years of follow-up (right column) in a woman aged 52 years with Alzheimer's disease and ***APOE*** ε3/ε3 genotype

A fluid-attenuated inversion recovery sequence showed prominent posterior atrophy at baseline in the sagittal (A) and axial (C) views that progressed swiftly over 2 years (B, D). In the coronal view the hippocampus was not greatly affected at baseline (E), and the increase in atrophy was moderate at 2 years of follow-up, especially compared with the degree of posterior atrophy (F).

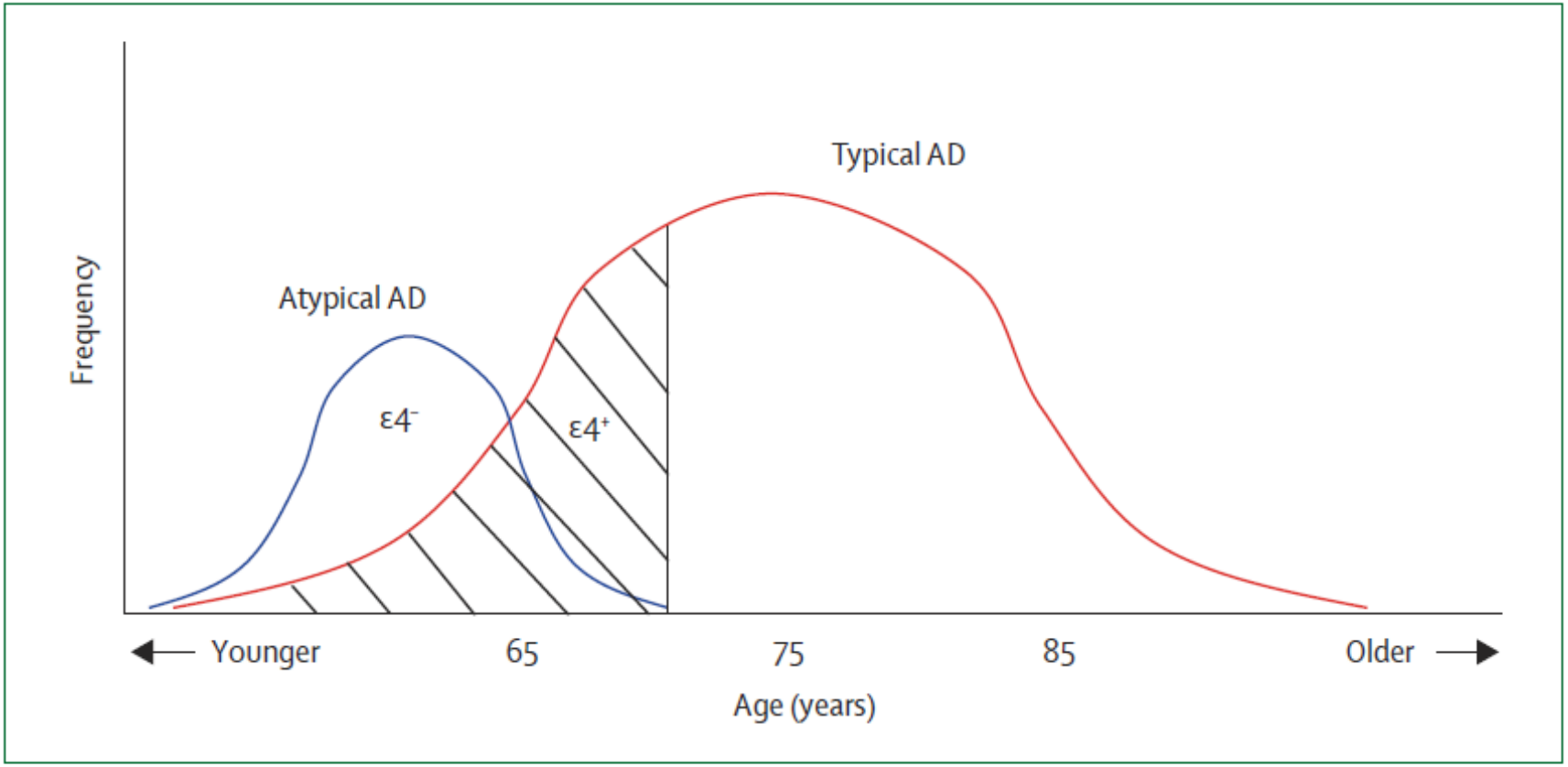

***Figure 2*: Hypothesised frequency distributions of the association between age at onset, absence or presence of *APOE* ε4 allele, and clinical phenotypes of AD**

Most patients have typical AD, which is characterised by prominent memory impairment and hippocampal atrophy, and has an average age at onset of 75 years. The presence of one or two *APOE* ε4 alleles predisposes for this type of disease but is associated with an earlier age at onset (hatched area, roughly 10 years). A smaller group of patients develop Alzheimer's disease at an early age and do not carry the *APOE* ε4 allele. These patients have an atypical clinical presentation of focal cortical, non-memory symptoms, and prominent atrophy in the posterior cortex. AD=Alzheimer's disease.

Cerebrospinal Fluid Analysis Should Be Considered in Patients with Cognitive Problems

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Hepatologists assay liver enzymes and cardiologists structural heart proteins in serum to diagnose and monitor their patients. This way of thinking has not quite made it into the memory clinics yet, in spite of the availability of validated cerebrospinal fluid biomarkers for key pathological events in the brain in neurodegeneration. Here, we argue that a spinal tap should be considered in all patients who seek medical advice for memory problems and list the highly relevant clinical questions CSF analyses can address.

1. Introduction

Memory problems may be caused by a wide range of neuropsychiatric diseases, including Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies, frontotemporal dementia (FTD), to mention a few [1]. Cognitive symptoms may also arise secondary to depression, neuroinflammation and various somatic illnesses. Today, patients with memory problems seek medical advice much earlier than 10 years ago. It is difficult to differentiate benign cognitive deficiencies from AD or other primary neurodegenerative diseases. Memory problems secondary to other diseases may also present a diagnostic challenge.

Patients with memory complaints most often undergo extensive clinical and neuropsychological assessments, and often also one or more brain imaging investigations. We argue that CSF analysis should be considered in the diagnostic work-up of all patients with memory problems to answer a number of highly relevant questions discussed below. Fear of spinal tap-related side-effects should not preclude CSF analyses, since complications are very rare in the elderly, provided that regular precautions well known to any trained physician are taken [2–4].

2. Does the Patient Suffer from Brain Amyloid Pathology?

The robust association of brain amyloid pathology with AD makes this question highly relevant. The easiest and most cost-effective way of giving it a reliable answer is to analyse CSF for the 42 amino acid form of amyloid β (Aβ1-42). Low CSF levels indicate retention of Aβ1-42 in the brain parenchyma [5–8]. This seems to be the earliest biochemical change during the course of AD [9–11]. Low levels of Aβ1-42 may be seen Creutzfeldt-Jakob disease (CJD), also in the absence of significant amounts of brain amyloid pathology [12].

3. Does the Patient Suffer from Neurofibrillary Tangle Pathology?

Tau expression is high in nonmyelinated cortical axons where it serves as a microtubule-stabilizing protein [13]. Hyperphosphorylation of tau causes the protein to detach from the microtubules. This process promotes axonal and synaptic plasticity in the developing brain [14, 15], but is pathological in the adult brain and specifically related

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