www.ftd-caregiver2016.de

Documentation

International FTD Caregiver Conference

Internationale FTD Angehörigen-Konferenz

2016

Donnerstag,
1. September 2016
9:30 – 17:30 Uhr

Thursday,
1. September 2016
9:30 a.m – 5:30 p.m.

Technische Universität München

Klinikum rechts der Isar

Deutsche Alzheimer Gesellschaft e.V.
Selbsthilfe Demenz

Welcome to Munich!

The International FTD Caregiver Conference 2016 takes place in conjunction with the „International Conference on Frontotemporal Dementias, ICFTD 2016“. Informal and professional caregivers as well as all interested people from Germany and all over the world are invited to Munich for mutual exchange and discussion.

In Frontotemporal Dementia (FTD) first symptoms in average occur in the late 50s. Early FTD is characterized by changes of behaviour and, in some cases, language. At the same time memory and orientation remain relatively intact during the early stages of the disease. Compared to dementia in Alzheimer‘s disease, FTD is a rather rare condition and is still not very well known among lay people and even medical staff. This might be one reason for frequent misdiagnoses. Treatment – pharmacological and non-pharmacological – is not very effective and it is difficult to find appropriate care facilities for the relatively young patients. Caregiver burden is high.

The aim of the International FTD Caregiver Conference 2016 is to display the state of the art of diagnosis and treatment and to give room for exchange. The speakers are experienced clinicians and internationally renowned FTD experts. Additionally, several heads of FTD patient and caregiver associations from Europe and the US will play an active role in the conference. The International FTD Caregiver Conference 2016 is a forum for discussion. It will raise the awareness for FTD nationally and internationally and points out the urgent need for patient oriented research and the development of patient care and support strategies.

Kind regards,

Prof. Dr. Janine Diehl-Schmid,
TU Munich, Klinikum rechts der Isar

Helga Schneider-Schelte,
German Alzheimer Society, Berlin

Organizer

Klinikum rechts der Isar
der TU Munich
Ismaninger Str. 22, 81675 Munich

in cooperation with
Deutsche Alzheimer Gesellschaft
Friedrichstr. 236, 10969 Berlin
www.deutsche-alzheimer.de

Program committee

- Sharon Denny, Association for Frontotemporal Degeneration (AFTD), USA
- Susan Dickinson, Association for Frontotemporal Degeneration (AFTD), USA
- Prof. Dr. Janine Diehl-Schmid; TU Munich, Klinikum rechts der Isar, Germany
- Helga Schneider-Schelte, German Alzheimer’s Association, Germany

Education points

This meeting is accredited by the registration of nursing professionals (Registrierung beruflich Pflegender GmbH) with 6 educational points. Furthermore the medical chamber of Bavaria accredited the meeting with 8 CME points.

Headsets

Main language at the FTD Caregiver Conference is German. Simultaneous translation into English (through headsets) will be provided.
Headsets are issued in Hörsaal A. Please remark your headset with one of your name badges. If you loose the headset you have to bear the costs of 200 €.

Certificate of Attendance

You will find the Certificate of Attendance in the conference binder.

Documentation

The documentation of the talks will be available October 2016 on
www.frontotemporale-demenz.de

Program Guide, September 1st 2016

Location: Klinikum rechts der Isar of the TU Munich, Ismaninger Str. 22, 81675 Munich, Lecture Hall A

9.30 – 10.00	Opening remarks, introduction	Prof. Dr. Janine Diehl-Schmid, Helga Schneider-Schelte, Susan Dickinson
FTD – State of knowledge and future directions		
10.00 – 10.40	FTD: A Medical overview	Prof. Janine Diehl-Schmid, *TU Munich*
10.40 – 11.10	Recent advances in research	Prof. Manuela Neumann, *DZNE, University of Tübingen* & Prof. Dr. Alexander Kurz, *TU Munich*
11.10 – 11.30	Clinical drug trials	Prof. Markus Otto, *University Ulm*
11.30 – 12.00	Discussion	

Lunch break 12:00 – 13:00

Patient-caregiver interaction		
13:00 – 13:30	Dealing with altered social behaviour *(English)*	Prof. Mario Mendez, *University of Los Angeles, USA*
13:30 – 14:00	Bridging the communication gap in progressive aphasia	Prof. Christina Knels, *MSH Hamburg*
14:00 – 14:40	FTD in the family – reports of a spouse – and a mother	Two caregivers
14:40 – 15:00	Discussion	

Coffee break 15:00 – 15:30

Patient and caregiver support: different countries – different customs?		
15.30 – 16:40	What can we learn from each other? *(English)*	Chair: Association for Frontotemporal Degeneration (AFTD), *USA*
	An intervention program for caregivers of early-onset dementia patients with frontal behavioural changes	Y.Pijenburg, *VU Medical Center, The Netherlands*
	PPA support group with speech therapy	J. Walton, *Rare Dementia Support, UK*
	The FTD Carer Peer Mentorship Model	M. Kettle, *AFTDA, Australia*
	Creating a Network of FTD Support Groups	S. Denny, *AFTD, USA*
	wohlBEDACHT – New ways of living for people with FTD	A. Arand /S.Brandtner, *wohlBEDACHT, Germany*
16.40 – 17:15	Panel discussion: Current needs *(English)*	Representatives of caregiver support groups and FTD advocacy groups
17:15 – 17:30	Wrap up and closing remarks	Helga Schneider-Schelte

Speaker Bios

Prof. Dr. Janine Diehl-Schmid, MD, is professor of psychiatry. She is senior consultant at the Department of Psychiatry of Technical University of Munich. Together with Dr. T. Grimmer she is Head of the Center of Cognitive Disorders, which is one of the largest memory clinic in Germany. Frontotemporal Dementias have been her clinical and research focus since more than a decade. In her FTD-clinics, which is part of the German FTLD-Consortium, more than 40 patients with FTD per year are newly diagnosed. She has authored numerous papers about various topics within FTD, including problems and needs of the family caregivers.

Susan L-J Dickinson, MS, CGC joined The Association for Frontotemporal Degeneration PA/US as Executive Director in February 2008. Under her leadership, AFTD has expanded dramatically in scale and impact. Today AFTD is a $ 3 million a $3 million organization with 15 full-time staff. During her tenure AFTD has expanded programs to meet and advocate for the needs of FTD families, and invested in specific strategies to advance FTD research and drug development, including a multi-year, $5 million initiative to identify biomarkers for FTD and a $10 million program to fund FTD clinical trials.

Prof. Dr. Christina Knels studied Clinical Linguistics at the University of Bielefeld and wrote her dissertation on primary progressive aphasia at the Ludwig-Maximilian-University in Munich. She worked as a speech and dysphagia therapist in neurological and geriatric rehabilitation clinics. Currently she is professor for Neurosciences and Neurolinguistics at the Medical School Hamburg.

Prof. Dr. Alexander Kurz has been active in the field of geriatric psychiatry as a clinician, teacher and researcher since 1985. His current scientific interests include the design and evaluation of non-pharmacological interventions including assistive technology for people with dementia and informal carers. He has contributed to the development of Alzheimer's associations on local, national, and European levels and is a board member of the German Alzheimer's Association.

Prof. Dr. Mario Mendez is the Director of the Behavioral Neurology Program at UCLA and the Director of Neurobehavior at the V.A. Greater Los Angeles Healthcare System. He has a background in experimental psychology and expertise in the behavioral and cognitive aspects of dementias. His research involves clinical and cognitive aspects of Frontotemporal Dementia and early-onset Alzheimer's disease variants. Dr. Mendez received his M.D. from the University of Texas and his Ph.D. from Case Western Reserve University, and he has co-authored three books and over 250 publications.

Prof. Dr. Manuela Neumann, M. D. is Professor of Neuropathology and Medical Director of the Department of Neuropathology at the University Hospital of Tübingen, Germany, and research group leader at the German Center for Neurodegenerative Diseases. Her main research focus is to unravel the molecular pathology and underlying pathomechanisms of neurodegenerative diseases by studying human tissues and animal models. Manuela Neumann serves as a member of the Board of Directors of the International Society for Frontotemporal Dementia (ISFTD).

Prof. Markus Otto is a clinical neurologist. He holds a professorship for Neurology at the University Clinic in Ulm. Beforehand he had a professorship for interdisciplinary dementia research at the University of Goettingen. He studied in Mainz, Zurich and London. His main research focus it the early diagnosis of neurodegenerative diseases and treatment approaches for frontotemporal lobar degeneration. In this field he published more than 200 research articles. Since 2011 he is the speaker of the german consortium for frontotemporal lobar degenerations. Since 2016 he is founding member and board member of the society for neurochemistry and CSF diagnostics.

Helga Schneider-Schelte joined the German Alzheimer Association in 2000. She set up and is managing the Alzheimer's Association helpline and is involved in several projects. For over ten years she has been committed to people with FTD and their families. She hosted a number of conferences in different cities to spread the knowledge about FTD in Germany. In 2007 she initiated the exchange of experience for FTD caregivers, which is held every year.

Online Materials
Speaker slides and handouts are available from October at: **www.frontotemporale-demenz.de**

Internationale FTD-Angehörigen-Organisationen
Caregiver Resources International Organizations Focusing on Frontotemporal Degeneration

Country	Organization	Website or Contact
Argentina	Institute of Cognitive Neurology	www.ineco.org.ar/demencia-frontotemporal
Australia	The Australian Fronto-temporal Dementia Association (AFTDA)	www.theaftd.org.au
England	Frontotemporal Dementia Support Group (FTDSG)	www.ftdsg.org
France	Association France-DFT	www.france-dft.org
Germany	Deutsche Alzheimer Gesellschaft e. V. Selbsthilfe Demenz	www.frontotemporale-demenz.de
Greece	FTDnet Website	www.ftdnet.gr
Italy	The Italian Association for Frontotemporal Dementias	www.frontotemporale.net/wordpress
Netherlands	FTD Lotgenoten	www.alzheimer-nederland.nl
Spain	Asociación de Demencia Frontotemporal (ADEF)	www.adef.es
United States	The Association for Frontotemporal Degeneration (AFTD)	www.theaftd.org
United Kingdom	Frontotemporal dementia support group (FDSG)	www.ftdsg.org
Webseite speziell für Kinder und Jugendliche:		
AFTD Kids and Teens: Explore. Learn. Connect		www.aftdkidsandteens.org

Sponsoren

Association for Frontotemporal Degeneration (AFTD), Radnor, PA/US

BKK ZF & Partner, Koblenz

MSD SHARP & DOHME GMBH, Haar

www.frontotemporale-demenz.de

Prof. Dr. Janine Diehl-Schmid, Psychiatrische Klinik
Department of Psychiatry

FTD – A medical overview

Munich, 01. Sep 2016

Technische Universität München

Overview

- Frontal lobe disorder
- Frontotemporal Dementia (FTD)
- Symptoms
- Diagnosis and differential diagnosis
- Caregiver burden
- Therapy

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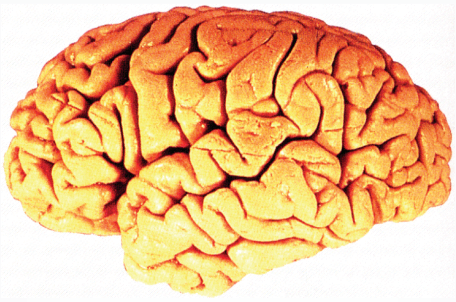

1400 grams
100 billion nerve cells / neurons
100 trillion synapses

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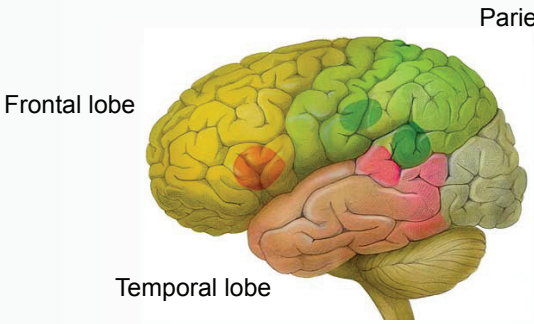

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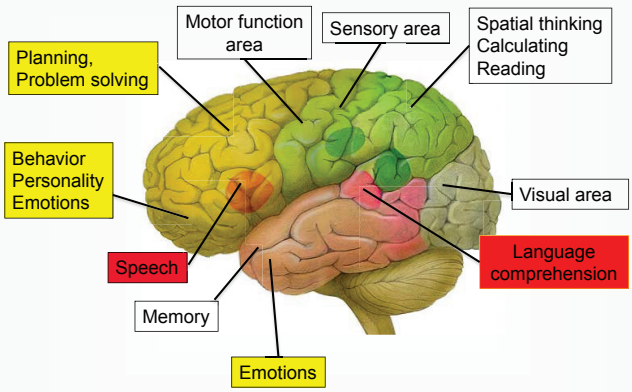

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Frontotemporal degeneration

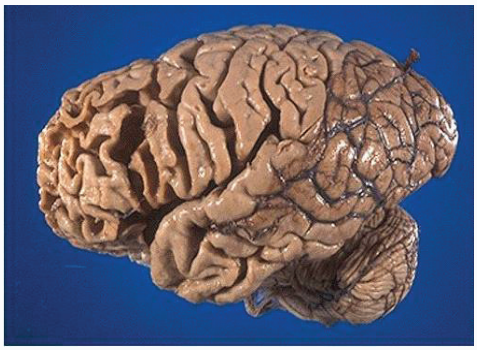
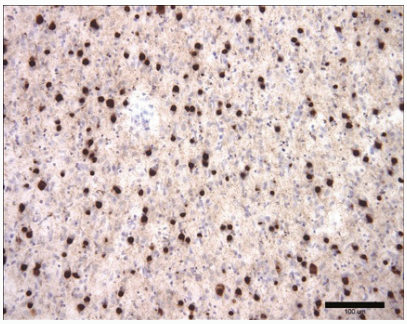
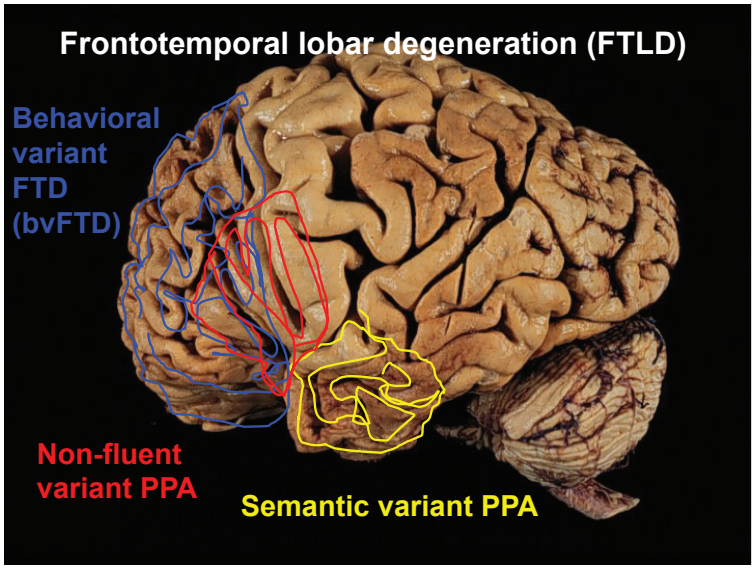


Image provided by courtesy of Prof. I.Mackenzie, UCB, Vancouver

Microscopic changes

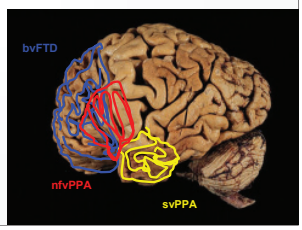


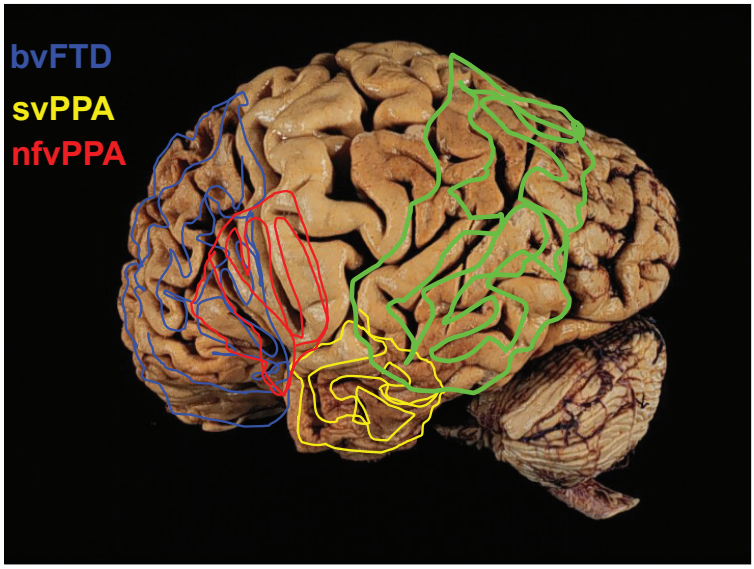
Protein disposits: Tau; TDP-43



Frontotemporal lobar degeneration (FTLD)

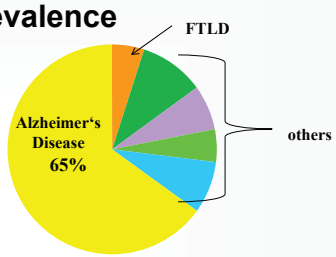
1. **Frontotemporal dementia, behavioral variant FTD (bvFTD)**
2. **Primary progressive aphasia (PPA)**
   - 2a. Semantic variant PPA
   - 2b. Non-fluent variant PPA





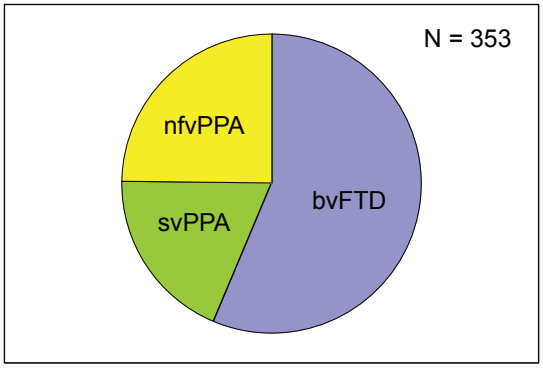
FTLD: Prevalence

- About 3 – 9% of all forms of dementia



- About 10 out of 100 000 persons between 45 and 65 years
- At least about 30 000 persons affected in Germany (?)

Distribution of diganoses



(Johnson, Diehl et al, 2004, Arch Neurol)

FTLD: Demographic data

	N	% male	Age of onset	
			mean	min - max
bvFTD	78	66%	58,6	37 - 81
svPPA	20	70%	61,1	57 - 74
nfvPPA	17	60%	66,4	44 - 83
FTLD in total	*115*	*65%*	*60,2*	*21 - 83*

Johnson J, Diehl J et al. (2005) *Arch Neurol*
Diehl-Schmid J et al. (2006) *Fortschr Neurol Psychiatr*,

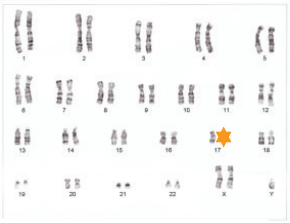
FTLD: Genetic risk factors

- Positive family history for neuropsychiatric diseases in 30 – 50% of the cases
- **Autososomal dominant** in about 10% (svPPA < nfvPPA/bvFTD)

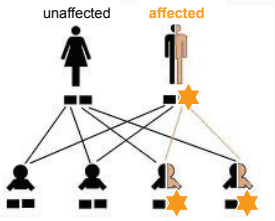
FTLD: Genetic risk factors

- Positive family history for neuropsychiatric diseases in 30 – 50% of the cases
- **Autososomal dominant** in about 10% (svPPA < nfvPPA/bvFTD)

DNA



Chromosomes



Probability of developing the disease: **50%**

Genetic risk factors

Symbol	Location	Gene name	Frequence in autosomal dominant FTLD
C9orf72	9p21.2	Chromosome 9 open reading frame 21	14 – 48%
GRN	17q21	Progranulin	3 – 26%
MAPT	17q21	Microtubule-associated protein tau	0 – 50%

(mod. Sieben et al., Acta Neuropathol, 2012)

Progression, survival time and causes of death

- Progression: chronic progressive
- Survival time: 8 - 14 years (1 – 29 years)
  (dvPPA > nfvPPA> bvFTD)
- Causes of death: Pneuomia
  Cardiovascular diseases
  Cachexia

(Nunnemann,…,Diehl-Schmid, 2010, *Neuroepidemiology)*

bvFTD: Symptoms

doi:10.1093/brain/awr179 Brain 2011: Page 1 of 22 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

Katya Rascovsky,[1] John R. Hodges,[2] David Knopman,[3] Mario F. Mendez,[4,5] Joel H. Kramer,[6] John Neuhaus,[7] John C. van Swieten,[8] Harro Seelaar,[8] Elise G. P. Dopper,[8] Chiadi U. Onyike,[9] Argye E. Hillis,[10] Keith A. Josephs,[3] Bradley F. Boeve,[3] Andrew Kertesz,[11] William W. Seeley,[6] Katherine P. Rankin,[6] Julene K. Johnson,[12] Maria-Luisa Gorno-Tempini,[6] Howard Rosen,[6] Caroline E. Prioleau-Latham,[6] Albert Lee,[6] Christopher M. Kipps,[13,14] Patricia Lillo,[2] Olivier Piguet,[2] Jonathan D. Rohrer,[15] Martin N. Rossor,[15] Jason D. Warren,[15] Nick C. Fox,[15] Douglas Galasko,[16,17] David P. Salmon,[16] Sandra E. Black,[18] Marsel Mesulam,[19] Sandra Weintraub,[19] Brad C. Dickerson,[20] Janine Diehl-Schmid,[21] Florence Pasquier,[22] Vincent Deramecourt,[22] Florence Lebert,[22] Yolande Pijnenburg,[23] Tiffany W. Chow,[24,25] Facundo Manes,[26] Jordan Grafman,[27] Stefano F. Cappa,[28,29] Morris Freedman,[24,30] Murray Grossman[1,*] and Bruce L. Miller[6,*]

bvFTD: Clincial diagnostic criteria

Three of the following (A-F) must be present to meet the criteria.

A. Early behavioral disinhibition

B. Early apathy or inertia

C. Early loss of sympathy or empathy

D. Early perseverative, stereotyped or compulsive/ ritualistic behavior

E. Early hyperorality or dietary changes

F.Neuropsychological profile: executive generation deficits with relative sparing of memory and visuospatial functions

Early: within 3 years after onset

(Rascovsky et al., 2011, *Brain)*

bvFTD: Clincial diagnostic criteria

A. Early* behavioral disinhibition
(one of the following symptoms A.1–A.3 must be present)

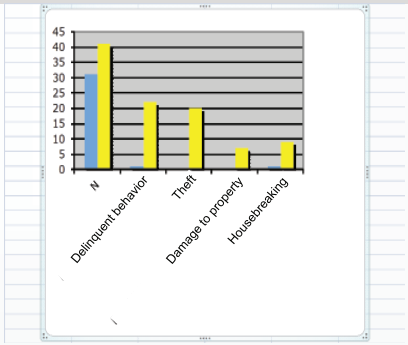
A.1. Socially inappropriate behavior

A.2. Loss of manners or decorum

A.3. Impulsive, rash or careless actions

bvFTD/svPPA/AD: Misdemeanor / criminal behavior

Differences between patients with AD (N = 31) and bvFTD/SD (N = 41)



(Diehl J et al., 2006, *Fortschr Neurol Psychiatr)*

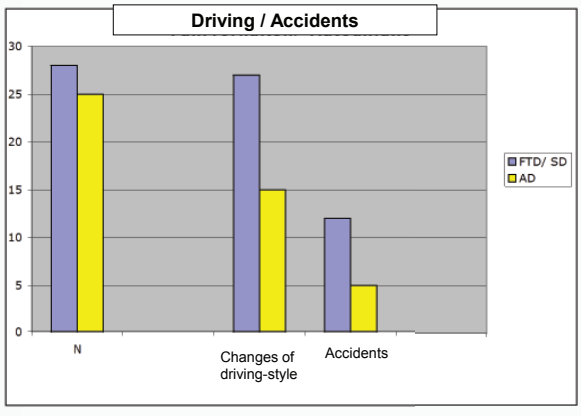
bvFTD: Clincial diagnostic criteria

A. Early* behavioral disinhibition
(one of the following symptoms A.1–A.3 must be present)

In September 1999 Dr. Allan Zarkin, an obstetrician from Manhattan, was so pleased with his Caesarean section he performed that he carved his initials in the patient' stomach.

During the $ 5 Million lawsuit it turned out that "Dr. Zorro" suffered from frontotemporal dementia.

(The Forensic Echo – Behavioral & Forensic Sciences in the Courts, 2000, Volume 4)



(Koch, …, Diehl-Schmid et al., 2010, *Nervenarzt)*

bvFTD: Clincial diagnostic criteria

B. Early* apathy or inertia
(one of the following symptoms B.1–B.2 must be present)

B.1. Apathy

B.2. Inertia

(Diehl-Schmid J et al. (2006): *Dement Geriatr Cogn Disord)*

bvFTD: Clincial diagnostic criteria

C. Early* loss of sympathy or empathy
(one of the following symptoms C.1–C.2 must be present)

C.1. Diminished response to other people's needs and feelings

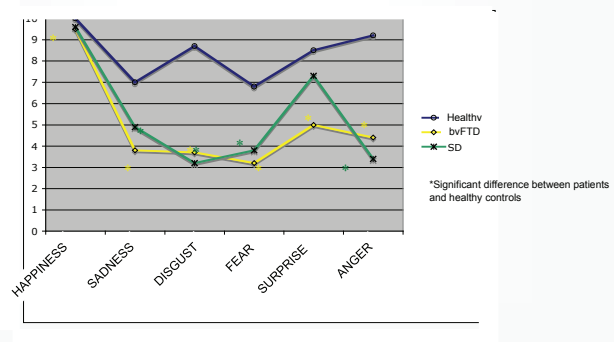
C.2. Diminished social interest, interrelatedness or personal warmth

(Diehl-Schmid J et al. (2006): *Dement Geriatr Cogn Disord)*

Ekman 60 Faces Test
(Ekman & Friesen, 1976)

FTD/SD: Recognition of emotional faces

Differences between healthy controls (N = 33; total: 50 points) and patients with bvFTD (yellow, N = 25; 30 points) and SD (green, N = 8; 32 points)



(Diehl-Schmid J et al., 2007, *Arch Clin Neuropsychol)*

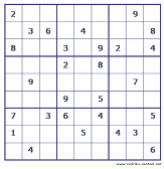
bvFTD: Clincial diagnostic criteria

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour
(one of the following symptoms D.1–D.3 must be present)

D.1. Simple repetitive movements
D.2. Complex, compulsive or ritualistic behaviours
D.3. Stereotypy of speech

bvFTD: Clincial diagnostic criteria

B	I	N	G	O
4	22	31	47	65
10	18	42	53	74
14	27	33	57	63
6	21	32	48	66
13	28	41	52	67



bvFTD: Clincial diagnostic criteria

E. Hyperorality and dietary changes
(one of the following symptoms E.1–E.3 must be present)

E.1. Altered food preferences
E.2. Binge eating, increased consumption of alcohol or cigarettes
E.3. Oral exploration or consumption of inedible objects

bvFTD: Clincial diagnostic criteria

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions
(all of the following symptoms F.1–F.3 must be present)

F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills

bvFTD: Clincial diagnostic criteria

Three of the following behavioural / cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
A.1. Socially inappropriate behaviour
A.2. Loss of manners or decorum
A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
B.1. Apathy
B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
C.1. Diminished response to other people's needs and feelings
C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
D.1. Simple repetitive movements
D.2. Complex, compulsive or ritualistic behaviours
D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
E.1. Altered food preferences
E.2. Binge eating, increased consumption of alcohol or cigarettes
E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills

(Rascovsky et al., 2011, *Brain*)

svPPA – Semantic dementia

- Progressive loss of comprehension of the meaning of words, faces, objects, etc.
- Disturbance of speech
  - Impaired speech comprehension
  - Loss of vocabulary, „thingy“
  - word finding difficulties
  - fluid language, for a long time grammatically correct
- Disturbance of perception
  - Inability to recognize faces or objects
  - Behavioral disorders (selfishness, loss of empathy, greed)

Non-fluent variant PPA

- Word finding difficulties
- Effortful speech, long pauses
- Grammatical errors
- Stuttering or apraxia of speech
- Impaired repeating of language
- Troubles with reading and writing
- Phonematic paraphrasing, impaired speech
- Relatively preserved language comprehension (at onset)

- Insight into the illness - depression
- Behavioral abnormalities late in the progression of the disease

Differential diagnosis

- Depression
- Manic episode
- Schizophrenia
- Addiction (alcohol)

Differential diagnosis

- Atypical Parkinson syndromes

  - Progressive supranuclear palsy (PSP)

  - Corticobasal degeneration (CBD)

- Amyotrophic lateral sclerosis (ALS)

Diagnosis

- Medical history by proxy
- Neuropsychological examination
- Laboratory values
- Structural Imaging (MRI)
- Positron emission tomography (PET)
- Examination of the spinal fluid (spinal tap)

Magnetic resonance imaging

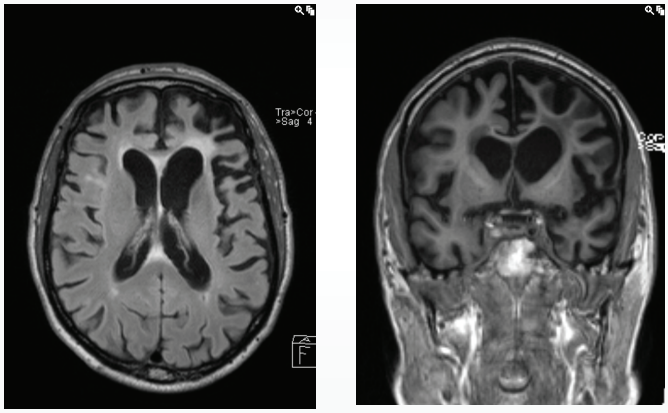
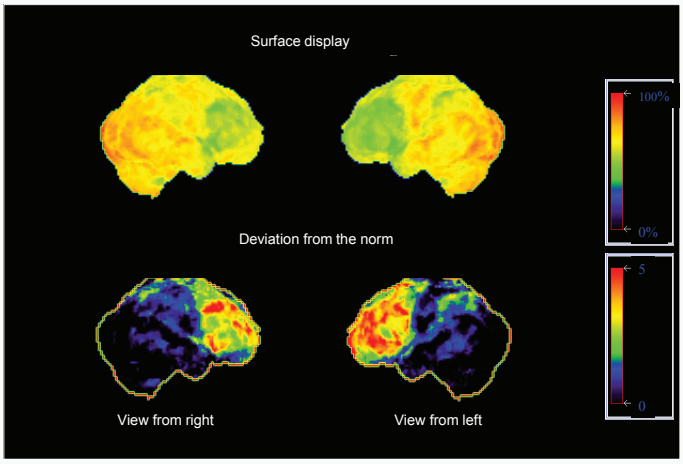


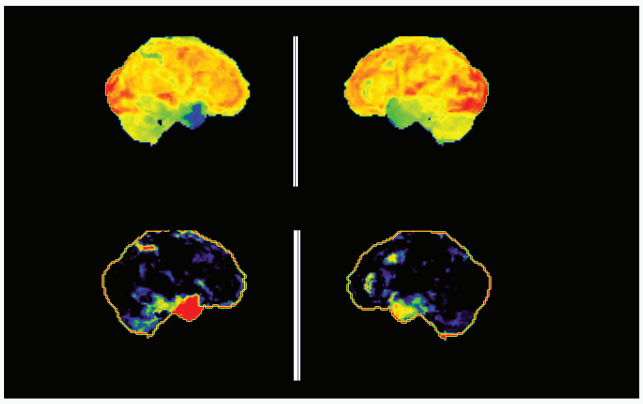
Image provided by courtesy of Prof. C. Zimmer, Institut für Neuroradiologie, TUM

Positron emission tomography (PET): bvFTD

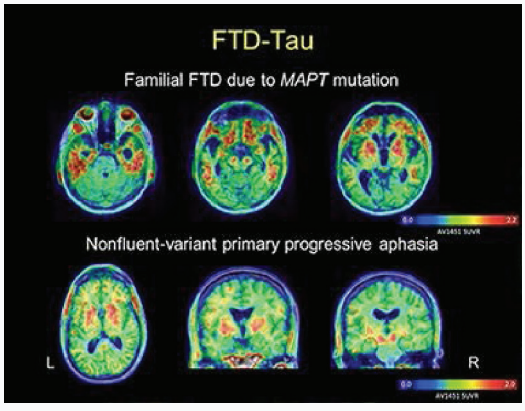


PET-Image provided by courtesy of Prof. A. Drzezga, Institut für Nuklearmedizin, TUM

PET: svPPA / Semantic dementia



Tau-PET



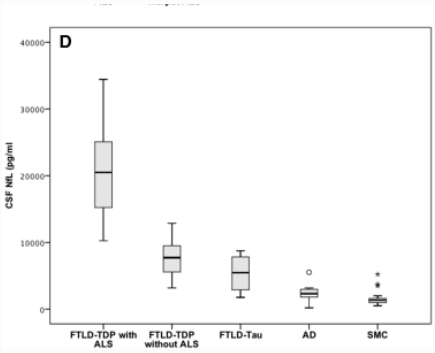
Images: UCSF, San Francisco, California

Technische Universität München

Spinal tap

1. Exclusion of inflammatory and infectious diseases
2. Determination of beta-amyloid/ tau/ phospho-tau
   → differentiating Alzheimer's disease
3. In the future: positive biomarkers for FTLD

CSF



Neurofilament light (NfL) chains

(Pijnenburg et al., 2015)

Caregiver burden

Questionnaire - goals

- To what extent and why are caregivers burdened?
- What are the problems?
- What are the needs?
- Which available and potential interventions / support services will / would be rated positively by the caregivers?

Questionnaire for caregivers of patients with FTLD (N=94)

Klinikum rechts der Isar

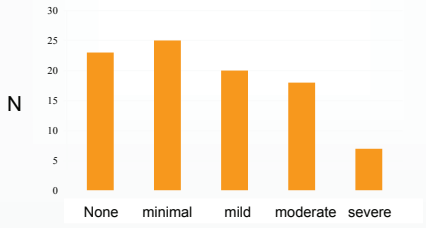
Technische Universität München

Questionnaire for caregivers of patients with FTLD: Problems and needs for support and assistance

(Diehl-Schmid et al: *J Ger Psychiatry Neurol, 2013)*

Caregiver burden

- Caregiver burden: **Caregiver Strain Index**: 7,8 ± 2.9 (0-13)
- Depression: **Beck Depression Inventory II (BDI-II):** 15,4 ± 8,7 (2 – 40)



Depression

Factors that influence depression

Carer	BDI-II
Sex (male / female)	p = 0,001* (f >m)
Age (spouses, partner)	r = -0,315; p = 0,006*
Reöationship (Partner vs. children)	p = 0,294
Hours of help (h/d)	r = 0,102 p = 0,384
Living together with the patient (y / n)	p = 0,572
Patient	
Sex	p = 0,002* (m > w)
Age	r = -0,195; p = 0,061
Age at onset of first symptoms	r = -0,207, p = 0,047*

* Korrelation signifikant

Factors that influence depression

	BDI-II
Care level 1, 2, 3	r = 0,058 p = 0,591
Living in a nursing home (yes / no))	p = 0,304
Number of persons involved in caregiving at the moment	r = -0,065 p = 0,535
Extent of change in the relationship	p = 0,001*
Financial problems	p = 0,069

* Korrelation signifikant

Factors that influence depression

*significant correlation

BDI-II	
Bedridden condition	Selfishness
	Aggression
	Addictive behavior
	Reduced need to sleep

The "worst" about the patient's disease

1. The loss of a loved one
2. Unstoppable progression of the disease
3. Own helplessness

Needs: What helps?

Information
Psychosocial support
Financial support for caregivers
Help through care outside from home
Help through support at home
…
Non-pharmacological therapies for the patients
Safety issues

An e-Learning-program for caregivers of dementia patients (onset before age 65)

RHAPSODY

JPND research
EU Joint Programme – Neurodegenerative Disease Research

Collaboration of 6 countries:
D, F, NL, SE, P, UK

Deutsche Alzheimer Gesellschaft e.V.
Selbsthilfe Demenz

RHAPSODY: Modules

Medical apects	Frequent problems and solutions	Challenging behavior	Family problems	Help availability	Self care
					

Additional: chat forum

Pharmacological therapy: symptomatic treatment

- Antidepresssants
- Antipsychotic drugs / neuroleptics
- Sedatives

BUT:

Which symptoms should be treated?
Possible environmental changes?
Side effects tolerable?

Pharmacological therapy: causal treatment

- There will be no (probable) single therapy for the treatment of all FTLD subtypes
- Treatments are developed for FTLD sub types (patholgically / genetically)
- Problems with clinical testing of drugs

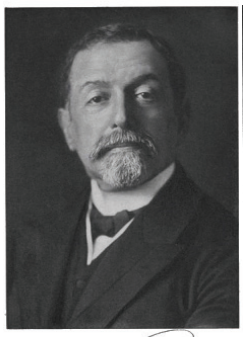
International
FTD Caregiver Conference 2016

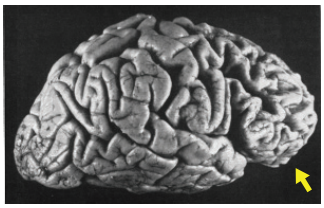
The 10th ICFTD

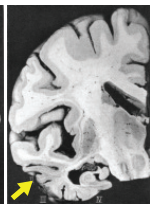
Recent advances in research

Prof. Dr. Alexander Kurz
Department of Psychiatry
Klinikum rechts der Isar
Technical University of Munich

It was simpler in the past: „Pick's disease“







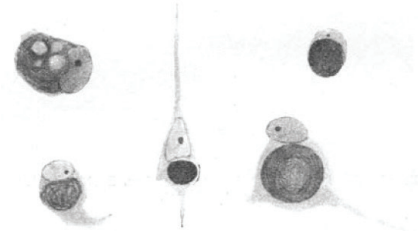
Changes of behavior and personal conduct caused by frontal lobe atrophy

Language disorder caused by temporal lobe atrophy

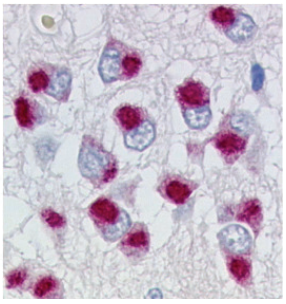
Arnold Pick (1851-1924)

H. Spatz: Z ges Neurol Psychiat 1937

It was simpler in the past: „Pick's disease“

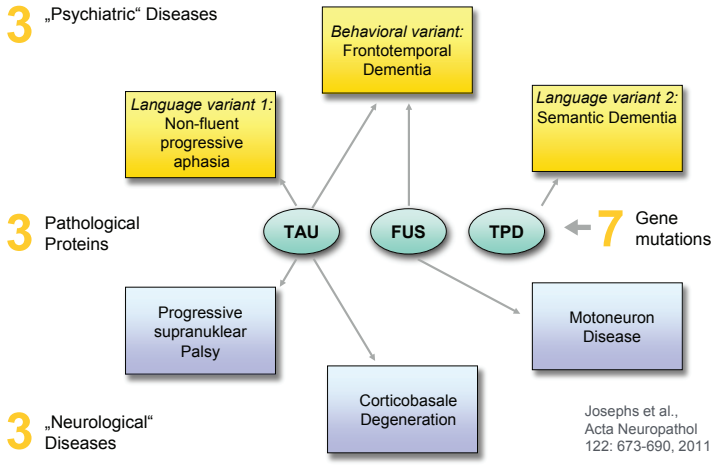


Alois Alzheimer (1911) „Eigentümliche Fibrillenveränderung der Ganglienzellen“



Pick-bodies (Tau) today (M. Neumann)

Today: Several diseases

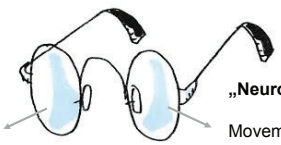


Josephs et al., Acta Neuropathol 122: 673-690, 2011

Diagnosis with both eyes

„Psychiatric“ Symptoms

Cognition
Behavior
Communication

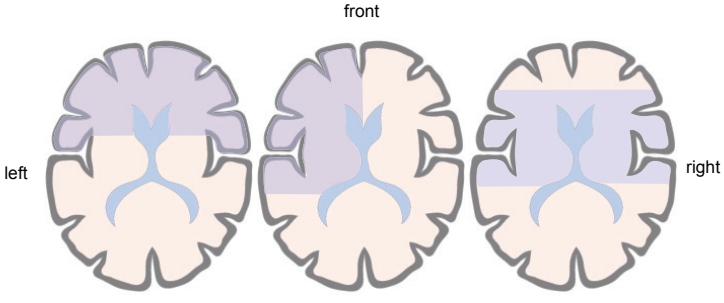


„Neurological“ Symptoms

Movement
Muscle strength and coordination
Posture

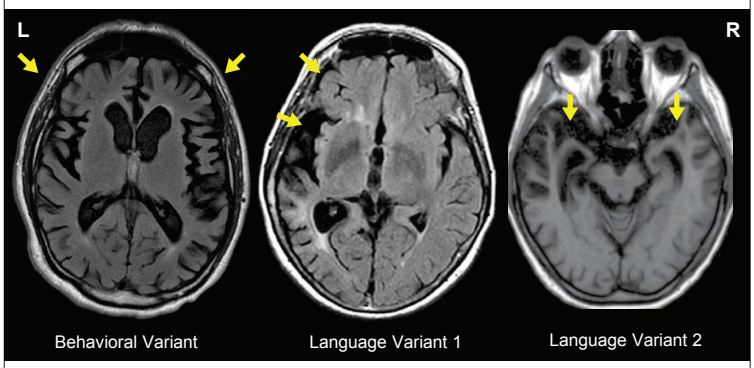
Warren et al. BMJ 2013: 347:f4827; Guennoc et al. Rev Neurol 169: 470-475, 2013;
Armstrong et al., Neurology 80: 496-503, 2013; 2013; Litvan et al., Neurology 47: 1-9, 1996

Symptoms are caused by the location of the brain changes, not by the underlying pathology



Behavioral variant	*Language variant 1*	*Language variant 2*
Frontotemporal dementia	Non-fluent progressive aphasia	Semantic Dementia

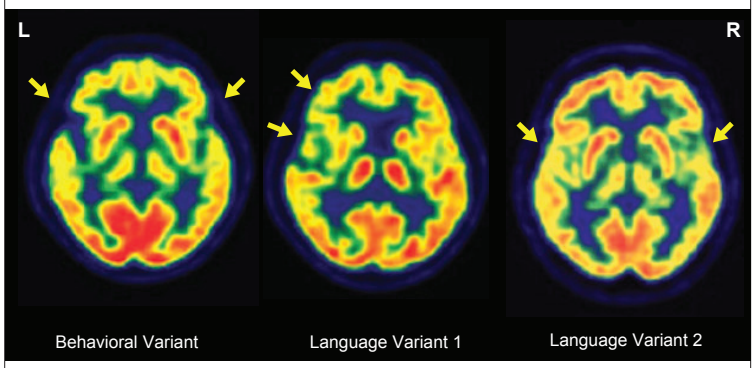
Look into the brain: Magnetic-Resonance-Imaging



Frontotemporal Dementia	Non-fluent, Progressive Aphasia	Semantic Dementia

radiopedia.org

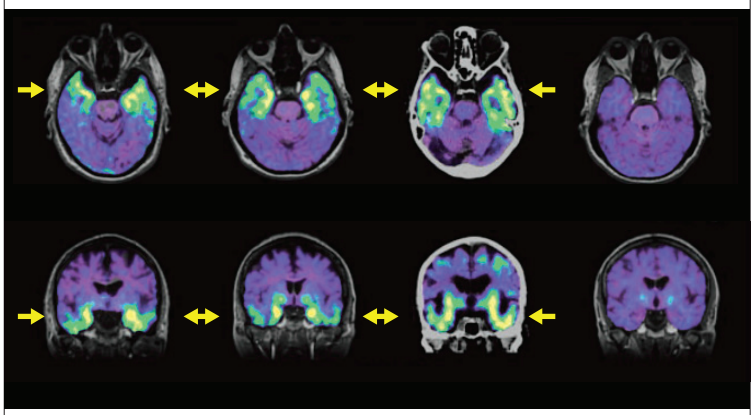
Look into the brain: Positron-Emission-Tomography



Frontotemporal Dementia	Non-fluent, Progressive Aphasia	Semantic Dementia

Abbildungen: Berti et al., Ann NY Acad Sci 1228: 81-92, 2011

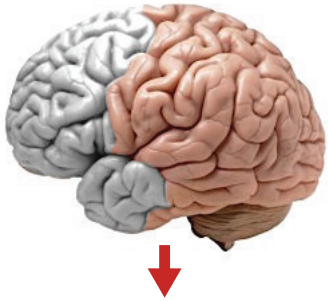
Look into the brain: Tau-PET



Frontotemporal Dementia — Healthy Control

Smith et al.: Brain, 29. Juni 2016

Consequences for patients and caregivers



Social perception and behavior
Apathy
Repetitive Behavior
Hyperorality or changed food preferences
Cognitive functions
Communication

Raskovsky et al.: Brain 134: 2456-2477, 2011; Gorno-Tempini et al., Neurology 76. 1008-1014, 2011

Non-pharmacological therapy

Form	Aim	Examples
Behavioral Management	Control and reduction of challenging behavior	Hobbies, games Occupation Physical activity
Modification of Environment	Control and reduction of challenging behavior	Avoiding overstimulation Constancy, clarity Daily routines Storage of food Safety precautions
Language therapy	Aufrechterhaltung der Kommunikationsfähigkeit	Video-based language training Personalized dictionary Communication folder Technical devices
Caregiver support	How to deal with the disease and its consequences	Information Attitudes Expectations Coping strategies

Shinagawa et al., J Alzheimer's Disease 45: 283-293, 2015; Tippett et al., Curr Treat Options Neurol 17;362, 2015

Recent advances in FTD research
- Basic research-

Prof. Dr. Manuela Neumann
Institute of Neuropathology
University Tübingen & German Center for Neurodegenerative Diseases

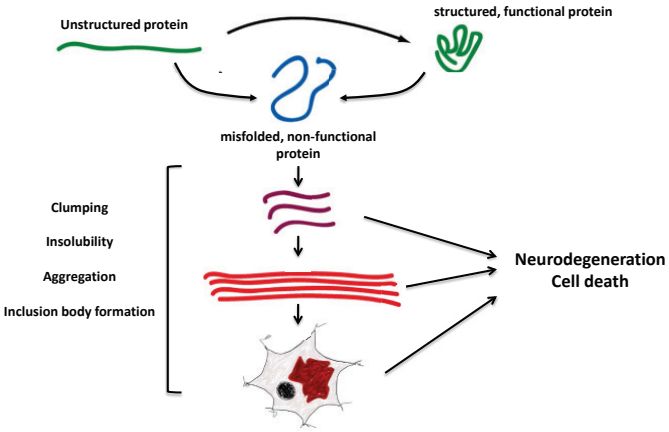
Neurodegenerative diseases are protein misfolding disorders

All biological functions in a living organism are almost entirely performed by proteins.

To be functional, each protein is present in a given structured state. A protein may have several functional structures.

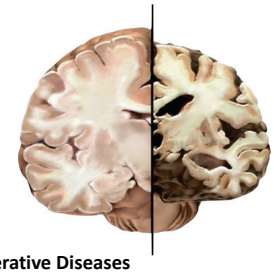
Various events lead to protein misfolding and clumping (aggregation)
-> Loss of function.

Neurodegenerative diseases are protein misfolding disorders



Neurodegenerative diseases are protein misfolding disorders

- Alzheimer disease
- Parkinson disease
- Dementia with Lewy bodies
- **Frontotemporal dementia**
- Amyotrophic lateral sclerosis
- Prion diseases
- …



Different neurodegenerative Diseases

↓

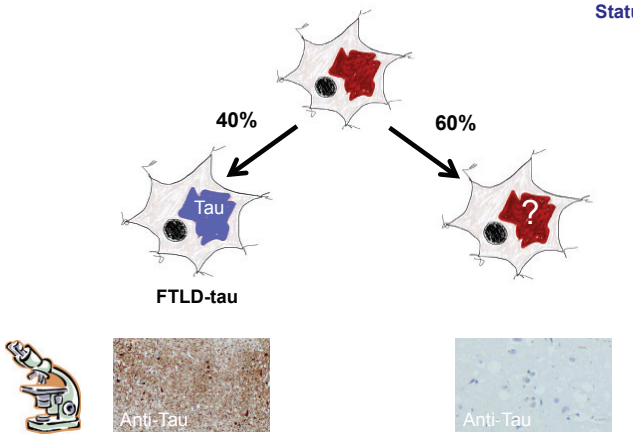
Different misfolded proteins

↓

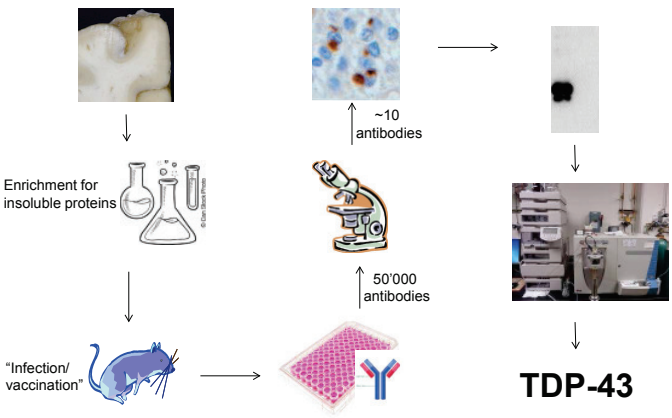
Different causes of cell death

Frontotemporal dementia–
Neuropathology: Frontotemporal lobar degeneration FTLD

Status 9/2006



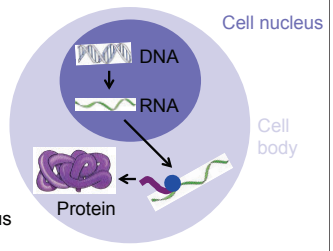
Procedure for identifying the unknown protein in FTLD



Manuela Neumann, Deepak Sampathu, Linda Kwong et al. 2006 Science

What is TDP-43 ?

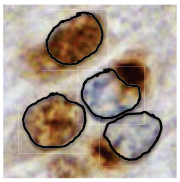
- RNA binding protein
- Localized predominantly in the nucleus
- Important for the correct production of > 6000 RNA molecules and transport of RNA molecules from the nucleus into the cell body.



DNA –> RNA –> Protein

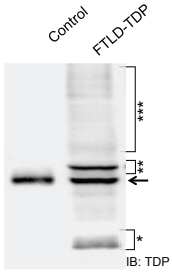
Characteristic changes of TDP-43 in the disease

Changes in localization



✓ Redistribution from the nucleus into the cell body

Changes on molecular level

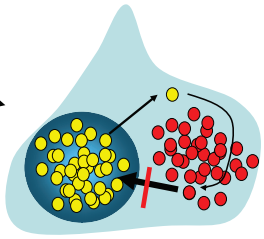


✓ Phosphorylation
✓ Cleavage
✓ Insolubility

Working hypothesis

Changes of TDP-43
Cleavage
Phosphorylation
misfolding/insolubility

Gene defects
- *Progranulin (2006)*
- *TDP-43 (2008)*
- *C9Orf72 (2011)*
- …



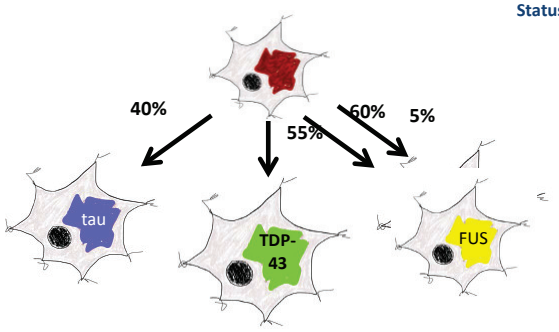
- Loss of TDP-43 function ?
- Toxic effect of pathological TDP-43 protein fragments ?

Cell death

Summary and Outlook

Frontotemporal dementia– FTLD
3 different protein misfolding disorders

Status 2016



Summary and Outlook

With the discovery of TDP-43 and FUS as new disease-causing proteins and the discovery of new disease genes (progranulin, C9orf72), all essential proteins and genetic defects that lead to FTD are now identified.

This opened up completely new avenues of research to unravel the underlying causes of ~ 60% of FTD.

The striking structural and functional similarities of TDP-43 and FUS suggest that changes in RNA processing play a key role in the pathogenesis of FTD.

Next steps: elucidating the normal function of TDP-43 and FUS in the brain, establishment of model systems that reflect the pathological changes in the human brain, clarify the interaction of progranulin, C9orf72 and TDP-43.

It is expected that these findings will lead to the development of new therapeutic approaches for the treatment of FTD.

Frontotemporale Lobardegenertion

Drug studies

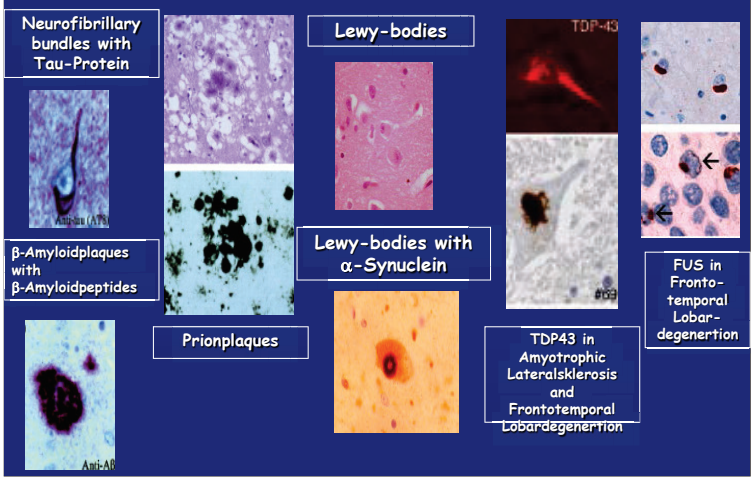
Markus Otto

Neurologische Klinik, Universität Ulm

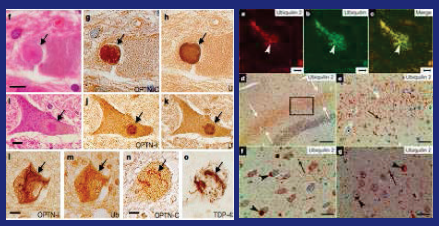
Which steps are necessary to develop a drug therapy

- a view of the molecular basis of the disease
- development of a model to investigate and/or to modulate single steps of disease stages
- testing of drugs in a model – development of an hypothesis
- development of tests, which mirrow the disease progression and monitor a drug effect (neuropsychology – neurochemistry),
- build-up an infrastructure, to diagnose patients early and obtain a relevant number of patients to perform a drug therapy study

Classification on molecular basis



Classification on molecular basis



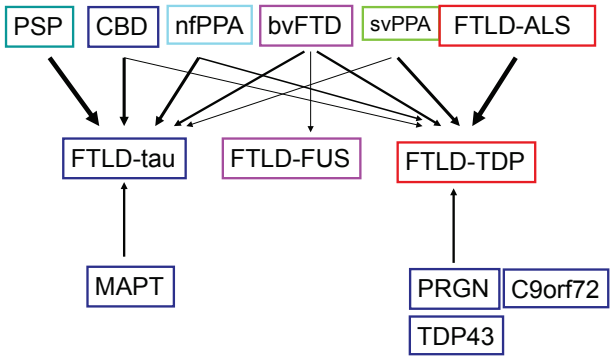
- Extracellular aggregates
  - Alzheimer´s disease
  - Prion disease
- Intrazellulare Aggregate
  - Tauopathies
    - Alzheimer´s disease
    - Frontotemporale dementia associated with chromosome 17
    - Progressive Supranuklear Palsy
  - Alpha-Synuclein diseases
    - Parkinson´s disease
    - Lewy-bodies disease
  - Ubiquitin - TDP43 - FUS
    - Amyotrophic Lateralsclerosis
    - FTD with Amyotrophic Lateralsclerosis
  - Polyglutamin disease
    - Huntington´s disease
    - spinocerebellar ataxia

The clinical spectrum of frontotemporal lobar degeneration

PSP | CBS | nfvPPA | bvFTD | svPPA | FTD-ALS

- Progressive supranuclear palsy (PSP)
- Corticobasal syndrom (CBS)
- non-fluent primary progressive aphasia (nfPPA)
- Behavioural variant of FTD (bvFTD)
- Semantic variant of primary progressive aphasia (svPPA)
- FTD with amyotrophic lateral sclerosis (FTD-ALS)

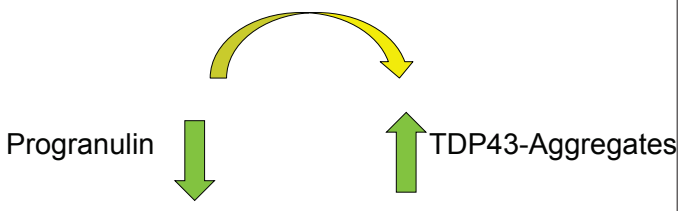
The clinical spectrum of frontotemporal lobar degeneration



Genetic

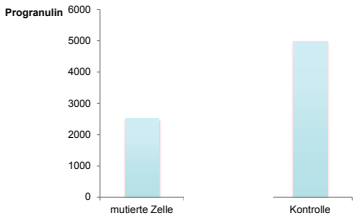
- MAPT (microtubule associated protein tau)
- GRN (Progranulin)
- VCP (valosin containing peptide)
- TARDBP (transactive response DNA binding protein)
- CHMP2B (charged multivescicular body protein 2B)
- C9orf72
- TBK-1

Development of an hypothesis



Neurobiology of Disease

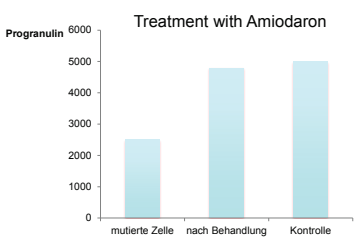
Rescue of Progranulin Deficiency Associated with Frontotemporal Lobar Degeneration by Alkalizing Reagents and Inhibition of Vacuolar ATPase



Modified from Capell et al. 2011

Neurobiology of Disease

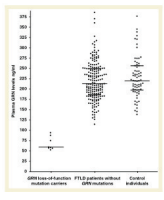
Rescue of Progranulin Deficiency Associated with Frontotemporal Lobar Degeneration by Alkalizing Reagents and Inhibition of Vacuolar ATPase



Modified from Capell et al. 2011

Therapeutic approaches

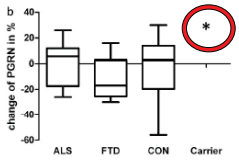
Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members



Progranulin as a candidate biomarker for therapeutic trial in patients with ALS and FTLD

2015

Nimotop Behandlung



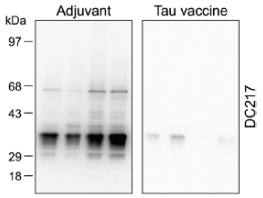
Therapeutic approaches

RESEARCH Open Access

First-in-man tau vaccine targeting structural determinants essential for pathological tau–tau interaction reduces tau oligomerisation and neurofibrillary degeneration in an Alzheimer's disease model

Eva Kontsekova[1], Norbert Zilka[1], Branislav Kovacech[1,2], Petr Novak[1] and Michal Novak[1*]

2015

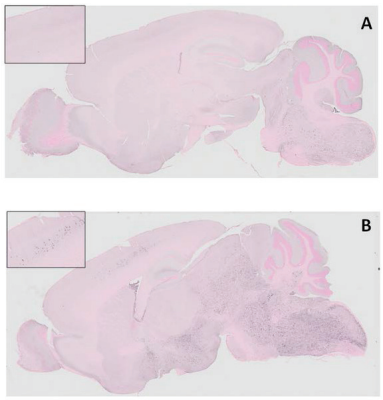


A pilot study of AADvac1 in patients with symptomatic nfvPPA

Synopsis of the study protocol

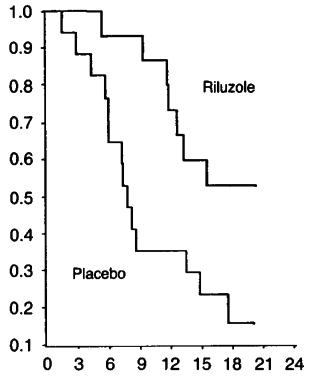
A 24-month open-label phase 1 pilot study of AADvac1 in patients with clinical symptoms of non-fluent primary progressive aphasia and temporoparietal glucose hypometabolism

Methylenblue in an animal model



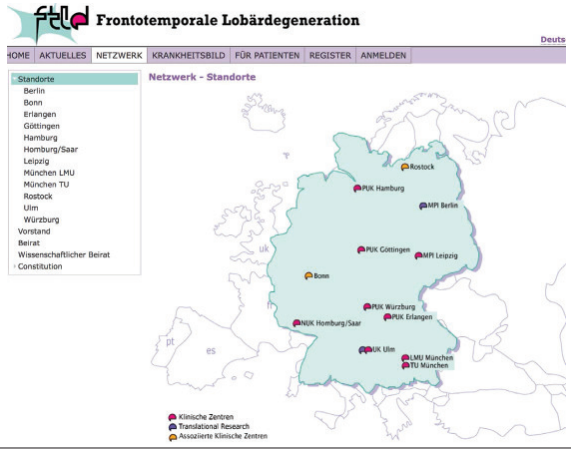
Hosokawa et al. 2012

Riluzole as candidate for a TDP-43 disease?

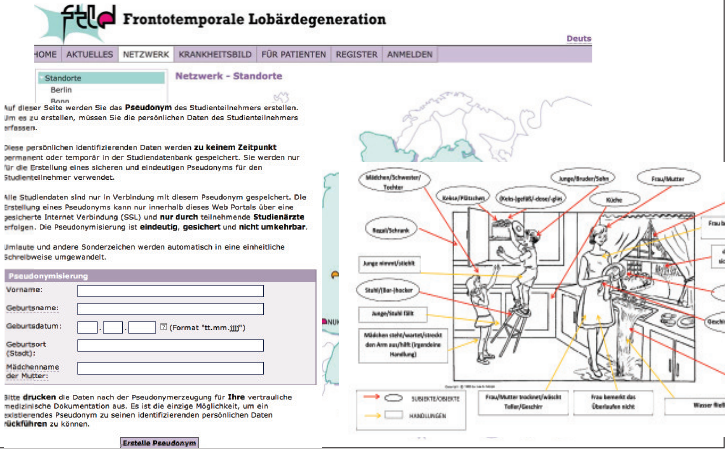


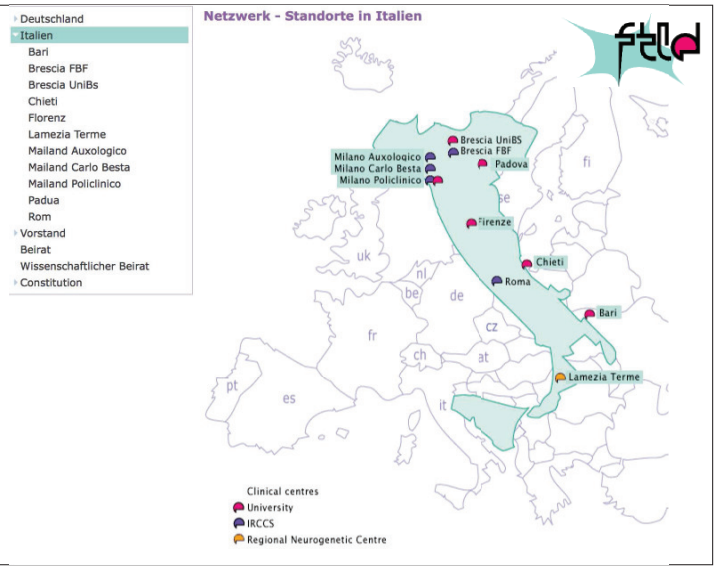
Bensimon et al. 1994

FTLD consortium www.ftld.de

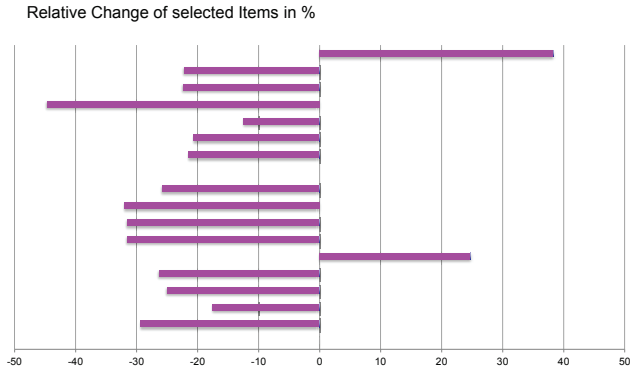


FTLD consortium www.ftld.de

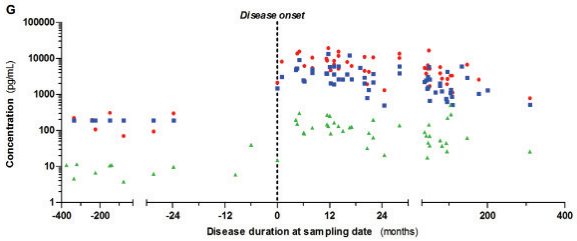




One year follow-up of nfvPPA patients

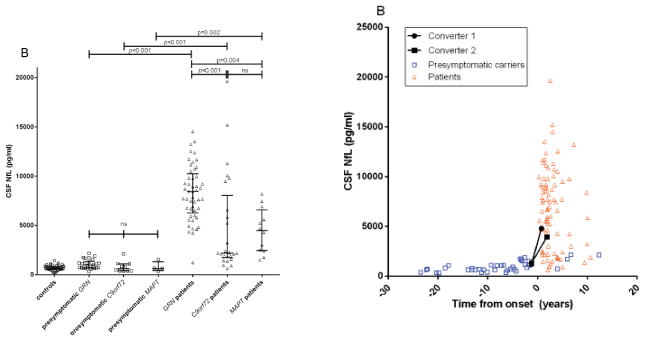


Neurofilaments as diagnostic marker in blood



Weydt et al. 2016, Annals of Neurology

FTLDc + Genfi



Meeter et al. 2016

Which steps are necessary to develop a drug therapy

- a view of the molecular basis of the disease
- development of a model to investigate and/or to modulate single steps of disease stages
- testing of drugs in a model – development of an hypothesis
- development of tests, which mirrow the disease progression and monitor a drug effect (neuropsychology – neurochemistry),
- build-up an infrastructure, to diagnose patients early and obtain a relevant number of patients to perform a drug therapy study

A look into the future

How could an individual therapy look like?

- Clinical diagnosis
- Differention of patients into Tau, FUS oder TDP-43
  - By genetic investigation or TAU-PET
- Tau (+) patients: Tau-Immunization
- TDP-43 (+): Riluzole – Progranulin-Enhancer (Nimotop)
- .....

Frontotemporal Degeneration: Dealing with Altered Social Behavior

Mario F. Mendez, M.D., Ph.D.
Departments of Neurology and Psychiatry & Biobehavioral Sciences,
David Geffen School of Medicine, University of California at Los Angeles;
and
Section of Neurology, V.A. Greater Los Angeles Healthcare Center,
Los Angeles, California USA

BvFTD is characterized by Altered Social Behavior

- Altered social behavior affects the psychological well-being and social life of families and caregivers.
- Understanding altered social behavior is critical for behavior management
- Accommodating the behavior in a calm, safe environment while providing education and support for the caregiver, is more important that extinguishing the behavior

Major Social Behavior Disturbances in BvFTD

1. Detachment: unmotivated, apathetic, "inertia"
2. Disinhibition: violate social norms/manners
3. Altered interpersonal connection or loss of empathy
4. Altered communication

Objectives

The ultimate objective: to m*aintain or enhance quality of life*

- What are the social behavior disturbances of FTD?
- What is their impact on patients?
- What is their impact on families and caregivers?
- What are non-drug management strategies?
  - Behavioral
  - Environmental
  - Caregiver
  - Educational

What is the impact on patients?

- Loss of independence
- Loss of role outside home (eg, occupation)
- Loss of role in family
- Social isolation and exclusion
- Decreased overall sense of self/identity

What is the impact on families?

- Altered balance between patient needs and family needs
- Altered family roles
- Ambiguity about the future and how to plan
- Family resilience and tensions about caregiving
- Children–discussing and helping them cope

Non-Drug Strategies for Intervention

Nonpharmacological interventions are more likely to be effective in managing behavioral symptoms than drugs (Ayalon et al, Arch Intern Med 2006;166:2182-8)

•Environmental adaptations

•Behavior management

•Caregiver training

•Education

Before anything, Check for Causes

FTD impairs their ability to communicate their needs or report physical health issues or other causes of altered social behavior.

- Check for unmet needs, eg, hunger, urge to urinate
- Make sure that even "mild" pain is managed
- Evaluate medical illnesses
- Evaluate medications and recent dosage changes
- Rule-out covert anxiety or depression

Think Proactive and Reactive Tools

- **PROACTIVE**
  - Plan ahead, the entire day and individual activities
  - Anticipate potential problems
  - Let others know of potentially altered social behavior
  - "Carer's card" to hand people in public that explains FTD
  - Plan environmental modifications
- **REACTIVE**
  - Have behavioral and other techniques ready to use
  - Invest others in preparation to respond when needed

Behavior Management
(Repeat, Reassure, Redirect)

- Approach with smile and a calm, soft, reassuring manner–avoid arguing
- Refocus them by distracting with conversation or objects
- Modify or eliminate potential triggers and frustrations
- Initiate enjoyable activities and comforting techniques
- Establish regular schedule, routine, sleep-wake cycle

Disengagement or Apathy

Apathy has the most impact on marital relationship (du Vugt et al., 2003)

- Provide structure - more effective than free time
- Offer or direct to individual or small group activities
- Do not force them; let the passively participate
- Ensure tasks are simple so that they can complete
- At onset, explain activities in simple language

Disinhibition

In Germany, behavioral disturbances were predominant reason for hospital admission among 58 patient with FTLD included FTD (Ibach et al, Dement Geriatr Cogn disord 2004;17:269-73)

- Identify trigger for disinhibition and interventions
- Avoid confrontation; gently redirect to another activity
- Reduce environmental stimulation
- Involve other family members and caregivers
- If disruptive, inform others, include what does or does not work

Altered Interpersonal Connection

FTD caregivers report a loss of emotional attachment leading to isolation and anger due to behavioral symptoms (Massimo et al, Geriatr Nurs 2013;34:302-6)

- Rethink expectation of emotional feedback; offer empathy without expecting reciprocity
- Provide them information about others' perspectives
- Encourage families to share what they did together
- Share moments of connection and special events
- Instruct others so they don't expect validation

Altered Communication

Many have little verbal output and single or short phrase answers and others are excessively talkative and jocular.

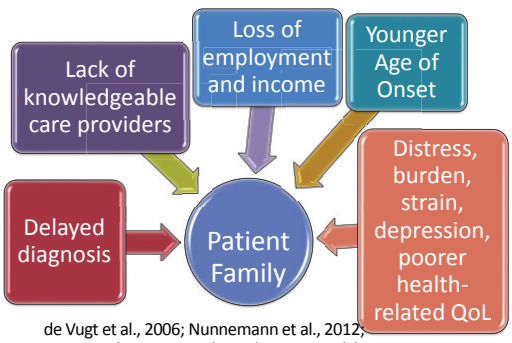
- Approach with calm, patient, pleasant tone of voice
- Reduce competing stimulation and distractions
- Use the same terms consistently for care issues
- Other forms of communication: touch and lead, hand motions, props, picture, sing, short written words
- Technology–iPads iwith communication apps and software programs like Proloquo2Go(www.proloquo2go.com)

Environment

- Create a safe, calm, and predictable environment
- Eliminate confusing, noisy, cluttered, or overstimulating environments
- Simplify social situations and number of people
- Provide safe wandering and ambulation
- Family may choose familiar public places

FTD Family Caregiving

(Darby Morhardt, PhD, LCSW
Northwestern University)



de Vugt et al., 2006; Nunnemann et al., 2012; Wong et al., 2012; Mioshi et al., 2009; Riedijk et al., 2006; Diehl-Schmid et al., 2013

Caregiver

Worse strain, emotional distress and lower perceived control among bvFTD caregivers. Levels of depression for FTD caregivers are twice that of AD caregivers (Wong et al, 2012 AMP 20;724-8) (Moishi et al, Dement Geriatr Cogn disord 2009;27:76-81).

- Practice caregiver wellness, self-care, and forgiveness
- Find balance: spend time together AND time apart
- Have realistic expectations
- Reach out and talk to others about what is happening
- Support groups with other caregivers of those with FTD

Education

- Education and coaching are effective in minimizing negative outcomes from behavioral symptoms
- Courses on behavior management
- Caregivers also benefit from courses on home safety, problem solving, stress reduction, health
- Coaching via phone calls regarding caregiver stress

I hope that this information helps you.
Thank you very much for your attention.

Communication with patients with progressive aphasia

Prof. Dr. Christina Knels

Language

4 modalities of language as a cognitive ability:

- production
- comprehension
- reading
- writing/spelling

4 levels of describing language functions

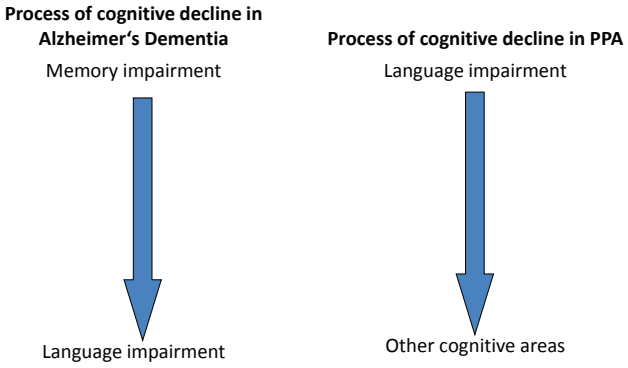
- speech sound (phonological level)
- lexicon (lexical level)
- comprehension (semantic level)
- grammar (syntactic level)

Primary progressive aphasia (PPA)

- Insiduous onset and gradual decline of speech/language functions (most prominent feature)
- These deficits are the principal cause of impaired daily living activities
- Aphasia ist the most prominent feature at symptom onset and for the initial phases of the disease

Gorno-Tempini et al.
2011, Mesulam 2001

Alzheimer‘s disease vs. primary progressive aphasia

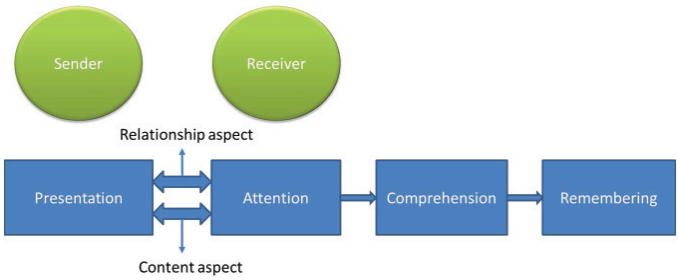


Variants of PPA

Nonfluent agrammatic variant	Semantic variant (semantic dementia)	Logopenic variant
Effortful, halting speech, sound errors	**Impairment of naming**	**Impaired single word production and naming (single-words)**
Impairment of grammar	**Impairment of single word comprehension**	**impaired repetition of sentences and phrases**
Impaired comprehension of syntactically complex sentences	Impaired object knowledge	Speech sound errors
Spared: single word comprehension, object knowledge	Spared: repetition, grammar, motor speech	Spared: grammar, articulation, single word comprehension, object knowledge

Gorno-Tempini et al.
2011

Communication model



Haberstroh et al. 2011

Aims of speech language therapy for PPA

Not an aim: restoration of impaired language functions

Aims:

- Preservation of language functions that are (still) intact
- Fortification of available ressources
- Consolidation and longest possible preservation of communication with caregivers/family (quality of life)

Adaptation of communication may be necessary in the course of the disease

HT, 63 years, semantic variant of PPA severe aphasia (production + comprehension)

Case study HT

- progressive impairment of language for over 5 years
- Severe word finding problems, incomprehensible speech production (“empty” speech), severe impairment of speech comprehension
- Nonverbal cognitive abilities: intact
- Intelligence/logical thinking: slightly above norm
- Severe reduction of active and passive vocabulary (estimated repertoire of 50 „active“ words)
- 4 nouns could be identified: dog (“Hund“), grandmother (“Oma“), son (“Sohn“), water (“Wasser“)

Communicative gestures

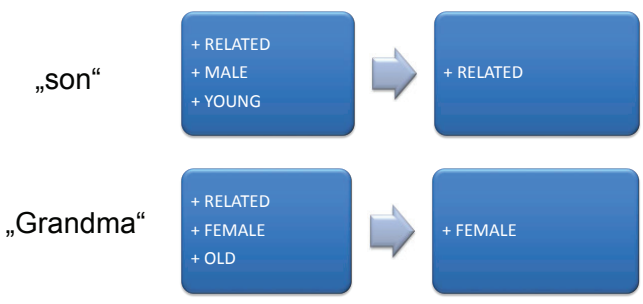
Pointing: positioning of communicative content regarding person (who?), space (where?) and time (when?)

- **Person (who?)**: points to where target person is usually „located“ (home, workplace), sometimes combination with „eam“ (general personal pronoun)
- **Space (where?)**: points to target location
- **Time (when?)**:
  - pointing forward in combination with “soon” (future tense),
  - pointing behind him + “learned” “little” “long (ago?)”

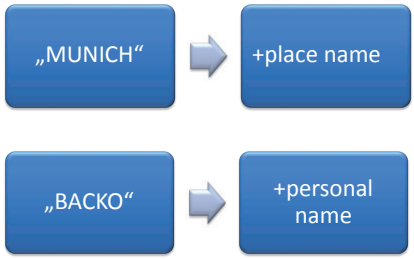
HT‘s lexicon

Produktion	Bedeutung
„water“	(to/the) water, (to/the) rain, wet, saliva, dirty, (to/the) shower, weather forecast, laundry, to clean („water off“)
„water“ (+ draws crosses in the air)	to water the flowers on the graveyard
„water“ (+draws flowers in the air)	To water the flowers in the garden
„cold“	cold, complicated, not functioning
„cold“ (+ grabs his nose)	it smells
„cold“ (+ looks at sun)	it is warm
„dog“	all animals
„dog“ (+ “piep“) „dog“ (+ flaps arms) „dog“ (+ “stupid“)	(singing) bird duck pigeon

Semantic shift of „son“ and „Grandma“



Semantic shift of proper names



Conclusion

- Language functions are **only one aspect** of communication
- Persons with PPA retain important **ressources** for communication (e.g. attentional processen, memory, nonverbal aspects of communication)
- In the course of progressive aphasia communication **changes** (nonverbal part increases)
- Communication can be maintained by **adapting to changed conditions**

Thank you!

Literature

- Haberstroh, J., Neumeyer, K., Franzmann, J., Krause, K., & Pantel, J. TANDEM: Communication training for informal caregivers of people with dementia. Aging and Mental Health; 2011
- Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76:1006–14
- Mesulam, M. Primary progressive aphasia. Ann Neurol 2001; 49: 425-432