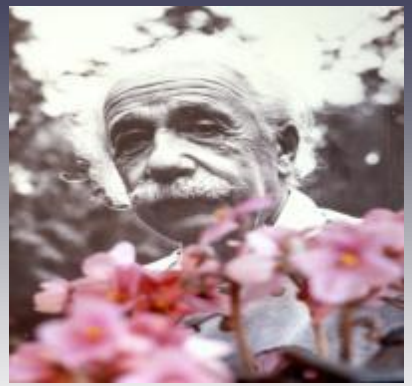

Albert Einstein
(1879 – 1955)

Muenster Cathedral
(1377, 161.4 m)

Ivory Lion Man
(~40000 y, ~30 cm)

ALS and other Motor Neuron Diseases: clues to diagnosis

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XXII Congress of the World Federation of Neurology, Santiago (Chile),

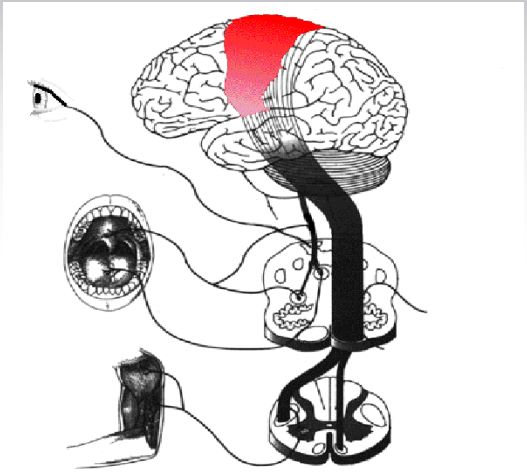
Wednesday the 4th of November 2015

I have nothing to disclose

Learning Objectives

1. ALS is a progressive disease primarily affecting motor neurons
2. ALS is a multisystem degeneration
3. Cognition, behavior, ocular movements, extrapyramidal systems are also affected by the disease process
4. Affection of these systems does not exclude ALS
5. Continuous spreading of the disease can be observed in most patients
6. Muscles are affected in a disease-specific pattern

A clinically defined disease: amyotrophic lateral sclerosis (ALS)



- rapidly progressive motor pareses with upper and lower motor deficits in most patients („motor neuron disease“)
- focal begin, continuuos spread, finally generalized pareses
- progression over 2-4 years
- patient finally „deefferentiated“ - „locked in“
- death by respiratory insufficiency
- incidence in Southern Germany 3.1/100000

An Early Report: a „strange disease“ 1848

Rechtfertigung

der

von den Gelehrten misskannten,

verstandesrechten

Erfahrungsheillehre

der

alten scheidekünstigen Geheimärzte

und

treue Mittheilung des Ergebnisses einer 25jährigen Erprobung dieser Lehre am Krankenbette

von

Johann Gottfried Rademacher.

Zweiter Band.

Dritte Ausgabe.

Berlin, 1848.

Druck und Verlag von G. Reimer.

I saw a very remarkable form of a strange paresis in the first year of my practice: I could not treat the patient, but presented him to my friends, because everything sememd to be strange:

The problem consisted of an incomplete paresis of the legs, and it was strange to see that - at the half paralyzed extremities – the patient had spontaneous muscle contractions causing wave-like movements of the skin.

Such a wave was about 5-10 cm long, and I reasoned that it must have its origin in a part of - not the entire - muscle, potentially originating from fiber bundles. It really looked as if frogs were jumping under the skin.

The poor man did not survive for a long time, the pareses spread to the entire body, he lost a lot of weight and died with a body weight of less than 40 kg.

„Forgotten“ Upper Motor Neuron Signs (Brooks et al., 2000)

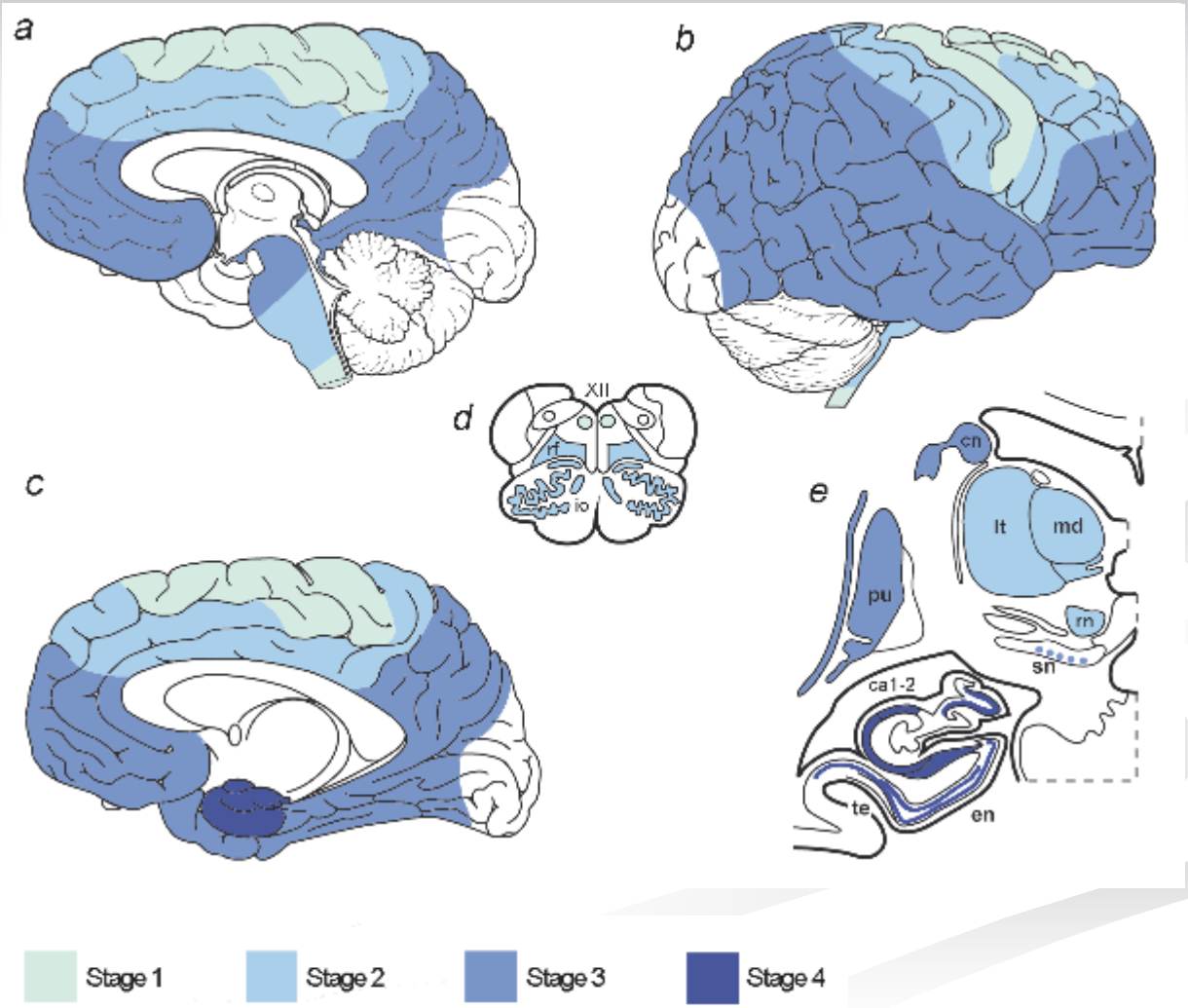
- Pseudobulbar features (forced yawning, clonic jaw jerk, gag reflex, exaggerated snout reflex)
- Tongue paresis without atrophy (and fasciculations)
- Preserved reflexes in weak wasted limb
- Spastic tone, rigidity
- Loss of superficial abdominal reflexes

The (pseudo)bulbar variant of ALS

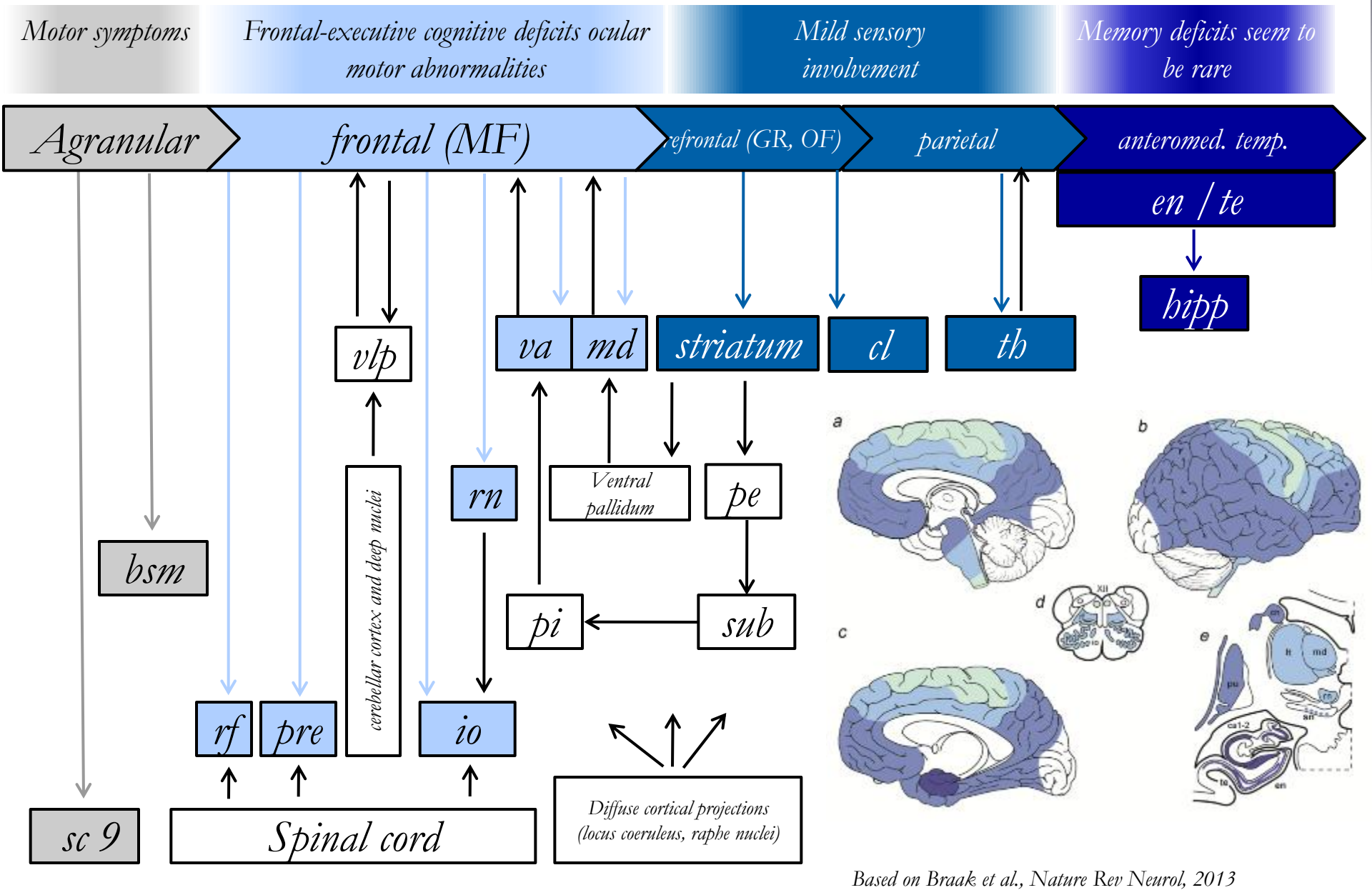
- Primary bulbar onset in about 25 % of patients (incidence)
- Women more frequently affected than men (60-80 years)
- Always generalizes into ALS

- Negative prognostic factor
- Pseudobulbar palsy – paresis, but no atrophy, and pathological crying and laughter

„Spreading“ of TDP-43 Pathology in ALS (Brettschneider et al., 2013, 2014) - Overview

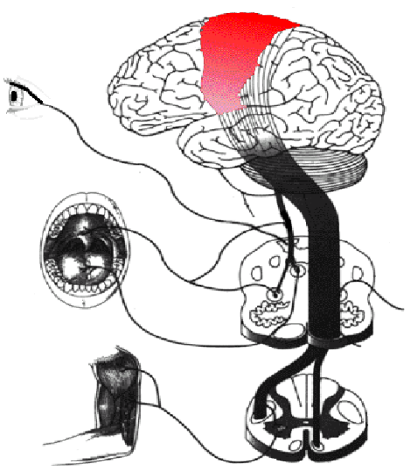


Summary: how we believe TDP-43 to spread



Based on Braak et al., Nature Rev Neurol, 2013

Groups of Neurons showing pTDP-43 neuropathology in group („stage“) II



I. *Prefrontal neocortex (middle frontal gyrus)*

II. *Precerebellar nuclei*

- *inferior olivary complex*

-- *dorsal accessory olivary nucleus*

-- *medial accessory olive*

-- *lateral reticular nucleus,*

-- *conterminal nucleus,*

-- *interfascicular nucleus,*

-- *nucleus of Roller,*

-- *vermiform nucleus,*

-- *subventricular nucleus,*

-- *dorsal paramedian reticular nucleus,*

-- *arcuate nucleus*

-- *pontobulbar body*

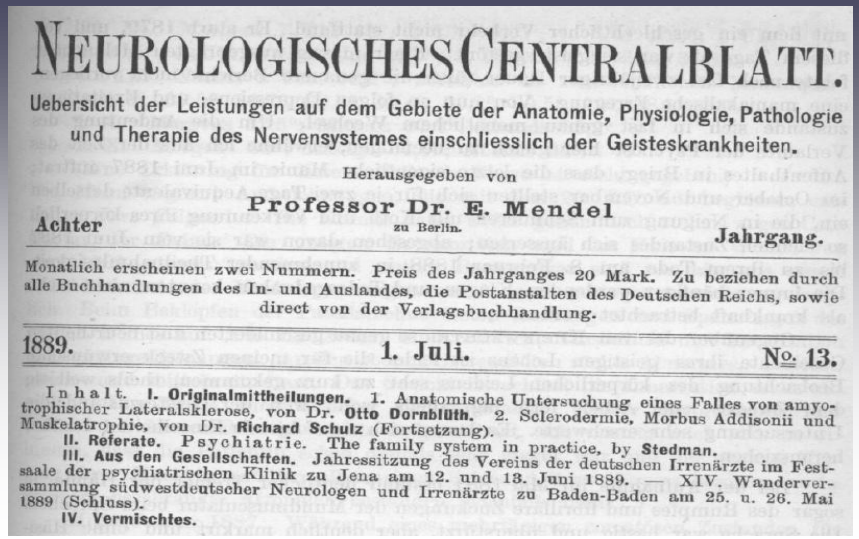
-- *parvocellular portion of the red nucleus*

III. *Reticular formation*

- *parvocellular portion*
- *magnocellular portion*

IV. *Others*

- *neuromelanin-containing cells of the pars compacta of the substantia nigra*
- *reticulate portion of the SN*
- *large neurons of the thalamus*



NEUROLOGISCHES CENTRALBLATT.

Uebersicht der Leistungen auf dem Gebiete der Anatomie, Physiologie, Pathologie und Therapie des Nervensystemes einschliesslich der Geisteskrankheiten.

Herausgegeben von

Professor Dr. E. Mendel

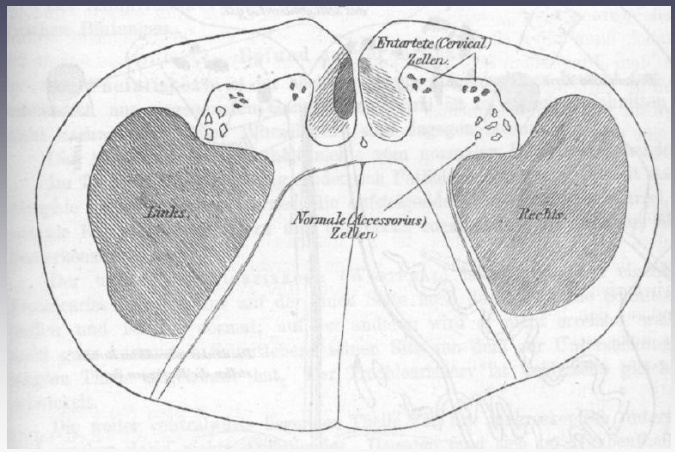
zu Berlin.

Achter Jahrgang.

Monatlich erscheinen zwei Nummern. Preis des Jahrganges 20 Mark. Zu beziehen durch alle Buchhandlungen des In- und Auslandes, die Postanstalten des Deutschen Reichs, sowie direct von der Verlagsbuchhandlung.

1889. 1. Juli. No. 13.

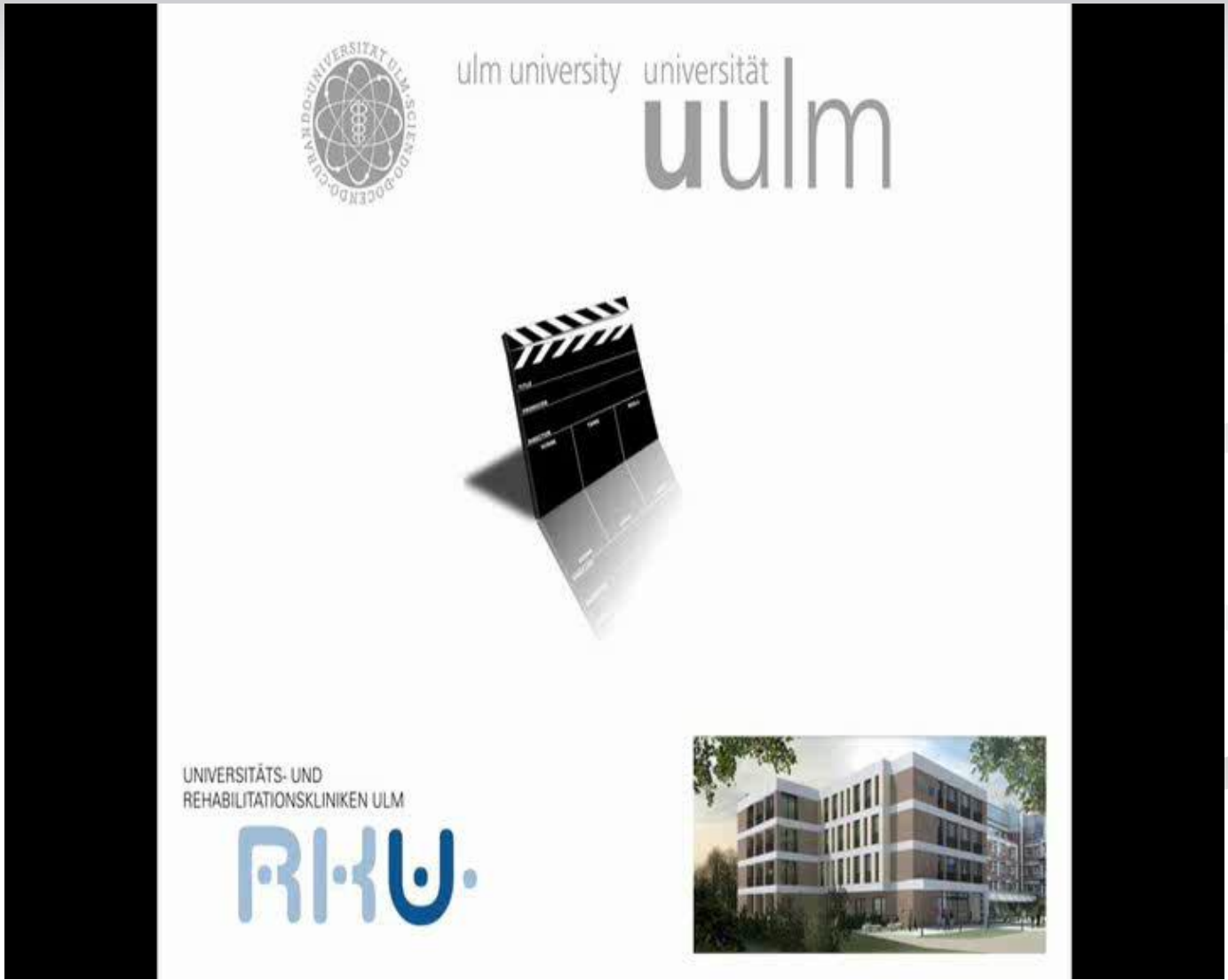
Inhalt. **I. Originalmittheilungen.** 1. Anatomische Untersuchung eines Falles von amyotrophischer Lateralsklerose, von Dr. **Otto Dornblüth.** 2. Sclerodermie, Morbus Addisonii und Muskelatrophie, von Dr. **Richard Schulz** (Fortsetzung).
II. Referate. Psychiatrie. The family system in practice, by **Stedman.**
III. Aus den Gesellschaften. Jahressitzung des Vereins der deutschen Irrenärzte im Festsaale der psychiatrischen Klinik zu Jena am 12. und 13. Juni 1889. — XIV. Wanderversammlung südwestdeutscher Neurologen und Irrenärzte zu Baden-Baden am 25. u. 26. Mai 1889 (Schluss).
IV. Vermischtes.



A 60 year-old woman; her brother died of paralytic, psychological disease……(„paralytische Seelenstörung“). After her husband died - when she was 54 - she developed a „psychosis“. During the course of the disease, she got apathic and withdrawn. At the age of 55, fibrillations of the tongue were observed and within 5 years she got completely paralyzed.

Autopsy: Degeneration of the pyramidal pathways, loss of anterior horn cells and bulbar motor neuron nuclei – however, the brain was not examined…….

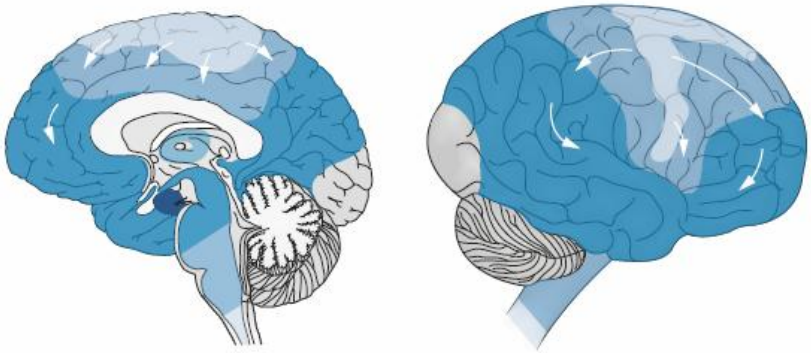
Executive Deficits in ALS: Word Fluency



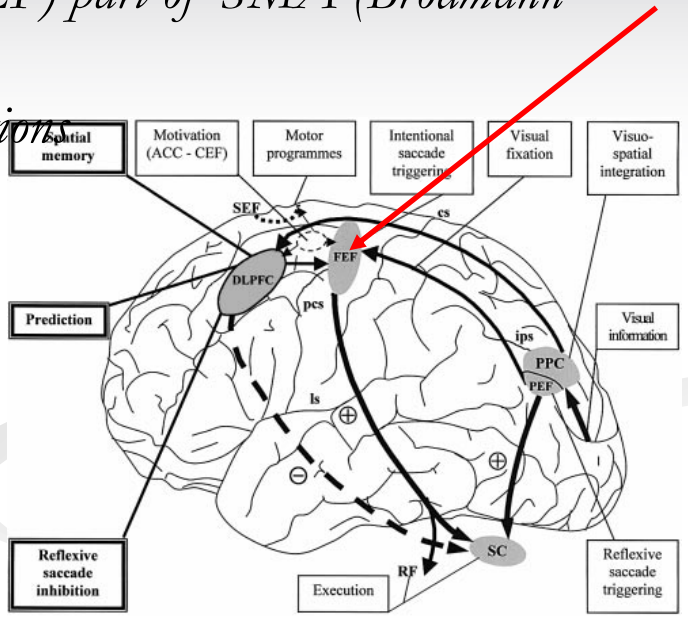
Stage 1 and 2: What to expect from oculomotor examination ?

Braak Stage 1: *agranular frontal neocortex (Brodmann areas 4&6) Supplementary Eye Field (SEF) part of SMA (Brodmann area 6)*

Braak Stage 2: olivocerebellar projections



H. Braak, et al., Nature Reviews Neurology, 2013.



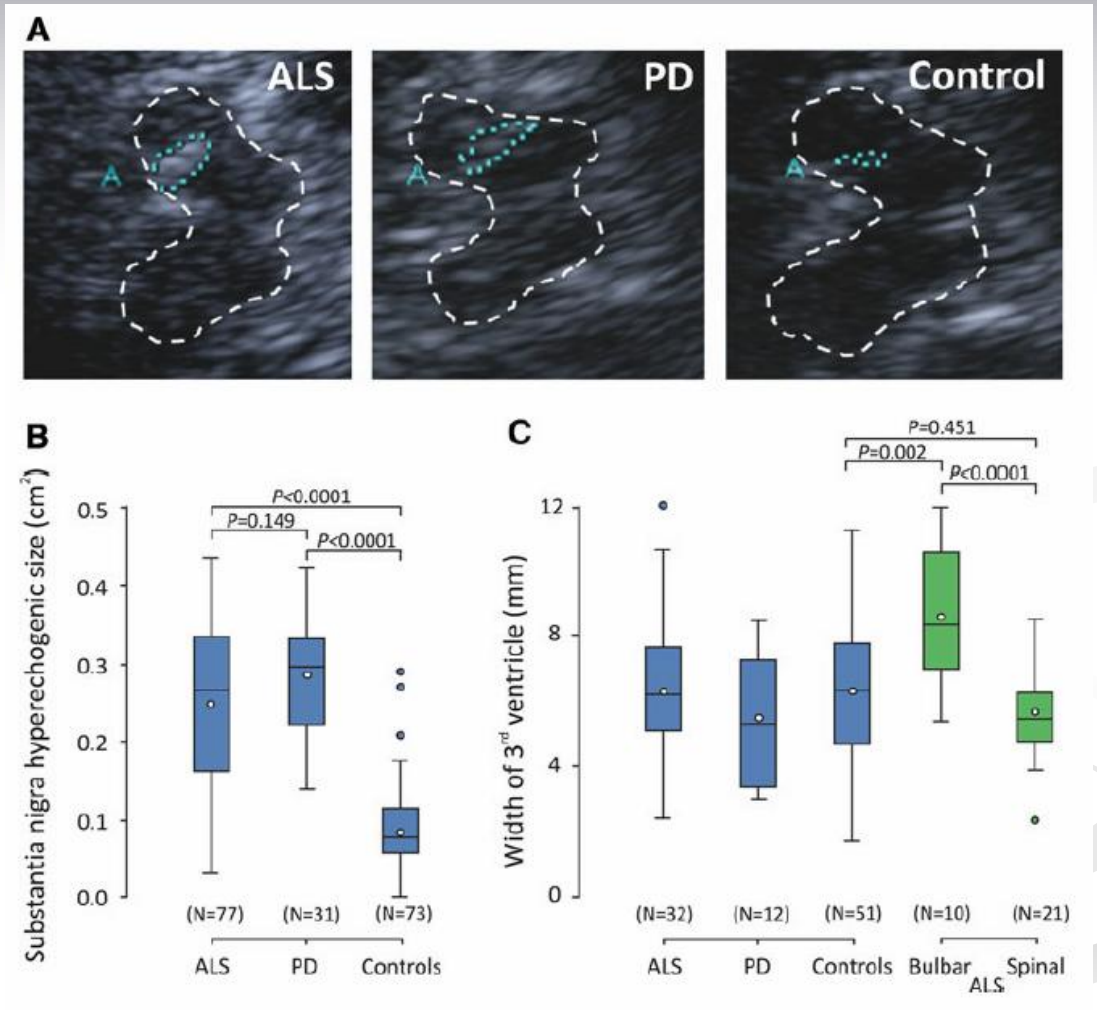
Pierrot-Deseilligny et al., Brain, 2003.

Microstimulation in the SEF changed monkeys' performance on a stop signal' task by delaying saccade initiation These results demonstrate that the supplementary eye field can exert contextual executive control over saccade generation.

Stuphorn, et al., Nature Neuroscience, 2006.

Parkinson's disease-like midbrain hyperechogenicity is frequent in amyotrophic lateral sclerosis

Panteha Fathinia · Andreas Hermann · Ulrike Reuner · Jan Kassubek · Alexander Storch · Albert C. Ludolph



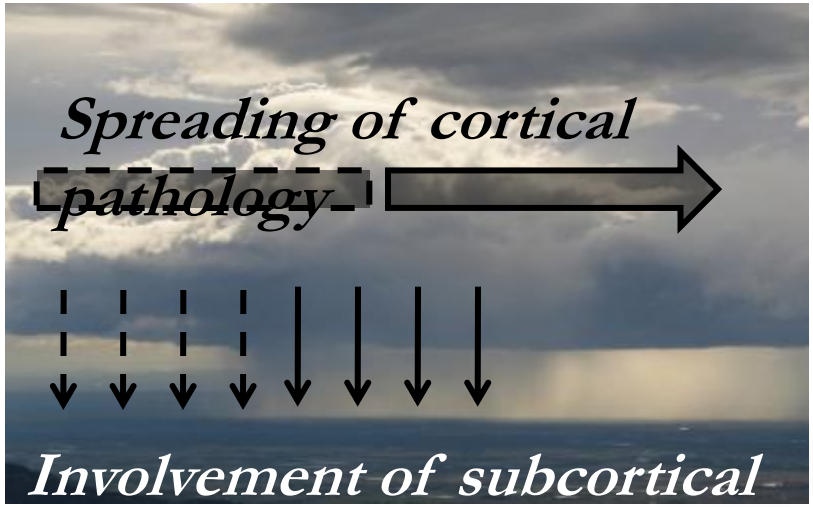
ALS starts focally and spreads continuuosly…

Neurons vulnerable to TDP-43 pathology (Braak et al., 2013)

Vulnerable subcortical neurons show strong and direct "monosynaptic" cortical input…

→ *The neurons which innnervate target structures are all glutamatergic*

→ *Is there an "All good things come from above"-principle in ALS?*



…neurons without direct cortical input are largely spared

- *locus coeruleus, raphe nuclei, ocular motor neurons…*

Specific muscle groups are more affected in ALS

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RKU

TESTING THE HYPOTHESIS – MONOSYNAPTIC CONNECTIONS

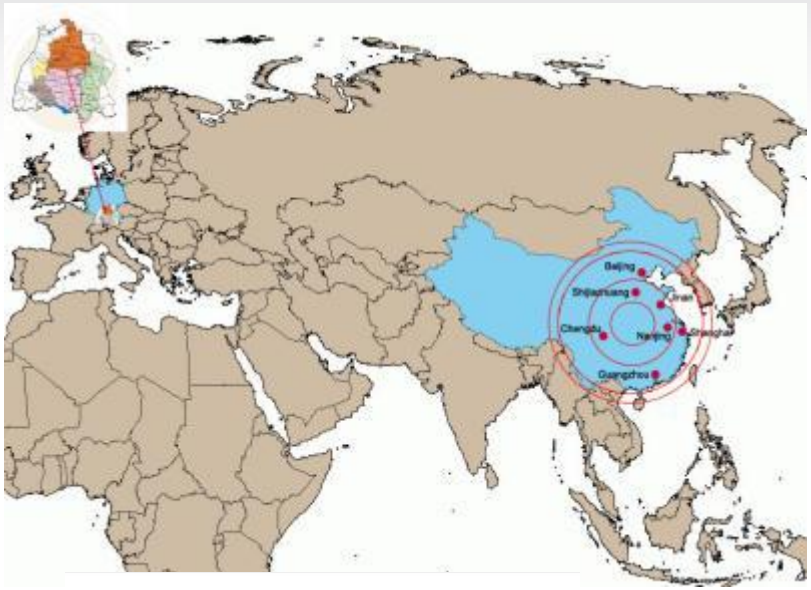
Monosynaptic pattern ?

965 retrospective patients

Biceps vs. Triceps	$p < 0.00001$
Hand extensors vs. flexors	$p < 0.000001$
Intrinsic hand musles vs. Triceps	$p < 0.00000001$
Foot extensors vs foot flexors	$p < 0.00001$

Clear evidence for a monosynaptic pattern

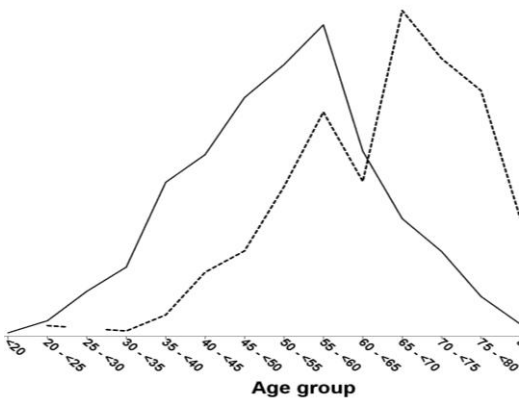
Are epidemiology and phenotype monomorphic in the world ? The example China (cooperation Prof. Cui Liying, Prof. Dongsheng Fan)



5 Chinese ALS Centers

614 vs. 680 patients

- *Incidence 1.8/100000*
- *Disease onset 51.1 (China) vs. 66.7 years*
- *M:F 1.3 vs. 1.7 (China)*
- *Bulbar Onset 19.5 %(China) vs. 32.7 %*



Age distribution

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Thank you for your attention.

Albert C. Ludolph