

# ALS Neuropathology and Spread: Synchronization, Desynchronization, and Saturation

VA National ALS Brain Bank Neuropathology Meeting  
Zoom  
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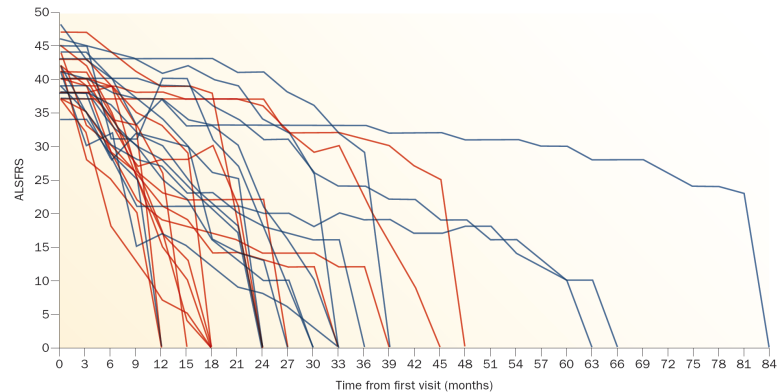
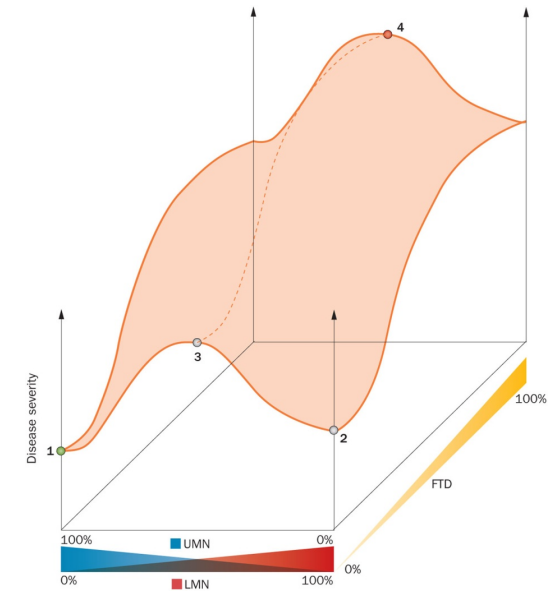
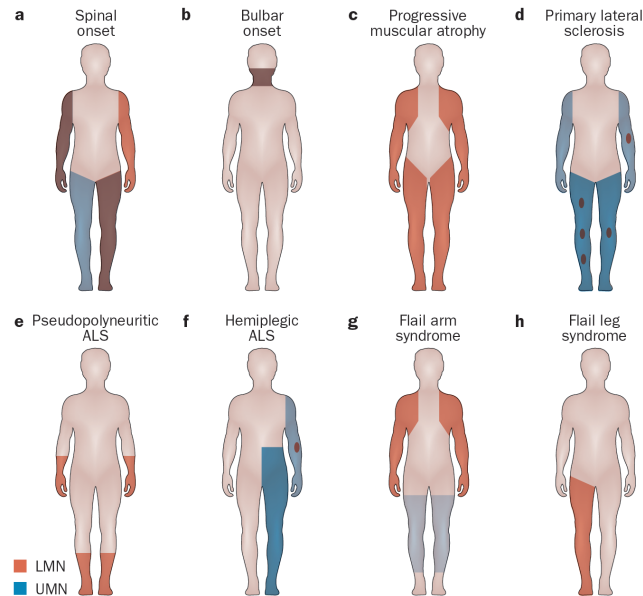
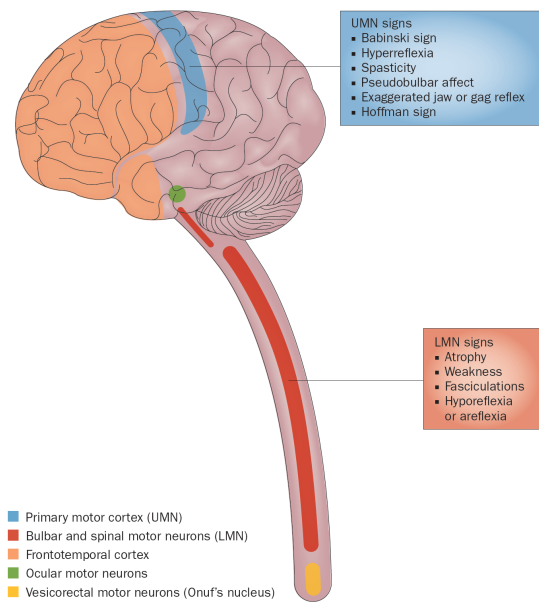
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SCHOOL OF MEDICINE

## Topics to be discussed

- Prime attributes of ALS onset and progression
  - Focality
  - Stochasticity
  - Neuroanatomic propagation (spread)
- Implications
- Respiratory constraints
- Implications of temporal-spatial summation
  - Neuropathology
  - Genomics

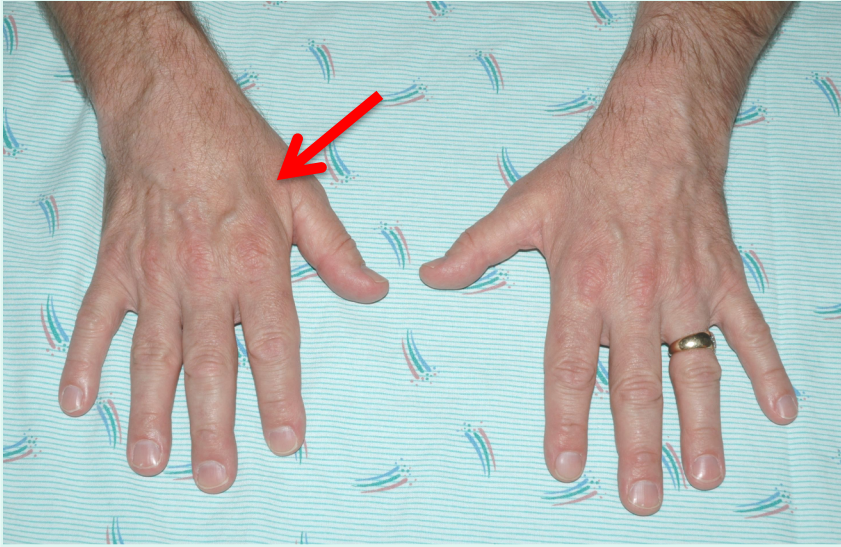
# ALS phenotypes: Continuous variation formalized in a scheme



Swinnen, B and Robberecht, W, Nature Reviews Neurology, 2014

53 year old male

Onset

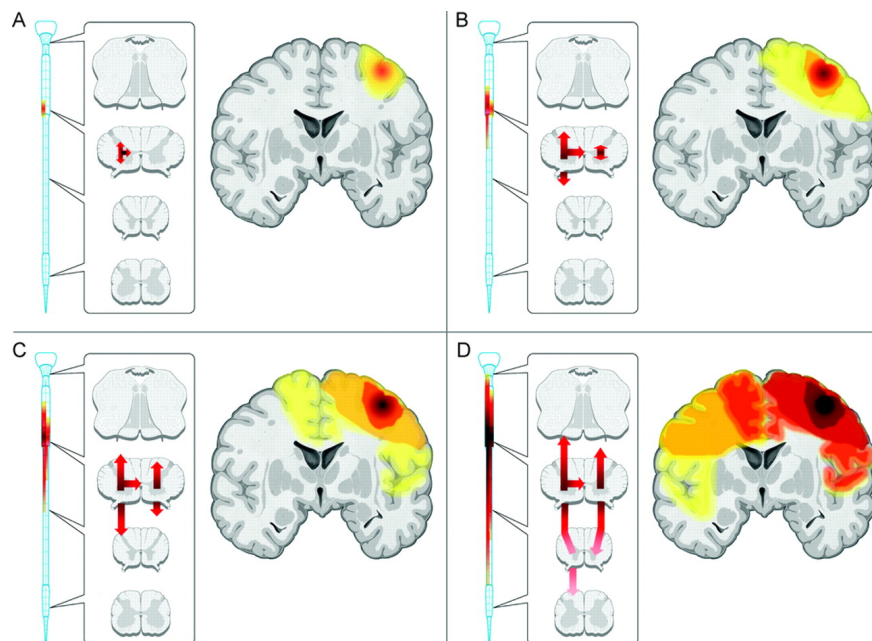


20 months later



# ALS focality, stochasticity and spread

## Spread



Ravits et al., 2009

Differences lead to “desynchronization”

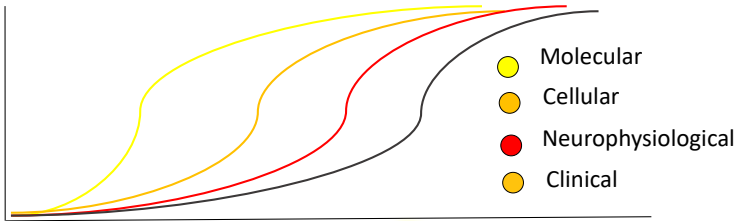
UMN & LMN contiguous  
UMN & LMN non-contiguous

## Prime determinants

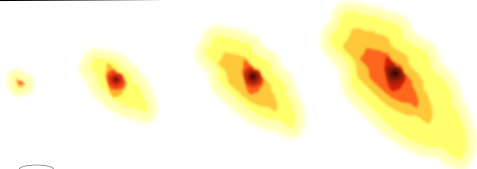
1. Focal
2. Stochastic
3. Converging network (hypocenter & epicenter)
4. Variably distributed between cortex (UMN) & spinal cord (LMN)
5. Contiguously and independently spreading
6. Variable kinetics



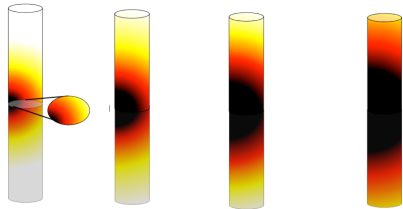
Time



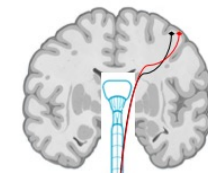
Space



Finite post-mitotic compartment with temporal-spatial summation



Ravits, Exp Neurol, 2014

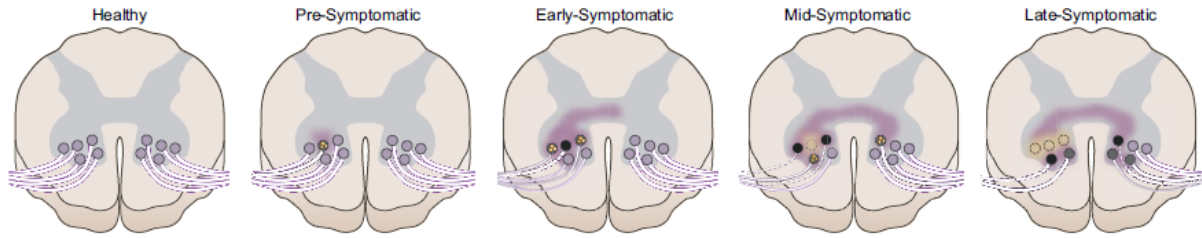
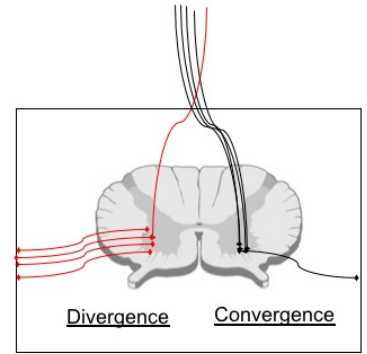


Contiguous Spread

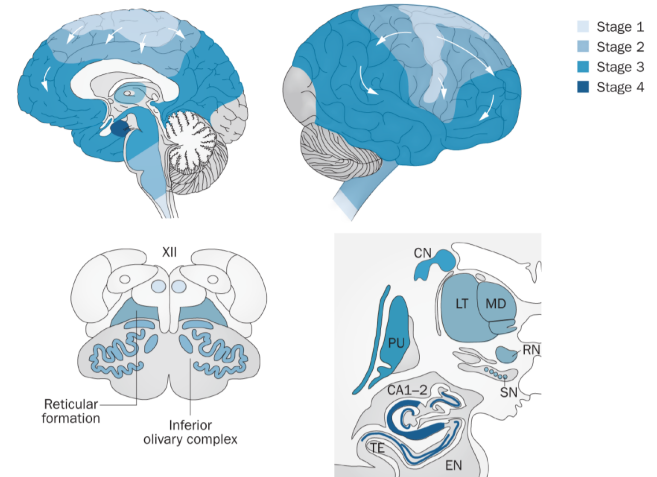
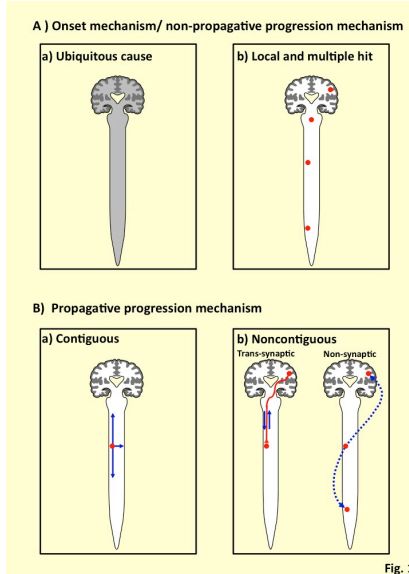
- Non-synaptic (side-to-side)
- Extracellular
- In parallel

Network Spread

- Trans-synaptic (end-to-end)
- Axonal
- In series

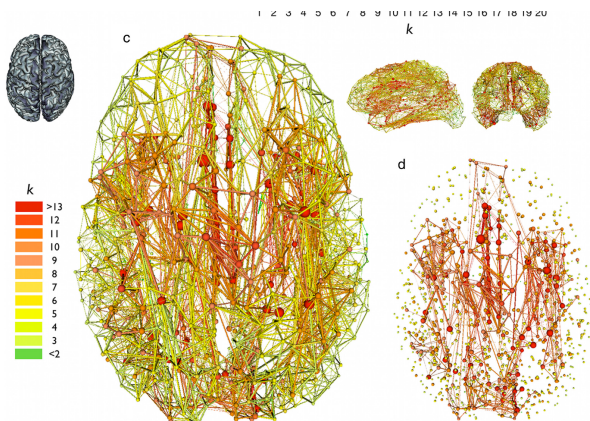


# Propagation in ALS: Alternative Models

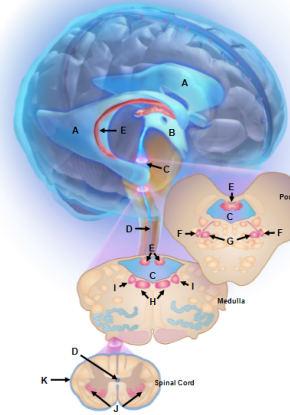


Braak H, Brettschneider et al, 2013

Kanouchi, Ohkubo, & Yokota, JNNP, 2012

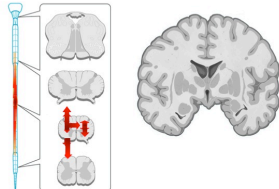


van den Heuvel et al, J Neurosci, 2011



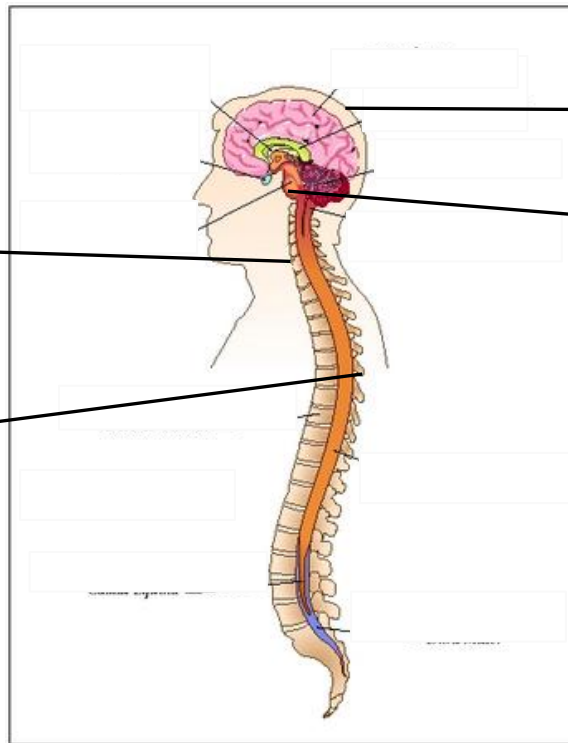
Smith RA et al, Medical Hypotheses, 2015

# Motor Anatomy of Respiration

ID	Clinical	Classification	Comment
<b>55M</b> <b>JM</b> <b>30106600</b>	Neck drop, shoulder/scapular weakness, and respiratory, ?FTD Onset: Sept, 2013 Exam: LMN>>UMN, ?FTD	Limb ALS (high cerv), phrenic LMN>>UMN, but FTD Course: >2 years FRS: 30/48 FVC: 27%	
<b>74M</b> <b>RB</b> <b>30121577</b>	Axial weakness, then generalizing incl. respiratory Onset: Nov, 2014 Exam: LMN>UMN, axial & abdominal	Thoracic onset, intercostals LMN>UMN Course: Dead at 1 yr FVC: 50% at 9 months, 0% at 12 mos	

Diaphragm muscle  
 Phrenic nerve  
 C3-5

Intercostal muscles  
 Intercostal nerves  
 T1-12



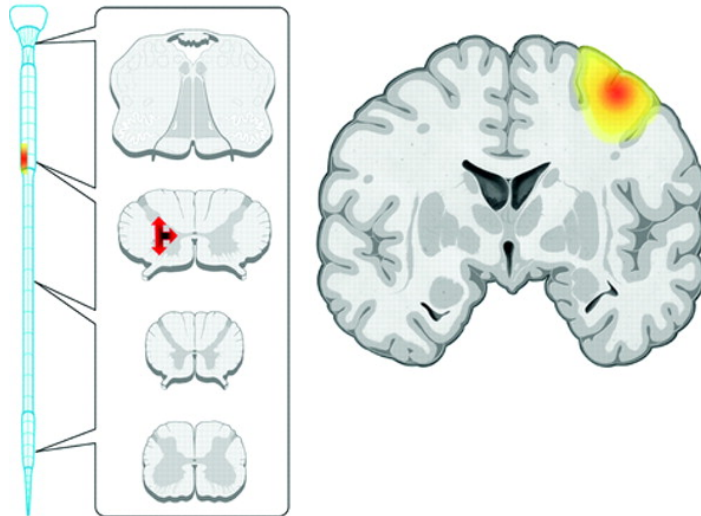
UMN

Regulatory

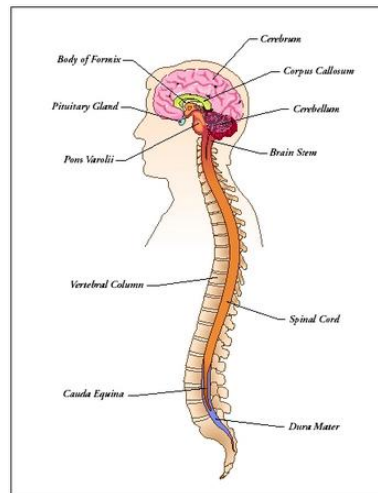
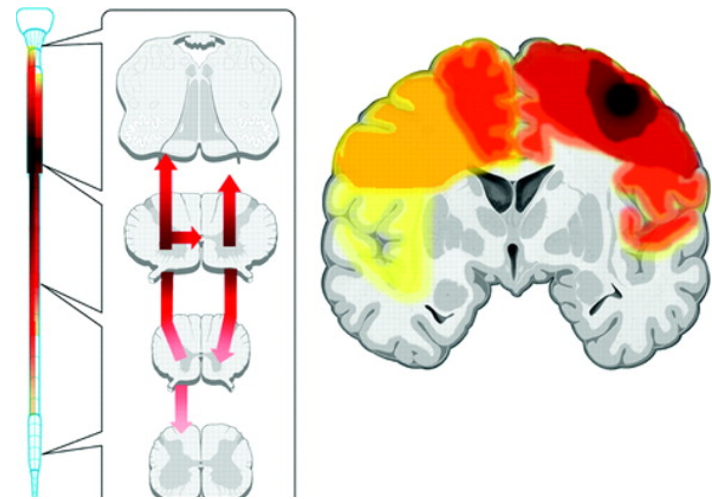


# ALS: Early vs Late Stages

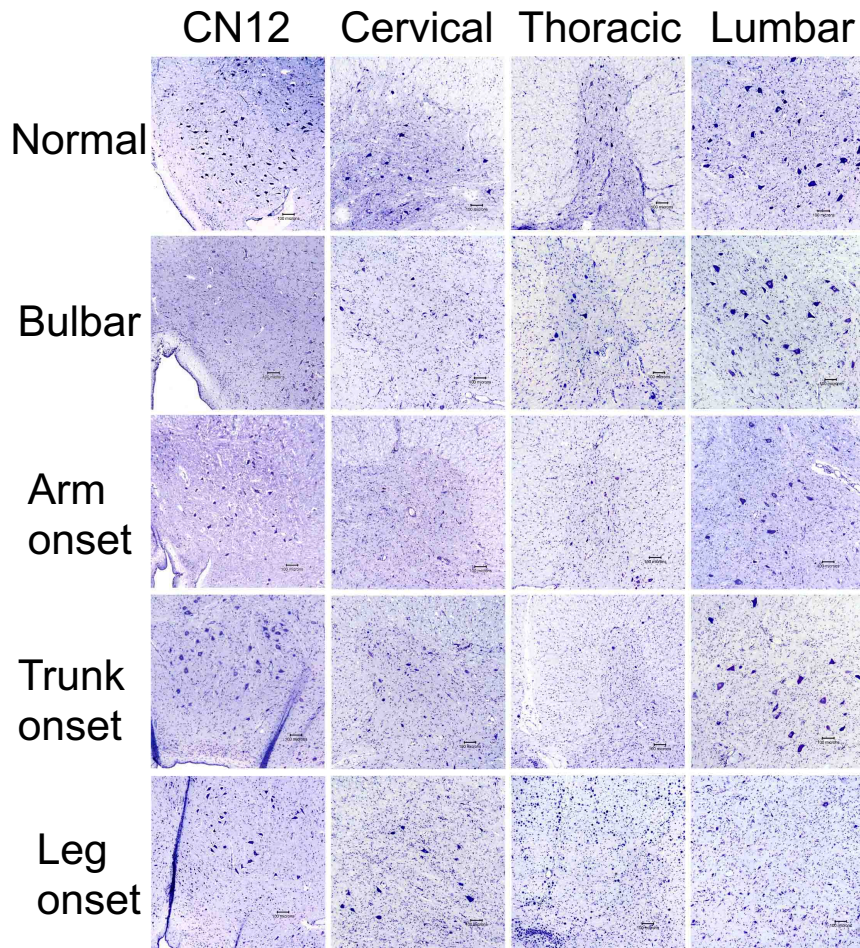
Clinical onset



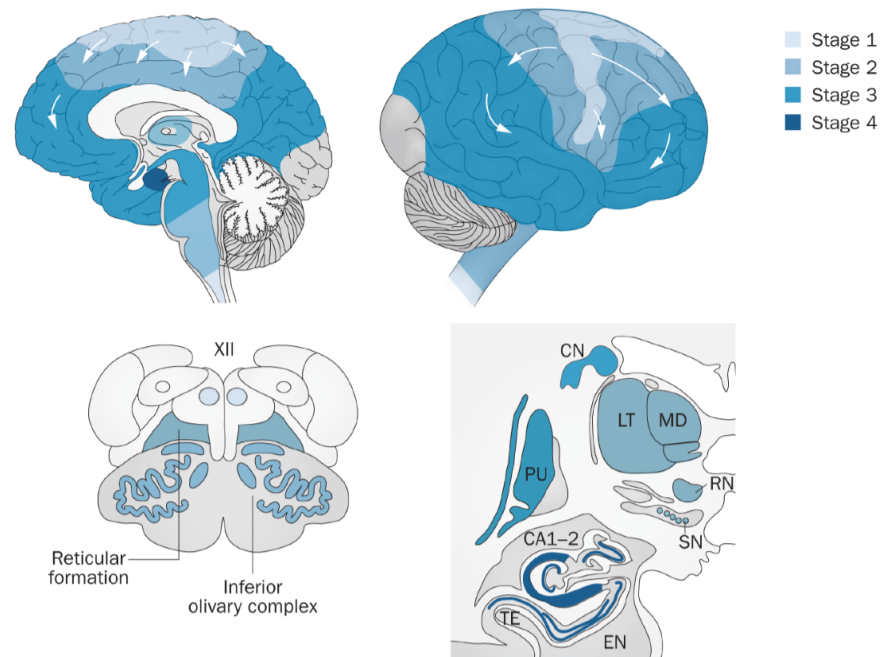
“End-stage neuropathology”



# Neuropathological staging is *relative*



Ravits et al, Neurology, 2007b



Braak H et al, 2013; Brettschneider J et al, 2013