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Primary Endpoints in “Alzheimer’s Dementia”

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Critique on Regulatory Decisions in Dementia

- **Trend to question the clinical relevance of improvement shown with AchEI and Memantine**
  - **All studies methodological flawed**
    - **Assessment tools**
    - **Endpoints**
    - **Drop outs/missing data**
    - **Statistical evaluation**
  - **Overestimation of effects of active treatment**
  - **Despite of these limitations treatment effects are small and not clinically meaningful**
  - **Long-term safety issues**

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Possible Cornerstones in the Treatment of Patients with Dementia

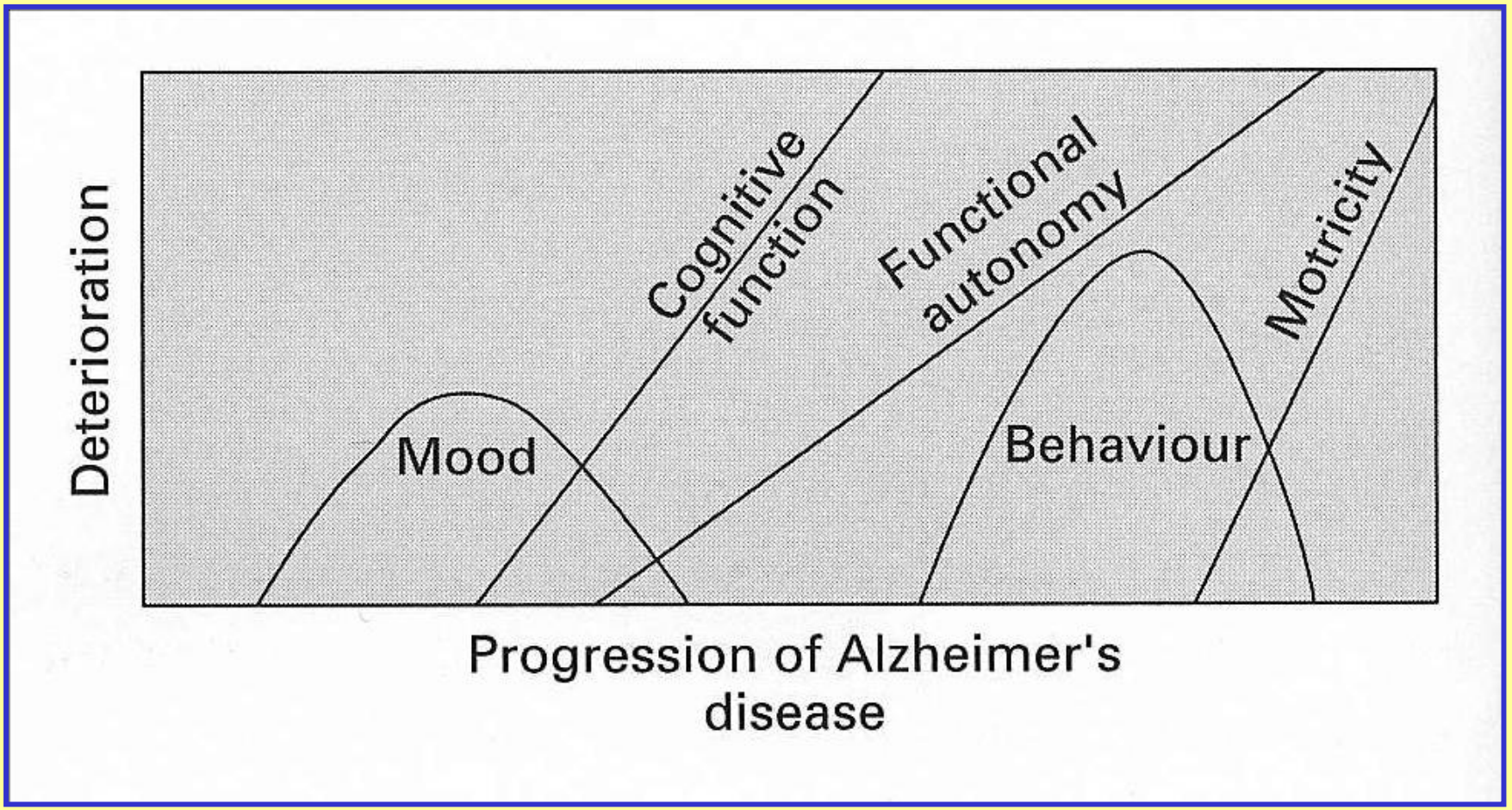
- **NfG on Medicinal Products for Treatment of Alzheimer‘s Disease**
  - **Symptomatic Improvement**
  - **Slowing or arrest of progression**
  - **Primary prevention**

NEW: http://www.emea.europa.eu

Clinical Milestones in Alzheimer‘s Disease

- Emergence of cognitive symptoms
- Conversion from amnestic MCI/preclinical dementia to diagnosable dementia
- Loss of „instrumental acitivities of daily living“
- Further deterioration in cognitive and functional domains to worse than expected
- Emergence of behavioural abnormalities
- Nursing home placement
- Loss of self-care ADL
- Death

Disease Course and Symptoms in the different domains

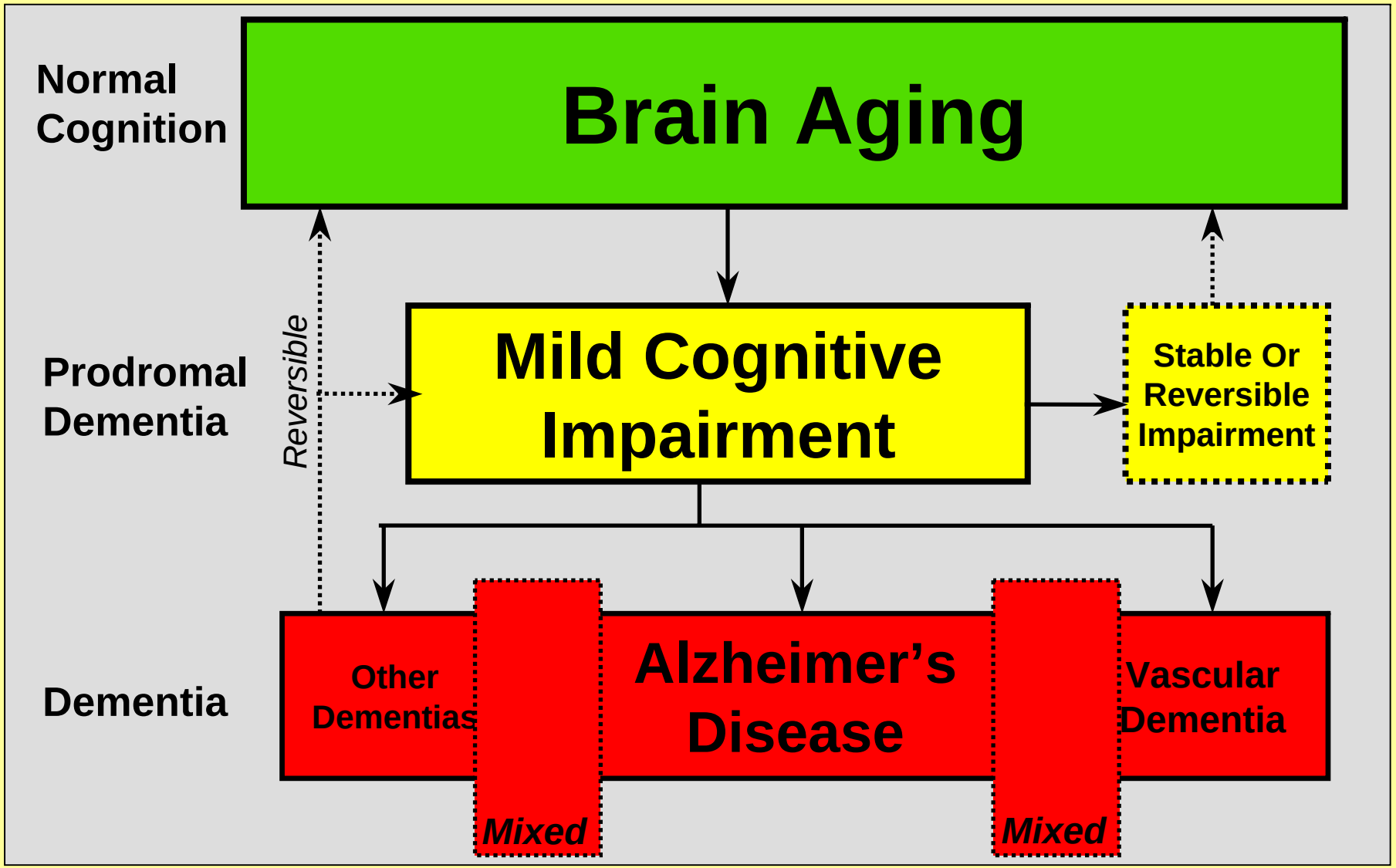


modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.38

Which population do we study ?

- **Diagnostic criteria**
  - MCI / aMCI / preclinical DAT / prodromal DAT
  - DAT
- **Severity**
  - Mild
  - Moderate
  - Severe
- **Study design**
  - Assessment tools
  - Domains of assessment
  - Duration of trials
  - Placebo/active comparator/add-on
  - Statistical evaluation
  - Clinical relevance

MCI is Prodromal Dementia ?



Clinical Heterogeneity of MCI

MCI
Amnestic

→ **Alzheimer's disease**

MCI
Single non-memory domain or Multiple domains slightly impaired

→ **Normal Aging**
Alzheimer's disease
Vascular dementia
Frontotemporal dementia
Lewy body dementia
Primary progressive aphasia
Parkinson's disease

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Revision of Diagnostic Criteria
Dubois B, Feldman HH, Jucova C et al. 2007

- **Core diagnostic Criterion:**
  Early and significant episodic memory impairment
- **At least one supportive criterion of**
  - **MTL atrophy shown with MRI**
  - **Abnormal CSF (amyloid-ß, tau, phospho-tau)**
  - **Specific pattern shown with PET**
  - **Proven DAT mutation**
- **Validation studies necessary !!!**

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Revision of the Guidance Document

- will address different types of dementia
- differences in severity
  - MCI/preclinical/prodromal/very mild
  - mild
  - moderate
  - severe
- disease modification
- discussion on biomarkers as surrogate endpoints
- discussion on adequate study designs

Alzheimer's Disease: Efficacy (Symptomatic Improvement)

- 2 primary Endpoints
  - mandatory: **cognitive** domain
    functional domain
  - both endpoints should show significant differences
- Response criteria for clinical relevance: proportion of patients with meaningful benefit ?
- Duration of treatment: at least 6 months
- secondary endpoints
  - global domain
  - additional symptoms

Scales used in Clinical Trials

- ***Cognition***
  - ADAScog
  - Neuropsychological Test Battery (NTB)
  - Severe Impairment Battery (SIB)
- ***Functional***
  - Alzheimer Disease Cooperative Study ADL Scale (ADCS-ADL)
  - Alzheimer‘s Disease Functional Assessment and Change Scale (ADFACS)
  - Disability Scale in Dementia (DAD)
  - Nurses Observation Scale for Geriatric Patients (NOSGER)
- ***Global***
  - CIBIC-plus

Assessment of overall benefit

- **Response-Criteria:**

  e.g.. ADAScog ≥ 4 + Score ≤ 3 of CIBIC + no change in DAD

- **Effect size**

- **Numbers Needed to Treat**

  (e.g. patients showing improvement of ADAScog ≥ 4)

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Alzheimer's Disease:
Efficacy (Disease Modification)

- 2 primary Endpoints
  - mandatory: **cognitive** domain
  - **functional** domain
  - both endpoints should show significant differences

- Response criteria for clinical relevance: proportion of patients with meaningful benefit ?

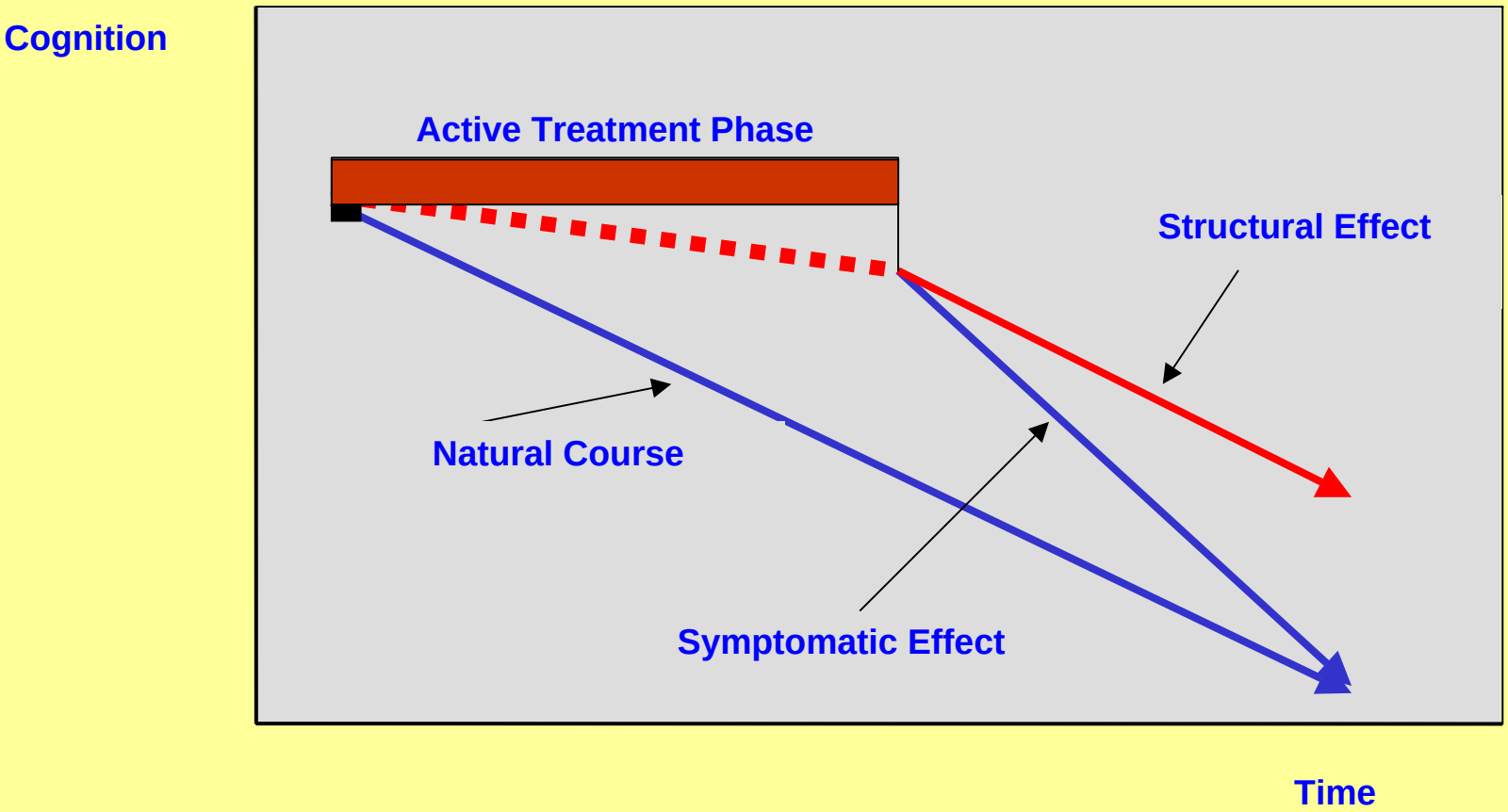
- Duration of treatment: 18 months (?)

- secondary endpoints
  - global domain
  - Biomarkers
    - **e.g. serial volumetric MRI**
  - Quality of Life
  - additional symptoms

Design Issues

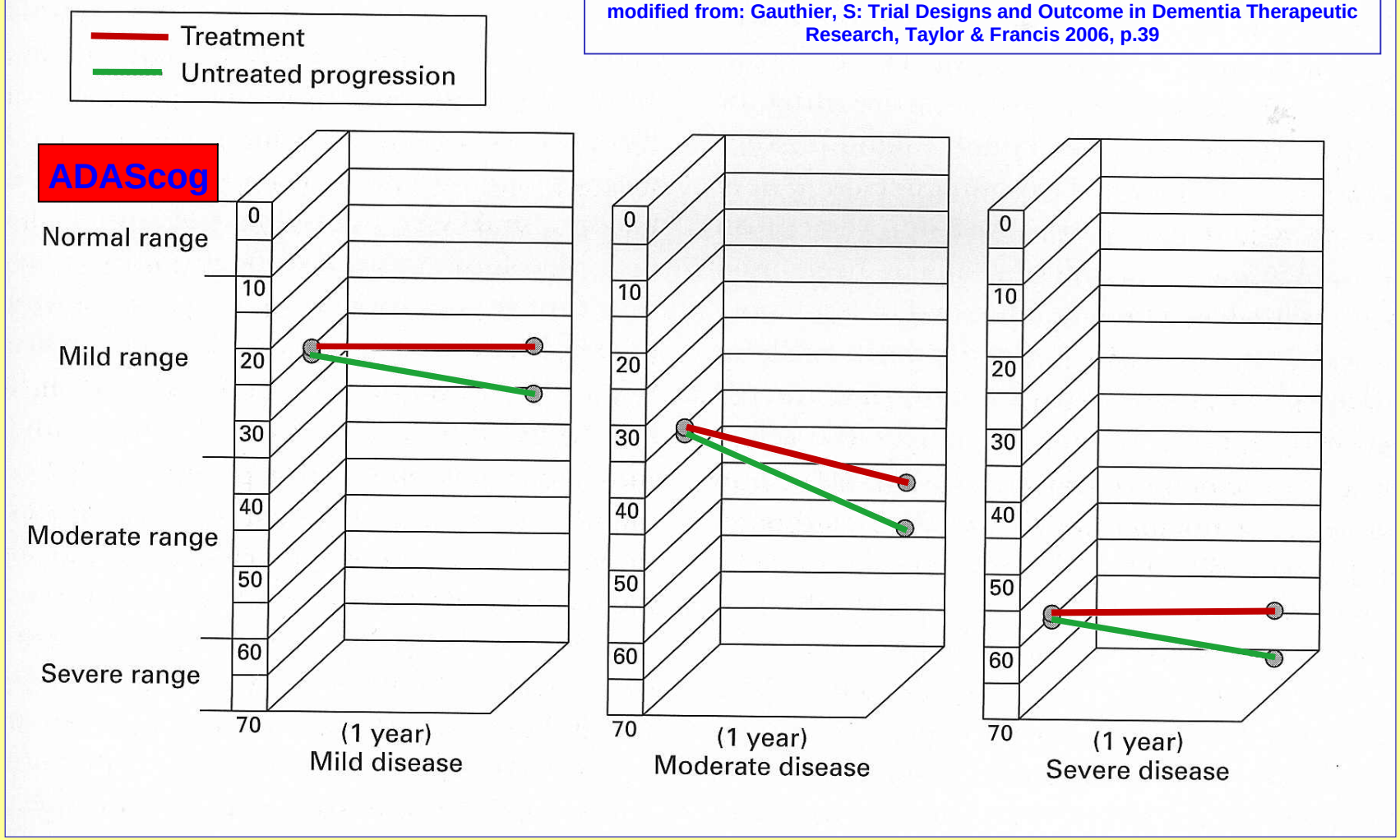
- study population/add-on populations
- study duration
- which type of endpoints
- type of analysis
  - slope analysis
  - survival analysis
  - randomized start designs /randomized withdrawal
  - missing data/drop outs/LOCF
- valid and reliable scales

„Randomized withdrawal design“

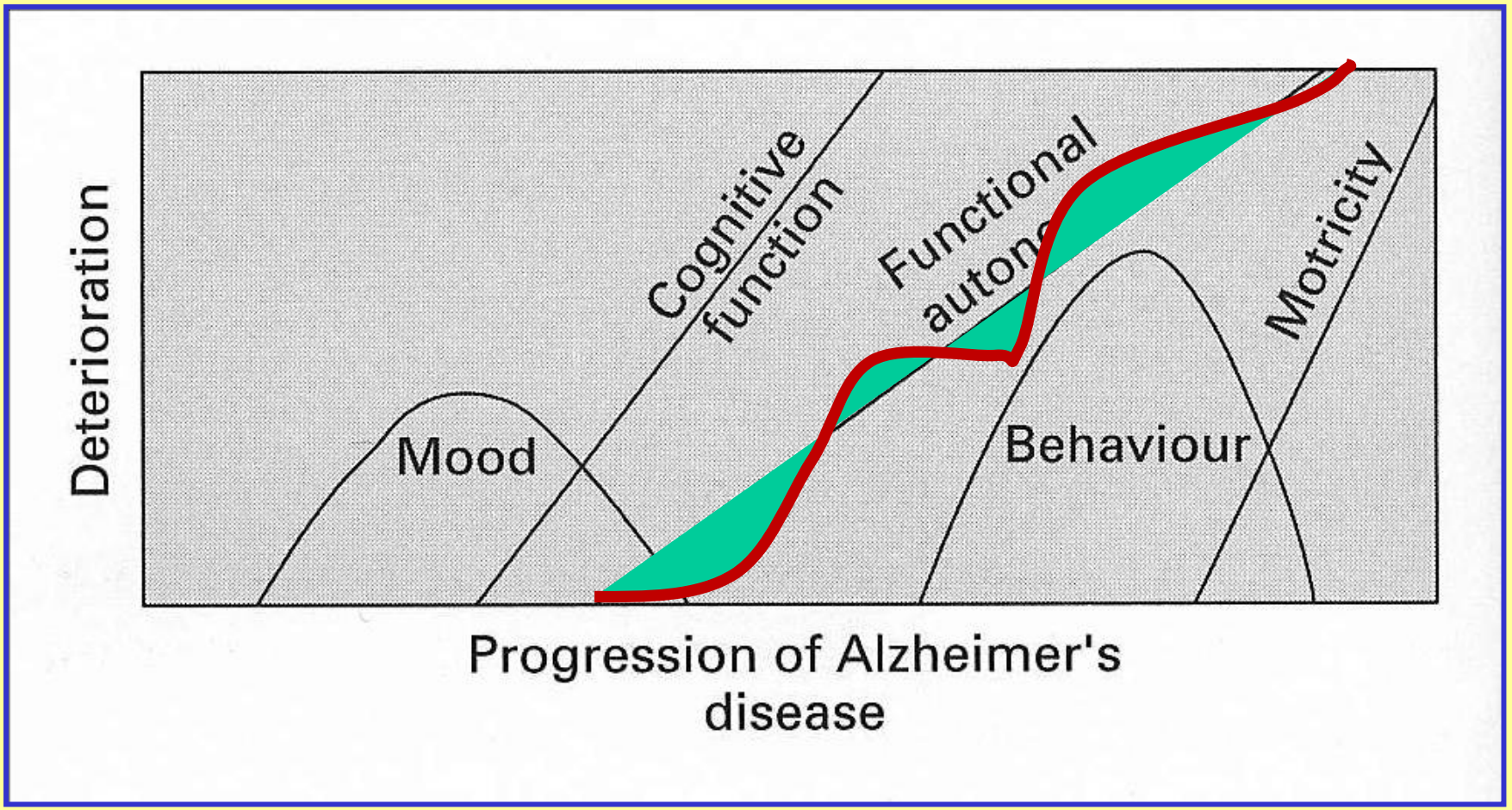


Deterioration in Cognition in different stages of Disease Severity

modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.39



Disease Course and Symptoms in the different domains



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Biomarkers can be used as tools to

- Understand the biology of a disease
- Understand the effects of medicinal products
- Provide information on sub-populations of patients that might respond to treatment or be susceptible to side effects (individualized medicine)
- Developing better diagnostics and medicinal products
- Improve methodology of clinical trials

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Primary Endpoints in Clinical Trials

- **Clinical Endpoints of interest may be difficult to use**
  - **Long follow-up measurement**
  - **Expensive measurements**
  - **Rare events**

- **Surrogate (replacement) Endpoint**
  - **Easier/quicker to measure**
  - **Reduce trial duration, size and expenditures**
  - **Should be measured accurately and reproducible**
  - **Change in proportion to what it represents**

- ***Common Misunderstanding: correlation between outcome and clinical endpoint reflects not a valid surrogate***

Ideal Surrogate Endpoints (1)

Temple R, JAMA, 1999

- …endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinical meaningful endpoint that measures directly how a patient feels, functions or survives

- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint

Ideal Surrogate Endpoints (2)

Fleming TR, Ann Int Med, 1996

- …proposed surrogate endpoint must ***not merely be a correlate*** of the true clinical outcome
- effect of intervention on a ***valid*** surrogate endpoint must reliably predict the effect on a clinical outcome of interest
- treatment effect on the clinical outcome should be explained by its effect on the surrogate marker

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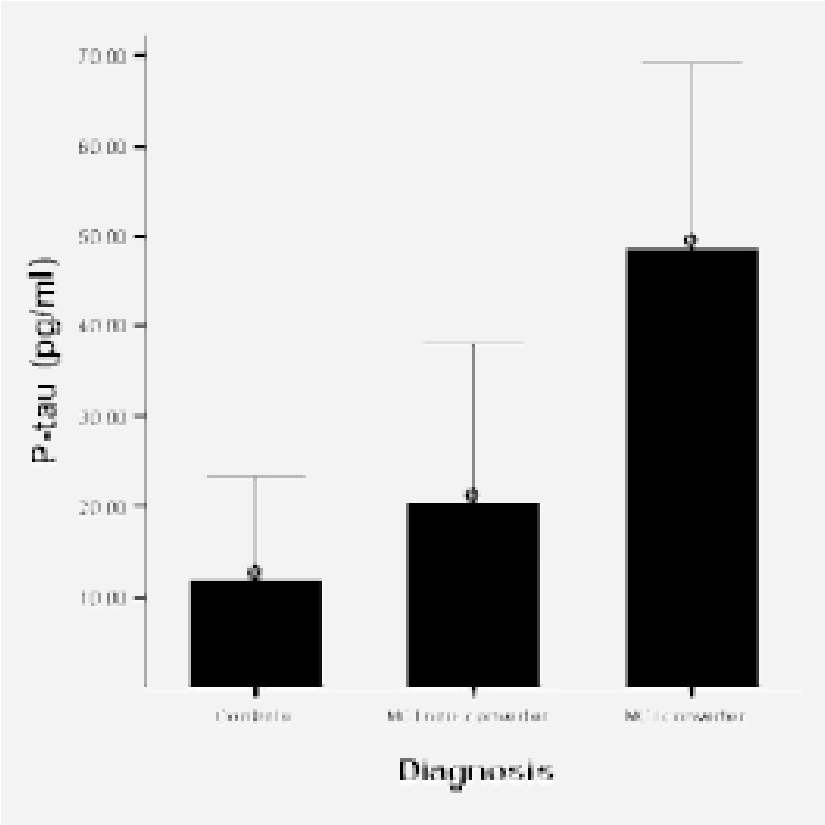
Questions on Surrogate Markers in Dementia

- for which clinical outcome the biomarker is used ?
- does the biomarker reliably predict the clinical outcome ?
- does the biomarker reflect effects on pathology and/or pathophysiology for a claim of disease modification ?
- are the effects seen in the biomarkers clinically relevant ?
- allow results seen short-term generalization to long-term ?

phospho-tau and MCI

Figure 1 Mean levels of p-tau$_{231}$ for healthy controls, mild cognitive impairment (MCI) nonconverters, and MCI converters at baseline



from:

Ewers M et al.

Neurology, 69, 2205-2212 (2007)

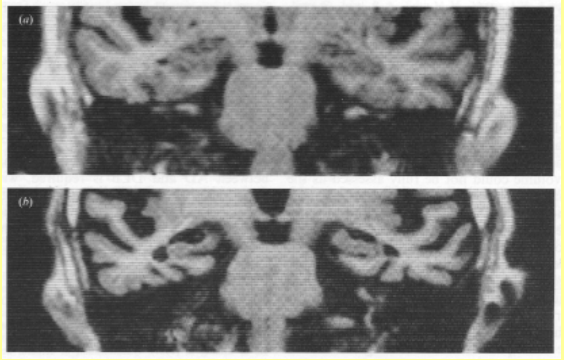
A priori cut off point:

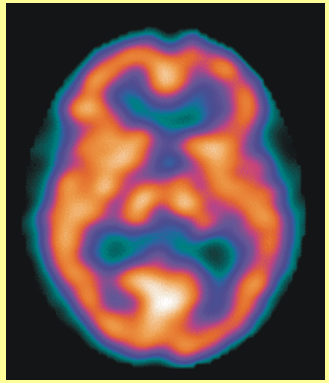
27,32pg/ml

Centers: München, Heidelberg, Amsterdam, Pitea

Surrogate Endpoints: Neuroimaging

- **Structural MRI**
  - **Hippocampus**
  - **Entorhinal cortex**
- **Functional Imaging**
  - **PET/SPECT**
  - **MRS**
  - **fMRI**





- **Links need to be established:**
  - **Imaging tool and desired clinical outcome**
  - **Imaging tool and disease modification**

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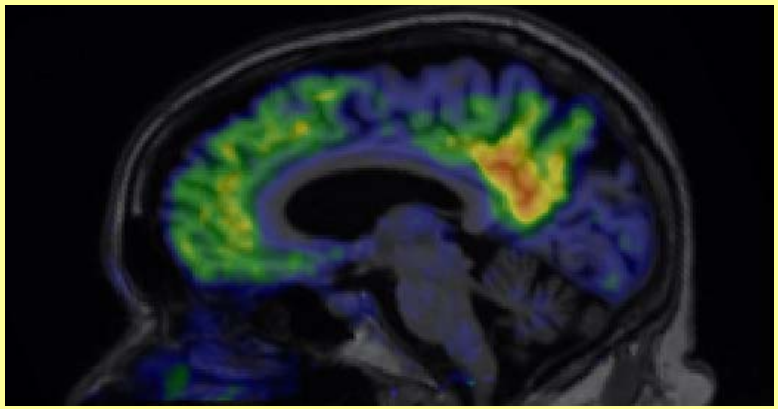
A new PET ligand for drug development in AD

- **PET radioligand [^{11}C]xyz**** for amyloid quantification**
- **Highly specific and reversible binding**
- **Early diagnosis and patient selection**
- **Confirm amyloid-lowering therapies at a biochemical level in man**



AD Patient

Cooperation Pharmaceutical Industry-Academic PET-Centers

Open Regulatory Issues

- **Study population / add-on populations**
  - Diagnostic criteria
    - Subtypes of dementia
    - Level of severity and impairment
  - Placebo / active control
- **Study design**
  - Which type of endpoints
    - Valid and reliable scales
    - Time to progression of ?
  - study duration
  - type of analysis
    - slope analysis
    - survival analysis
    - Randomized start designs /randomized withdrawal
    - missing data / drop outs / LOCF