„6 years follow-up of attentional and cognitive functions in early relapsing-remitting multiple sclerosis (RRMS) patients

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Background

Long-term investigations of cognitive disorders in MS are important because …

- Cognitive deficits in MS are correlated with **clinical progression, poorer quality of life** and **reduced social status.**

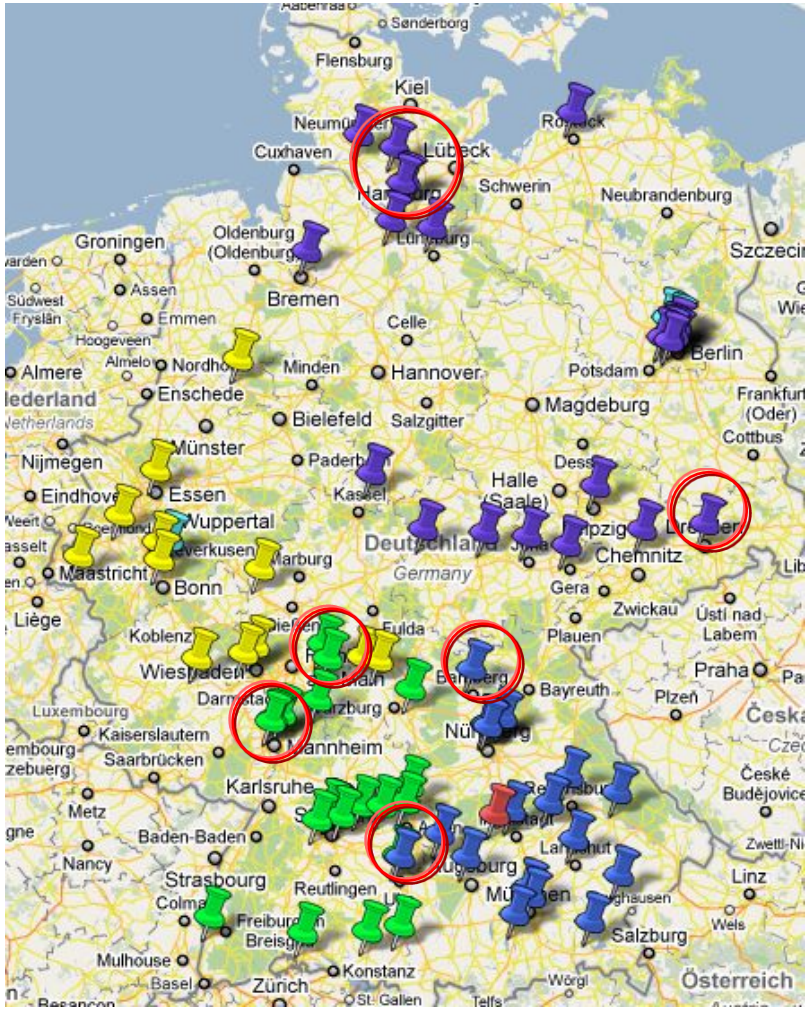
- **Long-term evolution** of cognition in MS is not well understood. Data from follow-up observations are limited. It remains to be clarified

  - to what extent cognitive decline occurs
  - at which stages and at which pace it occurs
  - what is the relation of cognitive to physical (motor/coordinative) decline
  - Which are the vulnerable patient subgroups
  - which cognitive functions are most vulnerable in the long run
  - which is the real effect of immune-therapy on cognition

Aim of study

- (1) to determine a cross-sectional profile of attentional and fronto-temporal cognitive functions in patients with early RRMS in a community-based environment
- (2) to observe the evolution of cognition over time in RRMS in comparison to healthy controls and in-between RRMS subgroups (DMT-treated vs untreated)
- (3) to specify the impact of disease evolution on cognitive subdomains (domain-specific vulnerability?)
- (4) to assess the influence of potential behavioral covariates on cognition, esp. depression and fatigue.

Study Organisation



78 NTD Centers in Germany
6 NTD centers collaborating in the study

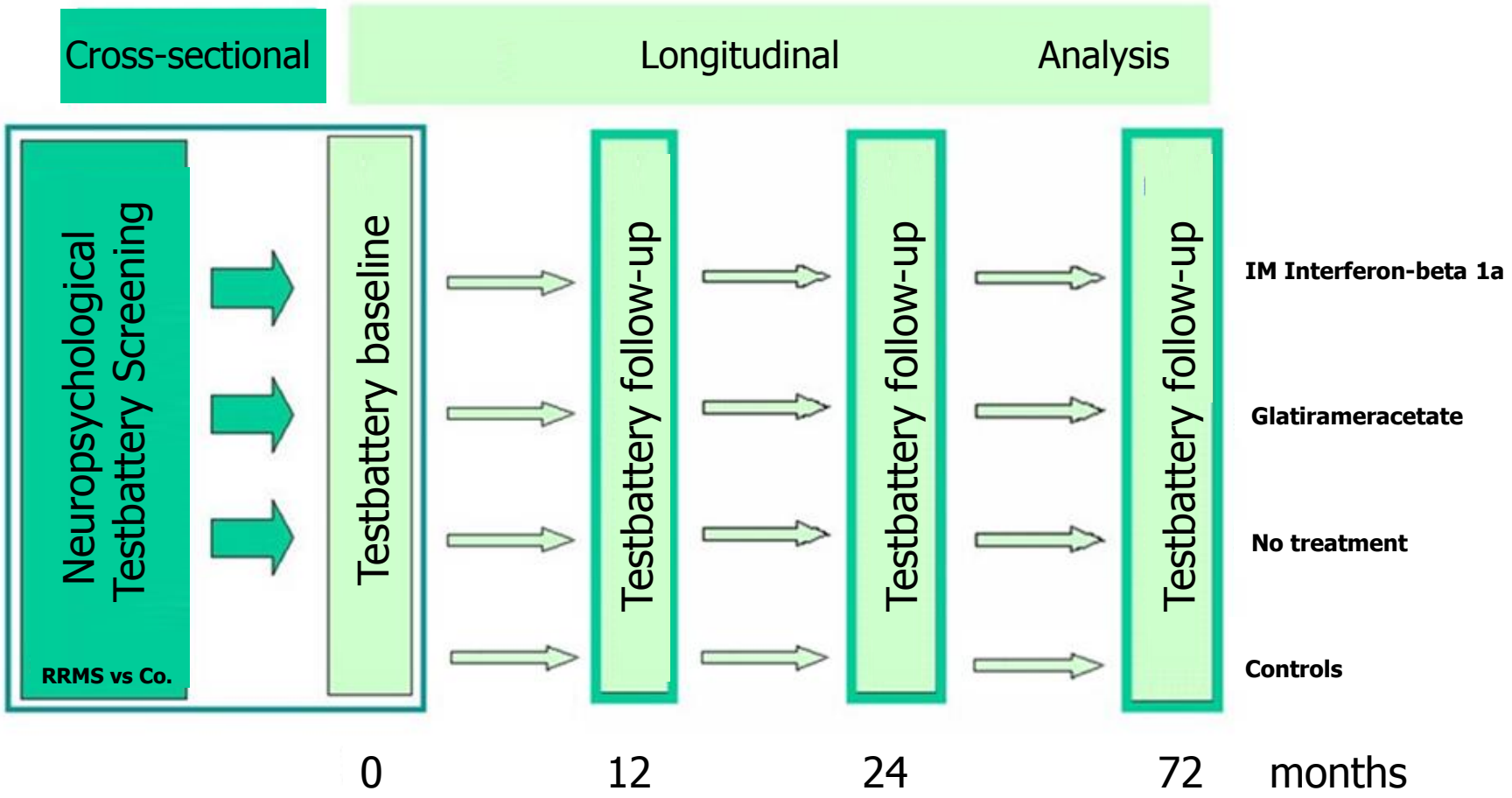
- **Inclusion criteria**
  - 18-55 yr
  - RRMS/Mc Donald on DMTs (GLAT/IM INFβ-1a)
  - EDSS 0-3.0
  - Disease duration <3yr
  - Controls (healthy or entrapment syndromes), no analgesics
  - No drugs qualified to compromise cognitive performance
- **Exclusion criteria**
  - DMTs changed to escalation therapy
  - Untreated patients starting therapy

Disease activity in RRMS subgroups

Selected parameters of disease activity at baseline (T0)

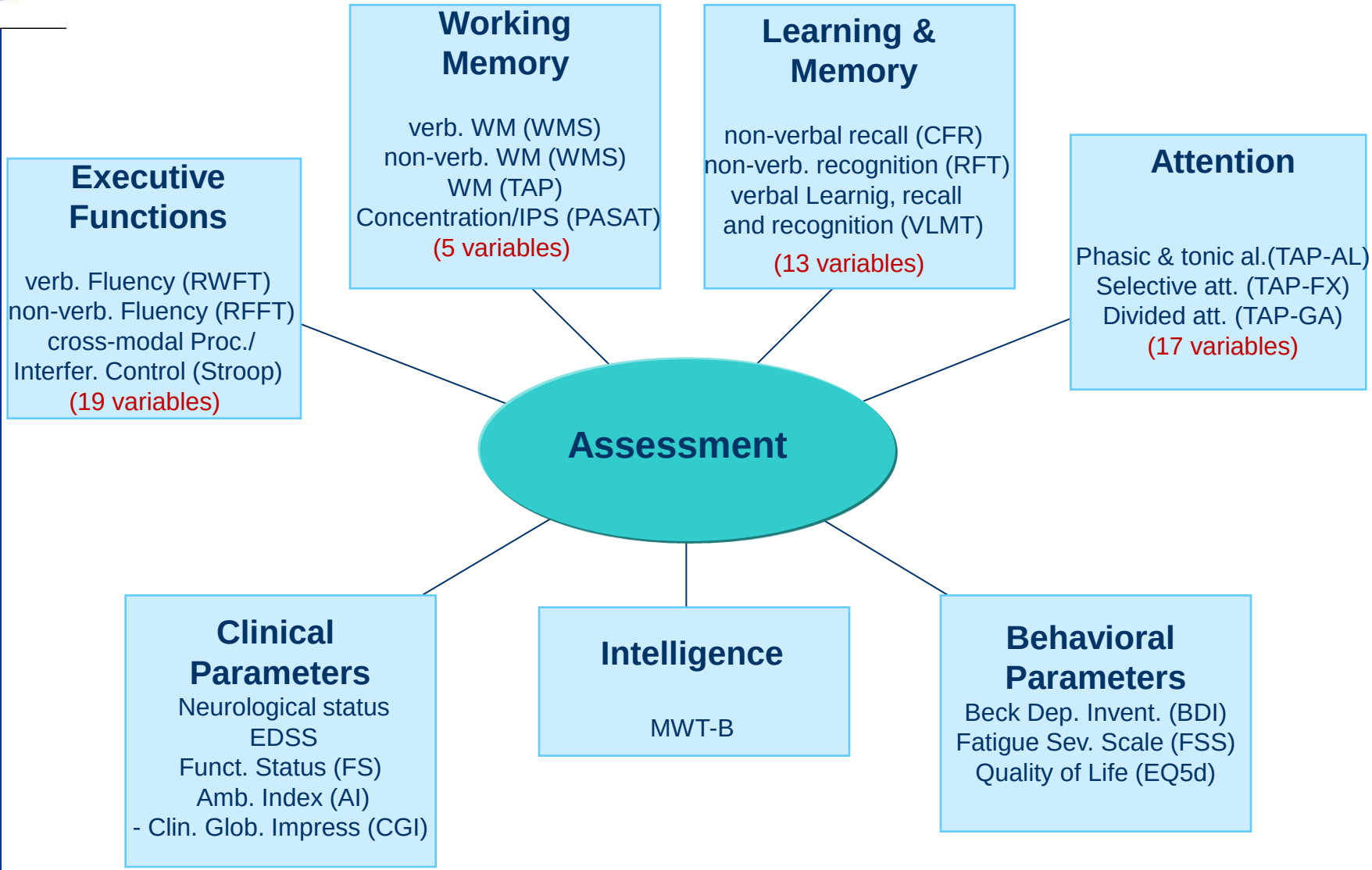
Baseline (T0)	**GLAT Mean** (SD)	**IM INFβ-1a Mean** (SD)	**Untreated Mean** (SD)
relapses	**2,9** (1,5)	**2,5** (1,2)	**2,5** (1,0)
Disease duration	**2,1** (1,4)	**2,2** (1,5)	**2,2** (1,4)
ARR ARR (T72)	**1,38 (0.48)**	**1,13 (0.48)**	**1,13 (0.29)**

Study design

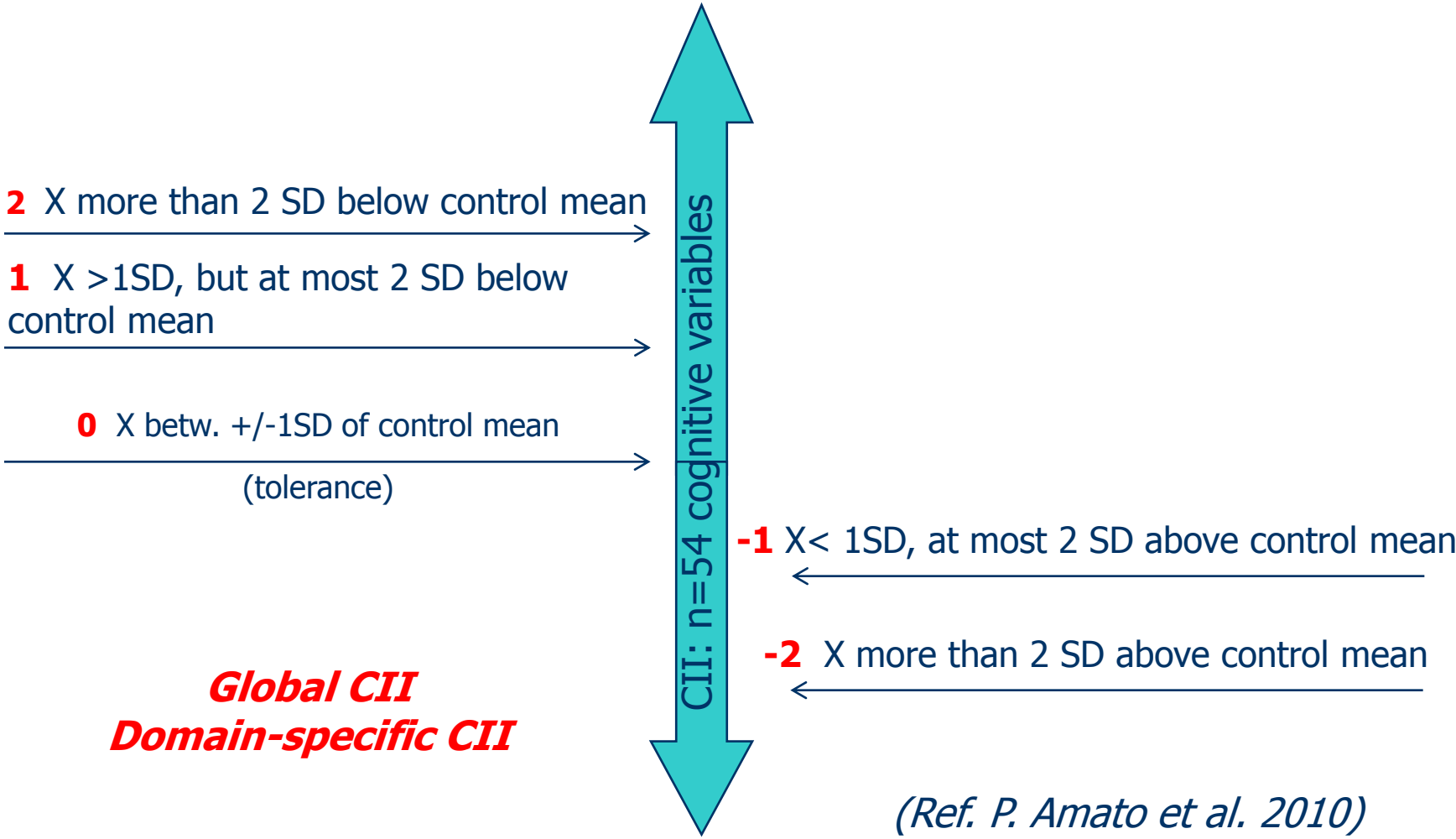


Data Profile

Neuropsychological, clinical and behavioral parameters



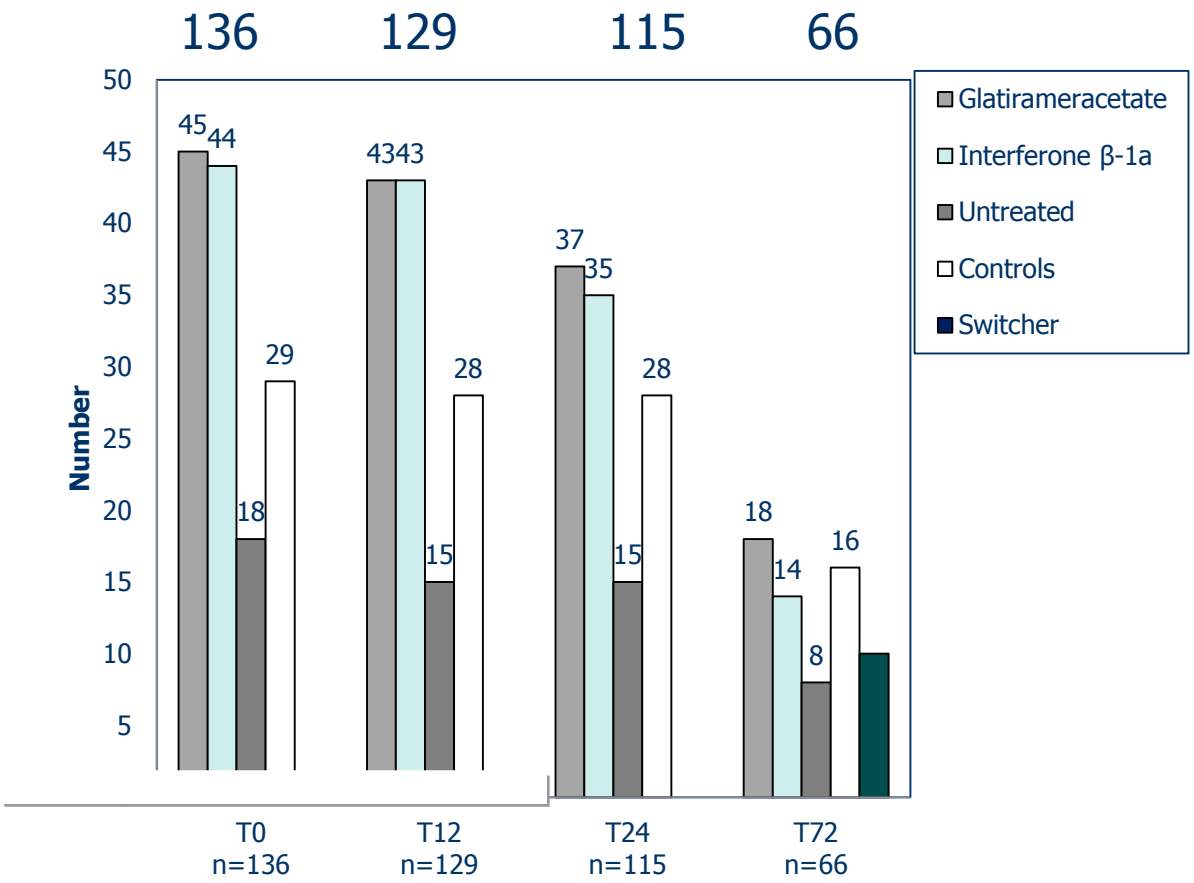
Cognitive Impairment Index (CII) Definition



Global CII
Domain-specific CII

(Ref. P. Amato et al. 2010)

Study recruitment over 6 years

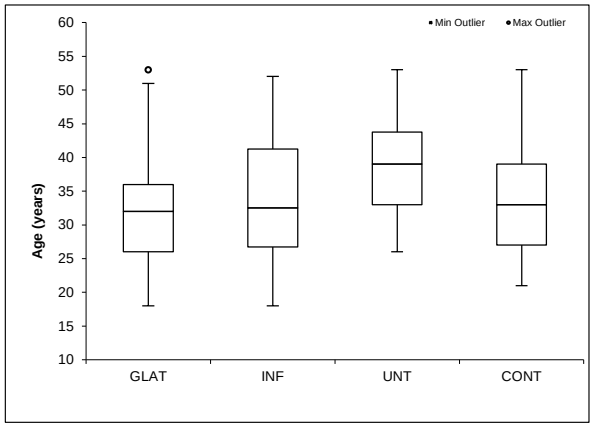


Recruitment of patients acc. to subgroups

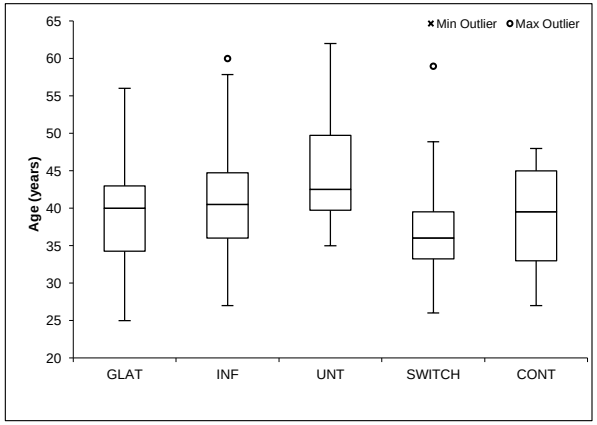
Matching of age, IQ and education

Matching of age

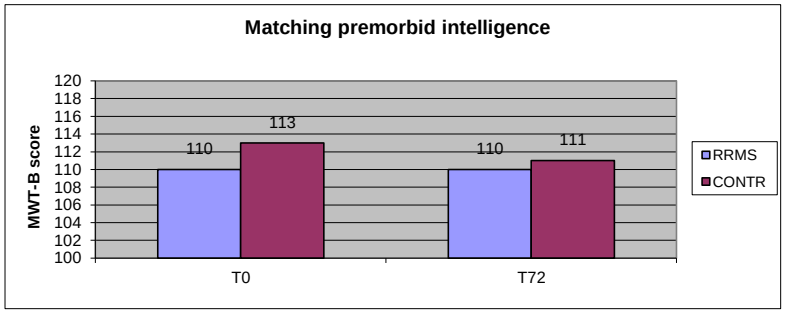
T0

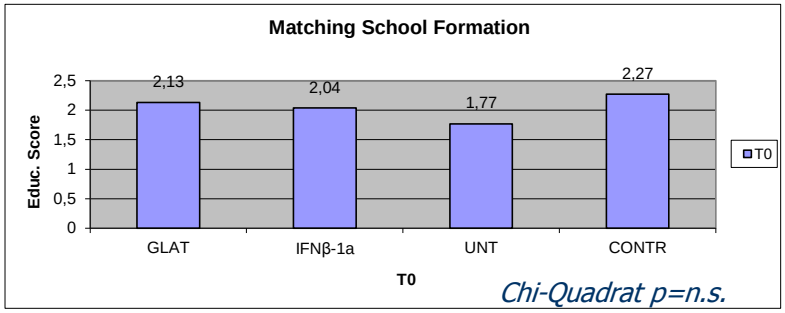


T72



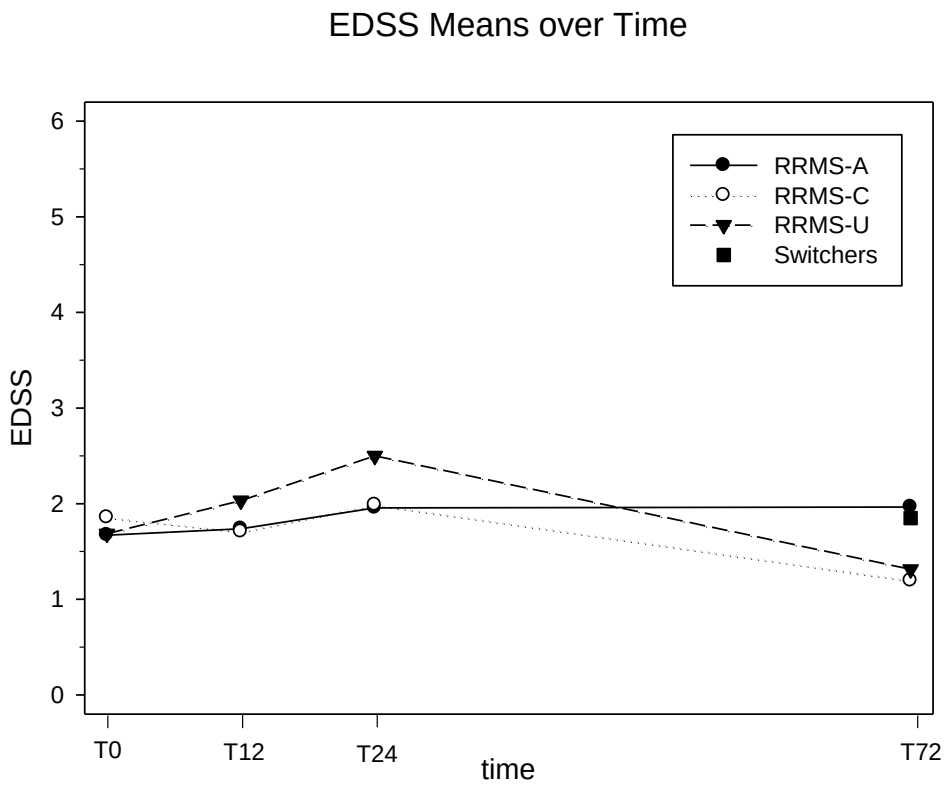
Matching of IQ and education (Baseline)





scored according to the 3 levels of the German school system at T0
(1=primary school, 2=secondary school, 3=grammar school/college)

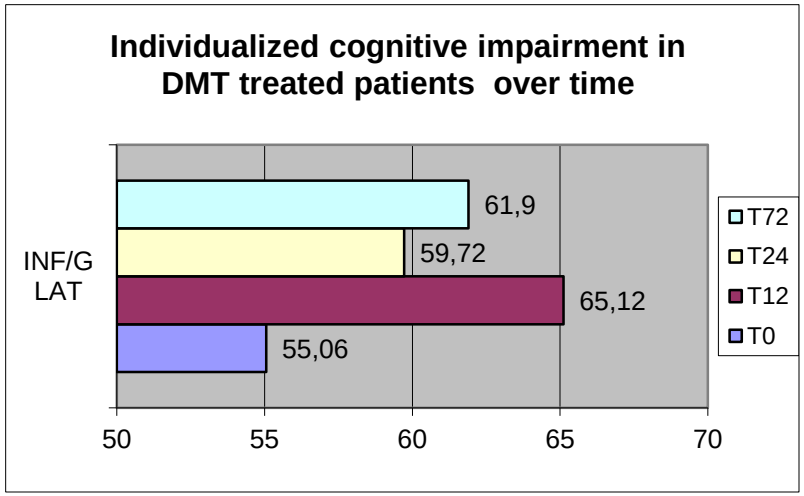
EDSS over time



n.s.

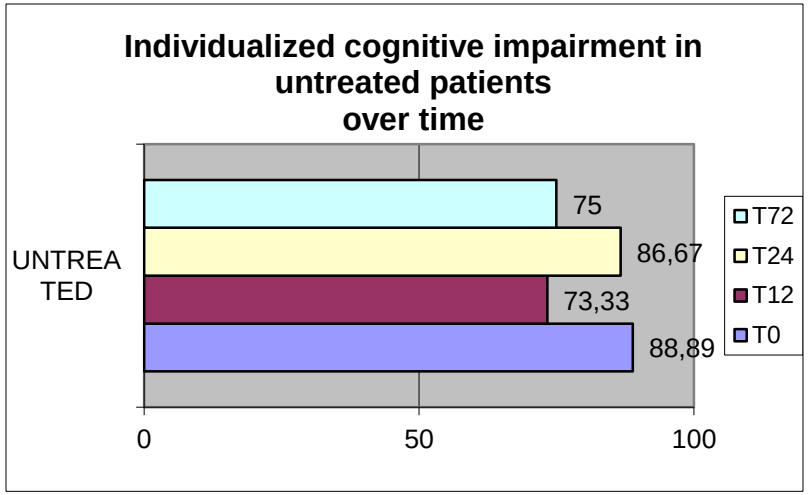
No relevant disease progression in the motor area over time

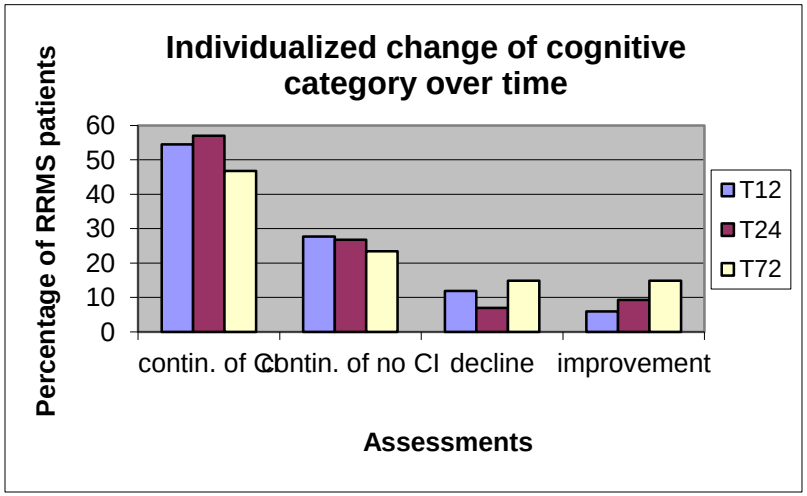
Individual cognitive performance over time



- **Individualized cognitive impairment in total RRMS over time**
  - **T0: 60,7%**
  - **T12: 66,3 %**
  - **T24: 64,3%**
  - **T72: 64,0%**

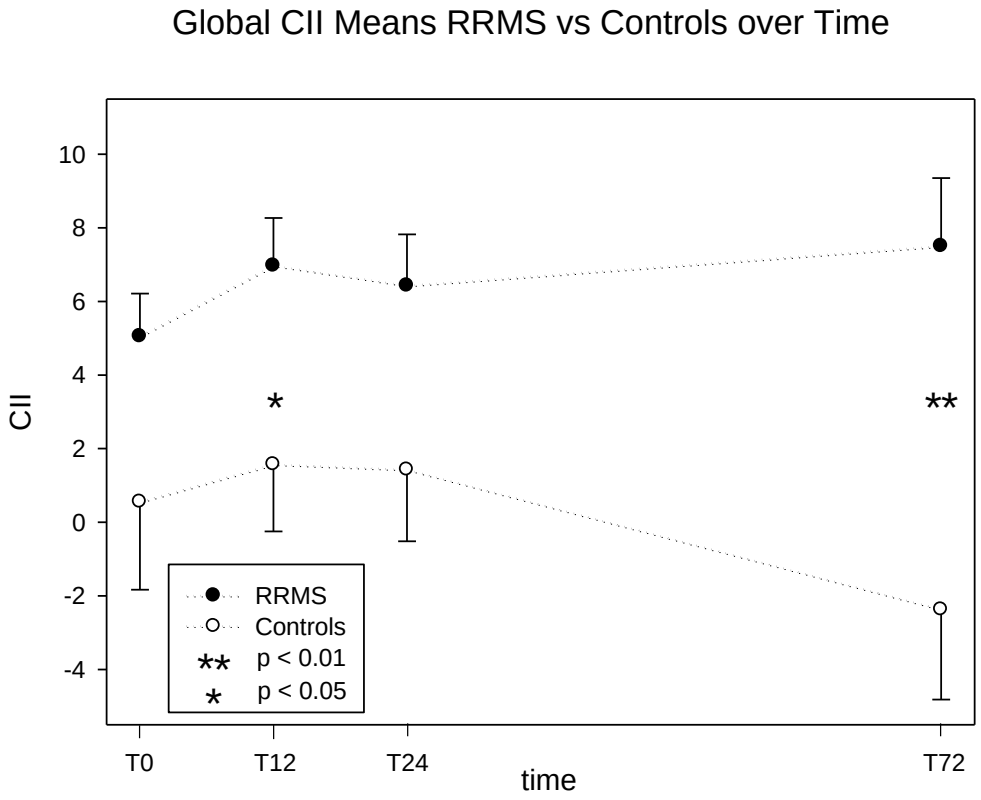
Crit: -1SD of control mean in two tasks





Evolution of cognitive performance (CII_{global}) over 6 years

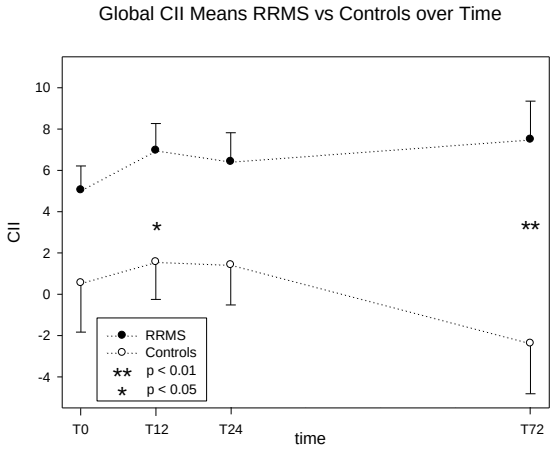
RRMS vs Controls

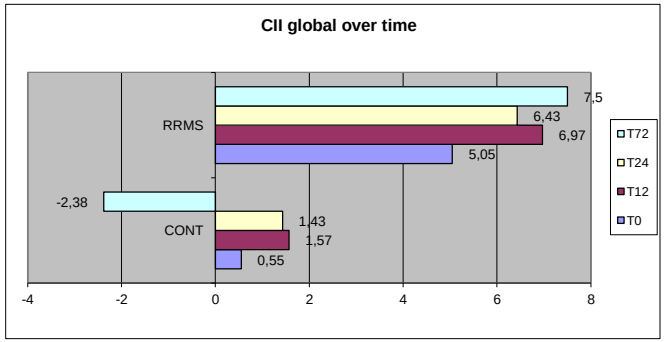


* 0.05, ** 0.01

Quantification of cognitive decline (CII_{global}) over time

RRMS vs Controls



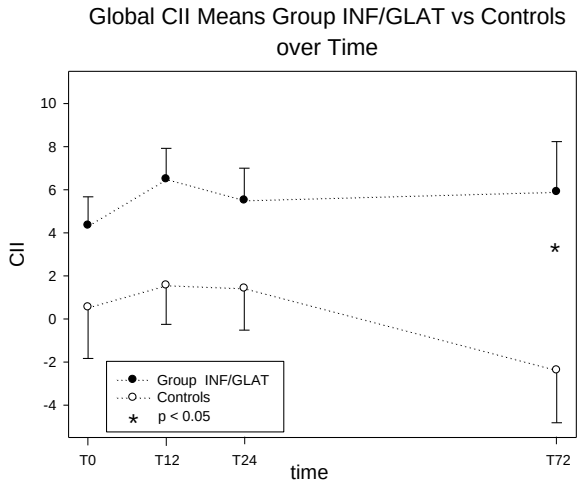


Stat analysis*					
Label	Estimate	SE	DF	t Value	Pr > |t|
MS-Patients vs Controls	**7.8317**	**3.9342**	**132**	**1.99**	**0.0486**

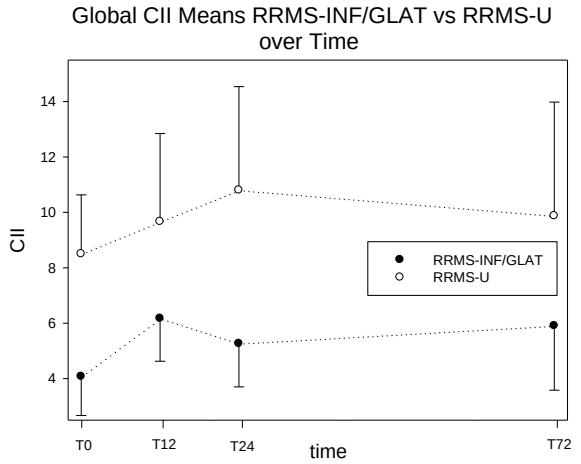
**mixed linear model, adj. Depr/Fatigue*

Quantification of cognitive decline in MS subgroups

DMT treated vs Control



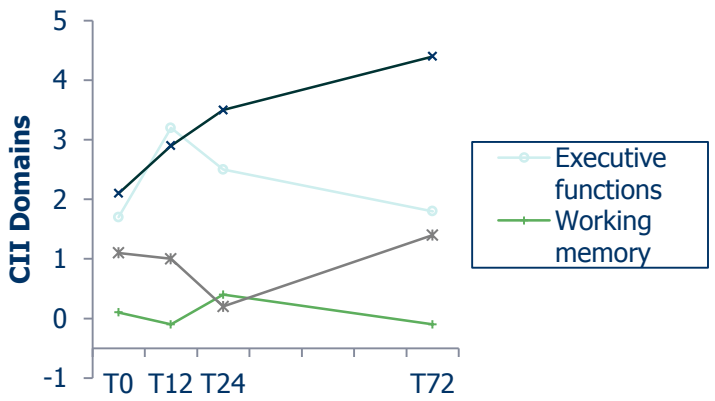
DMT treated vs Untreated

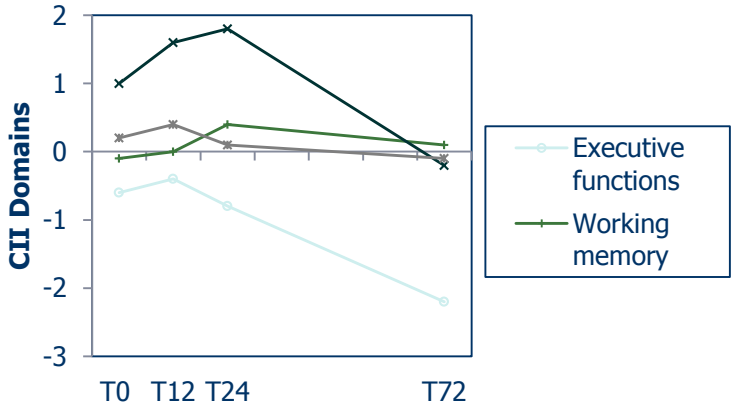


Stat. Analysis* – subgroup analysis					
Label	Estimate	Stand. Error	DF	t Value	Pr > |t|
DMT-treated vs UNTR	**-4.6430**	**2.9638**	**132**	**-1.57**	**0.1196**
DMT-treated vs Controls	**2.5446**	**2.4872**	**132**	**1.02**	**0.3081**
DMT-treated vs Switchers	**-3.3865**	**3.7565**	**132**	**-0.90**	**0.3690**
IM INFβ-1a vs GLAT	**1.2565**	**4.4337**	**132**	**0.28**	**0.7773**

**linear mixed model, adj for Dep./Fatigue*

Domain-related cognitive vulnerability over time





CII domains, adjust. for BDI, FSS; T0:T72

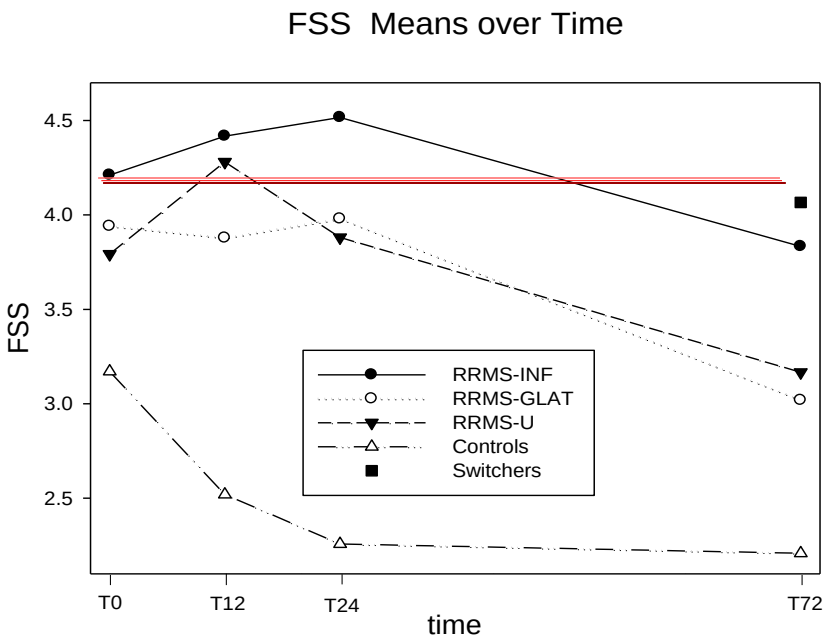
Least Squares Means						
Effect	domain	Estimate	Standard Error	DF	t Value	Pr > |t|
domain	Ex.Fct	**0.09702**	**0.03882**	**195**	**2.50**	**0.0133**
domain	**WM**	**0.02914**	**0.03921**	**195**	**0.74**	**0.4583**
domain	**Learn.& Mem.**	**0.1955**	**0.03918**	**195**	**4.99**	**<.0001**
domain	**Attent.**	**0.06477**	**0.03882**	**195**	**1.67**	**0.0968**

Ranking of cognitive vulnerability:
Learning & Memory > ex. Fct > Attent. > Work. Memory

Covariates of cognition

Fatigue

Clin cut-off



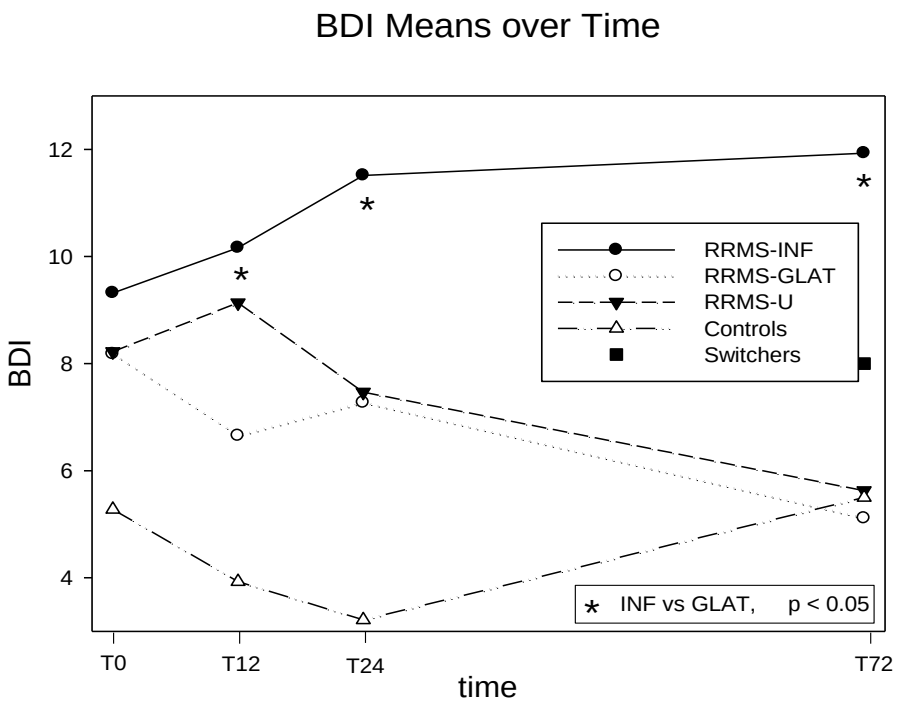
Inter-group differences (RRMS) n.s.

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
Zeit	**3**	**299**	**3.68**	**0.0126**
gruppe1	**3**	**132**	**1.75**	**0.1591**
BDI	**1**	**299**	**0.33**	**0.5672**
FSSMW	**1**	**299**	**8.42**	**0.0040**

Covariates of cognition

Depression

Clin cut-off 18



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FSSMW	**1**	**299**	**8.42**	**0.0040**

Conclusions

1. Cognitive and attentional deficits are prevalent and begin early in RRMS.

2. A negative performance profile over time is existing in RRMS patients compared to controls. Despite stable EDSS, the cognitive deficits increase over time while controls improve (repetition effects - facet of cognitive fitness?)

3. Although the cognitive deficit was clearly more expressed in untreated patients than those on stable DMTs, a significant treatment effect could not be validated (variance, drop-out bias).

4. Cognitive vulnerability seems to be domain-related with learning & memory > ex. Fct. > attention > working memory being affected.

5. Practice effects, drop-out bias and variance in performance put limitations on the interpretation of the data, and are principal problems in longitudinal studies of cognition.

≥≥

Thank you very much for your collaboration !

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- NTD support: **Arnfin Bergmann**

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Neuropsychology:
- **I. Uttner, I.M. De Winter, I.K. Penner**

- NTD MS-Centers:
- Ulm: **M. Lang, H. Schreiber, A. Kornhuber, M. Krauß, M. Krieck-Wiedenbauer, M. Engelberger**
- Kaltenkirchen: **M. Freidel**
- Aschaffenburg: **W. Hofmann**
- Hamburg: **W. Elias**
- Mannheim: **M. Bühler**
- Erbach: **G. Reifschneider, S. Ries**
- Dresden: **S .Tröger**

Statistics & Data management:
S. Schlegel, K. Ring, G. Berry, J. Ballasch, A. Kornhuber

Ulm cathedral

Ulmer Spatz