

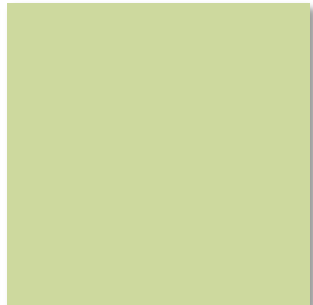
# Pharmakotherapie und andere körperbezogene Verfahren – Nutzen und Risiken



**Peter Falkai**

**LVR-Symposium  
"Psychisch erkrankt heute"**

**am 02. und 03. Februar 2017 in Köln**



# Übersicht

**Behandlung von psychischen Erkrankungen am Beispiel  
schizophrener Psychosen**

**Pharmakotherapie**  
**- Wirkung, Nebenwirkung**  
**- Neue Outcome-Parameter**

**Gehirnstimulationsverfahren**

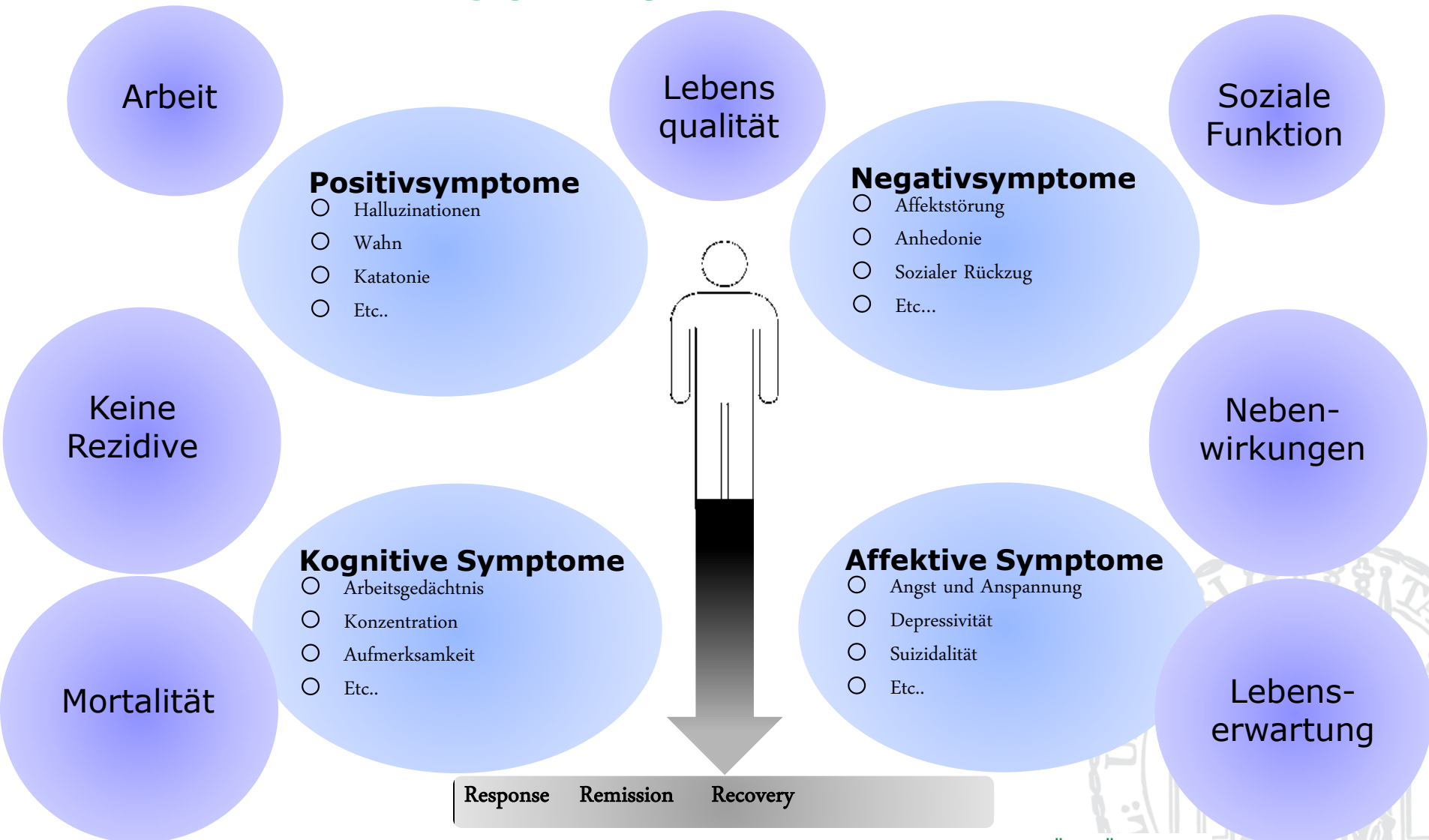
**Sport als Medikament**

**Lifestyle-Modifikationen**

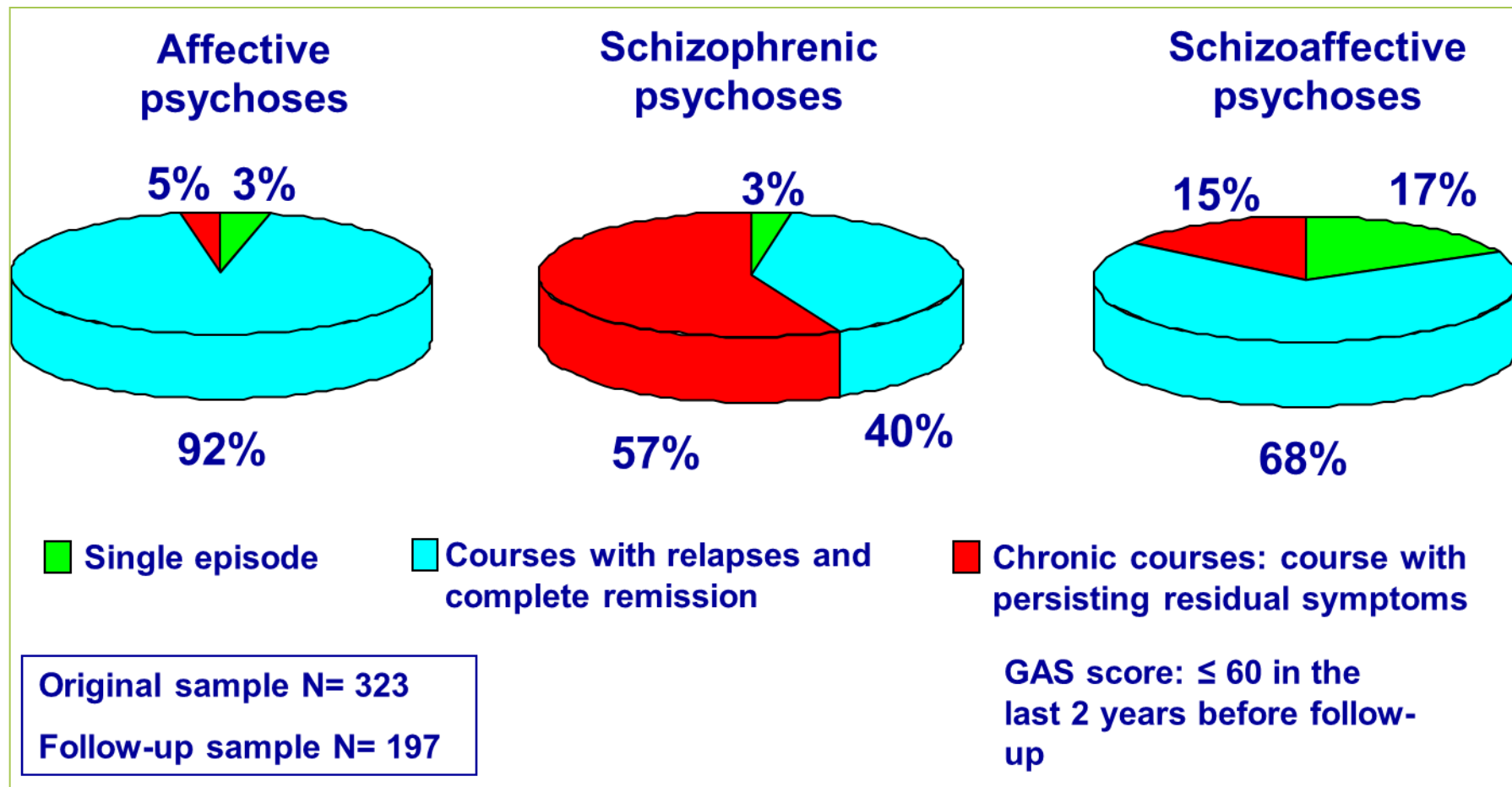
**Kombinationstherapie – Mehr ist mehr?**

**HDAC-Inhibitoren: komplett neue Medikamente**

# WAS SIND PATIENTENOUTCOMES BEI DER SCHIZOPHRENIE?



# Munich 15-year Follow-up Study (MUFUSSAD): Global outcome of first-admitted schizophrenic, affective and schizoaffective inpatients (ICD-10)



## Pharmakotherapie



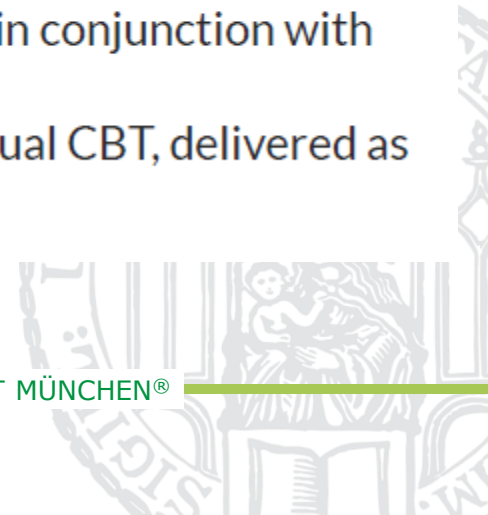
# OPTIMALE SYMPTOMKONTROLLE NICE 2014

1.3.4.1 For people with first episode psychosis offer:

- oral antipsychotic medication (see sections [1.3.5](#) and [1.3.6](#)) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in [section 1.3.7](#)). [new 2014]

1.4.2.1 For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer:

- oral antipsychotic medication (see sections [1.3.5](#) and [1.3.6](#)) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in [section 1.3.7](#)). [new 2014]

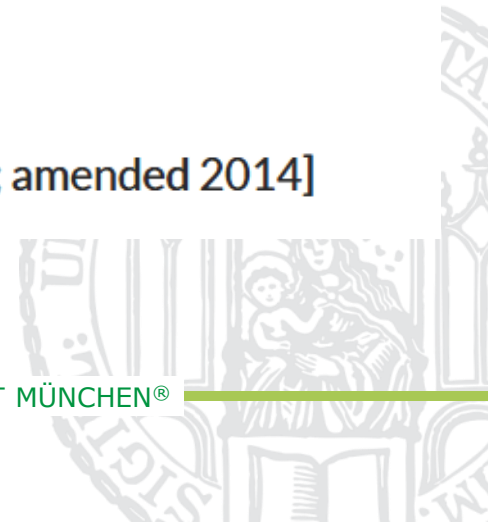


# OPTIMALE SYMPTOMKONTROLLE NICE 2014

## 1.3.5 Choice of antipsychotic medication

1.3.5.1 The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including:

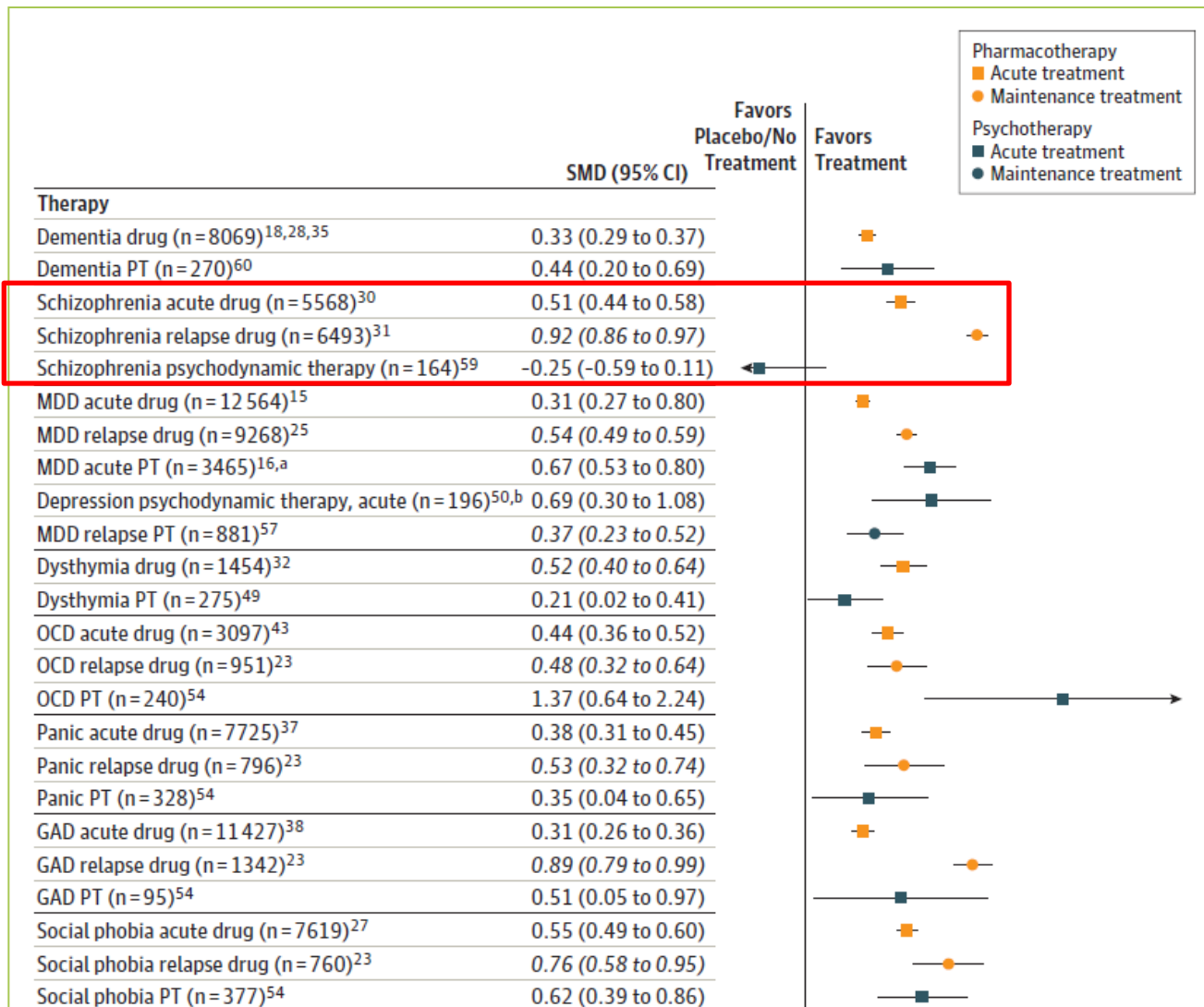
- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences). [2009; amended 2014]





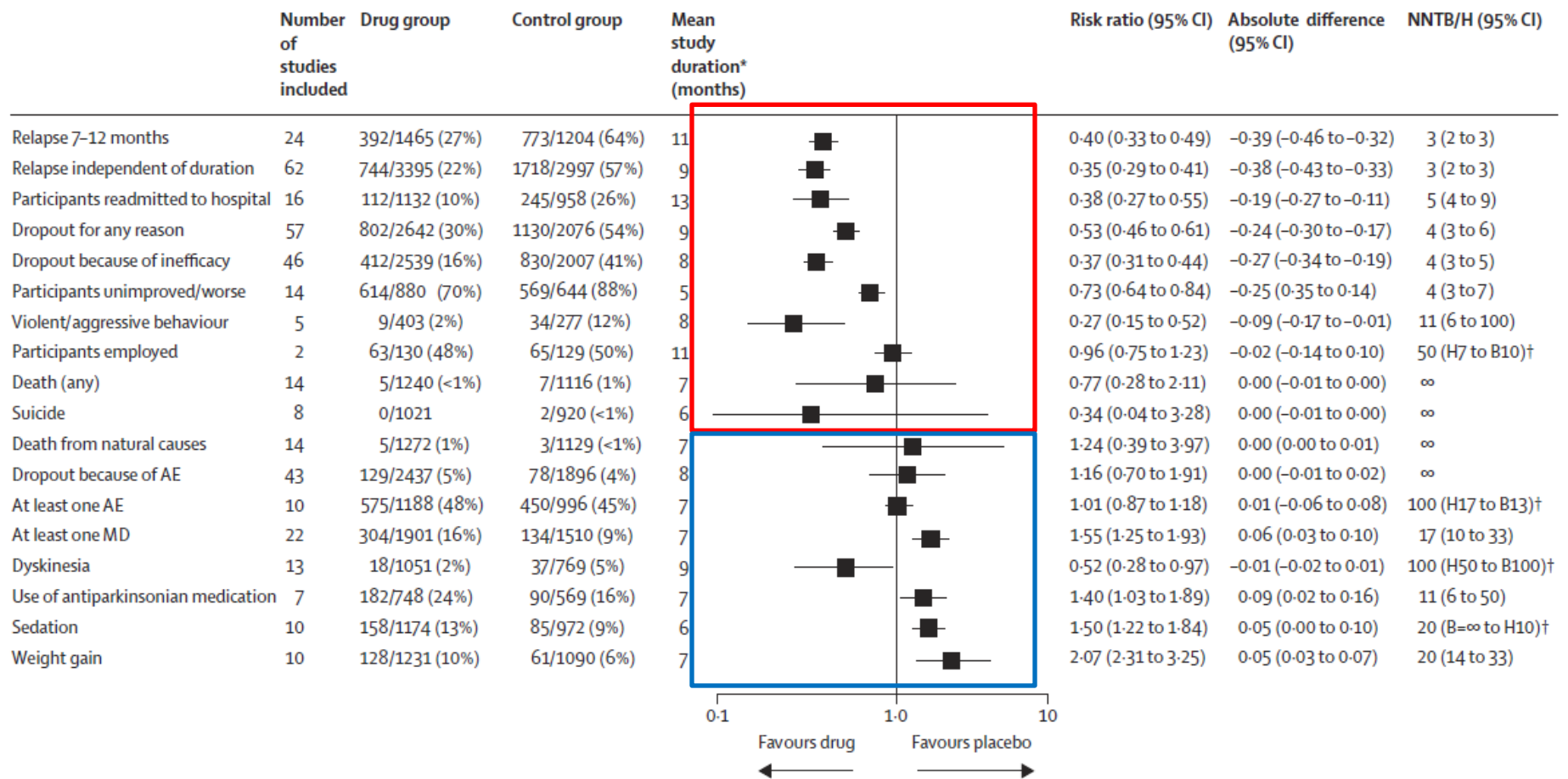
# What works?

## Comparison of effect sizes in meta-analyses of acute and maintenance treatment in pharmacotherapy and psychotherapy

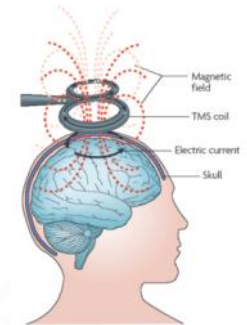




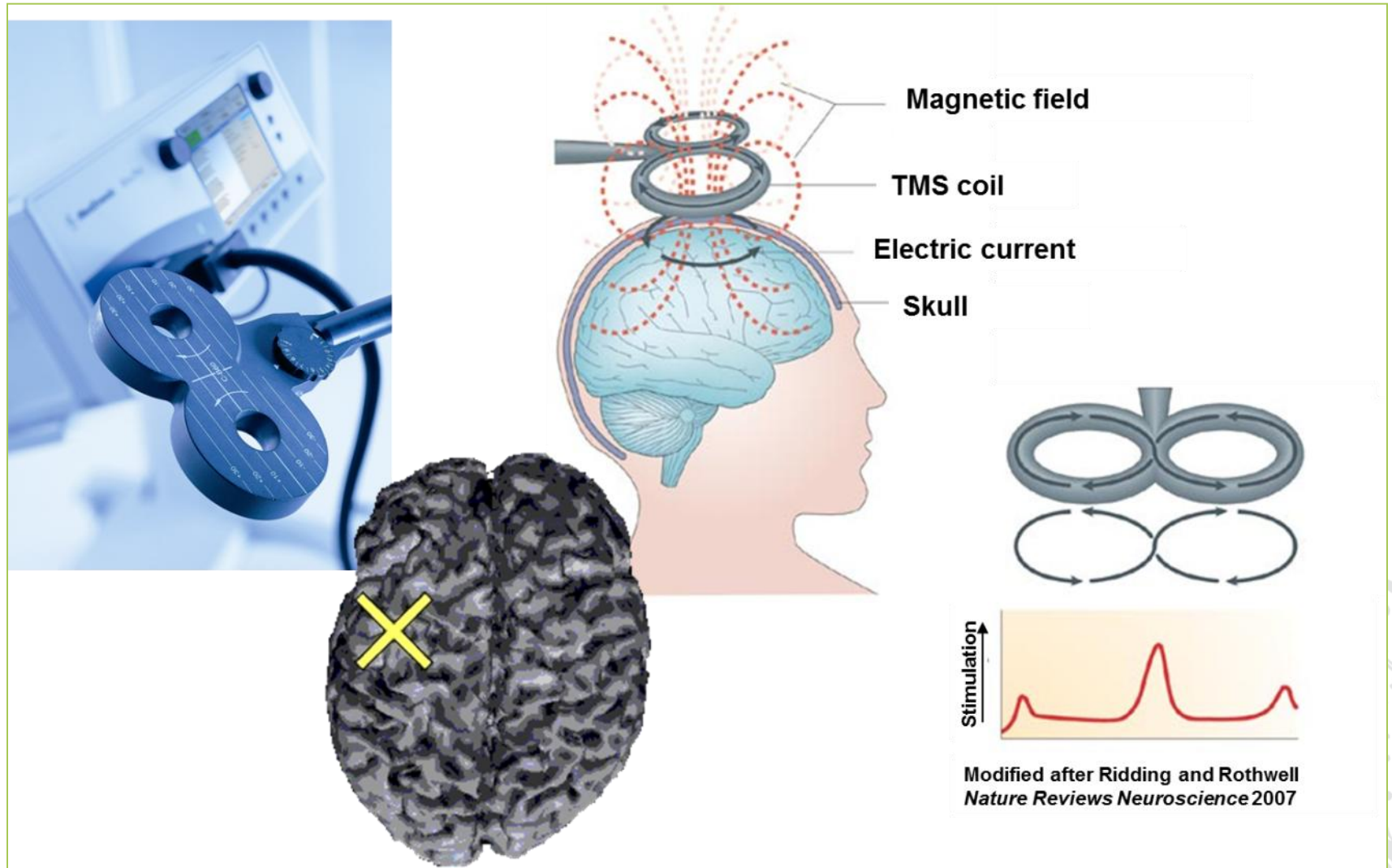
# RISIKO-NUTZEN EVALUATION



## Gehirnstimulationsverfahren



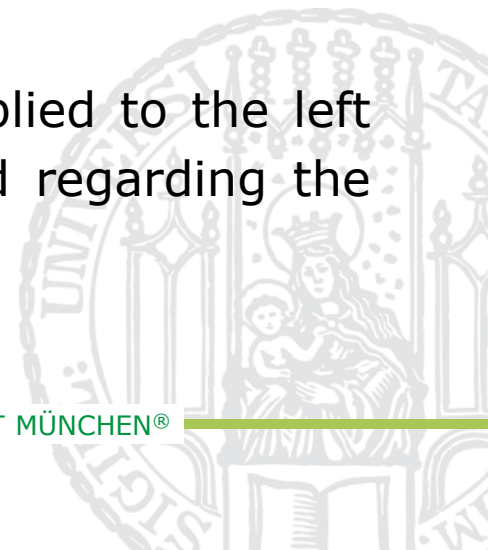
# Repetitive Transcranial Magnetic Stimulation (rTMS)



# NEGATIVE SYMPTOMS – SIMPLIFIED PATHOPHYSIOLOGY

- ‚Hypofrontality‘ and a ‚reduced activity‘ of the left dorsolateral prefrontal cortex have been discussed to underly the pathophysiology of negative symptoms
- Frontal cortex/lobe
  - Volume reduction
  - Reduced CBF
  - Reduced task-related activation
- Since more than 15 years, high-frequency rTMS applied to the left DLPFC in schizophrenia patients has been evaluated regarding the efficacy to improve negative symptoms.

‚Hypofrontality‘



# META-ANALYSIS

Before vs. After Treatment

Pooled Effect Size:

0.625

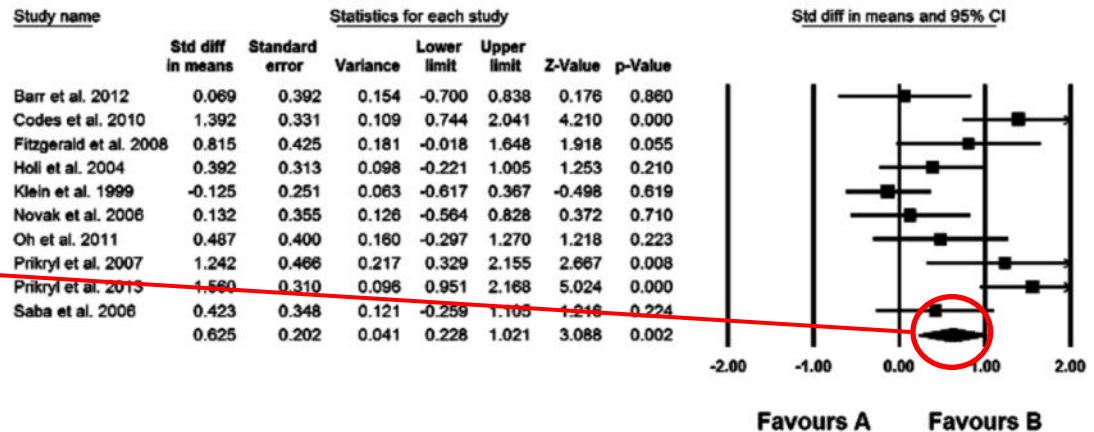


Fig. 2. Pooled effect size (before versus after treatment) for studies of rTMS effects on negative symptoms (random effect model).

Placebo vs. Active Treatment

Weighted Effect Size:

0.532

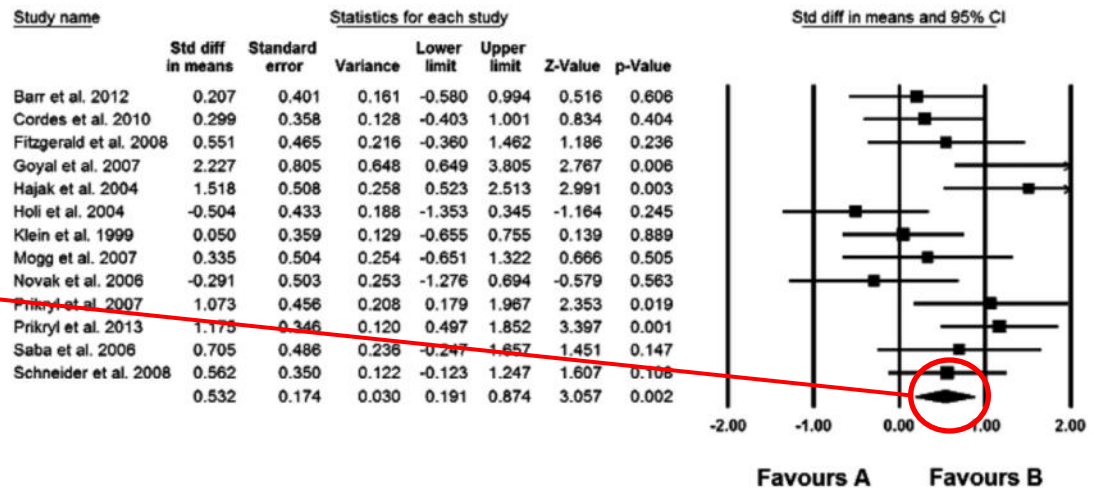
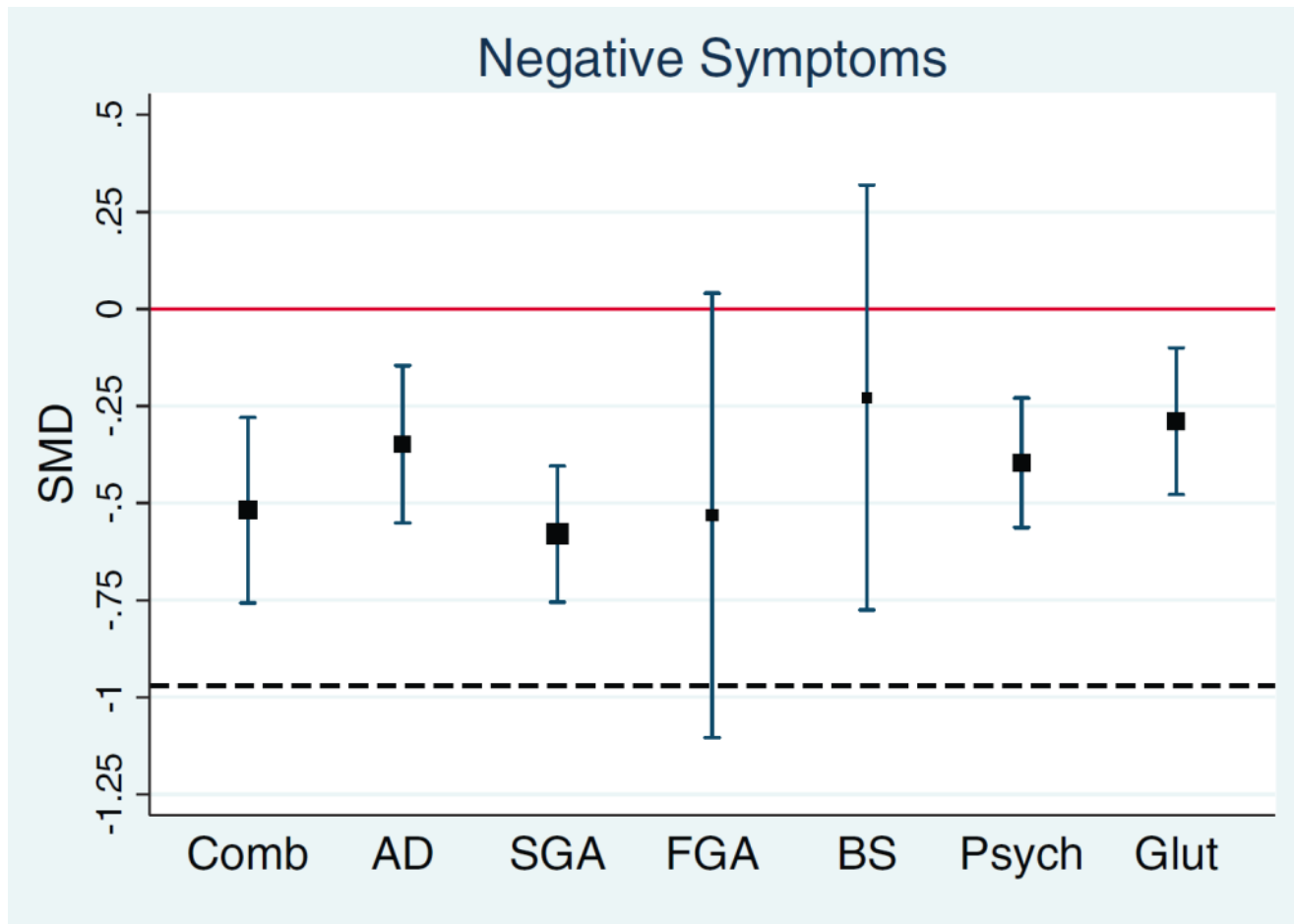


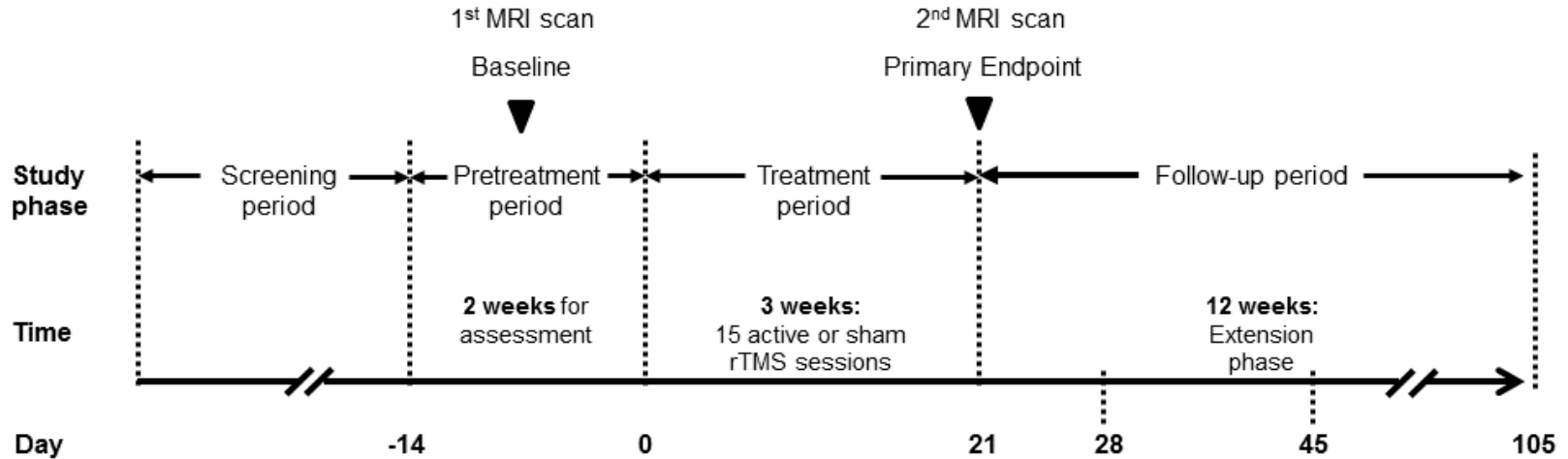
Fig. 3. Pooled effect size (placebo versus active treatment) for studies of rTMS effects on negative symptoms (random effect model).

# META-ANALYSIS



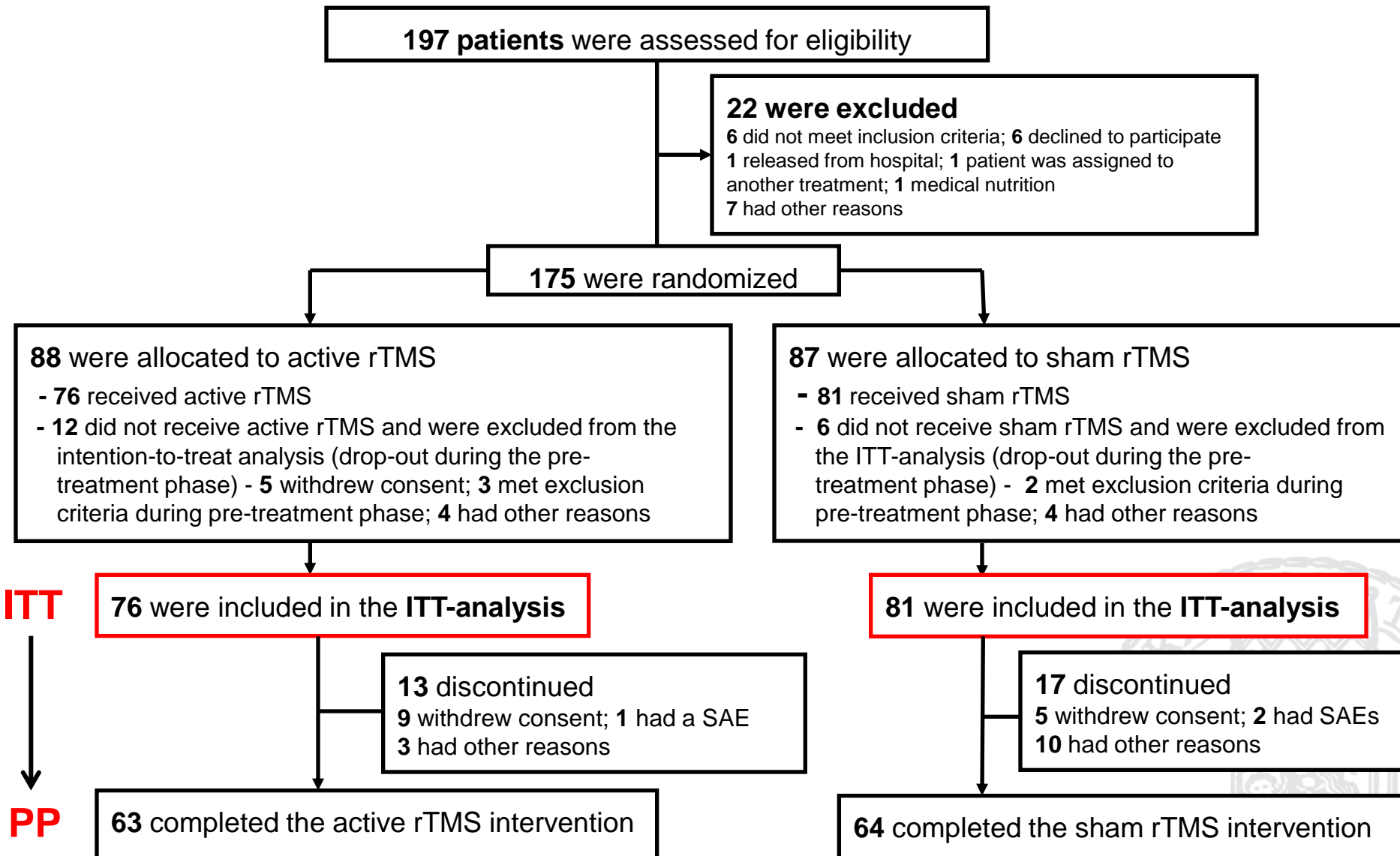


# THE RESIS – TRIAL





# THE RESIS – TRIAL: CONSORT CHART

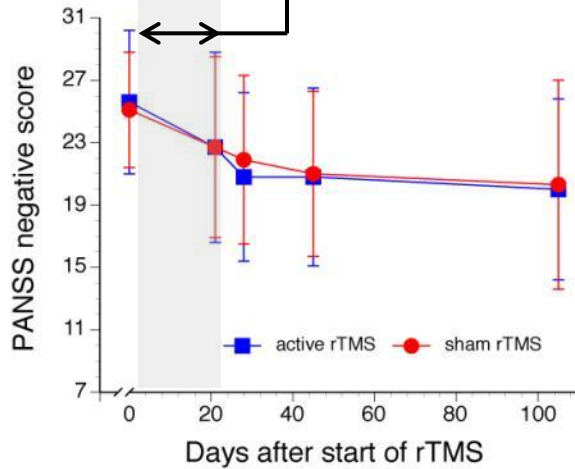


# CHANGE IN PSYCHOPATHOLOGY

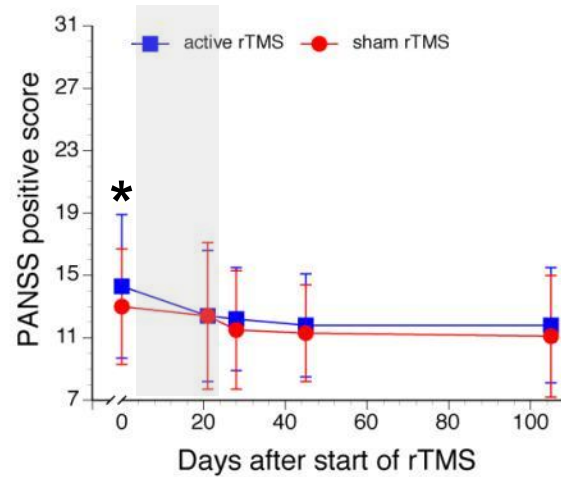
Primary outcome

Intervention period

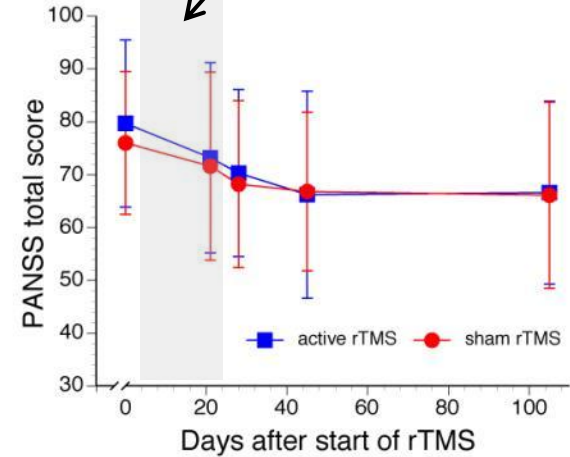
A Negative symptoms



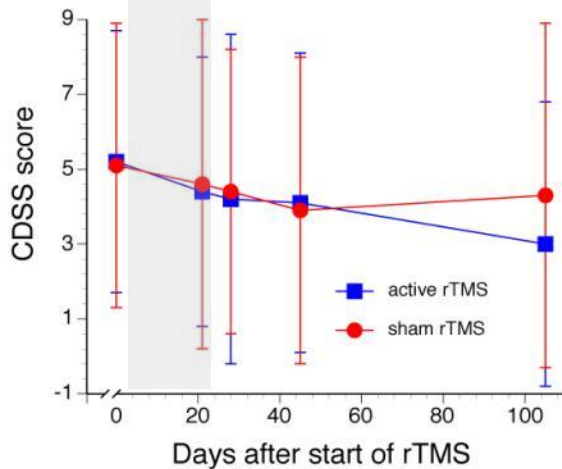
B Positive symptoms



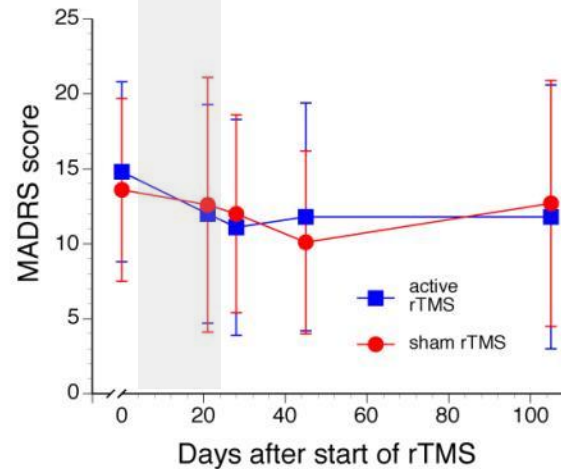
C Total symptoms



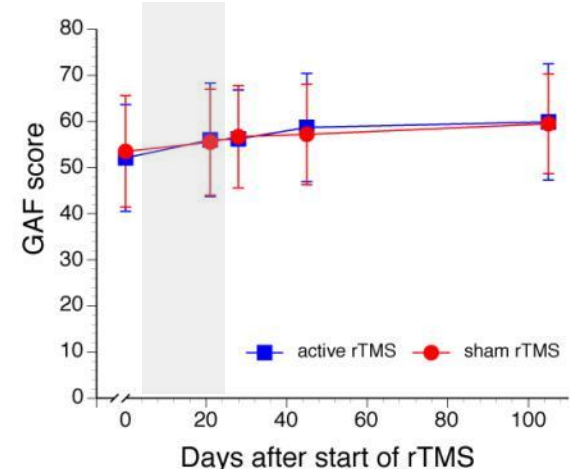
D Calgary Depression Scale for Schizophrenia



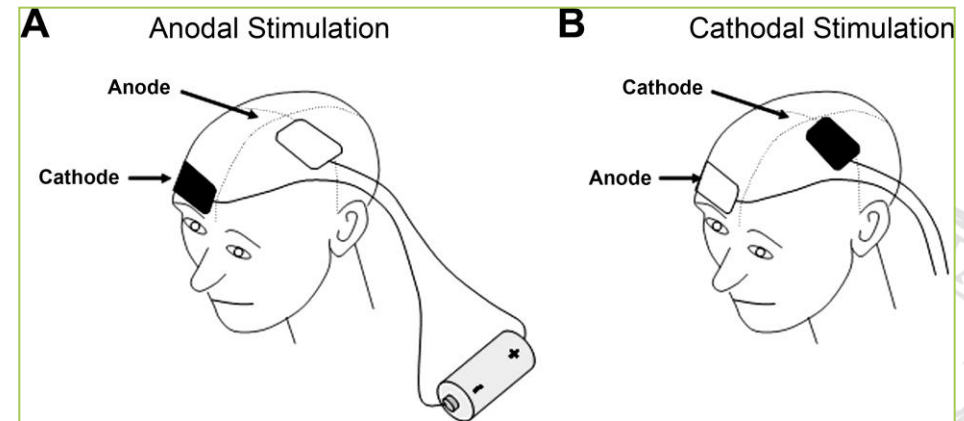
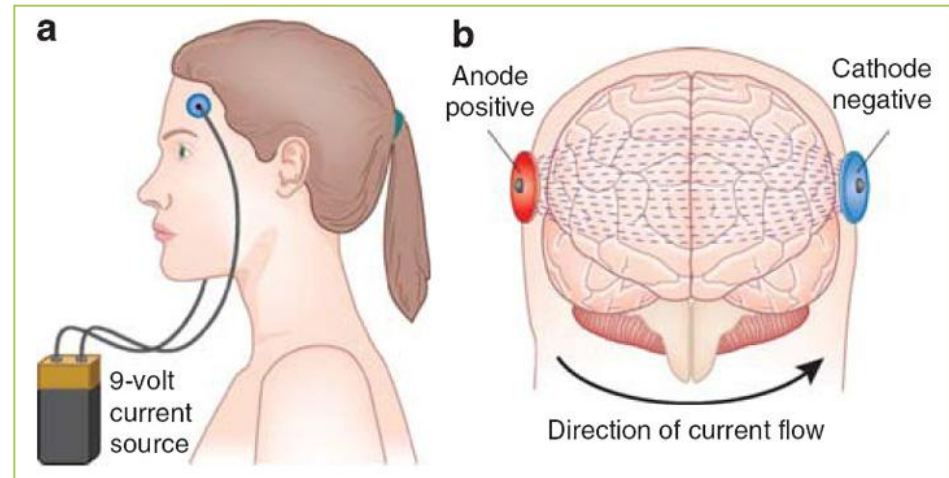
E Montgomery Asberg Depression Rating



F Global Assessment of Functioning



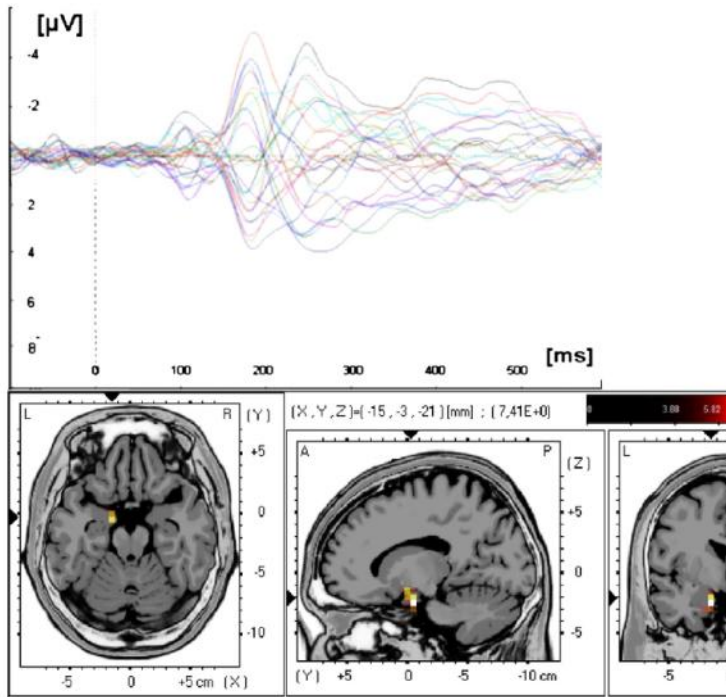
# New method: tDCS



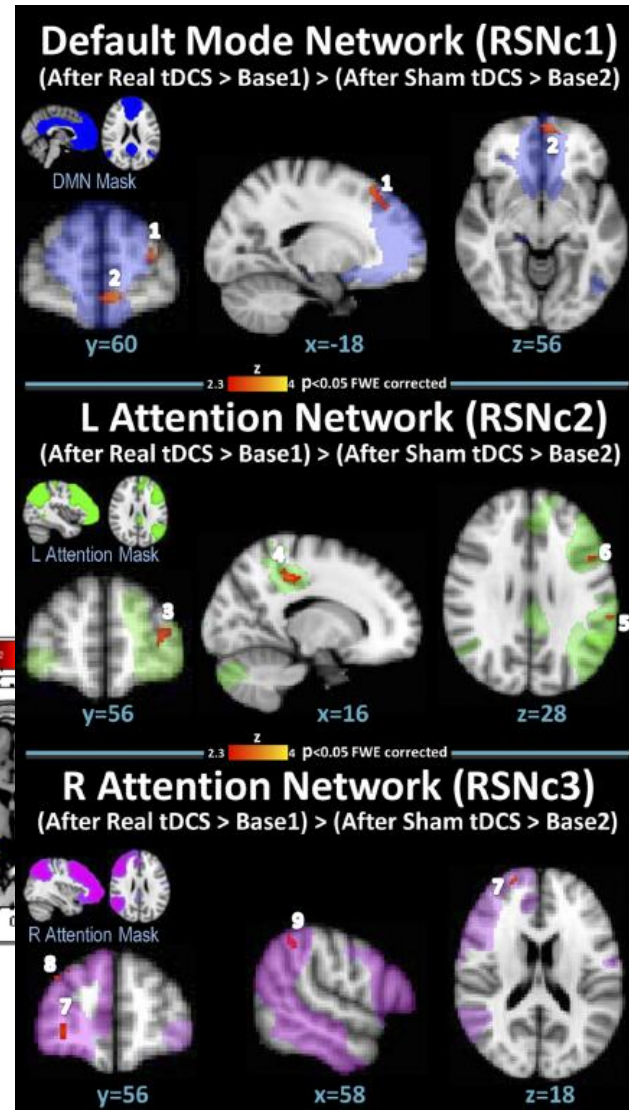
# Prefrontal tDCS changes connectivity within resting-state networks during fMRI

- Connectivity differences within the RSNs (RSNc 1–3) for the main contrast.

- Resting state connectivity differences for the main contrast (p < 0.05 FWE corrected) in the Default Mode Network (RSNc1)
- Resting state connectivity differences for the main contrast (p < 0.05 FWE corrected) in the L Attention Network (RSNc2)
- Resting state connectivity differences for the main contrast (p < 0.05 FWE corrected) in the R Attention Network (RSNc3)



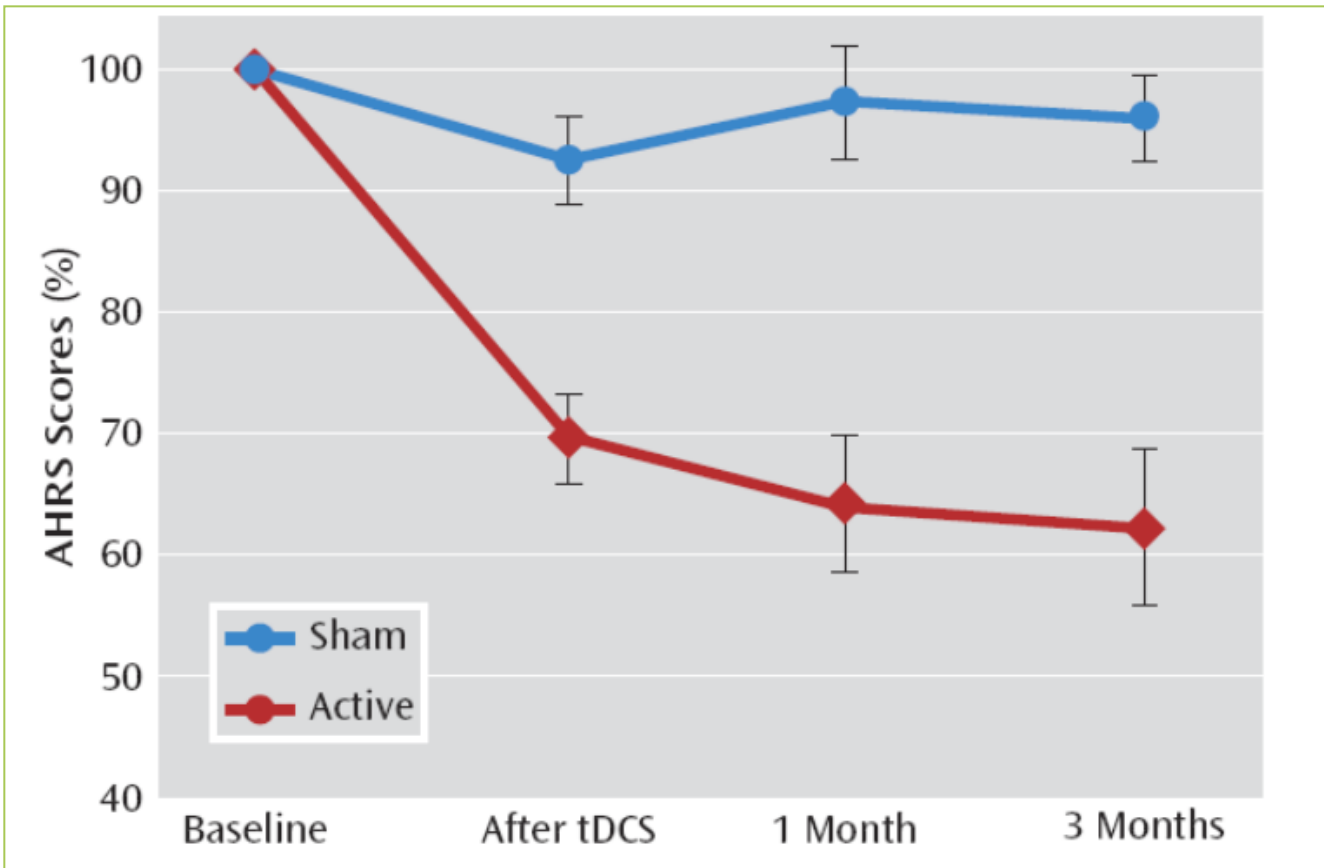
- \* Default mode network
- \*\* Frontal parietal network



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# Effects of tDCS on auditory verbal hallucinations



$p < 0.001$ .

The graph illustrates the significant interaction between the mean percentage change in Auditory Hallucination Rating Scale (AHRs) score in the two groups across the four assessments ( $F=10.97$ ,  $df=3, 84$ ,  $p < 0.0001$ ). Post hoc analyses showed significant differences between groups at each postbaseline assessment: after tDCS,  $t=-4.45$ ,  $p < 0.001$ ; 1 month after treatment,  $t=-4.48$ ,  $p < 0.001$ ; 3 months after treatment,  $t=-4.58$ ,  $p < 0.001$ . Error bars indicate standard error.

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# Summary: tDCS in schizophrenia

**2 case reports, 1 RCT, at least 1 ongoing study**

**improvement of auditory hallucinations by inhibitory stimulation of the left temporo-parietal cortex**

**improvement of positive/negative/depressive symptoms by excitatory stimulation of the left DLPFC**

**modest improvement in the disorganisation/cognitive dimensions**

**→ more/larger studies needed exploring:**

**different electrode positions (left/right hemisphere, extracephalic reference)**

**various stimulation protocols (current strength, duration, number of applications per day, total number of applications)**

**fMRI-controlled changes in resting state networks/arterial spin labeling**

**differences in dimensional changes/symptom heterogeneity**

## Sport als Medikament





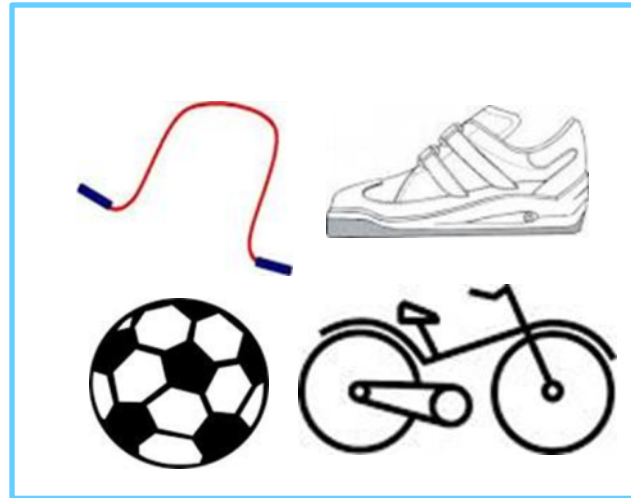
# Exercise promotes the functional and structural regeneration of cells in the hippocampus

**Exercise improved the Water Maze performance, enhanced the number of Bromodeoxyuridin-positive cells and extended alternatively the long-term-potential of the Gyrus dentate in mice**

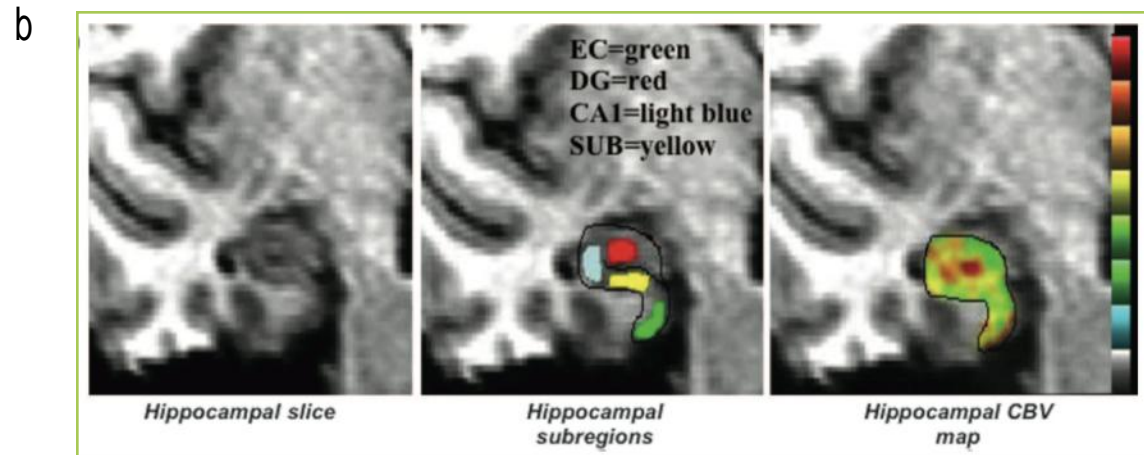
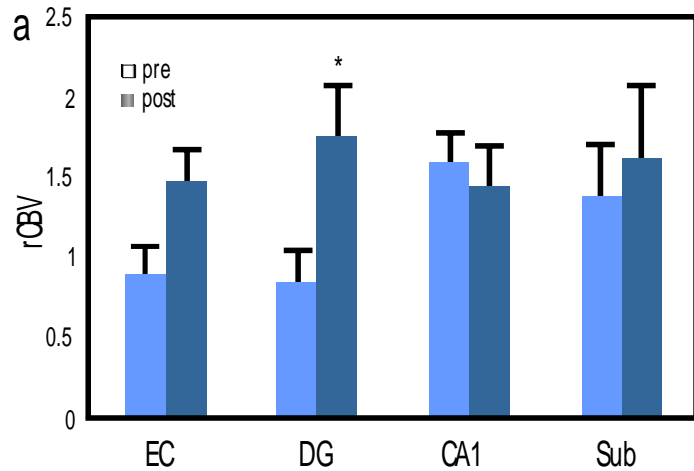


**Physical Activity can regulate neuroneogenesis of the hippocampus, equally synaptic plasticity and learning**

# Schizophrenia – translation neurogenesis and synaptic plasticity



Schizophrenia ?



# Exercise I Study – Effect of sports on physical capacity, cognition and neuronal processes in healthy subjects and schizophrenic patients

**Group: Patients with schizophrenia**

**Exercise: Cycling**



**Frequency: 3 times/week à 30 min**

**Duration: 3 months**

**Group: Patients with schizophrenia**

**Exercise: table soccer**



**Frequency: 3 times/week à 30 min**

**Duration: 3 months**

**Group: Controls**

**Exercise: Cycling**

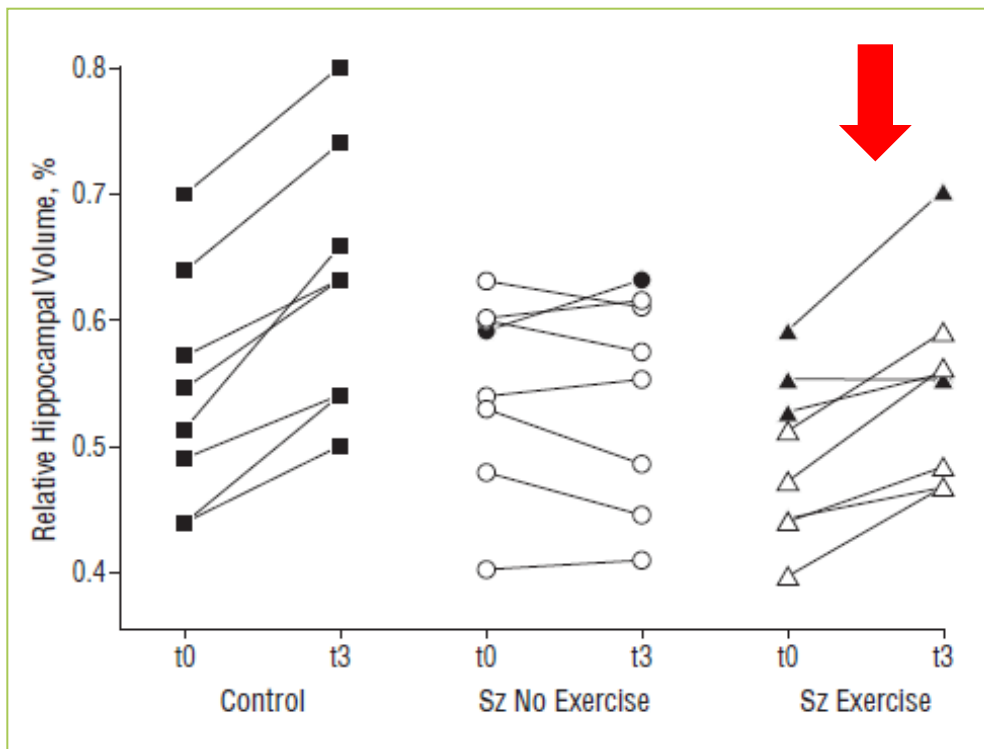


**Frequency: 3 times/week à 30 min**

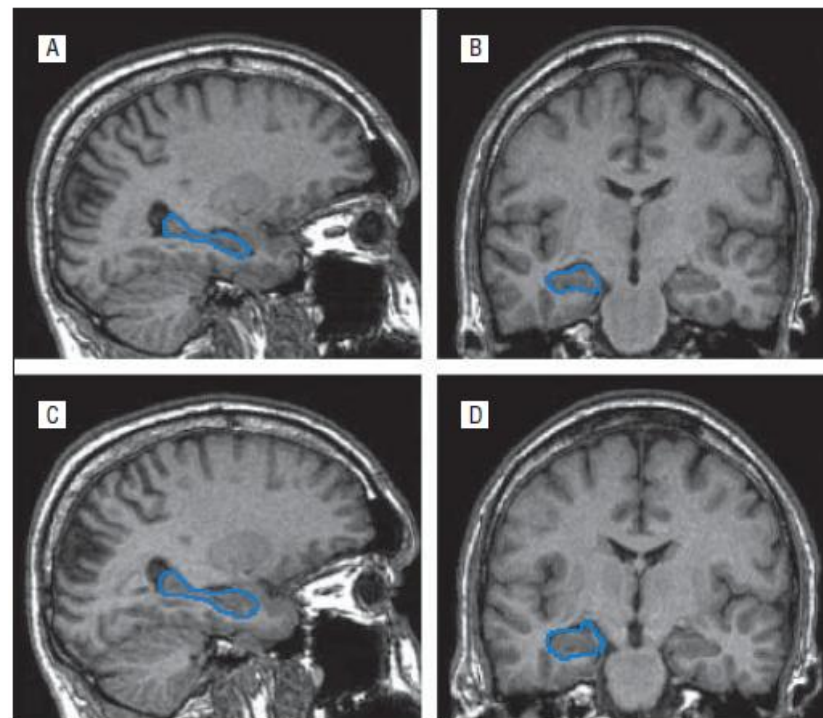
**Duration: 3 months**

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# Exercise normalises the hippocampus volume in schizophrenia



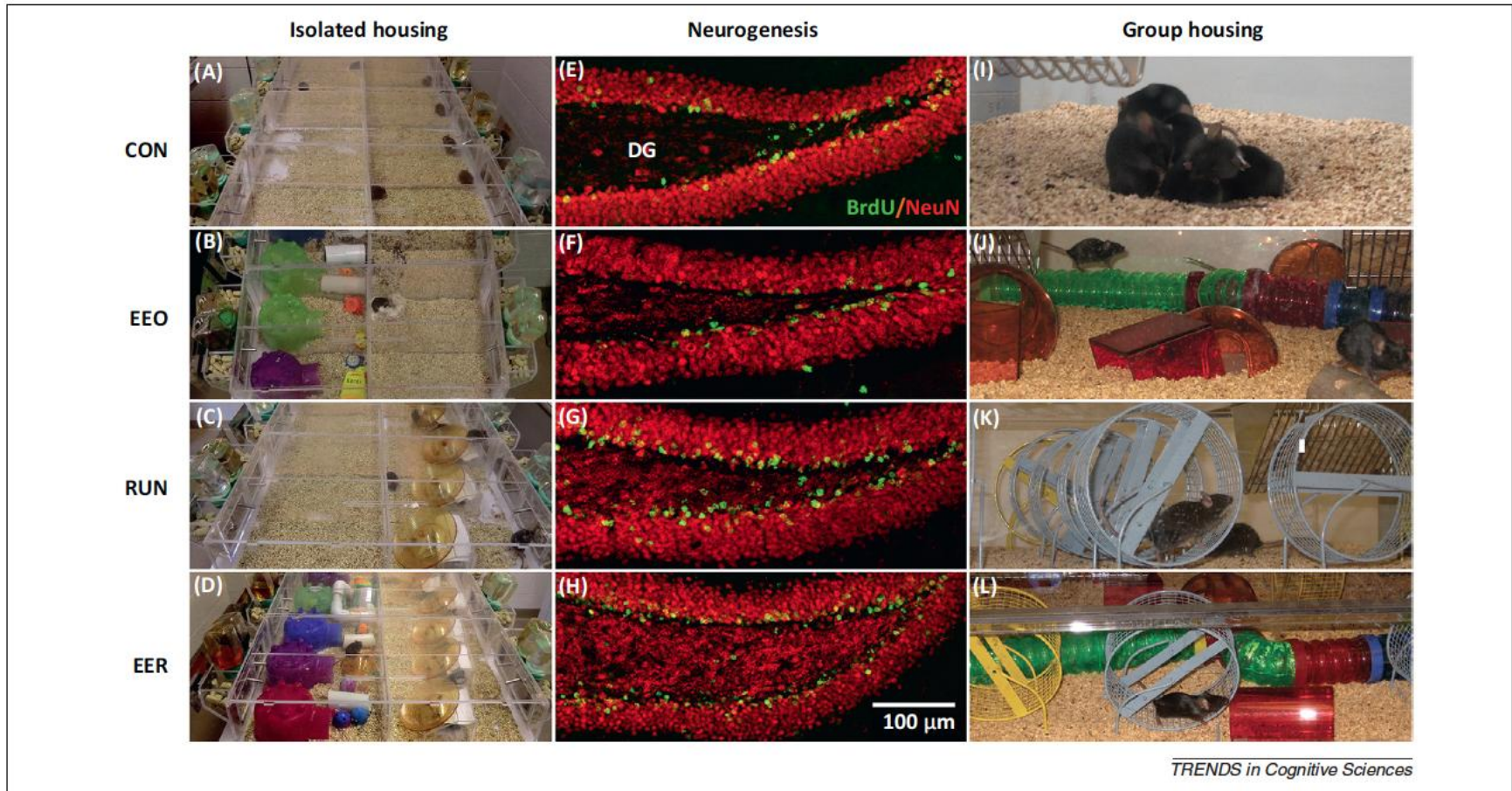
- Control subjects
- ▲ Sz exercise group, treated with antidepressants
- △ Sz exercise group, not treated with antidepressants
- Sz nonexercise group, treated with antidepressants
- Sz nonexercise group, not treated with antidepressants



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# Exercise II: Running and enriched environment leads to better functional improvements



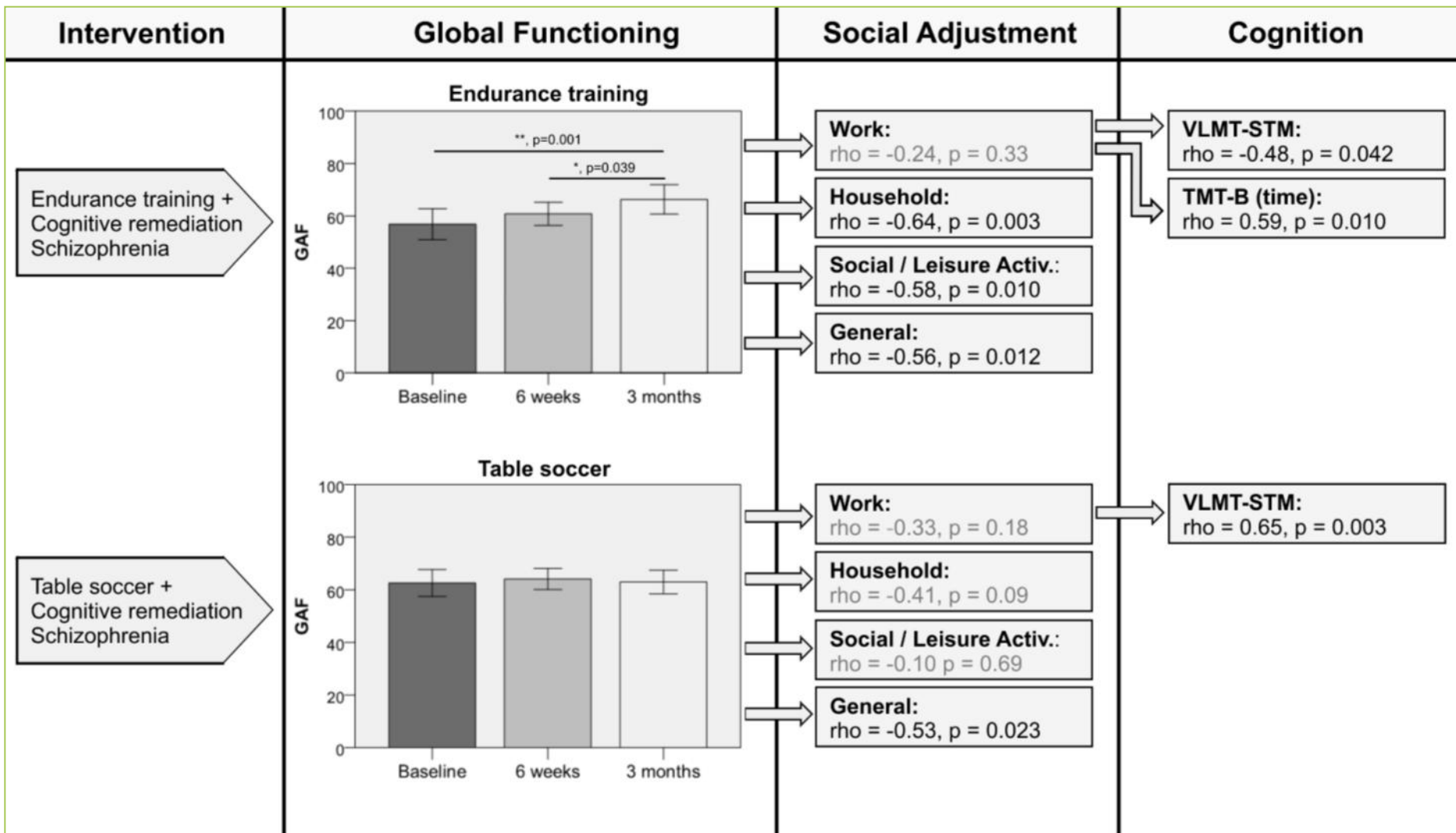
**Figure 1.** Exercise increases the production of new neurons in the dentate gyrus (DG) of the hippocampus. In two independent studies [18,19], mice were housed under (A,I) control (CON), (B,J) enriched environment only (EEO), (C,K) running (RUN), or (D,L) enriched environment and running (EER) conditions in (A–D) single or (I–L) group housing. Confocal images of bromodeoxyuridine (BrdU)-positive cells in the DG in sections derived from mice housed under (E) CON, (F) EEO (G) RUN, and (H) EER conditions. Sections were immunofluorescently double-labeled for BrdU (green) and NeuN (red) indicating neuronal phenotype (adapted from [18]). Panels (A–D) are reproduced with permission from [19]. Both studies show that adult DG neurogenesis is increased under the RUN and EER conditions but not under CON or EEO, indicating that running is the neurogenic stimulus.

# Exercise II: Study Design



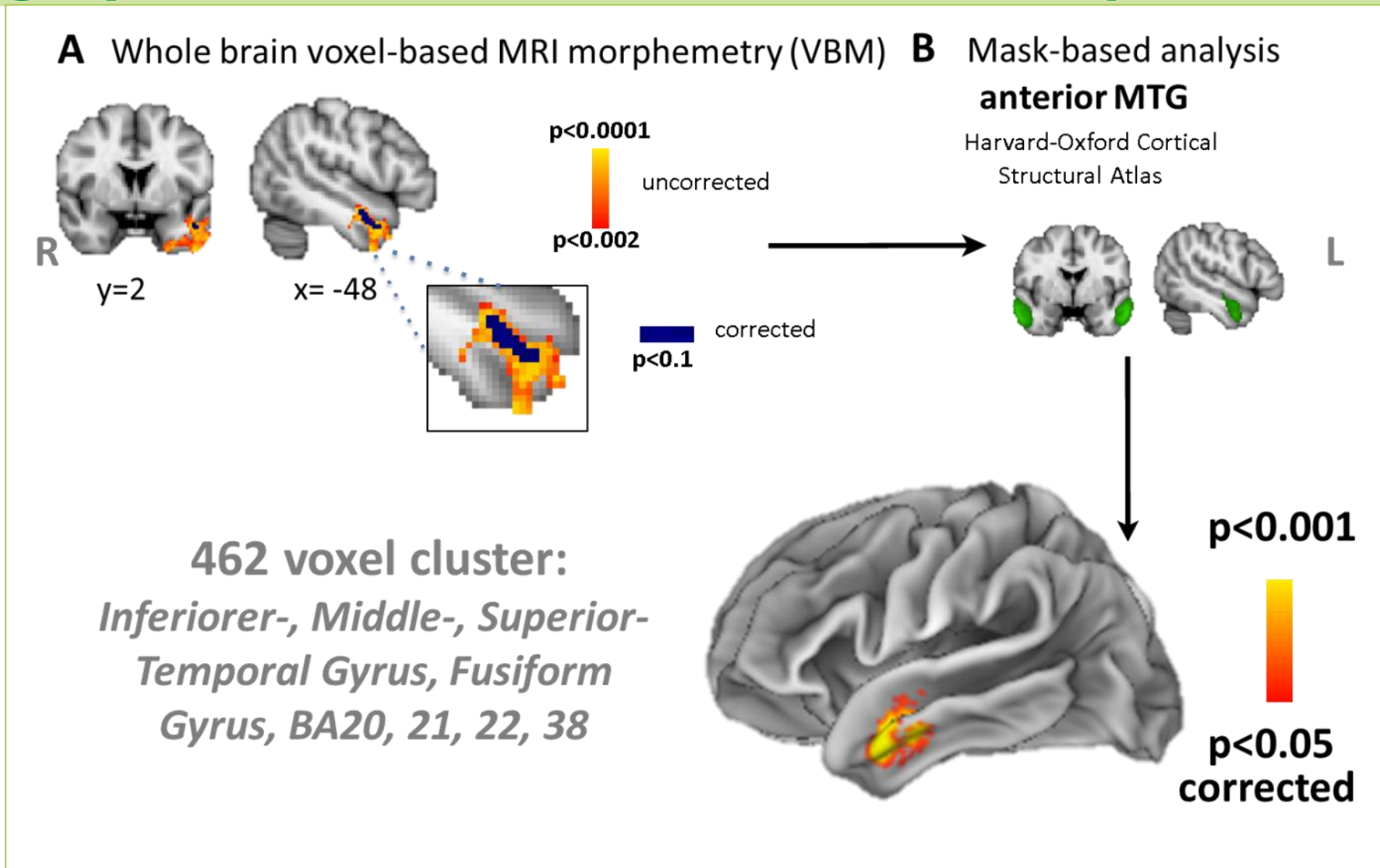
Timeline	Screening	Baseline/Intervention			Follow-up	
Visit-number	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Time point (Day)	-14	0 ± 2	42 ± 7	84 ± 7	182 ± 14	365 ± 14
Group 1 (SZ)		CYCLING				
			COGPACK			
Group 2 (SZ)		TABLE SOCCER				
			COGPACK			
Group 3 (Controls)		CYCLING				
			COGPACK			

# Exercise II: Main results of function (GAF, SAS)



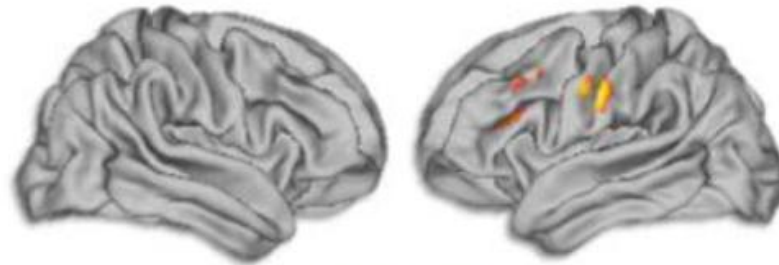


# Exercise II: Effects of endurance training: Increase in grey matter volume of the anterior temporal lobe



# Exercise II: Effects of table soccer on the brain - increase in grey matter volume of the ACC\* and the premotor area

**A** Whole brain voxel-based MRI morphometry (VBM) – 6 weeks table soccer vs. baseline



**R**  $p < 0.001$    $p < 0.05$  **L**  
*corrected*

**B** Whole brain voxel-based MRI morphometry (VBM) – 3 months table soccer vs. baseline



**R**  $p < 0.1$    $p < 0.06$  **L**  
*corrected*

\*anterior cingulate cortex



## Lifestyle-Modifikationen



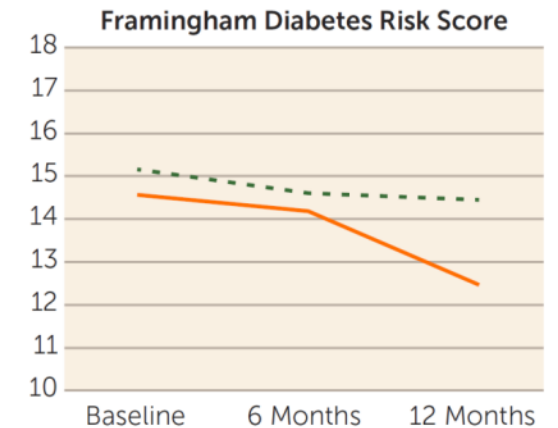
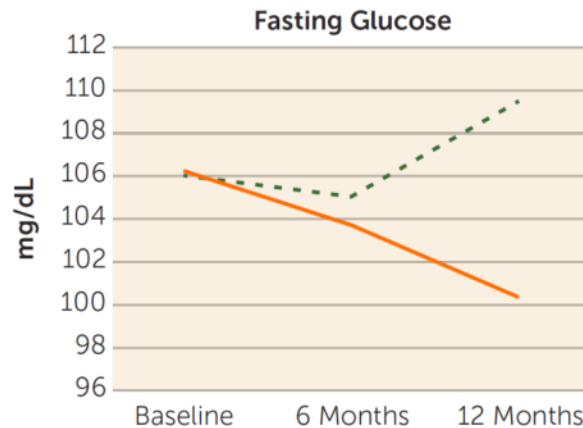
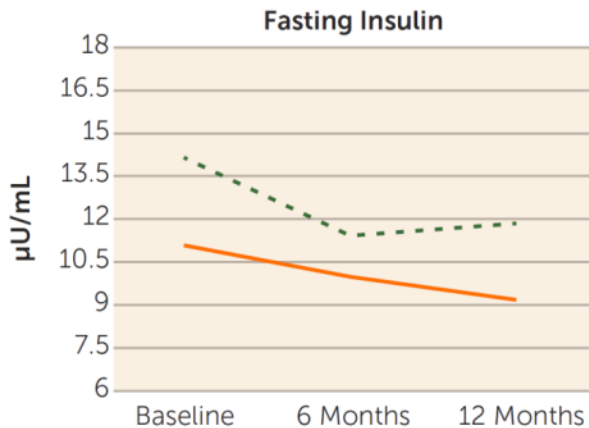
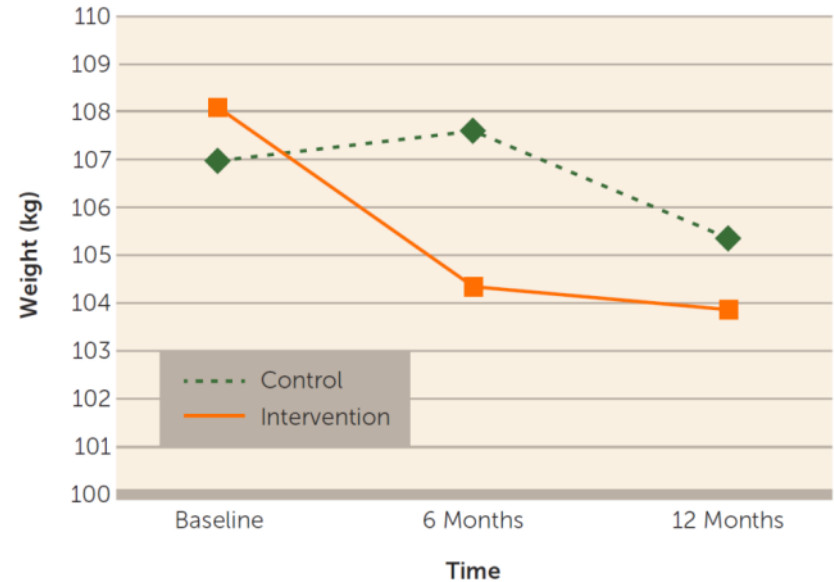
# Change of lifestyle – what is evident?

Element	Level of Evidence (adapted from the Canadian Best Practice Initiative Methodology Background Paper) <sup>a</sup>
<b>Diet</b>	
Caloric restriction is more important than macronutrient content for weight loss	Level 2
Diets that are low in cholesterol, total fat, and saturated fats lower total cholesterol and LDL	Level 1
The Portfolio diet has shown a reduction in LDL that is similar to statins	Level 2
Decreasing sodium intake lowers blood pressure	Level 1
The DASH diet lowers blood pressure and lipids	Level 2
The OmniHeart diet lowers blood pressure and lipids	Level 2
The Mediterranean diet has beneficial effects on weight, blood pressure, lipids, and blood sugar	Level 2
Diabetes risk is decreased by intake of fiber and complex carbohydrates	Level 1
<b>Exercise</b>	
Weight loss is proportional to duration of activity and amount of exertion	Level 2
Duration of exercise correlates with improvement in lipids	Level 1
The amount of physical activity required to lower blood pressure is controversial	Level 1
<b>Cognitive-behavioral therapy (CBT)</b>	
Successful strategies include goal setting, self-monitoring, structured curricula, and increasing self-efficacy	Level 2
<b>Other key elements</b>	
The use of multiple components (diet, exercise, and CBT) improves outcomes	Level 1
Personalization improves outcomes	Level 1
Duration of at least 4 months of active intervention is associated with greater success	Level 2
Higher-intensity programs show better results than lower-intensity programs	Level 2
Multidisciplinary treatment teams are associated with more significant outcomes	Level 2
Training of program leaders increases effect size	Level 2
Face-to-face interventions are more efficacious than virtual meetings	Level 1

<sup>a</sup>Level 1 equals systematic reviews (with or without meta-analysis). Level 2 equals nonsystematic reviews, including narrative reviews.  
Abbreviations: DASH = dietary approach to stopping hypertension, LDL = low-density lipoprotein.

# Die Stride-Studie

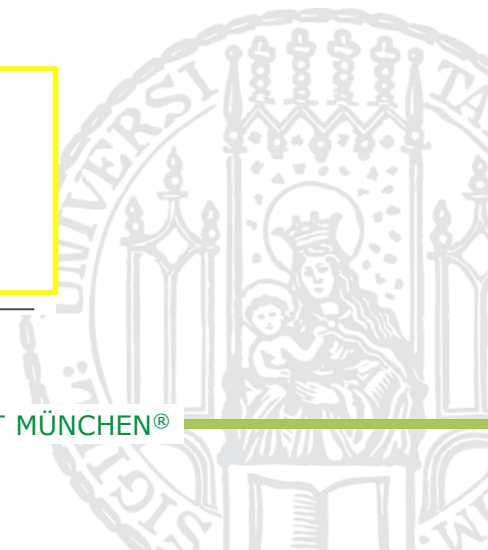
- Increasing awareness through monitoring: diet, physical activity, and sleep
- Creating personalized diet and physical activity plans
- Reducing calories
- Reducing portion sizes, identifying and choosing alternative foods, modifying meals
- Increasing consumption of fruits, vegetables, fiber, and low-fat dairy products
- Increasing physical activity
- Developing action plans for high-risk eating situations
- Graphing progress and making adjustments
- Addressing mental health effects on lifestyle-change efforts



# PHARMAKOLOGISCHE BEHANDLUNGSMÖGLICHKEITEN ZUR GEWICHTSREDUKTION – WFSBP-LEITLINIE II

Recommendation Table II. Recommendations for the psychosocial and pharmacological intervention to reduce weight gain and other metabolic side effects associated with antipsychotic treatment.

Intervention/Drug	Category of evidence <sup>a</sup>	Recommendation <sup>b</sup>
Psychosocial intervention	C	4 <sup>1</sup>
Switch to aripiprazole	A	2 <sup>2</sup>
Switch to ziprasidone	B	3 <sup>2</sup>
Amantadine	C	4
H2-receptor antagonists	C	4
Metformin	D	5
Modafinil	F	—
Orlistat	F	—
Rosaglitazone	F	—
Rosaglitazone + clozapine	C	4
Sibutramine	F	—
Sibutramine + olanzapine	C	4
Topiramate	C	4
Topiramate + olanzapine	B	3





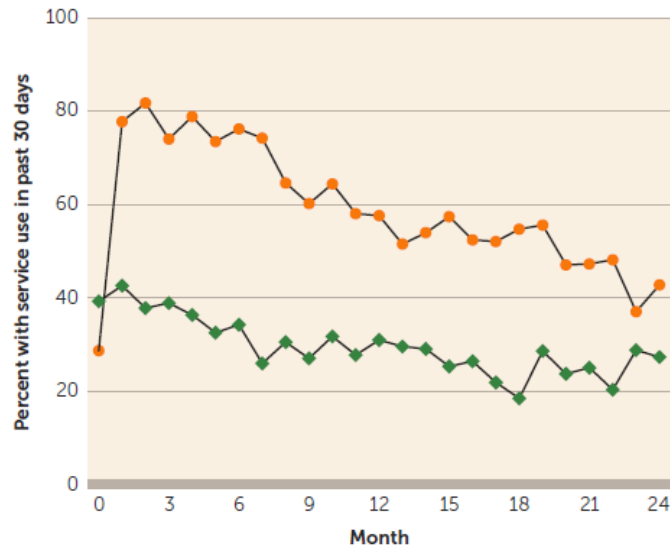
## Kombinationstherapie – Mehr ist mehr?



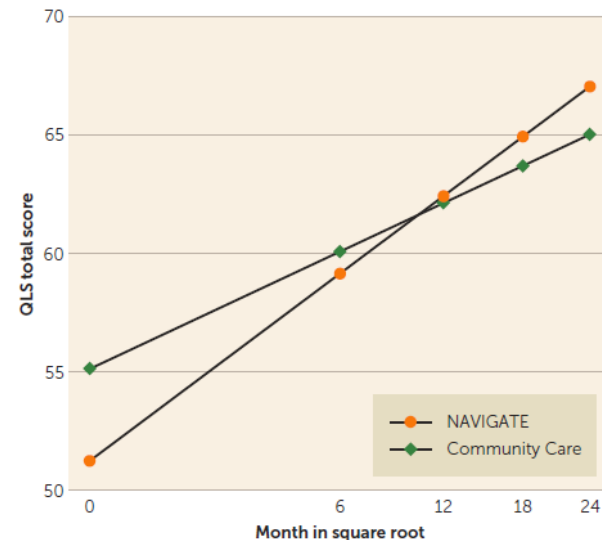
# The RAISE Study 2015 on FEP

- Intervention group included 4 elements:
  - Personalisierte Medikation (summary of the **evidenz for FEP**)
  - Psychoeducation for families
  - Resilience-focussed psychotherapy
  - Supported Employment
- 223 FEPs received the intervention and 181 Treatment as usual

B. Individual Resiliency Training: Have you had individual sessions with a mental health care provider who helps you work on your goals and look positively toward the future?

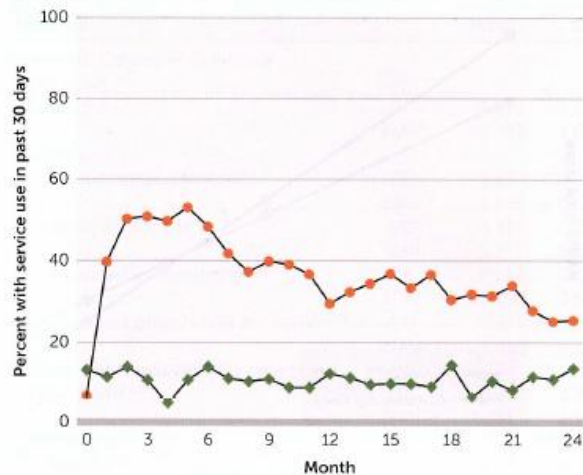


A. QLS total score<sup>b</sup>

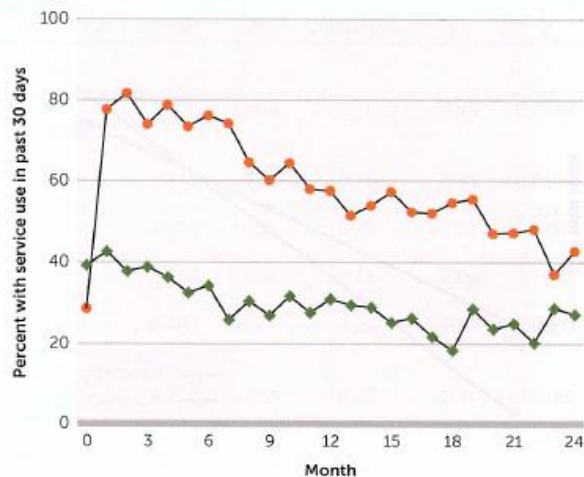


# The RAISE Study 2015 on FEP (2)

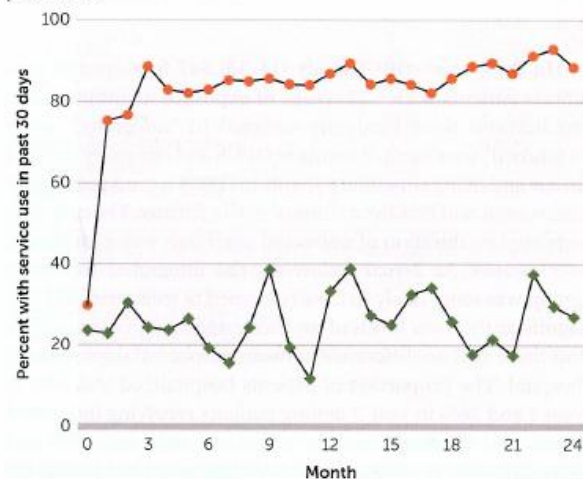
A. Supported Employment/Education: Have you met with a person who is helping you get a job in the community or furthering your education?



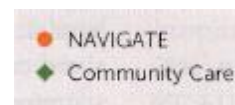
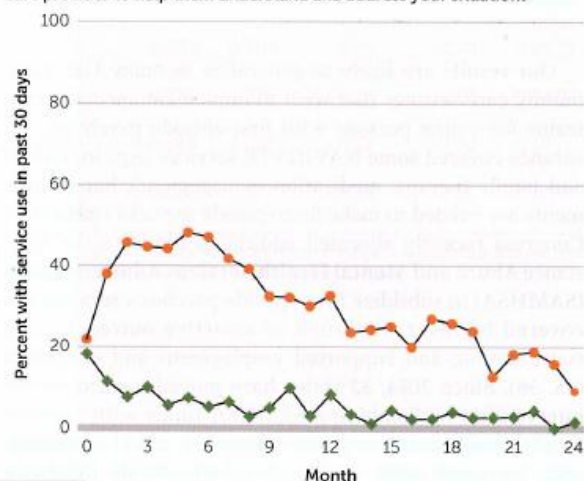
B. Individual Resiliency Training: Have you had individual sessions with a mental health care provider who helps you work on your goals and look positively toward the future?



C. COMPASS Decision Support: Were you asked to record your symptoms and side effects before you met with your psychiatrist or nurse practitioner?<sup>b</sup>



D. Family Psychoeducation: Has your family met with a mental health care provider to help them understand and address your situation?

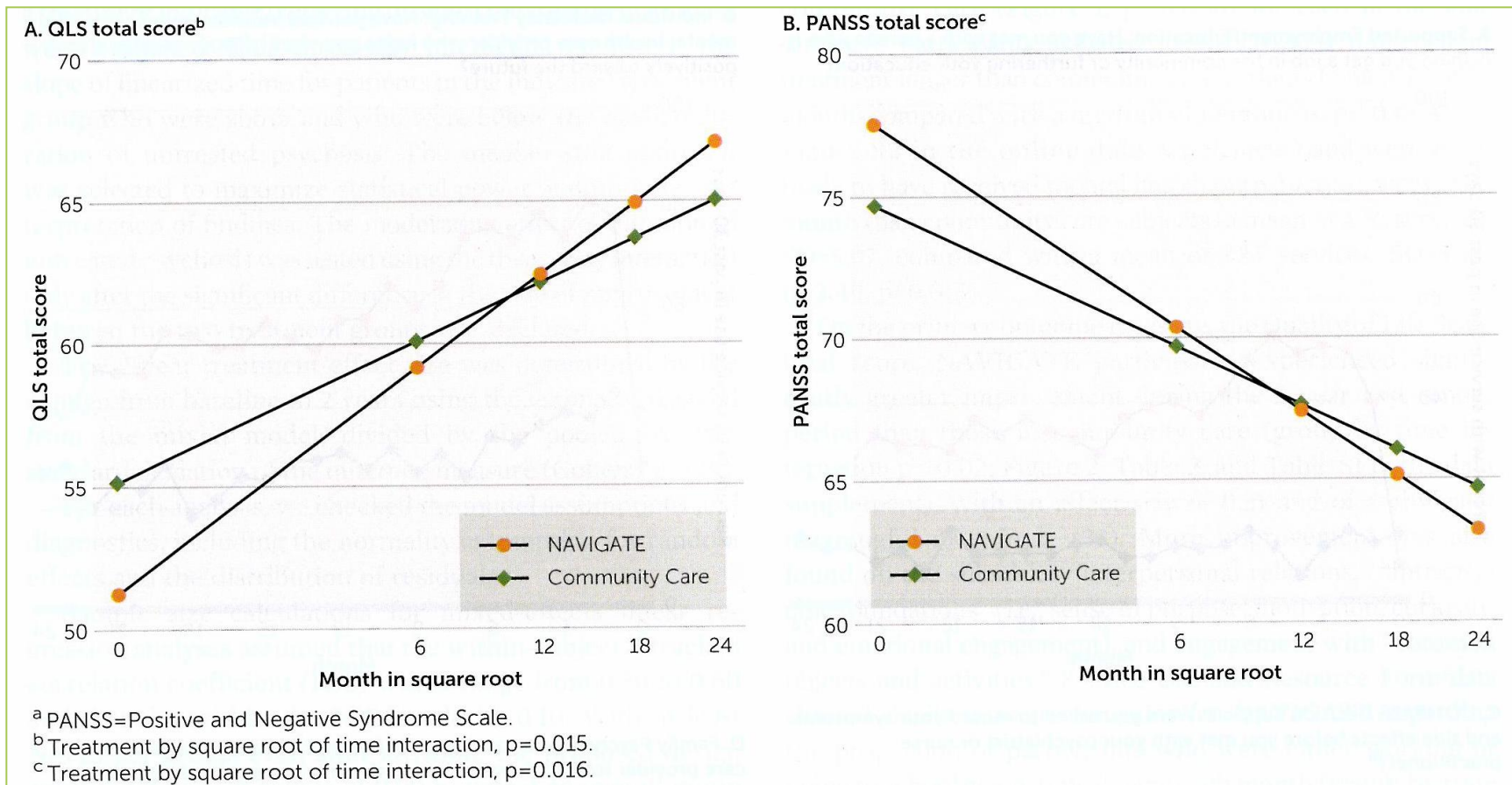


**Patient Self-reported use of NAVIGATE Model targeted Services during study period at NAVIGATE and community care sites**



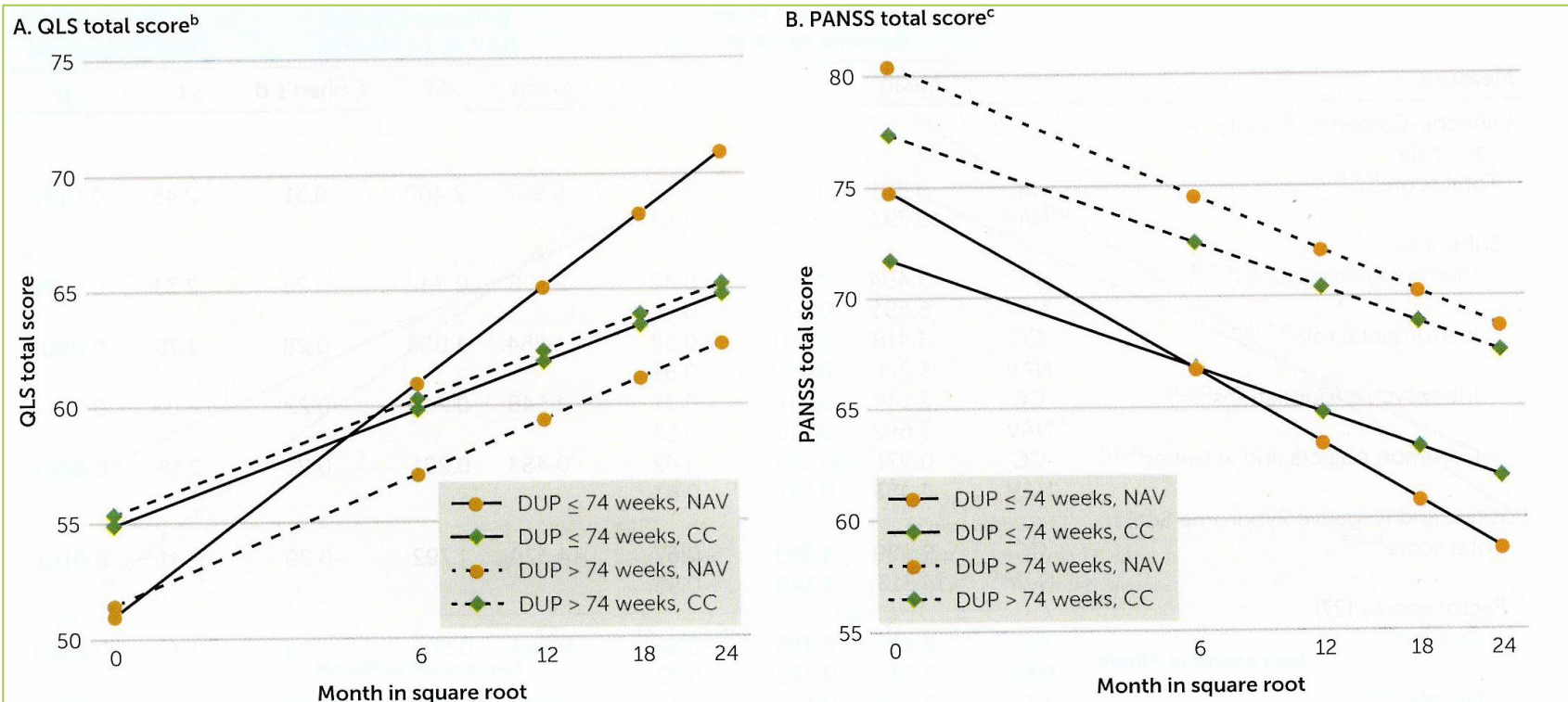
# The RAISE Study 2015 on FEP (3)

## Model-based estimates of Heinrichs-Carpenter Quality of life-scale (QLS) – total score and PANSS total score



# The RAISE Study 2015 on FEP (4)

## Model-based estimates of QLS – total score and PANSS total score – Effects of shorter and longer DUP



<sup>a</sup> In the model, DUP and DUP by square root of time by treatment terms were included as covariates in addition to the covariates listed in Table 2. The DUP by square root of time term was found not to be significant for either outcome. PANSS=Positive and Negative Syndrome Scale; CC=Community Care; NAV=NAVIGATE.

<sup>b</sup> DUP by treatment by square root of time interaction,  $p=0.003$ .

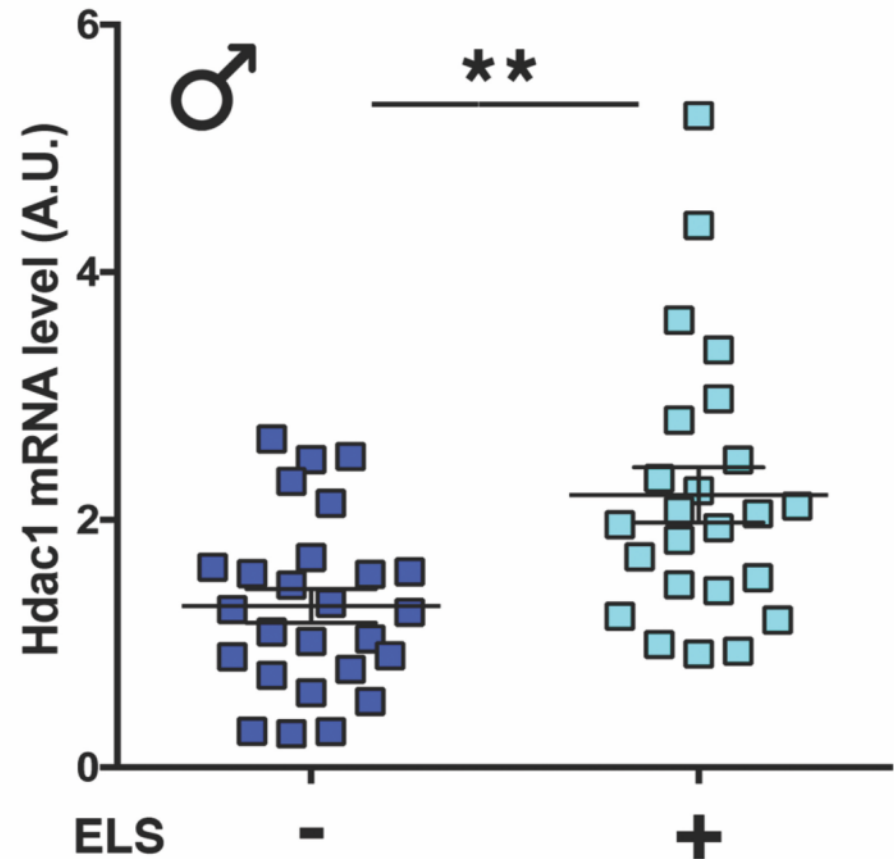
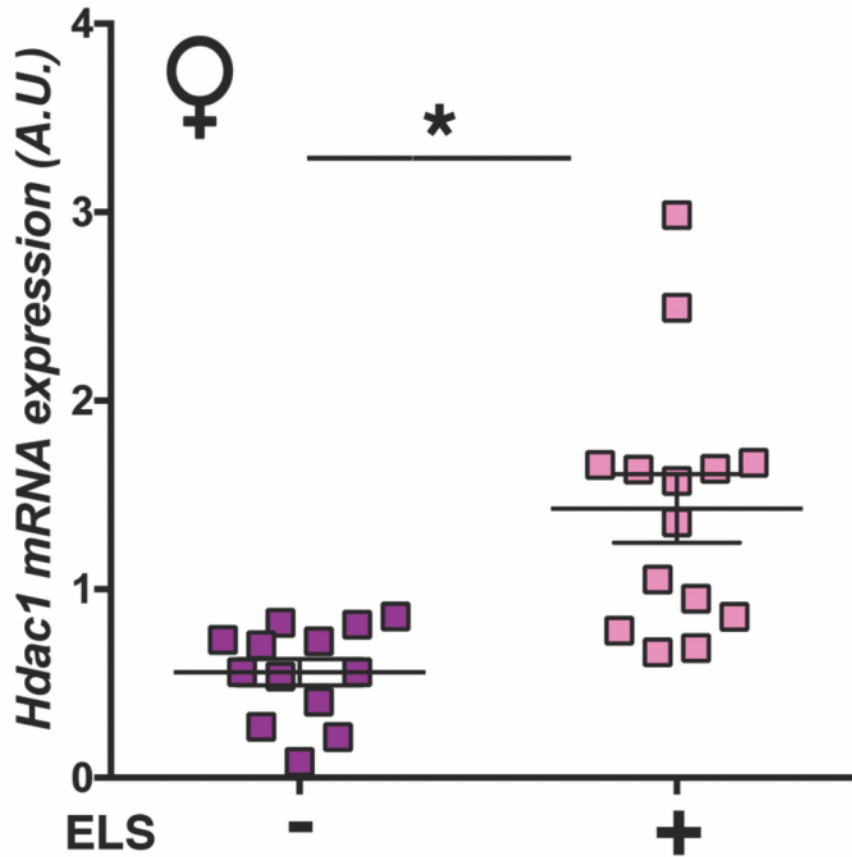
<sup>c</sup> DUP by treatment by square root of time interaction,  $p=0.043$ .

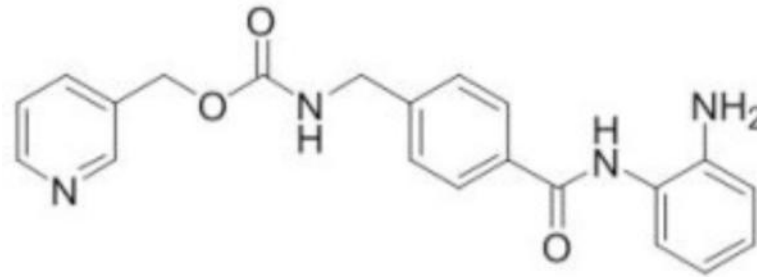




## Frühkindliches Trauma, Methylierungs-Status und HDAC-Inhibitoren

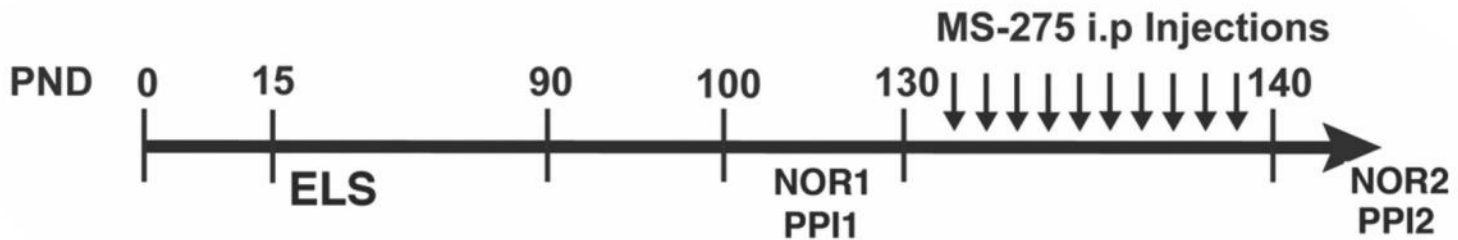




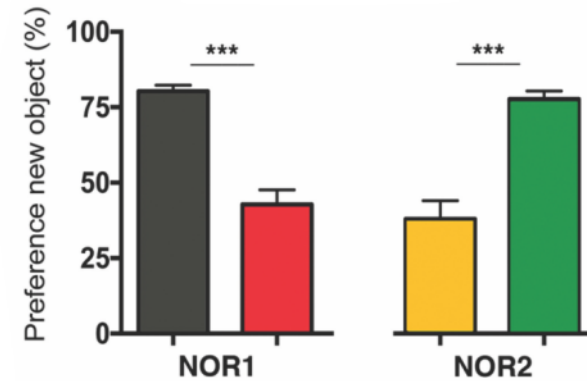
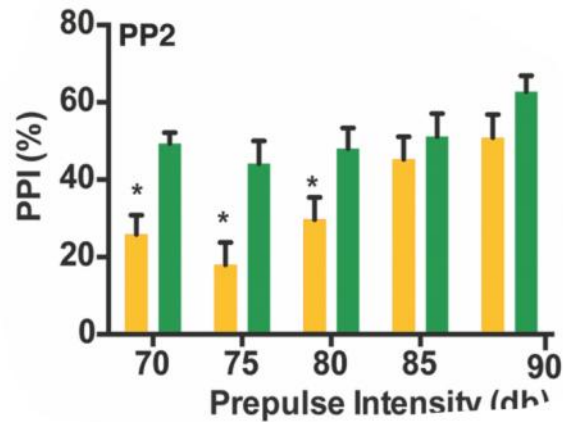
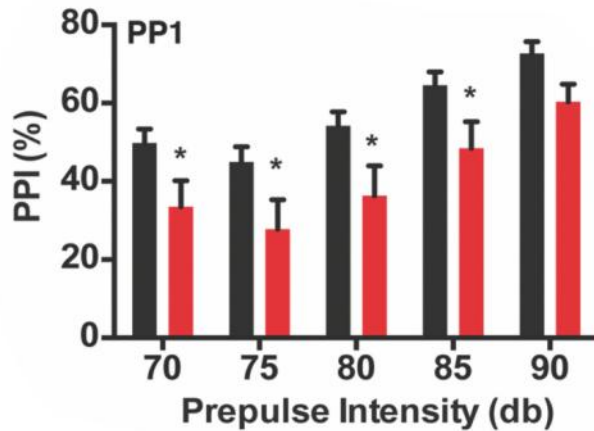
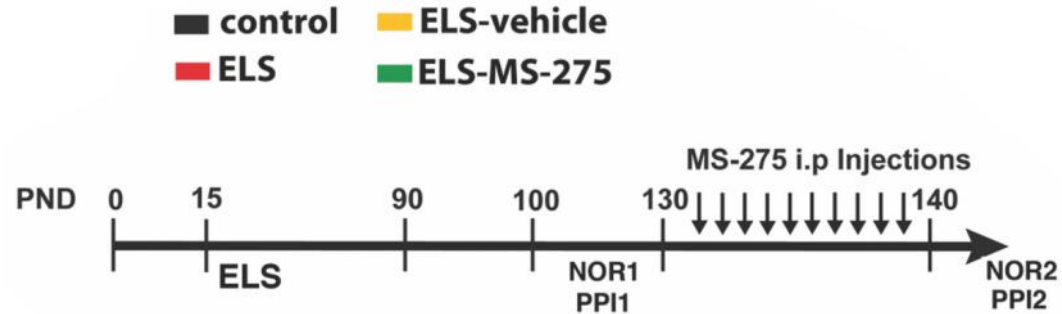


**Entinostat**

■ control    ■ ELS-vehicle  
■ ELS        ■ ELS-MS-275



# HDAC inhibitor Entonostat (MS-275) ameliorates ELS induced SZ-like phenotypes



# Übersicht

**Behandlung von psychischen Erkrankungen am Beispiel  
schizophrener Psychosen**

**Pharmakotherapie**  
**- Wirkung, Nebenwirkung**  
**- Neue Outcome-Parameter**

**Gehirnstimulationsverfahren**

**Sport als Medikament**

**Lifestyle-Modifikationen**

**Kombinationstherapie – Mehr ist mehr?**

**HDAC-Inhibitoren: komplett neue Medikamente**

# People doing the work

**AG  
Hasan**



**AG  
Rossner**



**AG  
Schulze**



**AG  
Schmitt**

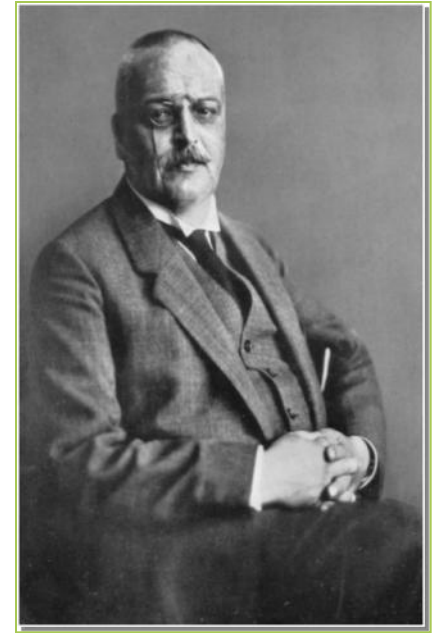


**AG  
Koutsouleris**



**AG  
Malchow**





**Vielen Dank für Ihre  
Aufmerksamkeit**

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