

PANIC-NET

Struktur, Funktionsweise und erste Ergebnisse

TMF – Münster 03-2011

Improving the Treatment of Panic Disorder -
From a Better Understanding
of Fear Circuit Mechanisms
to More Effective
Psychological Treatment and Routine Care

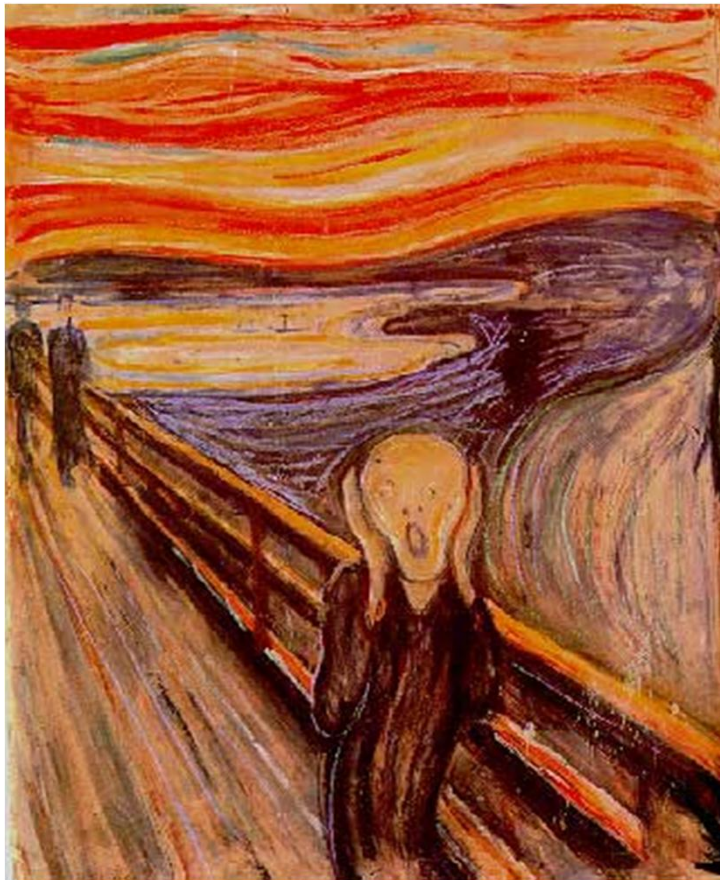
Prof. Dr. Volker Arolt, Münster

Panikstörung

- **Anfälle heftigster (!) Angst**
- **Angst vor Kontrollverlust**
- **Situationsunspezifisch, „aus h.Himmel“**
- **Ohne phobischen Stimulus**
- **Vegetative Begleitsymptomatik**

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1. Förderperiode (9/2006-9/2009)
2. Förderperiode (10/2009-10/2012)



Panikerkrankung

(mit Agoraphobie)

1. Symptome haben ein quälendes Ausmaß
 2. Symptome greifen in die Lebensführung ein
- ...ist häufig (PP 3%)
 - ...verläuft chronisch
 - ...beginnt früh (20 LJ.)

Panikattacke Panikerkrankung

- in > 70% Komorbidität mit **Agoraphobie**
- in > 50% Komorbidität mit **Depression**
- in > 25% **Alkoholmißbrauch/ -abh.**

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1st Funding Period (9/2006-9/2009)
2nd Funding Period (10/2009-10/2012)

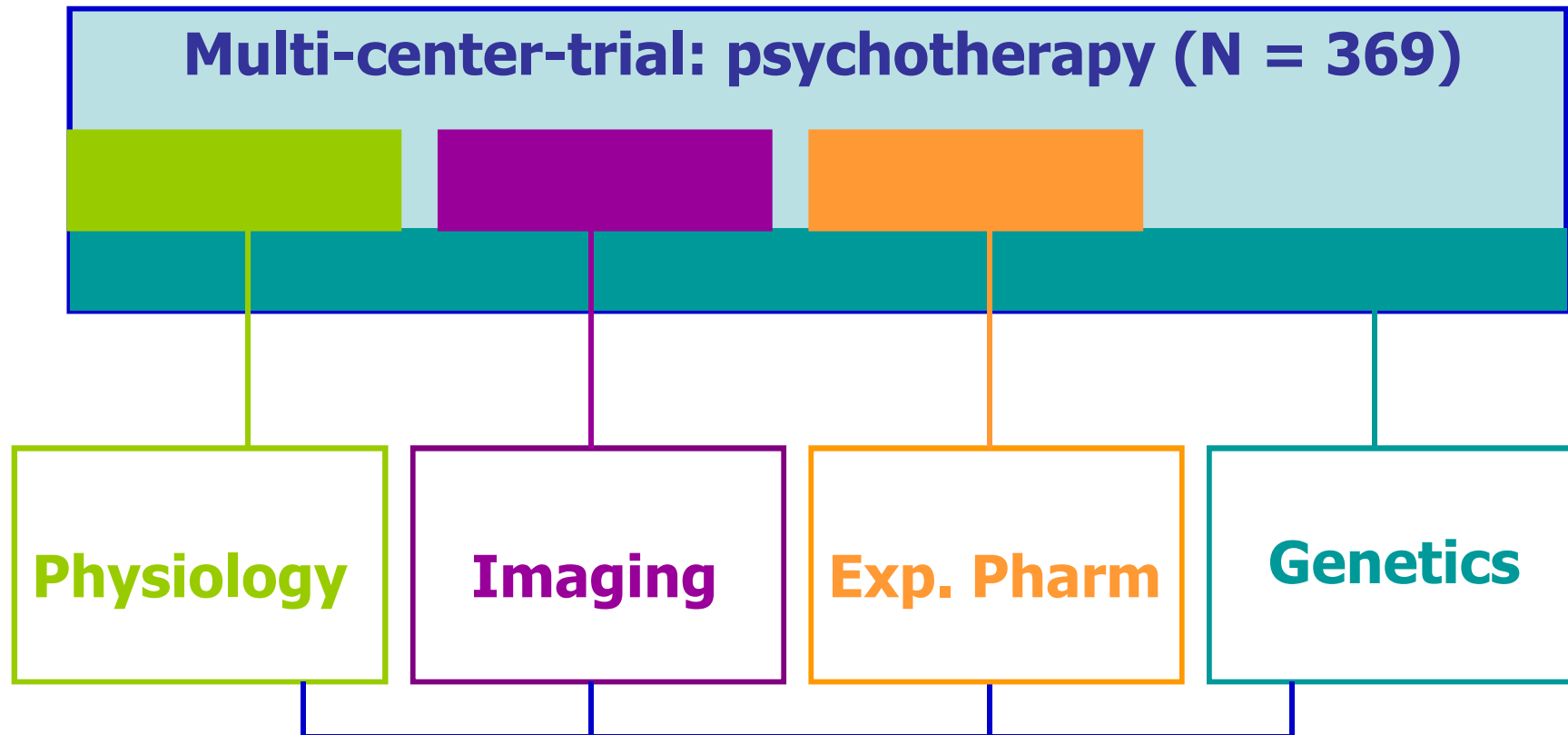
Panikerkrankung



Kognitive Verhaltenstherapie
ist effektiv...

warum ?

Multi Level Research Program:



The multicenter clinical trial (MCT)



Main Questions:

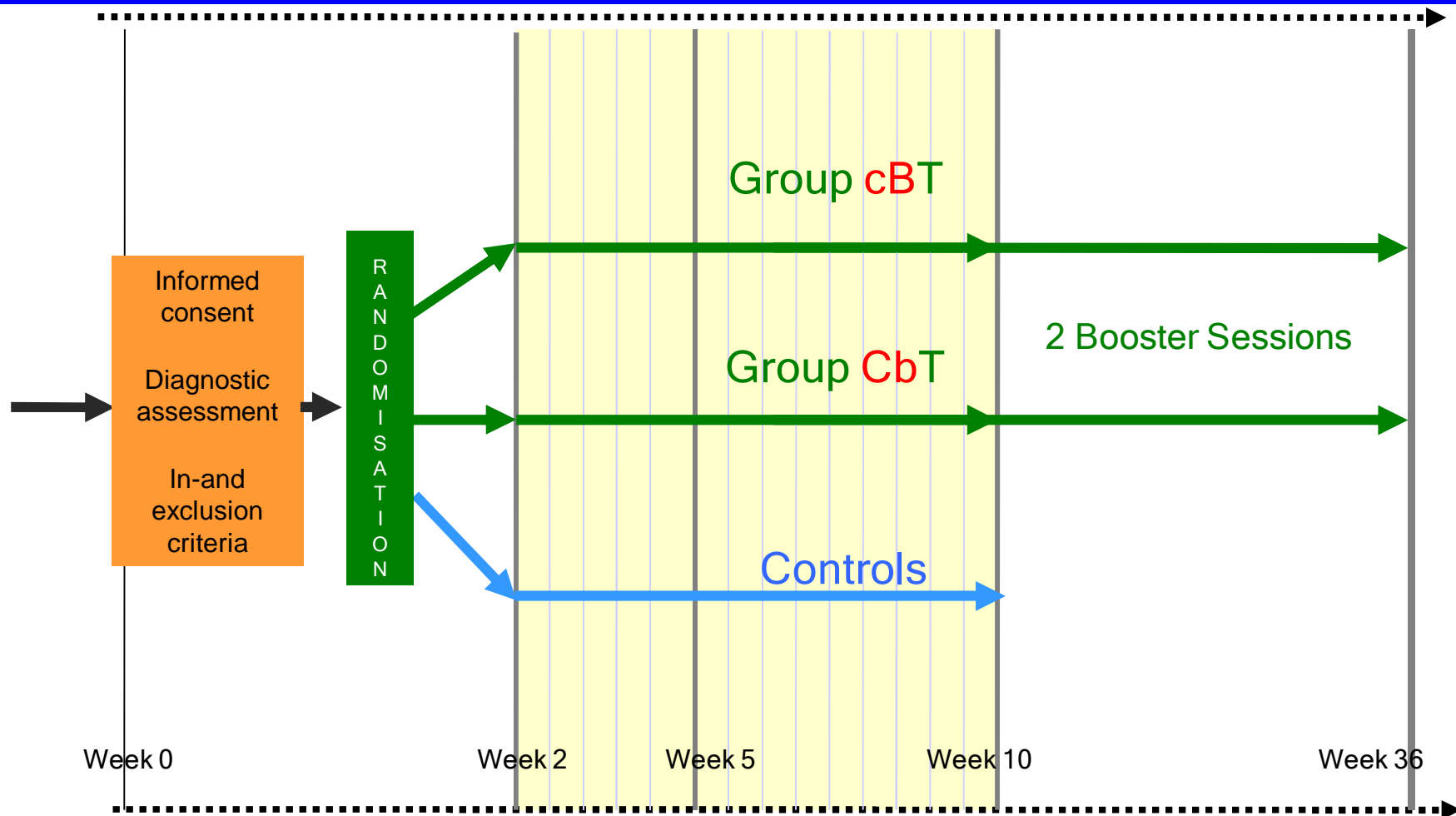
- “ What are the core active ingredients in therapeutic change?
- “ What is the role of (therapist-guided) exposition?

- “ Eight outpatient treatment centers
- “ experienced in methodology /CBT
- “ trained and licensed as part of study's certification procedures

1 Å Dresden (Director: Prof. Ulrich Wittchen)

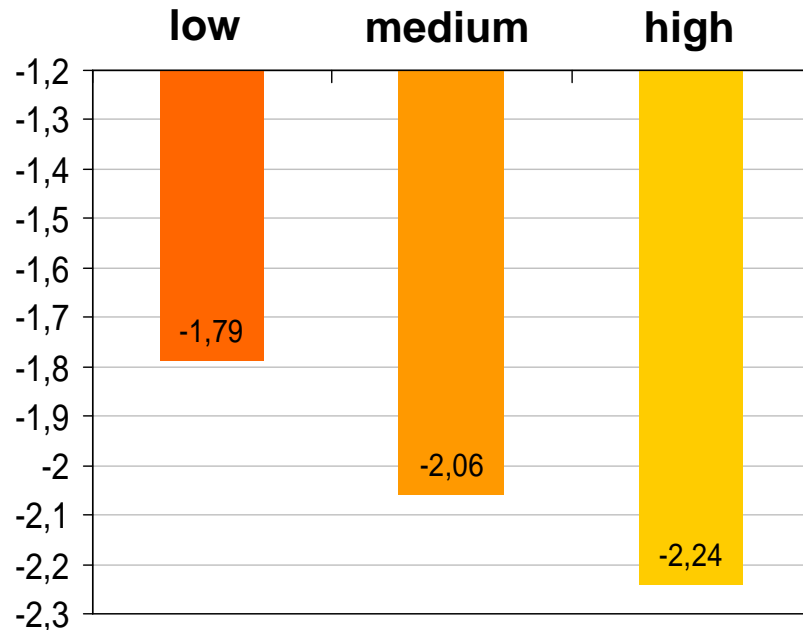
- 2 ö Berlin Charité
- 3 ö Berlin Adlershof
- 4 ö Münster
- 5 ö Aachen
- 6 ö Greifswald
- 7 ö Würzburg
- 8 ö Bremen

Design and Assessment



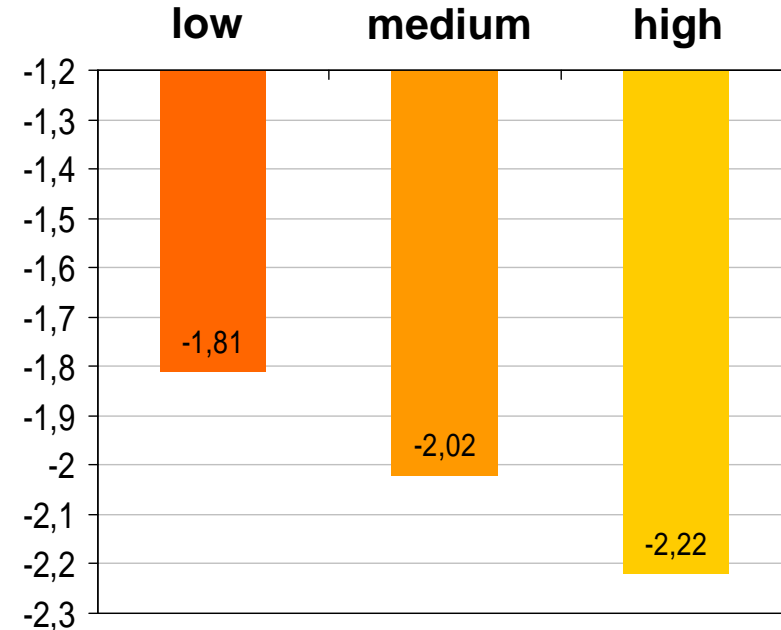
Project P2/3: Results of 1st funding period Frequency and Duration of Exposure in-vivo and Size of Treatment Effect (HAMA)

Exposure frequency (session 7-12)



Effect Size (Cohen's d on HAMA)

Exposure duration (session 7-12)

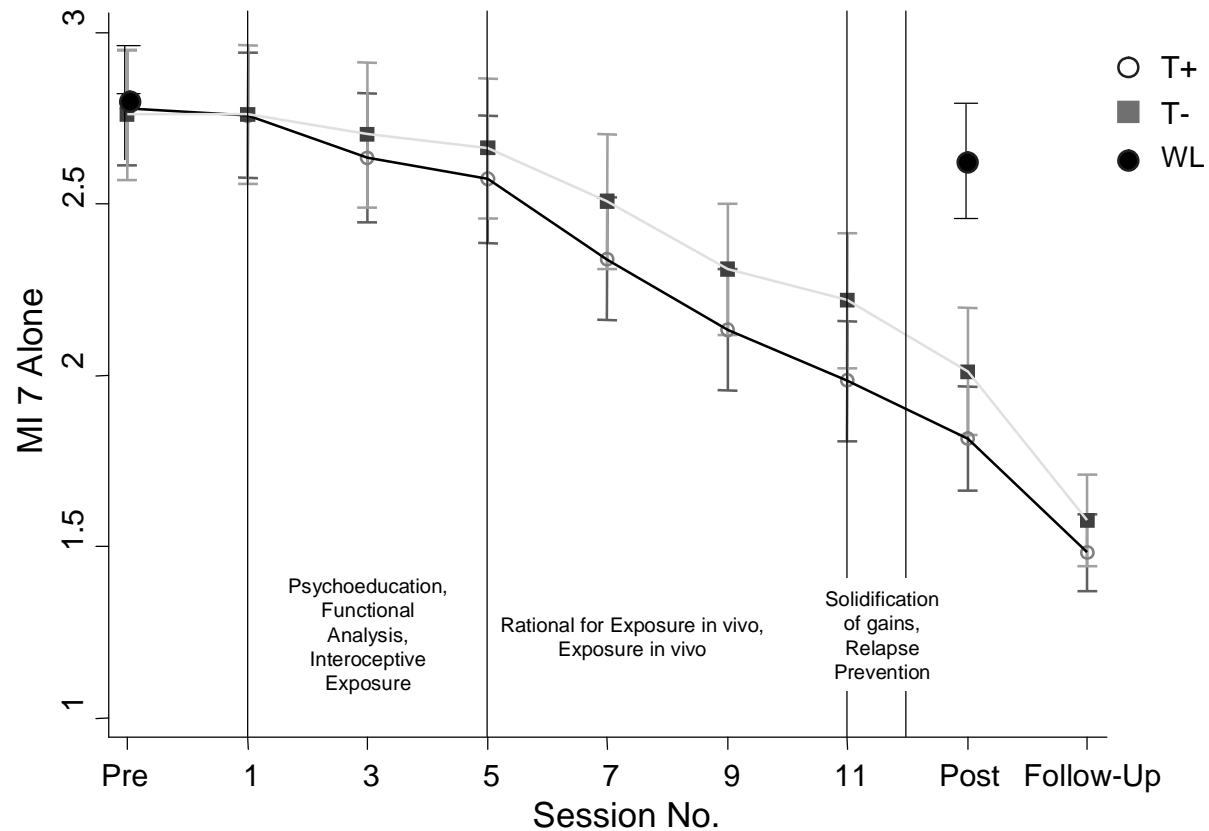


Effect Size (Cohen's d on HAMA)

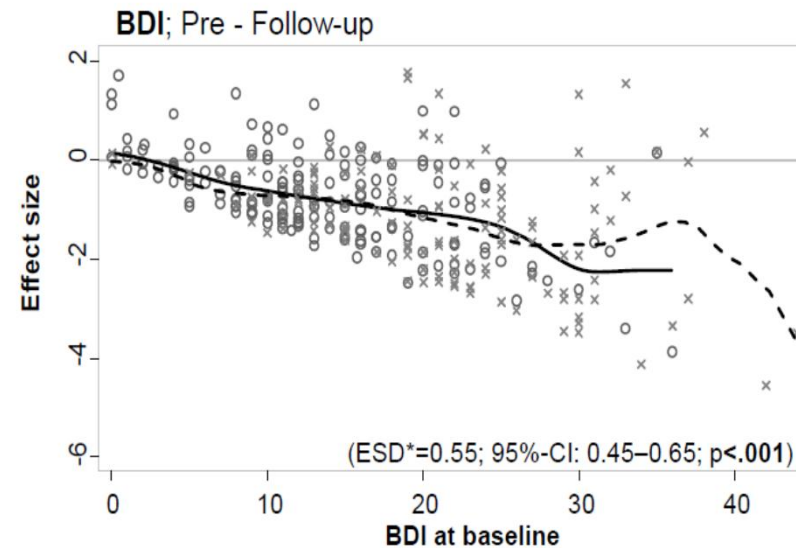
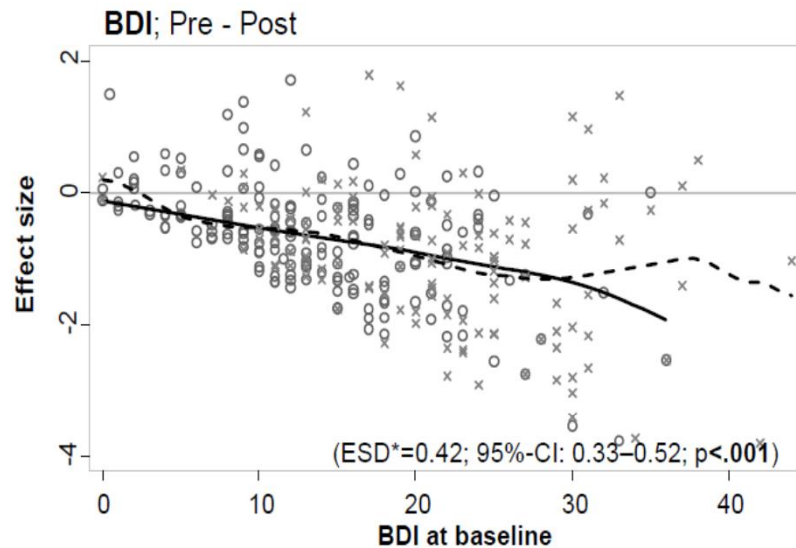
All differences: $p < .001$

**Pre-Post HAMA Effect size among patients with low, medium and high exposure frequency/duration
Exposure frequency and duration are highly associated with effect size on the HAMA (primary outcome criterion)**

Follow-up proposal: Continuation Cluster Project - Overview



Reduction of Depressive Symptomatology Throughout CBT for PD/AG

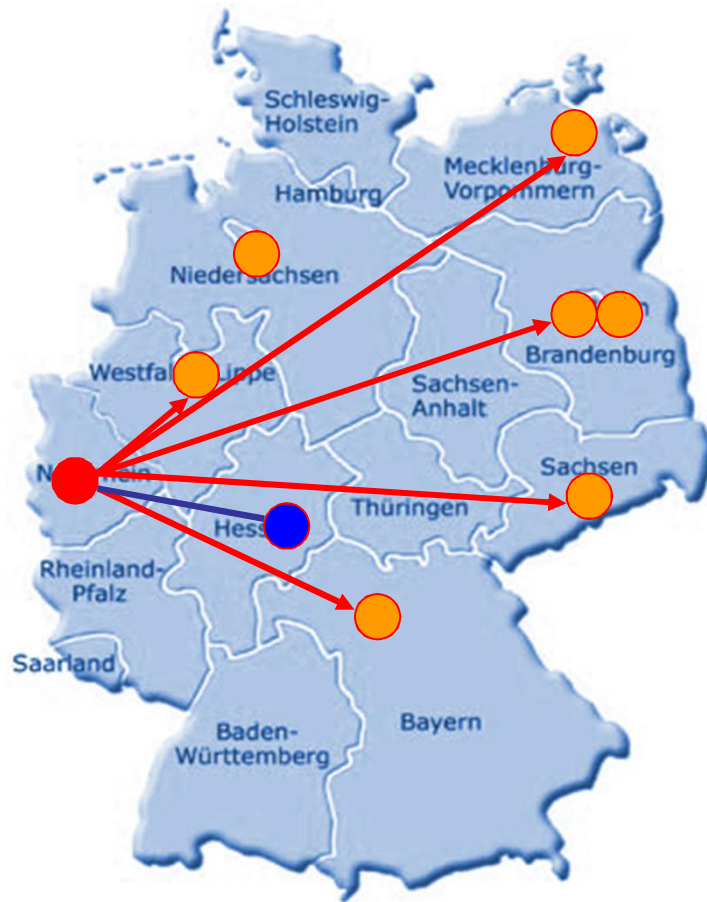


○ Represent one PD/AG patient without comorbid depression at baseline
 × Represent one PD/AG patient with comorbid depression at baseline
 — PD/AG patients without comorbid depression **
 - - - PD/AG patients with comorbid depression **

* ESD=effect size difference; one standard deviation more on the baseline BDI-II predicted higher effect sizes on the BDI-II
 ** Fitted curves from the nonparametric method of local polynomial approximation

Figure 2: Reductions in BDI-II by baseline BDI-II among those with or without comorbid depression (active treatment; n=301)
(lifetime-diagnosis)

Emotional processing / fMRI



“ Main Questions:

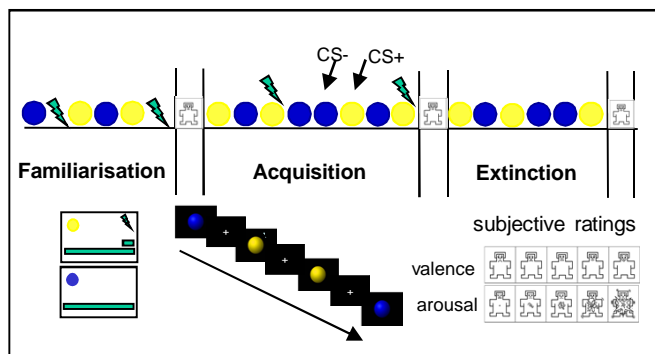
- “ Which brain areas/ components fear circuit involved in characteristics of PD ?
- “ Components modulated by CBT ?
- “ Outcome prediction by activation ?

1 Å Aachen /Marburg (Director: Prof. Tilo Kircher)

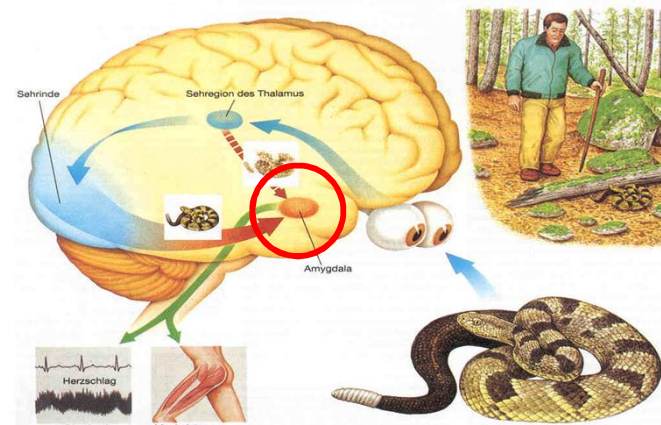
- 2 ð Berlin Charité
- 3 ð Münster
- 4 ð Dresden
- 5 ð Greifswald
- 6 ð Würzburg

Paradigm P7: Results of 1st funding period

Paradigm 1: Fear conditioning



Paradigm 1 (pooled) : Fear conditioning (preliminary results)

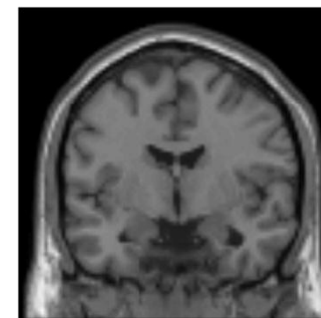


CS+ > CS- (activations t1 > t2):

Patients: reduction amygdala activation, NOT controls.



Patients n=33, p<0.05 FWE corr



Controls: n=18, p<0.01 uncorr

The role of genetic variation



“ Main Questions:

“ How does genetic variation modulate CBT and its outcome?

“ How does genetic variation influence clinical, psychophysiological, and fear-circuit mechanisms

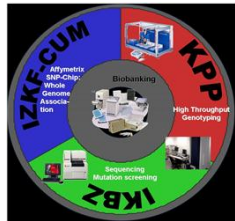
“ Efficacy of CBT on fear reduction in PD: the role of genetic variation (J. Deckert)

“ DNA from all Patients and Controls

1 Å Würzburg (Director: Prof. Jürgen Deckert)

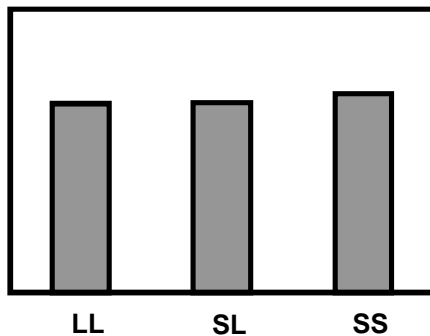
- 2 ð Berlin Charité
- 3 ð Berlin Adlershof
- 4 ð Münster
- 5 ð Aachen
- 6 ð Greifswald
- 7 ð Dresden
- 8 ð Bremen

P6: Results of 1st funding period BT on fear reduction in panic disorder: The role of genetic variation



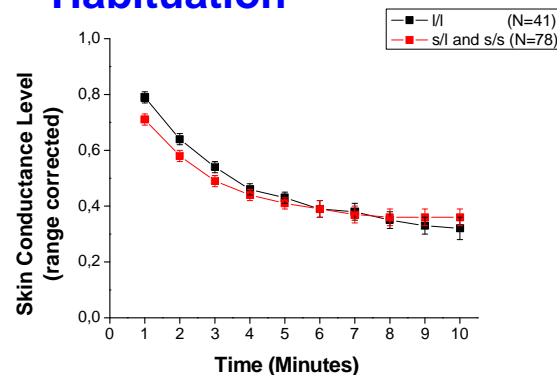
DNA from **n= 278 patients** (02/15/09), **n> 300 patients** until 09/30/09
Candidate (5-HTTLPR, 5-HT1A, MAO-A and COMT) genotyping for pre-intervention phenotypes, e.g. preliminary results with **5-HTTLPR**

Project P2/3 Anxiety Sensitivity



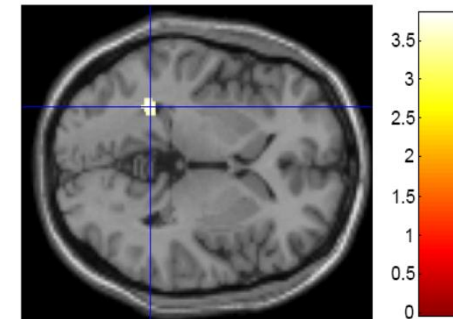
ll=sl=ss (total n=278)

Project P5 Habituation



ll(n=41) > ss+sl(n=78)

Project P7 Conditioning



ll(n=23) > ss+sl (n=35)

Plus: Genome wide association study using the Illumina 300 k microarray

PANIC-NET "Zusammenfassung"

- Erste Förderperiode: Studien abgeschlossen
- Etabliertes Forschungsnetzwerk / methodische Standards
- Netzwerk gut trainierter Psychotherapeuten
- Erste Ergebnisse zeigen die Bedeutsamkeit der Exposition

Follow-up:

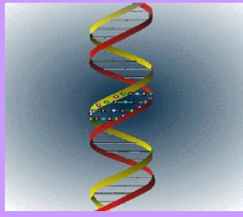
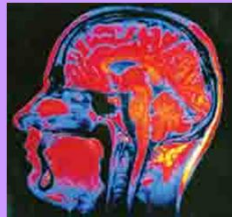
Die Mechanismen besser verstehen

Klinische Ebene, Psychophysiologie,

Furchtnetzwerk des Gehirns,

Genetischer Einfluß, Biologische Verstärkung der CBT

Let us go ahead!



Coordinator: Prof. Dr. Volker Arolt, Münster

TMF ?

BMBF: Förderung verbundübergreifender Forschung ?

Zwei übergreifende Problemstellungen:

- „Guidelines for Good Clinical Practice“ für Psychotherpiestudien
- Intensivierung und Vernetzung der molekulargen. Aktivität

Zwei Negativsignale...

PANIC-NET

Operational Structure, 1st Results,
Now: 2nd Funding Period (10/2009-2012)

Vielen Dank für Ihre Aufmerksamkeit!

Publikationen zur Netzwerkstruktur und Vorgehensweise:

Arolt V et al. Das Forschungsnetzwerk PANIC-NET . Von einem besseren Verständnis neurobiologischer Mechanismen der Furchtregulation zu effektiverer psychotherapeutischer Behandlung in der Praxis.

Psychother Psychosom Med Psychol. 2009 Mar-Apr;59(3-4):124-31.

Gloster AT et al. Mechanism of action in CBT (MAC): methods of a multi-center randomized controlled trial in 369 patients with panic disorder and agoraphobia.

Eur Arch Psychiatry Clin Neurosci. 2009 Nov;259 Suppl 2:S155-66.

Prof. Dr. Volker Arolt, Münster

Panic Disorder (with Agoraphobia)

Unmet research demands: Questions to ask

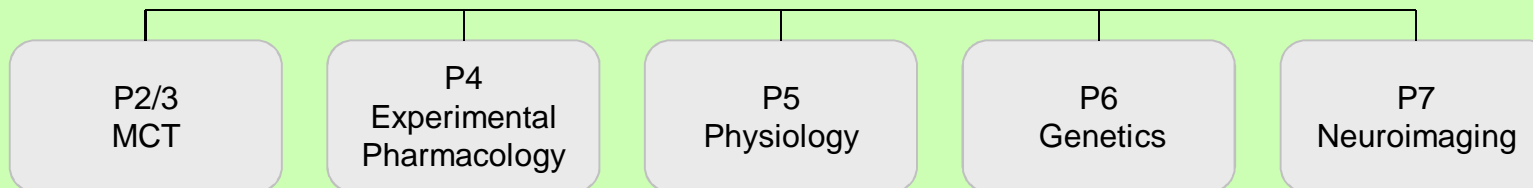
- Core factors of CBT efficacy - role of exposure ?
- Efficacy in subtypes / with comorbidity ?
- Proof of concept- / experimental therapies ?
- Psychophysiological correlates of CBT effects ?
- Fear circuit mechanisms underlying CBT effects ?
- Genetic control of fear/ relearning – CBT effects ?

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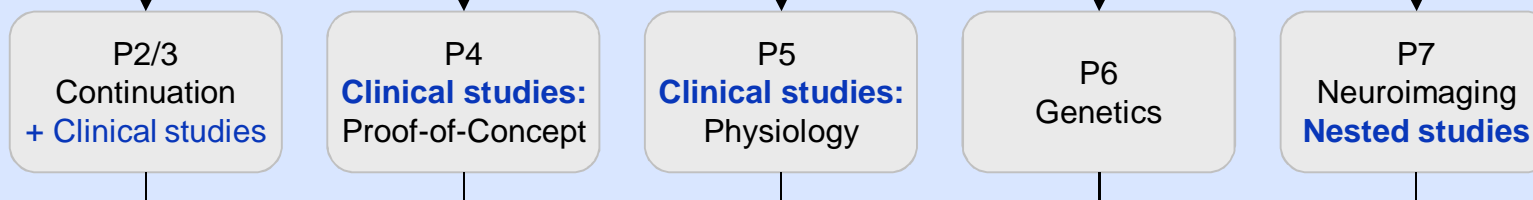
1st funding period

Why?



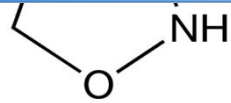
2nd funding period

How?

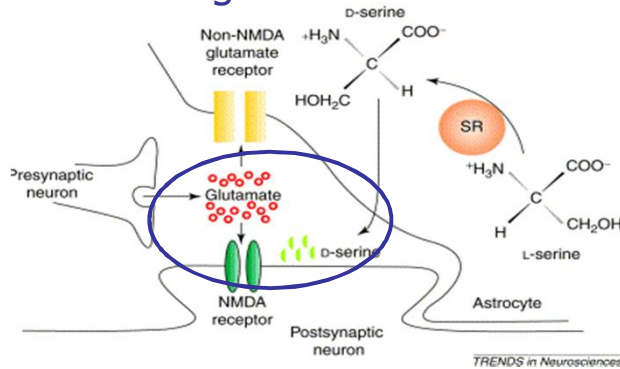


P4: Experimental Pharmacology

(and results of 1st funding period)

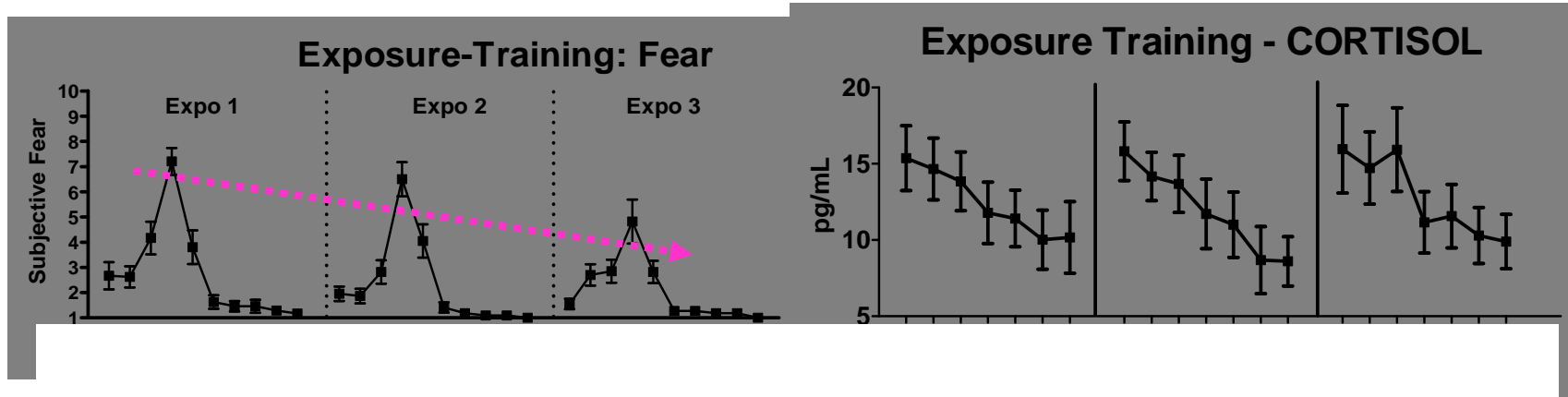


Glutamatergic Neurotransmission



Recruitment Status 01/09:
32 out of 44 patients treated

Baranano et al., Trends Neuroscience 24:99-106, 2004



P5: Results of 1st funding period Biological correlates of CBT treatment effects in PD: Overarching multicenter-project

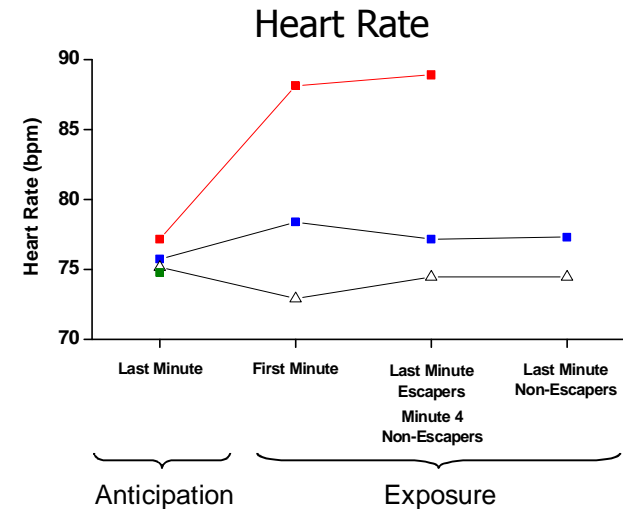
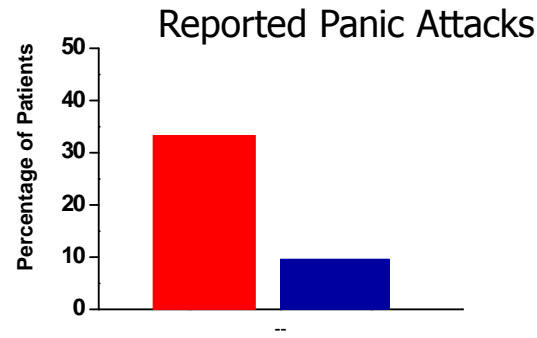
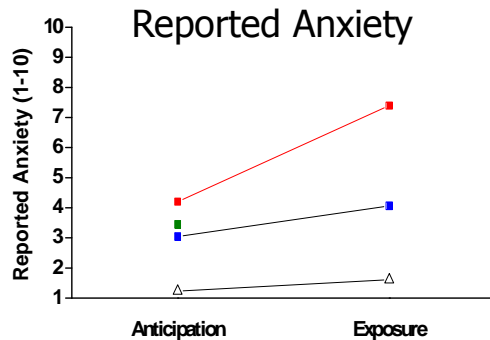
Behavioral Avoidance Test at all Centers

Exposure to a locked dark room for 10 minutes preceded by 10 minutes anticipation test at baseline:

N = 339 patients tested (from MCT)



Results 1st Funding Period

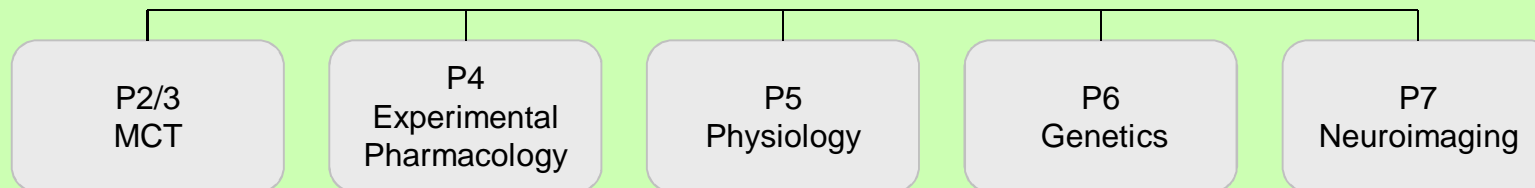


| | |
|---------------------------------|----------------|
| ■ Panic Patients - Avoiders | (N=38, 11,2%) |
| ■ Panic Patients - Escapers | (N=70, 20,6%) |
| ■ Panic Patients - Non-Escapers | (N=231, 68,2%) |
| △ Students Controls | (N=21) |

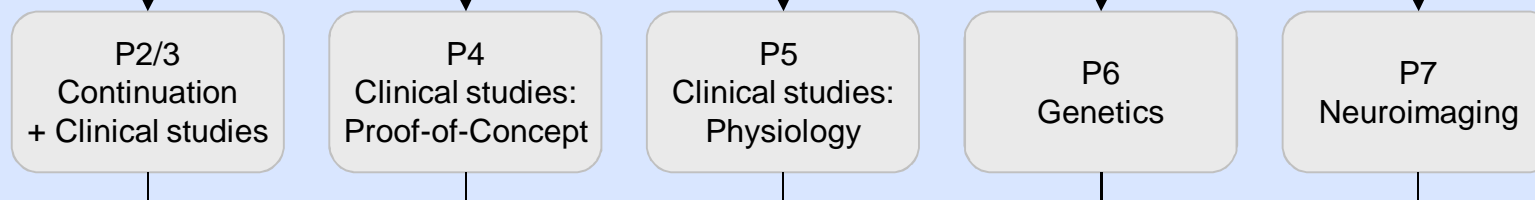
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1st funding period



2nd funding period



PANIC-NET

Zukunftsperspektive

Heute: CBT



Heute + : **cBT**



Mechanismen der Furchtverarbeitung verstehen



Morgen: **individualisierte** CBT!

Design and Methods - the Manual

How do the variants differ?

- “ Only and exclusively with regard to „therapist-guided exposure in vivo“
- “ Both variants refer to identical standard situations
- “ Both variants imply the same exposure dose (2 times 3 situations)
- “ Same rules and algorithms apply.

Sessions 1-3

Psychoeducation, Behavioral Analysis

Sessions 4-5

Interoceptive Exposure, Exposure Rationale

Sessions 6-8

Therapist-guided exposure: public transportation, shopping mall, forest

Sessions 6-8

Instruction/encouragement for exposure: public transportation, shopping mall, forest

Session 9:

Anticipatory Anxiety

Sessions 10-11

Therapist-guided exposure: two individual situations

Sessions 10-11

Instruction/encouragement for exposure: two individual situations

Sessions 12, Booster 1&2:

Summary and Relapse Prevention

Experimental Pharmacology



Main Questions:

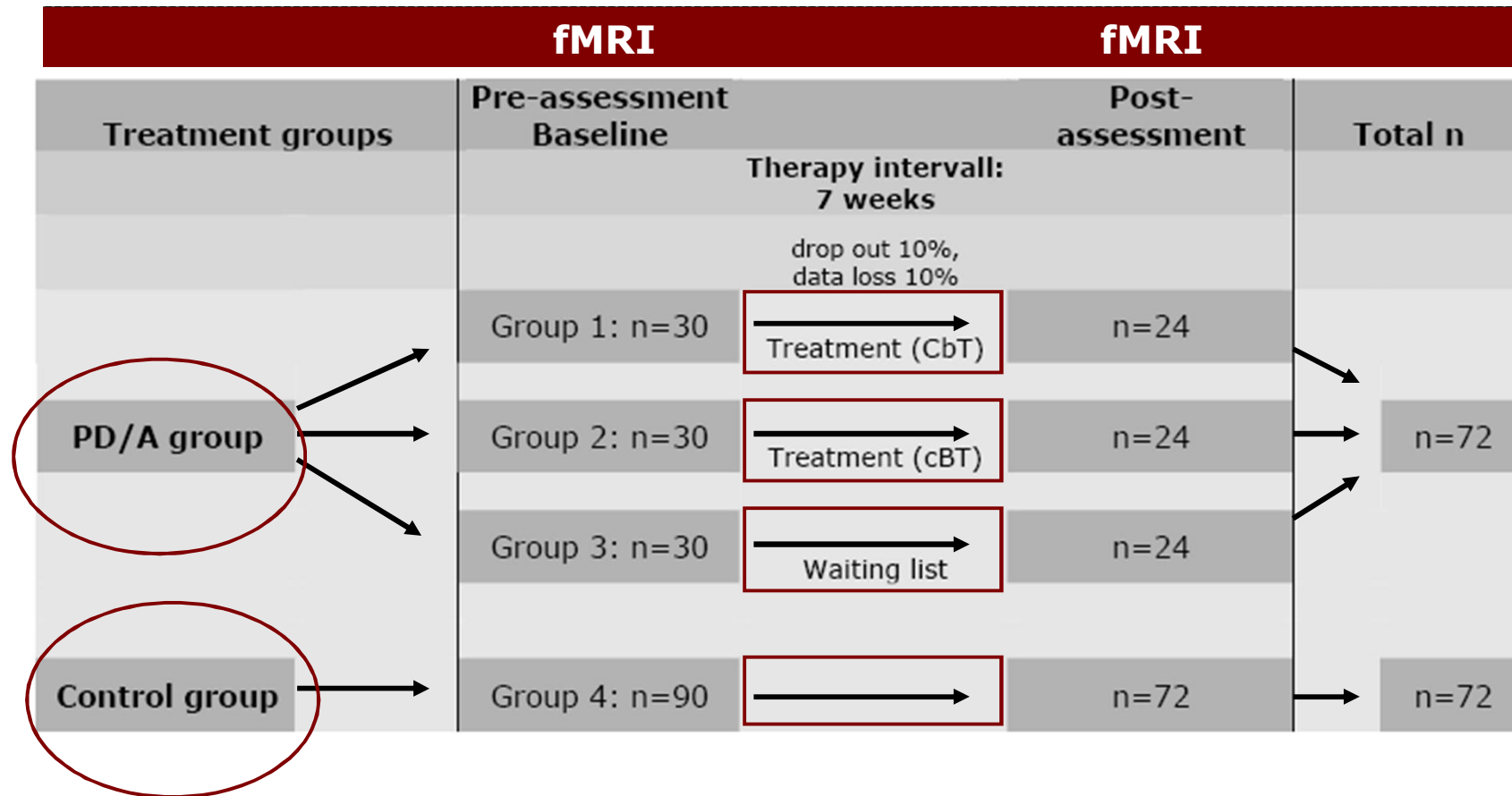
- “ Does co-administration of D-Cyclo to exposure increase the efficacy of CBT?
- “ Regulation of HPA during exposure ?

Planned: NIRS/TMS Münster - Würzburg

- 1 Å Berlin Charité (Director: Prof. Andreas Ströhle)**
- 2 ð Berlin Adlershof
- 3 ð Dresden
- 4 ð Würzburg
- 5 ð Münster

First funding period:
 Processing and the Fear Circuit in the course of CBT
 Center 3 Tesla fMRI Study in Panic Disorder
 (nested, pooled and oligo-site paradigms)

Design and methods



Psychophysiological Correlates of CBT treatment



“ Main Questions:

- “ Objective BT for fear activation (autonomic arousal, state response) ?
- “ Does anticipatory anxiety differentiate between psychophysiological response profiles?
- “ Biologically defined subtypes ?

1 Å Greifswald (Director: Prof. Alfons Hamm)

- 2 ö Berlin Charité
- 3 ö Berlin Adlershof
- 4 ö Münster
- 5 ö Aachen
- 6 ö Dresden
- 7 ö Würzburg
- 8 ö Bremen