# 5HTT Gene Transporter is Related to Psychological Flexibility

**Andrew T. Gloster, Hans-Ulrich Wittchen, Jürgen Deckert, & Andreas Reif**

**University of Basel**
**Technical University of Dresden**
**University of Wurzburg**

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# 5HTT Transporter Gene Variation is Related to Psychological Flexibility

# or

# Serendipity vs. False Positive?


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# What Is Known About Psychological Correlates of 5HHT Transporter Gene (short allele)?

| | |
|---|---|
| Fear Conditioning & Startle Response | Decision making |
| Attentional bias for anxious words | Response inhibition |
| Autonomic reactivity | Passive avoidance |
| Increased HPA axis reactivity | Risk aversion |
| Smoking, drinking, gambling | Motivationally speeded action |
| Excessive internet use | Attentional set-shifting |
| Social blushing | Reversal learning |
| Social aggression | Delayed matching-to-sample |
| Creative dancing | Probability discounting task |
| Social support | Delay discounting |

**(Homberg & Lesch, 2011)**

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# What Is Known About Psychological Correlates of 5HHT Transporter Gene (short allele)?

| Increased "Emotionality" | Improved "Cognition" |
|---|---|
| Fear Conditioning & Startle Response | Decision making |
| Attentional bias for anxious words | Response inhibition |
| Autonomic reactivity | Passive avoidance |
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# What Do We Know About 5HHT Transporter & Therapy?

| Pharmacology | Psychotherapy |
| --- | --- |
| Long Allelle > faster response (symptoms) to antidepressants in elderly suffering from MDD<br><br>(Durham et al., 2004) | Short Allelle < less response (i.e., symptoms) to CBT of PTSD<br><br>(Bryant, et al. 2010) |

# Another Study on Panic Disorder – WHY?!

- "CBT" for PD and Agoraphobia is one of, if not the, best studied disorder…
- …with some of largest effect sizes in the literature

**BUT…**

- Less is known about *why* patients-
  - remit
  - show only partial remission, or
  - fail to improve

- The Mechanisms responsible for treatment success (and failure) are not known – neither at psychological nor physiological level

# Design and Methods
## The study centers

8 outpatient (psychiatric and clinical psychological) treatment centers in Germany:

-Experienced in trial methodology and cognitive-behavioral treatment

- Trained and licensed as part of study's certification procedures


1 … Greifswald
2 … Berlin Charité
3 … Berlin Adlershof
4 … Münster
5 … Aachen
6 … Dresden
7 … Würzburg
8 … Bremen

**See also Gloster et al. 2009, 2011**


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# Design and Methods

## In- and exclusion criteria: Patients meeting DSM-IV-TR criteria for panic disorder with agoraphobia

### Inclusion criteria

- Age 18-65
- DSM-IV Panic Disorder
- DSM-IV Agoraphobia
- HAMA-Score ≥ 18
- CGI-Score ≥ 4
- be able for regularly attendance
- Informed Consent

### Exclusion criteria

- Significant medical (somatic/mental) conditions
- acute suicidality
- DSM-IV Bipolar Disorder
- DSM-IV Psychotic Disorder
- DSM-IV Borderline Personality Disorder
- current pharmacological or psychological treatment for an axis I-Disorder
- current alcohol-, BZD-, drug dependence

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Gloster et al. (2009)

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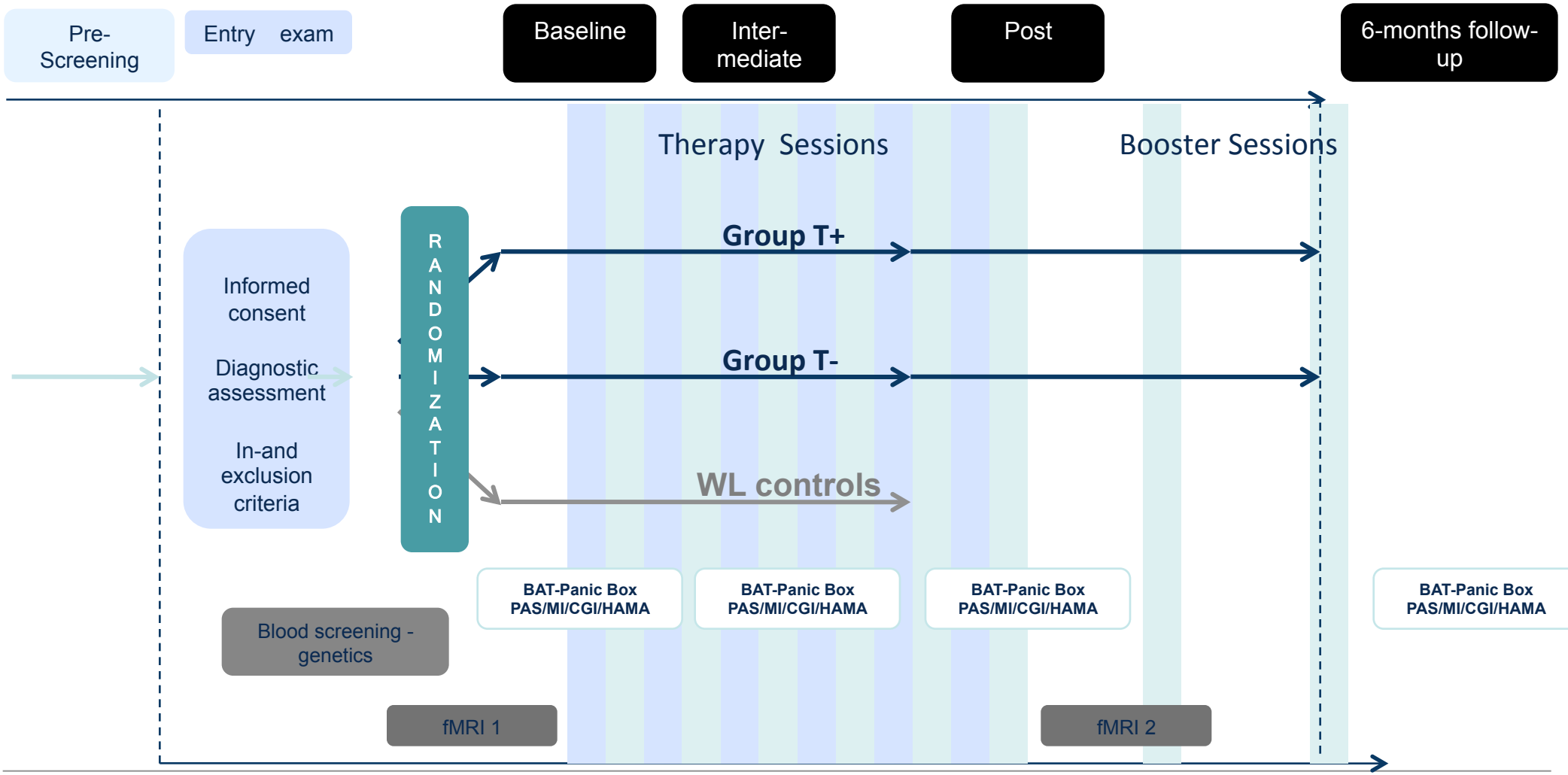


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# Design and Methods
## The Treatment

**Group T+**

**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 10-11**
Therapist-guided exposure: two individual situations

**Group T-**

**Sessions 6-8**
Instruction/encouragement for exposure: public transportation, shopping mall, forest

**Sessions 10-11**
Instruction/encouragement for exposure: 2 individual situations

**Session 9:**
Anticipatory Anxiety

**Sessions 12, Booster 1&2**:
Summary and Relapse Prevention

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# Less is More?

## State-of-the-art (old school)

– Lots of Exposure In Situ

– Much Interoceptive Exposure

– No Logical Disputation of Thoughts

– No Breathing Retraining

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# Results - Efficacy

Journal of Consulting and Clinical Psychology


0022-006X/11/$12.00 DOI: 10.1037/a0023584

# Psychological Treatment for Panic Disorder With Agoraphobia: A Randomized Controlled Trial to Examine the Role of Therapist-Guided Exposure In Situ in CBT

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Philipps-University Marburg

Jürgen Deckert
University of Würzburg

Peter Zwanzger
University of Münster

Michael Höfler
Technische Universität Dresden

Volker Arolt
University of Münster

***Objective:*** Cognitive–behavioral therapy (CBT) is a first-line treatment for panic disorder with agoraphobia (PD/AG). Nevertheless, an understanding of its mechanisms and particularly the role of therapist-guided exposure is lacking. This study was aimed to evaluate whether therapist-guided exposure in situ is associated with more pervasive and long-lasting effects than therapist-prescribed exposure in situ. ***Method:*** A multicenter randomized controlled trial, in which 369 PD/AG patients were treated and followed up for 6 months. Patients were randomized to 2 manual-based variants of CBT (T+/T−) or a wait-list control group (WL; $n = 68$) and were treated twice weekly for 12 sessions. CBT variants were identical in content, structure, and length, except for implementation of exposure in situ: In the T+ variant ($n = 163$), therapists planned and supervised exposure in situ exercises outside the therapy room; in the T− group ($n = 138$), therapists planned and discussed patients' in situ exposure exercises but did not accompany them. Primary outcome measures were (a) Hamilton Anxiety Scale, (b) Clinical Global Impression, (c) number of panic attacks, and (d) agoraphobic avoidance (Mobility Inventory). ***Results:*** For T+ and T− compared with WL, all outcome measures improved significantly with large effect sizes from baseline to post (range = −0.5 to −2.5) and from post to follow-up (range = −0.02 to −1.0). T+ improved more than T− on the Clinical Global Impression and Mobility Inventory at post and follow-up and had greater reduction in panic attacks during the follow-up period. Reduction in agoraphobic avoidance accelerated after exposure was introduced. A dose–response relation was found for Time × Frequency of Exposure and reduction in agoraphobic avoidance. ***Conclusions:*** Therapist-guided exposure is more effective for agoraphobic avoidance, overall functioning, and panic attacks in the follow-up period than is CBT without therapist-guided exposure. Therapist-guided exposure promotes additional therapeutic improvement—possibly mediated by increased physical engagement in feared situations—beyond the effects of a CBT treatment in which exposure is simply instructed.

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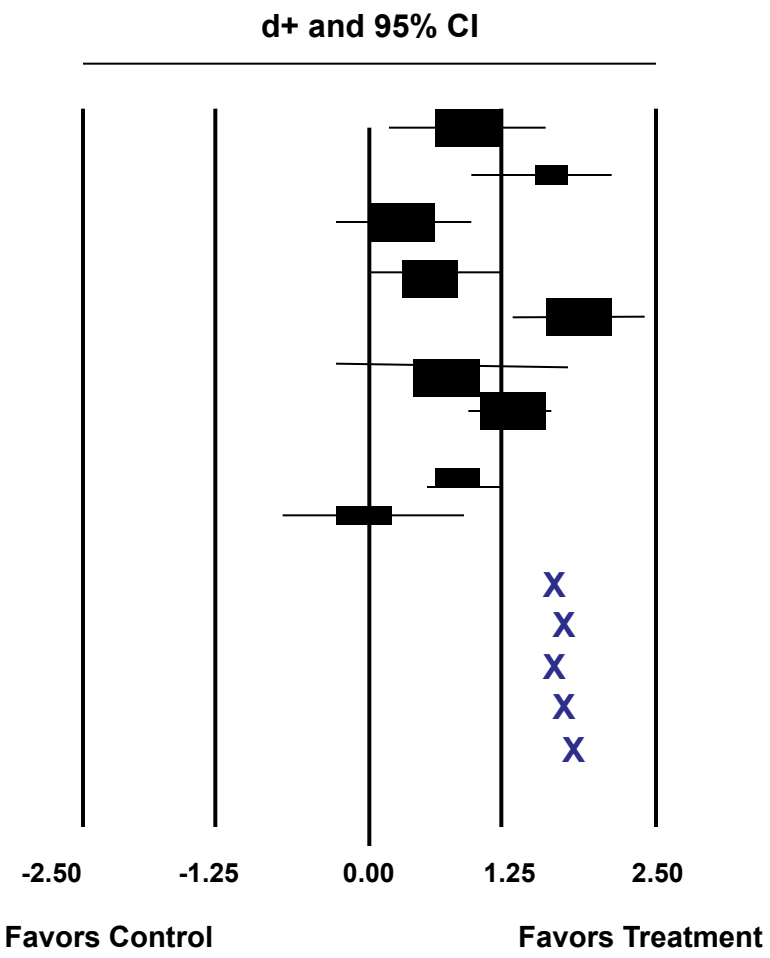
# Comparative Effect Size

| Treatment | d+ |
|---|---|
| Relaxation/Breathing (RB) | 0.86 |
| Exposure | 1.53 |
| Cognitive Therapy (CT) | 0.34 |
| EMDR | 0.61 |
| RB + Exposure | 1.84 |
| RB + CT | 0.70 |
| Exposure + CT | 1.29 |
| RB + Exposure + CT | 0.83 |
| Other techniques | -0.02 |
| **MAC Study at Post** | |
| Hamilton Anxiety | 1.59 |
| Clinical Global Impression | 1.70 |
| Panic Attacks | 1.56 |
| MI – Alone Subscale | 1.76 |
| PAS Total | 1.85 |



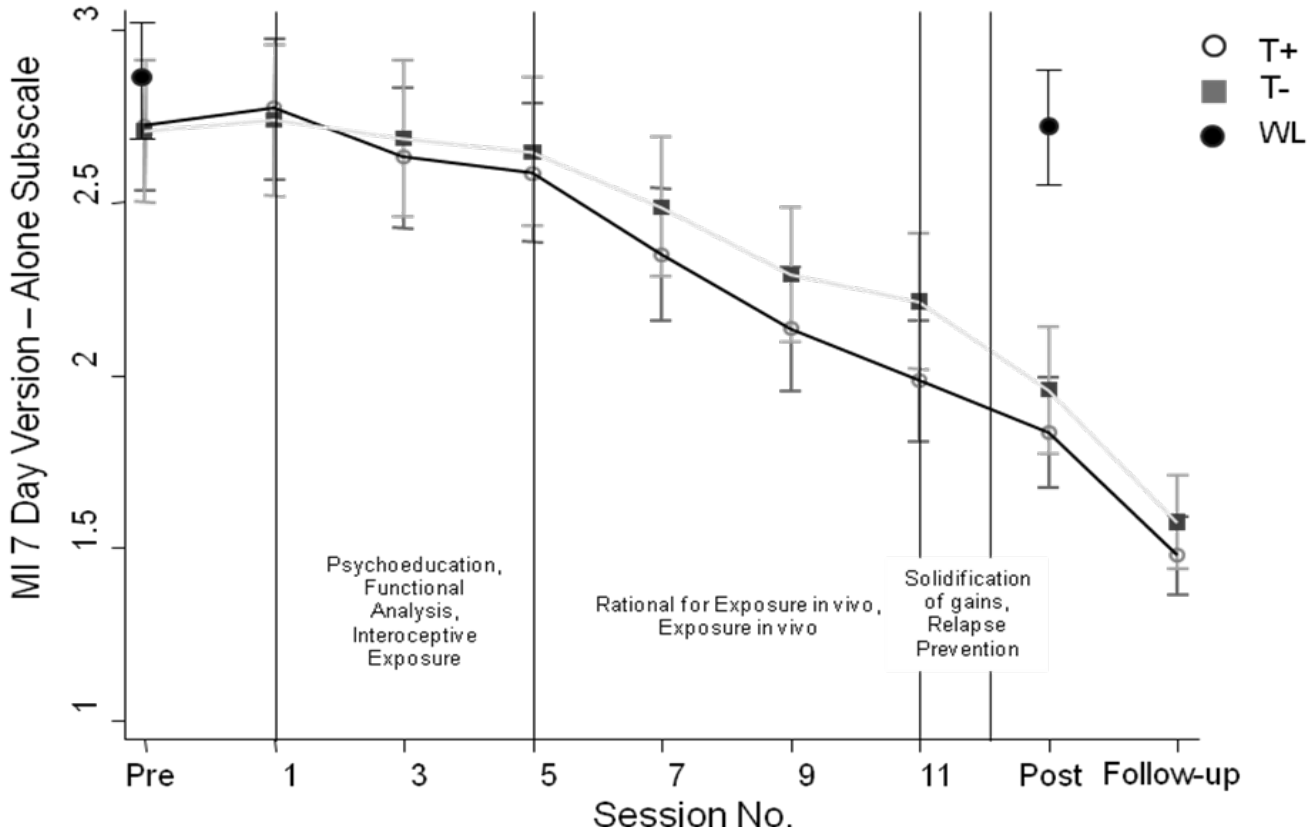

Sanchez-Meca et al., 2009

# Possible Mechanisms:

# Behavioral

# Is Therapeutic Change Associated with Specific Components? Reduction in Avoidance Seemingly Related to Therapy Components Over Time

## Situational Avoidance (MI-7) during past 7 days





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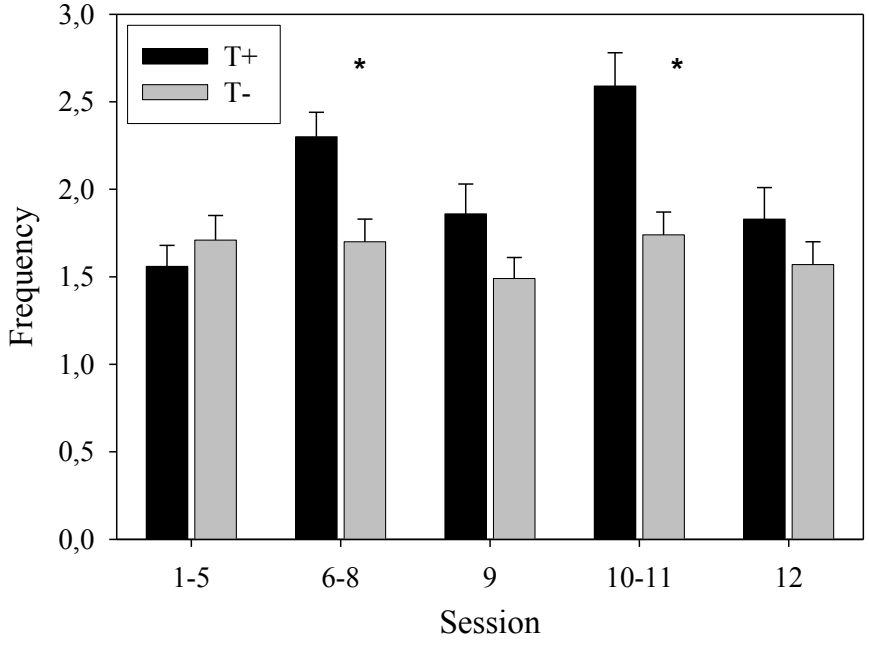
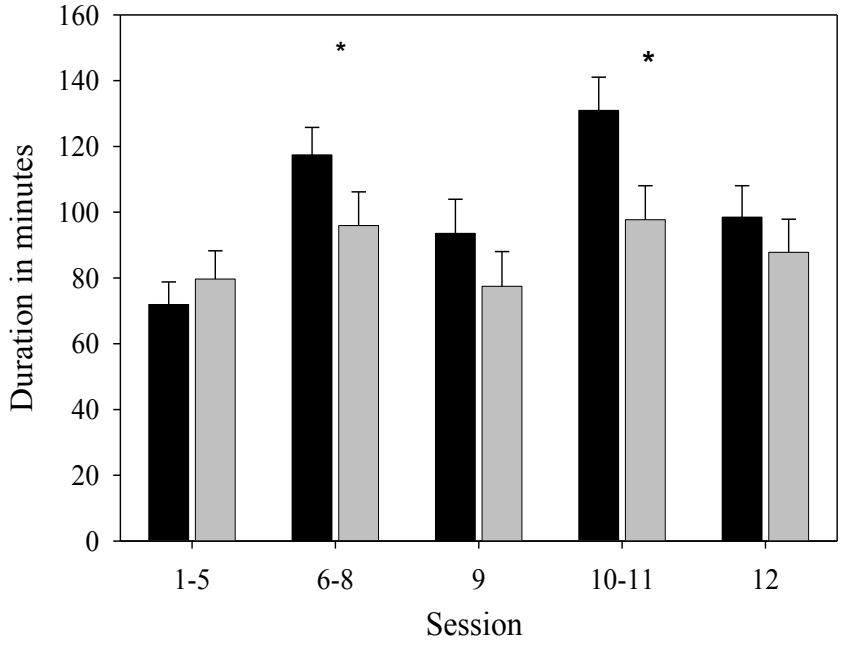
# Is therapeutic change associated with specific components?

## Number and duration of exposures and distress during the in-vivo exposure phase of treatment among completed sessions (n=268)

### Frequency and Duration of Exposure in Previous 24 Hours




**Mean scores across treatment sessions 7-12; T+ N = 145, T- N = 123**

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# Possible Mechanisms:

# Genetic

# Consistent with Genetic Findings?

**Treatment Effect Size by 5HTT Transporter Polymorphism**

| | LA/LA | | Not LA/LA | | | |
|---|---|---|---|---|---|---|
| | ES | SD | ES | SD | *F* | *p* |
| General Anxiety (HAMA-A) | -2.1 | 1.4 | -2.0 | 1.5 | 0.1 | 0.760 |
| Functioning (CGI) | -2.5 | 1.7 | -2.2 | 1.7 | 1.0 | 0.321 |
| Nr. Panic Attacks | -0.6 | 1.0 | -0.6 | 1.0 | 0.2 | 0.636 |
| Agoraphobic Avoidance (MI) | -1.0 | 0.8 | -1.1 | 0.9 | 0.9 | 0.338 |
| Anxiety Sensitivity (ASI) | -1.1 | 1.0 | -1.2 | 1.1 | 0.0 | 0.914 |
| Psychological Flexibility (AAQ-II) | 0.4 | 0.7 | 0.8 | 1.0 | 8.4 | 0.004 |

***d* = 0.5**

***Intent to Treat***

**(Gloster, Reif, et al., in prep)**

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# Endophenotype Criteria

An endophenotype is…

…associated with illness in the population

…heritable

…primarily state-independent (manifests in an individual whether or not illness is active)

Within families, endophenotype and illness co-segregate

- The endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population.

(Gottesman & Gould, 2003)

# Endophenotype Criteria

| Criteria | Psychological Flexibility |
|---|---|
| Assoc. Illness in Population | |
| Heritable | |
| State Independent (manifests whether or not illness active) | |
| Within families, co-occurs with illness | |
| Found in non-affected family members at higher rate than general population | |

# Possible Implications

- Context (short vs. long)
- Depth of Analysis
- Utility of Approach and Target Remains to be Seen
- Befriend your Favorite Geneticist

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# My Personal Plea

Please, try and replicate/ prove me wrong!

In a different population.

With ACT.

And you just might get a big grant in the process.

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