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

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Abstract
Cognitive behavioral therapy (CBT) is efficacious for panic disorder with agoraphobia (PD/A). Nevertheless, the active ingredients of treatment and the mechanisms through which CBT achieves its effects remain largely unknown. The mechanisms of action in CBT (MAC) study was established to investigate these questions in 369 patients diagnosed with PD/A. The MAC study utilized a multi-center, randomized controlled design, with two active treatment conditions in which the administration of exposure was varied, and a wait-list control group. The special feature of MAC is the way in which imbedded experimental, psychophysiological, and neurobiological paradigms were included to elucidate therapeutic and psychopathological processes. This paper describes the aims and goals of the MAC study and the methods utilized to achieve them. All aspects of the research design (e.g., assessments, treatment, experimental procedures) were implemented so as to facilitate the detection of active therapeutic components, and the mediators and moderators of therapeutic change. To this end, clinical, behavioral, physiological, experimental, and genetic data were collected and will be integrated.

Keywords Panic disorder, Agoraphobia, CBT, Exposure therapy, Mechanisms, Methods

Theoretical background

Cognitive behavioral therapy (CBT) across its many variations is efficacious for a wide range of mental disorders, with particularly strong effects for panic disorder and agoraphobia (PD/A) [5, 33, 36]. Despite the clear empirical support for CBT, numerous issues remain unclear. Primary among these is determining the mechanisms of action that lead to meaningful therapeutic change. The significance of identifying the active ingredients and mechanisms involved in the therapeutic process is manifold, with direct implications for the delivery of treatment, prediction of treatment response, understanding of factors that maintain therapeutic effects, and revealing possibilities for improvement of CBT as a psychotherapeutic method. Indeed, identification of the most relevant active ingredients and the core mechanisms involved in therapeutic improvement has implications for the definition of CBT itself.

As evidenced by numerous theoretical debates, the time is ripe to better understand what CBT is, what it changes, and how those changes are achieved [4, 30, 46]. To obtain such an understanding, a research design is needed that goes a step beyond those used in traditional efficacy trials. This means that an understanding of how CBT works necessitates the assessment of numerous factors not normally considered, and the more factors considered, the larger the required sample size. The mechanisms of action (MAC) study for panic and agoraphobia was established as a starting point to address these questions using a whole range of clinical and basic methods.

At the molar level (i.e., variables and constructs defined at a higher level of abstraction relative to lower-level molecular variables and constructs) hypotheses regarding possible mechanisms of therapeutic action abound [43]. They range from change in self-efficacy, to changes in "cognitive" constellations, to more precise hypotheses derived from learning theory such as habituation and extinction [15, 16, 36]. Fewer hypotheses exist at the molecular level, in part because the identification of therapeutic processes has seldom been a part of this research tradition. That said, preliminary research has implicated neural networks such as the so-called "fear circuitry" [18, 26, 27], the influence of functional genetic polymorphisms including the gene coding for the serotonin transporter protein [22, 23, 35], and psychophysiological processes [37]. Embedded in a large state-of-the art research platform, the MAC specifically targets molar variables in the form of objective and subjective ratings, molecular genetic variables, and those in-between of physiological measurements and functional magnetic resonance imaging (fMRI) approaches. Contrary to previous research, however, the MAC was structured such that the large number of dynamically interacting variables and levels can begin to be unraveled through the identification of salient processes that moderate and mediate treatment outcome. Emphasis in the first phase of the program was put upon the identification of active ingredients of CBT most likely involved in promoting therapeutic change.

Primary candidates for salient variables include the frequency, intensity, and type of administration of exposure in vivo exercises (i.e., under therapists guidance versus administration of intense cognitive exercises intended to induce behavioral change). Consistent with the available evidence, both variants of CBT are hypothesized to result in alterations of patients' cognitive appraisals and a reduction of panic and agoraphobia symptoms. Hypothesized differences between these two CBT variants relate to the speed, persuasiveness, and stability of changes as well as expectations that distal and proximal patient characteristics will be associated with differential treatment outcomes. Thus, the first aim of the MAC is to examine to what degree CBT with explicit exposure in vivo under therapist guidance outside the therapy room results in different changes as compared to a CBT variant where the therapist attempts to implement the same exercises without leaving the therapy room with the patient for the actual in vivo exposure exercises. Following an examination of the overall effectiveness of these two CBT variants (active tx) versus a wait list control group, the second phase of the research program will produce finer-grained analyses of putative mechanisms of change and the identification of predictors for sustained response and remission.

With these goals in mind, the MAC established a standardized treatment protocol and manual [34] utilized with all patients as a spring board from which to determine how therapeutic processes and outcomes are associated. In particular, the MAC targeted (a) learning processes involved in the startle reaction, anticipatory anxiety, and associated autonomic responses; (b) the processing of anxiety-relevant stimuli using paradigms of exteroceptive and interoceptive perception and conditioning/extinction; and (c) genetic variations.

Given that the MAC represents one of the first attempts to bridge traditionally isolated areas of research, it is worthwhile and necessary to examine the methods utilized and, en route, to clarify terms. It is to this task that we now turn our attention beginning with a description of the clinical trial concluding with experimental paradigms.

Methods of the overarching clinical trial

Research design

The MAC is a randomized, multicenter, clinical treatment outcome study with 369 outpatients who met DSM-IV criteria for panic disorder and agoraphobia. The study design was structured so that measures of treatment course and outcome could be related to specific treatment components. All patients were randomized to two active CBT treatment variants and a wait-list control group (WL). The distinguishing feature between otherwise identical CBT variants dealt with the administration of the exposure in vivo. The first active CBT condition included some sessions in which the therapist provided active guidance in exposure outside the therapy room (therapist guided exposure T+), whereas in the second active CBT condition the therapist was confined to the therapy room (no therapist guided T-).

Procedure

Patient recruitment, inclusion and exclusion criteria

Eight treatment centers in Germany participated (Aachen, Berlin-Adlershof, Berlin-Charité, Bremen, Dresden, Greifswald, Münster, Würzburg). Participants were recruited from ongoing clinical mental health care (i.e., 3 psychiatric clinics and 5 clinical psychological outpatient centers), physician referral (e.g., primary care physicians, neurologists, psychiatrists, cardiologists), and via additional advertisements in various media outlets (e.g., newspapers, internet, television). Participants who screened positive for the inclusion criteria were given an appointment to obtain written informed consent. Those who agreed to partake in the study scheduled a diagnostic appointment to determine whether all inclusionary criteria were met.

Inclusion criteria consisted of: (a) a current primary diagnosis of panic disorder and agoraphobia (PD/A) (as defined by the criteria of the diagnostic and statistical manual, fourth revision/text revision (DSM-IV-TR) [2] validated by a standardized computer-administered personal Composite International Diagnostic Interview (CAPI-WHO-CIDI; DIAX-CIDI version [47]); (b) a clinical interview score C18 on the structured interview guide for the Hamilton anxiety scale (SIGH-A [44] in anxiety and depression); (c) a score C4 on the clinical global impressions scale (CGI) [28]; (d) age 18–65 years; (e) ability and availability to regularly attend treatment sessions. The flow of patients into the study can be seen in Fig. 1. Nineteen patients from the WL were re-randomized to one of the active treatment conditions following the waitlist period. These patients met all inclusion criteria at the time of re-randomization.

Compared to previous studies, exclusion criteria were minimal to allow for the inclusion of patients with comorbid conditions commonly seen in daily practice. Exclusion criteria were (a) comorbid DSM-IV-TR psychotic or bipolar I disorder; (b) current alcohol dependence/current abuse or dependence for benzodiazepine and other psychoactive substances; (c) current suicidal intent, (d) borderline personality disorder, (e) concurrent ongoing psychotherapeutic or psychopharmacological treatment for PD/A or another mental disorder; (f) antidepressant or anxiolytic pharmacotherapy; (g) physician-verified contraindications of exposure-based CBT (i.e., severe cardiovascular, renal, and neurological diseases). The frequencies with which patients were not allocated to treatment because of these inclusion and exclusion criteria are listed in Table 1. As can be seen in Table 1, most patients were excluded because their scores on the clinical rating scales were too low, thus suggesting that the patients in the MAC are relatively severely affected.

Sample characteristics

Table 2 describes the sociodemographic characteristics of the 369 patients enrolled. The sample consisted overwhelmingly of patients with psychiatric comorbid conditions, with a mean of 3.5 comorbid diagnoses. Only 7.9% had no other diagnoses, whereas additional diagnoses were present as follows: 1–2 comorbid diagnoses (44.7%), 3–4 (33.9%), and 5 or more comorbid diagnoses (13.6%). The most frequent comorbid diagnoses were: specific phobias (69.4%), social phobia (41.7%), major depression (35.2%), harmful use of alcohol (37.4%), pain disorder (34.2%), and generalized anxiety disorder (20.3%).

Assessment

Assessments occurred at five primary time points chosen to capture changes in putative active ingredients in the treatment process (see Table 3): diagnostic (before inclusion), baseline (before treatment), intermediate (after the fourth session), post (immediately following treatment), and follow-up (6 months after the end of treatment). Each treatment session included a number of additional assessments, partly embedded within the therapy itself and tightly linked to add on studies. A description of the utilized measures can be seen in „Appendix". Patients in the WL group took part in all assessments from baseline to post-treatment.

Primary outcome parameters targeted domains of global anxiety and panic/agoraphobic-specific symptomatology [31]. These were assessed using both interview-rated outcome measures [SIGH-A total score (range 0–56) and the CGI (range 1–7)] and questionnaires completed by the patients assessing panic attacks [panic and agoraphobic scale (PAS)—mean number of panic attacks in the past week (subscale range 0–4)] and agoraphobic avoidance [mobility inventory original version (MI)]—mean of the alone subscale (range 1–5)]. Secondary outcomes were included to assess additional domains and answer secondary questions (see Table 3; Appendix). Among these, several behavioral measures (i.e., the amount of time the patient remained in the behavioral avoidance test, the frequency of exposures, duration of exposures, and distress experienced during exposures) were recorded.

Patients additionally completed self-monitoring forms throughout the treatment, especially before and after each exposure exercise. Prior to the exposure patients recorded information about the situation and anticipatory anxiety. Following the exposure, patients recorded the course of anxiety during the exercise, any use of safety behaviors, and their subjective conclusions regarding the exercise. Therapists separately recorded all safety behaviors utilized by the patient during the exercise.

Data collection and database

Assessments were directly entered by patients into an internet-based computer interface. Missing data were minimal due to the use of programmed algorithms that informed the interviewer and the patient of any missing data and prompted completion before continuing (around 2% across all items and assessments). Patients were trained by their therapist in the use of the computer program. All data was linked with the corresponding login password so that every change of the database was time-stamped and could be tracked. The database was saved at a central data coordinating center (study coordination center; KKS Dresden) that also insured data security. The database was checked regularly and the time of entry was compared against the scheduled entry time. Therapists and clinical directors of each center received regular feedback about the quality and timeliness of data for each of their patients.

Treatment

Treatment procedure

Therapy consisted of 12 individual sessions conducted over approximately 8 weeks. The therapy was implemented twice weekly with each session lasting approximately 100 min. The therapy was based on established manuals [15] previously evaluated as effective for patients with PD/A in several clinical trials [8] and developments in exposure-based CBT [6, 38, 42]. Based on these existing manual components a study manual—optimized for the study rationale and for component analyses—was written by experts for exposure therapy [34]. The manual focused on a clear differentiation between different techniques of exposure therapy as a basis for a better understanding of the mechanisms of action as well as an optimal separation between T+ and T-. It is again important to note that both active therapy variants T+ and T- contained exactly the same ingredients, were of identical duration, and differed only in the manner in which the exposure was implemented in vivo (therapist guided, supervised, and intensified vs. no therapist present during in vivo exposure exercises).

The manual was highly structured and detailed to minimize between-therapist variability. Details were conveyed in multiple levels (e.g., session overview, guiding principles, session take-home message, aims, session-specific exercises and forms). It included detailed descriptions of each procedure, provided sample dialogues, and anticipated typical problems with guidance for solutions. Figure 2 highlights the main components of each session.

The first treatment phase (sessions 1–5) was identical in both conditions (e.g., establishing therapeutic rapport, psycho-education, self-monitoring, functional analysis, interoceptive exposure). Only sessions 6–8 and 10–11 differed between the groups with respect to the implementation of exposure (T+ and T-). Although the T-condition discussed various aspects of exposure including barriers to effective implementation, no formal cognitive restructuring or disputation of thought content was implemented. Patients in both treatment groups were instructed to engage in three standardized exposure exercises (bus, department store, forest) followed by two individualized situations. In the T+ condition, exercises were carried out during the session with the therapist present. Prior to the next session, the patient was instructed to repeat this exposure exercise two more times. Patients in the T- group were instructed to complete three self-exposures between these sessions, thus holding the assigned number of exposure exercises constant between the two conditions. Quantification of all initiated exposures, whether assigned or not, were recorded at the next session in terms of the frequency, duration and experienced distress of all exposures. All self-exposures were reviewed in the following session in both conditions.

In both active treatment conditions, two booster sessions (sessions 13–14) were conducted. These sessions reviewed progress, addressed avoidance behavior—especially in stressful situations—and discussed additional exposure exercises that the patient could practice.

Manual training, certification of therapists, and supervision

All therapists were trained by experts in exposure-based CBT for P/A. All therapists were qualified at least at the level of advanced graduate student status in clinical psychology. Content of the manual was trained over a 3-day intensive and interactive course followed by a recorded role-play graded by experts. Therapists were only allowed to see study patients after

passing the role-play examination. Of 89 therapists trained in these procedures, 75 were certified as study therapists.

During this psychotherapy study, all therapists were involved in weekly manual specific supervision in their respective study center. Supervision was supplanted with a weekly telephone conference involving all centers in which problems with the manual and the study protocol were discussed.

Therapy integrity

All sessions were recorded on video cassettes or DVD. All violations of the protocol were documented and reported to the study coordination centers. Therapy integrity was assessed by independent raters. Over 15% of all sessions (n = 724/4,214 = 17.2%) were randomly selected and analyzed using the therapist adherence and competence rating scale for panic disorder and agoraphobia [24]. All raters took part in a two day training procedure and passed a qualification exam. The exam consisted of two videos, each of which had to be rated within one point of the expert rating on each item.

Core experimental components

Behavioral avoidance test

A behavioral avoidance test (BAT; darkroom paradigm) was executed at pre, intermediate, post, and follow-up in all patients to explore changes in symptom reports of avoidance behavior and physiological responding during anticipation (sitting 10 min in front of the cabinet) and exposure (10 min) in a narrow (120 9 75 cm) and dark room. The administration of this test aims to explore the mechanism of innervations at the behavioral and psychophysiological level [1]. Skin conductance and heart rate were obtained as measures of autonomic arousal while startle responses to acoustic probes (surface electromyography recordings over the left orbicularis oculi muscle) were measured as an index of subcortically mediated defense mobilization. Prior to therapy, 68% of all patients stayed in the dark room for the entire 10 min. 20% of the patients, however, escaped from the dark room with an average duration of 4 min. 12% of the patients refused to enter the dark and were thus categorized as avoiders. Overall, patients experienced 45 panic attacks within the dark room, with no differences between escapers and non-escapers. Overall, the heart rate was increased during exposure for escapers compared to non-escapers suggesting that increased physiological arousal might predict behavioral avoidance. On the other hand, those patients in the non-escaper group who reported comparably high levels of anxiety during exposure as the escapers also had significantly increased heart rates but did not leave the room.

Psychophysiological subtypes

In order to explore the value of respiratory and vestibular panic subtypes in the overall study, a subset of patients underwent two biological challenges [3]. In order to measure vestibular sensitivity, different visual flow stimuli were presented through a head-mounted display, thereby inducing a conflict between visual input and somatosensory information [32]. Anxiety and dizziness were assessed repeatedly by means of self-reports, while resultant body sway was measured continuously with a force plate that individuals stood on. In order to measure respiratory sensitivity, we measured responses to a hypoxic (12% O2) and a hypercapnic (7.5% CO2) laboratory challenge while measuring tidal volume, respiratory rate, the end-tidal CO2 concentration in the exhaled air, anxiety, and panic symptoms. The observed

physiological reactions will be related to previously identified latent class factors [3] with the aim of clarifying the impact of differential symptomatology on treatment efficacy, and to determine to what extent treatment should be tailored to these subtypes.

Fear circuitry mechanisms

Using three paradigms (aversive conditioning, interoception vs. exteroception, and anticipation of panic-relevant stimuli) before and after treatment, this project examines changes in the fear circuitry mechanisms associated with panic disorder and agoraphobia and potential activation pattern of treatment response [10].

Genetic variation and prediction

Functional risk polymorphisms for panic disorder such as those of the serotonin transporter, the monoamine oxidase or catecholamine-o-methyltransferase genes [19] or for novel genetic risk polymorphisms derived from animal models such as a neuropeptide S receptor gene polymorphism will be explored. Intermediate phenotypes for panic disorder will be examined under the premise that these correlate better with biological parameters like genetic variations. For example, heart rate in the BAT will be correlated to a functional polymorphism in the serotonin 1A receptor gene to determine whether this genetic variant exerts some of its effect via modulating vegetative parameters [21]. Additionally, genome-wide approaches will be utilized to define hitherto unknown genetic variants which increase the risk for panic disorder and/or influencing the therapeutic response to cognitive behavioral therapy.

Conclusion

MAC is a state-of-the-art collaborative and interdisciplinary research platform from which the mechanisms of therapeutic action in exposure-based CBT for patients with panic disorder and agoraphobia will be investigated. MAC promises to offer insights about a range of issues. The data will provide information about how variations in exposure-based CBT differentially affect a range of behavioral, cognitive, affective, and physiological outcomes. Necessary, salient, inactive, and even iatrogenic components can be identified and related to courses of symptomatology, maintenance of therapeutic gains, and relapse. In turn, the dynamic relationship between these results and molecular variables as well as variables from a systems-neuroscientific approach will be examined with the prospect of identifying moderator and mediator variables. Finally, MAC will generate hypotheses that will lead to a number of experiments that will focus on specific mechanisms of disease and therapeutic action. Evidence is already emerging that the sum total of the findings expected from MAC will significantly contribute to our understanding of the mechanisms of action in CBT.

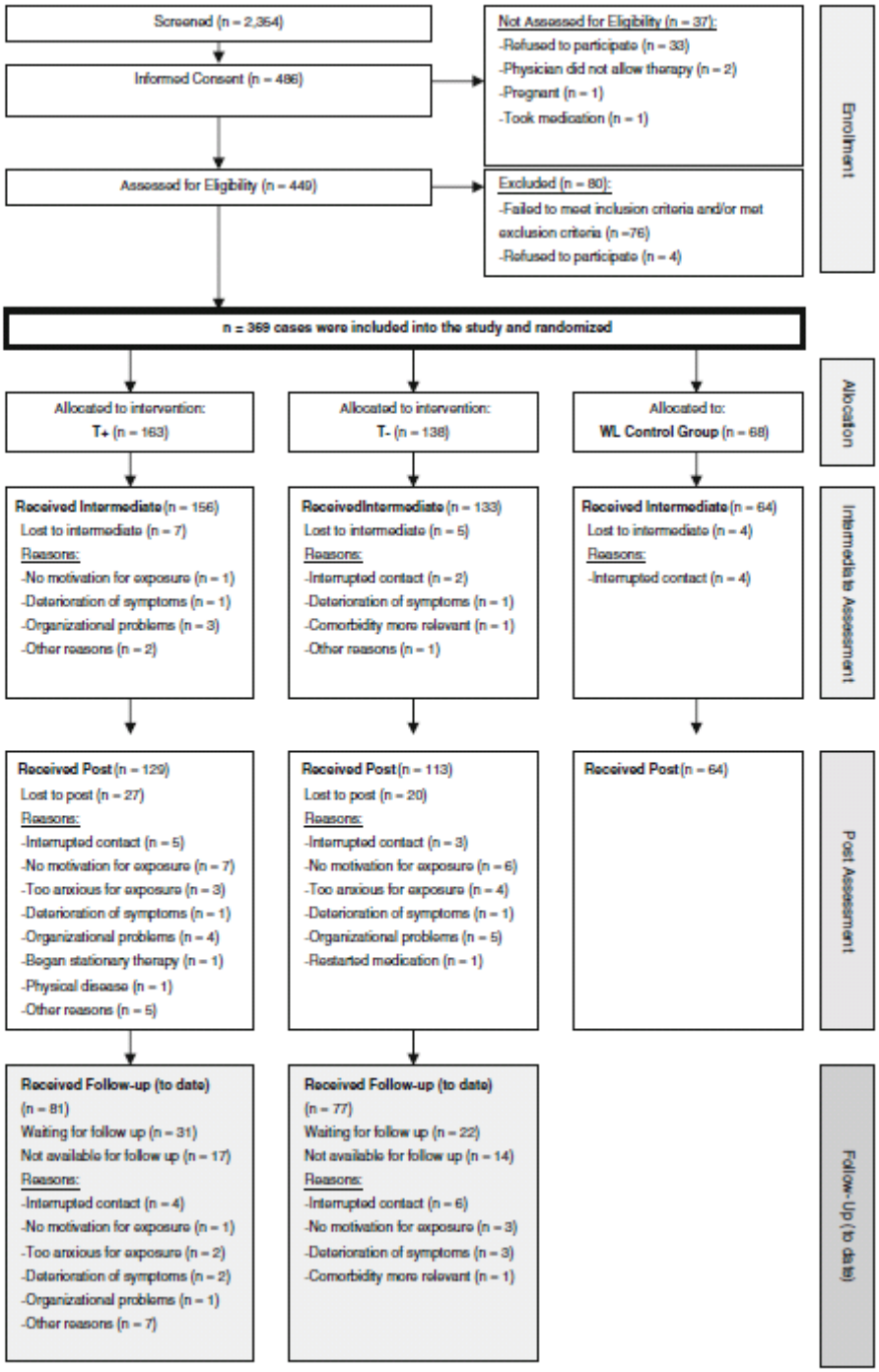

Fig. 1 Consort flowchart of the MAC randomized control psychotherapy study

Therapist Guided Exposure (T+)	No Therapist Guided (T-)
Sessions 1-3: Psychoeducation	
Sessions 4-5: Interoceptive exposure; Thought experiment	
Sessions 6-8: Exposure in vivo with the therapist in standard situations: bus, department store, forest	Session 6-8: Guidance for self-exposure in vivo in standard situations: bus, department store, forest
Session 9: Anticipatory anxiety	
Sessions 10-11: Exposure in vivo with the therapist in ideographically salient situations	Session 10-11: Guidance for self-exposure in vivo in ideographically salient situations
Sessions 12: Discussion of therapeutic gains and individual plans for continued exposure exercises during booster period; relapse prevention	
Booster 1-2: Discussion of individual exposure during booster period; relapse prevention	

Fig. 2 Overview of the therapy content in the active treatment conditions

Table 1 Reasons why patients assessed for eligibility were not allocated to treatment

	N	% of 80
Failed to meet inclusion criteria		
Age	0	0
Panic disorder	15	18.8
Agoraphobia	16	20.0
HAMA ≥ 18	45	56.3
CGI ≥ 4	14	17.5
Schedule	1	1.3
Met exclusion criteria		
Unable to comply with the study protocol	13	16.3
Suicidal intent	0	0.0
Bipolar	0	0.0
Psychosis	2	2.5
Borderline	0	0.0
Other axis I	6	7.5
Alcohol dependence	2	2.5
Other medical explanation for symptoms	4	5.0

Categories do not total 100% because multiple responses were possible

Table 2 Sample characteristics ($n = 369$)

	Mean	SD
Age	35.5	(10.8)
	n	%
Gender		
Male	87	23.6
Female	282	76.4
Years of education		
8	43	11.7
10	165	44.7
12–13+	150	40.7
No formal degree	11	3.0
Living arrangement		
With parents	19	5.2
Alone	70	19.0
With partner	258	69.9
Other	22	6.0
Employment		
University student	16	4.3
Job training	98	26.6
Employed	218	59.1
Unemployed	34	9.2
Other	3	0.8
Social class		
Lowest	18	5.0
Lower middle	81	22.4
Middle	223	61.8
Upper middle	39	10.8
Upper	0	0.0
Marital status		
Married	117	31.8
Divorced/widowed/ separated	50	13.6
Never married	201	54.6

Some variables do not total 100% due to missing values

Table 3 Assessment instruments and time of assessments of the randomized control psychotherapy study

Purpose	Instrument	Domain	Source	Diagnostic (before inclusion)	Baseline (before treatment)	Intermediate (after the fourth session)	Post (immediately following treatment)	Follow-up (6 months following the end of Tx)	Session-related assessments
Primary outcomes	SIGH-A	Somatic and psychic anxiety symptoms	Assessor/therapist	X	X		X	X	
	CGI	Severity of PD/A	Assessor/therapist	X	X	X	X	X	
	PAS	Number of panic attacks	Patient		X	X	X	X	
	MI (original)	Avoidance of situations	Patient		X	X	X	X	
Secondary outcomes	DIA-X	Diagnosis	Patient	X				X	
	BAT	Behavioral/physiological	Patient		X	X	X	X	
	ACQ	Catastrophic thoughts	Patient		X	X	X	X	
	BSQ	Anxiety of bodily sensations	Patient		X	X	X	X	
	MI-7	Avoidance of situations	Patient		X	X	X	X	X[a]
	MI-E	Characteristics of avoidance	Patient						X[a]
	EPA	Frequency of panic	Patient						X[a]
	SPA	Symptoms of panic	Patient		X				
	CLQ	Claustrophobic anxiety	Patient	X					
	ASI	Anxiety sensitivity	Patient	X			X	X	
	BDI-II	Depression	Patient	X		X	X	X	
	PANAS	Positive/negative effect	Patient		X				
	BSI	Psychological symptoms	Patient	X			X	X	
	AAQ-II	Psychological flexibility	Patient	X		X	X	X	
	HSQ	Health quality	Patient	X			X	X	
	IPAQ	Physical activity	Patient	X			X	X	
	SDS	Disability	Patient	X			X	X	
Process	EQ	Frequency, duration, and discomfort of exposures in the last 24 h	Patient	X	X	X	X	X	X[b]
	Process documentation	Problems during and between sessions	Patient/therapist						X[b]
	Process of exposure	Anxiety and behavior during exposure in vivo	Patient/therapist						X[c]

SIGH-A Structured interview guide for the Hamilton anxiety rating scale, *CGI* clinical global index, *PAS* panic and agoraphobia scale (PAS), *MI (original)* mobility inventory, *DIA-X* research version of the DIA-X computerized composite international diagnostic interview, *BAT* behavior avoidance test, *ACQ* agoraphobic cognitions questionnaire, *BSQ* bodily sensations questionnaire, *MI-7* mobility inventory 7-day version, *MI-E* MI expanded, *EPA* self-made questionnaire measuring the frequency and the severity of panic attacks in the last 7 days, *SPA* self-made questionnaire measuring symptoms during a panic attack, *CLQ* claustrophobia questionnaire, *ASI* anxiety sensitivity index, *BDI-II* Beck depression inventory-II, *PANAS* positive and negative affect schedule, *BSI* brief symptom inventory, *AAQ-II* acceptance and action questionnaire-II, *HSQ* health status questionnaire (detect), *IPAQ* international physiological activity questionnaire, *SDS* Sheen disability scale

[a] Following odd numbered sessions

[b] Following every session

[c] Following each exposure exercises

Appendix: Description of assessment instruments of the randomized control psychotherapy study

Abbreviation	Description
SIGH-A (HAMA)	The *Hamilton Anxiety Scale* [29] is a 14-item test measuring the severity of anxiety symptoms. Each item is rated on a five-point scale (range: 0—not present to 4— severe) by the therapist interviewing the patient
CGI	The *Clinical Global Impression Scale* [28] anchored for panic disorder is completed by the therapist to rate the severity of the patient's disorder and the therapeutic improvement. It yields five different measures: (1) the severity of patient's current symptomatology, (2) the extent of anxiety, (3) the extent of avoidance behavior, (4) the global functioning, and (5) an overall score. Each item is rated on a seven-point scale from 1 (normal) to 7 (amongst the most severely ill patients)
PAS	The *Panic and Agoraphobia Scale* [7] is a 13-item questionnaire that refers to the past week and assesses the extent of the severity of panic disorder as well as the existence and severity of agoraphobia by collecting information on phenomenology, frequency and severity of typical symptoms, e.g., panic attacks, anticipatory anxiety and avoidance behavior. All items were five-point scaled and scored from 0 to 4 as well
MI (original)	The *Mobility Inventory* [12] is part of the questionnaire of body related fears, cognitions and avoidance and comprises 27 items regarding avoidance in specific situations with or without accompaniment by a trust person. Each item is rated by patients on a five-point scale, ranging from 1 (never avoid) to 5 (always avoid)
DIA-X	The Research Version of the *DIA-X computerized Composite International Diagnostic Interview* [47] is a fully standardized diagnostic interview assessing symptoms and diagnosis of mental disorders by information about impairment, onset, duration and severity. Disorder-specific symptom lists and cognitive aids support the participant in answering questions
ACQ	The *Agoraphobic Cognitions Questionnaire* [13] comprises 14-items measuring maladaptive thoughts about the possible consequences of experienced anxiety or panic. Each item is rated by patient on a five-point scale, ranging from 1 (never) to 5 (always) and may be scored as a total scale, or according to its two subscales: loss of control and physical concerns
BSQ	The *Body Sensations Questionnaire* [13] comprises 17 items measuring frightened feelings of body sensation occurring in nervous or feared situations. Each item is rated by patient on a five-point scale, ranging from 1 (not at all) to 5 (extremely)
MI-7	The *Mobility Inventory- 7 days* ([25] is an adapted version of the Mobility Inventory and was developed for use in this study. The MI-7 days comprises 27 items regarding avoidance in specific situations with or without accompaniment by a trust person. Each item is rated by patients on a five-point scale, ranging from 1 (never avoid) to 5 (always avoid)
MI-E	The *Mobility Inventory- Expanded* [25] comprises 27 items measuring frequency and anxiety in and importance of situations in the last 7 days. Each item is rated by patient on frequency of occurrence and five-point scales of anxiety and importance, ranging from 0 (not at all) to 4 (extremely)
EPA	The *Evaluation of Panic Attack* questionnaire is a self-designed 3-item self-report measuring the frequency and the severity of panic attacks in the last 7 days. Symptoms of the worst and lowest panic attack are detected
SPA	The *Symptoms of a Panic Attack* questionnaire is a self-designed self-report. The first 10 items measure the kind and extension of bodily symptoms during panic attacks and are rated on a five-point anxiety scale ranging from 0 (not at all) to 4 (extremely). The other part involves three items measuring the frequency of visiting anxiety related situations and the level of stress in the last 24 h
CLQ	The *Claustrophobia Questionnaire* [40] is a 26-item self-report measurement assessing confinement and suffocation concerns relevant to claustrophobia. Each item is rated on a five-point anxiety scale ranging from 0 (not at all) to 4 (extremely)
ASI	The *Anxiety Sensitivity Index* [41] is a 16-item self-report measuring subjects beliefs about potential harmful consequences of anxiety related symptoms. Each item is rated on a five-point scale from 0 (very little) to 4 (very much)
BDI-II	The *Beck Depression Inventory-II* [9] is a 21-item self-report measuring severity of symptoms associated with depression. 19 items are rated on a four-point scale, 2 further items are assessed on a sevne-point scale

Appendix continued

Abbreviation	Description
PANAS	The *Positive and Negative Affect Schedule* [17] is a 20-item self-report measuring the extent of different feelings and emotions over the last days. Each word and phrase is rated on a five-point scale ranging from 0 (not at all) to 4 (extremely)
BSI	The *Brief Symptom Inventory* [20] is a 53-item self-report symptom inventory assessing the psychological symptom patterns of psychiatric and medical patients and non-patients over the past week. Each item is rated on a five-point scale from 0 (not at all) to 4 (extremely)
AAQ-II	The *Acceptance and Action Questionnaire* [11] is a 10-item self-report measure of psychological flexibility and acceptance. Each item is rated on a seven-point scale from 1 (never true) to 7 (always true)
HSQ (EQ5)	The *Health Status Questionnaire* [39] is a 12-item self report measuring the current state of health. One part of the HSQ consists of the EQ-5D involving five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is assessed on three levels of severity: 1 = no problems; 2 = moderate problems; and 3 = extreme problems. The other part comprises items regarding daily restrictions based on the status of health, frequency of consultation, intake of drugs and problems with handling health
IPAQ	The *International Physical Activity Questionnaire*-long form [14] is a self-report measuring a 7-day recall of habitual practice of physical activities divided into five parts: at work, at travel, in and around the house, in leisure time and sitting time
SDS	The *Sheean Disability Scale* [45] is a 3-item self report assessing functional impairment in work, social and family life. Items are rated on a 11 point scale translated into a percentage from 0 (not at all) to 100% (extremely)
EQ	The *Exposure Quantification Scale* is a self-developed scale consisting of three questions that measure the frequency, duration and associated discomfort of exposure exercises implemented by the patients, irrespective of whether or not they were assigned exercises or spontaneous

References

1. Alpers GW, Sell R (2008) And yet they correlate: psychophysiological measures predict the outcome of exposure therapy in claustrophobia. J Anxiety Disord 22:1101–1109
2. American Psychiatric Association (2000) Diagnostic and statistic manual of mental disorders, text revision, 4th edn. American Psychiatric Association, Washington, DC
3. Andor F, Glöckner-Rist A, Gerlach AL, Rist F (2008) Symptomspezifische Subgruppen der Panikstörung. Zeitschrift für Klinische Psychologie und Psychotherapie 37:161–171
4. Arch JJ, Craske MG (2008) Acceptance and commitment therapy and cognitive behavioral therapy for anxiety disorders: different treatments, similar mechanisms? Clin Psychol Sci Pract 15:263–279
5. Arch JJ, Craske MG (2009) First-line treatment: a critical appraisal of cognitive behavioral therapy developments and alternatives. Psychiatr Clin North America 32:525–547
6. Baker-Morrissette S, Spiegel DA, Heinrichs N (2005) Sensation-focused intensive treatment for panic disorder with moderate to severe agoraphobia. Cogn Behav Pract 12:17–29
7. Bandelow B (1999) Panic and agoraphobia scale (PAS). Hogrefe & Huber Publishers, Ashland
8. Barlow DH, Gorman JM, Shear MK, Woods SW(2000) Cognitive-behavioral therapy, imipramine, or their combination for panic disorder—a randomized controlled trial. JAMA 283:2529–2536
9. Beck AT, Steer RA, Brown GK (1996) Manual for the BDI-II. The Psychological Corporation, San Antonio
10. Blümel I, Jansen A, Kellermann T, Schüppen A, Kohn N, Gerlach A et al. (2009) Neural correlates of aversive conditioning (submitted)
11. Bond FW, Hayes SC, Baer RA, Carpenter KM, Orcutt HK, Waltz T et al. (2007) Preliminary psychometric properties of the acceptance and action questionnaire—II: a revised measure of psychological flexibility and acceptance (in review)
12. Chambless DL (1985) The mobility inventory for agoraphobia. Behav Res Ther 23:35–44
13. Chambless DL, Caputo GC, Bright P, Gallagher R (1984) Assessment of fear of fear in agoraphobics: the body sensations questionnaire and the agoraphobic cognitions questionnaire. J Consult Clin Psychol 52:1090–1097
14. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE et al (2003) International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35:1381–1395
15. Craske MG, Barlow DH (2007) Mastery of your anxiety and panic. University Press, Oxford
16. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A (2008) Optimizing inhibitory learning during exposure therapy. Behav Res Ther 46:5–27
17. Crawford JR, Henry JD (2004) The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. British Journal of Clinical Psychology 43:245–265
18. Davis M (2006) Neural systems involved in fear and anxiety measured with fear-potentiated startle. Am Psychol 61:741–756
19. Deckert J, Catalano M, Syagailo Y, Bosi M, Okladnova O, Di Bella D et al (1999) Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum Mol Genet 8:621–624
20. Derogatis LR (1993) Brief symptom inventory (BSI) administration, scoring, and procedures manual, 3rd edn. National Computer Systems, Minneapolis
21. Domschke K, Braun M, Ohrmann P, Suslow T, Kugel H, Bauer J et al (2006) Association of the functional -1019C/G 5-HT1A polymorphism with prefrontal and amygdala activation measured with 3T fMRI in panic disorder. Int J Neuropsychopharmacol 9:349–355
22. Domschke K, Hohoff C, Jacob C, Maier W, Fritze J, Bandelow B et al (2008) Chromosome 4q31-34 panic disorder risk locus: association of neuropeptide Y Y5 receptor variants. Am J Med Genet B Neuropsychiatr Genet 147B:510–516
23. Domschke K, Ohrmann P, Braun M, Suslow T, Bauer J, Hohoff C et al (2008) Influence of the catechol-O-methyltransferase val158met genotype on amygdala and prefrontal cortex emotional processing in panic disorder. Psychiatry Res 163:13–20
24. Gloster A, Einsle F, Lang T, Hauke T, Wittchen H-U (2009) The therapist adherence and competency rating scales for panic disorder with agoraphobia (in preparation)

25. Gloster AT, Klotsche J, Helbig S, Einsle F, Lang T, Hummel K et al. (2009) Expanding the assessment domain in agoraphobia: mobility inventory-expanded (MI-E) and mobility inventory 7-day (MI-7) versions (in preparation)
26. Gorman JM, Kent JM, Sullivan GM, Coplan JD (2000) Neuro-anatomical hypothesis of panic disorder, revised. Am J Psychiatry 157:493–505
27. Gorman JM, Liebowitz MR, Fyer AJ, Stein J (1989) A neuro-anatomical hypothesis for panic disorder. Am J Psychiatry 146:148–161
28. Guy W (1976) Clinical global impression. In: Guy W (ed) ECDEU assessment manual for psychopharmacology, revised. National Insitute of Mental Health, Rockville, pp 217–222
29. Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50–55
30. Hayes SC (2008) Climbing our hills: a beginning conversation on the comparison of acceptance and commitment therapy and traditional cognitive behavioral therapy. Clin Psychol Sci Pract 15:286–295
31. Hofmann SG, Alpers GW, Pauli P (2009) Phenomenology of panic and phobic disorders. In: Antony MM, Stein MB (eds) Oxford handbook of anxiety and related disorders. Oxford University Press, New York, pp 34–46
32. Hueweler R, Kandil FI, Alpers GW, Gerlach AL (2009) The impact of visual flow stimuli on anxiety, dizziness, and body sway in persons with and without fear of heights. Behav Res Therapy 47:345–352
33. Koch EI, Gloster AT, Waller SA (2007) Exposure treatments for panic disorder with and without agoraphobia. In: Richard DCS, Lauterbach DL (eds) Handbook of exposure therapies. Elsevier, Burlington, pp 221–245
34. Lang T, Helbig-Lang S, Westphal D, Gloster AT, Wittchen HU (2009) Kognitiv-behaviorale Behandlung der Panikstörung mit Agoraphobie. Ein Therapiemanual. Hogrefe, Göttingen
35. Lonsdorf TB, Weike AI, Nikamo P, Schalling M, Hamm AO, Öhman A (2009) Genetic gating of human fear learning and extinction–Possible implications for gene-environment interaction in anxiety disorder. Psychol Sci 20:198–206
36. McHugh RK, Smits JAJ, Otto MW (2009) Empirically supported treatments for panic disorder. Psychiatr Clin North Am
37. Melzig CA, Michalowski JM, Holtz K, Hamm AO (2008) Anticipation of interoceptive threat in highly anxiety sensitive persons. Behav Res Ther 46:1126–1134
38. Neudeck P, Wittchen H-U (2005) Die Vernachlässigung der Expositionsverfahren- ein Verstoß gegen die Regeln der Kunst!. In: Neudeck P, Wittchen H-U (eds) Konfrontationstherapie bei psychischen Störungen. Hogrefe, Göttingen, pp 7–14
39. Rabin R, de Charro F (1999, 2001) EQ-5D: a measure of health status from the EuroQol Group. Paper presented at the 12th Medical Symposium of the Yrjo-Jahnsson-Foundation, Finland
40. Radomsky AS, Rachman S, Thordarsona DS, McIsaaca HK, Teachman BA (1999) The claustrophobia questionnaire. J Anxiety Disord 15:287–297
41. Reiss S, Peterson RA, Gursky DM, McNally RJ (1986) Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Therapy 24:1–8
42. Richard DCS, Lauterbach D, Gloster AT (2007) Description, mechanisms of action, and assessment. In: Richard DCS, Lauterbach DL (eds) Handbook of exposure therapies. Elsevier, Burlington, pp 1–28
43. Shadish WR, Cook TD, Campbell DT (2002) Experimental and quasi-experimental designs for generalized causal inference. Houghton-Mifflin, Boston
44. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW et al (2001) Reliability and validity of a structured interview guide for the Hamilton anxiety rating scale (SIGH-A). Depress Anxiety 13(4):166–178
45. Sheehan DV (1983) The anxiety disease. Charles Scribner's Sons, New York
46. Wittchen H-U, Gloster AT (2009) Developments in the treatment and diagnosis of anxiety disorders. Psychiatr Clin North Am 32:xix–xiii
47. Wittchen H-U, Pfister H (1997) DIA-X Interview. Instruktionsmanual zur Durchführung von DIA-X-Interviews (Instruction manual for the DIA-X-Interview). Swets & Zeitlinger, Frankfurt