Original Article

Bridging the Gaps Between Basic Science and Cognitive-Behavioral Treatments for Anxiety Disorders in Routine Care

Current Status and Future Demands

Jan Richter,[1] Andre Pittig,[2] Maike Hollandt,[1] and Ulrike Lueken[3,4]

[1]Department of Physiological and Clinical Psychology/Psychotherapy, University of Greifswald, Germany
[2]Institute of Clinical Psychology and Psychotherapy, Department of Psychology, Technische Universität Dresden, Germany
[3]Center of Mental Health, Department of Psychiatry, Psychosomatics, and Psychotherapy, University Hospital of Würzburg, Germany
[4]Department of Psychology, Humboldt University of Berlin, Germany

Abstract: As a core component of cognitive-behavioral therapies (CBT), behavioral exposure is an effective treatment for anxiety disorders. Still, recent treatment studies demonstrate relatively high rates of treatment dropout, nonresponse, and relapse, indicating a substantial need for optimizing and personalizing existing treatment procedures. In the present article, we aim to address current challenges and future demands for translational research in CBT for the anxiety disorders, including (a) a better understanding of those mechanisms conferring behavioral change, (b) identifying important sources of individual variation that may act as moderators of treatment response, and (c) targeting practical barriers for dissemination of exposure therapy to routine care. Based on a recursive process model of psychotherapy research we will describe distinct steps to systematically translate basic and clinical research "from bench to bedside" to routine care, but also vice versa. Some of these aspects may stimulate the future roadmap for evidence-based psychotherapy research in order to better target the treatment of anxiety disorders as one core health challenge of our time.

Keywords: cognitive-behavioral therapy (CBT), anxiety disorders, exposure, individualized psychotherpy, routine care

With an estimated 12-month prevalence rate of 14.0%, anxiety disorders (AD) are the most frequent group of mental disorders (Wittchen et al., 2011). Due to their high prevalence and early onset predominantly during childhood and adolescence (Beesdo-Baum & Knappe, 2012), AD are a leading cause of disability with an exceptionally high individual and societal burden (Gustavsson et al., 2011; Wittchen et al., 2011). Untreated, AD are associated with a chronic or relapsing course and high comorbidity load. In fact, AD are the strongest known risk factor and precursor of depression, as well as of a more malignant course of depression and suicidality (Beesdo et al., 2007; Meier et al., 2015). As a result, developing effective treatments for AD, as well as for other mental disorders and disseminating them into routine care, is one core health challenge of our time (Wittchen et al., 2011).

In the last decades, concerted action to develop empirically supported treatments provided effective strategies to challenge pathological fear and anxiety. In this regard, cognitive-behavioral therapy (CBT) including exposure-based interventions represents a first-line treatment choice (Arch & Craske, 2009; Bandelow, Lichte, Rudolf, Wiltink, & Beutel, 2015; NICE, 2011). Using the gold standard of randomized controlled trials (RCTs), the efficacy of CBT-based interventions in treating AD patients has been repeatedly demonstrated by several meta-analyses (Butler, Chapman, Forman, & Beck, 2006; Deacon & Abramowitz, 2004; Hofmann & Smits, 2008; Norton & Price, 2007; Olatunji, Cisler, & Deacon, 2010; Tolin, 2010; Watts, Turnell, Kladnitski, Newby, & Andrews, 2015). Importantly, CBT protocols exclusively focusing on exposure-based interventions are also effective in reducing comorbid

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conditions such as depression with overall moderate to large effects (Acarturk, Cuijpers, Van Straten, & De Graaf, 2009; Cuijpers, Cristea, Karyotaki, Reijnders, & Huibers, 2016; Cuijpers et al., 2014; Emmrich et al., 2012; Hunot, Churchill, Teixeira, & Silva de Lima, 2007; Mitte, 2005; Sánchez-Meca, Rosa-Alcázar, Marín-Martínez, & Gómez-Conesa, 2010). Moreover, effectiveness studies demonstrated CBT to be successful in naturalistic settings with comparable effect sizes to those in RCTs (Hans & Hiller, 2013; Stewart & Chambless, 2009; van Ingen, Freiheit, & Vye, 2009). First studies also suggest long-term effectiveness of CBT for AD in clinical practice (DiMauro, Domingues, Fernandez, & Tolin, 2013; Wootton, Bragdon, Steinman, & Tolin, 2015). Combined, these findings highlight exposure-based CBT as an effective and long-lasting therapeutic intervention for ADs.

However, despite an impressive overall empirical support, the utility of CBT is still limited, as a substantial proportion of patients do not respond in a clinically meaningful way. This deficit is apparent in continuing high rates of treatment nonresponse (34–36%; Taylor, Abramowitz, & McKay, 2012) and dropouts (16–20%; Fernandez, Salem, Swift, & Ramtahal, 2015; Hans & Hiller, 2013; Swift & Greenberg, 2012) in studies of both efficacy and effectiveness. Furthermore, even after successful treatment, a return of pathological fear and anxiety (e.g., relapse) frequently occurs in the long run (Ginsburg et al., 2014) with rates of 50% and higher within 1 year after low-intensity CBT (Ali et al., 2017). Limitations posed by nonresponse and relapse are complemented by the insufficient availability of mental health resources in clinical practice, with only a minority of individuals in need of psychotherapy having access to appropriate evidence-based psychological treatments (Kazdin, 2017; Young, Klap, Sherbourne, & Wells, 2001). This lack of availability is especially true for exposure-based CBT (Böhm, Förstner, Külz, & Voderholzer, 2008; Freiheit, Vye, Swan, & Cady, 2004; Roth, Siegl, Aufdermauer, & Reinecker, 2004). Despite increasing mental health treatment utilization, the use of psychotherapeutic treatments has relatively decreased since the late 1990s, while rates of pharmacotherapy have increased (Gaudiano & Miller, 2013).

Thus, although CBT has generally been proven efficient for many AD patients, there are distinct challenges to clinical research and dissemination approaches that prevent obtaining optimal treatment outcomes for the individual patient. Current challenges include (a) increasing our knowledge about the underlying mechanisms of different therapeutic techniques to refine and optimize them in terms of a precision therapy approach, (b) increasing individual treatment outcomes by identifying evidence-based predictors that take into account individual differences associated with treatment response, and (c) increasing the health-related impact of evidence-based treatments by fostering their dissemination to routine care.

In the present article, we aim to address these challenges and present a critical perspective on the current status quo of psychotherapy research in AD. Using the example of exposure-based CBT, we will identify putative research constraints that may prevent further developments and discuss recommendations to overcome these gaps. Based on a recursive process model of psychotherapy research we will describe distinct steps to systematically translate basic to clinical research "from bench to bedside" to routine care, but also vice versa. Thus, we argue that research also needs to recursively incorporate observations and suggestions from clinical practice, which may help to develop innovative treatments coming "from bedside to bench." By means of a thorough scientific review, the underlying mechanisms of action, boundary conditions, and specific indications of new treatments can be thus identified.

A Recursive Process Model of Psychotherapy Research

The central goal of psychotherapy research is to provide recommendations for an *evidence-based practice* in clinical psychology by integrating "the best available research with clinical expertise in the context of patient characteristics, culture, and preferences" (American Psychological Association Presidential Task Force on Evidence-Based Practice, 2006; see also Kazdin, 2008). Evidence-based practice thus emphasizes three different sources to be considered during clinical decision-making in routine care: (i) knowledge about evidenced-based treatments, (ii) client preferences and values, and (iii) practical expertise that is needed to implement the current state of research (Spring, 2007). Following those demands, psychotherapy research so far focused mainly on developing *evidence-based psychological treatments* aiming to test the empirical efficacy of treatment protocols in RCTs that integrate different treatment components and systematically best-known practices. Indeed, evidence-based psychological treatments are currently available for almost all mental disorders (Chambless & Ollendick, 2001; Layard & Clark, 2014) and by now there is no doubt that comprehensive treatment programs generally work for the average patient. However, given the still limited utility illustrated above, the current focus of psychotherapy research – that relies on testing combined treatment protocols – needs to be balanced out by experimental approaches that are more capable of identifying the underlying mechanisms of specific active ingredients. In addition, research approaches that take into account the quite considerable amount of individual variation in

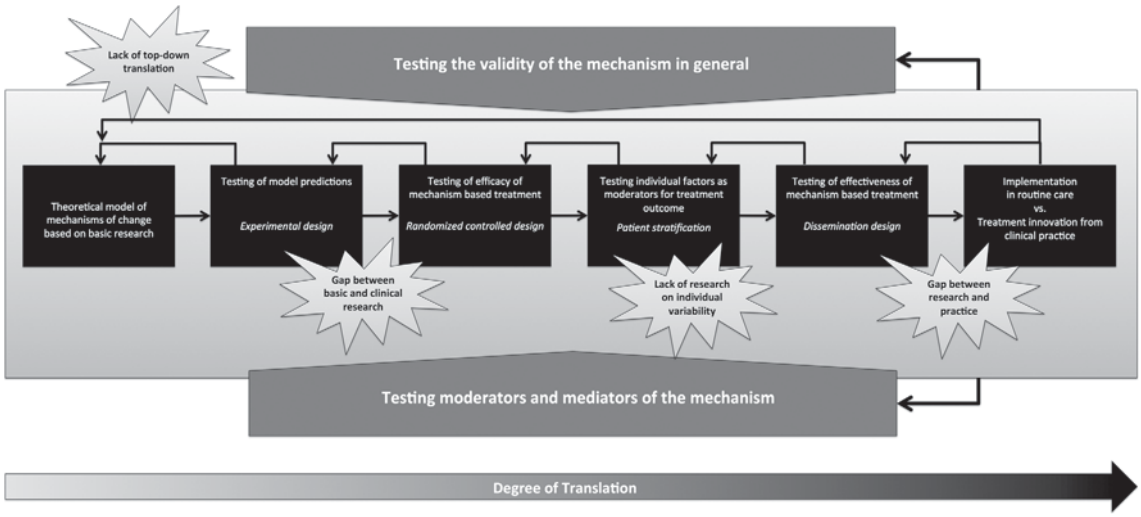

Figure 1. A recursive process model of psychotherapy research including different development steps from basic research to routine care and vice versa supplemented by the illustration of current research gaps.

patient characteristics possibly underlying differences in treatment response are needed.

As illustrated in Figure 1, a proposed recursive model of psychotherapy research describes a "bottom-up" (left-to-right) strategy from experimental approaches to test the underlying mechanisms and to translate findings into routine care. Following the mechanism-focused perspective, a behavioral exposure treatment is suggested to be a clinical analog of extinction learning of conditioned fear investigated in basic research studies (Kindt, 2014; Vervliet, Craske, & Hermans, 2013). This analog learning process may be a good example of how basic mechanisms can be translated to clinical application in a "bottom-up" manner. However, history has shown that new developments that have impacted the field of psychotherapy such as eye movement desensitization and reprocessing (Shapiro, 1989) are not always developed in a "bottom-up" manner, but often based on clinical observation and sometimes even serendipity ("top-down" strategy). As a consequence, experimental research was inspired by clinical observations in order to elucidate the underlying mechanisms and active ingredients (Ehlers et al., 2010; Lee, Taylor, & Drummond, 2006; Stickgold, 2002). As another example from the field of research on posttraumatic stress disorder, Imagery Rescripting and Reprocessing Therapy (Arntz & Weertman, 1999; Rusch, Grunert, Mendelsohn, & Smucker, 2000), which was also developed by practitioners for the treatment of intrusive memories, may indeed depend upon very basic mechanisms of memory reconsolidation that are well described on a neurophysiological level (Nader, Schafe, & Le Doux, 2000; Schwabe, Nader, & Pruessner, 2014). Although this disorder does not belong to the group of AD anymore after the revision of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), it shares some features with them and also responds to exposure-based treatments. These examples illustrate that the core mechanisms subserving behavioral change are commonly routed in basic processes of learning and memory, conferred via a brain that is highly neuroplastic. Experimental research is essential to follow up on such impulses from clinical observation to study the underlying mechanisms of action of novel techniques in order to optimize them based on mechanistic knowledge. This back-and-forth translation of basic and clinical findings thus constitutes a recursive approach.

Following the "bottom-up" logic, *experimental designs* on those principal mechanisms underlying behavioral change should subsequently be translated into *randomized controlled designs* as a central strategy for testing the efficacy of treatments under conditions of high internal validity (that should be supplemented by strategies enhancing external validity in RCTs). At the same time, *patient stratification* needs to test the dependence of RCT efficacy on patients' characteristics. In somatic medicine, stratification approaches take advantage of patients' individual characteristics (e.g., genetic make-up and molecular profiling) in order to assign a patient to a specific treatment alternative. By comparing randomized versus stratified allocation, the added value of this profiling can be tested. In order to increase clinical representativeness, effectiveness studies and *dissemination designs* are needed to translate research conditions of high internal validity to more naturalistic settings. Generally, dissemination designs involve all planned and proactive strategies to spread evidence-based information and treatment strategies to clinical practitioners

(Rabin & Brownson, 2012), including nonuniversity settings, patient referral, flexible structure, no therapist training for study purpose, more representative inclusion/exclusion criteria, allowing for concomitant medication, and no randomization (Shadish, Matt, Navarro, & Phillips, 2000; Stewart & Chambless, 2009). Finally, dissemination of evidence-based psychological treatments needs to be expanded to routine care to ensure the availability for the individual patient.

Supplementing the previous body of research on evidence-based psychological treatments, we here emphasize the additional need for identifying (1) evidence-based mechanisms of change in psychotherapy before they are translated to the RCT level (gap between basic and clinical research: which mechanisms work and why) taking suggestions into account from both basic research and clinical observations, (2) evidence-based predictors of treatment response that would allow for patient stratification (lack of research on individual variability: which treatments work for whom), (3) evidence-based methods to implement evidence-based psychological treatments in routine care (gap between research and practice: how can we make them work in routine care). Following our recursive process logic, these different phases of developing novel evidence-based treatments are interrelated and impact each other. Referring to the existing gaps and barriers in psychotherapy research, also illustrated in Figure 1, we describe new research perspectives below and discuss them in the example of exposure therapy.

Barrier 1: The Gap Between Basic and Clinical Research

As described above, efficacy and effectiveness of current evidence-based psychological treatments are still limited. In a "bottom-up" approach, optimization of already established interventions but also the development of novel treatment approaches should be based on identified mechanisms of change. However, our knowledge regarding those mechanisms is still in its infancy (Holmes, Craske, & Graybiel, 2014). In this regard, a need for identifying *empirically supported principles of change* instead of evidence-based psychological treatments by employing dismantling designs has already been highlighted (Rosen & Davison, 2003). In addition, major mediators and moderators of treatment outcome need to be identified to specify both the circumstances of most effective treatment procedures and specific target groups (Hayes, Long, Levin, & Follette, 2013; Kraemer, Wilson, Fairburn, & Agras, 2002; Murphy, Cooper, Hollon, & Fairburn, 2009).

To increase the grain size of research there is a need to identify and design particular treatment components tailored to specific mechanisms associated with symptom alleviation, rather than diagnostic categories (Hayes, Barlow, & Nelson-Gray, 1999; Hayes et al., 2013; King & Ollendick, 2008). However, the needed intensive translational exchange between basic science – also including animal research – and clinical science is still developing (Hayes et al., 2013). One central barrier between disciplines is the different focus of interest. The mechanism-oriented approach in basic science stands in contrast with traditional clinical science that is defining pathology by broad and heterogeneous clinical entities mainly based on patients' self-reported symptoms, thus applying a descriptive instead of a functional perspective. To overcome this conceptual gap the National Institute for Mental Health (NIMH) established the Research Domain Criteria project (RDoC) in 2009 aiming to develop – for research purposes – a novel classification approach based on intermediate biopsychological constructs more related to particular dysfunctions in mentally disordered patients than to broad diagnostic groups (Cuthbert, 2014, 2015; Cuthbert & Insel, 2013; Insel, 2014; Insel et al., 2010; Kozak & Cuthbert, 2016). This research focus explicitly aims to explain not only mechanistic heterogeneity within traditional diagnoses but also transdiagnostic similarities that were mostly neglected so far. Although this perspective is still developing, first examples start to illustrate the added value of this complementary approach (e.g., Hamm, Richter, & Pané-Farré, 2014; Hamm et al., 2016; Kaufman, Gelernter, Hudziak, Tyrka, & Coplan, 2015; Lang, McTeague, & Bradley, 2016). Future research needs to follow up on identifying those dysfunctions that are strongly related to specific clinical phenomena, such as escalating panic, lasting anticipatory anxiety, or avoidance behavior in ADs, whose individual significance for one's burden highly differs between patients. Although these dysfunctions are usually expressed in subjective experiences and observable behavior, they are also related to deviations in the system levels of genes, molecules, cells, neural circuits, and physiology (Deckert et al., 2017; Lueken et al., 2016; Richter et al., 2012). The holistic view of impairment based on these biopsychological interactions that is also explicitly taking desynchrony among different units of analyses (Kozak & Cuthbert, 2016) into account may better reflect the complexity of possible sources of maladaptive functioning. Such a comprehensive model of dysfunction may represent a good starting point for developing treatments that target specific dysfunctions rather than complex disorder entities. This biobehavioral perspective is complemented by current developments in cognitive-behavioral oriented models on (dys-) functions as constituting elements in mental disorders (Hofmann, 2014).

In sum, we argue that commencing with a theoretical rationale of clinical dysfunction and putative mechanisms

of change (rather than a mere diagnostic perspective) may facilitate the development of tailored treatment procedures supported by experimental findings. This first experimental proof of concept should act as a prerequisite before evaluating treatments using RCT methodology. The more detailed, specific, and comprehensive model predictions are tested the easier precise assumptions for therapeutic action can be drawn and proved. Thus, basic research is requested to deliver the theoretical basis of active ingredients in already established evidence-based psychological treatments and is asked to identify associated moderators and mediators.

In Depth: From Fear Extinction to Exposure – the Need for an Empirically Supported Model of Change Underlying Exposure Therapy

Treatment outcomes of exposure-based interventions are superior compared to other types of interventions (Marks & Dar, 2000; Tolin, 2010). As a consequence, exposure represents a key feature of CBT for anxiety patients (Clark, 1999; Hofmann, 2007, 2008; Lohr, Lilienfeld, & Rosen, 2012; Neudeck & Wittchen, 2012). Despite these promising findings, there are ongoing controversies regarding an empirically supported model of change.

Several psychological processes of change have been proposed to underly the positive effect of exposure including behavioral modification, cognitive change, counterconditioning, habituation, and extinction learning (Carey, 2011; Tryon, 2005). The emotional processing theory, as one of the most influential theories on the mechanism of exposure, assumes that fear reduction results from the integration of corrective, fear-incongruent information into a present fear memory during exposure (Foa, Huppert, & Cahill, 2006; Foa & Kozak, 1986; Foa & McNally, 1996; Rachman, 1980). For this integration, initial fear activation and within-session fear reduction are seen as prerequisites for between-session changes. However, past research failed to demonstrate a compelling association between within-session fear reduction and long-term treatment outcome (see Craske et al., 2008). In line with this, and based on an extant body of basic research (Dunsmoor, Niv, Daw, & Phelps, 2015), the inhibitory learning theory (Craske et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014) emphasizes the development of a new safety association with the original fear-inducing stimulus following the basic principles of extinction learning . Briefly, extinction learning occurs during extinction training, which typically follows fear acquisition. During fear acquisition training, a conditioned stimulus is repeatedly paired with an aversive event, thereby forming an excitatory CS-US association, or fear memory (see Lonsdorf et al., 2017, for a detailed description). During extinction training, the conditioned stimulus is subsequently presented in the absence of the aversive stimulus. During extinction training, an inhibitory extinction memory is formed (i.e., the fear conditioned stimulus now predicts the absence of the aversive stimulus). If successfully retrieved, this inhibitory memory competes with the original and still intact fear memory resulting in reduced fear reactivity. In contrast, return of fear may occur whenever the recall of the original fear memory is superior to the inhibitory memory. Such return of fear can be examined in the laboratory by distinct return of fear designs (i.e., spontaneous recovery, renewal, and reinstatement; see Lonsdorf et al., 2017). Following the analogy between exposure therapy and the basic model of extinction learning (Kindt, 2014) fear reduction in anxiety disordered patients during repetitive exposure is modeled by the degree of inhibitory memory generation and memory recall and, thus, treatment nonresponse is thought to be related to patients' deficits in these learning processes. In contrast, symptom relapse is affected by mechanisms of return of fear. Acknowledging individual differences between patients and associated moderators may bear the potential to optimize exposure procedure for current nonresponders. However, our understanding of individual differences especially in clinical populations is still limited (Lonsdorf & Merz, 2017; Lonsdorf & Richter, 2017).

Both emotional processing theory and the inhibitory learning theory aim to uncover the underlying mechanisms of change to improve exposure-based interventions. However, ccaution is warranted when treatment recommendations are derived prematurely. Based on the assumptions derived from the emotional processing theory, practitioners were urged to establish within-session fear reduction in exposure exercises. As mentioned above, these recommendations have been empirically questioned in the meanwhile (Craske et al., 2008, 2014). In a similar vein, numerous recommendations are already derived from the inhibitory model of fear reduction (Craske et al., 2014; Pittig et al., 2015; Pittig, van den Berg, & Vervliet, 2016). Several examples confirm the eligibility of the inhibitory learning theory in reducing pathological fear (Craske et al., 2014; Lass-Hennemann & Michael, 2014; Meuret et al., 2015; Shiban, Schelhorn, Pauli, & Mühlberger, 2015) also by testing pharmacological augmentations predicted by the model (Hofmann, Otto, Pollack, & Smits, 2015; Soravia et al., 2014). Still, empirical evidence for the translational value of experimental strategies for clinical practice is scarce. Clinical research has only started to address how to implement inhibitory learning strategies into clinical practice (e.g., effects of safety behavior during exposure therapy (Blakey & Abramowitz, 2016; Helbig-Lang & Petermann, 2010; Meulders, Van Daele, Volders, & Vlaeyen, 2016).

As discussed by Lonsdorf & Richter, (2017) in this special issue, the term extinction learning does not rely

on a unitary process but summarizes several learning mechanisms such as memory acquisition, consolidation, reconsolidation, recall, generalization, and retention. Future research in AD is necessary to disentangle mechanisms involved in the acquisition and consolidation of inhibitory memories from those involved in their recall and generalization. On a clinical level, dismantling studies are an appropriate method to test for the specific effects of particular variations in exposure protocols suggested by basic models of extinction learning (Dunsmoor et al., 2015). So far, RCTs investigating subtle but theoretically important variations in the practical implementation of exposure therapy are rare (but see Gloster et al., 2009, 2011; Heinig et al., 2017). Also, basic research is requested to increase the hitherto limited knowledge about specific mechanisms in extinction learning, such as generalization processes. These have already been investigated extensively for fear learning (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015) but less for fear-inhibitory learning (e.g., Vervliet, Vansteenwegen, Baeyens, Hermans, & Eelen, 2005; Vervliet, Vansteenwegen, & Eelen, 2005; Vervoort, Vervliet, Bennett, & Baeyens, 2014). Detailed insights into extinction generalization are of strong clinical relevance for the transfer of experiences during therapeutic exposure to patient's everyday life. Indeed, first studies demonstrated extinction generalization in the therapy context (Byrne et al., 2015; Rowe & Craske, 1998a, 1998b; Pace-Schott, Verga, Bennett, & Spencer, 2012; Preusser, Margraf, & Zlomuzica, 2017). Also, empirically based strategies are needed to prevent symptom relapse in initially successfully treated patients. Indeed, booster sessions following the actual treatment phase are already common in RCTs and might further affect positively symptom reductions from post to follow-up assessments usually observed in RCTs (e.g., Gloster et al., 2011). However, the specific effects of booster interventions are unclear; according to the inhibitory learning theory, several techniques might be possible and should be empirically tested. Finally, the inhibitory model has to integrate further possible mechanisms related to extinction learning such as active interference learning during fearful memory reconsolidation (Beckers & Kindt, 2017; Shiban, Brütting, Pauli, & Mühlberger, 2015; Telch, York, Lancaster, & Monfils, 2017) and has to specify similarities and differences between associated mechanisms.

In contrast to numerous studies on the acquisition and extinction of fear, basic research has only recently (re)discovered the essential role of instrumental avoidance learning for anxiety disorders (Servatius, 2016; Beckers & Craske, 2017). Persistent dysfunctional avoidance has been linked to increasing psychopathology (e.g., secondary depression; Beesdo et al., 2007) and individual impairments (Wittchen, Gloster, Beesdo-Baum, Fava, & Craske, 2010). Clinically, the reduction of avoidance is a necessary precondition for extinction learning as new learning cannot be initiated when exposure exercises are avoided. To understand the underlying mechanisms of avoidance behavior, basic research focuses on instrumental learning models. In these models, individuals learn to perform an instrumental action to prevent an aversive event whenever a potential occurrence of this event is signaled by a conditioned stimulus (CS+). As a laboratory analog of the detrimental effects of avoidance on exposure therapy, recent basic findings demonstrate that persistent avoidance prevents fear reduction because experience relevant to extinction learning is prohibited (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). Moreover, instrumental avoidance responses seem to persist despite successful fear extinction (Vervliet & Indekeu, 2015). This dissociation between fear and avoidance reduction exemplifies the need for detailed basic research modeling clinically relevant avoidance behavior. Still, innovative basic research in avoidance learning and its implication for reduction of maladaptive behavior is scarce and represents a crucial gap between clinical observation and basic science. Recent approaches to avoidance behavior highlighted the contribution of a variety of distinct mechanisms involving automatic action tendencies, instrumental learning, reflective decision-making processes, and habitual learning (Andreatta, Michelmann, Pauli, & Hewig, 2017; Arnaudova, Kindt, Fanselow, & Beckers, 2017; Krypotos, Effting, Kindt, & Beckers, 2015; Pittig, Schulz, Craske, & Alpers, 2014). The increasing interest raises hope that clear recommendations will be available soon how to modulate best clinically relevant avoidance behavior (e.g., Bublatzky, Alpers, & Pittig, 2017).

Barrier 2: The Gap Between the Average and the Individual Patient in Psychotherapy Research

Although CBT is a highly effective treatment for the average AD patient, clinically meaningful response is only seen in approximately 50–65% of the patients (Gloster et al., 2011; Taylor et al., 2012). Thus, CBT may leave over one third of patients as potential "nonresponders" toward the first-line standard treatment. Individual patient characteristics may act as one major source of variability underlying these differences in treatment response. Knowledge about baseline patient features that may bear predictive value for treatment outcome or relapse could thus open up new avenues for patient stratification where this information is used to support clinical decision-making on finding the optimal treatment for the individual patient: knowing a priori if a patient is likely to respond before a particular treatment is initiated could help in sparing ineffective

treatments, associated side effects on patient compliance, disease chronification or aggravation, as well as direct and indirect financial costs. Furthermore, predicting which patients may be vulnerable for showing clinical relapse could aid in planning special measures of relapse prevention for patients at risk.

Following the paradigm shift of personalized medicine in the domain of genetics and pharmacology "by steering patients to the right drug at the right dose at the right time" (Hamburg & Collins, 2010), research efforts are increasingly emerging on identifying those patient characteristics that modulate treatment response also in the field of mental health (Lueken et al., 2016; Uher, 2011). However, as outlined earlier (Lueken & Hahn, 2016; Lueken et al., 2016), the vast majority of studies targeting putative clinical or "biomarkers" of treatment response are most often restricted to investigations on the group level, which are inherently limited in translating these findings to the individual patient. While group comparisons are well suited to improve our mechanistic knowledge about putative mechanisms of change (see section "Barrier 1: The Gap Between Basic and Clinical Research" above), they do not necessarily translate into meaningful information for the individual patient (Lueken & Hahn, 2016). Personalized medicine approaches based on patient stratification are however only feasible if we can predict the diagnosis, course, or outcome of a proposed treatment on the single-case level. This "translational roadblock" may be overcome by novel methodological developments applying machine learning techniques to the field of predictive analytics in mental health (Hahn, Nierenberg, & Whitfield-Gabrieli, 2017) that allow for predictions on the individual patient level. Multivariate pattern recognition, embedded within a machine learning framework, is a technology that has strongly influenced medical research (Darcy, Louie, & Roberts, 2016; Libbrecht & Noble, 2015) and that bears potential to resolve these problems also for the field of mental health research and patient care (Doyle, Mehta, & Brammer, 2015; Orrù, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012; see section "In Depth: Using Machine Learning to Support Clinical Decision-Making" below).

Both researchers and clinicians sometimes wish to predict future outcomes: Which high-risk subject will convert to actual psychosis? Does the first onset of a major depressive episode indicate a unipolar or bipolar affective disorder – with consequences for the appropriate choice of treatment? Or will an AD patient respond to exposure-based treatment? Here, machine learning can aid in supporting clinical expert decisions by delivering single-case predictions with a quantifiable accuracy, sensitivity, and specificity. Emerging evidence suggests that machine learning techniques can deliver predictions on treatment outcome in major depression with high accuracy for cognitive treatments (Siegle et al., 2012), antidepressant medication response (Costafreda, Chu, Ashburner, & Fu, 2009), and electroconvulsive therapy (Redlich et al., 2016). In a similar vein, treatment response toward CBT crosscutting different AD diagnoses has been successfully predicted based on neuroimaging data with accuracy rates exceeding 80% (Hahn et al., 2015; Ball, Stein, & Paulus, 2014; Doehrmann et al., 2013; Månsson et al., 2015; Whitfield-Gabrieli et al., 2016). Although these initial findings appear to be promising, the search for valid and reliable (bio-)markers with sufficient sensitivity and specificity on the individual patient level is still in its infancy. Future challenges to the field encompass both methodological as well as practical issues (also see Lueken et al., 2016 and the next section for a summary).

In Depth: Using Machine Learning to Support Clinical Decision-Making

Multivariate pattern recognition is a field within the area of machine learning for automatic discovery of regularities in data through the use of computer algorithms. Multivariate readouts are treated as high-dimensional patterns and pattern recognition approaches are used to identify statistical properties within the data. Of particular relevance for medical research purposes are unsupervised and supervised machine learning algorithms. While the former allow for data-driven detection of regularities in the underlying data, the latter are dedicated to best differentiate between two or more groups of subjects and to predict a single-patient's status (e.g., the probability of this subject to be treatment-responder or nonresponder). In other words, while supervised machine learning gives exactly one answer that can support clinical expert decisions, unsupervised machine learning "gives a million answers" that may enrich our theoretic models (e.g., disease nosology) from a data-driven perspective (Libbrecht & Noble, 2015). For clinical purposes, supervised machine learning (e.g., to classify a patient to belong to two different groups such as cases or controls) is usually employed. In a first step, a model (or 0discriminating pattern) based on a group of patients (training sample) is constructed which in a second step is used to predict the characteristics of a new, previously not classified patient. By comparing the predicted with the "real-world" outcomes (diagnostic classification or response status), accuracy, sensitivity, and specificity measures of the given test (e.g., the discriminating pattern) can be calculated. Of note, machine learning is not restricted to one data modality, but can incorporate different modalities spanning from neurobiological (structural and functional magnetic resonance imaging [fMRI], electroencephalogram [EEG], or genetics) to behavioral (experimental or ecologic momentary assessments) to clinical data, thus increasing its appeal for different research domains from

deep (e.g., neurobiologically informed) to digital phenotyping (Oellrich et al., 2016).

Although first applications of machine learning algorithms to clinical problems appeared to show encouraging results, distinct methodological as well as practical problems need to be considered. First, and among others, the generalizability, or robustness of a classifier crucially awaits empirical validation. The vast majority of clinical studies currently employ validation procedures within a given sample, for instance leave-one-out cross-validations. While maintaining independent predictions by separating training and testing samples, leave-one-out cross-validations make most efficient use of a given dataset. However, as the underlying sample may be rather homogenous and prone to site-specific recruitment and assessment biases, we do not know yet how well the discriminating pattern will perform in other samples, or, ultimately, for the next given patient out there in clinical care. There is hence an increasing urge for out-of-sample validations that could be ideally conducted within a multisite study framework. Second, research so far predominantly focused on the neuroimaging data domain, which appears highly suitable for machine learning due to its inherent multivariate nature and proximity to the supposed underlying mechanisms of change on brain level. Limiting its utility from a health-economic and dissemination perspective, neuroimaging may however not become a low-cost, routine tool in clinical practice in the near future. Upcoming studies should thus consider other measures derived from digital phenotyping (which may be particularly suitable due to their multivariate nature and high ecological validity) and evaluate their utility for diagnostic screenings or predictions of treatment outcome on the individual level with an optimized cost-benefit ratio. For example, ecologic momentary assessments may be particularly suitable to track behavioral avoidance as a putative barrier for exposure therapy (see section "In Depth: From Fear Extinction to Exposure – the Need for an Empirically Supported Model of Change Underlying Exposure Therapy" above). Finally, in order to improve treatment response for otherwise nonresponsive patients, research has to inform clinical decision-making about evidence-based alternative treatment approaches or augmentation strategies. In this sense, innovative study designs are needed that deliver an empirical proof of evidence based on a priori patient stratification (which treatments [or combinations thereof] will work for whom).

Barrier 3: The Gap Between Clinical Scientists and Practitioners

Finally, despite considerable progress in demonstrating effective treatments, the great majority of patients do not receive appropriate care because evidence-based psychological treatments are used infrequently (Kazdin, 2017). Psychotherapy research started to challenge the scientist-practitioner gap in various ways (Forman, Gaudiano, & Herbert, 2016; Lilienfeld, Ritschel, Lynn, Cautin, & Latzman, 2013; McHugh & Barlow, 2010; Rakovshik & McManus, 2010; Stewart, Chambless, & Baron, 2012). Typically, dissemination efforts are based on informational strategies and trainings to spread the availability of skilled practitioners. While training in evidence-based psychological treatment does indeed increase the general utilization in routine practice (Harned et al., 2014; Sholomskas et al., 2005), a substantial number of practitioners, however, do not incorporate trained strategies into their practice at all or in a sustained manner (Becker, Zayfert, & Anderson, 2004). Thus, in addition to the transfer of skills and knowledge, distinct barriers need to be addressed. General concerns about evidence-based psychological treatment (e.g., utility of findings from strictly controlled RCTs for clinical practice) and attitudes toward specific interventions (e.g., exposure being unethical or harmful) may limit the willingness to adopt relevant treatment components. General dissemination barriers, for example, comprise a reluctance to use treatment manuals for various reasons (Addis, Wade, & Hatgis, 1999; Gunter & Whittal, 2010) or preferring clinical judgment to evidence-based recommendations (Stewart & Chambless, 2007). Moreover, distinct barriers in the clinical routine (e.g., patient load, time management) and systemic barriers of health care regulations (e.g., financial compensation) may hinder willing practitioners to fully implement evidence-based psychological treatment procedures. This set of barriers concerns economic and organizational differences between controlled research studies and routine care (Gunter & Whittal, 2010). Demands in routine care are typically higher (higher case load, efficient time schedules, etc.), thus practicability should be in the center of attention. In this regard, the view of evidence-based physical therapy (EBPT) as a one-way training strategy to transfer clinical research results into routine care disregards the naturalistic demands and subjective barriers of therapists in all-day practice (Gunter & Whittal, 2010). Finally, the frequent lack of attention toward novel treatment strategies derived from clinical developments in basic research supports an attitude of indifference toward evidence-based treatment guidelines. In addition to tailoring research agendas to practical needs, basic research should be informed by the extensive clinical experience of practitioners. Also, basic research needs to account for preconditions and boundaries by stakeholders (e.g., insurance companies) for conducting psychotherapy under routine care conditions that are often difficult to change (i.e., practice-based research). Following a recursive process model of psychotherapy research,

this information needs to be picked up and has to facilitate research that is able to answer the questions most important from the perspective of practitioners. In this line, dissemination processes may be better seen as a two-way bridge between research and practice (Goldfried, 2010; Goldfried et al., 2014) and should also foster the dissemination of practitioners' clinical experiences to research. Thus, "research-oriented practice" should always be complemented by "practice-oriented research."

In Depth: The Need for Reciprocal Dissemination of Exposure Therapy: Research-Based Practice and Practice-Based Research

Despite the high efficacy and effectiveness of exposure therapy demonstrated in the past and resulting recommendations for clinical practice, dissemination research strongly refutes a widespread utilization of exposure-based intervention. Compared to other therapeutic strategies, exposure is among the least utilized interventions of practitioners (Cook, Biyanova, Elhai, Schnurr, & Coyne, 2010). For anxiety and posttraumatic stress disorders, the portion of patients receiving exposure considerably varies depending on the targeted therapist and patient population. Some studies reported that only 17–37% of patients are offered exposure treatments (Becker et al., 2004; Böhm et al., 2008; Freiheit et al., 2004). One other study suggested that up to 80% of patients received exposure but, however, not appropriately delivered (Roth et al., 2004). Even by CBT therapists, exposure is rarely used (Hipol & Deacon, 2013) and seems to be the first strategy disregarded in routine care (Hoyer et al., 2017). These findings exemplify the ample need to optimize the utilization of exposure in routine care.

Within a research-based practice approach, the primary strategy to boost the dissemination of exposure is to train practitioners. On the one hand, controlled training approaches are effective to establish skills and therapeutic competence to deliver exposure and successfully increase the use of exposure in routine care (Harned, Dimeff, Woodcock, & Contreras, 2013; Harned, Dimeff, Woodcock, & Skutch, 2011; Harned et al., 2014; Sholomskas et al., 2005). On the other hand, a large group of trained therapists may still not accept and use exposure in their practice (Becker et al., 2004). Following trainings in manualized CBT, exposure may even be the first component to be disregarded when applying the manual in routine care (Hoyer et al., 2017). Thus, although training efforts have been shown to increase the dissemination of exposure, they may not suffice as a standalone strategy.

For exposure-based interventions, subjective barriers of practitioners such as negative attitudes toward exposure may drastically limit the use in routine care, but are hardly accounted for. Prominent negative attitudes, for example, include perceived risk of unspecific negative outcomes such as "decompensation," non-effectiveness for complex cases, or therapists' expectations that patients might not be motivated to undergo "distressing exposure" or should be excluded from exposure (Deacon & Farrell, 2013; Meyer, Farrell, Kemp, Blakey, & Deacon, 2014; Pittig & Hoyer, in press). Presence of such negative attitudes has been linked to less frequent, suboptimal, and less effective delivery of exposure (Deacon & Farrell, 2013; Farrell, Deacon, Kemp, Dixon, & Sy, 2013). Moreover, subjective believes about when exposure is indicated may lead to exclusion of patients that in contrast might greatly benefit (Meyer et al., 2014). For example, the presence of comorbid depression in AD patients is often perceived as a barrier to successfully conduct exposure therapy. In contrast, evidence from RCTs shows that comorbid depression in primary panic disorder with agoraphobia does not preclude patients to benefit from exposure and may even reduce the burden of depression (Emmrich et al., 2012). Even if comorbid psychosis is the number one exclusion criterion for exposure-based interventions, recent studies supported the efficacy of treating anxiety or trauma in patients with comorbid psychosis by means of exposure (Frueh et al. 2009; Halperin, Nathan, Drummond, & Castle, 2000; Kingsep, Nathan, & Castle, 2003; van den Berg & van der Gaag 2012). Finally, additional sources of subjective barriers have been identified, such as distress or anxiety sensitivity of therapists while conducting exposure (Harned et al., 2014; Pittig & Hoyer, in press). These attitudes and expectations are especially troublesome as they seem to persist (Deacon & Farrell, 2013) but, importantly, are not supported by empirical findings (e.g., as patients actually prefer exposure as the choice of treatment; Becker et al., 2004). In fact, a recent study identified therapist attitudes and knowledge as the primary dissemination barrier for exposure-based interventions (Harned et al. 2013).

Thus, standard training approaches may benefit from additional strategies to target subjective barriers of therapists. For example, adding motivational strategies to address therapists' attitudes is more effective than training alone (Harned et al., 2014). Different strategies, such as emotion-based appeals (Farrell et al., 2013), have been suggested but research is scarce. In addition, research on therapist barriers is mostly limited by small and/or selective samples and the assessment of single barriers, which do not allow a comprehensive estimation of their unique impact. Thus, there is need for future research addressing potential strategies to target subjective barriers of therapists.

Regarding the economic and organizational demands of routine care, an important objective of psychotherapy research is to provide effective exposure techniques that are cost- and time saving and easily implemented. In addition, health care regulations should be tailored to facilitate

the easy implementation of exposure (e.g., by offering adequate financial compensation for the necessary expenditure of time of exposure exercises during treatment). Again, good examples are rare so far but aspire toward more. For instance, a large RCT in patients with panic disorder and agoraphobia illustrated that self-guided exposure may also be effective, thus offering exposure techniques under conditions where therapist guidance may not be available (e.g., well-instructed standardized exercises with sufficient cognitive preparation; Gloster et al., 2011).

In sum, dissemination of evidence-based exposure interventions and novel optimization strategies is (still) a major goal. Although trainings are a major contribution to this dissemination effort, further strategies to address therapist reservations and practical barriers are needed. An equitable transfer between basic research and clinical practice may help to bridge the still existent gap.

Conclusions and Future Demands

Exposure-based CBT represents without doubt one of the major success stories in developing evidence-based treatments for the anxiety disorders. At the same time, existing barriers from basic to clinical research and to its dissemination to routine care emphasize the need for bridging translational gaps. Here we described a recursive process model of psychotherapy research and identified core challenges for future research, including (a) a better understanding of the underlying mechanisms conferring behavioral change, (b) identifying important sources of individual variation that may act as moderators of treatment response, and (c) target practical barriers for dissemination of exposure therapy to routine care. Importantly, we are convinced that in the future two perspectives need to be considered: a "research-oriented practice" and a "practice-oriented research."

Some of these aspects may stimulate the future roadmap for a closer interplay of clinical and basic science; however, recent calls for a mental health science (Holmes et al., 2014) clearly point out that – compared to efforts in pharmacological research – research on behavioral treatments is tremendously underfunded, thus preventing psychologists to sufficiently translate dramatic advances from basic neuroscience to the clinic. Thus, in addition to increasing our research efforts, relevant national and international stakeholders are requested to improve the visibility of our discipline.

In addition to this economic barrier and based on the recursion between basic research and clinical practice, we would like to strongly emphasize the need for practitioners to be well trained in scientific methods. This prerequisite for a successful translational science (bottom-up as well as top-down) should be already considered at the stage of developing novel training programs for psychotherapists.

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Jan Richter
Department of Physiological and Clinical Psychology/Psychotherapy
University of Greifswald
Franz-Mehring-Straße 47
17487 Greifswald
Germany
jan.richter@uni-greifswald.de