# CONTEMPORARY ISSUES IN DEFINING THE MECHANISMS OF COGNITIVE BEHAVIOR THERAPY

EDITED BY: Nikolaos Kazantzis, Lorenzo Lorenzo-Luaces, Daniel R. Strunk and Marcus J. H. Huibers

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# CONTEMPORARY ISSUES IN DEFINING THE MECHANISMS OF COGNITIVE BEHAVIOR THERAPY

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EDITORIAL
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# Editorial: Contemporary Issues in Defining the Mechanisms of Cognitive Behavior Therapy

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**Editorial on the Research Topic**

**Contemporary Issues in Defining the Mechanisms of Cognitive Behavior Therapy**

## INTRODUCTION

Cognitive behavior therapy (CBT) is an umbrella term that refers to psychological therapies founded on the premise that (a) cognitive and behavioral processes are implicated in the development and maintenance of psychopathology, and (b) those processes are likely to be present during the session and require the therapist to tailor the intervention to best assist the patient (1). CBT includes therapies that focus on attention and other processes of cognition (e.g., acceptance, tolerance), cognitive reappraisal (e.g., decentering, defusion), behavior change (e.g., activation, exposure), as well as emotion coping, and interpersonal skill development (2).

Various CBTs have well-documented efficacy (3, 4) that have led to considerable dissemination efforts (5), but the literature on mechanisms of action is less evolved (6–9). This literature can be classified into three groups: (1) research designed to identify patient features that may serve as prognostic predictors, as well as moderators or mediators of treatment effects (10–12); (2) research focused on generic relational processes in psychotherapy, such as foundational counseling skills, typically assessed as empathy, warmth, positive regard, and agreement on goals and tasks of therapy, comprising the combined construct of working alliance (13, 14); as well as (3) research aiming to examine specific aspects of the delivery of CBT, such as collaborative-empiricism, Socratic dialogue (15) and facilitation of homework assignments (16, 17). These various research efforts each involve methodological challenges including the indexing of patient characteristics and evaluation of therapist competence (18, 19).

In this Research Topic, we sought contributions from leading clinical scientists to contribute empirical, review, and conceptual issues in defining the mechanisms of change in CBT.

## NEW EMPIRICAL STUDIES OF MECHANISMS OF CHANGE IN CBT

Four papers examine in-session processes that might explain therapeutic gains in CBT. First, Lemmens et al. examine the processes that might contribute to sudden gains, large, stable improvements, in cognitive therapy (CT) for depression (20). Though primarily descriptive given the small sample size, they found the largest differences between a pre-gain and a control session emerged for their measures of behavioral changes. Interestingly, the working alliance was consistently high before and after the gain, suggesting it might not be a proximal determinant of sudden gains.

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Second, Don et al. examined the temporal associations of the working alliance and therapist adherence in CBT for depression. Initially, they failed to find that the alliance or a therapist-reported adherence item was associated with either subsequent or prior symptom change. In additional analyses, a perceived helpfulness component of the alliance alone was related to prior symptom change. Their work helps to reinforce the importance of carefully timing the assessment of therapy process variables and symptom change when working to understand how treatments achieve their effects.

Third, Feldmann et al. investigated potential mechanisms in CBT for chronic pain within routine inpatient treatment. They found that changes in the specific treatment processes of cognitive restructuring and relaxation were associated with changes in disability and depression. Their work highlights how data from routine care, which often can achieve larger samples than experimental studies, can be used to investigate mechanisms and pathways for improving CBT.

Finally, in a relatively large sample, Beierl et al. examined the relationship between the alliance and outcome in the context of treatment for post-traumatic stress disorder. Therapist and patient-rated alliance at session one were associated with symptom change from baseline to post-treatment. In a more sophisticated cross-lagged panel analysis that focused on prediction of subsequent change across sessions one, three, and five, findings using therapist-rated alliance supported a reciprocal relationship with both the alliance predicting symptom change and symptom change predicting the alliance. Neither of these relationships achieved significance using patient-rated alliance.

## CONCEPTUAL ISSUES IN THE SEARCH FOR MECHANISMS OF CHANGE IN CBT

Six papers examine important conceptual issues in the search for mechanisms of change in CBT, with some of these papers also describing newer methodological or analytic strategies. First, Hollon et al. explore how CBTs might fit into an evolutionary account of depression. They suggest that depression and anxiety are coordinated responses that helped individuals prepare to function adaptively in our ancestral past. Depression may have evolved to promote a type of rumination that may help to solve complex social problems. They suggest that, unlike medications which reduce the distress, CBTs may be better suited to facilitating the evolutionary function of depression in helping individuals ruminate more effectively.

Second, Verdonk and Trousselard address the question of how mindfulness works. They introduce the context-updating hypothesis, which posits that mindfulness facilitates optimal adjustment of prior beliefs to the context of present experience and thereby minimizes prediction errors. Prior beliefs are updated more effectively in light of the present context. They explore the clinical applications of this hypothesis and discuss how it could be tested.

Third, Huibers et al. provide an overview of the challenges in developing empirically-driven personalized psychotherapies. They introduce the concept of *personalized causal pathways* that highlight specific paths whereby therapeutic procedures lead to changes in therapeutic processes for patients with specific characteristics. They propose a research agenda that is designed to carefully characterize these pathways to facilitate development of an empirically driven personalization of CBT, including a call for research on both generic and CBT specific in-session processes.

Fourth, Zilcha-Mano and Webb extend prior reviews of processes in CBT and concentrate on studies that propose methodological and statistical approaches for disentangling within-individual (or state-like) effects and between-individual (or trait-like) effects. They effectively highlight the importance of the distinction, noting that it has not been considered in much of the existing psychotherapy process literature. They suggest that between-individual variables might be identified as prognostic or prescriptive factors, whereas within-individual variables are appropriate for evaluating potential active ingredients of treatment. They highlight how research making such distinctions particularly measured well and analyzed appropriately have the potential to substantially advance our understanding of how CBT works.

Fifth, Kaiser et al. report on a network analysis of follow-up effects of internet-delivered CBT. Using network intervention analysis, they were able to identify specific symptoms and aspects of quality of life that were directly impacted by iCBT (compared with care as usual) as well as additional symptoms that appeared to be impacted indirectly because they change following changes in other symptoms. Interestingly, in their study, patients who scored higher on the directly affected items experienced greater benefit from iCBT.

Finally, Southward and Sauer-Zavala discuss sequential multiple assignment randomized trial (SMART) designs as an approach to improving our understanding of treatment mechanisms. They describe their ongoing study in which patients are first randomized to receive the modules of the Unified Protocol in standardized or personalized order. At treatment mid-point, patients are further randomized to either discontinue treatment immediately or continue with the remaining sessions. They propose to test engagement of mechanisms such as distress aversion which might represent an important tailoring variable for whether to end or continue treatment. Their work highlights some innovative ways that experiments can evaluate personalized treatment decisions.

## NEW TECHNOLOGIES IN THE STUDY OF MECHANISMS OF CHANGE IN CBT

A final pair of papers examine the use of new technologies to investigate potential mechanisms of CBT. Wu et al. report on their systematic review and meta-analysis of virtual reality-assisted cognitive behavioral therapy (VRCBT) for anxiety. Drawing on data from a handful of available studies, VRCBT outperformed wait-list but did not differ significantly from "standard" CBT. The authors provide a discussion of the potential clinical benefits of VRCBT. Hehlmann et al. provide a preliminary test of ecological momentary assessments using heart

rate variability using fitness trackers every 3 min to investigate the role of stress in the process of change in CBT. They highlight how passive assessments might provide much more detailed information about change over time than traditional self-report measures.

## CONCLUSION

This Research Topic for *Frontiers in Psychiatry* provides a rich sample of contemporary work focused on advancing our understanding of the mechanisms of CBT. With the array of sophisticated methodological and analytic strategies being brought to bear, we are optimistic that a new generation of CBT research will substantially advance our understanding of how CBT achieves its effects and that such an understanding might ultimately be utilized to optimize CBT's benefits.

## AUTHOR CONTRIBUTIONS

All authors contributed to the ideas and have reviewed this Editorial.

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# Experimental Manipulations to Test Theory-Driven Mechanisms of Cognitive Behavior Therapy

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Despite decades of randomized-controlled trials demonstrating the efficacy of cognitive-behavior therapy (CBT), the mechanisms by which CBT achieves its effects remain unclear. Here, we describe how one adaptive intervention, the sequential multiple assignment randomized trial (SMART), can be used to randomize patients at multiple decision points in treatment to draw stronger causal claims about mechanisms unfolding in the course of CBT. We illustrate this design using preliminary data and case examples from an ongoing SMART in which we are testing the role of aversive reactions to negative emotions as a hypothesized mechanism of change in the Unified Protocol. Finally, we address common concerns with SMARTs and highlight how mechanistic research serves to personalize and optimize the delivery of CBT.

**Keywords: cognitive behavior therapy (CBT), mechanism, SMART, personalization, unified protocol (UP)**

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## INTRODUCTION

Hundreds of randomized controlled trials (RCTs) have shown that cognitive behavior therapies (CBTs) are efficacious for many psychiatric conditions (1–3). RCTs are the optimal experimental design to test the efficacy of a treatment relative to comparison conditions. Randomly assigning patients to condition (e.g., CBT vs. waitlist) provides confidence that any post-treatment differences between conditions are due to the effects of the intervention(s), rather than patient characteristics or other confounding variables. RCTs for psychological treatments, particularly CBTs, were especially informative following *DSM-III* (4), which included more reliable symptom criteria for each psychiatric disorder. These criteria allowed researchers to conduct RCTs to assess how well CBTs addressed specific constellations of symptoms, relative to other treatment conditions.

Given the established efficacy of many CBTs (5), there has been an increased push to characterize which mechanisms drive symptom improvement [e.g., (6)]. Mechanisms of change are defined as "…core psychological and biological processes … [that] explain specifically how characteristics of the dysfunction are altered by the intervention and how that translates to symptom change" [(7), p. 87]. The relations among treatments, associated therapeutic mechanisms, and symptom change has often been explored statistically, whereby a mediator variable accounts for the relation between an intervention and an outcome (8–11). However, to determine whether a particular process constitutes a *mechanism* of symptom reduction, rather than simply a statistical mediator, several criteria must be met. These criteria include: (a) a strong association between the mechanism of action and the outcome, (b) temporal precedence where change in the mechanism precedes change in the outcome, (c) manipulating levels of the mechanism to determine how they relate to outcomes, and (d) a dose-response relation such that greater change in a mechanism leads to better outcomes (7, 9, 10).

Treatment researchers have made great strides toward identifying mechanisms of CBTs by utilizing more intensive measurements (e.g., at each session rather than only pre- and post-treatment). Frequent measurement of candidate mechanisms and psychiatric symptoms can provide evidence for criteria (a) and (b) for establishing a therapeutic mechanism. However, even when researchers statistically determine temporal precedence, results remain observational and can at best reveal Granger causality (12), which indicates that a temporally-lagged variable ($X_{t-1}$) explains unique variance in another variable at the next timepoint ($Y_t$) above and beyond previous observations of that variable ($Y_{t-1}$).

To draw stronger causal conclusions about the processes driving therapeutic improvements, it is necessary to apply innovative research designs that leverage the advantages of random assignment. We argue that sequential multiple assignment randomized trials [SMARTs; (13)], a type of multi-stage, experimental design developed for adaptive interventions, are an elegant way to evaluate treatment effects and mechanisms within a single clinical trial. We will first provide an overview of SMARTs and then describe how they can be adapted to evaluate the hypothesized mechanism of an intervention. We will present illustrative data from a SMART we are currently conducting to highlight how this design can provide a stringent, experimental test of core mechanisms.

## SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIALS (SMARTS)

SMARTs are a framework for evaluating adaptive interventions in clinical trials. In contrast to traditional RCTs that involve one primary clinical decision (e.g., randomizing a patient to the treatment or control condition), SMARTs contain multiple randomizations. For example, Chronis-Tuscano et al. (14) conducted a SMART to characterize best practices for families in which mothers and their children exhibit ADHD symptoms. In the initial randomization, mothers received stimulant medication or behavioral training to test which treatment approach is relatively more efficacious to start with. The second randomization occurred 8 weeks later; patients were randomized to either continue initial treatment or receive the alternative intervention as a supplement to their initial treatment. Because patients are randomized to receive treatment adaptations, SMARTs enable researchers to draw stronger conclusions about optimal treatment planning decisions.

In addition to randomizations based solely on time (e.g., re-randomizing all patients at session eight), researchers may also use *tailoring variables* to determine whether to adapt treatment. For instance, patients whose anxiety symptoms do not a reach a pre-determined threshold by a particular point in treatment may be re-randomized to continue with current care or receive more intensive treatment.

## EVALUATING MECHANISMS OF ACTION USING SMARTS

Researchers implementing SMART designs are not limited to using symptoms as tailoring variables. In fact, we argue that to test hypothesized mechanisms of change in CBT, researchers should use the engagement of these mechanisms to guide treatment decision-making. Because changes in mechanisms should precede symptom changes, improvement in hypothesized mechanisms may represent an early indicator of eventual response. In this section, we describe the design of a pilot SMART we are currently conducting to evaluate methods for personalizing the delivery of the Unified Protocol [UP; (15)], an efficacious transdiagnostic CBT for a variety of psychiatric disorders (16, 17). In our initial randomization, patients with primary anxiety, depressive, or related disorders without imminent suicidal ideation are randomized to receive the modules (i.e., skills) from the UP in a personalized or standardized order. The second stage randomization occurs at mid-treatment (i.e., after 6 sessions), with patients assigned to either discontinue care immediately or receive the remaining six sessions. Patients randomized to discontinue immediately are sent weekly symptom measures to track their progress and are offered referrals as requested at the Week 12 follow-up assessment.

The developers of the UP have articulated a functional model of mood, anxiety, and related disorders in which these disorders are maintained by the transaction of frequent negative emotions (i.e., neuroticism) and aversive reactions to these emotions (18, 19). Aversive reactions may take many forms, including experiential avoidance, emotional suppression, worry, rumination, or distraction – any behavior used to escape or distract from one's emotions. Recent evidence suggests that reductions in certain forms of aversive reactions (e.g., experiential avoidance, anxiety sensitivity) precede and predict reductions in anxiety symptoms in CBT [(20–25); cf. (26)]. To measure aversive reactivity, participants in our SMART are completing the Distress Aversion subscale of the Multidimensional Experiential Avoidance Questionnaire [MEAQ-DA; (27)] before every weekly therapy session. The MEAQ-DA is a 13-item self-report measure designed to assess negative evaluations of and attitudes toward distress that has demonstrated good internal consistency across clinical samples (23, 27). The MEAQ-DA is sensitive to change in response to CBT for anxiety disorders [$d = 0.82$; (23)] and scores can range from 13–78.

We contend that our SMART design and, in particular, our secondary randomization (i.e., early termination vs. full course of care) are well-suited to evaluate aversive reactivity as a mechanism of change in the UP. The burgeoning evidence across independent treatment studies suggests the UP leads to changes in aversive reactivity. Variability in these changes indicate the degree to which the UP naturalistically manipulates different levels of this mechanism. Because patients are then randomized to receive 6 or 12 sessions, we can determine the degree to which aversive reactivity must improve in

early sessions to predict maintenance or continued symptom improvement for patients who terminate at mid-treatment. Adequate symptom reduction at week 12 follow-up in patients who discontinue after six sessions *and* demonstrate mechanism engagement provides clear evidence for the importance of targeting aversive reactivity. However, unlike symptom measures, which have established threshold scores to determine patient progress, "mechanism engagement" for aversive reactivity has not been operationally defined. Thus, thresholds indicating the degree of change in mechanisms that predicts continued symptom improvement must first be established for measures of hypothesized mechanisms of treatment. Our current SMART will allow us to operationally define adequate target engagement of aversive reactivity as measured by the MEAQ-DA, allowing us to use these results to define the bounds of a tailoring variable in subsequent SMARTs. Randomizing patients to discontinue treatment after achieving a pre-specified cutoff for target engagement provides a more stringent test of whether candidate mechanisms are associated with downstream symptom improvement.

In the following section, we will present illustrative data from this trial as an example of how to establish target engagement thresholds by examining: (a) variability in MEAQ-DA scores; (b) whether early session changes in MEAQ-DA scores precede later session symptom changes; and (c) the magnitude of change on MEAQ-DA scores needed in early sessions to predict maintenance or continued improvement in symptoms for patients who terminate at mid-treatment.

## Variability in Hypothesized Mechanisms

Variability in our hypothesized mechanism, MEAQ-DA scores, is assessed in two ways: within each decision point and from one decision point to the next. Variability within a decision point is necessary to ensure that all participants would not be assigned to the same decision condition. If all patients had the same MEAQ-DA scores at mid-treatment, we would not be able to use this variable to make discontinuation decisions. Variability from one decision point to the next is necessary, in this case, to ensure the hypothesized mechanisms of change are themselves responsive to the study treatment. In our sample to date ($n = 46$), we have found substantial variability at both pre- ($M = 45.00$, $SD = 11.06$) and mid-treatment ($M = 36.57$, $SD = 13.63$) in the MEAQ-DA. Further, MEAQ-DA scores significantly decreased from pre- to mid-treatment, $t(45) = -5.30$, $p < 0.01$, 95% CI [−11.64, −5.23]. It is important to note, however, that without a control comparison group, these changes may, to some extent, indicate participant regression to the mean.

## Changes in Mechanisms Preceding Symptom Change

We selected the Overall Anxiety Severity and Impairment Scale [OASIS; (28)] as our measure of symptoms. Like the MEAQ-DA, the OASIS was administered at pre-, mid-, and post-treatment. In preliminary analyses of relatively smaller samples, it can be useful to determine the proportion of the sample for whom changes in hypothesized mechanisms precede changes in symptoms. Decreases in MEAQ-DA scores from pre- to mid-treatment preceded decreases in OASIS scores from mid- to post-treatment for 18 participants (39%) and increases in OASIS scores for 9 participants (20%). Similarly, decreases in OASIS scores from pre- to mid-treatment preceded decreases in MEAQ-DA scores for 20 participants (43%). These findings suggest that reductions in MEAQ-DA scores tend to precede later anxiety symptom improvements and not deterioration, although anxiety symptom improvement may also precede mechanism change for a substantial number of participants. Although these preliminary results provide mixed evidence for aversive reactivity as the sole mechanism of action in the UP, they demonstrate (a) the importance of comparing alternative hypotheses in the same study (10) and (b) the potential to identify moderators to distinguish the patients for whom aversive reactivity or anxiety symptoms function as mechanisms of change. When possible, researchers conducting experimental manipulations of treatment mechanisms should include competing experimental conditions or measures of alternative mechanisms, as in our SMART, that can be compared to researchers' primary theorized mechanism to provide a more stringent and comprehensive test of the hypothesis.

## Degree of Engagement in Hypothesized Mechanisms

Determining how much change is needed to consider a hypothesized mechanism engaged remains an open question. Researchers may choose relatively conservative but standardized metrics such as the reliable change index (29) as the standard of mechanism engagement. Alternatively, they may estimate the degree of change preceding certain symptom outcomes in one sample and apply this estimate to an independent hold-out sample. Given the preliminary stage of our study, we will highlight three exemplar cases of mechanism engagement and downstream clinical outcomes.

### Patient 1

Patient 1 is a 61-year-old White female with primary generalized anxiety disorder (GAD) and specific phobia. She received UP modules in the standard order and discontinued treatment after six sessions. Thus, Patient 1 received the modules Understanding Emotions (UE), Mindful Emotion Awareness (MEA), and Cognitive Flexibility (CF; 2 sessions each) before discontinuing treatment. She demonstrated reliable change (Reliable Change Index [RCI] = −2.68) in MEAQ-DA scores from pre-treatment (46) to end-of-treatment (EOT; 30). However, she reported only a 1-point decrease in OASIS scores from pre-treatment (6) to EOT (5). Six weeks after treatment discontinuation, she reported a 40% decrease in anxiety severity (OASIS = 3; **Figure 1A**). This pattern of data suggests that achieving reliable change on the MEAQ-DA may predict continued symptom improvement even after treatment is withdrawn.

### Patient 2

Patient 2 is a 45-year-old Arab-American male with primary social anxiety disorder and GAD. He received UP modules in a personalized order and completed the full course of treatment. Thus, he received the modules Counting Emotional Behaviors

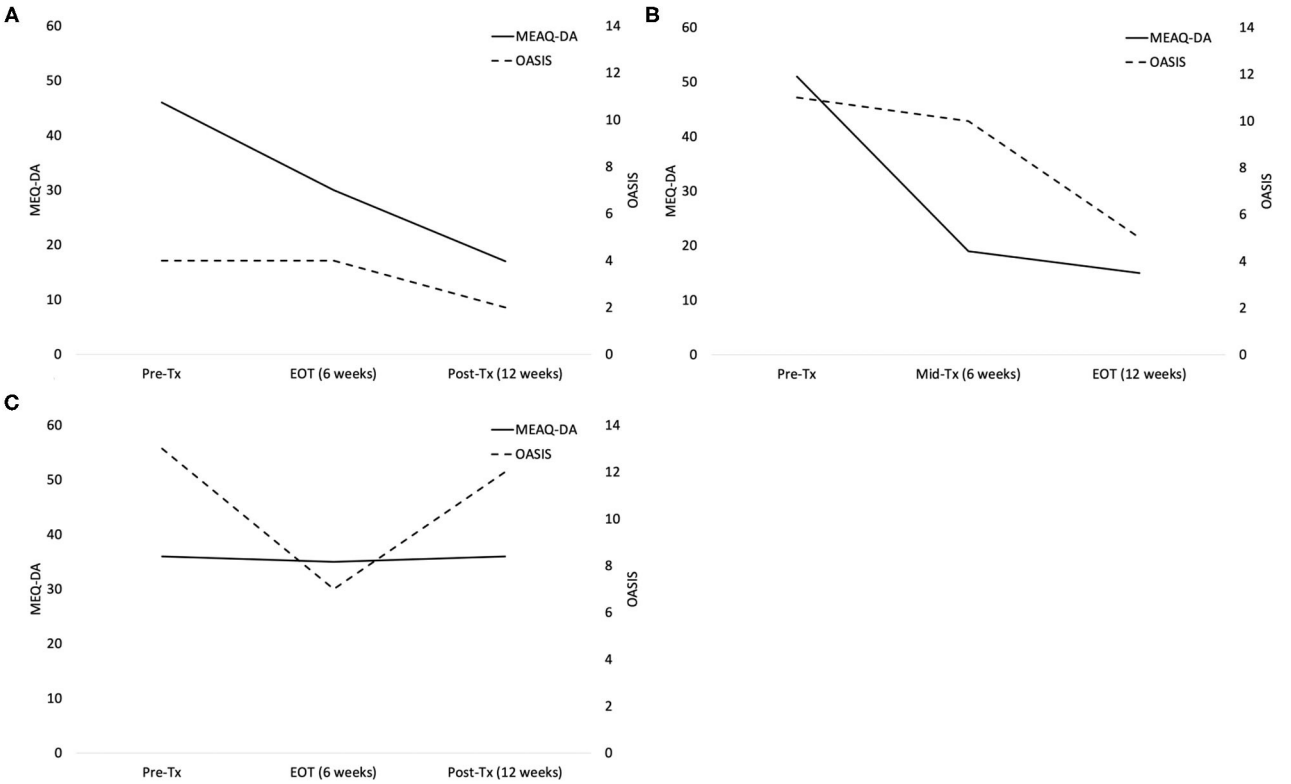


**FIGURE 1 | (A)** Patient 1 MEAQ-DA and OASIS data demonstrating decreases in MEAQ-DA scores from pre-treatment (PreTx) to end-of-treatment (EOT) and subsequent decreases in OASIS scores following treatment discontinuation from EOT to post-treatment (Post-Tx). **(B)** Patient 2 MEAQ-DA and OASIS data demonstrating greater decreases in MEAQ-DA scores from Pre-Tx to mid-treatment (Mid-Tx) followed by greater subsequent decreases in OASIS scores from Mid-Tx to EOT. **(C)** Patient 3 MEAQ-DA and OASIS data demonstrating decreases in OASIS scores from Pre-Tx to EOT without corresponding decreases in MEAQ-DA scores, followed by a return to Pre-Tx OASIS scores by Post-Tx.

(CEB) and UE in the first six sessions and MEA, CF, and Confronting Physical Sensations (CPS) in the last six sessions. He demonstrated reliable change on the MEAQ-DA (RCI = −5.35) from pre- (51) to mid- (19) treatment. Similar to Patient 1, Patient 2 demonstrated almost no change in anxiety severity from pre- (OASIS = 11) to mid- (OASIS = 10) treatment. Instead, after six more sessions, he also reported a 50% decrease in anxiety severity (OASIS = 5) at EOT (**Figure 1B**). Of course, because Patient 2 continued to attend sessions after he achieved reliable change on the MEAQ-DA, it is difficult to discern whether his symptoms would have continued to improve if treatment had been discontinued after session 6.

By contrast, some patients demonstrate symptom improvement before mechanism engagement. In traditional SMARTs that rely on symptom changes to make clinical decisions, this may indicate a patient is a good candidate for treatment discontinuation. However, symptom improvement without corresponding mechanism engagement may not be as durable.

## Patient 3

Patient 3 is a 33-year-old White female with primary GAD and body dysmorphic disorder. She received UP modules in a personalized order and discontinued treatment after six sessions. Thus, she received the CEB and CPS modules. She demonstrated substantial improvement in anxiety severity from pre- (OASIS = 13) to mid-treatment (OASIS = 7). However, her MEAQ-DA scores were little changed from pre- (36) to mid- (35) treatment (RCI = −0.17). Six weeks after treatment discontinuation, Patient 3 reported anxiety scores similar to pre-treatment (OASIS = 12), suggesting her symptom gains in treatment were not as durable (**Figure 1C**). This pattern of results suggests that changes in aversive reactivity to emotions may be an important therapeutic mechanism in the UP.

Of course, these are illustrative cases selected to demonstrate how our second-stage randomization (i.e., discontinue after 6 sessions or continue for 12 sessions) can be used to examine aversive reactivity as a mechanism of symptom improvement. Data from our full sample will allow us to establish the degree to which MEAQ-DA scores must improve to predict continued symptom reduction among participants randomized to discontinue treatment early. These data will be used to establish the thresholds necessary to use MEAQ-DA scores as a tailoring variable in future projects.

## DISCUSSION

As researchers and funding agencies shift from evaluating treatment outcomes to understanding the mechanisms by which treatments function, innovative trial designs are necessary. In particular, SMARTs allow for experimental manipulation of mechanisms within efficacy or effectiveness trials. Here, we have illustrated how our current SMART enables us to answer hypotheses about the timing and degree of change in a hypothesized mechanism needed for continued symptom improvement following treatment discontinuation. By examining different characteristics of mechanisms in treatment (e.g., variability, timing relative to symptom change, and degree of engagement), researchers can better characterize replicable and actionable mechanisms that can ultimately lead to more targeted interventions.

We have highlighted one current limitation of mechanistic SMARTs, namely the lack of a consensus definition of mechanism engagement. We believe this is appropriate, given the relatively nascent state of this research. However, it is essential that researchers first identify likely transtheoretical mechanisms of change and assess the degree of change necessary for a mechanism to be considered "engaged" by a patient. This degree of change will likely involve a range of values that vary based on individual differences, so we encourage researchers to pool resources when possible to collect these data. A second common limitation of SMARTs is the sample size needed to provide adequate statistical power. Given even two levels of randomization, it may appear that the sample sizes needed would be impossibly large. However, as Almirall et al. (30) note, researchers are rarely interested in testing differences among all randomization combinations. Instead, researchers should pre-specify which comparisons are of most interest and calculate the necessary sample size based on these comparisons. For instance, in our study, one comparison we will make is between participants randomized to continue or discontinue treatment, regardless of whether they received a personalized or standardized order of UP modules. Because we expect treatment discontinuation to exert a larger effect on outcomes than module ordering, we will collapse across participants in the personalization and standardization conditions to maximize our statistical power. Practically, we encountered no limitations in recruitment for this SMART, likely because all patients received some treatment immediately. We are currently replicating this study in a community mental health clinic to test the acceptability of discontinuing treatment to real-world providers, as this may be another limitation of SMARTs with treatment discontinuation.

We content that adaptive interventions, such as SMARTs, offer a promising way to personalize and optimize CBT. By characterizing which mechanisms are engaged by which treatment processes, how much change is needed in these mechanisms for a given patient, and when treatment can be reliably discontinued, these experimental designs can have a substantial influence on our understanding of core mechanisms of action in treatment. Rather than relying solely on symptom changes, which may be an unreliable indicator of progress, researchers can leverage experimental manipulations of treatment mechanisms to identify measures that clinicians can incorporate relatively easily into their practice to enhance the efficacy, efficiency, and accessibility of CBT (31).

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Kentucky Nonmedical Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

MS performed the data analysis and drafted the manuscript. SS-Z provided critical revisions. Both authors developed the manuscript concept, study design, collected the preliminary data, and approved the final version of the manuscript for submission.

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# On the Road to Personalized Psychotherapy: A Research Agenda Based on Cognitive Behavior Therapy for Depression

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In this conceptual paper, we outline the many challenges on the road to personalized psychotherapy, using the example of cognitive behavior therapy (CBT) for depression. To optimize psychotherapy for the individual patient, we need to find out how therapy works (identification of mechanisms of change) and for whom it works (identification of moderators). To date, psychotherapy research has not resulted in compelling evidence for or against common or specific factors that have been proposed as mechanisms of change. Our central proposition is that we need to combine the "how does it work?"-question with the "for whom does it work?"-question in order to advance the field. We introduce the *personalized causal pathway hypothesis* that emphasizes the links and distinction between individual patient differences, therapeutic procedures and therapy processes as a paradigm to facilitate und understand the concept of personalized psychotherapy. We review the mechanism of change literature for CBT for depression to see what we have learned so far, and describe preliminary observational evidence supporting the personalized causal pathway hypothesis. We then propose a research agenda to push the ball forward: exploratory studies into the links between individual differences, therapeutic procedures, therapy processes and outcome that constitute a potential causal pathway, making use of experience sampling, network theory, observer ratings of therapy sessions, and moderated mediation analysis; testing and isolation of CBT procedures in experiments; and testing identified causal pathways of change as part of a personalized CBT package against regular CBT, in order to advance the application of personalized psychotherapy.

**Keywords: personalized medicine, cognitive behavior therapy, depression, mechanisms of change, individual differences, moderated mediation**

## INTRODUCTION

Personalized or precision medicine has the potential to contribute greatly to the future of healthcare by delivering the most efficient patient-centered care that is acceptable both to patients and healthcare professionals (1). Personalized medicine may be broadly defined as treatment that is highly individualized for the patient based on biomarkers, processes that relate to etiology, or findings from data-driven methods. The approach has attracted considerable attention in recent years and is considered to be one of the main challenges for health care, although there is little empirical research that facilitates its application in most fields of medicine and health care.

Depression is one of those disorders for which a personalized medicine approach is still lacking (2, 3), and arguably one of the disorders that would benefit most from a personalized approach to treatment. Depression affects the lives of many and society as a whole (4–6) and is estimated by the World Health Organization (WHO) to be a leading cause of global disability (7). Treatment options such as psychotherapy and antidepressant medication (ADM) have comparable effects (8), even in severe depression (9), although the combination of psychotherapy and ADM might be somewhat more effective *on average* (10). However, ∼40–50% of patients do not respond to treatment (8, 11, 12). Those that respond remain at considerable risk for future relapse (13, 14), and even after 1 year of different treatments, about one third of patients has not remitted (15). At the same time, while some patients show almost no decrease in depression during treatment, other patients demonstrate large effects (3, 16). At this point, we do not know which patients will benefit from treatment, making treatment selection largely a matter of availability or trial-and-error (17).

In this paper, we propose a research agenda that will enable the personalization of psychotherapy for depression, in order to optimize treatment outcome for the individual patient. There are largely two distinct routes to improve the effectiveness of psychotherapy: identification of mediators to find out *how they work*, and identification of predictors and moderators to find out *for whom* they work. We propose that these two research lines need to be combined to advance personalized medicine in this area. Echoing the famous words of Paul (18), arguably the biggest scientific challenge in contemporary depression outcome research is to identify the causal pathways or *mechanisms of change* that reveal *how treatments works, and for whom*. For the context of psychotherapy, we add to this, *what works, for whom*, and *under which relational contexts*, as there are other theoretically important variables within the consultation session, not limited to generic and treatment specific elements of the therapeutic relationship. Mechanisms of change in psychotherapy for example are much debated, but poorly researched (19, 20). As a result, our knowledge is limited and the field needs innovative research methods to confirm how psychotherapy brings about its established effects (21).

In line with the focus of this special issue in *Frontiers in Psychiatry*, we will focus on cognitive behavior therapy (CBT) as the most widely studied evidence-based psychotherapy for depression. According to theory, CBT works through changes in the content and processes of cognition, emotion regulation and behavior (22). A recent review (23) of $N = 558$ meta-analyses concluded that the strongest support currently exists for cognitive ($n = 8$ meta-analyses) and behavioral ($n = 3$ meta-analyses) change processes in CBT for anxiety disorders and depression; though this evidence is still emerging and many questions remain unanswered about how to tailor these processes for the individual patient. We first describe mechanisms of change in psychotherapy research and focus on CBT for depression to illustrate what we do know about moderators and mediators. Finally, we propose a research agenda to advance the research of moderators and mechanisms and promote the development of personalized psychotherapy.

## MECHANISMS OF CHANGE IN PSYCHOTHERAPY

We recently reviewed the literature on mechanisms of change in *all forms of psychotherapy*, focusing on the common and specific factors that might explain how psychotherapy works and concluded that most studies to date are merely correlational (21). Mechanisms of change are the elements that constitute the causal pathways of psychotherapy. Understanding how therapy works will help us improve existing therapies, develop new ones, and tailor therapy to the needs of the individual. In order to establish that a mechanism or mediator (the statistical proxy for a mechanism) is indeed a *causal factor* in the recovery process of a patient, studies have to meet several methodological criteria as previously outlined by Kazdin (19). They include temporal precedence, plausibility, experimental manipulation, consistency, association, dose-response relation, and specificity.

In our review of psychotherapy process research, none of the common or specific factors we reviewed met the threshold and can thus be considered an empirically validated working mechanism, though this research has begun (23). More than 30 years after the introduction of mediation analysis (24), we still do not have compelling evidence for the common or specific factors that bring about change in psychotherapy (25). Moreover, by definition, psychotherapy is a complex process that involves multiple factors, dichotomies of common vs. specific factors are questionable (26), and simple causal models will not advance our understanding of the underlying mechanisms of change.

Our review (and previous overviews) also revealed that mechanism research is very challenging, and that most previous studies suffer from methodological shortcomings that limit the usefulness of findings. We have summarized the most important methodological problems and opportunities (21, 27, 28):

1 **Most mechanistic research has been conducted within the context of a randomized trial.** More experimental

studies in which the proposed *mechanism* (as opposed to the *intervention*) is directly manipulated would be more informative.

2 **CBT is treated as a black box**. Its therapeutic procedures (e.g., interventions aimed at cognitive change) and the change processes (e.g., the cognitive change itself) that follow from them are rarely distinguished.

3 **Most measurement is concurrent**. Temporality in research designs is needed to *establish a time line* that shows which of the constructs change first in order to rule out *reverse causality*.

4 **Little attention has been paid to individual differences**. Data on mechanism are mostly analyzed on the average group level. It is likely that patients differ in their response to therapeutic procedures offered to them, and these variations should be taken into account (i.e., *mediation moderated* by patient characteristics).

5 **Most previous studies relied on older approaches to mediation testing** (24). More modern approaches (29, 30) are more flexible and have more statistical power.

As a result, *how* CBT (or any other form of psychotherapy) works is still a ***black box,*** as was recently described in terms of a **personalized causal pathway hypothesis** (31).

The central proposition here is that therapeutic procedures (e.g., how therapeutic techniques are targeted and used to help patients change negative thinking) should be distinguished from (intra-individual) therapy processes (e.g., decrease in negative thinking) in order to crack the black box. Similar distinctions were proposed by Doss (32), who also underscored the importance of therapist change procedures (e.g., explaining the process to complete a thought record) and client change procedures (e.g., examining evidence for or against a belief). Moreover, mechanisms of change most likely differ between (subgroups of) individuals, and these individual differences need to be considered to unravel how psychotherapy works. It is not only about how psychotherapy works (mechanisms) but also for whom (moderators).

Moderators are prescriptive variables (i.e., patient characteristics) that predict a differential outcome in two or more treatments. Unlike general predictors (prognostic variables) they points us in the direction of the underlying mechanistic pathways that are active in specific subgroups of patients (19), without necessarily revealing what these pathways are. If certain patient characteristics predict a differential outcome depending on type of treatment, it must mean that something specific in the type of treatment is driving response in certain individuals and not in others. Further complexity exists because the clinician is tailoring therapeutic procedures (treatment processes) within the treatment and their mode of delivery (in-session process) as a function of patient characteristics (33). Thus, finding moderation is ipso facto evidence of *differential* mediation, i.e., pathways of change that differ between two or more treatments. It also implies that mediation analyses should take individual differences into account, since proof of moderation also means that subgroups of patients are responding differently to the mechanisms that are triggered in treatment. We will later return to this issue of *moderated mediation*.

# WHAT DO WE KNOW? THE EXAMPLE OF CBT FOR DEPRESSION

## Cognitive Behavior Therapy and Its Putative Mechanisms

Of all psychotherapies for depression, ***cognitive (behavior) therapy*** (CBT) is the most extensively researched (34, 35). CBT is an effective treatment in the acute phase of depression (36), can prevent future relapse (37, 38) and is a recommended choice of treatment in clinical guidelines (39).

According to Beck's cognitive theory (40), dysfunctional beliefs about the self, the personal world and the future, incorporated in stable and enduring schemas, lie at the root of depression. When activated by stressful events, these (implicit) schemas produce negative thoughts and depressive symptoms.

CBT aims to change negative thinking and alter dysfunctional behavior, by restructuring thoughts and increasing physical activity. Central to CBT is the assumption that *cognitive change* is the mechanism that leads to recovery in CBT (41). If cognitive change *is* the central mechanism in CBT, how exactly does it work? Barber and DeRubeis proposed three different models (42):

- ***Accommodation model***: CBT changes (explicit) negative thoughts and (implicit) underlying schemas directly, in such a profound way that the individual's depressive symptoms, and the risk for relapse, are reduced.
- ***Activation-deactivation model***: CBT merely deactivates (implicit) underlying schemas temporarily, leaving the underlying vulnerability for future depressive episodes untouched.
- ***Compensatory skills model***: CBT leaves the (implicit) underlying schemas unchanged, but promotes the use of certain compensatory skills for dealing with distressing thoughts and events.

The empirical support for any of these models is weak, as only a handful of studies provide preliminary, typically indirect evidence (28, 41), though cognitive change is the best "contender" for a working mechanism of CBT. Tang and DeRubeis (43) found so-called "sudden gains" in CBT, sudden improvements in depression following substantial change in negative thinking in the *preceding* therapy session, which indicates that cognitive change might drive the observed improvement. Dozois et al. found that CBT was associated with greater change in schemas than antidepressants (44). Schmidt et al. (45) applied a fine-grained session-to-session analysis to demonstrate that the relation between immediate cognitive change in a previous CBT session and subsequent depression change in a following session was mediated by the sustained cognitive change measured at the beginning of the following session. Moreover, both immediate and sustained cognitive change predicted subsequent symptom change, and the only variable that predicted immediate cognitive change was therapist adherence to cognitive methods. This not only reveals that cognitive change may be a predictor of symptom change, but also highlights cognitive change as a potentially important mechanism of change, at least in CBT.

Other studies found that change in negative thinking is *not specific* to CBT, and can also be observed in other psychotherapies and antidepressant treatment (41). However, the question of whether measures are sufficiently specific to target the spectrum of change in cognitive content and process (e.g., attentional refocusing, beliefs about intrusive thoughts and ruminative processes) and the concomitant comprehensiveness of the assessment strategy remains a matter for debate. For example, acquiring certain skills as a result of therapy (e.g., examining one's own thoughts) has been linked to symptom decreases and relapse prevention after therapy (46, 47), yet patients are likely to develop different beliefs about their thought processes through this work that were not assessed. While promising, most of these findings are merely *observational* and do not provide strong support for causal inferences, and also are technically unable to tap the full spectrum of changes that each patient experiences as they benefit from therapy. *Experimental studies* in which a putative mechanism is manipulated to provide a direct test of causality are almost completely lacking, with the exception of an older study (48) in which it was found that attempts to *change* thinking processes led to a greater reduction in negative thoughts and depressive symptoms, relative to efforts to *explore* thinking processes.

In recent years, treatments that focus solely on behaviors have received renewed attention. *Behavior therapy* was developed in the 1950's, but was overshadowed by the "cognitive revolution" in the 1970's that followed from the work of Beck and others (49). However, findings suggest that *behavioral activation* (BA, the behavioral component of CBT) *alone* is as effective as a full package of CBT (50–52). A heated debate on what these results tell us about the underlying mechanisms of change continues to this day. Some have argued that the equivalence of BA and CBT proves that both BA and CBT work only through behavioral changes (53). Others have pointed out that we cannot draw this kind of conclusion from comparative treatment studies (49).

In our view, it is still entirely possible that both BA and CBT work through changes in negative thinking, as studies with carefully planned assessments of the relevant behavioral and cognitive change processes are lacking. A further possibility is that there are other features of CBT such as empiricism that exist to a lesser extent in therapies that have a behavioral focus, or are adopted differently. If these features of CBT are not measured within trials contrasting "behavioral" and "cognitive" components, unmeasured variability within conditions could explain the comparable findings. As long as we cannot determine *which process changes precede changes in depression symptoms*, it is impossible to determine which mechanisms account for the effects of CBT (or BA), and even temporal precedence does not provide conclusive evidence that these processes are the actual cause of the change in depression.

CBT theory assumes that CBT works through *specific*, CBT-related elements. However, there is a competing model that has gained considerable popularity among therapists especially that claims that the effects of therapies are realized predominantly by so-called *common factors*. These common factors are those factors that all therapies have in common, such as the therapeutic alliance between the patient and the therapist, expectations, and a rationale that helps the patient understand his problems (21). The most modern common factors model is the *contextual model* (54), according to which a patient and a therapist first have to create a basic bond to work together. The contextual model and common factors hypotheses are supported indirectly by correlations between the therapeutic alliance and treatment outcomes, but there are no experiments that have manipulated this therapy process directly (21), there are concerns about the conduct of the meta-analyses used as support for the model (55) and serious concerns about the validity of the conceptual model across therapeutic modalities with those correlational findings (56).

A further problem is that common factors may be used in CBT in specific ways that mean they are no longer "common" and comparable to what occurs in other therapies (57). For example, understanding with empathy and interpersonal effectiveness are part of the operationalization of therapist skill in CBT delivery, as they require a specific focus on understanding the patient's cognitive internal reality in a manner that is highly professional. Yet these aspects are also part of the therapeutic alliance as conceptualized in scales such as the Working Alliance Inventory (58). Lorenzo-Luaces et al. (57) found evidence that the effect of the alliance varies by prior episodes markedly in CBT, but not in psychodynamic therapy, suggesting that this supposedly "common" therapy element may operate in different ways across different treatment. Evidently, there is a need to reliably assess modality specific elements of the therapeutic interaction, determine if they predict CBT outcomes over and above the effects of common factors, and then conduct experimental studies where they are experimentally manipulated in order to validate their importance for CBT.

## Mechanisms and Moderators in CBT: Implications From the STEP-D Study

To illustrate the intrinsic links between mechanisms and moderators, we describe the results of a randomized trial comparing CBT and interpersonal psychotherapy (IPT) for depression from the first author's research group, the STEP-D study that was conducted at Maastricht University. Depressed patients seeking help ($n = 182$) at an academic mental health clinic were randomized to a maximum of 20 sessions of CBT and IPT and monitored up to 2 years after the start of the study. CBT and IPT demonstrated comparable effectiveness in the reduction of depression severity *on average* in the acute phase (59) and in the long term (60).

Using latent-difference score models, we then examined the role of five (common and specific) therapeutic processes (dysfunctional attitudes, interpersonal functioning, rumination, self-esteem, and therapeutic alliance) that were repeatedly measured during therapy as potential mediators of outcome (61). Although processes were associated with outcome and changed in the expected direction, change in processes was remarkably smaller than change in symptoms. More importantly, no *temporal relations* between processes and outcome or mediational paths were found, which led us to conclude that the theoretical models for CBT and IPT could not be confirmed.

On the other hand, we found evidence for moderation in this study, which suggests that different mechanisms are active in CBT and IPT. In one paper, we identified general baseline predictors and moderators of treatment outcome that were then combined in a so-called Personalized Advantage Index PAI (62) to determine which of two treatments is predicted to produce the best result for the individual patient (63) [1]. Five moderators predicted a better outcome in CBT while only one moderator predicted a better outcome in IPT. A high PAI score indicates a large predicted difference in outcome between two treatments, in this case CBT or IPT, and the average PAI in our sample was 8.9 BDI-II points, with larger PAI scores for those who were predicted to do better in CBT than for those who were predicted to do better in IPT. In additional analyses, comorbid anxiety (diagnoses and symptoms) and higher cluster A/B personality traits were also associated with better acute outcomes in CBT compared to IPT (64, 65). Moreover, it was found that "sudden gains" occurred significantly more often in CBT compared to IPT (27), which also may point at differential mechanisms being active in the two psychotherapies.

Taken together, the STEP-D findings suggest that CBT and IPT may work (partly) through different mechanisms, but which mechanisms remains unclear (66). Given the many moderators predicting favorable outcome in CBT, the larger PAI scores favoring CBT and the occurrence of sudden gains, it might be implied that these mechanisms are more active and pronounced in CBT compared to IPT (at least in these data), which speaks to the specificity of CBT. There are several possible explanations why we did not find evidence of differential mediation: the statistical power was lacking, the theories might be wrong, we might have measured the wrong constructs or used the wrong methods and design. We think one important and very likely explanation is that we did not factor in individual differences, in the form of moderators. One alternative may be to use PAI scores as indices of individual differences in the relative likelihood of benefitting from the mechanisms of one treatment vs. the other. The evidence of moderation in the absence of evidence for mediation means that we now know that mechanisms exist, but that we do not know what they are or in which patients they work. Testing for *moderated mediation*, mediation moderated by patient characteristics, might then be the answer.

[1]In this earlier study, we used linear regression models for within-sample predictions, which might have led to statistical overfitting. Modern machine learning approaches are now used to produce more stable and generalizable prediction models (17).

## Pathways and Individual Differences in CBT

A central proposition in this paper is that we should break down the elements that constitute the (potentially causal) pathways of a CBT intervention in order to understand what is inside the black box. We should distinguish certain individual ***patient profiles*** or subgroups that are associated with individual differences in outcomes and processes of therapy, therapeutic ***procedures*** that are applied in therapy, therapy ***processes*** that follow from the procedures applied, and ***outcome*** in terms of depressive symptomatology (**Figure 1**).

Is there evidence to support this ***personalized causal pathway hypothesis***? Recent observational CBT findings (**Table 1**) seem to point in this direction. Lorenzo-Luaces et al. (67) found that for individuals with fewer than three prior episodes of depression there was a moderate correlation between *observer-rated* therapeutic alliance (a process) and outcome, whereas there was essentially no relation in the subgroup of patients with three or more episodes. This pattern of results was replicated in the CBT condition of another RCT, but not in psychodynamic therapy (57). This pattern of results suggests that specific (e.g., CBT vs. PDT) and "common" therapy factors (e.g., working alliance) interact to predict outcomes.

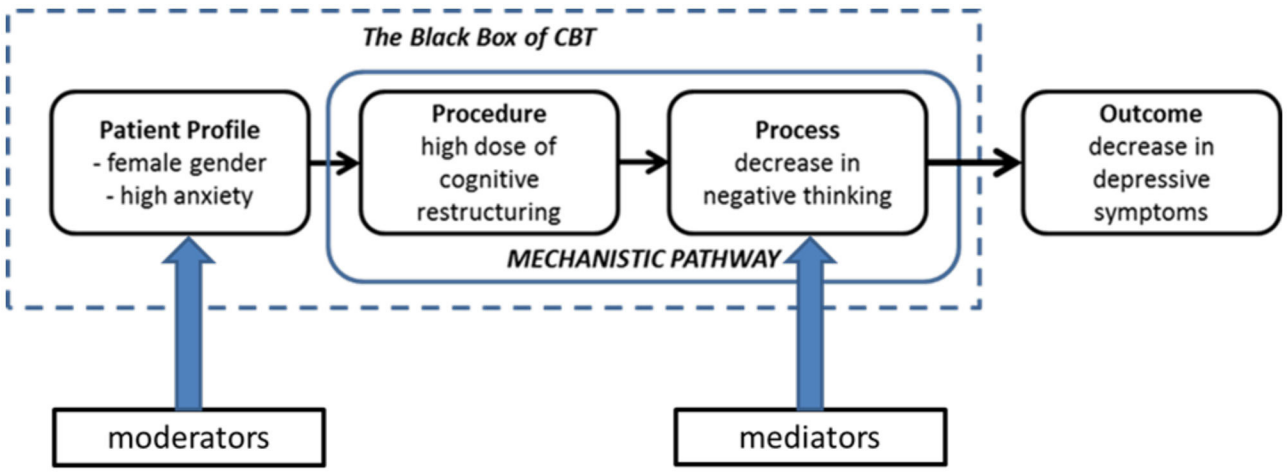


**FIGURE 1 |** Hypothetical causal pathway linking profile-procedure-process-outcome in CBT. Procedures and processes have often been lumped together under the term "mechanism." Note that the temporal precedence (what follows from what?) is important here.

**TABLE 1 |** Overview of identified links between profiles, procedures, processes, and outcome.

| Study | Profile | Procedure | Process | Outcome |
|---|---|---|---|---|
| Lorenzo-Luaces et al. (57) | Prior episodes | CBT vs. PDT | Alliance | Symptoms |
| Lorenzo-Luaces et al. (67) | Prior episodes | n.a. | Alliance | Symptoms |
| Zilcha-Mano et al. (68) | Not intrusive, but cold | n.a. | Alliance | Symptoms |
| Sasso et al. (69) | Women | CBT methods | n.a. | Symptoms |
| Webb et al. (70) | Severity | Adherence | n.a. | Symptoms |
| Keefe et al. (71) | Personality disorder | Schema work | n.a. | Symptoms |
| Forand et al. (72) | "Moderate" prognosis | Engagement/adherence | n.a. | Symptoms |

In an analysis of the relationship between therapist adherence to cognitive therapy methods and symptom changes in a depressed sample, Sasso et al. (69) found that cognitive methods were more strongly related to next session change for women compared to men. In addition, fewer prior depressive episodes and higher pre-treatment anxiety predicted stronger relationships between use of behavioral methods and change in symptoms. Similarly, Webb et al. (70) found evidence that therapist adherence to CBT techniques was most strongly associated with response among individuals with more severe depression. Keefe et al. (71) found that depressed patients with personality disorders benefitted from a therapeutic focus on maladaptive core beliefs but did not experience benefit from other procedures.

Moreover, there is also evidence that multiple patient variables may interact to predict outcomes. Utilizing a data-driven approach, Zilcha-Mano et al. (68) used machine learning techniques to identify patient characteristics that moderate the alliance-outcome association. They found this association to be strongest in a subgroup of patients "rated as not overly intrusive but who were overly cold in their affect toward others." This suggests that research may need to move beyond considering isolated variables.

Using data from an earlier RCT on web-based CBT for depression (73), Forand et al. (72) tested the *prognosis moderation hypothesis*, which states that patients with a "moderate" prognosis will evidence stronger process-outcome relationships than patients with a "good" or "poor" prognosis (56). Specifically, they used multiple patient pre-treatment variables to create a prognostic index. Results showed that those in the "good prognosis" group improved regardless of the therapy procedures received while those in the "poor prognosis" group remained depressed and were not affected by therapy procedures. Conversely, for patients with a moderate prognosis, there was an association between adherence to the intervention and treatment outcomes, in line with the prognosis moderation hypothesis.

All of these studies are *post-hoc* analyses with a limited power and publication bias cannot be ruled out here, but the findings might form bits and pieces of a promising puzzle regarding the mechanisms of change in CBT. However, studies **directly** linking patient profiles, exact procedures, processes, and outcome are still lacking to this day, and there is no unifying account of change in CBT.

# WHAT DO WE NEED? A RESEARCH AGENDA

In this section, we describe three related research objectives that will help to discover the mechanisms of change that are active in psychotherapy and that should be targeted in a sequential order, by which each step informs the next step: the identification of mechanisms using large observational datasets, the experimental isolation of specific therapy procedures to assess their effect on processes and outcome and the development and testing of personalized psychotherapy packages. We continue to use CBT for depression as an example, but this framework can also be applied to other forms of psychotherapy.

## Identification of Mechanisms

Most process research essentially demonstrates how difficult it is to determine the processes that account for outcomes in psychotherapy, mainly because the research design falls short (25). One likely reason is that the utility of questionnaires to capture process changes is limited (28), while day-to-day assessments of single symptoms and processes might be more appropriate to capture the fluctuations of mood and mind states. Moreover, we have failed to distinguish therapeutic procedures and subsequent therapy processes in a clear way, although more recent work has begun to disentangle these related but distinct phenomena (28, 33, 74).

How *can* we open up the black box of CBT? We propose an exploratory study framework that combines daily assessments of relevant constructs ("experience sampling") and observer-rated assessments of procedures during the course of CBT to establish the (potentially causal) links between therapeutic procedures, therapy processes and subsequent outcome, and investigate whether these links differ in subgroups of patients. DeRubeis et al. (56) noted that for some subgroups of patients the therapy procedures they receive will have a greater impact on outcome. They hypothesize that patients who are pre-disposed to have a favorable prognosis, will obtain positive outcomes regardless of the quality of therapy they receive, while another group of patients will not respond to therapy regardless of its quality. This supposes the existence of a third group of patients who will only respond to therapy if the quality is sufficient. In this latter group, therapy procedures will most likely be related to outcomes, but process-outcome associations for this subgroup are lost in the aggregate of (trial) data. The statistical concept

of *moderated mediation* (75) captures the idea that there are differential mediational processes across subgroups of patients. In other words, "different folks need different strokes," and recent studies have just begun to explore these associations (28, 67, 68).

## Network Theory

The *network theory of psychopathology* was introduced by Borsboom and Cramer (76, 77), who state that mental disorders likely result from the causal interplay between individual symptoms that involve feedback loops, wherein symptoms fuel each other. In their terms, "causal meaningful relations are the stuff of which mental disorders are made." They also propose that *therapeutic procedures* should be targeted at these core symptoms and the relations between them, and conclude that this approach would sit especially well with an intervention like CBT. In collaboration with the Borsboom group, we used data to characterize a network connecting depression symptoms measured before each session in the course of psychotherapy, with some symptoms being more "central" than others (78). We propose to extend this approach to link symptoms and processes. We also propose to link this network of symptoms and processes to observer-rated procedures, to determine if and how therapeutic procedures break the connections of maladaptive symptoms and processes that perpetuate depression. The advantage of the network approach is that it seeks to identify (potentially causal) *within-person* changes, whereas standard nomothetic approaches, based on between-person changes, assume that all individuals respond in the same way to therapeutic procedures. Distinguishing between-person variability (e.g., degree of negative thinking) and within-person variance (e.g., change in negative thinking over time) is of great importance to assess how changes within a patient in the course of treatment lead to individual outcomes.

Use of advanced methods such as experience sampling (ESM) might be very helpful to track down change processes of individual patients before and during treatment that can then be linked to outcome [see for e.g., Fisher (79)]. In ESM (80), participants are asked to rate their momentary experiences daily at random times, using an electronic device (i.e., smartphone). The set of single items refers to concrete experiences, such as "how sad do you feel right now?" or "how much are you bothered by negative thoughts right now?" Collected over longer time periods, ESM results in a very large number of observations per individual. The advantage of ESM is that it has a high ecological validity, takes the dynamics of daily life into account and yields high statistical power. In our example, single items to be assessed daily address depressive symptoms (e.g., sadness, guilt, restlessness, concentration), well-being, negative thinking (e.g., dysfunctional cognitions, rumination, intrusive images) behavior (e.g., activity, avoidance, use of therapy skills), and interpersonal functioning (e.g., social relations and activity).

However, ESM also comes with its challenges. The use of single items makes it difficult to account for measurement error. Moreover, the use of session-by-session assessments in combination with intensive ESM might be a burden for participants, which underlines the need to keep participants engaged in the study. ESM needs rich and dense data to robustly model time series, also because the time between sessions is rather short and violations of stationarity can become a problem. However, we think the advantages of ESM outweigh these challenges.

## Processes to Be Investigated

As said, CBT is assumed to work through cognitive and behavioral procedures that lead to less *negative thinking* and more *positive reinforcement* and *activation*. But there are other *candidate mechanisms* too. In recent years, research has highlighted the role of *therapy skills*, i.e., skills and strategies that are acquired as a result of therapy. Barber and DeRubeis (42) proposed that these compensatory skills (defined as the ability to identify and challenge depressive, dysfunctional thoughts or beliefs) can become an automated process as a result of continued practice and might form the central process in CBT. Moreover, they suggested that either the activation of other more functional cognitions and schemas (and deactivation of the dysfunctional ones) or cognitive change could be explained as a result of the repeated use of these skills. CBT skill acquisition has been shown to be associated with greater depression reduction during therapy, as well as resistance to relapse after therapy is terminated (46, 47, 81).

Related to therapy skills are the *learning processes* that take place in therapy, particularly the role of *memory* (74). Harvey et al. (82) proposed to improve therapy outcomes by improving memory for in-session therapy information and content. We have proposed that therapy outcomes can be improved by increasing the frequency of therapy sessions (from once- to twice-weekly), with increased learning processes that lead to better skills as the underlying mechanism (83), a hypothesis we are currently testing in the context of a large randomized trial (84). Other phenomena that are relevant in this context are *mental imagery* and *rumination*. Depressed patients report having intrusive negative images about past experiences (85), and imagery is known to enhance memory (86). Rumination is defined as "repetitive thinking about the causes, meanings and implications of depressed feelings, symptoms, problems, and upsetting events" and has been shown to play an important role in depression (87, 88). Studying these cognitive processes *in conjunction* will likely advance our understanding of the mechanistic pathways that are engaged in CBT.

Finally, the *therapeutic alliance* between the patient and therapist has been championed as the essential mechanism according to the *common factor theory*, that states that a-specific elements present in all types of therapy are responsible for the effects (20, 89). Several meta-analyses show that a strong therapeutic alliance is linked to treatment success in psychotherapy, although the association is modest (90, 91). Findings like these have been presented as evidence for the common factor model, but associations cannot be used to infer causation. More recent studies (in CBT and other therapies) have tried to push the ball forward by disentangling the temporal sequence of change, but the evidence remains far from conclusive, as we reviewed (20).

To expose to the pathways that link profiles and procedures to processes and symptom change in CBT, large observational

studies in depressed patients who receive CBT that is considered to be of high therapeutic quality are needed. An observational study is preferred because randomized trials are designed to diminish the individual variability we are interested in and leaves out the (potentially large) group of patients that is not willing to be randomized for treatment. First, it should be identified which processes account for recovery, and whether this differs between subgroups. Second, it should be investigated how processes and individual symptom changes are dynamically interconnected in time using network analysis (77, 78). Third, it should be investigated whether observer-rated CBT procedures can be linked to the identified processes and process-symptom connections. Fourth, the findings from these different explorative steps should be combined to *determine distinct pathways* of profiles, procedures, processes and outcome, and determine which kinds of patients need which procedures to engage which processes that drive recovery from symptoms.

### Observer Ratings of In-session Procedures and Processes

In order to acquire observer ratings of the relevant procedures and processes, all therapy sessions in the observational study should be videotaped. Tapes can then be studied by independent raters, who rate the occurrence and magnitude of process changes and the procedures that are applied in-session, and the overall quality of therapy, using pre-defined rating scales such as Collaborative Study Psychotherapy Rating Scale (92) and the Cognitive Therapy Rating Scale (93). Because of the complexity and expert level needed to do this, procedures, processes and therapy quality should be rated by different groups of raters. Obviously, rating all sessions is a tremendous amount of work, and the method is not consistently applied in the psychotherapy literature. However, this laborious behavioral analysis method has been successfully applied in several studies (43, 94–97), as it provides the strongest test of therapy adherence, therapist competence, in-session process changes and the delivery of procedures. One alternative to make the process of rating more feasible is the use of thin-slicing or related procedures that only rate a portion of the therapy session. Another alternative is to rate the content of internet-based therapy procedures where a substantial amount of therapy content occurs via text exchanges. In a recent study, 90,000 therapy hours from 17,000 patients receiving internet-enabled CBT were analyzed using deep learning methods to associate therapist utterances with outcome. It was found that increased quantities of CBT techniques, especially CBT change methods, were positively associated with reliable improvement, while the quantity of non-therapy-related utterances was negatively associated (98). Although it is not clear whether the techniques that came up in therapy were actually delivered appropriately, the methods applied in this large-scale study might also advance our understanding how therapists' behaviors are linked to processes and outcome.

### Hypotheses

The ***default hypothesis*** that is usually tested in most studies is that CBT works through its theoretically assumed working mechanisms, namely that CBT procedures lead to changes in negative thinking and (depressive) behavior, which leads to a reduction of depression symptoms. However, the ***personalized causal pathway hypothesis*** we propose states that CBT works through its theoretically assumed working mechanisms, but that causal pathways differ between subgroups of patients, and that these pathways contain interactions of procedures and processes that are more complex than traditional CBT theory states. For instance, *cognitive restructuring* may lead to *cognitive change*, but only if the *therapeutic alliance* is strong, and only if patients have a high *educational level*. The ***alternative hypothesis*** is that CBT does not work through its theoretically assumed working mechanisms, but because of "common factors" present in all forms of psychotherapy, such as the therapeutic alliance.

An overview of the main points that were made in section identification of mechanisms is presented in **Table 2**.

**TABLE 2 |** Main points of section identification of mechanisms of change.

| | |
|---|---|
| 1 | Exploratory and observational study frameworks to study the links between therapeutic procedures, therapy processes and outcome, relying on not only self-report assessments but also observer ratings of procedures and processes that are manifested in session. |
| 2 | Careful consideration of the therapy processes that are the strongest candidates to reflect actual mechanisms of change according to theory, such as CBT processes, learning processes and the therapeutic alliance. |
| 3 | Moderated mediation analyses to find out for whom certain procedures and processes matter most. |
| 4 | Network analyses that link the (potentially causal) connections between symptom change and process change by means of rich experience sampling data. |

## Isolating CBT Procedures in Experiments

A much-echoed criticism regarding existing mechanisms studies is the lack of experimental designs in which the putative mechanism (or mediator, in statistical terms) is isolated and *directly* manipulated to assess a possibly *causal* effect on outcome (19, 21) (**Figure 2**). Here too, it is essential to distinguish procedures and processes, as sequential parts of the mechanistic pathway. The second line of research we propose is a series of experiments in which the most important CBT procedures are isolated and compared to a non-active control condition in a sample of depressed patients so that the effect on relevant processes and outcome can be assessed. For example, cognitive restructuring (using Socratic questions to evaluate negative thoughts, using dysfunctional thoughts records with guided therapist support) could be compared to merely monitoring negative thinking (using dysfunctional thoughts records), while in another experiment behavioral activation (increasing pleasurable activities, using activity registration) can be compared to merely monitoring daily activities (using activity scheduling). Study participants who experience at least mild depression symptoms would receive a series of tightly scheduled sessions (e.g., six 30-min sessions in 2 weeks, to optimize the effect of the manipulation) that focus solely on the isolated procedure. Experience sampling methods can be added in the

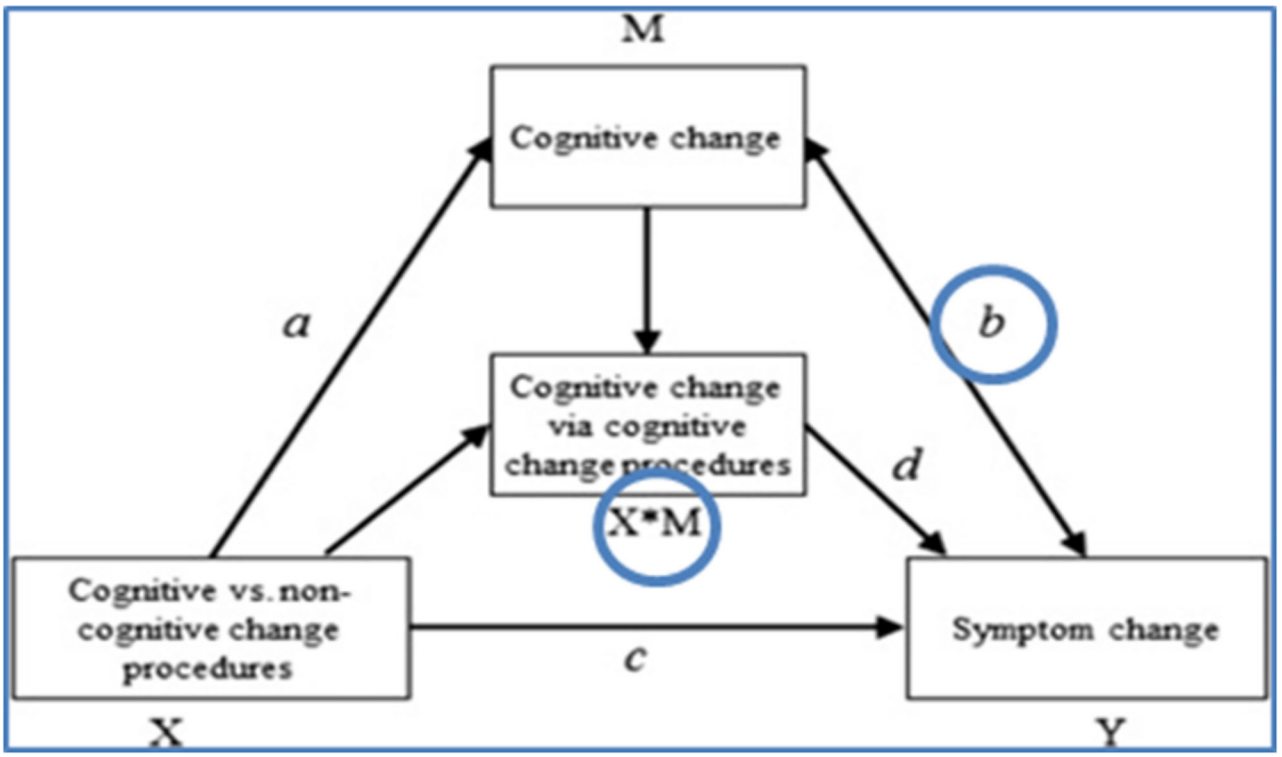


**FIGURE 2 |** Mediation model to be tested in an experiment (28).

course of the experiment to collect rich momentary data on daily experiences, processes and symptoms.

To illustrate, we describe a few preliminary experiments recently conducted at the *Experimental Psychotherapy Lab Amsterdam* in which we have begun to conduct such mechanistic experiments with (distressed) students. In the first experiment, the effects of cognitive therapy skill acquisition ($n = 36$) were compared to no procedure ($n = 36$) in response to induced distress following a social stress test. Participants reported more cognitive therapy skills after the procedure focused on the acquisition of cognitive therapy skills compared to no procedure, but there were no differences in dysfunctional thinking, distress and mood between the groups (99). In a second experiment, distressed students were randomized to an experimental condition focused on the acquisition of cognitive therapy (CT) skills ($n = 27$) or a control condition focused on being exposed to theories of automatic thinking ($n = 25$), after which all participants were exposed to a sad mood induction. Participants in the experimental group used more CT skills compared to participants in the control group, but there were no differences between conditions in the decrease of the credibility of idiosyncratic dysfunctional beliefs and strength of emotions. However, in participants with low levels of depression, those who underwent the experimental procedure showed larger decrease in the credibility of their most malleable belief (i.e., mostly automatic negative thoughts) compared to those that received the control procedure (100). In the third experiment designed to test the role of memory of therapy content, individuals with moderate levels of distress were randomized into retrieving (memory test, $n = 46$) or rehearsing (restudying, $n = 49$) four weekly sessions of online problem-solving therapy (PST). Retrieval led to overall higher recall, but this difference disappeared when controlling for the time spent on retrieval vs. rehearsal (101). Retrieval did not lead to better problem-solving skills or less distress, compared to rehearsal. Baseline working memory performance did moderate the effect of condition on recall.

Taken together, these *preliminary experimental studies* shed new light on the required dose and intensity of CBT procedures, the impact of initial depression severity, the advantages in conducting these experiments, and the importance in extending this research program to clinical populations. Using designs like these, we might be able to test the direct effects of isolated CBT procedures on therapy processes and depression symptoms in patients with depression.

## Testing Personalized CBT

Once we have collected sufficient findings along multiple, converging lines of research on the patient profiles, procedures, processes, and outcome that might constitute the individual pathways of change in CBT, we can use these new empirical insights to develop personalized CBT packages based on

procedures that are deemed to be crucial for certain individuals or subgroups of patients. Of course, the ultimate experimental test to demonstrate whether these personalized pathways are truly causal in nature would be an RCT in which a personalized CBT package based on the identified pathways of change that can be matched to the individual patient outperforms a standardized CBT package, in terms of both process change and outcome.

Let's assume we have found *one* potentially causal pathway linked to a certain subgroup and that this subgroup consists of female patients with high anxiety that is predicted to respond best to a (single) CBT procedure (i.e., a high dose of cognitive restructuring) that leads to a change in process (i.e., less negative thinking) and a subsequent decrease of depressive symptoms (see **Figure 1**). In this simplified hypothetical example, personalized CBT would consist of a higher dose of cognitive restructuring delivered with a specific timing (e.g., in session 3–12) compared to standard CBT, and less focus on behavioral activation or other procedures, based on the potentially causal pathway we found. In case we find two or more causal pathways linked to other subgroups as well, we could include these in the trial, with the characteristics of the subgroups as additional inclusion criteria. In fact, it makes sense to compare several personalized CBT packages (that are likely to be highly variable and to contain more carefully planned interventions than in this simplified example) to standardized, one-size-fits-all CBT in a randomized trial if we want to demonstrate that selecting specific therapeutic procedures for specific patients leads to better and perhaps also faster recovery from depression.

## CONCLUSION

In this paper, we described the many challenges on the road to develop personalized psychotherapy that fits the needs of the individual patient and presented our ideas how to improve our understanding of the mechanisms of change in psychotherapy. We used the example of CBT for depression because it is the most extensively researched form of psychotherapy with a relatively large evidence base on outcomes, predictors and processes involved. We left out the statistical analysis considerations that come with complicated designs such as these as the field is likely to follow the rapid developments in statistical methods such as network modeling (76) and machine learning approaches (17). We also did not provide an overview of alternative designs that might be particularly useful to study mechanisms of change, such as single-case series designs (102).

The topic of our paper is a timely one, and many others are presently contributing to the debate. As part of the Lancet Psychiatry Commission on psychological treatments research, Holmes et al. (103) described the many difficulties of mechanism research, such as the lack of rigorous methodology that plagues many mediation studies. They too promote the study of moderators to improve precision in treatment matching but also to learn more about the (differential) mechanistic pathways in psychotherapy, and the "unpacking" of psychotherapy packages by focusing more on therapeutic strategies (i.e., procedures). Future studies should demonstrate whether matching mechanistically focused treatments to individual profiles enhances treatment outcome. Kazantzis (33) proposed the "matrioshka process," a testable model of the different therapeutic techniques and in-session processes that are involved in CBT as a means to understand their true relations and provide an empirical basis to tailor therapy to a particular patient at a particular point in therapy. Hofmann and Hayes (104) have suggested that the future of intervention science should be focused on therapy processes. They state that the medical illness model of psychopathology has lost its utility (and as a result the term CBT perhaps as well), and that we should move forward toward process-based therapies that target core mediators and moderators directly based on testable theories, that link evidence-based therapeutic procedures to evidence-based processes and that are ideographic rather than nomothetic in nature, consistent with the overall trend toward more person-centered approaches. Watkins et al. (105) described an innovative study framework to distinguish therapeutic procedures and processes and investigate causal pathways of change. They propose to use (fractional) factorial designs to identify the active ingredients of internet-delivered CBT for depression, framed within the Multiphase Optimization Strategy (MOST) approach. The optimization phase is used to select the candidate components that should be included in the optimized intervention, which can then be tested against the standard intervention in the evaluation phase. This of course resembles our proposal to test personalized CBT, albeit without matching the optimized intervention to the profile of individual patients. The factorial design also provides a strong test of the relative contribution of specific vs. common factors, which is another advantage. The design proposed by Watkins et al. is currently being used in an ongoing large-scale RCT and the results are underway (106).

Some psychotherapists will say that personalization of therapy is their everyday work, so who needs such a research agenda? They will adapt the therapy to their individual patients based on what they feel is the right combination of therapeutic procedures, based on their clinical intuition. But as Meehl (107) already demonstrated in 1954 and as we recently confirmed (108), clinical intuition is an unreliable source of input for the clinician. Therapists have their own thoughts and preferences on why and how to deviate from treatment protocols to treat their patients best, but such choices are most often not substantiated by empirical evidence. In the worst scenario, it can become a case of "therapist-centered psychotherapy," where therapists deliver an eclectic therapy that "feels" best to themselves mostly. We strongly urge psychotherapists to take a more empirical stance toward their profession.

Our main message centers around the personalized causal pathway hypothesis that emphasizes the distinction between procedures and processes and calls for moderated mediation analyses or other approaches that take individual differences

into account. We described the type of research that we think will be needed to advance our understanding of the mechanisms of change in psychotherapy, acknowledging that there are more roads that lead to Rome. Holmes et al. (103) concluded that advances in this field will depend on funding opportunities and greater collaboration among clinical researchers to establish the sample sizes that are required for this kind of research. We agree with these authors and invite researchers to engage in multi-lab collaborations to pool large datasets that can be used explore questions about personalizing CBTs.

## DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

MH drafted a first version of the manuscript. LL-L, PC, and NK provided feedback and additions to the text. All authors contributed to the article and approved the submitted version.

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# The Temporal Associations of Therapeutic Alliance and Manual Adherence With Depressive Symptom Change in Cognitive Behavioral Therapy for Adult Outpatient Major Depression

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**Background:** The therapeutic alliance is considered an important causal agent of psychotherapy efficacy. However, studies in cognitive behavioral therapy (CBT) for depression have suggested that alliance might be more of a consequence rather than a cause of depressive symptom change, while adherence to CBT specific techniques was found to be associated with subsequent depression change. We aimed to add to this body of literature by assessing the temporal associations of both therapeutic alliance and manual adherence with depressive symptom change in a relatively large sample of depressed adult outpatients over the full course of CBT.

**Methods:** Adults with a major depressive episode ($n = 98$) participating in a randomized clinical trial were offered 22 weeks of CBT and rated the Penn Helping Alliance Questionnaire (HAq-I) at weeks 5 and 22. Therapists rated their adherence to the CBT manual after each session and observers assessed the Hamilton Depression Rating Scale scores at weeks 0, 5, 10, and 22. Linear mixed model analyses were used to assess the associations of alliance and adherence with prior and subsequent depression change.

**Results:** HAq-I Relationship and manual adherence ratings were not significantly associated with prior nor with subsequent depression change ($p > 0.14$). Prior depression change was associated with the HAq-I subscale Perceived helpfulness at the end of treatment ($r = 0.30$, CI = 0.03–0.56, $p = 0.03$).

**Conclusion:** We were not able to replicate prior depression change in CBT for depression to be associated with improved quality of the therapeutic alliance when using a more "pure" measure of the therapeutic relationship. Limitations of this study include



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the subjective alliance and adherence assessments. Our findings indicate the need to appropriately distinguish between the perceived helpfulness and the relationship factors when examining therapeutic alliance.

**Keywords: therapeutic alliance, manual adherence, cognitive behavioral therapy, depression, temporal associations**

## INTRODUCTION

Cognitive behavioral therapy (CBT) is one of the best-known and empirically supported psychological treatments for depression. Although CBT has shown to be efficacious in the treatment of depression (e.g., 1), still, up to 50% of patients fail to achieve an adequate response, and even fewer achieve remission following an acute treatment trial (1). Thus, the efficacy of CBT for depression needs to be improved.

One possible way to enhance efficacy is to investigate which treatment factors in CBT result in symptom change (2, 3), so that "we can direct better, stronger, different, or more strategies that trigger the critical change process(es)" (2). Two theories pose how CBT results in depressive symptom change: the behavioral activation theory (4) and the cognitive theory (5). Lewinsohn et al. (4) theorize that depression is caused or maintained by a reduction in satisfying activities. Patients are therefore encouraged to engage in activities that positively influence their mood. On the other hand, the cognitive theory posits that inaccurate beliefs and maladaptive information processing play a causal role in the development and maintenance of depressive symptoms (5). According to this theory, correcting these beliefs and processes is the core working mechanism in CBT for depression. In order to capitalize on these theorized effective treatment factors, it is important that therapies are being conducted as intended, i.e., that the therapist is adherent to the treatment manual (6, 7).

Besides the specific CBT factors mentioned previously, there is a more general—or non-specific—factor that is supposed to contribute to CBT efficacy. The quality of the therapeutic alliance is considered an important factor that can enhance the efficacy of psychotherapy in general (8, 9). According to Bordin's (10) influential definition, therapeutic alliance implies that therapist and patient (a) agree on treatment goals, (b) define a set of therapeutic tasks used to achieve the goals, and (c) form a positively toned emotional bond.

In an attempt to assess the associations of therapeutic alliance as well as therapist's adherence to the treatment manual with treatment effect, Castonguay et al. (11) found treatment adherence and the alliance—both as assessed at the end of treatment—to be associated with a better response to CBT for depression. However, in this study the temporal relation of adherence and alliance with symptom change was not adequately established (2). It did not rule out reverse causality: that it was symptom change that drove adherence and alliance rather than the other way around. Adequately taking reverse causality into account requires addressing the temporal relationship between treatment factors and outcome.

DeRubeis and Feeley (12) were the first to use this strategy when investigating process factors in CBT associated with alleviation of depressive symptoms. In a sample of 25 depressed outpatients, they found that the extent to which therapists adhered to the manual, i.e., they used concrete symptom-focused CBT in an early session, was associated with subsequent change in depression. This finding was replicated by Sasso et al. (13), Strunk et al. (14), and Brotman (15), and provides support for the behavioral activation and cognitive theories of depression. However, an investigation by Snippe et al. (16) among depressed diabetics following CBT failed to identify a significant association between adherence and treatment effect.

DeRubeis and Feeley (12) also found that therapeutic alliance was not correlated with subsequent change in depression, but was correlated with prior symptom change, suggesting that the quality of the therapeutic relation was more of a consequence rather than a cause of depression symptom change. This finding is particularly interesting, because it is contrary to the conventional wisdom that the quality of the therapeutic relation is an important causal agent of psychotherapy efficacy. It received only marginal support in a replication study by the same authors, where prior symptom change predicted therapeutic alliance at trend level only (17), but it was replicated in larger samples by Strunk et al. (14) and by Strunk et al. (18). However, the last two investigations were restricted to the first five and three sessions, respectively, leaving unanswered which changes may have taken place in later phases of treatment. Using a sophisticated repeated-measures design, Falkenström et al. (19) also found that improvement in alliance was associated with a reduction of depressive symptoms in the next CBT or IPT session, but the authors note the relatively small sample size as a limitation of their study (43 patients underwent CBT). Together, the findings of these studies suggest that in CBT for depression, quality of the therapeutic relation might be a consequence of depression symptom change. This is in contrast with studies investigating the alliance in treatments other than CBT for depression, which generally found the alliance associated with subsequent symptom change (20–28). It should be noted, however, that several studies also have failed to find a significant relationship between alliance and symptom change in CBT for depression (29, 30) even when applying a high-quality mediator study design. A meta-analysis among several kinds of psychotherapies and disorders by Flückiger et al. (31) revealed a significant relation only in investigations with a specific interest in the alliance.

In this study, we aim to add to the literature mentioned previously by investigating the temporal associations of both therapeutic alliance and manual adherence with depressive

symptom change in CBT for adult outpatient major depression in a relatively large sample of patients over the entire course of the treatment. We hypothesize that prior symptom change will be positively associated with therapeutic alliance, but that therapeutic alliance will not be associated with subsequent symptom change. Furthermore, we hypothesize that early manual adherence will be associated with subsequent symptom change, but not with prior symptom change.

# MATERIALS AND METHODS

## Design

This paper draws upon data from the CBT condition of a randomized clinical trial in the outpatient treatment of major depression (32). The study design was approved by the Dutch Union of Medical-Ethic Trial Committees for mental health organizations and the study protocol was published (33). Of the 341 participants randomized to treatment in the clinical trial, 164 were assigned to the CBT condition. Of these, 66 had a baseline HDRS score >24 and were offered additional antidepressant medication.

## Participants

Participants were referred by their general practitioner for depression treatment to one of three outpatient mental health clinics in Amsterdam, the Netherlands. Inclusion criteria were: (34) main diagnosis of depressive disorder according to DSM-IV criteria (35) as assessed by the MINI-International Neuropsychiatric Interview—Plus (36), (1) a score of 14 or above on the Hamilton Depression Rating Scale (HRSD, 30), (2) age between 18 and 65 years, and (3) a written informed consent after having received a complete description of the study.

Exclusion criteria included presence of psychotic symptoms or bipolar disorder, severe suicidality warranting immediate intensive treatment or hospitalization, substance misuse or abuse in the past 6 months, pregnancy, inability to meet trial demands due to for example medical conditions, and use of psychotropic or other medications that might influence mental functions. Patients on an antidepressant regimen were included only if the medication they were currently taking was judged to be inefficacious by both the patient and the intake psychiatrist. If so, the medication was tapered off under medical supervision, and baseline assessment took place after a washout period of at least 1 week after the medication was completely stopped. Patients with very severe depression (HDRS score >24) at baseline were offered additional antidepressant medication administrated by a psychiatrist. We excluded these patients for this work, because the effects of CBT could not be disentangled from those of the antidepressant medication.

Separate random allocation sequences were generated for each of the three clinics by one of the authors (J.P.) using SPSS random number generator (SPSS, Chicago). Randomization was stratified by gender and age (<32.5 and >32.5 years). Research assistants, aware of the allocation sequence, enrolled participants, and assigned them into interventions.

## Intervention

CBT comprised 16 individual sessions within 22 weeks, with the first 10 sessions taking place weekly and the final six taking place 2-weekly. CBT was conducted according to a published treatment manual (37) and consisted of an introductory session, three treatment phases and a concluding session. In the introductory session, acquaintance with the therapist was made, therapy conditions were explained, and a treatment contract was signed by both the patient and the therapist. The first treatment phase (sessions 2–4) focused on behavioral activation by means of planning and registering activities and concurrent mood levels. In the second CBT phase (sessions 5–7), the cognitive model was explained and patients kept a thought diary to identify automatic thoughts. These thoughts were challenged in the third phase (session 8–15), when they were tested on their validity and utility by logical reasoning. Patients were encouraged to identify reasoning errors in their own thinking. In addition, a behavioral experiment was designed and conducted to test the identified automatic thoughts in real life. Depending on the patient's needs, sessions 13–15 could be spent on complementary challenging techniques or conducting additional behavioral experiments. The final session (session 16) concluded treatment by evaluating the therapy and the therapeutic goals, and discussing strategies of action in case of relapse.

CBT therapists were psychiatrists or psychologists with at least a master's degree who completed a 100-h basic CBT training course accredited by the Dutch Association for Behavioral and Cognitive Therapy. Moreover, all therapists adequately conducted at least one intensively supervised therapy case in accordance with the treatment manual as judged by a study supervisor. Although no formal assessments were conducted, treatment fidelity was checked by means of biweekly supervision sessions, chaired by a study supervisor, in which audiotaped material was discussed. All study supervisors were registered supervisors with the Dutch Association for Behavioral and Cognitive Therapy.

## Measures

An overview of the assessments included in this work is provided in **Table 1**.

Depression severity was assessed with the Dutch version of the 17-item HRSD (38, 39) at weeks 0, 5, 10, and 22. The HRSD is a structured interview designed to quantify the severity of depressive symptoms in patients already diagnosed as suffering from a depressive disorder. Its items cover different depressive symptoms, such as mood, sleep problems, lack of appetite, weight loss, suicide intentions, and feelings of guilt, which are rated on either a 0–2 or 0–4 scale. Trained research assistants (master's-level graduate students in clinical psychology) assessed the HRSD according to the Dutch scoring manual (40). Assessors participated in biweekly 1-h peer supervision sessions, in which audiotaped interviews were discussed. The average intraclass correlation coefficient over 46 audiotaped assessments scored by multiple assessors was 0.97. The HRSD showed good reliability (Cronbach's alpha:0.82).

Therapeutic alliance was assessed from the patient's perspective at weeks 5 and 22 by means of the Penn Helping

**TABLE 1 |** Timeline of assessments during CBT treatment.

| Week | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Session | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | | 11 | | 12 | | 13 | | 14 | | 15 | | 16 |
| Depression severity | X | | | | | X | | | | | X | | | | | | | | | | | | X |
| Therapeutic alliance | | | | | | X | | | | | | | | | | | | | | | | | X |
| Manual adherence | | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | | X | | X | | X |

Alliance Questionnaire Method (HAq-I), which assesses the extent to which the patient experiences the therapist and the therapy as helpful (41, 42). The HAq-I is a self-report instrument including 11 items that are rated on a 6-point scale from −3 ("No, I strongly feel that it is not true") to 3 ("Yes, I strongly feel that it is true"). The total score equals the sum of the item ratings. The HAq-I correlates well with other measures of therapeutic alliance (43–45) and the strength of the association between alliance and outcome assessed with HAq-I is comparable with other measures (46). The Penn Helping Alliance Scales distinguish two types of helping alliance. Helping Alliance Type 1 refers to the patient's perceived helpfulness of the therapist, whereas Helping Alliance Type 2 is defined as the patient's collaboration or bonding with the therapist. The HAq-I Type 2 subscale items have shown to form an independent factor (43, 47) that measures the collaborative nature of the therapeutic relationship. We used this subscale for the main analyses in this study, because, in our opinion, it better reflects Bordin's (10) definition of the therapeutic alliance. The reliability of both the total scores and Type 1 & 2 subscales of the HAq-I was good (Cronbach's alpha: type 1 alliance, 0.92; type 2 alliance, 0.92; total alliance 0.94).

CBT manual adherence was assessed by the therapist, who rated the extent to which he or she had been able to adhere to the treatment manual for that session on a scale from 1 ("not at all") to 10 ("completely") after each session.

## Data-analysis

We first calculated raw prior depression change scores for each patient by subtracting the HRSD score at week 0 from the HRSD scores at week 5, week 10, and week 22. Similarly, we calculated raw subsequent depression change scores by calculating the differences between the HRSD score at weeks 0, 5, and 10, and the end-of-treatment HRSD score at week 22. Next, we transformed the raw change scores to residualized change scores. More specifically, we used ANOVA to predict each patient's change based on their HRSD-score at week 0. We calculated the difference between the predicted score and the patient's actual change score resulting in a residual. A positive sign of this residual signifies a better-than-expected effect, while a negative sign indicates the effect is less than expected. We added the group mean change to the residuals and transformed these scores into z-scores to center the residual change around the group mean change (48)877–883.

With regard to therapeutic alliance, following Lorenzo-Luaces et al. (49), we used the sum score for the Relationship (Type 2)-subscale (items 1, 6, 7, 8, 9, and 10) for our main analyses, because this measures the collaborative nature of the therapeutic relationship, and not the perceived helpfulness that characterizes items from the Type 1-subscale. However, we also conducted sensitivity analyses using the HAQ-I total and the Type 1 (Perceived helpfulness) subscale sum scores.

With regard to manual adherence, mean adherence scores were calculated for sessions 1–5, sessions 6–10, and sessions 11–16, corresponding with treatment weeks 0–5, weeks 6–10, and weeks 11–22, respectively. We visually inspected Probability-Probability plots and judged all variables to be normally distributed.

We then assessed the associations of alliance and adherence with prior and subsequent depression change using linear mixed model analyses with a two-level structure (patient and therapist). In analyses of prior symptom change, alliance, or adherence served as the dependent variable and symptom change as the independent variable. In analyses of subsequent depression change, this variable served as the dependent variable and alliance or adherence as the independent variable. By design, alliance at week 22 (end of treatment) could only be related to prior depression change. Similarly, adherence in sessions 1–5 could only be related to subsequent symptom change and adherence in sessions 10–16 could only be related to prior symptom change.

In analyses including therapeutic alliance, the number of prior episodes was added as a covariate, because this variable has been found to moderate the alliance-outcome association in CBT for depression (49). In addition, we examined possible other confounders separately for each analysis, by testing whether the independent variable was significantly associated with one of the baseline characteristics (**Table 2**) using one-way ANOVA. As a result, we added gender as a covariate in the analysis of therapeutic alliance at week 5 and subsequent depression change (**Table 3**). Before computing the estimate of fixed effects, results were standardized into z-scores in order to get an *r*-type effect size following Strunk et al. (12, 730), where 0.20 represents a small effect 0.30 a medium sized effect and 0.50 representing a large effect (50). All analyses were conducted using SPSS version 22.0. The significance level used was alpha $< 0.05$, 2-sided.

Missing data for the different measures were imputed at item-level by means of multiple imputation, using the MICE package in "R" statistical software [version 2.25; (51)]. The default settings for the imputation method were applied, meaning that predictive mean matching was used for the imputation of missing numeric data, logistic regression imputation for binary data, polytomous regression imputation for unordered categorical data, and proportional odds model imputation for ordered categorical data. Variables with more than 50% missings were not imputed.

Twenty imputed datasets were created. Density plots showed the distribution of the imputed data following the distribution of the original data, indicating adequate imputation. The analyses were performed on the 20 imputed datasets separately, and these results were combined using Rubin's rules (52) in SPSS. We used the imputed data for our main analyses, but we conducted sensitivity analyses using the observed (unimputed) data only. We also conducted sensitivity analyses in which the HRSD-scores at week 22 were not imputed but the other variables were, as imputation of the outcome variable has been disputed (53).

As an additional analysis we examined whether there was an interaction effect between the alliance at week 5 and manual adherence up to that point on subsequent symptom change in order to investigate whether manual adherence has more effect in the context of a good therapeutic alliance.

# RESULTS

## Participants

From April 2006 to December 2009, 4,866 patients were assessed for eligibility during a standard intake procedure. Ninety-eight participants were included in the present study, 67 (69.8%) of which were female. Their mean age was 37.3 years (SD = 10.79; range 22–64) and their mean pre-treatment HRSD score was 19.96 (SD = 2.68), indicating severe levels of depression (54). The majority of the participants were never married (54.2%), had intermediate (36.5%) to high (42.7%) education levels, were unemployed (54.2%), had a depressive episode duration of <6 months (34.0%), and had reported two or more prior depressive episodes (46.2%). Detailed characteristics of the study sample are described in **Table 2**.

Thirty-five therapists treated on average 2.8 patients (range 1–9). The majority of patients had a female therapist (75.5%) with a mean age of 40.9 years (SD = 10.2, range 27–57). The average number of CBT sessions attended was 10.8 (SD = 5.5).

**TABLE 2 |** Baseline characteristics of 98 patients assigned to cognitive behavioral therapy for depression.

| | M | SD |
|---|---|---|
| Baseline HRSD | 19.96 | 2.68 |
| Age | 37.29 | 10.79 |
| | *n* | % |
| **Gender** | | |
| Female | 69 | 70.4 |
| Male | 29 | 29.6 |
| **Marital status** | | |
| Married | 26 | 26.5 |
| Divorced | 16 | 16.3 |
| Widowed | 2 | 2.0 |
| Never married | 54 | 55.1 |
| **Educational attainment** | | |
| Low | 18 | 18.3 |
| Intermediate | 36 | 36.7 |
| High | 42 | 42.9 |
| Unknown | 2 | 2.0 |
| **Employment status** | | |
| Employed | 41 | 41.8 |
| Student | 4 | 4.1 |
| Unemployed or "other" | 53 | 54.1 |
| **Episode duration** | | |
| <6 months | 33 | 33.7 |
| 6–12 months | 22 | 22.4 |
| 1–2 years | 14 | 14.3 |
| +2 years | 16 | 16.3 |
| Unknown | 13 | 13.2 |
| **Prior episodes** | | |
| 0 | 35 | 35.7 |
| 1 | 16 | 16.3 |
| 2+ | 44 | 44.9 |
| Unknown | 3 | 3.1 |

## Therapeutic Alliance and Symptom Change

The associations of therapeutic alliance with prior and subsequent depression change after imputation of missing data are shown in **Table 3**. Therapeutic alliance, as assessed with the Type 2 (Relationship) subscale at both week 5 ($r = 0.14$, CI: −0.15–0.43, $p = 0.34$) and week 22 ($r = 0.20$, CI: −0.07 to 0.47, $p = 0.14$) was not associated with prior symptom change. Nor was therapeutic alliance Type 2 at week 5 associated with subsequent symptom change ($r = 0.14$, CI: −0.16 to 0.45, $p = 0.35$).

Sensitivity analyses with the Type 1 (Helpfulness) and HAq-I total sum scores also indicated no significant association between prior depression change and therapeutic alliance at week 5 (**Table 3**). However, prior symptom change was significantly associated with therapeutic alliance Type 1 at week 22 ($r = 0.30$, CI: 0.03–0.56, $p = 0.03$), and a similar association was found at the level of a non-significant trend for the HAq-I total score ($r = 0.25$, CI: −0.01 to 0.54, $p = 0.06$). HAq-Type 1 at week 5 predicted subsequent change at the level of a non-significant trend ($r = 0.24$, CI: −0.01 to 0.50, $p = 0.06$).

Sensitivity analyses using the observed data only and using the dataset in which all but the HRSD-score at week 22 were imputed are described in the (**Supplementary Tables 1, 2**). In the analysis of the unimputed data only, HAq-I Type 2 at week 22 was significantly associated with prior symptom change ($r = 0.43$, CI:0.13–0.68, $p = 0.01$), but not when imputing all variables but the HDRS at week 22 ($r = 0.23$, CI: −0.09 to 0.58, $p = 0.15$). We found no association between alliance at week 5 and prior or subsequent change in both sensitivity analyses ($ps > 0.10$), though HAq-I Type 2 at week 5 was associated with subsequent depression change at the level of a non-significant trend ($r = 0.27$, CI: −0.05 to 0.74, $p = 0.08$) when using the observed data.

## Manual Adherence and Symptom Change

The associations of CBT manual adherence with prior and subsequent depression change after imputation of missing data are shown in **Table 3**. Mean CBT manual adherence scores in the first 5 weeks of treatment were not associated with subsequent depressive symptom change ($r = -0.05$, CI: −2.36 to 1.70,

**TABLE 3 |** Associations of therapeutic alliance and manual adherence with prior and subsequent change in depression imputing all variables.

| Comparison | *n* | *r* | *95% CI* | *p* |
|---|---|---|---|---|
| **Therapeutic alliance—Type 2 (Collaboration/Bonding)** | | | | |
| Prior depression change—Therapeutic alliance week 5 | 56 | 0.14 | −0.15 to 0.43 | 0.34 |
| Prior depression change—Therapeutic alliance week 22 | 37 | 0.20 | −0.07 to 0.47 | 0.14 |
| Therapeutic alliance week 5—Subsequent depression change | 48 | 0.14 | −0.16 to 0.45 | 0.35 |
| **Therapeutic alliance—Type 1 (Perceived helpfulness)** | | | | |
| Prior depression change—Therapeutic alliance week 5 | 56 | 0.23 | −0.05 to 0.52 | 0.11 |
| Prior depression change—Therapeutic alliance week 22 | 37 | 0.30 | 0.03 to 0.56 | 0.03* |
| Therapeutic alliance week 5—Subsequent depression change | 48 | 0.24 | −0.01 to 0.50 | *0.06* |
| **Therapeutic alliance—Total** | | | | |
| Prior depression change—Therapeutic alliance week 5 | 56 | 0.20 | −0.09 to 0.49 | 0.18 |
| Prior depression change—Therapeutic alliance week 22 | 37 | 0.25 | −0.01 to 0.54 | *0.06* |
| Therapeutic alliance week 5 – Subsequent depression change | 48 | 0.21 | −0.08 to 0.49 | 0.15 |
| **Manual adherence** | | | | |
| Prior depression change—Manual adherence weeks 6–10 | 49 | 0.11 | −0.19 to 0.41 | 0.47 |
| Prior depression change—Manual adherence weeks 10–22 | 40 | 0.04 | −0.22 to 0.31 | 0.75 |
| Manual adherence weeks 1–5—Subsequent depression change | 51 | −0.05 | −0.35 to 0.25 | 0.75 |

*N = 98. *p < 0.05.*

$p = 0.75$). Mean adherence scores in weeks 5–10 and weeks 10–22 were not associated with prior symptom change up until these weeks either (5 and 10, respectively) ($r = 0.11$, CI: −0.19 to 0.41, $p = 0.46$ and $= 0.04$, CI: −0.22 to 0.31, $p = 0.71$). Sensitivity analyses using the observed data and the dataset in which all variables but the HRSD-scores at week 22 were imputed are described in the (**Supplementary Tables 1, 2**) and showed similar results. Again, no significant associations were found between manual adherence and prior or subsequent depressive symptom change ($p$s > 0.15).

There were no interaction effects between therapeutic alliance (HAq-I type 1, HAq-I type 2, and HAq-I total score) at week 5 and manual adherence up to that point on subsequent symptom change ($p$s> 0.05).

# DISCUSSION

## Findings

We examined the temporal associations of therapeutic alliance and manual adherence with depressive symptom change in adult outpatients receiving CBT for depression. We found no association of CBT manual adherence with prior nor with subsequent symptom change. Similarly, we did not find therapeutic alliance to be related with prior nor with subsequent depression change in our primary analyses, in which we used the HAq-I type 2 subscale containing the items that purely tap the collaborative nature of the alliance. We did find prior depression change to be associated with the HAq-I type 1 subscale that assesses the perceived helpfulness, as well as for the total HAq-I scores (which is the sum of both subscales) at the level of a non-significant trend. We take this finding to indicate that patients who have experienced more depressive symptom alleviation over the course of their 22 week treatment also perceive their therapy and therapist as more helpful. Similarly, the perceived helpfulness subscale scores at week 5 were associated with subsequent depression change at the level of a non-significant trend, meaning that patients that perceive their therapist as helpful also may experience more symptom reduction.

Thus, we were not able to replicate previous studies finding prior symptom change to be associated with therapeutic alliance in CBT (12, 14) and CBT combined with antidepressant medication (18), when using a measure that, in our opinion, purely taps the collaborative nature of the alliance. Rather, our findings are in line with previous work in which no significant relationship between alliance and symptom change in CBT for depression was found (29, 30). We also did not find that the alliance is associated with subsequent depression change, which was also found in previous studies in CBT for depression (12, 14, 18), but not for other treatments like alliance fostering therapy (e.g., 15, 16) and supportive-expressive psychotherapy or clinical management combined with pharmacotherapy or clinical management combined placebo (27, 28). Maybe the therapeutic alliance plays a less important role in CBT for Depression than it does in other therapies (19). Concerning manual adherence, we also were not able to replicate prior studies finding adherence in CBT to be associated with subsequent depression change (e.g., 12, 50, 51), but our findings are in line with other work reporting no significant relation between adherence and treatment effect in CBT for depression (16).

## Strengths and Limitations

The study has a number of strengths. First, the study includes a relatively a large sample. Second, several elements contribute to the generalizability of the study's findings to general clinical practice. Treatment was provided in regular psychiatric outpatient clinics by a large number of therapists with different experience levels. Patients were not recruited by advertisement but instead were referred by general practitioners,

no selection criteria with regard to previous treatment or suitability for psychotherapy were applied, and patients with relatively low socioeconomic status were included. Third, we carefully distinguished the collaborative nature of the therapeutic relationship and the perceived helpfulness of the therapist/therapy in our analyses. Fourth, our study design allowed us to examine the temporal relation between treatment effect and process variables and we used sophisticated statistical techniques to do so, controlling for patient and therapist variance.

This study also has a number of limitations. First, although depression symptom severity was assessed by independent observers, manual adherence and therapeutic alliance were subjectively assessed by, respectively, therapists and patients. Although the patient's perspective is frequently used in alliance research [e.g., (19, 55)], patients and therapists may be biased in their judgements by the improvement (or lack thereof) they experience. Independent raters, blind to outcome (56), may assess alliance and adherence more objectively. Second and related, symptom change and therapeutic alliance were rated later in treatment than in some other studies (e.g., 48) and we cannot rule out the possibility that an interaction between alliance and outcome might have already taken place at week 5. Third, although our research design allowed us to study the temporal associations of therapeutic alliance and manual adherence with symptom change, our design did not allow us to identify either of these variables as mechanisms of change (2). Neither does our study rule out possible third variable causality (that some unmeasured patient characteristic facilitated both the process variable and symptom change with no direct causal link between the two). Fourth, no control condition was included in the study.

### Clinical and Research Implications

The fact that we did not find a relation between treatment effect and the alliance does not mean that the alliance is irrelevant in CBT. It has been long suggested that in CBT for depression the alliance is necessary but not sufficient for therapeutic change to take place (e.g., 6). Rather, to put it in the words of DeRubeis and Feeley (1990), our well-trained and "empathetic therapists may undoubtedly have created a proper environment for therapeutic change."

Concerning the limitations of this study, we recommend researchers investigating relations of alliance and adherence with symptom change to use more objective measures. Recent work has suggested that working mechanisms might be too complex to be captured in simple causal models (57) and this might also apply to the alliance and adherence. Indeed, for example Sasso et al. (58) found that protocol adherence has different aspects and may work differently in specific subgroups. Additionally, Lorenzo-Luaces et al. (49) found that the alliance-outcome association was moderated by the number of previous depressive episodes, also suggesting that the relationship between alliance and outcome can be different for different patients. We advocate further investigation of moderators of alliance-outcome and adherence-outcome relationships. Most importantly, however, our work underlines the importance of distinguishing the perceived helpfulness from the more pure relationship items of the HAq-I when examining therapeutic alliance and we recommend future investigations of therapeutic alliance to use an instrument not containing items that may also measure therapeutic progress as this can potentially bias results.

### Conclusions

We examined the temporal associations of therapeutic alliance and manual adherence with depressive symptom change in adult outpatients receiving CBT for depression. We found no association of CBT manual adherence with prior nor with subsequent symptom change. Similarly, we did not find therapeutic alliance to be related with prior nor with subsequent depression change in our primary analyses, in which we used the HAq-I type 2 subscale containing the items that purely tap the collaborative nature of the alliance. Thus, we were not able to replicate prior depression change in CBT for depression to be associated with improved quality of the therapeutic alliance. Our findings indicate the need to appropriately distinguish between perceived helpfulness and the more pure relationship items of the HAq-I when examining therapeutic alliance.

## DATA AVAILABILITY STATEMENT

The dataset presented in this article can be accessed upon request. Requests can be directed to Jack J. M. Dekker, jack.dekker@arkin.nl.

## ETHICS STATEMENT

This study was reviewed and approved by Dutch Union of Medical Ethics Trial Committees for mental health organisations. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

FD and ED wrote the manuscript. ED coordinated the data acquisition. JP performed the statistical analyses. MB performed the imputations. RD contributed to the research design. JD an JS lead the research project. All authors provided comments and read and approved the final manuscript.

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# Disentangling Trait-Like Between-Individual vs. State-Like Within-Individual Effects in Studying the Mechanisms of Change in CBT

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Hofmann et al. argued that "[w]hile the clinical field has produced a dizzying number of treatment models and treatment protocols for virtually every psychiatric and psychological problem imaginable, increases in understanding of the processes of change in psychotherapy has been slow to arrive." We propose that one of the reasons for the slow progress is that prior psychotherapy research conflates trait-like and state-like components of mechanisms of change. Trait-like components can serve as prescriptive or prognostic variables, whereas state-like components reflect within-client processes of change, and may highlight active ingredients of successful treatment. Distinguishing between the two is essential for clarifying the underlying processes of change in psychotherapy, and ultimately identifying empirically-derived individualized treatment targets. We review studies that implement methodological and statistical approaches for disentangling the two. These studies clarified particular mechanisms of change that may operate in a given treatment, highlighted differences in the processes of change between different treatments, and explored the within-individual interplay between different mechanisms of change during treatment. Examples include studies investigating the therapeutic role of behavioral, cognitive, and interpersonal skills, as well as emotional processing. We conclude with suggestions for future research, including attention to diversity, improved measurement to facilitate a reliable and valid estimation of trait-like and state-like components, the use of appropriate statistical approaches to adequately disentangle the two components, integration of theory-driven and data-driven methods of analysis, and the need to experimentally manipulate the state-like changes in a given mechanism of change to strengthen causal inferences.

**Keywords: personalized treatment, mechanisms of change, process of change, between-individual effects, within-individual effect, State-like, Trait-like**

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## INTRODUCTION

Theoretical conceptualizations of the mechanisms underlying psychotherapeutic change refer to dynamic, multivariable processes which unfold over the course of treatment (1). Within-client state-like changes in theory-specified mechanisms of change are assumed to contribute to reductions in symptoms and improvements in well-being. Researchers in many fields of science have shown that the trait-like qualities of a construct and state-like changes in it over time

are meaningfully distinct entities and critical to disaggregate (2). One commonly used example illustrating the importance of disentangling trait-like and state-like components of the same construct is the association between typing speed (number of words typed per minute) and the percentage of typing errors made (3). At the between-individual or trait-like level, there is an inverse association: individuals who type faster tend to make fewer mistakes than those who type more slowly. In contrast, at the state-like level (i.e., within individuals), the association between typing speed and typos is positive: the faster one types, the more errors one is likely to make. As another example of the need to disentangle trait vs. state level effects, individuals who exercise more are, on average, at decreased risk of a heart attack relative to those who do not. However, at the individual level, one is at a higher risk of a heart attack during intensive exercise relative to at rest (4). A third example in which trait-like and state-like effects show opposite directions is of the effect of self-efficacy on performance. Whereas the trait-like effect of self-efficacy on performance is positive [individuals with higher self-efficacy show better performance; (5)], the state-like effect is negative [a state-like boost in self-efficacy may result in poorer performance; (6)], due, perhaps, to overconfidence in one's abilities.

As these three examples demonstrate, effects examined at the trait-like vs. state-like level can not only be inconsistent, but even opposite in direction. In addition, as described in more details below, trait-like level characteristics may moderate state-like effects (e.g., the within-individual association of exercise on heart attack risk is moderated by pre-existing cardiovascular risk factors). Below, we discuss the importance of disentangling trait-like and state-like effects to clarify the mechanism of change in CBT and for informing treatment selection and targets.

## KEY CHALLENGE IN THE STUDY OF MECHANISMS OF CHANGE IN CBT: CONFLATING TRAIT-LIKE AND STATE-LIKE EFFECTS

Reviews and meta-analyses on the mechanisms of change in CBT for depression suggest that CBT may improve dysfunctional thinking (7), and in turn, that cognitive change is associated with better treatment outcomes (8). However, most studies on the mechanism of change in CBT, including those focused on the core question of the role of cognitive change, are constrained in the causal inferences they can draw due to methodological limitations and have yielded mixed findings (9). For example, in the treatment of depression, a meta-analysis suggested that adherence and competence are, on average, not significantly associated with treatment outcome, with mixed findings across the included studies (10). Mixed results have also been obtained for treatments of anxiety disorders. For example, Foa and Kozak's emotional processing theory (11) was supported by some studies (12, 13) but not by others (14, 15). Similarly, the inhibitory learning theory of Craske et al. (16) produced mixed results, with some studies supporting it (14, 17) and others describing a more complex picture (18). The mixed results are so profound that in their systematic review of the literature on common factors across psychotherapies, Cuijpers, Reijnders, and Huibers (19) concluded that: "It is as if we have been in the pilot phase of research for five decades without being able to dig deeper" (p. 224).

An important factor that may help account, at least in part, for the mixed results is that most studies conflate trait-like and state-like components. As others have emphasized, it is critical to disentangle trait-like (between-individuals variance) and state-like (within-individual variance) components (2, 20), especially with the type of data generated in psychotherapy research (21). Inferences drawn from studies that do not disaggregate trait-like and state-like components can be strikingly different relative to those that do. As has been argued by Fisher and colleagues (21): "… conclusions drawn from aggregated data may be worryingly imprecise" (p. 6106). Trait-like variability refers to any variance between individuals in their traits or relatively stable characteristics. For example, within psychotherapy, trait-like characteristics may describe relatively enduring, automatic pre-treatment patterns of thoughts, feelings, and behaviors that are consistent across similar situations. Trait-like components may refer to relatively fixed entities (like many demographic variables) or to a recurring, dynamic pattern that characterizes the individual [i.e., predicable diurnal cycles in anxiety; (22)]. State-like changes may include reductions or increases in a trait-like characteristic (e.g., reduction in previously stable levels of anxiety) or deviations from a previously stable dynamic pattern (e.g., attenuation of a strong diurnal pattern of anxiety), potentially as the result of treatment. The trait-like components may serve as (a) "prognostic" (i.e., treatment non-specific) predictors – stable client characteristics that influence one's ability to benefit from any treatment (e.g., cognitive impairment or interpersonal pathology) or as (b) "prescriptive" variables (i.e., moderators) – variables that predict differential response to one treatment vs. another (e.g., CBT vs. antidepressants). In contrast, state-like components refer to within-individual variation in a construct that occur over time, such as in a mechanism of change as a result of implementing therapeutic techniques that target those mechanisms. State-like changes in those mechanisms are in turn expected to bring about changes in symptoms. The trait-like vs. state-like distinction may shed light on inconsistent earlier findings.

## BENEFITS OF DISAGGREGATING TRAIT-LIKE AND STATE-LIKE COMPONENTS

### Clarifying the Mechanisms of Change

A core feature of CBT is the focus on the acquisition of cognitive (e.g., identifying and interrogating negative automatic thoughts) and behavioral (e.g., behavioral activation) skills. To what extent does client use of cognitive and/or behavioral skills in fact contribute to depressive symptom change? To adequately address this question, the state-like component (i.e., variance in

cognitive and behavioral skills *within* clients over the course of treatment) needs to be isolated from the trait-like component (i.e., stable, between-client differences in the tendency to report generally high vs. low levels of cognitive or behavioral skills) (see **Figure 1** for a simulated example to illustrate state-like vs. trait-like effects). In a recent study, Webb et al. (23) found that client-reported use of behavioral – but not cognitive – skills predicted symptom change in CBT for depressed adolescents. The latter finding emerged when using conventional analyses (i.e., not disaggregating state-like and trait-like components). However, when disaggregating these two components, only the state-like components were significant. Specifically, and consistent with a causal interpretation, greater state-like within-individual levels of behavioral skills predicted greater depressive symptom change. The same pattern of findings emerged whether client skills were assessed from the perspective of the client themselves or from the therapist. Importantly, and similar to the abovementioned typing speed and heart attack examples, one could certainly imagine how trait-like and state-like effects could operate in opposite directions. For example, those individuals with trait-like deficits in behavioral activation (BA) skills may be more likely than those with relatively high levels of skills to benefit from BA therapy, given that the latter treatment specifically targets that skill set (i.e., *lower* trait-like skills predicts relatively enhanced response to BA). In contrast, greater state-like within-individual increases in BA skills may predict better outcomes within treatment (i.e., the opposite relation for the state-like effect). An example for such opposite directions of trait-like and state-like components comes from a study by Rubel and colleagues (24). In their study, higher levels of state-like in-session affective experiences and involvement were associated with a greater subsequent reduction in symptoms. However, the trait-like effects were in the opposite direction: higher overall levels of affective experiences were associated with higher overall symptom severity.

Disentangling trait-like and state-like components is also important for identifying which techniques bring about changes within individuals. For example, when using conventional analyses (i.e., not disentangling trait-like and state-like components), both adherence to identifying and evaluating automatic thoughts and adherence to negotiating therapy content with the client and structuring the session were significant predictors of treatment outcome (25). In contrast, with the trait-like vs. state-like distinction, only state-like changes in adherence to identifying and evaluating automatic thoughts predicted next-session symptom change. Such findings may help inform which techniques therapists should consider implementing in a session to bring about better treatment outcomes (26). Another example for distinct effects at the trait-like and state-like levels comes from the research on non-verbal synchrony. Recent findings suggest that at the between-individual level, trait-like non-verbal synchrony was not associated with either problem actuation or motivational clarification. However, at the within-client level, state-like non-verbal synchrony was associated with both problem actuation and motivational clarification (27).

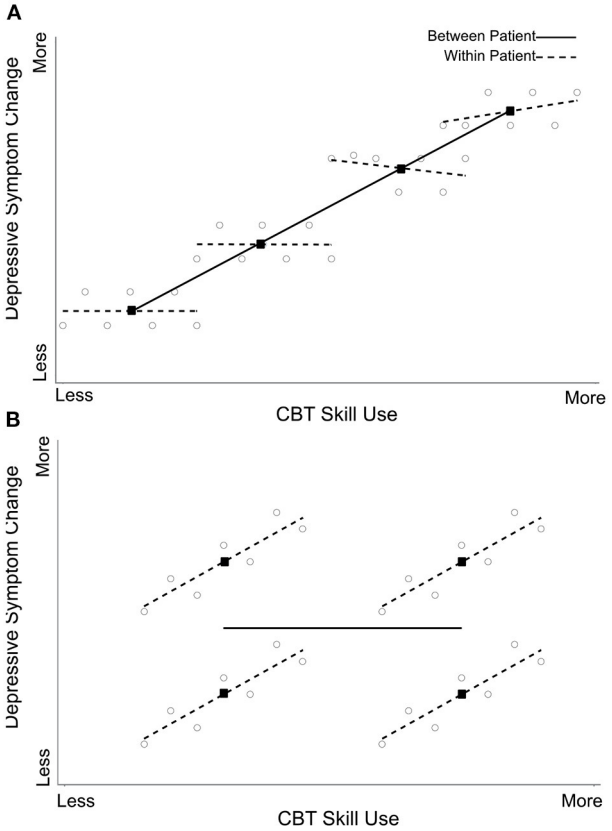


**FIGURE 1 |** Webb et al. (23) American Psychological Association. Reprinted with permission. The figure displays simulated data from four clients (seven time points per client) showing a between-client (dark line), but no within-client (dotted lines), effect of skills on symptom improvement **(A)** vs. a within-client, but no between-client, effect of skills on outcome **(B)**. Circles represent skill scores for each client at each time points, and black squares refer to each client's mean skill score.

## Identifying Differences in Mechanisms of Change Between Treatments

One of the most replicated findings in psychotherapy research is that treatments conceptualized as working via different mechanisms often show similar outcomes at the end of treatment [commonly referred to as the *Dodo Bird Verdict*, (28, 29)]. Based on this finding, many scholars have argued that all treatments work through the same mechanisms, and consequently questioned the claim that different treatments have unique mechanisms of change. We argue that the trait-like vs. state-like distinction may have the potential to reveal different mechanisms of change underlying distinct treatments. Of relevance, a recent study (30) comparing exposure-based cognitive therapy (EBCT) and cognitive-behavioral therapy (CBT) for depression found that although EBCT augments CBT by the addition of exposure-based strategies, no significant differences between the two conditions emerged in their treatment outcomes. After making the trait-like vs. state-like distinction (using a centering approach), however, EBCT was

found to result in greater state-like increases in emotional processing during treatment and higher self-efficacy during follow-up relative to CBT, both of which were associated with better long-term depression outcome (31). One potentially fruitful avenue for future research is to identify individuals who may benefit most from integrating emotional processing strategies. For those individuals, EBCT may result in better outcomes than CBT, given that the former treatment directly targets emotional processing. Another example comes from research on the working alliance, which is commonly referred to as a non-specific common factor. Studies suggest that trait-like differences in the alliance between patients are indeed associated with treatment outcome across different treatments, with stronger alliances being linked to better outcomes (32). However, in treatments that directly focus on the alliance as a mechanism of change (e.g., brief relational treatment), SL changes in alliance were stronger predictors of subsequent treatment outcome, than in treatments where the alliance is typically not considered a main mechanism of change (33, 34).

## The Longitudinal Interplay Between Different Mechanisms of Change

Although studies commonly focus on a single mechanism of change, the reality of clinical practice teaches us that for a given individual a variety of factors – and complex interactions among them – are contributing to symptom change. For example, state-like changes in one mechanism may be moderated by trait-like levels of another, suggesting that the processes or mechanisms of change may differ as a function of identifiable client characteristics, and thus answering the question for whom a given therapeutic procedure may be most beneficial. For example, Fitzpatrick et al. (35) explored the question of who benefits most from cognitive change in cognitive therapy for depression. After disaggregating state-like and trait-like components of cognitive change, using a centering approach (20), the authors found that clients with poorer trait-like interpersonal skills and greater trait-like interpersonal problems exhibited a stronger relation between state-like changes in cognition and symptom improvement.

Moreover, state-like changes in one mechanism may be moderated by state-like changes in another. This type of interaction may suggest *how* two mechanisms of change interact to bring about therapeutic change. Interactions between state-like components of two or more mechanisms or other process variables may also guide clinical decisions on *when* to target a specific mechanism. Specifically, state-like changes in process variables may provide useful and actionable information about the optimal timing for implementing procedures that target a specific mechanism of change. In this case, the interaction may suggest *when* (i.e., at which levels of the process variable) state-like changes in a particular mechanism of change are most beneficial in bringing about therapeutic change. For example, Zilcha-Mano (36) found that state-like improvements in alliance at a given session result in subsequent reduction in symptoms only in the case of higher sense of life satisfaction at that session, thus suggesting when it may be most therapeutically beneficial to implement techniques for strengthening the alliance.

Interactions between trait-like and state-like components of the same construct may be of particular interest, because they may contribute to progress toward precision medicine (37). Such interactions serve as a test of two contrasting hypotheses: building on clients' relative weaknesses vs. capitalizing on their strengths (38). A recent meta-analysis based on individual level data from 5,350 individuals suggested that the effect of state-like changes in alliance on outcome was stronger for individuals with stronger trait-like alliance (39). This finding supports the capitalizing on the clients' strengths hypothesis: those with stronger trait-like alliance are the ones who derive the most therapeutic benefit from state-like gains in the alliance. Building on the BA example above, individuals with relatively higher baseline competency in BA skills may be more likely to take advantage of a BA treatment that capitalizes on their pre-existing strengths (40, 41). Whereas the latter example is consistent with a "capitalization" model, one could also imagine a "compensatory" model [i.e., individuals with trait-like deficits in BA skills benefit the most from a treatment (BA) that directly targets their deficit].

The examples so far focused on moderation. However, another way in which state-like changes in two variables can relate to each other is by one preceding the other, in a within-client mediation model, to delineate the *temporal process of how therapeutic change occurs*. For example, Schmidt et al. (42) found that immediate state-like cognitive changes predicted sustained cognitive changes, which in turn predicted treatment outcome.

# WHAT DOES THE FUTURE HOLD?

Below we highlight several promising directions for future treatment research disentangling state-like within-person vs. trait-like between-person effects.

## Better Measurement Will Facilitate a More Reliable and Valid Estimation of the Trait-Like and State-Like Components

When distinguishing between trait-like and state-like components, the ability to capture dynamic patterns is critical. Based on an accurate assessment of baseline trait-like dynamics, it is possible to investigate not only whether the individual's average values of a construct have changed, but also whether the trait-like dynamics have changed. For example, mean level of negative affect (NA) may change as a result of effective treatment, and the dynamic pattern of the individual may change as well (e.g., attenuated fluctuations in NA; **Figure 2**). Capturing this dynamic before, during the course of, and after treatment requires frequent sampling of NA in the daily lives of individuals. Given the omnipresence of smartphones, ecological momentary assessment (EMA) has become increasingly popular in psychological research and holds promise for psychotherapy studies investigating relevant state-like within-person vs. trait-like between-person processes.

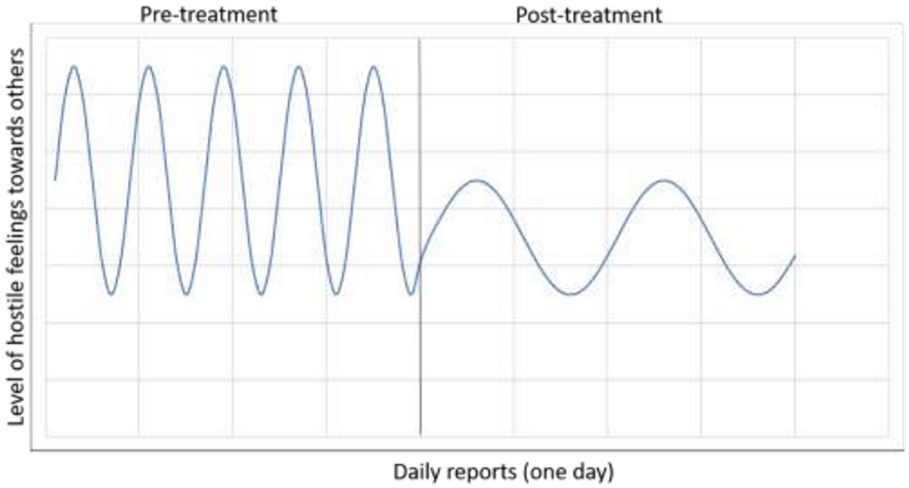


**FIGURE 2 |** A demonstration of change in both the overall mean level of a construct and in its dynamic pattern as the result of treatment. The client started treatment with a generally high level of negative affect, and specifically, higher levels of hostile feelings toward others, characterized by a pattern of frequent and extreme daily reports of hostility. In the course of treatment, the overall mean level of hostile feelings was reduced. The dynamic pattern changed as well, the client displaying less frequent and less extreme hostility toward others.

In addition to EMA, the expansion of "passive" (i.e., no user input required) measurement methods also holds promise for examining predictors and processes of change, including sensor data (e.g., activity levels and movement from accelerometer and GPS, proxies of social interaction from call and text meta-data) from smartphones and wearables (43), as well as other markers based on motion (44, 45), acoustic and language style (46–48) and physiology (49). The extent to which biological variables, such as hormones (50), neuroimaging (51–53) and inflammatory biomarkers (54), provide incremental predictive validity above conventional (and less costly and time-consuming) self-report measures is also an important area of research (55).

## The Use of Appropriate Statistical Analyses for Disentangling Trait-Like and State-Like Components

The trait-like vs. state-like distinction requires specialized statistical approaches to disaggregate and analyze these two components. First, it is important to use the appropriate methods to make the distinction, which fit the type of the data collected (20), and it is equally important to use appropriate statistical methods in analyzing each of the two components. Many statistical methods currently being used to analyze psychotherapy data are suitable for handling the trait-like components of mechanisms of change, but not the state-like components. For example, the analyses conducted to identify factors at the basis of the majority of available self-report scales are appropriate for trait-like components, but not for state-like components, and yet the same scales are often used to assess within-subject, should be within-individual. Factor structures of a scale for trait-like and state-like components of the same construct may differ (56). It is essential, therefore, to use the factor analyses that are suitable for state-like data. As another example, Group Iterative Multiple Model Estimation [GIMME; (57)], based on a unified structural equation modeling [uSEM; (58)] framework, integrates within-individual (idiographic) and conventional between-individual (nomothetic) modeling. Specifically, GIMME estimates subject-specific associations, as well searches for commonalities between individuals in those relations (59). With sufficient data points per individual (e.g., repeated EMA of relevant mechanism of change variables and outcome assessments), GIMME may allow psychotherapy researchers to estimate common patterns in mechanisms of change across clients, while simultaneously capturing individual-level heterogeneity in those variable relations (i.e., client-specific patterns). A detailed discussion of GIMME, and related approaches, is beyond the scope of this review. However, it is important to note that there are a number of assumptions that should be met with such time series data (e.g., stationarity, approximately equal time intervals between assessments, continuous variables; see (59, 60).

## Integration of Theory-Driven and Data-Driven Methods of Analysis

Data-driven approaches have been increasingly common in psychotherapy research in recent years and may have fruitful applications for research focused on trait-like vs. state-like distinctions (40, 61, 62). As one example from relationship science, a team of researchers recently sought to predict the construct of relationship quality (63). Using a machine learning approach with a total sample of 11,196 and 2,413 potential predictors, the researchers discovered a similar pattern of findings to those that have accumulated in many fields of science: the trait-like and state-like components of relationship quality produce distinct patterns. Up to about half the variance in the trait-like component of relationship

quality can be explained by the individual's baseline trait-like predictors (e.g., attachment avoidance). By contrast, the variance of the state-like component of relationship quality (that is, relationship quality change) was largely unpredictable. Similar results demonstrating the differences in predicting trait-like vs. state-like components were obtained regarding other constructs [e.g., (64–66)]. With regards to research investigating mechanisms of change in psychotherapy research, recent work has revealed the challenges in identifying predictors of the state-like effect of alliance on outcome (62), although some promising results have been obtained when a variety of potential interpersonal predictors were used (67). Promising results have also been obtained in a recent study using a machine learning approach to predict client-specific skill-affect associations based on baseline clinical and demographic characteristics (59). These preliminary findings on the implementation of machine leaning approaches to identifying predictors of state-like effects stress the importance of thoughtful selection of relevant predictors in future trial designs, as well as consideration of a variety of machine leaning-related analytical approaches. It is also worth noting that computational models of psychological change and recovery that attempt to directly emulate the psychological mechanisms occurring within each individual client may contribute to progress in psychotherapy research toward precision medicine (68).

### Demonstrating Causality

Establishing a correct temporal relationship between state-like changes in a mechanism of change and subsequent symptomatic change is important in progress toward inferring causality, but a more direct (experimental) test of the effect of state-like manipulation is needed. Examples of direct manipulation of mechanisms of change include the administration of D-cycloserine and hydrocortisone as facilitators of inhibitory learning in exposure therapy (18), as well as the direct modulation of brain function connectivity using approaches such as transcranial magnetic stimulation (TMS) of the cerebellar midline (69).

### Attention to Diversity

Different mechanisms of change may be at play for different populations. As Hollon (70) has argued, moderated mediation models can improve the precision of the tested mediation model because they take into account the different processes that may come into play for different individuals. Potential moderators may include clinical symptoms [e.g., therapists adherence to cognitive techniques may play a relatively more prominent role in contributing to symptom change among clients with more severe depressive symptoms, (71); whereas the reverse may be the case with regards to the alliance, (39)] and socio-demographic variables [e.g., adherence to cognitive techniques may be more critical for women than men (72)]. Attention to such diversity may contribute to more contextually appropriate implementations of therapeutic procedures to bring about state-like changes in specific mechanisms of change.

## SUMMARY

Although studies focused on the mechanisms of change in psychotherapy have been published at a rapid rate, our understanding of underlying processes of change has made slow progress and produced contradictory results. In the present article, we propose that one contributing factor to the slow advance and the mixed results is the conflation of trait-like and state-like components of individual mechanisms of change. As has been demonstrated before, the two components have distinct meanings and play different roles in treatment (37), and studies can yield very different findings depending on whether these two components are conflated or disaggregated (21, 32).

As reviewed, studies leveraging methodological and statistical approaches to disaggregate trait-like and state-like components can yield important findings on the processes of psychotherapeutic change, including: (a) clarifying within-client mechanisms of change in CBT (as in the example of state-like changes in behavioral skills predicting a reduction in depressive symptoms, **Figure 1**); (b) identifying differences between treatments in putative mechanisms of change (as in the example of the mechanisms targeted in ECBT vs. CBT); and (c) exploring the interplay between mechanisms of change in the process of bringing about therapeutic change, with the aim of clarifying the optimal circumstances and timing for targeting any given mechanism or a series of mechanisms (such as interactions between trait-like and state-like components of multiple mechanisms of change to answer the questions for whom, when, and how to implement given therapeutic procedures). It is of course important to note that disaggregating state-like and trait-like effects is relevant to psychotherapy research more broadly, and not just CBT (37).

We are optimistic about the future of psychotherapy science implementing the trait-like vs. state-like distinction using interdisciplinary approaches. The accumulation of data making this distinction will be instrumental in building clear and detailed links between evidence-based procedures (e.g., exposure, mindfulness practices) and evidence-based mechanisms and processes (e.g., cognitive flexibility and diffusion/distancing)(1).

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

SZ-M and CW contributed equality to conceiving the presented ideas and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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GENERAL COMMENTARY
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# Commentary: A Computational Theory of Mindfulness Based Cognitive Therapy from the "Bayesian Brain" Perspective

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**A Commentary on**

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## INTRODUCTION

In their seminal paper, Manjaly and Iglesias (1) introduce a theoretical model of the neurocomputational underpinnings of Mindfulness Based Cognitive Therapy (MBCT). Taking a "Bayesian brain" perspective, they propose a promising framework that seeks to answer a question that remains at the frontier of neurosciences: "How does mindfulness work?". The authors claim that mindful functioning increases the precision of likelihood (i.e., the precision of incoming sensory information), but decreases the precision of prior (i.e., the precision of internal model prior to receiving new sensory evidence), thus reducing the significance of prediction error (which is the discrepancy between the prior and the likelihood).

Manjaly and Iglesias propose that the being mode in mindfulness (i.e., accepting whatever sensations arise) may enhance the precision of likelihood by promoting attentional skills, notably the ability of focused attention, which enables individuals to access an extensive sensory experience (2). In our own recent work, we suggested that attentional amplification in mindfulness could result in a lower consciousness threshold, thus facilitating the access of sensory information to the global neural workspace [(3); for a review of the global neural workspace theory, see (4)]. Consequently, the increased quantity of (sensory or metacognitive) evidence that is consciously processed may improve the precision of information (likelihood).

Nevertheless, we disagree on a second point, which argues that mindfulness could be associated with prior that is less precise (i.e., less informative), resulting in low reactivity (1). Even though such a computational mechanism could account for reduced reactivity (in the sense of active inference), we believe that it is clearly inconsistent with the first computational mechanism—the increased precision of likelihood. The brain is a dynamic system in which events are intrinsically dependent—one experience will impact the next. Thus, a more precise likelihood at time $t$ is expected to lead to a more precise prior at time $t+1$. Indeed, the process of updating beliefs integrates new and old information (from present and past experience, respectively) to improve future predictions. Consequently, the precision of priors should gradually increase as mindful experience accumulates (**Figure 1**).

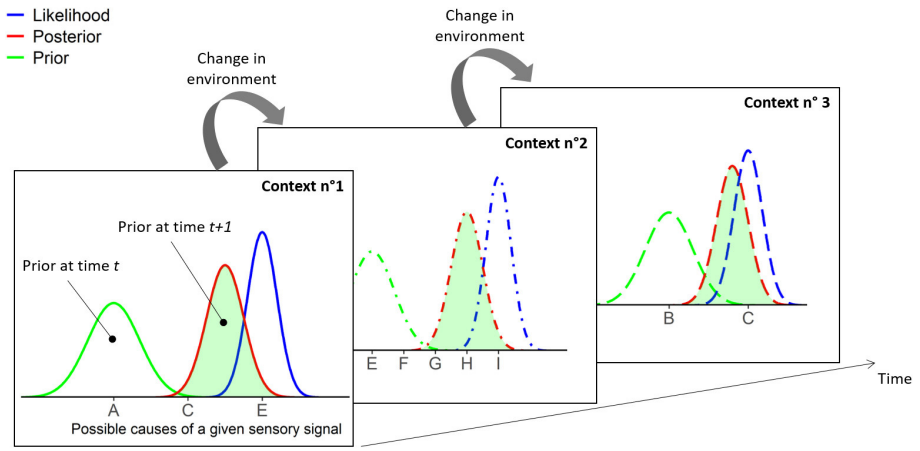


**FIGURE 1 |** Graphical summary of two neurocomputational mechanisms through which mindfulness may work. First, mindfulness increases the precision of likelihood (i.e., the precision of incoming sensory information), by decreasing the threshold of conscious access through attentional amplification. Thus, at time *t*, belief is updated by integrating the more precise likelihood and the prior (i.e., the internal model prior to receiving new sensory evidence), which leads to a more precise posterior. Consequently, the newly updated prior at time *t+1* (green area), which is equivalent to the posterior at time *t*, shows an increased precision. Second, the attentional pattern of mindfulness, which is executed "moment to moment," enables the prior belief to be optimally adjusted to the context of present experience. Thus, prior beliefs are iteratively updated as changes in environment occur over time. This dynamic process makes it possible to continuously minimize prediction error, which is the discrepancy between the prior and the likelihood, as the former is the best suited to the present context.

It should be noted that, to keep behavior adaptive, the prior precision must not exceed the likelihood precision. Indeed, in cases in which prior becomes more precise than likelihood, one would expect that individuals become less adaptive because they are less inclined to change when receiving new information.

## THE CONTEXT-UPDATING HYPOTHESIS

Learning from (sensory) experience contributes to make an agent's prior (internal model) more precise, by reducing the range of possible causes of an input in relation to the context of experience. In other words, given an input and a context, possible causes are limited on the basis of contextual elements of past experience. Consequently, the probabilities of (remaining) causes increase, as well as the precision of prior, as experience accumulates.

Here, we argue that mindfulness is characterized by optimal adjustment of prior beliefs to the context of present experience, which contributes to minimizing prediction error. The attentional pattern of mindfulness, which is executed "moment to moment" (2, 5), could enable prior beliefs to be timely updated as a function of the present context.

Sensory information is continuously processed unconsciously. Conscious access, on the other hand, is thought to start when attention amplifies a given piece of information and allows it to access the global neural workspace (4). The context-updating theory suggests that a belief (mental representation) is updated when the individual receives a new piece of information indicating a change in the environment. After initial sensory processing, a process of comparison evaluates the representation of the previous context and, if new evidence is detected, the representation is updated (6). By linking the global neural workspace model and context-updating theory, we propose that the attentional pattern of mindfulness, which is executed "moment to moment," may enable gradually more precise priors to be optimally updated as a function of the context of present, conscious experience. This dynamic, moment-to-moment process could help to minimize the prediction error by limiting the discrepancy between the likelihood and the prior, as the latter is expected to be the most appropriate given the present context. Our hypothesis may be represented graphically by iterative updating of prior beliefs as changes in environment occur over time (**Figure 1**). This dynamic process makes it possible to continuously minimize the distance between the likelihood and the prior, which reflects the significance of the prediction error.

This computational strategy is of particular interest in our ever-changing environment, because it enables continuous adjustment of cognitive and physiological reactivity. The flexibility that is cultivated through mindfulness practice could relate to this strategy when switching between modes (being vs. doing), depending on which has greater relevance to the present context. Returning to the clinical focus of Manjaly and Iglesias' article, depression relapse is thought to result from self-reinforcing rumination, which corresponds to repetitive, negative thoughts. Within the "context-updating" framework, rumination could be described as resulting from the lack of updating of the prior, which remains fixed on a negative mental representation (belief) irrespective of emotional changes in the present context (7). Furthermore, we suggest that the efficiency of MBCT in the treatment of depression relapse, including reduced rumination (8), could rely on better

updating (flexibility) of priors as a function of the present, emotional context.

Manjaly and Iglesias provide several experimental recommendations for future empirical work testing their theoretical model. The context-updating hypothesis presented in this commentary can be tested using the hierarchical gaussian filter, which derives update equations for beliefs in considering their time-varying structure (9). Context flexibility (i.e., the ability to adjust belief as a function of current context) in mindfulness can be tested by estimating separate parameters (for priors, likelihood and prediction errors) on different temporal hierarchies. Finally, it should be noted that the context-updating framework may be applicable to other psychiatric disorders that can be seen in terms of a deficiency in context processing (i.e., context rigidity), such as the Post-Traumatic Stress Disorder (10) and schizophrenia (11).

## CONCLUSION

Manjaly and Iglesias propose a theoretical, computational framework that offers a promising way to investigate the mechanisms through which mindfulness improves health and well-being. However, it appears to us that a core mechanism in their model—namely, the decreased precision of prior—conflicts with the mechanism of increased precision of likelihood. We suggest that mindfulness could be characterized by the increased precision of prior, because of the increased precision of likelihood, and the dynamic updating of prior beliefs to the context of the present experience, which ultimately lead to optimal active inference.

## AUTHOR'S NOTE

The opinions or assertions expressed herein are the private views of the authors and are not to be considered as official or as reflecting the views of the French Military Health Service.

## AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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# The Use of Digitally Assessed Stress Levels to Model Change Processes in CBT - A Feasibility Study on Seven Case Examples

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In psychotherapy research, the measurement of treatment processes and outcome are predominantly based on self-reports. However, given new technological developments, other potential sources can be considered to improve measurements. In a feasibility study, we examined whether Ecological Momentary Assessments (EMA) using digital phenotyping (stress level) can be a valuable tool to investigate change processes during cognitive behavioral therapy (CBT). Seven outpatients undergoing psychological treatment were assessed using EMA. Continuous stress levels (heart rate variability) were assessed via fitness trackers (Garmin) every 3 min over a 2-week time period (6,720 measurements per patient). Time-varying change point autoregressive (TVCP-AR) models were employed to detect both gradual and abrupt changes in stress levels. Results for seven case examples indicate differential patterns of change processes in stress. More precisely, inertia of stress level changed gradually over time in one of the participants, whereas the other participants showed both gradual and abrupt changes. This feasibility study demonstrates that intensive longitudinal assessments enriched by digitally assessed stress levels have the potential to investigate intra- and interindividual differences in treatment change processes and their relations to treatment outcome. Further, implementation issues and implications for future research and developments using digital phenotyping are discussed.

**Keywords: ecological momentary assessments, digital phenotyping, process and outcome research, outcome monitoring, abrupt changes**

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## INTRODUCTION

The effectiveness of psychotherapy for the treatment of mental disorders has already been demonstrated in numerous meta-analyses, with outcomes comparable to and in some cases more durable than pharmacotherapy [e.g., (1–3)]. However, there is still room for improvement. Currently, about two thirds of all patients benefit from psychological treatments, yet some patients do not and 5–10% of patients even show deterioration (4). Furthermore, a significant number of patients (ranging from 18.5 to 46.5%) will experience a recurrence of their symptoms, even if they initially responded to treatment (5). These findings underline the urgency of improving psychological treatments, including cognitive behavioral therapy (CBT).

One attempt to increase the chances of treatment success for the individual patient is the call for a transdiagnostic treatment personalization [e.g., (6, 7)]. Accordingly, interventions should be personalized and adapted to each patient, consistent with patients' specific intake profiles, idiographic needs or therapists' skills [e.g., (8–12)]. This implies moving away from using treatment packages in a uniform manner and adapting CBT treatment based on patient-specific factors. Another aspect of personalization is to take a closer look at patient's' change processes[1] over the course of treatment by repeatedly assessing outcome variables and monitoring progress [e.g., (13)]. Thereby, patients at risk of treatment failure may be identified at an early stage, which can then be reported directly back to the therapist. Monitoring therapy is particularly relevant in view of the assumption that psychotherapy progress is often non-linear and characterized by abrupt changes in symptom reduction, i.e., sudden gains (14) or sudden losses (15). Research has shown that both of these abrupt changes have a significant impact on treatment outcome. Sudden gains are associated with larger pre-post effect sizes, while sudden losses are predictive of negative outcome (16, 17). Identifying those two groups and giving feedback regarding problematic developments could help therapists adapt treatment individually (6). One example of providing personalized information to support therapists in their everyday decision-making is the Trier Treatment Navigator (TTN). Therapists are provided with personalized pre-treatment recommendations, prediction of drop-out risk, prediction of the optimal treatment strategy, a dynamic risk index to identify patients at risk for treatment failure as well as clinical problem-solving tools for personalized treatment adaptation (13, 18).

In addition to sudden symptom changes, emotional dynamics such as resistance to emotional change or inertia have been identified as potential and useful candidates to provide an early warning signal for change in depression symptoms (19). For instance, higher levels of inertia in both positive and negative affect have been found to be associated with depression and lower self-esteem (20). Furthermore, Nelson et al. (21) found higher levels of inertia in negative affect in depressed patients than in healthy controls.

One promising strategy applied to capture inertia is the use of intensive repeated measures of clinically-relevant constructs via Ecological Momentary Assessments [EMA; (22, 23)]. This method tracks participants' experiences over time in real-time and real-life situations. Self-report variables are usually collected using mobile devices several times a day and over several days. The advantages of EMA include potentially enhancing the description of within-person processes and dynamics due to overcoming retrospective biases, more frequent measurements, greater ecological validity, and increased accuracy (24). In clinical psychological research, EMA has been recently used to track a variety of patients' experiences such as perceived stress (25), symptom-related distress (26), mood and anxiety symptomatology (27), and more. Furthermore, pre-treatment fluctuations in positive and negative affect collected via EMA have been shown to predict early treatment response (28) and the prediction of patients' dropout probability has been improved using network analysis based on EMA (29). However, so far, the concept of inertia has not been extended to biological rhythms such as stress level.

To date, EMA have predominantly relied on self-report data. Recently, other sources of information have come into the picture, e.g., using passive data from personal digital devices such as smartphones to quantify moment-by-moment data. The collection of data from patients in their naturalistic settings via smartphones or other personal digital devices is defined as digital phenotyping (30). The large amount of data collected by smartphone-based digital phenotyping provides an opportunity to develop precise disease phenotypes or diagnostic markers (30) and to enhance EMA (31). Since physical activity, heart rate variability, and sleep are often associated with health outcomes, recent studies have focused on using digital phenotyping to examine their significance in psychotherapy (32, 33). For instance, Jacobson et al. (34) used actigraphy data to identify participants' diagnostic group, i.e., major depressive disorders and bipolar disorders, due to their specific and notable patterns of movement and light exposure. While depressed patients mostly showed decreased activity levels, increased levels of activity were found in patients with bipolar disorder (34). Besides identifying diagnostic groups, Jacobson and Chung (35) used passive sensor data from smartphones and wearable sensors to predict major depressive disorder severity and changes in severity across days and weeks. In view of the results and conclusions of the above-mentioned studies, it can be assumed that the integration of digital phenotyping will provide useful contributions to psychotherapy research. Nevertheless, there has been little research on how individual change in digital phenotypes (e.g., stress level) could enhance the investigation of change processes and their relation to treatment outcome.

The aim of the present feasibility study was to examine whether digitally assessed stress levels via EMA can be a valuable tool to investigate change processes during CBT. A recent model to detect both gradual and abrupt changes (36) in biological inertia is applied to passive stress data to detect individual differences. In addition, the relationship between assessed stress levels and outcome measures is being investigated to examine the predictive validity of the digital parameter.

# METHODS

## Participants and Study Design

The sample consisted of seven patients who started CBT treatment between December 2019 and March 2020 in the outpatient clinic of the University of Trier. The two-week EMA period was integrated into the clinic's regular care process and took place within the diagnostic phase. All patients filled out pre-treatment questionnaire packages, along with questionnaires every fifth session as a part of the clinic's routine assessment.

[1]In the following, we will not investigate a specific psychotherapeutic process or mechanism of change. Rather, our focus is on small steps of the change process itself, measured by a psychological distress variable. In other words, we do not investigate variables, which might causally influence change, such as cognitive change or the therapeutic alliance. Instead, we investigate the within-patient change process in a fine grained way (12).

A detailed description of the pre-treatment and the progress assessments can be found in the measures section, while **Figure 1** is portraying the study design. In addition, the Structured Clinical Interview for DSM-IV-TR Axis I Disorders [SCID-I; (37)] was conducted by trained therapists to assess diagnoses during the diagnostic phase.

The invitation to participate in the study, detailed patient information, a declaration of consent and terms of use were sent to the patients by mail upon agreement to the regular initial interview appointment, which was conducted by experienced psychotherapists in training or licensed CBT therapists. During the initial interview, willingness to participate in the study, the exclusion criteria, and the acute need for treatment were clarified. Exclusion criteria for study admission were (a) current suicidal tendencies, (b) current mania and (c) current psychosis. All patients who did not meet the exclusion criteria were invited to participate in the study. Before the study, each patient was informed that he or she can stop the study at any time without giving reasons and without suffering any disadvantages. Following the regular initial interview, patients who agreed to participate in the study received an introductory meeting (see **Figure 1**). Here, the participants were handed out the fitness tracker, the app was installed and linked to the fitness tracker, furthermore the handling of the tracker and the app were explained. In addition, a hotline was made available to patients in case of open questions or technical difficulties.

## Measures

### Pre-assessment and Progress Measurements Every Five Sessions

This section describes all relevant measures that are included in the study and are part of the clinic's routine assessment. The routine assessment includes questionnaire packages before and after treatment as well as every five sessions. The Hopkins Symptom Checklist-11 [HSCL-11, (38)], an 11-item self-report inventory for the assessment of symptomatic distress, is a brief version of the Symptom Checklist-90 [SCL-90-R; (39)] that correlates highly with the global severity index of the SCL-90-R ($r = 0.91$), and has high internal consistency [$\alpha = 0.92$; (37)]. The Outcome-Questionnaire-30 [OQ-30; (40)] is a 30-item self-report measure designed to assess patient outcomes during the course of therapy, which can be aggregated to create a total score. It is a short form of the OQ-45 with which it demonstrates high levels of congruence (40). The Patient Health Questionnaire-9 [PHQ-9; (41)] is a widely used, reliable and valid assessment of depression severity. It consists of nine self-reported items and is rated from 0 to 3, resulting in an overall severity score ranging between 0 and 27. The Generalized Anxiety Disorder Scale-7 [GAD-7; (42)] is a symptom-specific instrument measuring anxiety disorder severity. It consists of seven items and is rated from 0 to 3, resulting in an overall severity score between 0 and 21 (42). Additionally, socio-economic data, such as age, gender, employment, and education status, were collected.

### EMA Variables

EMA data was collected using a fitness tracker (Garmin *vivo* smart 4) and the corresponding app (Garmin Connect) for digital phenotyping. During the 2-week period, participants were encouraged to only take off the fitness tracker to recharge it. Heart rate, stress level, intensity minutes, movement (in steps and distance), calories, sleep duration and phases such as lighter sleep, deep sleep, being awake or REM sleep were measured. Stress level was measured every 3 min (6,720 measurements) and was based on heart rate variability. To measure stress level, Garmin is using Firstbeat Technologies Ltd., which analyzes stress from heart rate measurements. To detect heart rate, Garmin is using photophlethysmography (PPG). PPG utilizes an emitter that emits light and a detector that measures how much light is

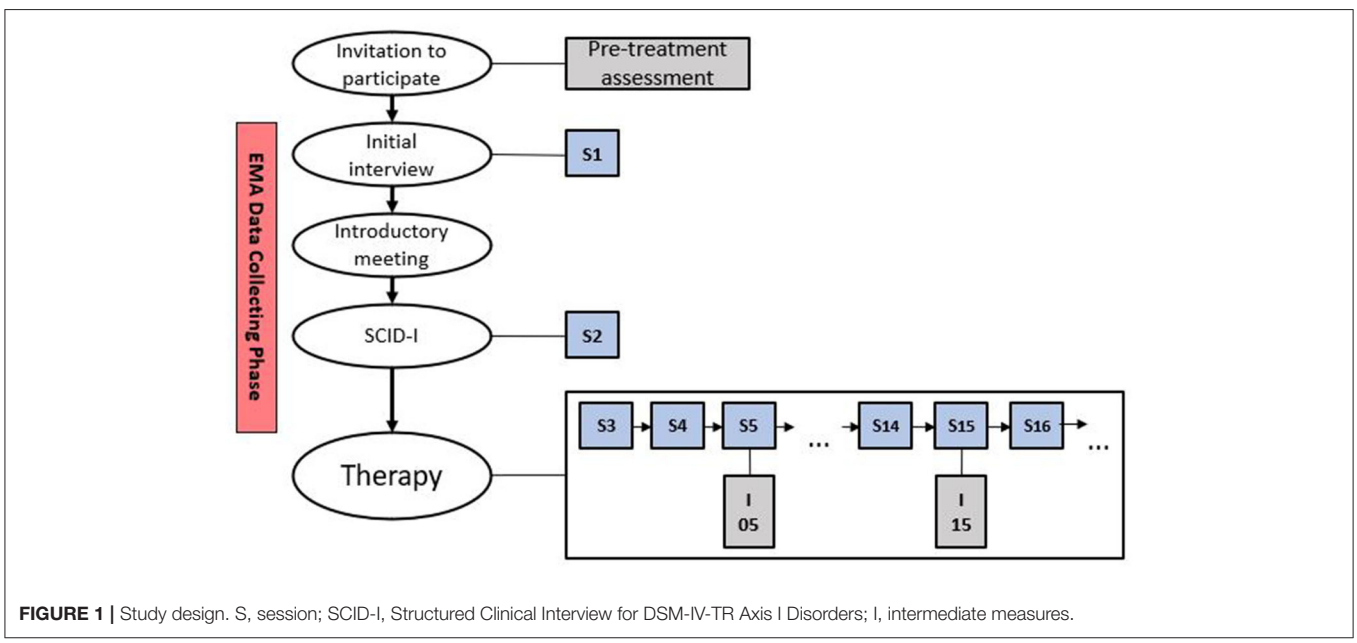


**FIGURE 1 |** Study design. S, session; SCID-I, Structured Clinical Interview for DSM-IV-TR Axis I Disorders; I, intermediate measures.

reflected, to estimate heart rate. Several factors influence the reflection of light, e.g., blood arteries absorb light better than the surrounding body tissue. The intensity of reflected light rises and falls with the contracting and swelling of the arteries as the blood pulsates. To get an insight into the performance and reliability of wearable devices, several studies have compared the results of those devices with electrocardiography (ECG) chest straps that were used at the same time (43–46). Collins et al. (44) and Bent et al. (46) found accurate results for resting heart rate when investigating several devices, among others, the Garmin *vivo* smart. However, devices differed when responding to change in activity (44, 46). Pasadyn et al. (45) investigated the response of different devices during six different treadmill speeds. The Lin's concordance correlation of the Garmin *vivo* smart and the ECG was $R_c = 0.89$ (45). The heart rate variability within each monitored period serves as indicator for the calculated stress level. To detect stress, several factors must first be excluded such as physical activity, exercise movement, recovery from exercise or changes in posture (47, 48). The obtained stress level value reports the average stress level of the monitored 3 min period. Here, values of 0–25 are considered as rest or no stress, values of 26–50 as low stress, values of 51–75 as medium stress, and values of 76–100 represent high stress. Missing values occur due to physical activity or because there is not enough data to calculate the average value. Before the analysis, the EMA data were examined for suitability. The data were suitable, when participants wore the fitness tracker more than 50% of the time. The data was downloaded as CSV. First, the Garmin UTC time stamp was converted into standard Excel date-time serial numbers. Missings were coded as –1 when there was not enough data to calculate the average stress within one monitored period, and as –2 when the participant was physically active. However, the data had to be checked for further missings in the form of entire time points missing that have not been coded accordingly.

## Statistical Analysis

The calculation of inertia trough autocorrelation or by fitting an autoregressive model [e.g., (49)] brings the drawback of assuming stationarity. However, inertia is able to change over time (50). The "critical slowing down" approach examines such changes, more specifically the increase of the autocorrelation of the symptoms, and uses this as an early warning signal [e.g., (51)]. Gradual increase in autocorrelation can also be seen as an early warning signal, but since previous methods concentrated on either modeling only abrupt or only gradual changes, a method is needed that is able to detect both changes.Time-varying change point autoregressive models (TVCP-AR, 36) were employed to detect both gradual and abrupt stress level changes for each patient. The TVCP-AR model is based on the generalized additive model framework (52), which allows both intercept and slope to change gradually over time. Further, the model is also based on the structural change point model (53, 54) in which the data are divided into regimes before and after change points (CPs). The regimes differ only in the value of the intercept, which can be extended to differences in autoregressive effects. Hamilton (53, 54) uses a transition matrix to describe the probability of moving from one regime to another for each time point. The combination of these models results in the TVCP-AR model, which allows both gradual and sudden changes in the dynamics. As the exact locations of CPs for our cases were unknown, all possible options had to be considered and an exploratory search was conducted in accordance with Albers and Bringmann (36). To find sudden changes, two models were fit to the data of each patient, one model that assumes a gradual course and one that considers a CP. After fitting the model assuming gradual change to the data and denoting the corresponding Akaike Information Criterion (AIC), the second model considering CPs was fitted and the AIC value denoted. Then, the AIC value of the gradual change model was subtracted from the AIC value of the model including a CP. If results showed no or only a small AIC improvement, there was no indication of a CP. As a threshold, we chose −15 to avoid too many false positives, which is in accordance with Albers and Bringmann (36). When two CPs are too close to each other, it implies that the number of measurements between the two CPs are too low to obtain robust estimates. It is not possible for one regime to have only one measurement. CPs that are too close to boundaries of certain intervals are difficult to detect. Furthermore, a small amount of measurements within one regime hinders the next step of the TVCP-AR model, namely modeling gradual change in the autocorrelation.

Besides presenting the case examples and their gradual and abrupt changes in stress levels, exploratory analyses concerning the associations of abrupt changes with the outcome measures at session 15 were performed. First, Pearson correlations between the number of CPs resulting from the TVCP-AR models and the outcome measures as well as between stress level and outcome measures were applied. Second, to control for initial impairment, partial correlations were computed for outcome measures at session 15 with the number of CPs as well as with stress level, adjusted for the pre-treatment assessment measured with the respective instrument. All analyses were run in *R* version 3.6.2 (55) using the package *mcgv* version 1.8-33 (56).

# RESULTS

TVCP-AR models were applied and results for the seven patients are displayed in **Figure 2**. Autoregressive effects of stress level are shown for each patient and CPs are marked by vertical lines. **Table 1** first reports the mean values and standard deviations (SD) of the comparative sample from Lutz et al. (18) for the used outcome measures (HSCL-11; OQ-30; GAD-7; PHQ-9). Means for the pre-treatment assessment and outcome at session 15 are also portrayed for each outcome measure. In addition, product moment correlations of the number of CPs and of stress level with the outcome measures are shown. Furthermore, partial correlations controlling for initial impairment are presented. The pre-treatment assessment of every participant can be seen in **Table 2**, along with the session 15 assessment, which was available for six of the seven participants.

For the six patients, who provided data at session 15 (A, B, C, D, E, and G), results revealed higher correlations for the symptom specific instruments than for the HSCL-11 and OQ-30 (**Table 1**). The highest correlation of $r = 0.84$ was found between the

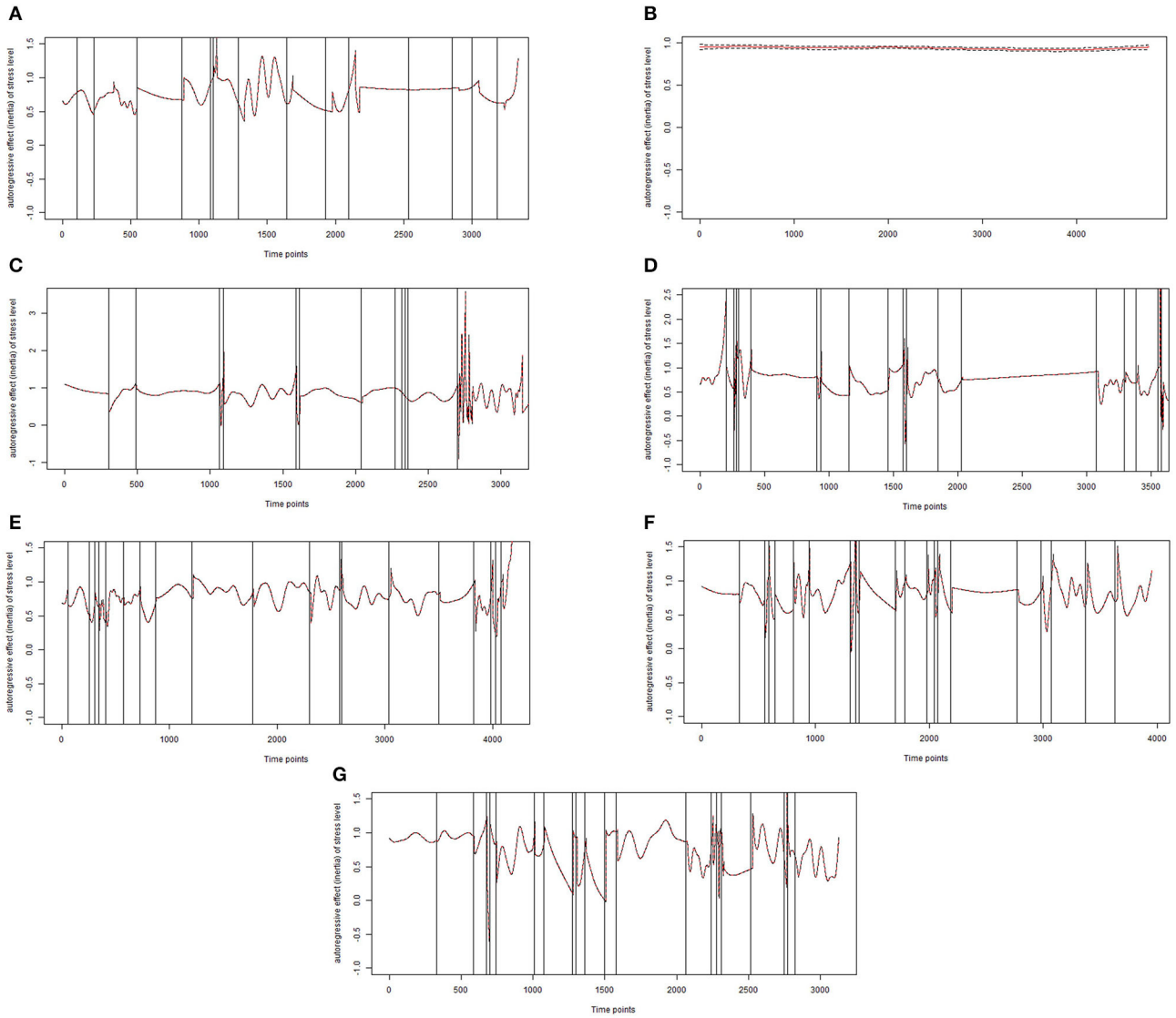


**FIGURE 2 |** Final models of inertia for stress level for patients **(A–G)**. Each vertical line represents the exact time point of a change point.

number of CPs and GAD-7. Although only the correlation with GAD-7 was statistically significant, all outcome measures were negatively associated with the number of CPs on a descriptive level at pre-treatment assessment and at session 15. Furthermore, all outcome measures were positively correlated with stress level on a descriptive level also at both pre-treatment assessment and at session 15.

Patient A was female, 24 years old[2], currently employed, and diagnosed with post-traumatic stress disorder (PTSD) and recurrent depressive disorder, current episode moderate. The patient reported in the initial interview a relatively high tension level, with tension quickly intensifying due to external stress factors such as conflicts at work or in social situations. With an HSCL-11 score of 2.09 and a GAD-7 score of 9, the patient was just below the average impairment of the comparison sample. However, according to the OQ-30 (2.03) and the PHQ-9 (15) she tended to score higher than the comparison sample. In the course of the first 15 sessions, the patient showed slightly reduced values in HSCL-11 and GAD-7 but also slightly higher values in OQ-30 and PHQ-9 (see **Table 2**). For patient A, both gradual and abrupt stress level changes were found. After excluding, the points that were too close together, a total of 15 CPs were identified during the 2-week period (**Figure 2A**). For example, two CPs were identified on day 4, at 17:54 (AIC difference of −18.96) and 20:21 (AIC difference of −28.83) and two CPs on day 6, at 08:39 (AIC difference of −40.97) and 08:48 (AIC difference of −40.41). The largest AIC difference found for patient A was −51.91 on day 14

[2]In order to preserve data protection, some of the socio-demographic variables have been slightly modified.

**TABLE 1 |** Product-moment and partial correlations of number of change points, stress level and outcome measures.

| | | Pre-Treatment | | | Session 15 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Number of CPs | Stress level | | Number of CPs | | Stress level | |
| **Outcome measure** | ***M* (SD)[a]** | ***M* (SD)[b]** | ***r*** | ***r*** | ***M* (SD)[b]** | ***r*** | ***r* partial** | ***r*** | ***r* partial** |
| HSCL-11 | 2.20 (0.65) | 2.29 (0.53) | −0.24 | 0.29 | 2.08 (0.44) | −0.18 | 0.08 | 0.13 | −0.31 |
| OQ-30 | 1.90 (0.56) | 1.99 (0.45) | −0.48 | 0.52 | 1.87 (0.37) | −0.19 | 0.24 | 0.43 | 0.10 |
| GAD-7 | 11.02 (5.06) | 12.33 (3.27) | −0.62 | 0.56 | 12.83 (5.95) | −0.84* | −0.97* | 0.68 | 0.55 |
| PHQ-9 | 12.48 (5.73) | 14.17 (4.83) | −0.58 | 0.66 | 16.00 (4.86) | −0.76 | −0.64 | 0.57 | 0.01 |

*M, Mean; SD, Standard deviation; r, Pearson product-moment correlation coefficient; $r_{partial}$ = partial correlation; HSCL-11, Hopkins Symptom Checklist-11; OQ-30, Outcome Questionnaire-30; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; CPs, change points; *p < 0.05.*

[a]*comparative sample from Lutz et al. (18), N = 377.*

[b]*N = 6, includes only patients that provided data at pre-treatment and session 15.*

**TABLE 2 |** Outcome measures at pre-treatment and session 15.

| | | Pre-treatment | | | | Session 15 | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient** | **Number of CPs** | **HSCL-11** | **OQ-30** | **GAD-7** | **PHQ-9** | **HSCL-11** | **OQ-30** | **GAD-7** | **PHQ-9** |
| A | 15 | 2.09 | 2.03 | 9 | 15 | 1.91 | 2.17 | 8 | 16 |
| B | 0 | 2.36 | 2.27 | 16 | 18 | 2.09 | 1.87 | 22 | 21 |
| C | 12 | 2.70 | 2.17 | 14 | 17 | 2.36 | 1.97 | 16 | 21 |
| D | 18 | 2.77 | 2.40 | 15 | 13 | 2.73 | 1.83 | 15 | 16 |
| E | 19 | 2.50 | 1.93 | 12 | 17 | 1.91 | 2.20 | 10 | 14 |
| F | 21 | 3.05 | 2.17 | 14 | 14 | | | | |
| G | 20 | 1.34 | 1.14 | 8 | 5 | 1.45 | 1.17 | 6 | 8 |

*N = 7 for pre-treatment; N = 6 for session 15; HSCL-11, Hopkins Symptom Checklist-11; OQ-30, Outcome Questionnaire-30; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9: CPs, change points.*

at 09:21, which clearly goes beyond our threshold of −15. When looking at **Figure 2**, the CPs occured almost regularly except for one period of time around time point 2,200–2,800, which was during the weekend when the patient did not have to go to work.

Patient B was a currently unemployed female, 22 years old, diagnosed with recurrent depressive disorder, current episode severe without psychotic symptoms, and harmful use of alcohol. Noteworthy were the patient's compulsive behavioral tendencies to control everyday life and thus, avoid stress and the tendency to withdraw in unpleasant situations. She started the treatment with higher initial impairment scores in every outcome measure (HSCl-11, OQ-30, GAD-7, and PHQ-9) compared to the outpatient sample. In addition, the GAD-7 score at session 15 was noticeably higher (total score of 22) than at the pre-treatment assessment (total score of 16; see **Table 2**). The PHQ-9 also revealed higher values at session 15, however, the values for the HSCL-11 and the OQ-30 decreased. In contrast to patient A, the TVCP-AR model for patient B detected two CPs at day 1 at 14:39 (AIC difference of −18.97) and at 15:18 (AIC difference of −15.05), which are too close to each other and to the starting point, resulting in too few measurements to obtain robust results. Therefore, the final model for patient B portrays no signs of change in autocorrelation (**Figure 2B**), which fits the patient's tendency of avoiding any kinds of stressful situations. This example shows the most constant level of inertia compared to the other patients.

Patient C was female, 23 years old, currently employed, and was diagnosed with PTSD, an eating disorder, and recurrent depressive disorder, current episode moderate. Accordingly, the patient described handling stressful situations and tending to prevent unpleasant feelings with the help of her eating habits. She tended to be more highly impaired than the average outpatient from the comparative sample, since all of the outcome measures portrayed higher scores. **Table 2** shows a slight decrease in the HSCL-11 and OQ-30 scores and a slight increase in the GAD-7 and PHQ-9 scores for patient C. Patient C showed both gradual and abrupt stress-level changes, with a total number of 12 CPs during the 2-week period (**Figure 2C**). For patient C, CPs also had to be excluded, as they were too close together, for example on day 5 at 15:18 (AIC difference of −17.5) and at 15:54 (AIC difference of −18.61). On day 13 at 14:48, the largest AIC difference of −33.16 was found. Notable are recurring longer phases without abrupt changes. Additionally, the level of inertia decreased over the course of the 2 weeks, toward the end more CPs were identified, and the AIC differences varied more widely.

Patient D was male, 44 years old, held a University degree and was currently employed, and diagnosed with recurrent depressive disorder, current episode moderate, and pain disorder exclusively related to psychological factors. Patient D also presented higher scores for the HSCL-11, OQ-30 and GAD-7 than the average of the outpatient sample. The PHQ-9 score was close to the average with a score of 13. He was the only patient who

dropped out of treatment immediately after session 15. The outcome measures HSCL-11, GAD-7 and PHQ-9 did not reveal improvement in the course of treatment, only the score of the OQ-30 was descriptively lower at session 15. After excluding CPs that were too close together, 18 CPs were identified for patient D (**Figure 2D**). He displayed abrupt and gradual changes over the course of the assessment. On day 6, five jump points took place very close to each other at 18:24 (AIC difference of −28.29), at 18:39 (AIC difference of −34.63), at 18:48 (AIC difference of −53.51), at 21:15 (AIC difference of −24.76), and at 22:09 (AIC difference of −56.01), which was the largest AIC difference for this patient. The final model included CPs at 18:24 and at 22:09 on day 6. **Figure 2** shows that, for example, for patients D (**Figures 2C,D**), besides the abrupt changes, there were also longer phases without abrupt changes compared to the other patients. Especially at the beginning of the assessment, patient D showed several CPs close to each other. However, toward the end of the assessment, a longer period of time without any CPs was observed.

Patient E was male, 25 years old, a University student, and diagnosed with recurrent depressive disorder, current episode moderate. He reported having mood swings that were associated with external stressors, e.g., work or certain social situations. The HSCL-11 score (2.50) and the PHQ-9 (17) for patient E were higher than the average of the outpatient sample. The OQ-30 and the GAD-7 scores were close to the average. The outcome measures HSCL-11, GAD-7 and PHQ-9 revealed decreased values, only the score of the OQ-30 was descriptively higher at session 15. For patient E, a gradual and abrupt pattern with 19 CPs was detected (**Figure 2E**). This patient displayed the largest AIC difference (−78.37) across the entire study, which was found on day 13 at 23:51. Especially at the beginning and end of the assessment period, several CPs were found quite close together. Additionally, in contrast to patients C and D, no longer periods of time without CPs were found for patient E.

Patient F was a currently employed male, 58 years old, and diagnosed with recurrent depressive disorder, current episode moderate, panic disorder without agoraphobia, and obsessive-compulsive disorder. Unfortunately, for patient F, process data assessed every fifth session were missing. Therefore, **Table 2** only contains his pre-treatment assessment. He revealed the highest HSCL-11 value (3.05) of the seven patients, which was one SD higher than the average HSCL-11 outcome of the comparative sample. The remaining instruments also presented scores that were higher compared to the average of the outpatient sample. Patient F displayed the highest number of CPs (21) and showed both gradual and abrupt changes (**Figure 2F**). The largest AIC difference of −69.15 was located on day 12 at 07:18. Compared to patients A, B, C, and D, CPs could be found more often and quite regularly.

Patient G was female and the oldest participant (65 years old). She was diagnosed with a moderate depressive episode. Further, she portrayed the lowest scores of the seven patients at pre-treatment assessment and at session 15 on the HSCL-11, OQ-30, GAD-7, and PHQ-9 (see **Table 2**). All outcome measurement scores were also lower than the average of the outpatient sample, specifically one SD lower for the HSC-11, OQ-30 and PHQ-9 scores. The outcome measures HSCL-11, OQ-30 and PHQ-9 did not reveal any improvement in the course of treatment and even showed slightly higher values, only the GAD-7 score was descriptively lower at session 15. Additionally, patient G showed gradual and abrupt changes, while 20 CPs were found. The CP with the largest AIC difference (−61.85) was on day 11 at 20:45. More gradual changes were observed at the beginning, at the end, and between days 8 and 10, whereas for the rest of the assessment, many CPs were visible. It is noteworthy that patients E, F and G displayed the highest number of CPs as well as the largest AIC differences for their CPs. To summarize, stress level changed both gradually and abruptly in patients A, C, D, E, F, and G, each with varying numbers of total CPs, whereas patient B showed no signs of change. Additionally, the level of inertia varied between patients with patient B portraying the highest constant level. Finally, all patients had often or constant high levels of inertia.

## DISCUSSION

The present feasibility study investigated whether individual differences of change patterns over time in digitally assessed stress rhythm can be detected using TVCP-AR models. The TVCP-AR model fitted two models to the data of each patient over the course of time, one model assuming a gradual course and one assuming an abrupt change point (CP). If the AIC improved when comparing the two models, this indicated the presence of a CP. When a CO was identified, the time series was split at the CP and both newly formed sections were also examined. This procedure was repeated for each new CP that was identified. Results showed abrupt changes in six of the seven participants, no change point was found in the time series of patient B. Furthermore, the number of CPs varied between the six participants. For patient A 15 CPs were identified, 12 CPs for patient C, 18 CPs for patient D, 19 CPs for patient E, 21 CPs for patient F, and finally 20 CPs for patient G. Such data collected from seven cases over a 2-week period was able to uncover individual differences in gradual and abrupt changes over time and differences in the number of CPs.

Correlations of stress level and change points with the strength and the development of patients' impairment over the course of treatment could also be shown. Although the number of patients was small, the findings suggest that the number of CPs is negatively correlated with several symptom measures, indicating that less change in physiological stress levels (i.e., inertia) tends to be associated with more self-reported symptoms. Furthermore, consistently higher stress levels correlated with higher self-reported symptoms. Specifically, the digitally assessed stress levels and the number of change points significantly correlated with the self-reported anxiety assessments via GAD-7 (at pre-treatment as well as at session 15).

These results, even so on a very limited database, are in line with previous studies that examined inertia of positive and negative affect and found higher levels of inertia to be associated with higher levels of psychological impairment, e.g., in depression and lower self-esteem as well as the onset of future symptoms (20, 21, 57). Inertia of emotional resistance has been

identified as a potential candidate for an early warning signal for change in depressive symptoms (19). The results of this feasibility study suggest that physiological inertia may provide similarly useful information.

Of course, the potential of individual differences in patterns of abrupt changes in physiological and digitally assessed stress or digital phenotyping parameters should be further investigated in larger samples. Future research might benefit from taking a closer look at the patterns of individual patient differences in gradual and abrupt change over time not only related to symptoms, but also to process measures of psychotherapy. These patterns could be generated for varying parameters of change and analyzed in association with within- and between-patient change processes [e.g., (12)]. Future studies with larger samples will allow a better investigation of how those parameters can predict outcome or how they might be influenced by specific clinical techniques or strategies during treatment. Knowledge about process variables that might influence physiological inertia (or other digital parameters) could provide meaningful information on detecting mechanisms of change in psychotherapy. To increase the probability of identifying such mechanisms, change in physiological stress parameters could be investigated over a longer period of time or even for the entire duration of treatment. Finally, the quality of the physiological data collected and the psychological changes found could be further investigated by examining the relationship to psychological variables assessed simultaneously.

## LIMITATIONS AND CONCLUSION

Digital phenotyping offers some new potential to investigate change processes in psychotherapy, however, it is at a preliminary stage and thus, several limitations have to be considered. First, as mentioned above, larger studies must be conducted to get a clearer picture of such digitally assessed parameters of inertia, their potential to investigate change processes, and their potential function as an early warning signal for negative or positive treatment outcome. One aspect that contributed to the small sample size was the first-time implementation of that particular pilot study into routine processes of the outpatient clinic. First, patients had to be made aware of the project, also there were many missings among some patients due to a lack of commitment to wear the watch more than 50% of the time. In the end, the introductory meeting was the main contributor for the small number of participants, as it took place face-to-face, which was only possible to a limited extent during the Covid-19 pandemic. Furthermore, all digital phenotyping results (e.g., stress, sleep, physical activity) depend on the accuracy of the fitness tracker used. Fitness tracker measurement errors and differences between different products need to be considered. Several studies already examined the accuracy of wearable devices measuring physiological parameters (43–46). However, more studies are required to investigate the current state of different wearables. More specifically, studies are needed that compare the performance of wearables with the performance of already validated methods, not only for heart rate or activity measured in steps, but also for sleep duration, sleep phases, and calories. Finally, one also should be aware of possible technical problems when using fitness-trackers. In order for the data from the fitness tracker to be uploaded to the server, a connection with the app must be established via Bluetooth. If participants do not establish the Bluetooth connection with the app before returning the fitness tracker, data will be lost. In addition, there are occasional missings during data transfer in the form of time points that are missing and that are not coded accordingly. This must be taken into account when cleaning the data.

One advantage of measuring digital parameters is the large amount of data that is passively measured for a longer period of time. For example, stress level was measured continuously and displayed for every 3-min section in this study resulting in a maximum of 6,720 measurements per patient. However, an issue that occurred with patients in our study related the closeness of some change points. The TVCP-AR model needs enough data to identify change points and change in small periods of time between change points that are very close to each other seem harder to identify. Therefore, the model is unable to identify the exact time point of change in autocorrelation but only gives an approximation. This might be especially a problem for parameters, which are assessed less frequently over time. Finally, several patients show autocorrelation values $> 1$, which could be attributed to the method since it happens mostly around change points (vertical lines, see **Figure 2**) and the data might still contain non-stationarity.

To conclude, this feasibility study was able to present the preliminary potential of digital phenotyping by finding individual differences in stress level inertia and connecting it with clinical as well as psychometric parameters. This is the first study to examine the inertia of digitally assessed stress levels in order to investigate fine-grained change processes in CBT. First, replication in larger samples is required. Thereafter, future research should further investigate the potential of digital phenotypes to display treatment change processes and their relation to treatment outcome. Furthermore, not only biological rhythms such as stress level should be considered as predictors or parameters of psychological change, but also other digital phenotyping candidates, e.g., activity and sleep. Additionally, the potential of digital phenotyping to predict diagnostic groups could be considered (34, 35).

An improved outcome prediction based on digitally assessed stress levels could enhance prognosis and clinical decision-making. Providing therapists with this information could support them in identifying patients at risk for poor treatment outcomes early in therapy and adapting their clinical strategies accordingly. Using this new source of information on individual change might lead to direct applications in personalized treatment and monitoring processes, e.g., by integrating it into a comprehensive feedback system and reporting this information back to the therapist (13).

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Patients provided written, informed consent

for the publication of the study. No patient was under the age of 16. Cases were modified to preserve data protection. Therefore, these cases do not represent original case vignettes. Requests to access these datasets should be directed to Miriam I. Hehlmann, hehlmann@uni-trier.de.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics commission of the University of Trier. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MH was responsible and main contributor to the concept, writing, data management, data analyses, and data interpretation. BS contributed to writing, literature analyses, data management, preparation, and data interpretation. TL contributed to the analyses of the data and data interpretation. JG and JR consulted in the literature analyses and contributed to the writing of the manuscript. WL was contributor to several of the main concepts, writing, literature analyses, and data interpretation. All authors contributed to the article and approved the submitted version.

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# Therapy Processes Associated With Sudden Gains in Cognitive Therapy for Depression: Exploring Therapeutic Changes in the Sessions Surrounding the Gains

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**Background:** The frequency and clinical impact of *Sudden Gains*—large symptom improvements during a single between-session interval—in psychotherapy for depression have been well established. However, there have been relatively few efforts to identify the processes that lead to sudden gains.

**Aim:** To explore therapy processes associated with sudden gains in cognitive therapy for depression by examining changes in the sessions surrounding the gains, and the session preceding the gain in particular.

**Methods:** Using ratings of video-recordings ($n$ = 36), we assessed the content, frequency and magnitude of within-session cognitive-, behavioral-, and interpersonal change, as well as the quality of the therapeutic alliance in the session prior to the gain (pre-gain session), the session after the gain (post-gain session) and a control session. After that, we contrasted scores in the pre-gain session with those in the control session. In addition, we examined changes that occurred between the pre- and post-gain session (between-session changes) and explored patients' attributions of change.

**Results:** Although not statistically significant, within-session changes were more frequent and stronger in the pre-gain session compared to the control session. The largest difference between the pre-gain and control session was found in the behavioral domain, and reached the level of trend-significance. There were more, and more impactful between-session changes in the interval during which the gain occurred as compared to a control interval. Exploratory analysis of attributions of change revealed eight subcategories, all corresponding with the cognitive-, behavioral- and interpersonal- domain. The quality of the therapeutic alliance was high and almost identical in all sessions.

**Conclusion:** In spite of its small sample size, our study provides relevant descriptive information about potential precipitants of, themes related to, and attributions given for sudden gains. Furthermore, our study provides clear suggestions for future research.

A better understanding of session content in the sessions surrounding sudden gains may provide insight into the mechanisms of change in psychotherapy, hereby suggesting treatment-enhancing strategies. We encourage researchers to conduct research that could clarify the nature of these mechanisms, and believe the methods used in this study could serve as a framework for further work in this area.

**Keywords: cognitive therapy, major depression, sudden gains, mechanisms of change, time-course research**

## INTRODUCTION

The frequency and clinical impact of *Sudden Gains* (1) in psychotherapy for depression have been well established [see meta-analyses of Aderka et al. (2) and Shalom and Aderka (3) for an overview]. Sudden gains, large symptom improvements during a single between-session interval, are observed in ∼40% of depressed patients (range 25.9–50.0%), and those with sudden gains consistently report better acute and long-term treatment outcomes as compared to those without sudden gains (2, 3). Studies aimed at explaining why sudden gains occur have often focused on the predictive value of baseline characteristics (3). However, so far, no robust predictors of sudden gains have been identified, even in studies in which multiple predictors and their interactions were examined [e.g., (4)]. An explanation for this might lie in the strong association between sudden gains and treatment outcome, which suggests that this phenomenon is driven by important breakthroughs that occur during treatment that are difficult to predict using pre-treatment characteristics. One way to identify these breakthroughs is by meticulously analyzing the content of the sessions on either side of the gains, and the session preceding the gain (the so called pre-gain session) in particular. In only a few studies have researchers examined session content preceding sudden gains, and in those studies, the main focus has been on the role of cognitive change.

In the initial studies in cognitive therapy (CT), Tang and DeRubeis (1) and Tang et al. (5) examined the content of the pre-gain session and contrasted this to a control session. They found that the pre-gain session closely resembled the control session on most examined variables, including therapist competence and therapeutic alliance, but that there were differences in the cognitive domain. More specifically, they observed more cognitive change in the pre-gain session as compared to the control session, suggesting that cognitive changes might trigger sudden gains (1, 5). Researchers reporting on efforts to replicate this finding have concluded that cognitions were not related to sudden gains (6–9). It should be noted though, that Andrusyna et al. (7) examined this question in the context of psychodynamic therapy, and in the other studies, the role of cognition that was examined was substantially different than the one proposed and tested by Tang et al. For example, (6) tested the ability of a baseline self-report measure of cognition (prior to the initiation of a course of treatment) to predict which patients would experience sudden gains, and Kelly et al. (8) included a measure of self-reported self-esteem assessed at the beginning of the therapy session as a proxy of cognitive change, and associated this with sudden gains. Similarly, Vittengl et al. (9), amongst other methodological differences, also assessed process variables at the same point in time as they assessed depressive symptoms. Since in none of these studies the assessment of change was conducted in such a way to support, or rule out, the role of the purported mediator in the generation of a sudden gain, the relation between sudden gains and preceding cognitive changes still needs to be elucidated.

In addition, there is a growing body of research that collectively identifies sudden gains in a variety of other (non-cognitive) psychotherapeutic treatments for depression, or at a point in treatment in which cognitive techniques have not yet been addressed (7, 8, 10, 11). This suggests that other factors may be associated with sudden gains as well. Factors that have been suggested but that are lacking clear research support include, amongst others, behavioral- and interpersonal change, and the quality of the therapeutic alliance [e.g., (1, 6, 9, 12, 13)]. Additional research is necessary to examine the role of these factors more closely as well.

The current study focused on the identification of cognitive, behavioral, interpersonal, and relational precipitants of sudden gains in CT. Using the original studies by Tang and DeRubeis (1) and Tang et al. (5) as a starting point, video recordings of relevant sessions (pre-gain, post-gain and a control session) were watched and rated by independent raters, and the therapeutic changes that occurred in the pre-gain session (within-session change) were contrasted with observations obtained by viewing and rating control sessions. We also examined changes that occurred between the pre- and post-gain session (between-session change) and explored patients' attributions of change in the post-gain session. As such, we tried to identify crucial processes in and outside of therapy that might help us better understand how sudden gains occur. We expected that within-session changes would occur more frequently and with greater magnitude in the pre-gain session as compared to the control session, and that the most and most impactful between-session changes would be reported in the post-gain session. Because of the nature of CT we expected that most change would occur in the cognitive and the behavioral domain. However, because sudden gains have been found across psychotherapeutic interventions for depression, and at points in treatment in which cognitive techniques have not yet been addressed, we did not rule out that changes in the other domains could play a role as well.

## METHODS

### Data Source

Data were collected by rating video recordings of relevant therapy sessions of 17 patients treated with CT who were identified as "*sudden gainers*" in a previous study in which we examined the

frequency, magnitude, clinical impact and baseline predictors of sudden gains (14) and who gave consent for videotaping their sessions and for using these recordings for research purpose[1]. Participants were adult outpatients (nine women, mean age = 44.76 years; SD = 9.56) referred to the mood disorder unit of the Maastricht Academic Community Mental Health Centre in the Netherlands. All patients had received a primary diagnosis of major depressive disorder and 52.9% was diagnosed with recurrent depression. The majority of the patients (70.6%) was educated at intermediate vocational level (vs. 17.6% lower and 11.8% higher), and over half of the patients had a partner (58.8%) and was actively employed (52.9%) at the start of treatment. Baseline depression severity levels were assessed with the Beck Depression Inventory-II [BDI-II: (15)] and ranged from 17 to 54. The mean BDI-II score at baseline was 29.29 (SD = 9.96), which marks the border for "severe depression" (15). Treatment consisted of 16–20 individual 45-min sessions (mean = 15.76, SD = 4.10) and was based on the manual by Beck et al. (16). Sessions were offered weekly, but the protocol allowed flexibility in scheduling fewer appointments later on in treatment. The quality of therapy given was rated as very good to excellent and treatment dropout was low (17). The study is registered at the Netherlands Trial Register, part of the Dutch Cochrane Centre (ISRCTN 67561918). More details about the study design, participants, procedures, assessment instruments (quality of the), interventions and overall outcomes can be found in earlier publications (17–19).

Sudden gains were examined using the *original* criteria as defined by Tang and DeRubeis [see (14) for more details]. Of the 17 patients included in the current study, 11 patients had one sudden gain and the other six experienced two. The average magnitude of the gains was 10.48 BDI-II points (SD = 4.12) and the median pre-gain session was session 6 (range 2–18). In order to collect data on processes that were hypothesized to be related to sudden gains, three sessions were selected for each patient, representing the session prior to the gain (pre-gain session), the session after the gain (post-gain session) and a within-subject control session. Following Tang and DeRubeis (1) and Tang et al. (5) we chose the session immediately before the pre-gain (the pre-pre-gain session) as the control session, because this session is most likely to resemble the pre-gain session (see **Figure 1**). For the six patients with two sudden gains, only the first gain was included, resulting in only one data point per patient [average magnitude (SD) of the gains = 10.59 (4.32) BDI-II points; median pre-gain session = 5]. Of the 51 selected sessions (3*17), recordings of 15 sessions were unavailable (missing or damaged), leaving 36 recordings available for analyses (12x pre-, 15x post-, and 9x control session). For eight patients, a full set of ratings was available, eight patients had data for the pre-gain and control session (same eight), and a total of 12 paired pre- and post-gain comparisons could be made.

## Measures

The frequency and magnitude of therapeutic changes in the pre-gain session, post-gain session and the control session were rated on three domains (1) the cognitive domain, (2) the behavioral domain, and (3) the interpersonal domain. In addition, the quality of the therapeutic alliance in each session was assessed. Cognitive-, behavioral- and interpersonal- changes were assessed using an adapted and extended version of the Patient Cognitive Change Scale [PCCS; (1, 5)] that was composed for the current study[2]. We included nine items of the original PCCS: six items assessing potential cognitive change, and three items reflecting behavioral change. Unlike the original studies, in which all nine items were fitted in the cognitive domain, we created a separate behavioral domain, including two additional items of the Activation subscale of the Behavioral Activation for Depression Scale [BADS; (20)]. Furthermore, following the structure of the cognitive items of the PCCS, we created comparable items for the interpersonal domain using the IPT manual by Klerman et al. (21). An overview of the items used can be found in **Table 1**. The complete instrument including its rating instructions can be found in **Supplementary Data I**. Items reflected either preparation for change (indicated with an * in **Table 1**) or actual change achieved. For each item, raters first indicated whether such change was observed in the session (frequency rating; yes/no). If this was the case, they specified its content and indicated whether the (preparation for) change was achieved during the session (within-session change) or whether it reflected a discussion of change that occurred prior to the session (between-session change). After that, following the original guidelines from the PCCS, the personal significance of the change (magnitude rating) was rated on a five-point scale ranging from 0 (no change/not applicable) to 4 (change with extraordinary personal significance). Any of the items could receive multiple ratings in a given session, as long as they clearly differed in content. However, if the same type of progress was acknowledged more than once, only one score was given. Raters were instructed never to infer changes. Only when any of the changes were explicitly acknowledged, raters would classify it by its content and rate its magnitude. Total scores per domain

[1]Readers familiar with our study (14) might notice that the initial study identified 27 patients with sudden gains in CT and also included an Interpersonal Psychotherapy (IPT) arm. However, since there were insufficient IPT tapes available to make statements about precipitants of IPT and/or to compare both interventions (less SG's in IPT, many missing tapes, complete data for only two patients), we decided to only focus on CT here. Furthermore, as mentioned in the paper, for CT, 8 out of 27 patients experienced gains that occurred in between-session intervals that were more than 14 days apart. To ensure the *suddenness* of the gain, for the present study, we selected only those patients whose gains occurred within a 14-day timeframe leaving us with 19 participants. As two of them did not give consent for videotaping their sessions, this resulted in a sample of 17 patients. There were no relevant differences between the sample of excluded ($n = 10$) and included ($n = 17$) patients in terms of the sociodemographic factors, depression- and treatment specifiers, and sudden gains characteristics described in the "Data Source" section.

[2]Item selection took place as follows: first an extensive literature search was conducted to gain insight in the topics, scales and items that were used in each of the domains and in related studies. Subsequently, the selected topics and scales were discussed and carefully examined in expert meetings, and items were deducted until only the most important items remained. In doing this, attention was paid to both item content as well as the number of items per domain.

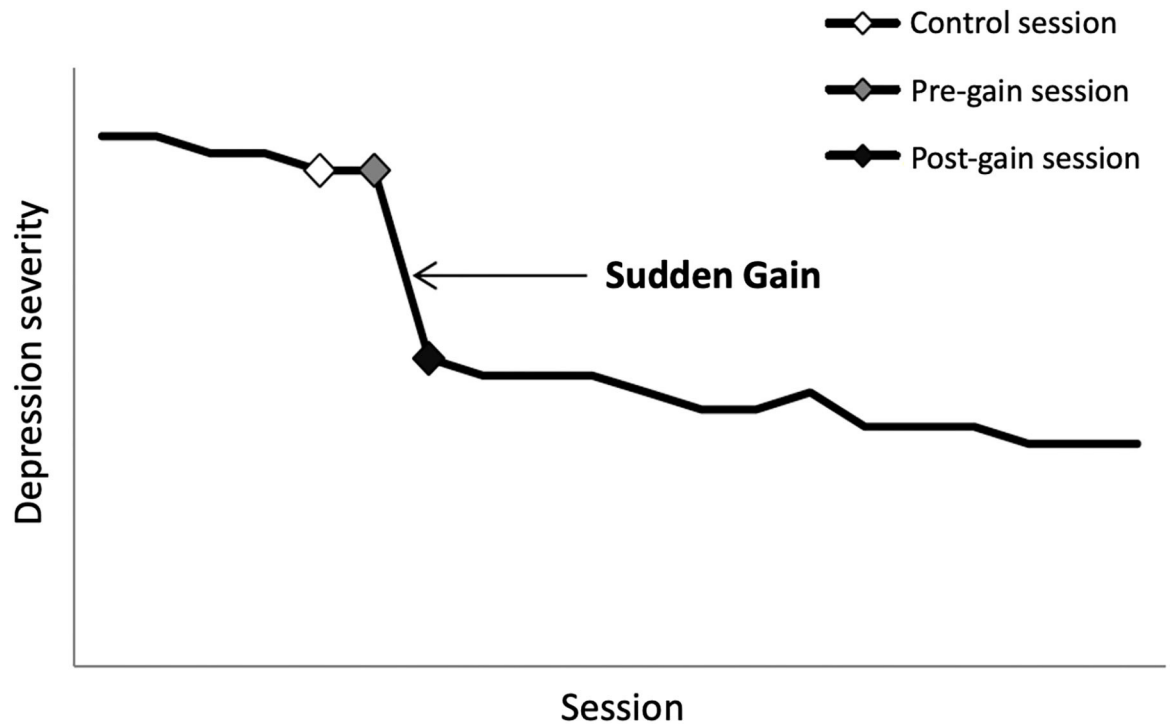


**FIGURE 1 |** Illustration of the concept of sudden gains and the critical sessions surrounding the sudden gain. Note: the Y-axis represents depression severity with increasing severity from bottom to top; the X-axis represents session number with ascending session number from left to right. The black line represents the course of depression (simulated data; one data point per session). The large drop in symptoms between the gray and black diamond represents the sudden gain. The gray diamond represents the pre-gain session. The black diamond represents the post-gain session, and the white diamond represents the control session.

(separate sum scores for frequency and magnitude ratings) were obtained by summing up all item scores per category.

The quality of the therapeutic alliance was assessed with the observer-rated version of the Working Alliance Inventory Short [WAI-O-S; (22, 23)], which is based on Bordin's (24) conceptualization of working alliance. According to Bordin, a strong alliance forms if the therapist and client agree on (1) the *goals* of therapy and (2) the *tasks* that are needed to meet those goals, and (3) have a *bond* between them that facilitates this process. The instrument consists of 12 items (four for each subscale) that are rated on a 7-point scale (1 = never, to 7 = always), with higher scores indicating a stronger alliance. A total score is obtained by summing up all item scores. Psychometric properties of the WAI-O-S are good (7, 25, 26).

Patients' attributions for change in the post-gain session were explored using a rater-based modified version of the Symptom Change Attribution Interview [SCAI; (27)]. Raters indicated whether (1) there was a discussion between therapist and client about an improvement in mood (yes/no); (2) whether the patient reported reasons for change, and if so, which reason(s) was/were reported; (3) whether the patient report on anything from the previous session that stood out for him/her, and if so, what stood out; and (4) whether the patient reported that during/since the last session (s)he (a) realized something not realized before, arrived at new perspective on something, or changed beliefs or ideas, (b) learned new techniques that (s)he found helpful, (c) learned other things, or (d) has noticed that (s)he has been doing anything different, plus specification.

## Procedure

Each session was watched and rated by two independent raters under the supervision of the first author (LL) who was trained by TT and RD. Raters were clinical psychology students (1 undergraduate, 1 MSc) from Maastricht University (Netherlands). Individual scores on all items were discussed afterwards with the first author until consensus was reached. Consensus scores were used as the final scores. Prior to the study, raters individually orientated on the topic by means of an extensive literature search (8 h). In addition, raters received an elaborate training (9 × 2 h) in which they were taught about the concept of sudden gains, the instrument, the rating guidelines, and the complexities of rating psychotherapeutic processes. Throughout the 3 month rating period, weekly consensus meetings were scheduled to optimize reliability and minimize rater's drift. In each session, a subset of tapes was discussed, and the conclusions from each session were implemented in the strategy for the next subset of tapes. All identifying information was removed from the recordings to make sure that all of those involved in the rating process were blind for the session number, symptom changes before and after the session, and treatment outcome. Due to the specific therapeutic interventions and the

**TABLE 1 |** Overview of items for the cognitive, behavioral and interpersonal domain.

| Domain | Items |
|---|---|
| Cognitive change | 1. The patient became aware of the relationship between cognition and mood*<br>2. The patient became aware of a belief behind negative feelings*<br>3. The patient changed his/her belief<br>4. The patient became aware of schema*<br>5. The patient changed his/her schema<br>6. The patient accepted a new cognitive technique* |
| Behavioral change | 1. The patient accepted alternative behavior*<br>2. The patient decided to increase pleasurable activities*<br>3. The patients made plans for pleasurable activities*<br>4. The patient engaged in a wide and diverse array of activities<br>5. The patient structured his/her day's activities |
| Interpersonal change | 1. The patient became aware of the relation between interpersonal functioning and mood*<br>2. The patient became aware of dysfunctional patterns in interpersonal functioning*<br>3. The patient became aware of the need to improve interpersonal functioning*<br>4. The patient decided to change interpersonal functioning*<br>5. The patient made plans for changing interpersonal functioning*<br>6. The patient changed interpersonal functioning |

**Items reflect preparation for change (vs. actual change achieved). For each item, raters first indicated whether such change was observed in the session (frequency rating; yes/no). If this was the case, they specified its content and indicated whether the (preparation for) change was achieved during the session (within-session change) or whether it reflected a discussion of change that occurred prior to the session (between-session change). After that, the significance of the change (magnitude rating) was rated on a five-point scale (0 = no change/item not applicable; 1 = possible/potential change; 2 = definite change; 3 = important change; 4 = change with extraordinary personal significance).*

visual character of the study, it was not possible to blind raters for patients and therapist. Whenever raters heard that change was explicitly acknowledged in the session, they were asked to specify this as clearly as possible and to provide their line of reasoning for selecting a certain magnitude rating. This was important for both the training phase as well as the rating phase as this facilitated the consensus discussions. There were no written transcripts available. Instead raters were instructed to press pause and/or rewind the recording if necessary.

## Data Analysis

We replicated and extended the method used by Tang and DeRubeis (1) and Tang et al. (5). First, using all available data of all 17 patients, we mapped out the frequency and magnitude (mean, SD) of within-session and between-session changes that were observed in the relevant sessions. After that, for those with complete data, frequency and magnitude of within-session changes in each domain were compared between the pre-gain session and the control session using paired samples $t$-tests ($n = 8$). Similar to the original studies, if the frequency or magnitude of an observed variable in the pre-gain session was significantly ($p < 0.05$) higher than its level in the control session, we considered this a suggestion that this factor might be associated with the sudden gain. To gain insight in important changes that happened between the pre- and post-gain session, we took a closer look at the between-session ratings in the post-gain session, and contrasted them to the scores in the pre-gain session using paired-samples $t$-test (paired data only; $n = 12$) Finally, we explored and manually categorized the content of the attribution questions in the post-gain session, to learn more about patients' own attributions of change (see **Supplementary Data I** for more details).

# RESULTS

## Data Exploration

An overview of all available within- and between-session changes in each of the three domains (frequency and magnitude ratings) and alliance scores (M, SD) in the pre-gain, post-gain and control session are presented in **Table 2**. A total of 103 within-session changes were identified; 44 in the pre-gain, 40 in the post-gain, and 19 in the control session. Although in general, magnitude ratings were in the lower end of the range, the largest magnitude ratings were observed in the pre-gain sessions, with highest overall domain scores in the behavioral domain, followed by the interpersonal and cognitive domain. The control sessions showed the smallest overall within-session change. There were five items that were not observed in any of the sessions. For three of them (engaging in a wide and diverse array of activities, structuring activities, and changing interpersonal functioning), we did not expect within-session changes, since they require action outside of the session. For the other two items (becoming aware of/changing a schema), within-session change was possible, but did not occur. The total number of between-session changes that was observed was 162; 54 for the pre-gain session, 70 for the post-gain session, and 38 for the control session. Largest magnitude ratings were observed in the post-gain session, with a similar pattern for the various domains as was found in the within-session ratings (i.e., highest overall domain score in the behavioral domain, followed by interpersonal and cognitive domain). All items were rated at least once in any of the sessions, except for the cognitive items becoming aware of and/or changing a schema, which were not observed at all. The quality of the therapeutic alliance was high and almost identical in all sessions.

**TABLE 2 |** Overview of all available data: within- and between-session cognitive, behavioral and interpersonal change (frequency and magnitude) and within-session alliance data (M, SD) in the pre-gain, post-gain and control session.

| (*n* = 17) | Within-session change | | | | | | Between-session change** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-gain session (*n* = 12) | | Post-gain session (*n* = 15) | | Control session (*n* = 9) | | Pre-gain session (*n* = 12) | | Post-gain session (*n* = 15) | | Control session (*n* = 9) | |
| **Domain** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Frequency (Sum)** | **Magnitude (M, SD)** |
| **Cognitive domain total** | **13** | **2.17 (2.66)** | **16** | **2.07 (2.40)** | **9** | **1.56 (1.33)** | **12** | **1.42 (2.50)** | **12** | **1.80 (2.73)** | **3** | **0.89 (1.36)** |
| - Becoming aware of relation cognition and mood* | 1 | 0.08 (0.29) | 4 | 0.53 (1.13) | 3 | 0.33 (0.50) | 3 | 0.33 (0.65) | 2 | 0.20 (0.56) | 0 | 0.00 (0.00) |
| - Becoming aware of belief* | 3 | 0.50 (0.90) | 3 | 0.33(0.72) | 2 | 0.44 (0.88) | 3 | 0.25 (0.45) | 5 | 0.67 (1.11) | 1 | 0.33 (1.00) |
| - Changing a belief | 6 | 1.08 (1.56) | 3 | 0.47 (1.06) | 0 | 0.00 (0.00) | 3 | 0.42 (1.44) | 2 | 0.40 (1.06) | 1 | 0.33 (1.00) |
| - Becoming aware of schema* | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) |
| - Changing a schema | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) |
| - Accepting a new cognitive technique* | 3 | 0.50 (0.90) | 6 | 0.73 (1.28) | 4 | 0.78 (1.09) | 3 | 0.42 (1.16) | 3 | 0.53 (1.13) | 1 | 0.22 (0.67) |
| **Behavioral domain total** | **17** | **2.67 (3.28)** | **5** | **0.60 (1.59)** | **1** | **0.22 (0.67)** | **23** | **3.08 (2.91)** | **36** | **5.07 (4.06)** | **20** | **4.22 (4.27)** |
| - Accepting alternative behavior* | 7 | 1.25 (1.66) | 3 | 0.33 (0.72) | 1 | 0.22 (0.67) | 7 | 0.92 (1.08) | 10 | 1.53 (1.41) | 9 | 1.89 (1.83) |
| - Deciding to increase pleasurable activities* | 5 | 0.75 (0.97) | 1 | 0.13 (0.52) | 0 | 0.00 (0.00) | 3 | 0.33 (0.65) | 7 | 1.00 (1.13) | 2 | 0.44 (0.88) |
| - Making plans for pleasurable activities* | 5 | 0.67 (1.07) | 1 | 0.13 (0.52) | 0 | 0.00 (0.00) | 4 | 0.42 (0.67) | 7 | 1.00 (1.20) | 3 | 0.56 (0.88) |
| - Engaging in a wide and diverse array of activities | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 5 | 0.83 (1.11) | 10 | 1.40 (1.18) | 3 | 0.78 (1.30) |
| - Structured day's activities | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 4 | 0.58 (1.00) | 2 | 0.13 (0.35) | 3 | 0.56 (1.01) |
| **Interpersonal domain total** | **14** | **2.33 (3.98)** | **19** | **2.33 (3.75)** | **9** | **1.67 (2.35)** | **19** | **2.50 (3.34)** | **22** | **3.33 (4.88)** | **15** | **3.00 (2.87)** |
| - Becoming aware of relation int. func. and mood* | 1 | 0.17 (0.58) | 3 | 0.27 (0.59) | 0 | 0.00 (0.00) | 4 | 0.67 (1.15) | 6 | 0.93 (1.28) | 5 | 1.11 (1.17) |
| - Becoming aware of dysfun. patterns in int. func* | 3 | 0.50 (1.00) | 5 | 0.73 (1.10) | 3 | 0.44 (0.73) | 5 | 0.75 (1.06) | 3 | 0.53 (1.13) | 5 | 1.00 (1.00) |
| - Becoming aware of need to improve int. func* | 3 | 0.50 (1.00) | 4 | 0.53 (0.92) | 2 | 0.33 (0.71) | 3 | 0.33(0.65) | 3 | 0.33 (0.72) | 2 | 0.33 (0.71) |
| - Deciding to change interpersonal functioning* | 3 | 0.58 (1.00) | 4 | 0.47 (0.92) | 2 | 0.44 (0.88) | 2 | 0.33 (0.78) | 2 | 0.33 (0.90) | 1 | 0.11 (0.33) |
| - Making plans interpersonal change* | 4 | 0.58 (1.08) | 3 | 0.33 (0.90) | 2 | 0.44 (0.88) | 1 | 0.08 (0.29) | 4 | 0.53 (1.13) | 1 | 0.22 (0.67) |
| - Changed interpersonal functioning | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 4 | 0.33 (0.49) | 4 | 0.67 (1.40) | 1 | 0.22 (0.67) |
| **Therapeutic alliance total** | | **66.83 (2.86)** | | **66.60 (2.23)** | | **65.89 (4.51)** | | | | | | |
| - Bond | | 21.92 (1.51) | | 21.60 (1.18) | | 22.11 (2.03) | | | | | | |
| - Goal | | 23.00 (0.74) | | 22.93 (0.88) | | 22.78 (1.09) | | | | | | |
| - Task | | 22.25 (1.14) | | 22.53 (1.13) | | 21.22 (1.79) | | | | | | |

**Items reflect preparation for change (vs. actual change achieved). For each item, raters first indicated whether such change was observed in the session (yes/no; frequency rating). If this was the case, they specified its content and indicated whether the (preparation for) change was achieved during the session (within-session change) or whether it reflected a discussion of change that occurred prior to the session (between-session change). After that, the significance of the change (magnitude rating) was rated on a five-point scale (0 = no change/item not applicable; 1 = possible/potential change; 2 = definite change; 3 = important change; 4 = change with extraordinary personal significance). **since alliance was only rated within the session, there is no between-session alliance data available.*

**TABLE 3 |** Within-session cognitive, behavioral and interpersonal change (frequency and magnitude) and alliance data (M, SD) in the pre-gain and control session, and their comparison ($n = 8$).

| | Within session change | | | | |
|---|---|---|---|---|---|
| | Pre-gain session | | Control session | | |
| **Domain** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Pre vs. control (*p*)** |
| **Cognitive domain total** | **7** | **1.63 (2.50)** | **6** | **1.25 (1.04)** | **0.76** |
| - Becoming aware of relation cognition and mood* | 1 | 0.13 (0.35) | 2 | 0.25 (0.46) | 0.60 |
| - Becoming aware of belief* | 2 | 0.50 (0.93) | 1 | 0.25 (0.71) | 0.60 |
| - Changing a belief | 2 | 0.50 (0.93) | 0 | 0.00 (0.00) | 0.17 |
| - Becoming aware of schema* | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| - Changing a schema | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| - Accepting a new cognitive technique* | 2 | 0.50 (0.93) | 3 | 0.75 (1.16) | 0.70 |
| **Behavioral domain total** | **8** | **2.00 (3.07)** | **1** | **0.25 (0.71)** | **0.09** |
| - Accepting alternative behavior* | 4 | 1.13 (1.64) | 1 | 0.25 (0.71) | 0.09 |
| - Deciding to increase pleasurable activities* | 2 | 0.50 (0.93) | 0 | 0.00 (0.00) | 0.17 |
| - Making plans for pleasurable activities* | 2 | 0.38 (0.74) | 0 | 0.00 (0.00) | 0.20 |
| - Engaging in a wide and diverse array of activities | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| - Structured day's activities | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| **Interpersonal domain total** | **8** | **2.00 (3.51)** | **9** | **1.88 (2.42)** | **0.82** |
| - Becoming aware of relation int. func. and mood* | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| - Becoming aware of dysfun. patterns in int. func* | 2 | 0.38 (0.74) | 3 | 0.50 (0.76) | 0.60 |
| - Becoming aware of need to improve int. func* | 2 | 0.38 (0.74) | 2 | 0.38 (0.74) | 1.00 |
| - Deciding to change interpersonal functioning* | 2 | 0.63 (1.19) | 2 | 0.50 (0.93) | 0.35 |
| - Making plans interpersonal change* | 2 | 0.63 (1.19) | 2 | 0.50 (0.93) | 0.35 |
| - Changed interpersonal functioning | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| **Therapeutic alliance total** | | **66.25 (3.24)** | | **66.63 (4.21)** | **0.75** |
| - Bond | | 21.88 (1.81) | | 22.38 (2.00) | 0.47 |
| - Goal | | 22.75 (0.71) | | 23.00 (0.93) | 0.52 |
| - Task | | 21.88 (1.13) | | 21.50 (1.69) | 0.50 |

**Items reflect preparation for change (vs. actual change achieved). For each item, raters first indicated whether such change was observed in the session (yes/no; frequency rating). If this was the case, they specified its content and indicated whether the (preparation for) change was achieved during the session (within-session change) or whether it reflected a discussion of change that occurred prior to the session (between-session change). After that, the significance of the change (magnitude rating) was rated on a five-point scale (0 = no change/item not applicable; 1 = possible/potential change; 2 = definite change; 3 = important change; 4 = change with extraordinary personal significance).*

## Within-Session Changes

**Table 3** presents frequency and magnitude ratings (M, SD) of within session changes on each of the three domains in the pre-gain and control session for those with complete data ($n = 8$). Furthermore, alliance scores (M, SD) for these sessions are presented. There were more within-session changes in the pre-gain session as compared to the control session (23 vs. 16 for pre-gain and control session, respectively). Magnitude scores in the cognitive-, behavioral- and interpersonal domain were larger in the pre-gain session as compared to the control session. The largest difference between the pre-gain and the control session was found in the behavioral domain, followed by the cognitive and the interpersonal domain. Paired-samples *t*-tests indicated that none of these differences were statistically significant, but the difference in the behavioral items reached trend level ($p = 0.09$). The average magnitude rating of behavioral change in pre-gain session (2.0) was equivalent to one "definite change" in behavioral items, whereas the average control session (0.25) represented almost no change in behavioral items.

A closer look at the item level, indicated that the effects in the behavioral domain seemed mainly driven by within-session acceptance of new behavior, the decision to increase pleasurable activities, and making plans for these pleasurable activities. All of these items represented preparation for change. The largest contrast reflecting actual change achieved in the session was found in the cognitive domain (changing a belief). The quality of therapeutic alliance was similar in the pre-gain and control session.

## Between-Session Changes

**Table 4** presents the frequency and magnitude ratings (M, SD) of between-session changes, i.e., changes that were discussed in the session but that occurred outside the therapy, on each of the three domains between the two session in which the gain occurred for patients with complete data in these sessions ($n = 12$). As can be seen in the table, more (frequency rating) and more impactful (magnitude rating) between-session changes

**TABLE 4 |** Between-session cognitive, behavioral and interpersonal change (frequency and magnitude) in the pre-gain and post-gain session, and their comparison ($n = 12$).

| | Prior to session change | | | | |
|---|---|---|---|---|---|
| | Pre-gain session | | Post-gain session | | |
| **Domain** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Frequency (Sum)** | **Magnitude (M, SD)** | **Pre vs. post (*p*)** |
| **Cognitive domain total** | **12** | **1.42 (2.50)** | **12** | **2.25 (2.90)** | **0.36** |
| - Becoming aware of relation cognition and mood* | 3 | 0.33 (0.65) | 2 | 0.25 (0.62) | 0.78 |
| - Becoming aware of belief* | 3 | 0.25 (0.45) | 5 | 0.83 (1.19) | 0.13 |
| - Changing a belief | 3 | 0.42 (1.44) | 2 | 0.50 (1.17) | 0.79 |
| - Becoming aware of schema* | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| - Changing a schema | 0 | 0.00 (0.00) | 0 | 0.00 (0.00) | 1.00 |
| - Accepting a new cognitive technique* | 3 | 0.42 (1.16) | 3 | 0.67 (1.23) | 0.46 |
| **Behavioral domain total** | **23** | **3.08 (2.91)** | **33** | **5.92 (4.03)** | **0.07** |
| - Accepting alternative behavior* | 7 | 0.92 (1.08) | 9 | 1.75 (1.42) | 0.03 |
| - Deciding to increase pleasurable activities* | 3 | 0.33 (0.65) | 7 | 1.25 (1.14) | 0.05 |
| - Making plans for pleasurable activities* | 4 | 0.42 (0.67) | 7 | 1.25 (1.22) | 0.09 |
| - Engaging in a wide and diverse array of activities | 5 | 0.83 (1.11) | 8 | 1.50 (1.24) | 0.10 |
| - Structured day's activities | 4 | 0.58 (1.00) | 2 | 0.17 (0.39) | 0.21 |
| **Interpersonal domain total** | **19** | **2.50 (3.34)** | **19** | **3.58 (5.37)** | **0.37** |
| - Becoming aware of relation int. func. and mood* | 4 | 0.67 (1.15) | 5 | 1.00 (1.35) | 0.34 |
| - Becoming aware of dysfun. patterns in int. func* | 5 | 0.75 (1.06) | 2 | 0.42 (1.00) | 0.17 |
| - Becoming aware of need to improve int. func* | 3 | 0.33 (0.65) | 2 | 0.25 (0.62) | 0.72 |
| - Deciding to change interpersonal functioning* | 2 | 0.33 (0.78) | 2 | 0.42 (1.00) | 0.84 |
| - Making plans interpersonal change* | 1 | 0.08 (0.29) | 4 | 0.67 (1.23) | 0.15 |
| - Changed interpersonal functioning | 4 | 0.33 (0.49) | 4 | 0.83 (1.53) | 0.24 |

**Items reflect preparation for change (vs. actual change achieved). For each item, raters first indicated whether such an change was observed in the session (yes/no; frequency rating). If this was the case, they specified its content and indicated whether the (preparation for) change was achieved during the session (within-session change) or whether it reflected a discussion of change that occurred prior to the session (between-session change). After that, the significance of the change (magnitude rating) was rated on a five-point scale (0 = no change/item not applicable; 1 = possible/potential change; 2 = definite change; 3 = important change; 4 = change with extraordinary personal significance).*

were observed in the post-gain sessions as compared to the pre-gain session. For the behavioral domain, this difference was at the level of a non-significant trend (overall domain score $p = 0.07$). At the item-level, patients accepted significantly more alternative behavior ($p = 0.03$). Furthermore, patients reported more plans for pleasurable activities, and engaged in a wider and more diverse array of activities between the two sessions, at the level of a non-significant trend ($p = 0.09$ and $p = 0.10$, respectively).

## Patients' Attributions for Change

In all 12 post-gain sessions, there was a spontaneous discussion about improvements in mood that occurred prior to the session. In all but one of the sessions, the patient reported one or more reasons for symptom improvement; eight patients reported that they realized something they had not realized before, and/or arrived at a new perspective or changed ideas/beliefs during/since the last session; seven patients indicated that they learned something that they found helpful; and five patients reported noticing themselves doing things differently. Attributions could be sorted into the following:

Eight subcategories, all corresponding with the cognitive-, behavioral- and interpersonal- domain: behavioral activation, exercise, shift in belief(s)/perspective(s), absence of negative thoughts, work/work-life balance, asking for help, setting and communicating boundaries and other (see **Table 5** for examples). Two patients explicitly linked their improvement to the previous session ("*I realized last session that I don't know if my negative thoughts will influence my future*" and "*I realized last week that my depression worsens if I stay inactive. I have to get up and do things.*"

# DISCUSSION

The present study explored therapy processes associated with sudden gains in CT for depression by examining the role of cognitive, behavioral, and interpersonal change and the quality of the therapeutic alliance in the sessions surrounding the gains. More specifically, using ratings of video-recordings, we assessed the content, frequency and magnitude of within-session changes in each of the three domains, and the quality of the therapeutic alliance in the session prior to the gain (pre-gain session), the session after the gain (post-gain session) and a control session. After that, we contrasted scores in the pre-gain session with those in the control session. In addition, we examined changes

**TABLE 5 |** Patients' attributions for change as reported in the post-gain session (categories and examples) ($n = 12$).

| Category | Examples |
|---|---|
| - Behavioral activation | Had more things to do this week (mentioned by two patients); Did a lot of pleasurable things; Took up old activities; Went shopping; Got up and did things. |
| - Exercise | Started going to the gym. |
| - Shift in belief/perspective | Future is brighter than expected; It's not my fault; I cannot know if negative thoughts will influence future. |
| - Absence of negative thoughts | Had no negative thoughts this week. |
| - Work and work-life balance | Things are going well at work; Job application going well; Getting used to combination work/private life. |
| - Asking for help | Asked husband to make coffee; Asked husband to help with laundry. |
| - Setting/communicating boundaries | Has set clearer boundaries; Has set new rules and communicated them to partner. |
| - Other | Had a nice holiday. |

that occurred between the pre- and post-gain session (between-session changes) and explored patients' attributions of change in the post-gain session.

Although the sample size was small, absolute magnitude scores were in the lower end of the range, and several constructs were not observed at all, within-session changes were observed more frequently and with greater magnitude in the pre-gain session as compared to the control session, albeit not statistically significant. The largest difference between the pre-gain and the control session was found in the behavioral domain, and reached the level of trend-significance, which is interesting and in line with a C(B)T context. Other within-session changes in the pre-gain sessions were mainly preparation for change (i.e., awareness, openness, realizations). The most promising item that reflected actual change achieved during the pre-gain session was the item "change of belief," which also matches a C(B)T setting. Although not statistically significant, possibly because of the limited statistical power, our pattern of findings is similar to those reported by Tang and DeRubeis (1) and Tang et al. (5).

The fact that independent raters observed more between-session as compared to within-session changes was not totally unexpected given that several items (those reflecting actual change) could not be rated as within-session change since they required action outside of the therapist's office. For between-session change, all items could potentially be rated. Furthermore, the period for assessing between-session changes (a full between-session interval) was a lot longer than that for within-session change (a 45-min session), which allowed for more opportunities for change. It should be noted that this also increases chances of recall bias. The frequency and impact of between-session changes were larger for the post-gain session as compared to the pre-gain session. Although not statistically significant, this indicated the changes in the between-session interval in which the gain occurred were more frequent and stronger as compared to those in the control interval. Rudimentary analysis of attributions of change revealed eight subcategories of explanations for change, all corresponding to each of the three investigated domains. The quality of the therapeutic alliance was high and almost identical in all sessions.

## Scores in the Cognitive, Behavioral and Interpersonal Domain

Although consistent with previous studies conducted by Tang and DeRubeis (1), Tang et al. (5), and, scores in the various domains were on the lower end of the range. More specifically, even though the magnitude scale ranged from 0 to 4, ratings higher than 2 were rarely given. The question that remains is why this was the case. Though speculative, some reasons are more plausible than others and deserve further discussion. First, our findings could indicate that treatment was not powerful enough to elicit important changes in the examined domains. However, this explanation is unlikely since an extensive integrity check confirmed high therapy quality and integrity [see (17)]. It is more likely that magnitude of change in this study is underrepresented because of the specific rating instructions that were used. Similar to Tang and DeRubeis (1) and Tang et al. (5), raters were instructed not to infer, but rather only rate change that was explicitly acknowledged in the session. As a result, changes that were more implicit were not detected, despite potentially contributing to change. A third reason for the relatively low ratings might lie in the scale that was used for the magnitude scores. The most information seemed to be in the differentiation between 0 (no change) and 2 (definite change). The fact that scores higher than two were rarely given, indicates that it is difficult—or even unnecessary—to further differentiate between 2 (definite change), 3 (important change) and 4 (change with extraordinary personal significance). Alternatively, our findings could point toward the possibility that the domains that were examined in this study were not important for sudden gains, but that other therapy processes that were not investigated in this study are crucial for these large and sudden drops in depressive symptoms.

When taking a closer look at the specific domains that were included, particularly the scores in the cognitive domain were lower than expected. In fact, items related to identifying and changing schemas were not even rated at all (either as within- or between-session change). This is remarkable when taking into account that the cognitive domain is a central part of CT. Although the possibility that cognitive changes are not important for sudden gains in CT cannot be fully ruled out, it is more

likely that behavioral and interpersonal changes were easier to detect. One reason for this might be that therapists relied more on behavioral techniques instead cognitive techniques within the therapeutic framework, or that schema change is very difficult to track by raters. Since the independent raters were instructed not to infer, they had to follow the discussion as it emerged during the session. The difference between the domains might be further reinforced by the fact that, contrary to several other studies, we combined the various domains in one study. During the rating process, we noticed that several examples would fit in multiple domains (e.g., cognitive change and interpersonal change). In our case, we had to decide which category fitted best. Moreover, in a way, one could even argue that in well-delivered CT, all behavioral/interpersonal change follows from or leads to cognitive change. Unfortunately, our research design did not allow us to further differentiate here.

A final potential explanation that cannot remain undiscussed is the fact that with our approach we made a critical assumption: namely that explicit changes in the pre-gain session (either in terms of preparation for change, or actual change) are responsible for the gains. Although this framework is more plausible than for instance the idea that sudden gains are predicted by baseline levels of hypothesized therapeutic processes, it gives a very central position to the session itself and rules out various other options, such as the possibility that during the pre-gain session a "seed" is planted that is followed-up later on during the week, or that sudden gains are not linked to the therapy sessions at all. If this would be the case, it is not remarkable that we only observed little changes. Although we tried to shed light on this by also looking at changes that occurred in the between-session interval in which the gain occurred, and by exploring the patients' own attributions for change, we did not do this systematically enough to provide clear cut answers about this. In order to get a clearer view about this one would need more fine-grained research on the patients' lives outside of the session, as well as more structured information about attributions of change. Furthermore, it would be interesting to differentiate between procedures (interventions used by the therapist) and processes [changes experienced by the patient, presumably following from procedures; (28)]. Because if the therapist uses more specific techniques in the session prior to the gain, this could also inform us about important precipitants of sudden gains.

## The Role of Therapeutic Alliance

Contrary to the rather low scores in the behavioral, cognitive and interpersonal domains, alliance scores were very high and almost identical in every session. What does that tell us about the role of alliance in sudden gains? The fact that there were no differences between nor changes during the sessions makes it unlikely that alliance is a process that drives sudden gains. However, the high scores might point toward alliance as a prerequisite for sudden gains. Contrasting the quality of the therapeutic alliance between those with and without sudden gains could shed more light on this. Unfortunately, those data were not available. Alternatively, as suggested by Zilcha-Mano et al. (4), it could also point toward alliance as an important ingredient of an upward spiral in which sudden gains lead to a further strengthening in alliance, which in turn predict further improvements in well-being, which in may result in sustained sudden gains.

## Methodological Considerations

To our knowledge, our study was the first to test and replicate the original hypothesis regarding cognitive change proposed by Tang and DeRubeis (1) and Tang et al. (5). Furthermore, we extended the work of Tang et al. by examining the role of changes in the behavioral and interpersonal domain as well. Other strengths of the study include the line-by-line analysis of video recordings by independent raters, exploration of changes that occurred in the between-session interval in which the gain occurred and the inclusion of a rudimentary attribution analysis. However, several limitations should be mentioned as well. First, our study was a secondary analysis of an existing trial that was not specifically designed to answer questions about precipitants of sudden gains. Therefore, our design also had some restrictions. For example, there was no systematic attribution interview. Furthermore, a systematic and fine-grained analysis of changes that happened in-between sessions was lacking and we cannot completely guarantee that all between-session changes and that that were discussed actually happened in the single between-session interval that was examined. Although CT is a present-focused treatment by nature, and therapists were instructed to specifically ask for change since the last session, there were instances for which the interval was not made explicit. In addition, although our instrument was largely composed from existing and validated instruments, the psychometric properties of the instrument in its composed form have not been examined. The largest limitations of the study, however, are its small sample size ($n = 17$), and the fact that only for a subset of the included patients a full set of ratings was available due to the relatively high proportion of missing data. This, together with the fact our data were highly skewed, and the risk of type-1 error due to multiple comparisons, constrained our statistical analyses. Results should therefore be interpreted with caution, and follow-up studies are extremely important.

## Implications and Suggestions for Future Research

In spite of its statistical limitations, our study provides relevant information about potential precipitants of, themes related to, and attributions given for sudden gains. The merit of this study therefore lies mainly its descriptive value. Furthermore, it laid out difficulties that one can encounter in this type of research and points toward several specific suggestions for future research. First, larger samples and more sophisticated statistical tests are needed. Second, in order to conduct a more detailed within-person analysis that focuses on proximal causes of sudden gains, one would need a more fine-grained assessment of both within- and between-session change in a larger sample of patients. Experience sampling methods (ESM) might be promising in this regard. In doing this, it might be relevant to differentiate between procedures and processes, to focus on the differentiation between the different domains, and to critically evaluate the scales of the instruments that are

used. Furthermore, it is important to assess patients' attributions for change more systematically. Under ideal circumstances therapists would track sudden gains on a session-by-session basis during the study, and in case a gain is detected they would ask the client to fill out an attribution questionnaire or administer a structured interview to learn more about this. Other interesting avenues for future research might be to contrast those with and without sudden gains, especially to shed more light on the role of alliance as a prerequisite for change, and to examine whether different processes contribute to sudden gains at different time points. This might add to the generalizability and representativeness of our findings. Additionally, future research should include other potential therapy processes that are relevant to sudden gains as well, such as self-esteem (8), positive and negative life events (13), and treatment adherence (29). This might increase both generalizatility as well as representativeness of findings. To conclude, the large proportion of missing and damaged videotapes points toward the importance of optimization of procedures for in-session-recordings and video storage. In the current study, therapists used handycams with mini DV tapes that they had to set up before each session. Each tape was manually digitalized afterwards. This allows for noise in both the recording- as well as the digitalization process. Fixed, automated digital systems in which the therapist only needs to press a button to start and stop the recording and automatic encrypted upload to a secured server after the session might be helpful to solve this issue.

### To Conclude

Although the literature on sudden gains has grown substantially in the past decade, with ∼100 additional studies on sudden gains published since the first meta-analysis in 2011 (3), almost none of them has focused on identifying the processes that happen in the sessions surrounding the gains. Sudden gain process research is an example of detailed time-course research. This type of research provides a powerful tool for testing mechanism hypotheses but is time-consuming and labor intensive. Probably because of this, these types of studies are rarely carried out, leaving this to be a neglected area in therapy mechanism research. Increased utilization of this approach may provide insight into the mechanisms of change in psychotherapy and thereby contribute to treatment enhancing strategies. We would therefore like to encourage other researchers to conduct follow-up research. Our study could serve as a framework for this.

## DATA AVAILABILITY STATEMENT

The anonymized raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The study was reviewed and approved by Maastricht University's Ethical Board. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MH and LL obtained funding for the study. LL, RD, TT, and MH designed the study. LL conducted the study and supervised the raters, in consultation with RD, TT, and MH. LL performed the data analysis, with assistance from JS-S, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.576432/full#supplementary-material

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# The Relationship Between Working Alliance and Symptom Improvement in Cognitive Therapy for Posttraumatic Stress Disorder

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**Background:** Working alliance has been shown to predict outcome of psychological treatments in multiple studies. Conversely, changes in outcome scores have also been found to predict working alliance ratings.

**Objective:** To assess the temporal relationships between working alliance and outcome in 230 patients receiving trauma-focused cognitive behavioral treatment for posttraumatic stress disorder (PTSD).

**Methods:** Ratings of working alliance were made by both the patient and therapist after sessions 1, 3, and 5 of a course of Cognitive Therapy for PTSD (CT-PTSD). Autoregressive, cross-lagged panel models were used to examine whether working alliance predicted PTSD symptom severity at the next assessment point and vice versa. Linear regressions tested the relationship between alliance and treatment outcome.

**Results:** Both patients' and therapists' working alliance ratings after session 1 predicted PTSD symptom scores at the end of treatment, controlling for baseline scores. At each assessment point, higher therapist working alliance was associated with lower PTSD symptoms. Crossed-lagged associations were found for therapist-rated alliance, but not for patient-rated alliance: higher therapists' alliance ratings predicted lower PTSD symptom scores at the next assessment point. Similarly, lower PTSD symptoms predicted higher therapist working alliance ratings at the next assessment point. Ruminative thinking was negatively related to therapists' alliance ratings.

**Conclusions:** Working alliance at the start of treatment predicted treatment outcome in patients receiving CT-PTSD and may be an important factor in setting the necessary conditions for effective treatment. For therapists, there was a reciprocal relationship between working alliance and PTSD symptom change in their patients during treatment, suggesting that their alliance ratings predicted symptom change, but were also influenced by patients' symptom change.

**Keywords: posttraumatic stress disorder, cognitive therapy, working alliance, cross-lagged associations, treatment outcome**

## INTRODUCTION

The working alliance, an important aspect of the therapeutic relationship, defined broadly as the "collaborative and affective bond between the therapist and patient" (1), has long been considered an essential component in the successful delivery of psychological therapy (2). Research findings have generally supported this assumption, with moderate but consistent associations found between alliance ratings and treatment outcome across different therapeutic approaches and disorders (1, 3). However, effect sizes are often in the small to moderate range; Horvath et al. (4) estimated an effect of $r = 0.28$ based on 190 alliance-outcome relationships reported in 201 studies. This is similar to results reported in previous meta-analyses with estimates of $r = 0.26$ [24 studies (3)] and $r = 0.22$ [79 studies (1)]. These associations are found whether the alliance rating is made by the patient, therapist or an observer. Some, but not all, studies have found that patients' alliance ratings are better predictors of outcome than therapists' or observers' (1, 3). Similarly, patients' ratings tend to be more consistent across therapy sessions than therapists' (1), suggesting that patients view the alliance as more stable. This finding requires replication, as few studies include ratings taken from both patient and therapist at multiple time points.

Studies investigating the predictive power of the working alliance have found differing effects depending on the time point at which the alliance is recorded. DeRubeis and Feeley (5) found that observer-rated working alliance measured in an early session of treatment for depression did not predict subsequent symptom change. However, symptom reduction during treatment predicted alliance later in therapy, raising the intriguing possibility that it is improvement in therapy which predicts how positively the alliance is viewed, rather than the other way around. Many studies have averaged alliance ratings taken across therapy (4) obscuring the temporal order, and therefore the causation relationship between alliance and outcome.

Studies which have investigated the temporal relationship between alliance ratings and outcome have produced mixed findings, with some reporting a relationship between alliance and treatment outcome (6–9), while others did not find evidence for a significant association (10, 11). The possibility that symptom change predicts later alliance ratings has also been replicated in several studies (7, 9, 12). A reciprocal relationship, whereby alliance is found to predict symptom improvement and vice versa has also been demonstrated (13, 14).

A number of studies have shown that a good working alliance predicts better treatment outcome in patients with PTSD [see (15) for a review]. However, most of these studies have used a pooled or single point measure of working alliance and have not examined the relationship in the opposite direction (i.e., symptom change influencing alliance). This study aims to assess both directions of the relationship by taking ratings of working alliance at three time points (after sessions 1, 3, and 5) within the treatment arc. This allows a more rigorous examination of the longitudinal relationships between the working alliance and treatment outcome in the early phase of treatment where the greatest changes in symptoms are observed (Ehlers et al., 2021)[1]. Ratings taken by both patients and therapists will be analyzed in a cohort of patients being treated for posttraumatic stress disorder (PTSD) using Cognitive Therapy for PTSD [CT-PTSD (16)], which is based on (17) cognitive model of PTSD. Working alliance has only been assessed in CT-PTSD in one previous study, where Brady et al. (18) compared high and low treatment responders on an observer-rated version of the Working Alliance Inventory (WAI) and found that the alliance/agreement component of the scale (comprising items on the task and goals of therapy), but not the relationship (or bond) component predicted better outcome. Brady et al. (18) also found that a perseverative thinking style (ruminative thinking) was related to lower working alliance and poorer outcomes. This study will explore these findings with a larger cohort and with patient and therapist ratings, including analysis of sub-scales of the WAI. Given the importance of ruminative thinking identified in Brady et al.'s study, we will also explore its association with working alliance and outcome, by analyzing whether rumination correlates with ratings of working alliance.

There may be reason to argue that the working alliance is particularly important in treatment for PTSD [e.g., (15)]. CT-PTSD, and most other evidence-based treatments, are trauma-focused, relying on the disclosure of intensely personal and painful experiences. Furthermore, avoidance of reminders of the trauma, as well as cognitive and emotional avoidance, are symptoms of PTSD, so a strong therapeutic alliance is needed to encourage patients to overcome their avoidance of talking about or thinking about their trauma. Lastly, many people with PTSD have experiences of interpersonal trauma, interpersonal difficulties and poor trauma-related social support, which have been shown to impede the development of a trusting alliance (19, 20). In this study, the effect on working alliance of interpersonal vs. non-interpersonal traumas will be assessed, and entered as a potential moderator in the relationship between working alliance and outcome.

The study investigated three questions:

1. **Prediction of treatment outcome**: In line with previous research, we predicted that higher working alliance rated by patients and therapists at the end of session 1 of CT-PTSD would predict better treatment outcome, measured by PTSD symptom severity at the end of treatment, controlled for baseline PTSD severity.
2. **Does working alliance drive symptom improvement during treatment or vice versa:** As previous research has yielded inconsistent results about the direction of changes in symptoms and working alliance, we investigated whether working alliance predicts symptom improvement a later session and/or vice versa (see **Figure 1**).
3. **Relationship of alliance with ruminative thinking**: In addition, we explored the relationship between patients' ruminative thinking style and patient and therapist ratings of working alliance, building on Brady et al.'s (18) results that ruminative thinking is associated with lower agreement/confidence, a component of alliance.

[1] Ehlers A, Wild J, Warnock-Parkes E, Stott R, Grey N, Cullen D, et al. Effectiveness of cognitive therapy in routine clinical care: Second phase implementation. (2021).

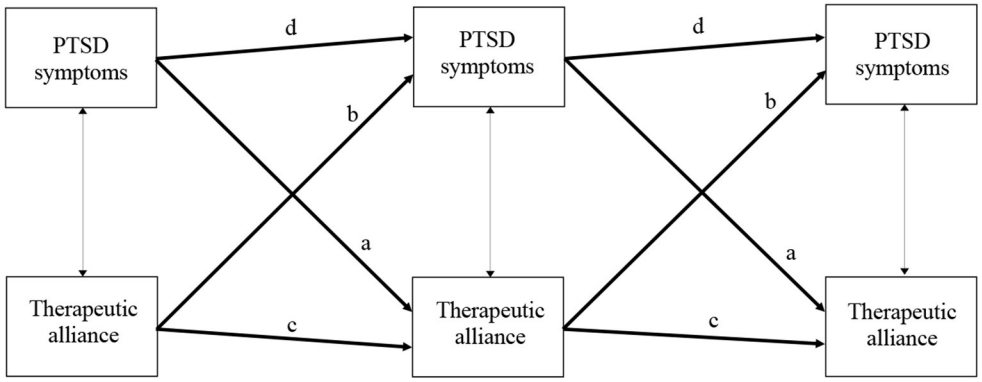


**FIGURE 1 |** Schematic figure of the hypothesized autoregressive, cross-lagged models. Thick paths with arrows in one direction, such as **a** ($PDS_t \rightarrow WAI_{t+1}$; t refers to the respective treatment session and t+1 to 2 sessions later) and **b** ($WAI_t \rightarrow PDS_{t+1}$) indicate cross-lagged effects, paths **c** ($WAI_t \rightarrow WAI_{t+1}$) and **d** ($PDS_t \rightarrow PDS_{t+1}$), indicate autoregressive effects; thin paths with arrows in both directions represent correlations at the same session ($PDS_t \leftrightarrow WAI_t$).

# METHODS

## Participants and Procedure

The current study is a secondary analysis of an effectiveness study of a cohort of 343 consecutive patients treated in routine clinical care (Ehlers et al., 2021)[1] with CT-PTSD (16). Patients had experienced a range of traumas, including various forms of interpersonal violence, accidents, and death of others.

Treatment was delivered by clinical psychologists, trainee clinical psychologists, and CBT therapists and trainees with other professional backgrounds (i.e., psychiatry, nursing) with a range of clinical experience. Patients completed PTSD symptom measures weekly before every treatment session (assessing their symptoms over the preceding week) and patients and therapists both completed working alliance measures at the end of sessions 1, 3, and 5. The measure was given to the patient by a research assistant, and not seen by the therapist.

Working alliance scores and the corresponding PTSD symptom severity for the week following sessions 1, 3, and 5 were used for the analysis of the bidirectional relationships, and the interval between assessments was thus two treatment sessions. Data were available for 230 patients for whom at least one patient or one therapist alliance measure and one PTSD symptom measure was available at the respective sessions. Demographics for the study sample of $N = 230$ are presented in **Table 1** and descriptive statistics are presented in **Table 2**.

Posttraumatic stress disorder symptom data at their final treatment session and at baseline was available for all patients. Exploration of any possible patterns of missing data for the other measures is reported in the preliminary analyses. Patients received on average $M = 9.95$ ($SD = 4.57$) treatment sessions in total.

## Measures

### PTSD Symptom Severity

Patients completed the Posttraumatic Diagnostic Scale [PDS (21)], which assesses the severity of the 17 PTSD symptoms specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition [DSM-IV (22)]. Patients rated the extent to which they were bothered by each of the 17 symptoms during the last week (4-point Likert scale) before each treatment session. Cronbach's α at session 1 was 0.88.

### Working Alliance

Therapeutic working alliance was assessed by the patients and therapists using the short version (23) of the WAI at the end of sessions 1, 3, and 5. The original version of the WAI was developed by Horvath and Greenberg (24) according to Bordin's (25) three components of alliance (tasks, goals, and bond). The short version consists of 12 items (7-point Likert scale), Cronbach's $\alpha$ at session 1 was 0.95 for the patient ratings and 0.96 for the therapist ratings. For the prediction of treatment outcome, sub-scores of the WAI (Task, Goal, Bond) were also calculated to aid interpretation.

### Ruminative Thinking

Ruminative thinking was measured at session 1 with the 6-item rumination subscale of the Response to Intrusions Scale (26, 27). Cronbach's $\alpha$ for this subscale was 0.86.

## Treatment

Cognitive Therapy for PTSD (CT-PTSD) aims to reduce the patient's sense of current threat by changing problematic meanings of the trauma and its consequences, elaborating and updating the memories of the trauma with information that gives them a less threatening meaning at present, discriminating triggers of intrusive memories, and changing behaviors and cognitive processes that maintain PTSD, such as rumination and safety behaviors.

Core interventions in CT-PTSD are: the collaborative development of an individualized case formulation; reclaiming/rebuilding your life assignments to address the clients' perceived permanent change after trauma by re-engagement with activities and relationships; changing problematic appraisals of the traumas and their sequelae via information, guided discovery and behavioral experiments; updating trauma memories by

**TABLE 1 |** Patient characteristics ($N = 230$).

| Variable | n | % | M *(SD)* |
|---|---|---|---|
| Age (in years) | 230 | | 37.77 (11.63) |
| Months since traumatic event | 228 | | 52.38 (78.88) |
| Gender | | | |
| Male | 100 | 43.5 | |
| Female | 130 | 56.5 | |
| Ethnicity | | | |
| White | 146 | 63.0 | |
| Ethnic minority | 84 | 37.0 | |
| Relationship | | | |
| Married/Cohabiting | 83 | 36.1 | |
| Divorced/Separated/Widowed | 35 | 15.2 | |
| Never married | 104 | 45.2 | |
| No information | 8 | 3.5 | |
| Education | | | |
| University | 67 | 29.1 | |
| A-levels | 29 | 12.6 | |
| GCSE | 49 | 21.3 | |
| Professional qualification | 20 | 8.7 | |
| No formal qualification | 19 | 8.3 | |
| No information | 46 | 20.0 | |
| Employment | | | |
| Employed/Self-employed | 104 | 45.2 | |
| Sick leave | 10 | 4.3 | |
| Disability/Retired | 14 | 6.1 | |
| Unemployed | 73 | 31.7 | |
| Other | 5 | 2.2 | |
| Student | 10 | 4.3 | |
| No information | 14 | 6.1 | |
| Type of main traumatic event | | | |
| Interpersonal violence | 150 | 65.2 | |
| Accident or disaster | 44 | 19.1 | |
| Death or harm to others | 24 | 10.4 | |
| Other | 12 | 5.2 | |

*n, number of available responses for each variable; %, percentage of study sample.*

**TABLE 2 |** Descriptive statistics of PTSD symptoms and working alliance ($N = 230$).

| Assessment | Measure | *M (SD)* | *n* |
|---|---|---|---|
| Initial | PDS | 33.78 (9.66) | 230 |
| After session 1 | PDS | 30.10 (11.22) | 210 |
| | $WAI_{Patients'rating}$ | 70.89 (11.28) | 152 |
| | $WAI_{Therapists'rating}$ | 65.06 (11.21) | 179 |
| After session 3 | PDS | 26.40 (12.20) | 193 |
| | $WAI_{Patients'rating}$ | 73.62 (9.01) | 130 |
| | $WAI_{Therapists'rating}$ | 67.06 (12.25) | 150 |
| After session 5 | PDS | 21.52 (12.73) | 179 |
| | $WAI_{Patients'rating}$ | 75.12 (9.68) | 105 |
| | $WAI_{Therapists'rating}$ | 68.88 (11.21) | 132 |
| Final session | PDS | 15.60 (14.12) | 230 |

*Sum scores for all measures are reported; 17 PDS items rated on a 4-point Likert scale ranging from 0 to 3; 12 WAI items rated on a 7-point Likert Scale ranging from 1 to 7; n = number of available responses for each variable.*

elaborating and updating the worst moments of the memory; discrimination training with triggers of reexperiencing; a site visit (returning to the scene of the trauma); dropping unhelpful behaviors and cognitive processes; a blueprint summarizing what the client has learned in treatment and planning for any setbacks. Throughout treatment, the work on appraisals is closely interwoven with memory work and is tailored to the case formulation. The specific cognitive therapy techniques depend on the client's pattern of emotions and underlying cognitive themes. For further details of treatment procedures and measures see https://oxcadatresources.com.

## Statistical Analysis

Preliminary analyses investigated any effects of PTSD symptom severity or degree of working alliance on the occurrence of missing data (coded as "1") vs. not missing (coded as "0") using logistic regressions; unstandardized parameter estimates are reported for these analyses. Welch tests were used to investigate any potential differences between patients who experienced interpersonal (coded as "−0.5") compared to non-interpersonal traumas (coded as "0.5") with regards to therapeutic alliance at the beginning of treatment and PTSD symptom severity at baseline and at the end of treatment. Moderation and simple slope analyses using multiple linear regressions investigated any effects between trauma type and alliance ratings on treatment outcome, controlled for baseline severity.

The first research question (prediction of treatment outcome by initial working alliance, controlled for baseline PTSD symptom severity) was tested using multiple linear regressions and we report unstandardized and standardized coefficients.

To investigate the second research question (whether working alliance drives symptom improvement during treatment or vice versa), autoregressive, cross-lagged panel models (28) were specified. As shown in **Figure 1**, these models tested effects of time for each of the variables (i.e., symptom improvements over time) and any causal effects between both variables (i.e., if working alliance drives improvement in symptoms, we would observe effects of the WAI on symptom scores at two sessions later, i.e., WAI at session 1 on symptoms at session 3, and from WAI in session 3 on symptoms at session 5, paths **b** in **Figure 1**; and vice versa if symptom change drives alliance change, paths **a** in **Figure 1**). Autoregressions (paths **c** and **d**) and cross-lag effects across sessions (paths **a** and **b**), and correlations within the same sessions were each set to be equal and freely estimated. In addition to reporting standardized (β) parameter estimates for the main research questions, unstandardized parameter estimates (b) are reported for these panel models (see **Table 3**). Model fit was evaluated based on the $\chi^2$-test statistic (29, 30) and the fit indices CFI (31), RMSEA (32), and SRMR (33). We set the criterion that at least one patient alliance score and one PTSD symptom score at the relevant sessions (either after session 1, 3, or 5) should be available for a patient to be included in the

**TABLE 3 |** Autoregressive and cross-lagged effects.

| Model | Effects | *b* | *SE* | β | *p* |
|---|---|---|---|---|---|
| Patients' alliance[a] | (a) $PDS_t \rightarrow WAI_{t+1}$ | −0.05 | 0.03 | −0.05 | 0.173 |
| | (b) $WAI_t \rightarrow PDS_{t+1}$ | −0.06 | 0.04 | −0.06 | 0.142 |
| | (c) $WAI_t \rightarrow WAI_{t+1}$ | 0.72 | 0.04 | 0.79 | <0.001 |
| | (d) $PDS_t \rightarrow PDS_{t+1}$ | 0.82 | 0.06 | 0.76 | <0.001 |
| Therapists' alliance[b] | (a) $PDS_t \rightarrow WAI_{t+1}$ | −0.12 | 0.04 | −0.12 | 0.001 |
| | (b) $WAI_t \rightarrow PDS_{t+1}$ | −0.14 | 0.04 | −0.13 | 0.001 |
| | (c) $WAI_t \rightarrow WAI_{t+1}$ | 0.76 | 0.04 | 0.75 | <0.001 |
| | (d) $PDS_t \rightarrow PDS_{t+1}$ | 0.84 | 0.05 | 0.77 | <0.001 |

*(a) and (b) indicate cross-lagged effects; (c) and (d) indicate autoregressive effects (see **Figure 1**).*
*[a] n = 185; [b] n = 213.*

respective panel analysis ($n = 185$ patients). Similarly, at least one therapist alliance rating and one PTSD symptom score had to be available at the relevant sessions for a patient to be included in the panel model investigating therapist alliance ($n = 213$ patients). In order to include all patients within those two sub-samples (symptom or alliance data only available at one or two of the three respective sessions) into the respective panel analyses, Robust Maximum Likelihood estimation (34) was used together with Full Information Maximum Likelihood (35).

The third research question (association between working alliance and ruminative thinking) was assessed with Pearson correlations ($r$).

Data were analyzed using *RStudio* (36) and the packages *lavaan* (37), *psych* (38), *sjmisc* (39), *skimr* (40), *emmeans* (41), and the *tidyverse* set of packages (42). R code for data analysis can be accessed at ETB's Open Science Framework repository (https://osf.io/4dqyx/).

# RESULTS

## Preliminary Analyses

### Missing Data

Whether PTSD symptom data after session 5 were missing or not did not depend on: PTSD symptom severity after session 1, $b = -0.01$, $SE = 0.01$, $b_p = -0.16$, $p = 0.352$; the degree of patients' alliance after session 1, $b = -0.01$, $SE = 0.02$, $b_p = 0.06$, $p = 0.779$; or therapists' alliance after session 1, $b = -0.03$, $SE = 0.02$, $b_p = -0.31$, $p = 0.091$.

### Trauma Type

Patients who experienced interpersonal traumas rated their therapeutic alliance after session 1 lower than patients who experienced other types of trauma, $t_{(130.04)} = -2.80$, $p = 0.006$, whereas there was no significant difference for therapist ratings, $t_{(154.46)} = -1.74$, $p = 0.084$. Patients who experienced interpersonal compared to non-interpersonal traumas did not differ in their PTSD symptom severity at baseline, $t_{(170.74)} = -1.17$, $p = 0.243$, or at the end of treatment, $t_{(181.70)} = 1.95$, $p = 0.053$.

Trauma type (interpersonal vs. non-interpersonal) did not significantly moderate any influence of patients' alliance ratings after session 1 on PTSD symptom severity at the end of treatment, controlled for baseline PTSD symptom severity, $b = 0.37$, $SE = 0.21$, $\beta = -0.29$, $p = 0.077$, $R^2_{adj} = 0.15$. However, a simple slope analysis revealed that, for patients who experienced interpersonal traumas, patients' therapeutic alliance after session 1 had a significant effect on reduction of PTSD symptom severity at the end of treatment, controlled for baseline severity, $b = -0.31$, 95% CI [−0.51, −0.11]. This relationship was not significantly different from zero for patients who experienced non-interpersonal traumas, $b = -0.06$, 95% CI [−0.29, 0.42].

Trauma type (interpersonal vs. non-interpersonal) also did not significantly moderate any effect of therapist' alliance ratings after session 1 on PTSD symptom severity at the end of treatment, controlled for baseline PTSD symptom severity, therapists' WAI: $b = -0.13$, $SE = 0.17$, $\beta = 0.10$, $p = 0.460$, $R^2_{adj} = 0.27$. For both patients with interpersonal and non-interpersonal traumas, the relationship between therapists' working alliance after session 1 had a significant effect on treatment outcome, controlled for baseline severity, interpersonal trauma: $b = -0.32$, 95% CI [−0.51, 0.14]; non-interpersonal trauma: $b = -0.45$, 95% CI [−0.74, 0.16].

## Analyses of the Main Research Questions

### Question 1: Prediction of Treatment Outcome by Early Working Alliance

Both higher patient-reported and therapist-reported working alliance after the first treatment session predicted better outcome, i.e., lower PTSD symptom severity at the final treatment session (controlled for symptom severity at baseline); patients' WAI: $b = -0.23$, $SE = 0.09$, $\beta = -0.19$, $p = 0.008$, $R^2_{adj} = 0.13$; therapists' WAI : $b = -0.36$, $SE = 0.08$, $\beta = -0.29$, $p < 0.001$, $R^2_{adj} = 0.28$. The results were the same if the three WAI sub-scales were considered independently (patients: Task sub-scale $p = 0.018$, Goal sub-scale $p = 0.004$, Bond sub-scale $p = 0.018$; therapists: Task $p < 0.001$, Goal $p < 0.001$, Bond $p < 0.001$).

### Question 2: Prediction of PTSD Symptom Severity by Prior Working Alliance and Prediction of Working Alliance by Prior PTSD Symptom Severity

#### *Fit Measures of the Autoregressive, Cross-Lagged Models*

Both cross-lagged, autoregressive panel models for the patients' and therapists' alliance ratings fit the data well; model for patients' WAI: $\chi^2_{(10)} = 12.61$, $p = 0.247$, CFI = 0.99, RMSEA [95% CI] = 0.04 [0.00, 0.10], SRMR = 0.05; model for therapists' WAI: $\chi^2_{(10)} = 22.16$, $p = 0.014$, CFI = 0.97, RMSEA [95% CI] = 0.08 [0.04, 0.13], SRMR = 0.06. In the patients' alliance model, 64% of variance was explained in PTSD symptom severity and 60% of variance in patient-reported working alliance after session 5. In the therapists' alliance model, 70% of variance was explained in PTSD symptom severity and 67% of variance in therapist-reported working alliance after session 5.

### *Parameter Estimates of the Autoregressive, Cross-Lagged Models*

***Patient-reported working alliance and PTSD symptom severity.*** A higher working alliance reported by patients (see **Table 3** and **Figure 1**) was not associated with lower PTSD symptom severity at the same session, $r = -0.08$, $p = 0.122$. Higher alliance scores after sessions 1 or 3 predicted higher alliance at the next assessment (i.e., alliance ratings after the session 1 predicted higher alliance ratings after the session 3 and alliance ratings after the session 3 predicted higher alliance ratings after the session 5; paths **c** in **Figure 1**), $\beta = 0.79$, $p < 0.001$. Lower PTSD symptom severity in the week after sessions 1 or 3 predicted lower PTSD symptom severity at the next assessment (i.e., PTSD symptom severity after the session 1 predicted PTSD symptom severity after the session 3 and PTSD symptom severity after the session 3 predicted PTSD symptom severity after the session 5; paths **d** in **Figure 1**), $\beta = 0.76$, $p < 0.001$. Thus, preceding levels of patient-reported therapeutic alliance predicted subsequent levels of patients' alliance and preceding levels of PTSD symptom severity predicted subsequent levels of symptom severity.

Taking into account these autoregressive coefficients, patients' self-reported PTSD symptom severity in the week after sessions 1 or 3 did not significantly predict a higher patient-reported alliance at the next assessment (i.e., PTSD symptom severity after the session 1 did not predict alliance after the session 3 and PTSD symptom severity after the session 3 did not predict alliance after the session 5; paths **a** in **Figure 1**), $\beta = -0.05$, $p = 0.173$. A higher patient-reported alliance after sessions 1 or 3 also did not predict lower PTSD symptom severity at the next assessment (i.e., alliance after the session 1 did not predict PTSD symptom severity after the session 3 and alliance after the session 3 did not predict symptom severity after the session 5; paths **b** in **Figure 1**), $\beta = -0.06$, $p = 0.142$. Thus, preceding levels of patient-reported therapeutic alliance did neither drive subsequent improvement in PTSD symptom severity, nor vice versa.

***Therapist-reported working alliance and PTSD symptom severity.*** A higher working alliance reported by therapists (see **Table 3** and **Figure 1**) was associated with lower PTSD symptom severity after the same session, $r = -0.16$, $p < 0.001$. Higher therapist-reported alliance after sessions 1 or 3 predicted higher therapist-reported alliance at the subsequent assessment (i.e., after the session 3 or 5; paths **c** in **Figure 1**), $\beta = 0.75$, $p < 0.001$, and lower PTSD symptom severity in the week after session 1 or 3 predicted lower PTSD symptom severity at the successive assessment (i.e., after the session 3 or 5; paths **d** in **Figure 1**), $\beta = 0.77$, $p < 0.001$. Thus, similar to the results from the auto-regressions in the patients' alliance model, preceding levels of therapist-reported alliance predicted subsequent levels of therapist-reported alliance and preceding levels of PTSD symptom severity predicted subsequent levels of symptom severity.

Taking into account these auto-regressions, lower PTSD symptom severity in the week after session 1 or 3 significantly predicted higher therapist-reported working alliance at the subsequent assessment (i.e., after the session 3 or 5; paths **a** in **Figure 1**), $\beta = -0.12$, $p = 0.001$, and higher therapist-reported alliance after session 1 or 3 predicted significantly lower PTSD symptoms at the subsequent assessment (i.e., after the session 3 or 5; paths **b** in **Figure 1**), $\beta = -0.13$, $p = 0.001$. Thus, unlike to the results from the cross-lagged parameters in the patients' alliance model, preceding levels of therapist-reported alliance did drive subsequent PTSD symptom improvement and vice versa.

### Question 3: Relationships With Ruminative Thinking

Therapist alliance ratings in the first session showed a negative relationship with patients' ruminative thinking about the trauma in the same session, $r = -0.19$, $p = 0.015$, whereas patient alliance ratings showed a non-significant positive relationship with rumination, $r = 0.13$, $p = 0.131$.

## DISCUSSION

This study aimed to assess whether higher working alliance predicted better treatment outcomes in patients receiving CT-PTSD. Higher working alliance at the start of treatment, as rated by both patients and therapists after session 1, was associated with greater symptom improvement, measured by symptom scores at the end of treatment, controlled for baseline scores. This extends the earlier findings of Brady et al. (18), who found that patients reporting a stronger working alliance were more likely to respond well to CT-PTSD, and replicates the findings of numerous other studies which have found a positive association between working alliance and therapy outcome, including in PTSD treatment (15). Although the effect sizes in our study were of small to medium size, they are in line with those of other studies in a range of different disorders (1, 3, 15). These results support the importance of establishing a good working relationship with patients in trauma-focused psychological therapies for PTSD, which is associated with treatment outcomes, although other processes such as reduction of negative appraisals also play a role (43). Higher ratings in the total score and all the three subscales Bond, Goal, and Task were predictive of better outcomes, suggesting that a positive relationship and agreement on mutual goals as well as agreement on concrete steps to be taken in therapy may be important in facilitating change. The alliance ratings were consistently high for both patients and therapists. The collaborative therapeutic style of CT-PTSD may have facilitated a positive working alliance.

Secondly, we aimed to find whether working alliance led to improved symptom scores or vice versa. The results from autoregressive, cross-lagged panel models in this study provided support for a bidirectional relationship between the patients' symptom improvements and working alliance rated by therapists during treatment. A measure of working alliance completed by therapists after sessions 1 and 3 of treatment predicted subsequent symptom severity (i.e., after session 3 and 5; see **Figure 1**), with a better alliance predicting lower symptoms scores, taking into account the preceding symptom scores. During treatment, therapist-rated alliance after session 3 and 5 was predicted by symptom scores at the preceding time point (i.e., after session 1 and 3; see **Figure 1**), as well as by preceding alliance ratings. This fits with other studies suggesting a reciprocal relationship between alliance and outcome (13, 14); a positive alliance leads to better therapy outcomes, and

better outcomes encourage therapists to view the alliance more positively. The reciprocal relationship found for working alliance contrasts with studies showing a unidirectional relationship between changes in negative cognitions about the trauma and symptom change in the treatment of PTSD. Cognitive change preceded symptom change in studies of CT-PTSD (43) and other trauma-focused cognitive behavioral treatments (44), and a reverse relationship was found in only a small minority of studies. Taken together, these findings suggest that cognitive change drives symptom change, but a good working alliance both facilitates, and is a result of, symptom change.

However, despite the overall relationship between patient-rated working alliance at the session 1 and improvement of PTSD symptoms during therapy, no significant cross-lagged associations between patients' alliance and symptoms were found in the early sessions of therapy when taking into account the significant effects of preceding symptom scores on subsequent symptom levels, and preceding alliance scores on subsequent alliance levels. Preceding levels of patients' alliance (i.e., after sessions 1 or 3; see **Figure 1**) did neither predict subsequent levels of PTSD symptom severity (i.e., after session 3 or 5; see **Figure 1**), nor vice versa (PTSD symptom scores in the week after session 1 or 3 did not predict the working alliance at the subsequent assessment, i.e., after session 3 or 5; see **Figure 1**), controlled for the respective auto-correlations of symptoms scores and alliance scores over time. Thus, the results for patient-rated alliance were mixed, which is in line with the literature. Some studies have shown that working alliance rated by PTSD patients is predictive of treatment outcomes [e.g., (45, 46)], but Forbes et al. (47) and van Minnen et al. (48) reported no association between working alliance and outcome in their PTSD samples.

One potential reason for this discrepancy is methodological. In contrast to earlier studies, the cross-lagged analyses used in this study controlled for autocorrelations within each measure, which were high. The sample that provided patient alliance ratings was somewhat smaller than that for therapist ratings, restricting power. There was also some indication of restricted variance in patient alliance ratings in the later sessions and ceiling effects, and is in keeping with previous studies which have found that patient ratings of alliance tend to be fairly stable during treatment (1). Indeed, the patients' ratings of alliance in this study were consistently fairly high after all the three sessions 1, 3, and 5. It may be that their early first impressions of the therapeutic alliance, based on a first session of therapy that was engaging and collaborative, changed very little as treatment progressed and did not affect, nor was affected by, changes in their symptoms. Beck (49) wrote that a good therapeutic alliance is "necessary but not sufficient" to effect change in cognitive therapy. It may be that the "good enough" working alliance for most of the patients in this study was sufficient for engagement with treatment, but that the major influence on symptom change did not lie in their perception of the therapeutic relationship, but in the tasks and techniques used in treatment to produce cognitive change. This could suggest that therapists should prioritize establishing a solid working alliance in early sessions as a foundation for other aspects of treatment.

The reason for the discrepancy between the cross-lagged associations of PTSD symptoms of therapist and patient alliance ratings is unclear. Therapists do have more experience in the process of therapy than patients, and may be more likely to pick up on aspects of the alliance that will prove beneficial for future outcomes. Other studies, however, have found the opposite effect, with patients' ratings of alliance more predictive of outcome than therapists' [e.g., (1, 3, 50)]. Due to the methodological properties of the autoregressive, cross-lagged panel models (51) it cannot be ruled out that the alliance ratings partly reflected some trait-like stability. This might have led to the lagged parameters not only representing within-person relationships over time, but also between-person processes. This methodological problem may have been more pronounced for patients, some of whom had PTSD-related problems trusting other people in general which may have influenced their ratings. Indeed, a history of interpersonal trauma was related to lower initial ratings of the therapeutic alliance, which is in keeping with other studies that have suggested that people with a history of interpersonal trauma may particularly struggle to form a strong therapeutic alliance [e.g., (52)], but trauma type did not moderate the relationship between the working alliance and treatment outcome. However, the finding from the simple slopes analysis did indicate a potential effect of interpersonal trauma on the alliance-outcome relationship. This relationship requires further investigation.

Finally, the study aimed to explore the relationship between ruminative thinking and working alliance, following Brady et al.'s (18) finding that observer-rated ruminative thinking was associated with lower working alliance and predicted poorer outcomes in CT-PTSD. In this study, negative correlations between patient-rated ruminative thinking and therapist ratings of working alliance were found, but a non-significant positive correlation was found when patients rated the alliance. This indicates that therapists, but not patients, see rumination as an unhelpful strategy and thus rate alliance lower when this happens. The differential effect of ruminative thinking on patients' and therapists' rating may thus have contributed to the different pattern of results for the cross-lagged relationship with symptom reduction, as therapists are more effectively spotting that rumination is an unhelpful strategy, linked to poorer treatment outcome. Potential clinical implications of this finding are that therapists should address ruminative thinking in a manner which preserves the working alliance, such as collaboratively establishing the effect it has on the maintenance of PTSD symptoms.

A strength of this study was that it was drawn from a consecutive cohort of PTSD patients with a wide range of traumas and ethnic backgrounds who received an evidence-based psychological treatment in routine care and that the direction of the relationship between working alliance and symptom change during treatment could be investigated by repeated assessments.

Methodological limitations of the study include ceiling effects in the alliance measure that may have potentially masked effects, as a possible restriction in variance restricts magnitude of correlations and correlation-based parameters. The sample was of a similar size to other studies in this area, but would benefit from replication with a larger sample due to more complex

analysis and estimation methods used in this study compared to previous studies. Another possible limitation is that the time lag between the therapy sessions was not always exactly 1 week, which may have led to some noise in the parameter estimates (53).

Despite these limitations, the study provides further insight into the relationship between working alliance and treatment outcome amongst patients receiving treatment for PTSD. It highlights the importance of a strong working alliance at the very start of treatment, possibly particularly with patients who have experienced interpersonal trauma and in addressing rumination. The mixed findings also indicate the importance of using ratings from multiple raters (therapist and patient) at multiple time points in treatment to fully understand the relationship between alliance and outcome in future studies.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because, we did not obtain consent to share patient data at the time of data collection but share the data analysis code and details of results. Requests to access the datasets should be directed to anke.ehlers@psy.ox.ac.uk.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by King's College and South London and Maudsley Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

EB wrote and revised manuscript, designed statistical analysis plan, and conducted statistical data analysis. HM wrote and revised manuscript, involved in literature review, contributed to treatment, data collection, and data analysis plan. MW involved in data management, contributed to data analysis plan, and critical revision of write-up. EW-P, JW, and RS contributed to treatment and clinical supervision, data collection, and critical revision of write-up. NG was the co-director of clinical treatment and clinical supervision, contributed to data collection, and critical revision of write-up. DC was the co-grant holder and contributed to critical revision of write-up. AE was the primary investigator of study and grant holder, designed and supervised data collection, clinical supervision, contributed to write-up, and critical revision. All authors contributed to the article and approved the submitted version.

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# Maintaining Outcomes of Internet-Delivered Cognitive-Behavioral Therapy for Depression: A Network Analysis of Follow-Up Effects

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**Background:** Depression is a highly prevalent mental disorder, but only a fraction of those affected receive evidence-based treatments. Recently, Internet-based interventions were introduced as an efficacious and cost-effective approach. However, even though depression is a heterogenous construct, effects of treatments have mostly been determined using aggregated symptom scores. This carries the risk of concealing important effects and working mechanisms of those treatments.

**Methods:** In this study, we analyze outcome and long-term follow-up data from the EVIDENT study, a large ($N$ = 1,013) randomized-controlled trial comparing an Internet intervention for depression (Deprexis) with care as usual. We use Network Intervention Analysis to examine the symptom-specific effects of the intervention. Using data from intermediary and long-term assessments that have been conducted over 36 months, we intend to reveal how the treatment effects unfold sequentially and are maintained.

**Results:** Item-level analysis showed that scale-level effects can be explained by small item-level effects on most depressive symptoms at all points of assessment. Higher scores on these items at baseline predicted overall symptom reduction throughout the whole assessment period. Network intervention analysis offered insights into potential working mechanisms: while deprexis directly affected certain symptoms of depression (e.g., worthlessness and fatigue) and certain aspects of the quality of life (e.g., overall impairment through emotional problems), other domains were affected indirectly (e.g., depressed mood and concentration as well as activity level). The configuration of direct and indirect effects replicates previous findings from another study examining the same intervention.

**Conclusions:** Internet interventions for depression are not only effective in the short term, but also exert long-term effects. Their effects are likely to affect only a small

subset of problems. Patients reporting these problems are likely to benefit more from the intervention. Future studies on online interventions should examine symptom-specific effects as they potentially reveal the potential of treatment tailoring.

**Clinical Trial Registration:** ClinicalTrials.gov, Identifier: NCT02178631.

**Keywords: depression, network analysis, maintenance, internet interventions, health-related quality of life**

# BACKGROUND

## Internet-Delivered Psychotherapy

Depression has become one of the greatest challenges to public health, especially in Western, industrialized societies. An increasing number of persons with mental health problems seek treatment. However, structural barriers prevent many of those affected from getting the best help possible (1, 2). Depending on the health care system, a major structural barrier results from financial reasons (treatment costs or lack of insurance coverage), lack of time for undergoing treatment, or lack of clarity about where to get an appointment. Patients' attitudes can also prevent them from getting treatment, mainly because mental health problems are expected to improve without treatment by a mental health professional, but also due to fear of stigmatization or involuntary hospitalization (3).

As a result, the need for evidence-based and cost-effective treatments that are easy to disseminate becomes evident. Internet-delivered psychotherapy could have the potential to overcome the aforementioned barriers, as accessing them is easy and practically anonymous (4), while being cost-effective compared to care as usual (5). In-depth interview studies with patients show that internet-based treatment components also increase accessibility when blended with in-person treatment settings (6). For psychiatric and psychosomatic disorders, internet-delivered interventions show effects that are comparable to face-to-face treatments (7). Massoudi and colleagues showed that interned-delivered psychotherapy is moderately effective compared to waiting list control groups while small effects can still be observed when compared to care as usual (8). They also summarized four studies reporting cost-effectiveness, concluding that online interventions reduce healthcare costs by significant amounts. Internet-delivered psychotherapy can therefore be regarded as a useful addition to the mental health care system and could be implemented in stepped-care approaches as well as blended interventions in routine care (9, 10). In their review, Massoudi et al. found the most evidence for Internet-delivered cognitive-behavioral therapy (iCBT). iCBT can currently be considered the most promising alternative to traditional face-to-face approaches. Patients use specially designed secure websites or mobile applications over a specified period of time. Most of these programs consist of systematic presentation of therapy content through text, instructions for independent practice of learned techniques ("homework"), and accompanying materials such as videos or audio recordings. Some programs include contact to therapists via e-mail or video conferencing software, but many completely self-guided programs exist (11). While these analyses show promising results, there are cases in which internet-delivered psychotherapy shows small or unsatisfactory effects. A recent meta-analysis on iCBT for anxiety and depression in adolescents and young adults showed moderate effects for post-treatment symptom scores, but only small effects at follow-up (12). Generally, follow-up effects of iCBT tend to be small and non-significant. While it is possible that the effects of these interventions diminish after some time, another reason may also lie in the way symptoms are measured in most studies.

## Current Issues in the Measurement of Treatment Effects

In studies evaluating the effects of psychiatric and psychotherapeutic interventions, it is common practice to report mean differences. The reported mean values typically consist of the sum or average scores of psychometric scales to measure the severity of symptoms. However, Fried and Nesse (13) argued that symptoms of mental disorders should be analyzed on the item level, because important information is lost when using sum scores. They provided several examples for this in the example of depression. First, research on biomarkers for depression revealed that many of its biological correlates are symptom-specific (14). Second, many treatments are effective for specific symptoms only. For example, antidepressants were found to reduce depressive mood, anhedonia and feelings of worthlessness while their side-effects often mimic other symptoms like sleep problems, fatigue and suicidal ideation (15, 16). Psychotherapy might target different symptoms and could also have side-effects. Fournier et al. (17) found that cognitive psychotherapy reduced atypical-vegetative symptoms like hypersomnia, weight gain or changes in appetite. Bekhuis et al. (18) analyzed the effects of psychotherapy compared to psychotherapy combined with antidepressants and found that combined therapy was significantly more effective in reducing symptoms of feeling entrapped, emotional lability, worry, hopelessness, obsessive thoughts, blue mood, and feeling low in energy. Regarding side-effects, a qualitative analysis of a large sample found that patients receiving iCBT frequently report increases of anxiety, stress or insomnia (19). Thus, using sum scores could lead to inaccurate assessments of the efficacy of available treatments. Third, symptoms of depression are differentially associated with overall psychological functioning. Changes on the item level can be manifold but lead to the same changes on the scale level. Clinically, however, changes on a scale value can have various meanings. Using an example from a depression scale, a decrease in suicidality has completely different clinical implications than a change in eating behavior. The different

arguments against the use of scale values were followed by an increase of research on symptom-specific intervention effects. For example, Hieronymus and colleagues (15) have shown that the apparent ineffectiveness of antidepressants in less severe depression is no longer detectable when examining the symptoms included in the 6-item Hamilton Depression Rating Scale. For depressed mood, feelings of guilt, impairment of work and loss of interest, psychomotor retardation, psychic anxiety, and general somatic symptoms, antidepressant effects were independent of baseline severity.

## Network Analysis

A promising method that is suitable for analyzing symptom-specific effects of psychological and psychiatric interventions, which has gained great popularity in recent years, is network analysis (20). When applied to psychopathology, mental disorders are treated as systems of interrelated symptoms. Typically, a correlation matrix for the items is calculated and transformed into a partial correlation matrix. Partial correlations indicate the pairwise relationship between two symptoms after possible confounding influences of other items in the network model have been removed. These partial correlations can be used, for example, to better understand the structure of the co-morbidity of mental disorders (21, 22).

The usefulness of the network approach is not limited to epidemiology but can also provide interesting insights for the therapy of mental disorders. In addition to symptoms, a binary "treatment" variable can be included in a network model. Symptoms that correlate negatively with this variable are directly affected by the intervention. We refer to this as "direct effects." Symptoms that in turn correlate with the directly affected symptoms may also change, which we refer to as "indirect effects."

Following this approach, Boschloo et al. (23) performed a network analysis and found that Deprexis directly targets a subset of depressive symptoms (feelings of guilt, concentration problems, fatigue and sleep problems) and that participants with high scores on these symptoms benefit more from the intervention. Blanken and colleagues (24) introduced a new network-based method to investigate such symptom-specific treatment effects: Network Intervention Analysis (NIA). In their study of patients suffering from insomnia, network models were used to analyze the sequential effects of an internet-delivered cognitive-behavioral intervention for insomnia compared to a waiting list control group over the course of several points of assessment. They could not show that the intervention primarily reduced insomnia symptoms and that these effects followed a certain temporal order. First, early morning awakening was reduced in the first week, followed by suicidal thoughts an the second week and difficulty maintaining sleep in week 3 and dissatisfaction with sleep in week 4. Depressive symptoms correlated with these symptoms reduced as well, suggesting indirect effects that result from an improvement of insomnia symptoms caused by the intervention.

Only recently has this field of research been looking at the effects of interventions beyond symptoms commonly associated with depression. A study by Cervin et al. (25) used network intervention analysis to study the symptom-specific effects of congnitive-behavioral therapy, antidepressant medication and their combination in pediatric anxiety disorders. They could show that, in addition to symptom reduction, all treatments achieved their effects also by a reduction of family interference and avoidant behavior. NIA therefore offers important insights into the working mechanisms of psychiatric treatment that would be concealed if using scale values to determine treatment effects.

## The Current Study

The analysis presented here is based on the EVIDENT study, a large randomized controlled trial on the effects of an online cognitive-behavioral intervention for depression (Deprexis). Symptom-specific effects of Deprexis were already studied using data from this study (23) and in another data set (26). However, only depressive symptoms directly after the intervention were considered. Thus, we will include a measure of health-related quality of life in our analysis, which will potentially reveal treatment effects that go beyond symptom reduction. In addition, while Klein et al. (27) reported that Deprexis continues to show small but significant long-term scale-level effects until up to 1 year, symptom-level effects in the follow-up period have not yet been studied.

In summary, the goals of this study were two-fold: first, we were interested in the direct and indirect effects of this intervention both on depressive symptoms as well as health-related quality of life. Second, our goal was to examine symptom-level effects over an extended period of time of up to 12 months. Based on previous network intervention analysis studies, we hypothesized that (a) Deprexis usage is linked to a reduction to a limited set of symptoms, (b) that a significant portion of the Deprexis effect is expressed indirecty and (c) that direct treatment effects become less pronounced in the follow-up period while changes in item means remain relatively stable.

# METHODS

## Trial Design and Participants

We analyzed data from the "Effectiveness of Internet-based Depression Treatment" (EVIDENT) trial (28). EVIDENT was a large ($N = 1{,}013$) multicenter randomized controlled trial comparing an internet-delivered cognitive-behavioral intervention (Deprexis) with care as usual (CAU) for mild to moderate depressive symptoms. Patients scoring between 5 and 14 on the Patient Health Questionnaire-9 [PHQ-9 (29)] were included in the study. Participants were randomized equally to one of those conditions. Participants of this trial were free to use any form of treatment, including medication and psychotherapy. The treatment group received access to the Internet intervention in addition to their usual treatment. The internet-delivered cognitive-behavioral intervention "Deprexis" is a 12-week individually-tailored self-help programme based on cognitive-behavioral therapy. It consists of 10 modules covering a variety of techniques, like cognitive restructuring, behavioral activation, acceptance, mindfulness exercises, problem solving. Deprexis can be used with or without guidance by a mental health professional. In the EVIDENT trial, participants with

mild depressive symptoms [PHQ-9 sum score 5 to 9 (30)] received the unguided version, while participants with moderate symptoms (PHQ-9 sum score 10 to 14) were contacted once a week by a trained supporter via e-mail. After the 12-month randomized-controlled trial (RCT) period, the CAU group had access to Deprexis as well. A more detailed description of the Deprexis programme is given by Meyer et al. (31).

Depression symptoms and overall impairment were measured before trial onset (baseline), directly after the trial (post treatment) and over a follow-up period. Full assessments were conducted at three, 6 and 12 months after randomization. Additionally, monthly assessments of depressive symptoms were conducted between the post-assessment and the twelve-months follow-up. Then, an extended follow-up period of 18, 24, 30, and 36 months was offered to participants. In this period, the control group also had access to the Deprexis treatment. **Figure 1** shows the study flow chart and sample sizes. While the EVIDENT trial conducted intention-to-treat analyses, we analyzed only the available data of every assessment. Sample sizes for all assessments included in this study are specified in **Table 1**.

## Instruments

The nine-item Patient Health Questionnaire (PHQ-9) (29) was used as a primary outcome measure. The PHQ-9 is a relatively short, but highly reliable and well-validated self-report questionnaire for depression severity. In a validation study on the German general population, it was shown to have a one-factor structure and a high internal consistency (Cronbach alpha:.88).

The "Short Form-12" (SF-12) (32) was included to measure the perceived health status. It includes 12 items assessing the impact of impairment by physiological and psychological problems on health-related quality of life. The SF-12 has an acceptable internal consistency (Cronbach alpha:.89 for physical health,.76 for mental health) and was shown to be predictive of various health conditions (32).

## Statistical Analysis

In order to analyze the symptom-specific effects of the treatment, we used Network Intervention Analysis (24). We closely followed the proposed method by Blanken and colleagues (24), using Mixed Graphical Models (MGM) to estimate network models. For each assessment, we estimated a LASSO-regularized network that included the psychometric scales as well as a binary treatment allocation variable. Regularization methods like LASSO reduce the occurrence of false-positive edges in network models (33), thus minimizing spurious findings while increasing the interpretability of networks. The LASSO tuning parameter was selected using 10-fold cross-validation. We included all symptom items of the PHQ-9 and the SF-12 as continuous variables and added a binary treatment allocation variable (0: care as usual, 1: Deprexis intervention). The SF-12 included four yes/no items that were also treated as categorical binary variables. Because the CAU group got access to Deprexis after the 12-month follow-up, the extended follow-up assessments were excluded from network intervention analysis. If not stated otherwise, all analyses use the available data and missing data were removed using listwise deletion.

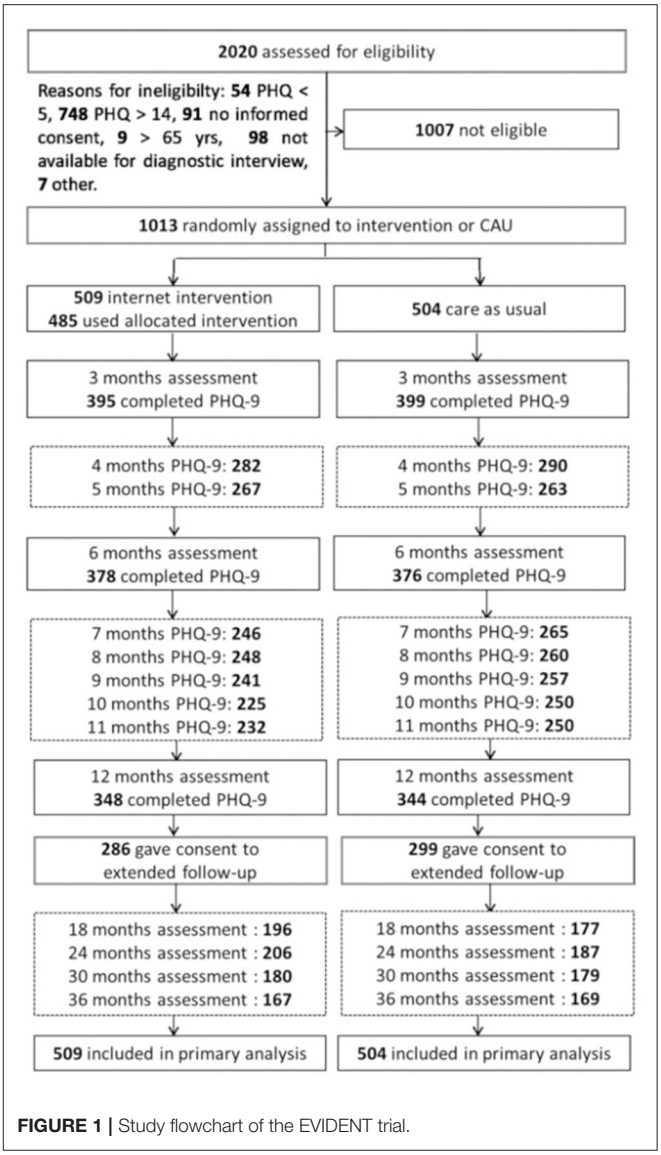


**FIGURE 1 |** Study flowchart of the EVIDENT trial.

We used the resampling function implemented in the MGM package to conduct a bootstrap analysis of network edge stability. For every network model, we drew 100 bootstrap samples for which we fitted the models. We then plotted the sampling distribution for every edge weight. The plots show the number of times an edge was estimated to be non-zero when resampling, as well as the 5 and 95% quantiles of the estimates. We will report the stability estimate (i.e., the percentage of bootstrap runs in which the edge was estimated as being non-zero) for the reported edge weights. For example, a stability of 98% indicates that the edge was found to be non-zero in 98 of 100 bootstrap runs. Full result plots for the resampling procedure of every model are available in the online supplement.

### Graphical Representation

We used the R package qgraph (34) to plot the network models. In these plots, the nodes represent the symptoms and treatment

**TABLE 1 |** Overview of assessments, sample sizes, between-group standardized mean differences (Cohen's *d*) for main assessments and intermediary PHQ-9 assessments, including 95% confidence intervals.

| Timing of the assessment | PHQ-9 | SF-12 mental | SF-12 physical |
|---|---|---|---|
| 3 months (post; *N* = 794) | −0.40 [−0.54; −0.26] | −0.45 [−0.30; −0.16] | −0.08 [−0.22; 0.06] |
| 4 months (*N* = 572) | −0.44 [−0.61; −0.28] | - | - |
| 5 months (*N* = 530) | −0.45 [−0.62; −0.27] | - | - |
| 6 months (follow-up; *N* = 754) | −0.36 [−0.50; −0.21] | −0.21 [−0.35; −0.06] | −0.04 [−0.18; 0.11] |
| 7 months (*N* = 511) | −0.32 [−0.49; −0.14] | - | - |
| 8 months (*N* = 508) | −0.28 [−0.46; −0.11] | - | - |
| 9 months (*N* = 498) | −0.23 [−0.41; −0.05] | - | - |
| 10 months (*N* = 475) | −0.17 [−0.35; 0.01] | - | - |
| 11 months (*N* = 482) | −0.11 [−0.29; 0.06] | - | - |
| 12 months (follow-up; *N* = 692) | −0.27 [−0.43; −0.11] | −0.24 [−0.40; −0.07] | −0.08 [−0.24; 0.09] |
| 18 Months (follow-up*; *N* = 373) | −0.14 [−0.35; 0.06] | −0.08 [−0.29; 0.13] | −0.17 [−0.38; 0.04] |
| 24 Months (follow-up*; *N* = 393) | −0.14 [−0.34; 0.06] | −0.16 [−0.36; −0.04] | 0.06 [−0.14; 0.26] |
| 30 Months (follow-up*; *N* = 359) | −0.06 [−0.26; 0.15] | −0.01 [−0.22; 0.20] | 0.08 [−0.22; 0.20] |
| 36 Months (follow-up*; *N* = 336) | −0.03 [−0.18; 0.25] | 0.02 [−0.19; 0.24] | 0.14 [−0.08; 0.35] |

*The SF-12 is not available for the monthly assessments. Negative values indicate lower scores for the Deprexis group compared to the CAU group. *: participants from the CAU group had access to the intervention at this point.*

allocation, while the edges represent partial correlations between nodes. Edges can be green, indicating a positive correlation between two nodes, or red, indicating a negative correlation. The thickness of edges is proportional to the strength of the correlation. For example, red connection between the Treatment node and a symptom indicates that a reduction of this symptom can be explained by using Deprexis. The node size changes if a mean score changes relative to its baseline over and above changes in the CAU group. Graph layout was done using a fixed, three-layer structure: on top, the "intervention" variable was placed. Below, items directly affected by the treatment are positioned. The third layer contains all other items. To ease the interpretation of successive graphs, the layout from the baseline graph was used for all other graphs as well.

### Estimation of Direct and Indirect Effects

Network models can be analyzed by calculating a number of node centrality measures (33). These measures are used to estimate the influence of single nodes in a model on other nodes. For example, by summing the absolute edge weights of one node, its "strength" can be calculated. "Betweenness" indicates how often one node lies on the shortest path between two other nodes. To determine direct as well as indirect effects of the intervention, we used the centrality measure "bridge expected influence" (BEI) (35). This measure is defined as the sum of signed edge weights that connect nodes from two predefined communities. We defined the treatment allocation variable as one "community" and PHQ-9 and SF-12 items as another. Thus, the direct effect of Deprexis usage on the measured symptoms is the BEI of the treatment allocation variable. The BEIs of the symptom nodes show how the overall effect can be broken down into symptom-specific effects. The "two-step BEI" can be computed by taking into account the influence of nodes affected by the intervention on other nodes. For example, if the treatment reduces "depressive mood" and the "depressive mood" item is correlated with "suicidality," the two-step BEI would include the connections between those symptoms because a reduction of "depressive mood" is likely to reduce "suicidality" as well. Thus, the "two-step BEI" can be used as an estimate of additional indirect treatment effects.

### Visualizing Treatment Effects on Symptom Severity

As proposed by Blanken et al. (24), we standardized item values at each assessment to the baseline value and subtracted the standardized differences of the treatment group from those of the control group. This way, we can visualize the symptom reduction that can be attributed to the intervention. Smaller nodes in the network plots are those most affected by the intervention.

### Predicting Treatment Effects From Baseline Score Profile

Similar to Boschloo et al. (23), we were interested in the predictive utility of item scores affected by the treatment in the network models. Thus, we calculated a baseline severity indicator by averaging item scores of those items affected by the treatment in the "post" model. As a control, we calculated another index consisting of all items not directly affected by the treatment. We then correlated this indicator with symptom reductions at all assessment points.

## RESULTS

## Outcome

The between-group effect sizes on the PHQ-9 and the two subscales of the SF-12 are summarized in **Table 1**. It shows that the mean mental health symptom burden is stable for up to 12 months after the start of the study. These effects were not found in the extended follow-up period in which the CAU group also had access to Deprexis.

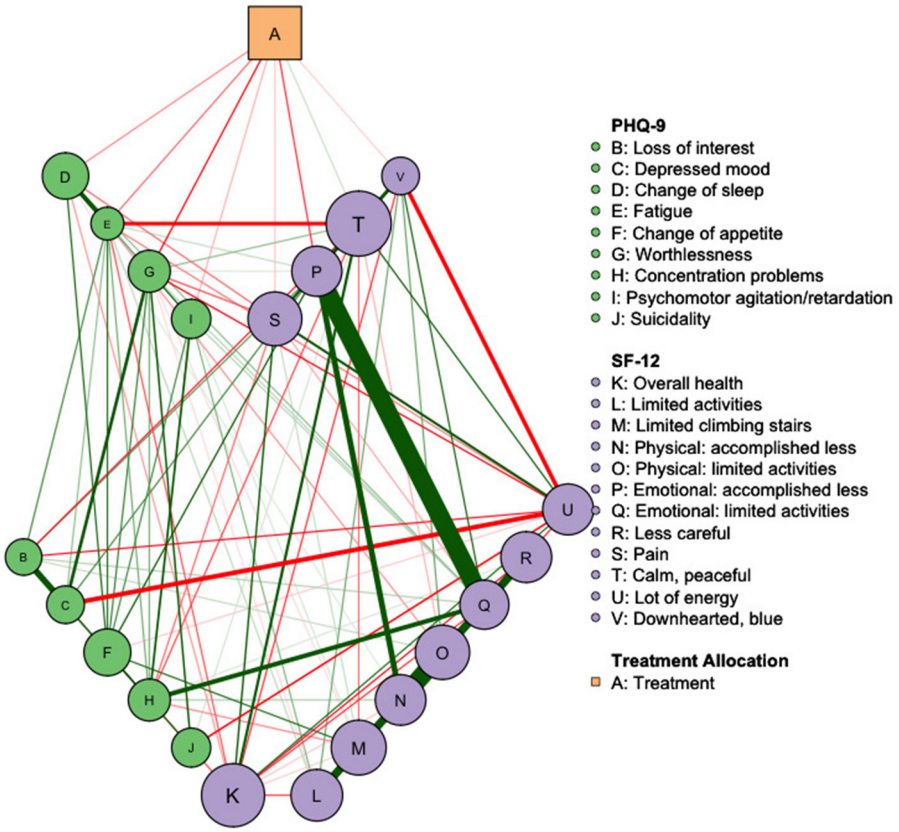


**FIGURE 2 |** Network diagram of treatment allocation, depressive symptoms and health-related quality of life at post-treatment assessment. Red edges indicate negative correlations, green edges indicate positive ones. Smaller nodes have greater pre-post mean reductions compared to the control group. Nodes directly affected by the treatment are arranged in the first line. $N = 794$.

## Network Intervention Analysis

Despite the modest effects at the scale level, it is possible that the long-term effects can only be seen on certain items. In order to gain a more detailed insight into the effects of deprexis and to be able to distinguish indirect from direct effects, NIA was used. Some BEI values are used for interpreting treatment effects. See **Appendix A5** for a full summary of BEI values for each item and assessment. For the sake of reproducibility, correlation matrices of all network models are provided in the online supplement.

The network model revealed that the effect of Deprexis was directed at a subset of symptoms. As depicted in **Figure 2**, using Deprexis directly reduced a subset of seven item scores: "worthlessness" (BEI: −0.12, stability of the edge, measured by percentage of non-zero estimates in bootstrap runs: 100%), "accomplished less because of emotional problems" (BEI: −0.09, stability: 74%), "fatigue" (−0.06, stability: 82%), "change of sleep" (−0.05, stability: 74%), "psychomotor agitation" (−0.03, stability: 71%), "pain" (−0.02, stability: 72%) and "downhearted, blue" (−0.02, stability: 52%). The item "Calm, peaceful" showed a slight increase that can directly be explained by using Deprexis (0.02, stability: 62%). Additionally, indirect treatment effects can be observed. For example, Deprexis use was most strongly associated with reduced "worthlessness," which is positively correlated with "depressed mood." This suggests that reductions of "depressed mood" can be explained by the direct reduction of "worthlessness." A reduction of "fatigue" on the other hand will lead to an increase in "calm peaceful," as indicated by a negative connection between these two items.

The BEI of the treatment node was −0.36 in the first step and −0.62 in the second step, suggesting that a significant proportion of the treatment effect is indirect.

As depicted in **Figure 3**, network models for the intermediary PHQ-9 assessments at 4 and 5 months again revealed the association of Deprexis treatment with "Worthlessness" (stability: 98%), "Psychomotor agitation" (stability: 95%), "Fatigue" (91%) and "Change of sleep" (stability: 82%). In the 5 months-assessment, treatment was most strongly associated with "Change of sleep" (stability: 99%), while reductions of other symptoms, as well as the overall network structure, remained relatively stable. First- and second-step BEIs of the treatment variable were −0.34/−0.62 after 4 months and −0.32/−0.39 after 5 months. As shown in **Figure 4**, this effect was also observed after 6 months.

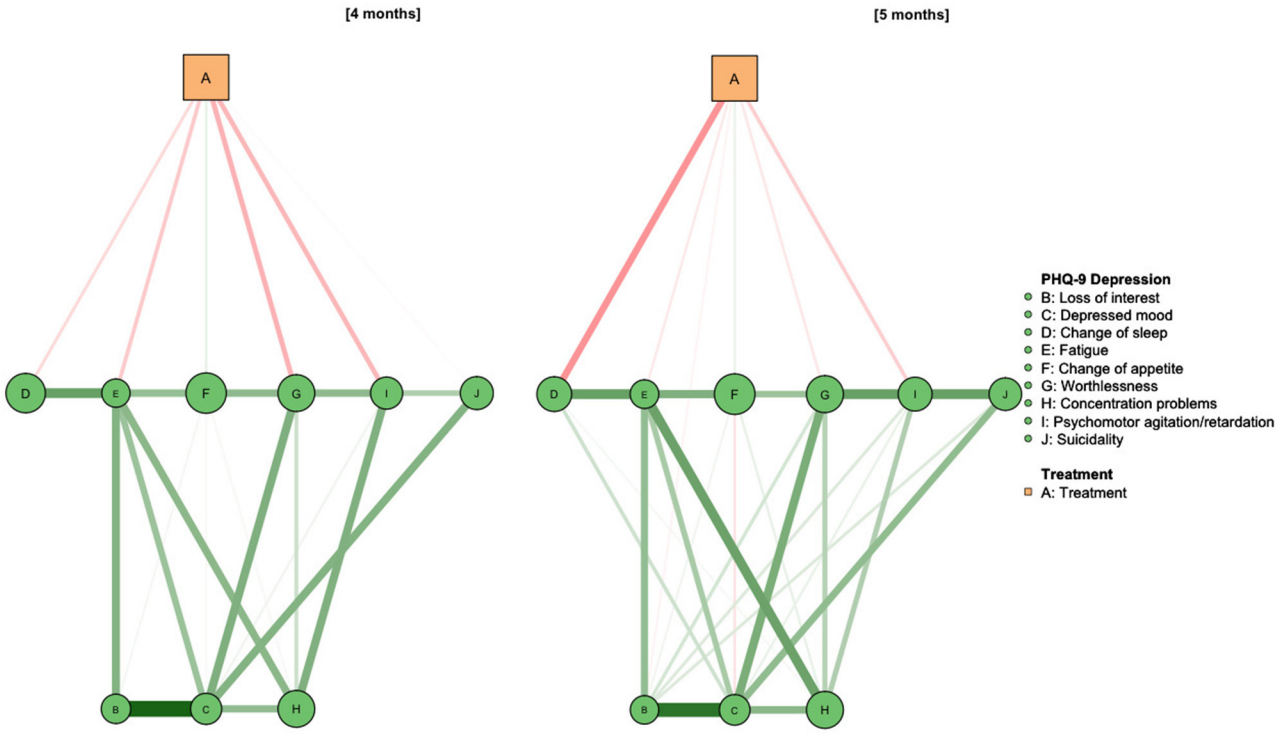


**FIGURE 3 |** Network diagram of treatment allocation, depressive symptoms and health-related quality of life at 4 and 5 months after study onset. Ns = 572 (4 months) and 530 (5 months).

At this point, Deprexis usage was associated with "Change of sleep" (BEI: −0.12, stability: 98%), "Worthlessness" (−0.01, stability: 61%), "Concentration problems" (−0.04, stability: 73%), "Psychomotor agitation" (−0.05, stability: 86%), and "Suicidality" (−0.04, stability: 67%).

The treatment effects decrease continuously in the course of the further follow-up time. This can be seen in **Figure 5** and is indicated by the drop in BEI at 7 months (−0.24) to −0.09 at 11 months. The last follow-up assessment we analyzed was conducted at 12 months and is depicted in **Figure 6**. Here, effects on the PHQ-9 were comparable to the previous assessments (treatment BEI: −0.10) and the overall effects can be explained by small effects on "Fatigue" (BEI: −0.05, stability: 67%) and "Suicidality" (BEI: −0.03, stability: 73%). When taking account indirect effects, the BEI of the treatment variable increases to −0.28.

## Prediction of Treatment Outcomes and Stability by Baseline Severity Indicator

As shown in **Table 2**, the baseline severity indicator was significantly correlated with greater PHQ-9 symptom reductions in the Deprexis group, with the exception of the 6 months-assessment. In the CAU group, the indicator was correlated with stronger outcomes in the 36 months-assessment. The control indicator was not significantly associated with outcomes at any time point (All $|r| < 0.16$, $p > 0.18$).

# DISCUSSION

In this study, we applied a novel approach to evaluating long-term treatment efficacy to a data set from the EVIDENT trial (EffectiVeness of Internet- based DEpressioN Treatment) which has examined the effectiveness of "Deprexis," an online intervention for depression. This is the first study using Network Intervention Analysis for studying long-term follow-up effects of internet-delivered treatments of depression. Our findings can be summarized as follows:

First, effects of Deprexis in addition to CAU are likely to result by affecting activity patterns (indicated by direct treatment effects on "fatigue" and "psychomotor agitation/retardation"), sleep behavior ("change of sleep") and depressive cognitions ("worthlessness").

Second, patients who score higher on the directly affected items ("worthlessness," "accomplished less because of emotional problems," "fatigue," "change of sleep," "psychomotor agitation," "pain," "downhearted, blue" and "Calm, peaceful") at baseline profit more from Deprexis throughout the whole study period. This could indicate a patient subtype that benefits particularly from Deprexis.

Third, a large portion of treatment effects can be better explained by changes in other symptoms than by assignment to the treatment group. We examined this relation of direct to indirect treatment effect size by comparing one-step and two-step expected influence values. This means that Deprexis

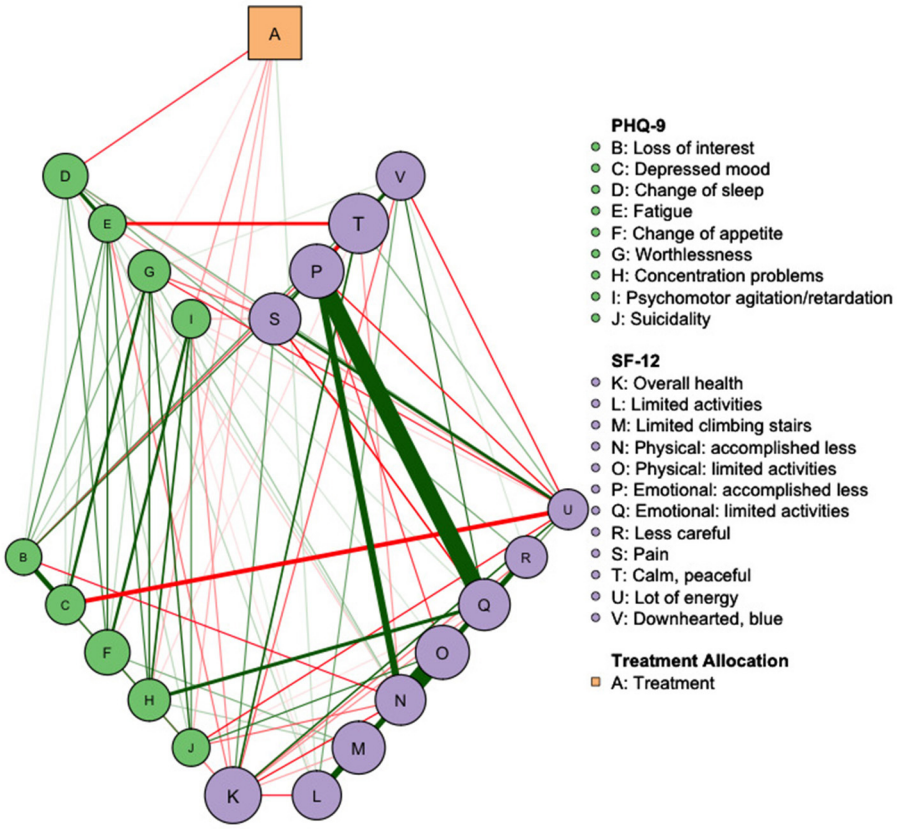


**FIGURE 4 |** Network diagram of treatment allocation, depressive symptoms and health-related quality of life at 6 months after study onset. $N = 754$.

tackles only a small subset of problems but is successful in reducing many other symptoms as a secondary effect. For example, "Depressed mood" was significantly correlated with "Worthlessness" and also decreased after treatment. Similarly, "Fatigue" was directly affected and correlated with "Loss of interest" as well as "Change of appetite," both of which showed decreases in the treatment group.

Fourth, Deprexis usage affects health-related quality of life by reducing depressive feelings, increasing feelings of calmness, reducing functional impairment by emotional problems, and pain.

These results presented increase the understanding of the effects of online interventions on depression by also evaluating follow-up data. They also reveal how changes at the symptom level affect the health-related quality of life.

## Scale and Item-Level Treatment Effects

Small to moderate between-group effects were found on the scale level until up to 12 months after study onset for depressive symptoms measured by the PHQ-9 and for mental health related quality of life measured by the SF-12. No effects were found for the physical health related quality of life. In the extended period, CAU participants could also access Deprexis. During this period, group differences on the scale level disappeared completely, indicating that even this delayed treatment with Deprexis had at least some effects for the CAU group as well.

At the item level, it was found that different PHQ-9 items reacted differently to the treatment. Between-group effects were smaller and more transient for some items (e.g., "Change of appetite," "Change of sleep," "Concentration problems," and "Worthlessness") than for others (e.g., depressed mood, fatigue, loss of interest and suicidality). It is noteworthy that the strongest and longest lasting effect could be demonstrated for the suicidality item. Given the high scalability of online interventions like Deprexis, even the modest effects observed in this study can be relevant.

Interestingly, participants scoring higher on the items affected by Deprexis at the post assessment showed stronger treatment outcomes throughout the whole trial period, including the follow-up period, a finding that could have implications for further personalization of this intervention. For example, while patients reporting higher values for "Worthlessness", "Fatigue", "Psychomotor agitation" and "Change of sleep" might be directed to the standard version of Deprexis, while a modified version

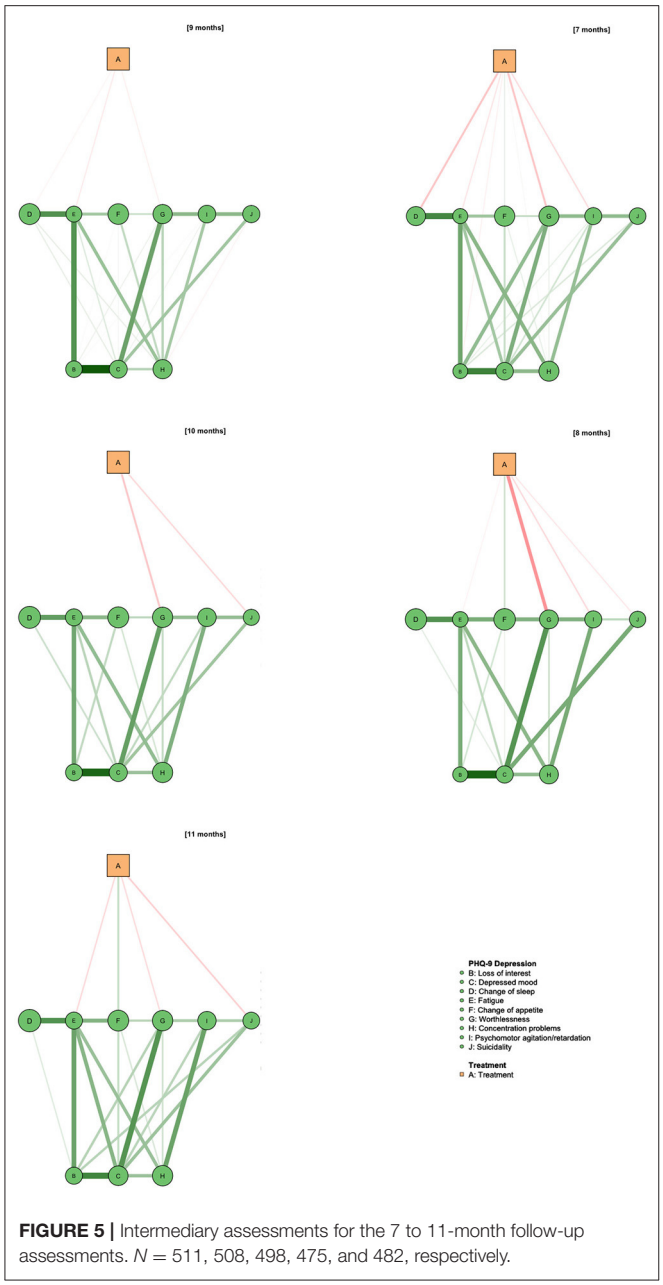


**FIGURE 5 |** Intermediary assessments for the 7 to 11-month follow-up assessments. *N* = 511, 508, 498, 475, and 482, respectively.

of the treatment could be developed for patients reporting higher scores on the other items. This modified version might be specifically tailored to address problems that we did not find to be directly affected by Deprexis treatment. Those symptoms include "Loss of interest" and "Lot of energy" from the SF-12, so the modification could be more effective by emphasizing techniques that focus on behavioral activation (36) more strongly. The fact that the baseline severity index also correlated with the effect in the CAU group at the 36 months assessment can possibly be explained by the fact that the CAU group could access Deprexis after the 12 months follow-up.

## Network Analysis

By using network analysis and including a treatment variable, we were able to isolate direct and indirect effects of Deprexis. In contrast to the mere analysis of changes in mean scores, this type of analysis goes beyond looking at symptom reduction and can provide information about possible mechanisms of action. Although connections in the network and symptom reduction correlate at the item level, not every item that showed a decreased mean value must also have a connection in the network. Instead, the items tend to have a connection to the treatment, the reduction of which cannot be explained by the reduction of other symptoms. The strong direct effect on self-devaluating cognitions (measured by the PHQ-9 item "Worthlessness") is expected from cognitive-behavioral therapy, as changing depressive cognitions are the main focus of CBT (37). Similarly, reductions in "Fatigue" and "Accomplished less because of emotional problems" could be in line with behavioral activation and reduction of avoidant behavior, both of which are well-established working mechanisms in CBT for depression (38).

Indirect (second-step) treatment effects were more diverse and encompassed most of the PHQ-9 items. Since we were only able to distinguish Deprexis and CAU group, we can only speculate which specific ingredients of the intervention led to these effects. Assuming that "worthlessness" predominantly captures depressive cognitions, the effect in the network model could be explained by exercises in cognitive reappraisal.

While the symptom-specific effects on the depression questionnaire PHQ-9 were clearly visible in the analysis, there were less pronounced effects for the general health questionnaire SF-12. Deprexis users reported being constrained by emotional problems less frequently, but other symptoms were not directly linked to the treatment. Indirect effects also revealed negative associations between Deprexis usage and SF-12 items reflecting depressive symptoms ("downhearted, blue"). Since BEI only involves up to two "steps" in the network, treatment effects may be more indirect or caused by variables not included in our model. However, given our results it can be assumed that Deprexis works mainly by reducing depressive symptoms directly, which leads to a subsequent increase of quality of life. This finding is expected, as the PHQ-9 was found to be highly correlated with most items of the SF-12 (39). Also, there were strong intercorrelations of SF-12 items that are most likely due to the structure of the questionnaire. For example, items asking if a participant "Accomplished less than they would like" and "Were limited in the kind of work or other activities" (items N and O in network graphs), a very high correlation is almost guaranteed, especially with a binary item format.

By applying the network intervention analysis approach to follow-up data, we identified symptoms responsible for the maintenance of treatment effects over 1 year after study onset. Interestingly, those symptoms were different to those associated with treatment in the first assessment. It could be speculated that effects on this aspect of depression need several months to unfold although further studies including more intense repeated assessments are needed to substantiate this.

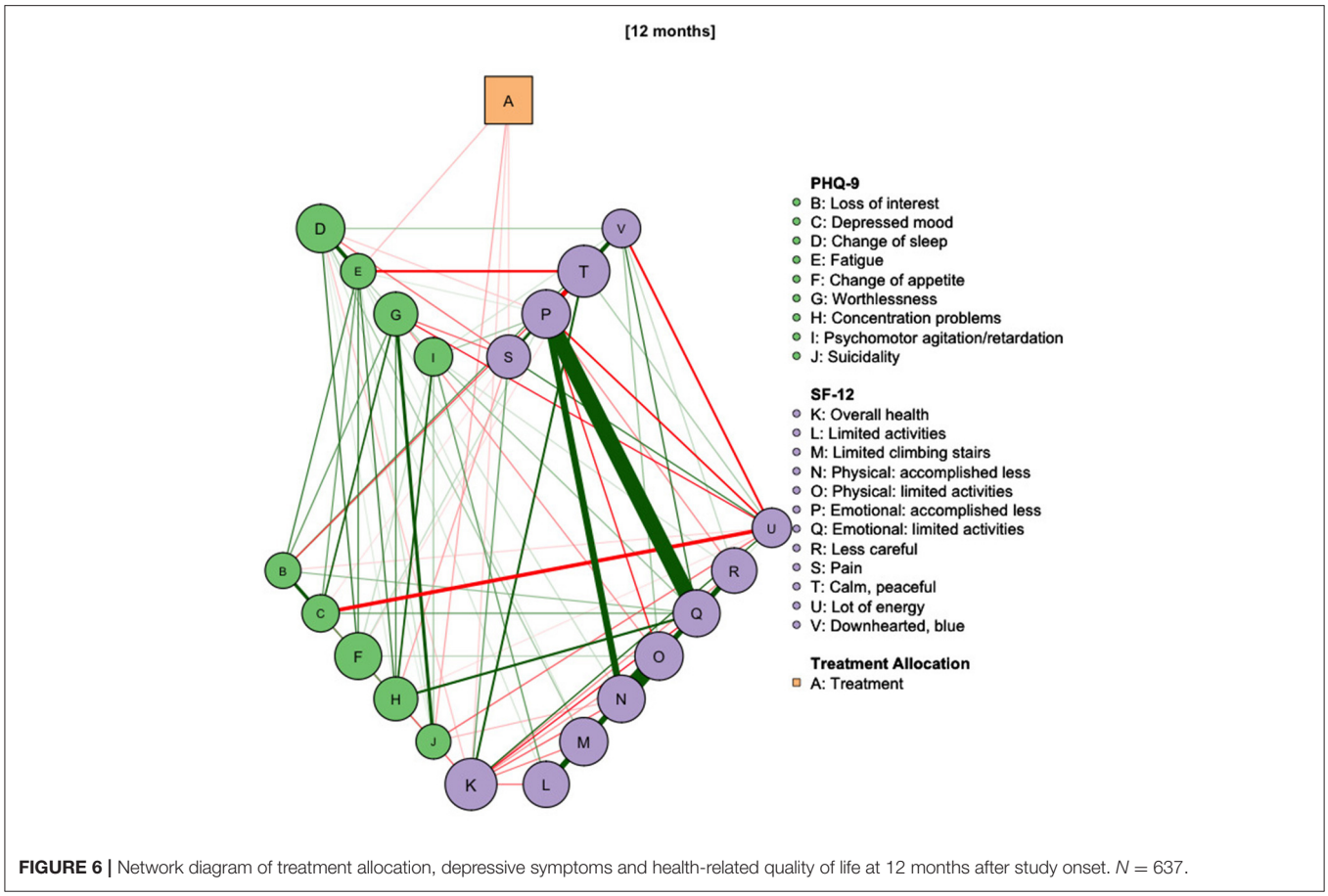


**FIGURE 6 |** Network diagram of treatment allocation, depressive symptoms and health-related quality of life at 12 months after study onset. $N = 637$.

**TABLE 2 |** Correlations of baseline severity indicator with symptom reductions at different time points.

| Time (months) | Deprexis | CAU |
|---|---|---|
| 3 | −0.23* | −0.07 |
| 6 | −0.13 | −0.07 |
| 12 | −0.21* | −0.15 |
| 18 | −0.26* | −0.15 |
| 24 | −0.25* | −0.18 |
| 30 | −0.35* | −0.17 |
| 36 | −0.24* | −0.35* |

*, *Holm-adjusted* $p < 0.05$.

## Limitations

Some limitations to our findings should be considered. Especially in the follow-up period, there was a considerable number of drop-out cases. This could have led to less accurate estimates of network edges and false-positive results. Since this study is a secondary data analysis, no a priori simulation study for power calculation was possible. However, as our bootstrap analysis shows, many edges estimated for treatment effects show imperfect stability, possibly reducing the confidence once should put in these effects. On the other hand, no agreed-upon cutoff values for satisfactory edge stability in network intervention analysis exist and the stability of treatment effect edges obtained in this study are comparable and often surpass those reported by Blanken et al. (24).

Regarding treatment effects, we decided to analyze complete cases because the network modeling approach we chose does not support incomplete data. This could have led to inaccurate effect size estimates. In fact, effect sizes from the previously reported intention-to-treat analysis by Klein et al. (27) were lower and less stable at follow-up.

The attribution of treatment effects observed in our sample is somewhat complicated due to a number of factors. Because participants were able to continue with their current psychiatric or psychotherapeutic treatment, a part of the effect might be attributable to these ongoing treatments. Subgroup analyses conducted in the original study (28) showed that the treatment effect of DEPREXIS was smaller in those patient groups. However, the proportion of patients receiving treatments elsewhere was the same in both groups by randomization, allowing the cautious conclusion that the impact of these treatments was not significantly greater in either group. While higher symptom severity normally predicts slightly larger effects in low-intensity interventions (40), this moderator is likely have been washed out because individual treatments were started long before participating in the EVIDENT study. Thus, including

participants that already underwent other treatments is likely to have led to an underestimation of treatment effects. On the other hand, participants with higher PHQ-9 scores (sum score of 10 to 14) were contacted by a supporter once per week, which could have led to increased effects for this group. Because symptom severity and access to e-mail support are confounded, it is hard to separate the influences of these two conditions. Future studies should consider randomizing supporter conditions to make this possible.

Compared to the work by Blanken et al. (24), we could not study the effects during the ongoing treatment because there were no assessments during that time. The processual nature of therapeutic interventions is lost in cross-sectional designs because intraindividual variation are not captured (41, 42). This requires study designs with high frequency measurements of the therapeutic process. For example, Santos et al. (38) used repeated measures during behavioral activation-focused residential treatment to show that the extent of behavioral activation is in fact associated with treatment outcomes. Future studies on the working mechanisms of online interventions should include adequate measures of intraindividual variation.

### Outlook

Future studies could extend the network intervention analysis approach to studies comparing two or more treatment approaches. This way, important information about the symptom-specific effects of different treatments could be uncovered, possibly leading to personalized treatment recommendations. Ideally, researchers considering using this approach should design their clinical studies in a way that NIA can be carried out adequately. This includes adding ongoing symptom assessments to the design of clinical studies so that the unfolding of treatment effects can be observed during interventions. Also, a priori statistical power calculations should include network models in order to guarantee stable estimates.

### Conclusion

Online interventions can help participants to manage their symptoms more effectively. In the case of Deprexis, this is accomplished most likely by reducing depressive thoughts and fatigue. Network intervention analysis is a promising tool to help clinical psychologists to design and evaluate interventions that lead to a broadening of knowledge about treatment effects and, thus, to greater benefits for participants.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the findings are not publicly available, as the publication of the collected primary data is not covered by the informed consent. For the sake of reproducibility, correlation matrices of all network models are provided in the online supplement. Requests to access these datasets should be directed to philipp.klein@uksh.de.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The article is a secondary data analysis of the EVIDENT trial. This trial has been approved by the Ethics Committee of the German Psychological Association (DGPs, reference number SM 04_2012). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

TK developed the concept of the paper, the first draft, the final manuscript and performed all steps of the data evaluation. LB has made key methodological and theoretical contributions as well as contributing to the revision of the manuscript. TB made a decisive contribution to the revision of the manuscript. BM, CS-N, JS, FH, and SM all provided important remarks on the first draft. JK provided important theoretical and methodological contributions and coordinated communications between co-authors. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

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# Cognitive Behavior Therapy for Depression From an Evolutionary Perspective

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Evolutionary medicine attempts to solve a problem with which traditional medicine has struggled historically; how do we distinguish between diseased states and "healthy" responses to disease states? Fever and diarrhea represent classic examples of evolved adaptations that increase the likelihood of survival in response to the presence of pathogens in the body. Whereas, the severe mental disorders like psychotic mania or the schizophrenias may involve true "disease" states best treated pharmacologically, most non-psychotic "disorders" that revolve around negative affects like depression or anxiety are likely adaptations that evolved to serve a function that increased inclusive fitness in our ancestral past. What this likely means is that the proximal mechanisms underlying the non-psychotic "disorders" are "species typical" and neither diseases nor disorders. Rather, they are coordinated "whole body" responses that prepare the individual to respond in a maximally functional fashion to the variety of different challenges that our ancestors faced. A case can be made that depression evolved to facilitate a deliberate cognitive style (rumination) in response to complex (often social) problems. What this further suggests is that those interventions that best facilitate the functions that those adaptations evolved to serve (such as rumination) are likely to be preferred over those like medications that simply anesthetize the distress. We consider the mechanisms that evolved to generate depression and the processes utilized in cognitive behavior therapy to facilitate those functions from an adaptationist evolutionary perspective.

**Keywords: depression, evolution, rumination, cognitive behavior therapy, antidepressant medications**

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## INTRODUCTION

In the early 1900's Emil Kraepelin, widely considered the father of modern psychiatry, stated, "it is almost impossible to establish a fundamental distinction between the normal and the morbid mental state (p. 115) (1)." Over a century later, the latest edition of the American Psychiatric Association's Diagnostic and Statistics Manual (DSM-5) meekly echoed Kraepelin's statement: "[I]n the absence of clear biological markers or clinically useful measurements of severity for many mental disorders, it has not been possible to completely separate normal and pathological symptom expressions contained in diagnostic criteria (p. 21) (2)." A century of stagnation on such a fundamental issue is an alarming lack of progress for any scientific field and it speaks to a failure to rigorously adhere to a hypothesis disconfirmation approach (3).

In particular, there has been significant debate as to whether modern diagnostic criteria for depression accurately distinguish between normal and pathological states. Not all unpleasant reactions or experiences are necessarily diseases or disorders. Fevers and diarrhea are unpleasant to experience, but they are not diseases in and of themselves; rather, they represent a coordinated effort to rid the body of dangerous pathogens (in the body generally in the case of fever, and in the gut specifically in the case of diarrhea). Unless they become too pronounced (too high a fever can produce brain damage in infants although that is rare, and people do die of dehydration in the event of protracted diarrhea) they increase the chances of survival for those who are "afflicted."

A similar case can be made that those non-psychotic psychiatric "disorders" that are marked by strong states of negative affect (depression and anxiety especially) represent adaptations that evolved to serve a function in our ancestral past. In that sense they are neither "diseases" nor "disorders" but instead coordinated responses to external challenges or threats that increase the chances of passing on one's gene line (inclusive fitness). They may be distressing to experience and even disrupt life at times, but if they increased reproductive fitness they would have been selected by evolutionary pressures. It should be noted that evolution selects for the "*survival of the fittest gene line*" and not the *"fittest individual."* Inclusive fitness is the sum of the reproductive fitness of the individual (direct fitness) and his or her biological relatives (indirect fitness). There are instances in which acting in ways that lessens the odds that the individual will reproduce increases the odds that his or her gene line will reproduce.

Clinicians often refer to behaviors that do not serve the individual as being "maladaptive" without recognizing that if a trait advanced the inclusive fitness of his or her ancestor's gene line in their evolutionary past then it would have been selected for by evolution and psychological mechanisms "baked in" that are there to be expressed in modern life. That will have implications for the ways in which terms like "maladaptive" are used; from an evolutionary perspective "maladaptive" means that the trait reduces inclusive fitness, whereas from a clinical perspective "maladaptive" implies that the trait is not helpful to the individual. The key point is that evolution may have selected for certain traits that are adaptive for the propagation of one's gene line but that are not propitious for the individual him or herself. Think of risk-taking and the men who live fast and die young, but leave offspring with the women who were attracted to them.

The fact that a trait evolved in our ancestral past does not mean that we necessarily have to adhere to it today if it does not suite our current purposes (most reproductively capable adults practice birth control at times), but it does facilitate the therapeutic process for the clinician to recognize and discuss with the patient that some behaviors that seem "maladaptive" may have been selected for in our ancestral past. This is a point to which we will return later in the article.

Psychiatry, especially through the DSM and psychopharmacology, has had an outsized influence on the understanding, research investigation, categorization, and treatment of mental illnesses. That is being challenged, especially with the use of an evolutionary approach. The non-psychotic disorders may be aversive to experience but motivate adaptive defenses that serve to propagate the gene line (4). It is the gene line that is selected via evolution, not the individual.

Retrospective epidemiological studies estimate that 16% of all people will experience an episode that meets modern criteria for major depression at some time in their lives (5), whereas cohort studies that follow people from birth on put that number three times as high, with the majority of those extra instances coming in response to major life stressors among people who are unlikely to experience subsequent episodes (6). Prevalence rates of that magnitude raise concerns that the diagnostic criteria for major depressive disorder are inaccurate and overinclusive (7, 8). Women are twice as likely as men to experience episodes of depression, a disparity that first emerges in early adolescence and that is maintained across the lifespan (9). That is an unusual time course for a "true" disease to follow; most kill you in your infancy or your dotage (10).

The decision to eliminate the bereavement exclusion from DSM-5 generated considerable controversy precisely because grief is widely recognized to be a "normal" response to the loss of a loved one (11–13). Almost anyone will experience a grief reaction following such a loss and that grief is largely homologous with depression. High prevalence and near universality in response to loss suggest that depression is "species typical" (something that can happen to anyone) and its gender disparity (women are twice as likely to get depressed as men), and age of onset (half of all first episodes occur in the teens) suggests that it evolved to solve life challenges relevant for young women as they enter their reproductive years (14). Women cannot "muscle" their way out of stressful situations and grip strength is inversely correlated with risk for depression (15).

In this article, we explore the implications of depression as an evolved adaptation and consider the proposition that aspects of cognitive behavior therapy (CBT) may be particularly well-suited to advance the functions that depression evolved to serve. We focus especially on the notion that melancholic depression (and perhaps most other clinical depressions as well) evolved to facilitate the process of analytical rumination (the careful consideration of the causes of and possible solutions to) complex social problems that are particularly likely to arise as young primates first take on adult responsibilities (16). "Depression" is a catchall term that encompasses multiple, evolutionarily related phenotypes (including sickness depression, starvation depression, and clinical melancholia) that share sadness and anhedonia in common, as well as some genes and neurocircuitry, but that differ in other symptoms and the situations that trigger them.

There are reasons both anatomical and biological (see below) to prefer the analytical rumination hypothesis (ARH) to other possible evolutionary explanations for melancholia (17) and other phenotypes characterized by rumination like atypical depression (18, 19) and reasons to prefer CBT or other related psychosocial interventions (also described below) to antidepressant medications (ADMs) to the extent that those anatomical and biological implications are true (20).

It is *a basic principle of evolutionary medicine that any intervention that facilitates the functions that a negative affect evolved to serve is more likely to be successful in the long run than one that merely anesthetizes the distress.* We think that CBT facilitates the functions that depression evolved to serve (it makes rumination more efficient) whereas ADMs only suppress the distress and leaves the problem that triggered the depression largely unaddressed.

To illustrate how CBT may work within the context of the ARH, we raise nine questions likely to be of interest to clinicians, and we discuss how our evolutionary approach provides insight into each. We have addressed these questions in greater detail elsewhere, and we refer interested readers to our previous articles for more in-depth considerations (16, 17, 21, 22).

## QUESTION 1: WHY DO PEOPLE HAVE PAINFUL FEELINGS? IT IS ALL ABOUT THE SQUIDS AND THE SEA BASS

Most evolutionary accounts of aversive feelings propose that they are triggered by harmful events and that they motivate behavior and learning that promote avoidance of those events. Anger motivates avoidance of social exploitation (23), anxiety motivates avoidance of an imminent threat (24), jealousy motivates avoidance of romantic infidelities (25), and pain motivates avoidance of damage to bodily tissues (26). It is also commonly thought that emotional adaptations produce coordinated whole-body responses to meet the various adaptive challenges of the different situations (27–29). Even though negative emotions share a functional commonality in that all are thought to promote avoidant behavior and learning, the precise whole-body response that is triggered depends on the specific harm to be avoided. Avoiding a predator requires a different whole-body response than avoiding infidelity, a pathogen, or social ostracism.

In each instance, the external challenge is different, and the body is readied to respond in a different fashion to each so as to maximize inclusive fitness. From the perspective of evolutionary biology, such syndromes are neither diseases nor disorders. Unlike a disease, the physical structure of the body is intact and doing what it was shaped by natural selection to do. The affects that emerge coordinate a "whole body response" (thought, feeling, physiology, and behavior) that is anything but disordered.

Low prevalence, high heritability disorders like the serious mental illness (SMIs) (schizophrenia, bipolar I, and autism) may well represent "true" diseases in the classic sense of the term, but the high prevalence modestly heritable non-psychotic "disorders" that revolve around distressing affects like depression and anxiety likely represent adaptations that evolved in our ancestral past because they enhanced reproductive fitness (30).

We illustrate this point with a study on the adaptive value of physical pain. Sea bass eat squid and, as best as we can tell, squid prefer not to be eaten. Crook and colleagues conducted an elegant trial to evaluate the survival value of pain (31). In that study, quartets of squids either had a swimmer surgically removed (or not) under anesthesia (or not) in a 2x2 factorial design and were then placed in a tank with a hungry sea bass 6 hrs later (long enough for the effects of the anesthetic to wear off) with rates of predation monitored. Human observers could not detect which of the squids had been operated on, but the sea bass could (that is the kind of thing that predators evolved to do). The squids that were physically intact were the least likely to be eaten (whether they had been anesthetized or not), whereas the squids that had been operated on under anesthesia were the most likely to be eaten, largely because they began evasive maneuvers no sooner than the squids that were intact. Those squids that had been operated on without anesthesia began evading the sea bass sooner than the squids that were intact and were more successful in avoiding predation than the squids that had been maimed but felt no pain. The moral of the story is that pain may hurt, but it motivates the organism to avoid further harm and facilitates survival.

Melancholic depression is distressing, but that is not necessarily bad. If it is a normal emotional adaptation, the issue is to figure out what negative circumstances it evolved to avoid.

## QUESTION 2: WHAT IS THE EVIDENCE THAT MELANCHOLIA IS AN ADAPTATION?

Demonstrating that a trait such as melancholia is an adaptation is an onerous burden, and we refer readers to our other papers for more thorough treatments (21, 32, 33). Natural selection is the only known force in nature capable of producing highly organized and coordinated traits, and the only workable explanation for the architecture of the brain (34, 35). As a consequence, the search for adaptation essentially involves recognizing highly organized and coordinated traits.

When faced with a trait with unknown evolutionary origins, such as melancholia, the researcher should engage in a two-step reverse engineering process. The first step involves identifying as many features of the trait as possible, including neurological and physiological components, but also cognitions, feelings, and behaviors. The second step involves attempting to identify an effect that non-randomly organizes the features. Vision non-randomly organizes all the features of the eye (cornea, lens, pupil, iris, trabecular meshwork, vitreous humor, retina, etc.), and so vision is the evolved function of the eye. A systematic failure to find evidence of organization or coordination increases confidence that other explanations are required.

As we have argued in detail elsewhere, the classic description of melancholic depression exhibits a high degree of order and coordination for promoting Type 2 avoidant learning in response to serious failures or mistakes (21). By "avoidant learning" we mean that melancholia is an emotional response to serious missteps, and that it promotes a learning style whose function is to avoid similar events in the future. By "Type 2" we refer to one of two basic information processing styles that are widely studied in cognitive psychology. Type 1 processing is quick and requires little more than instinct or a conditioned stimulus-response. That is the kind of thinking that leads one to assume that the rustle in the bushes is a predator intent on a meal and not something more benign or tasty. The premium in such instances is on rapidity of response and little time is spent in careful contemplation. In

contrast, Type 2 thinking is more contemplative and deliberative. It's essential feature is the use of working memory in which information is kept in an active state because it is useful in ongoing processing (36). The employment of working memory is time-consuming, attentionally-demanding, and energetically expensive, so Type 2 thinking is better suited to solving complex social problems that do not require an immediate response. This distinction is what Daniel Kahneman refers to as "thinking, fast, and slow" (37).

Sadness, which is a crucial symptom of melancholia, is well-known to promote a Type 2 processing style (16, 38). Many other symptoms of melancholia can be non-randomly organized around the time-consuming, attentionally-demanding, energetically expensive nature of Type 2 thinking (21). For instance, one will be unable to effectively engage in Type 2 processing if one is continuously distracted by thoughts of food or sex, so the symptom of anhedonia may help one engage in Type 2 processing without interruption. Also, chronic activation of the HPA axis tends to direct energy to the brain, which can be used to support Type 2 processing.

Furthermore, many of the neurological changes that support Type 2 processing—working memory, distraction-resistance, the reallocation of energy to brain activity, an attentional focus on a threat or problem, and a loss of interest in other activities (anhedonia)—are coordinated by an increase in serotonin transmission to various forebrain regions. The idea that melancholia involves an increase in serotonin transmission may seem like the fatal flaw that refutes our hypothesis, because the conventional wisdom is that depression is associated with a reduction in serotonin transmission. However, the low serotonin hypothesis arose as a result of trying to explain how ADMs reduce symptoms, and it is widely recognized that their mechanisms of action are not well-understood (39). We have reviewed extensive evidence elsewhere that serotonin is upregulated in unmedicated depressed people, and in rodent models of depression (17).

In short, melancholia exhibits signs of adaptation for promoting Type 2 processing. We refer readers to our other work for a more in-depth treatment of this issue (16, 17, 21). Because Type 2 processing is analytical, we refer to this as the *analytical rumination hypothesis* (ARH) (16, 21). We have shown that the ARH applies directly to melancholia, but that it also may be useful in explaining atypical depression or other depressive phenotypes (21).

When an evolutionary biologist tries to tease apart the ancestral conditions that might have given rise to an adaptation, s/he engages in a process called "reverse engineering" in which the current manifestation is taken apart to see how the mechanisms works (an analogy is often made to deconstructing a watch to see what it was designed to do) (32). When attempting to reverse engineer a trait with unknown evolutionary origins, it is useful to follow the distribution of metabolic resources (energy), much as when "Deep Throat" advised Woodward and Bernstein to "follow the money" in Watergate. Evolutionary biologists "*follow the energy*" when they can.

There are at least three syndromes that involve depressed affect and a loss of interest in hedonic pursuits (anhedonia). When someone gets an infection, energy is directed away from cognition and the brain and toward the immune system. When someone is starving, energy is directed away from the immune system and growth and toward the maintenance of the vital organs, particularly the brain (17). When someone gets depressed (extrapolating from the classic melancholic form of depression) energy is directed away from the immune system and maintenance of vital organs and toward the cortex. These differential energy transfers are all coordinated by serotonin, a very ancient neurotransmitter that co-evolved with mitochondria (the energy-generating "blast furnaces" within each cell), and that is the target of nearly every ADM.

All the neurons in the brain that use serotonin as a neurotransmitter have their cell bodies in the raphe nucleus. The raphe nucleus is itself buried deep in the brainstem, suggesting that it developed a very long time ago in our ancestral past; serotonin is over 600 million years old and is present in almost all central nervous systems (40). When the raphe nucleus fires, it activates the amygdala, so as to keep the organism focused on the source of its current distress, as well as the hippocampus, so as to bring working memory online, the lateral prefrontal cortex, so as to make the organism resistant to distraction, the nucleus accumbens, so as to dampen down hedonic pursuits (anhedonia), and the hypothalamus, so as to tamp down growth and reproduction. In short, when the raphe nucleus fires it redistributes energy throughout the brain in a manner that facilitates rumination (17). *Avoidant learning is the effect that non-randomly organizes the features of depression and non-random organization must be a consequence of natural selection.*

Jeffrey Gray mapped out two coordinated neurobiological systems: (1) avoidance of threat, the behavioral inhibition system (BIS), largely noradrenergic in nature; and (2) the pursuit of pleasure (appetitive stimuli), the behavioral activation system (BAS), largely dopaminergic in nature (41). It is the latter that seems to be most directly suppressed in depression. Imminent threat requires an immediate response, whereas the pursuit of appetitive rewards can be delayed until the timing is propitious. Any organism must do two things as it goes through its day; it must get lunch without becoming something else's lunch, and the former always will take precedence over the latter (42). What is most relevant for our immediate discussion is that serotonin, the primary target of nearly all of the antidepressant medications, moderates the distribution of energy between inhibition (BIS) and activation (BAS) and as such largely coordinates the relative balance of these disparate types of activities and the affective syndromes they reflect.

## QUESTION 3: WHAT IS THE CONTENT OF RUMINATION AND WHAT IS ITS FUNCTION?

Clinicians tend to think of rumination as merely a symptom of depression or, even worse, a causal process in its own right (43). In point of fact, it is clinicians who have given rumination a bad name. Merriam-Webster's *New Collegiate Dictionary* defines rumination as to "go over in the mind repeatedly and often casually or slowly … to engage in contemplation" (44), whereas

that same company's *Medical Dictionary* defines rumination as "…obsessive thinking about an idea, situation, or choice especially when it interferes with normal mental functioning; specifically: a focusing of one's attention on negative thoughts or feelings that when excessive or prolonged may lead to or exacerbate an episode of depression" (45).

Clinicians associate rumination with depression and assume that it serves no useful function, despite the fact that that is what the brain seems to be predisposed to do when loss or failure has occurred or is anticipated. Most episodes of depression remit on their own in the absence of treatment (something known as "spontaneous remission") and that is not the case for most other non-psychotic disorders. Someone with a fear of heights tends to stay afraid of heights throughout his or her lifetime unless he or she takes specific action to resolve the fear (situational but not temporal) whereas someone who is depressed tends be depressed across situations until the episode remits (temporal but not situational) which it almost always does. That brings us to the question: Why do depressions go away? In our ancestral past, before the advent of treatments, something must have accounted for what appears to be such "spontaneous remission."

Normal emotions are evolutionarily ancient, and they evolved because they motivate adaptive responses to specific situations. Positive emotions motivate the pursuit of fitness-enhancing opportunities (BAS), whereas aversive emotions motivate the avoidance of fitness-reducing harms (BIS). Normal emotions resolve when the opportunity or problem that triggered the emotion resolves (21). Because normal emotions promote adaptive responses to the situation that triggered them, they generate the source of their own resolution. The evidence that melancholia is an adaptation for promoting Type 2 thinking therefore suggests that depressive thinking may contribute to such "spontaneous remission" via resolving the triggering problem.

Depressive thinking (aka rumination) has self-blaming themes of worthlessness and culpability. How could it be adaptive to have such thoughts after a loss or failure? Is that not self-defeating? How could focusing on one's own inadequacies help one resolve the problems caused by loss or failure? Indeed, it might seem maladaptive to engage in any cognitive effort about a loss or failure, because one cannot reverse time to avoid an event that has already occurred.

Our starting point is that thinking about a loss or failure is not wasted effort if it helps you redress a social problem that still continues or to avoid similar such events in the future. Redressing such events or avoiding them in the future requires understanding why the loss or failure happened, which in turn requires reconstructing the causal chain of events that led to the bad outcome. Moreover, not all causes are equal. Those causes that you could have done nothing about are of less use than those for which you could have taken preventable action. Analyzing the chain of events that led to a loss or failure and focusing on those points in the causal chain where one could have taken preventable action, is called a root cause analysis (RCA). Such an RCA is often employed to reduce the risks of mistakes and errors in the business world and health care.

RCA requires Type 2 processing because reconstructing the causal chain of events that led to the failure or loss will occupy working memory and our capacity for storing things in working memory is no greater than that for our primate cousins (46). Additionally, the load on working memory is exacerbated by the fact that one must consider different hypothetical actions that could have been taken to understand if any one or more could have prevented the loss or failure.

One outcome of RCA is the development of *upward counterfactual thoughts* (21) that take the following form: "If only I had done X, then harmful event Y would not have happened to me." They are *counterfactual* because they reflect a belief about how the present situation could have turned out differently if different action had been taken. And they are *upward* because they focus on how the situation could have turned out better than it did. Counterfactual thoughts reflect a belief about what caused the harmful event, and the action that could have been taken to prevent it. Clinicians will recognize that such thoughts are common in their depressed patients. Note also that counterfactual thoughts often have a self-blaming bias. When redressing an existing problem, it is often helpful to take responsibility for one's own actions and when attempting to avoid similar losses or failures in the future, a biased search for self-blaming causes is more adaptive than blaming external events because one has the most control over one's own future actions (47).

A natural explanation for the guilt and remorse that occur in melancholic rumination is that they display regret for past actions and motivate the search for root causes when preventable action could have been taken, and they lead to upward counterfactual thoughts that help one reduce the risk of recurrences. As we describe in detail elsewhere, the melancholic symptoms of low self-esteem (worthlessness) and pessimism (negative expectations) also play motivational roles in the search for root causes and the development of upward counterfactual thoughts (21). As Leary and Baumeister have described beliefs about one's character ("I am worthless" or "I am unlovable") are beliefs about oneself that have a social component (48). Sociometric theory proposes that self-esteem evolved to monitor social acceptance, not so much as to maintain self-esteem, and that it serves to detect cues indicating that the individual is not adequately valued. As such, it motivates behaviors that enhance one's value to important others in one's social world. Beliefs about the self that lack any social context are unlikely to be acted on by evolution, since it is natural selection (operating through inclusive fitness) that shapes how organisms interact with their environment. Beliefs must affect social behavior in order to be shaped by evolution.

In summary, Type 2 avoidant learning of harmful events non-randomly organizes all the major symptoms of melancholia (sadness, anhedonia, chronic HPA activity, rumination, guilt, worthlessness, pessimism) and quite possibly serves a social function in interpersonal conflict. The promotion of Type 2 avoidant learning is therefore the evolved function of melancholia (21).

## QUESTION 4: WHAT IS THE RELATIONSHIP BETWEEN RUMINATION AND SPONTANEOUS REMISSION?

As just described, melancholic rumination often focuses on understanding the causes of problems, with a particular focus on self-blaming causes. This is hypothesized to be useful in figuring out how to solve those problems (e.g., redressing complex social problems that already exist and taking preventative action that reduces the risk of recurrences). Once those problems are solved, the depressive episode is predicted to resolve. In other words, under the ARH, depressive episodes are predicted to resolve through a sequential two-step rumination process (16, 49, 50). In this model, depressive symptoms first promote RCA, which then promotes problem-solving analysis (PSA). In turn, PSA leads to the resolution of the triggering problem or reduces the likelihood of its recurrence and thus reduces depressive symptoms, thereby contributing to spontaneous remission, which is, in fact, anything but "spontaneous" but instead the outcome of a process. In engineering terms, the ARH predicts that melancholia is part of a "closed system" that responds to disturbances and then returns the system to equilibrium. Problems drive depression that in turn drives causal analysis that then facilitates problem solution that then resolves the depression. In essence, spontaneous remission can be viewed as an "unaided resolution" in which depression does its job (motivating steps that lead to problem resolution) and then goes away, much like a fever resolves when it has contributed to the death of the invasive pathogen.

We have found consistent support for this model in a series of papers involving both clinical and non-clinical samples (51–53). Specifically, RCA is more temporally proximate to depression than PSA (52), and it acts as a mediating variable between depression and PSA (50, 52), both of which are consistent with our sequential model. We also found consistent evidence that PSA exerts negative feedback on depressive symptoms, which suggests that PSA may play a role in spontaneous remission (50, 52). Finally, in a sample hospitalized for major depression, we found that higher levels of PSA 1 week after admission were associated with lower levels of depressive symptomatology 5 weeks later, also consistent with spontaneous remission (53).

## QUESTION 5: WHY DO DEPRESSED PEOPLE OFTEN HAVE RECURRENCES?

As noted earlier, depression appears to be far more common than our retrospective epidemiologic studies would lead us to believe. According to cohort studies that follow samples prospectively from birth, its actual incidence may be up to three times higher than standard psychiatric estimates, and the bulk of those additional instances occur in response to major life stressors among people who do not go on to become recurrent (6). These are the persons referred to by Monroe and colleagues as "depression possible" and that designation is virtually synonymous with "species typical." Few individuals ever make it into treatment in their first episode unless it goes on long enough to be considered chronic (currently defined as 2 years or more). What this suggests is that the majority of individuals who ever get depressed get out of their episodes on their own with no subsequent recurrence. That suggests the operation of some kind of evolved adaptation that serves its function and then desists. That is the very definition of a "closed system" in engineering terms, and that is exactly how the ARH is presumed to operate.

What to make of the individuals who are "recurrence prone"? Multiple explanations are possible. First, according to Monroe and colleagues, there is no reason to suspect that simply experiencing an episode of depression increases an individual's risk for having another (the widely accepted "kindling" hypothesis is based solely on the observation that it is easier to identify a precipitant for initial episodes than for later ones). Rather, according to Monroe and colleagues, the fact that the number of prior episodes predicts the likelihood of subsequent episodes is simply an artifact of mixing "depression possible" and "recurrence prone" individuals in heterogeneous samples (6). It is likely that elevated risk either can be inherited or acquired (the latter likely prior to adolescence), but it does not necessarily grow across repeated episodes.

Second, if melancholic depression is a normal emotion, the quandary dissipates, because all emotions are recurrent experiences. As humans, we experience love, anger, fear, and most other emotions multiple times in our lives, and it is no mystery. Recurrences of emotions take place because people are exposed to the events that trigger them multiple times in their lives.

Third, people also appear to differ in their capacity for *experiential avoidance* (i.e., the use of distraction, thought suppression, self-medication, or other tactics to avoid experiencing painful feelings). Experiential avoidance is associated with worse outcomes from depression [for reviews, see: (16, 21, 54)], which suggests that a higher propensity for recurrences could be associated with a greater tendency to utilize experiential avoidance when one is depressed. In essence, if one does not learn from experience (painful though it may be), one is prone to repeating the same mistake.

Fourth, some problems may be so complex that their solution may require slowly grinding away at them over the course of years in bursts and bouts of intense melancholic mental activity, punctuated by periods of respite and rest. Why? Often, the only feedback people get that their mental model of their social world is inadequate is that they fail to achieve their social goals. However, it may not be obvious what aspects of their mental model are problematic. Does their whole understanding need to be revised, or does the model simply need to be tweaked? Usually, it is better to tweak the mental model unless substantial evidence indicates wholesale revision is required. After all, the current model is the product of years of experience and may have worked well in the past. The individual may need to develop different hypotheses about which parts of their mental model need to be refined, and then test them systematically until feedback improves. People who are prone to depression are not unique in terms of being conservative when it comes to changing their beliefs, that is a characteristic common to the species. New information that contradicts an existing belief is viewed with greater skepticism than information that confirms what one already believes (55). If "insanity" is doing the same thing over

and over again and expecting different results, then the bulk of the human race is functionally "insane," since most of us operate in that fashion. It is not that new ideas do not win out in the end (if they do a better job of representing the external realities), it is just that a critical mass of anomalies must accumulate and be noticed before an existing paradigm begins to shift. Having an alternative that can better account for the anomalies is usually required to facilitate such a paradigm shift (56).

Most depressed patients seen in clinical settings appear to have latent schema regarding unlovability or incompetence that get triggered by negative life events. The difference between the "depression possible" and the "recurrence prone" may be the ease with which subsequent episodes get triggered (patients with Axis II personality disorders appear to be at particular risk since they tend to engage in "compensatory strategies" to protect themselves from loss or failure that annoy other people), but any and all would benefit from the type of careful Type 2 thinking (rumination) that moves the process along to resolution. People who have lost a loved one through no fault of their own (grief) still have many realistic problems to resolve and those who come into adolescence with a latent belief that they are unlovable are especially prone to making errors in relationships or interpreting occasional conflicts that arise as reflections of their worth.

Similarly, people who have experienced a major vocational setback or achievement-related failure would be well-advised to consider what steps if any they could have taken to avoid that failure as a prelude to what steps they will take in the future to move their prospects along and those who are schematic for incompetence even more so. Physicians who make medical errors often respond by becoming depressed and as a consequence exercise greater care in their future practice (21). Once again, this process is helped along by an apparent shift into Type 2 thinking (rumination) that is motivated by their affective distress.

In keeping with the notion that depression is an adaptation that evolved because it served a function, it is interesting to note that the symptoms expressed tend to differ as a function of the triggering life event; death of a loved one and romantic breakups elicit sadness, anhedonia, appetite loss, and guilt (with the latter restricted to breakups), whereas chronic stress and failure are associated with fatigue and hypersomnia (57).

The majority of people that we see in treatment (and by extension in clinical trials) are "recurrence prone" who themselves represent a minority of the people who ever get depressed. A major feature of many such patients is the operation of latent schemata that lie dormant until activated by negative life events (20). The beliefs at the core of those schemas are often "stable" trait theories about the self ("unlovable" for those concerned with affiliation and "incompetence" for those invested in achievement). We put "stable" in quotes because we think these are actually conditional beliefs. Patients would not bother to come to treatment if they did not think these propensities could not be changed or at least worked around. From an evolutionary perspective, it is adaptive for people who get depressed to consider ways in which they may have contributed to the problems that they face. That is part of the root cause analysis, and if their actions contributed in any way to the genesis of the problems, then those actions can be avoided in the future.

One of the major strategies in CBT is to encourage the patient to consider other explanations than a trait-like defect in the self (conditional or otherwise), and most often that is that they were simply pursuing the wrong strategy. This is what Salkovskis refers to as pitting "Theory A" ("I am defective") vs. "Theory B" ("I chose the wrong strategy") (58). As we indicated above any consideration of the causes of a problem should include consideration of the role one might have played since it is one's own behavior that is easiest to modify in future problem situations. Distress drives the search for causes; changing behaviors is often the solution. As indicated above, self-referential beliefs are best understood as reflecting one's perceived value to others and the behaviors they motivate are those that impact on one's social environment (48).

We know that people who get depressed tend to generate more life stress in terms of events that could be "dependent" on their own problematic behavior (e.g., a divorce or getting fired as opposed to the death of a loved one), a phenomenon referred to as stress generation (59). Since these studies are based on clinical samples and since clinical samples tend to skew toward the "recurrence prone" what we think that means is that people who have an underlying diathesis (inherited or acquired) tend to generate behaviors that increase the number of stressors that they face. It is not that they necessarily confront more stressors because they tend to get depressed (although that likely happens too since people cope less well when depressed) but rather that they get depressed more often than other people because they inadvertently generate more life stress.

There is nothing about stress generation that is incompatible with an adaptationist perspective. If some people inadvertently generate life stressors, they would be expected to get depressed more often than others who do not, and that is exactly what appears to happen. We also know that individuals who are prone to making internal, stable, global attributions for the problems that they encounter are more likely to become depressed when things go wrong than those who tend to make other types of causal attributions (60). What we think this means is that individuals with an underlying diathesis (inherited or acquired) are at greater risk of becoming depressed in response to life stressors that would not be depressogenic for others who do not share that underlying diathesis (the "depression possible"). Again, there is nothing about the notion that having a particular attributional style is depressogenic that is incompatible with an adaptationist perspective or evolutionary theory. If having a particular attributional style increases the likelihood of becoming depressed in response to the same negative life event then that simply means that those individuals will have more need to shift into Type 2 thinking in order to solve what they perceive to be a bigger problem than other people perceive that problem to be.

What we think this all means in aggregate is that depression is an evolved adaptation that works both for those people who confront only the occasional major life stressor (the "depression possible") and for those people who inadvertently generate an overabundance of negative life stressors or who overreact to less severe stressors (the "recurrence prone"). It is just that it will have to "kick in" more often for the latter. There is no evidence that episodes last any longer (on average) for one group than

the other or that spontaneous remission is any more or less likely to occur for either. What is likely is that people who are "recurrence prone" are more likely to find their way to treatment since they know from prior experience that even though each episode tends to go away on its own it often takes many months to do so. For the "depression possible" clinical intervention may not be necessary but (depending on its nature) not necessarily problematic. CBT may be overkill (analytical rumination will likely help them resolve the triggering problem before it occurs to them to enter treatment) whereas ADM may be unnecessarily iatrogenic (if it prolongs the episode and leads to relapse when the medications are taken away) (22).

For those among the "recurrence prone" CBT is likely to be preferred for those who will respond to it (not all will) since it seems to facilitate the processes that depression evolved to serve with respect to resolving the problem that triggered the episode in the first place and to have an enduring effect that reduces risk for future episodes (22). We think this is a consequence of either dismantling existing depressogenic schema (accommodation) or teaching compensatory skills (compensation) that allow patients to short-circuit the episode before it starts (61). For those among the "recurrence prone" who do not respond to CBT or some other empirically supported psychosocial interventions like behavioral activation (BA) or interpersonal psychotherapy (IPT), then ADM may still be the treatment-of-choice by necessity. In an earlier trial we found that patients with depressions superimposed on Axis 2 personality disorders were more likely to respond to ADM than to CBT but especially likely to relapse when ADM was discontinued (62). For such patients, who are particularly likely to engage in behaviors that generate problems in affiliative and achievement related endeavors, short-term psychotherapy might not be sufficient. There are things that can be done with such patients in lieu of or in addition to medications, but they generally take months or years instead of weeks and require addressing the behavioral strategies that patients have developed to compensate for perceived inadequacies (63).

There are several types of life events that appear to increase risk that someone will develop a depressogenic schema, childhood trauma, and death of a parent among them, and the greatest lasting impact seems to occur when those events occur prior to or early in adolescence. The strategies used in CBT largely revolve around encouraging clients to use their behaviors to test the accuracy of their beliefs (run experiments) and catch themselves when they start to slide into Type 1 thinking, such as "all-or-none thinking" or the rigid application of "shoulds" (64). None of this would work if the patient were not capable of generating alternative explanations for a given negative event ("Theory A vs. Theory B") and weighing the evidence for and against each.

We argue elsewhere that sadness motivates introspection, and that such introspection is a useful tool when things go wrong, especially when that negative event could have been the consequence of one's own problematic behavior (21). Negative affects clearly play an important motivational role. If you did not feel distress in response to something going wrong, you would not be motivated to fix whatever caused the problem. To the extent that the stress generation hypothesis is true, then those who are "recurrence prone" likely carry in their heads an internal recipe for making inadvertent mistakes in life, likely as a consequence of generating self-fulfilling prophecies in which their own negative beliefs lead them to engage in self-defeating behaviors that generate the very outcomes that they fear (20).

## QUESTION 6: DOES CBT DISRUPT RUMINATION OR MAKE IT MORE EFFICIENT?

If depression is an evolved adaptation that serves to motivate efficacious problem-solving, then it is likely better to promote that process than to disrupt it. From an adaptationist perspective *it is not the distress that is the problem, but rather the problem that generated the distress*, and it is the problem that needs to be resolved. If so, then thinking about the triggering circumstances in a careful and deliberative fashion (rumination) is one step in the process of problem resolution. A case can be made that CBT teaches people how to ruminate more efficiently (64). Everyone engages in both Type 1 (rapid judgments dominated by heuristics and biases) and Type 2 (careful, methodical, analytical deliberation) thinking, it is just that depression tends to motivate more of the latter. Much of what passes for positive self-esteem in those who are not depressed is based on positive illusions and such an "illusory glow" only works when things are going well (65).

What we think we do in CBT is to take advantage of the depressed patients' proclivity for ruminating about the problems in their lives. However, ruminating about the causes of one's problems does not necessarily mean that the causes considered will be correct or that the solutions generated will necessarily be efficacious. Although most episodes will resolve over time (often as a consequence of the one's own efforts at resolution whether recognized or not), some patients get "stuck" and when they do it is usually because they have settled on a causal explanation that focuses on some defect in the self (incompetence or unlovability) that does not readily suggest a behavioral solution that will solve the problem.

This is wholly consistent with our evolutionary view that suggests that negative characterological explanations are a normal part of our evolved psychology in response to serious failures and losses. For instance, as we describe in more detail below (see Question 9), characterological explanations may have a motivational function (21). Moreover, there are a number of normal factors and constraints on human cognition that may make it difficult for people to see non-characterological explanations following losses and failures (20, 21) and may make them appear to be cognitively "stuck."

In this context, CBT may be particularly useful in helping people identify and consider non-characterological alternatives. If the essence of an adaptationist theory is that depression is an evolved adaptation that motivates the person to ruminate about the causes of their distress so that an efficacious solution can be found, the essence of cognitive therapy is helping persons who get stuck along the way by helping them correct errors in their thinking; that is, to ruminate more efficiently and to a better end.

One of the authors (JAT) worked with a 30-something graduate student in the natural sciences who has been chronically depressed for 3 years. The problem was that he was in a very difficult program of studies that few of us could master, not that he was depressed as a consequence. The patient had come to believe that he was a "failure," and his psychotherapist was pushing the author (a psychiatrist) to medicate the patient so as to resolve the depression. There was nothing "characterological" about his depression and his proclivity to look for self-referential explanations likely served a motivational purpose. That said, it was likely that the cause of this instance was that his program was simply very difficult and something few of us could master.

Integral to that process is encouraging patients to ask themselves three questions whenever they catch themselves having an automatic negative thought: (1) ***evidence:*** what is my evidence for that belief? (2) ***alternatives:*** are there any other explanations for that event other than the first one I came up with? and (3) ***implications:*** are the real implications as dire as I first presumed? In effect, CBT therapists do not so much try to disrupt rumination as to facilitate it and to give it structure (64). The alternatives question, in particular, invites the patient to consider multiple possible explanations for the problems that they face. This is analogous to what Salkovskis has described as pitting Theory A (the patient's explanation for his or her distress that in the case of depressed patients usually focuses on some kind of perceived defect in the self) vs. Theory B (an alternative rationale that typically looks to see if the patient has simply adopted the wrong behavioral strategy) (58). The evidence question then prompts the patient to review the existing facts and encourages him or her to gather new information to test between the competing theories, often by virtue of conducting behavioral experiments in real life that the therapist cannot control. Finally, the implications question prepares the patient to parse out what the likely consequences (if any) will be of the problems that they face. The goal is not simply to relieve distress (that can be done more rapidly with ADMs), but rather to first accurately identify the cause of the problem that is causing the distress (root cause analysis) and then come up with a plan to resolve it (problem solving analysis). This process is wholly consistent with the ARH. Moreover, it teaches the patient a strategy that they can follow in future instances if they do again become depressed, and that is likely what accounts for CBT's long-term enduring effects (66).

In an earlier article we described two patients who both were treated in this fashion (20). Both were severely depressed at the time they started treatment, but one was a patient with a relatively uncomplicated case of depression whereas the other had a depression superimposed on a host of problematic interpersonal behaviors that looked at first to be consistent with a borderline personality but turned out to be more a case of complex PTSD. That being said, the treatment of each followed a very similar format (albeit requiring only a matter of months with the first and a matter of years with the second), with more purely behavioral self-monitoring giving way to training more efficient rumination (as described in the preceding paragraph) that was framed in each case around conducting a set of ongoing tests of opposing theories (Theory A vs. Theory B).

The first patient was a 40-something sculptor who had lost his job teaching in a liberal arts college about 3 years earlier through no fault of his own when his entire art department was let go during an economic downturn. He had been working as a handyman in a condominium complex for the last 3 years following his dismissal and been depressed for the bulk of time, a fact he attributed to his "dead end" job. He viewed his distress as being a reality-based depression and could not imagine getting better until he was employed again in academia. Simply asking him to monitor his moods and activities between the first and second session quickly revealed that he felt his best when he was at work and his worst when he was at home on the weekends and in the evenings thinking about how much he hated his "dead end" job. It also quickly became apparent that he blamed himself for being stuck in his current situation, which he attributed to being an "incompetent loser" who "always screwed things up" (Theory A), the evidence for which being that he had yet to apply for another teaching job or pay his taxes during the last 3 years while depressed. Simple behavioral strategies such as graded task assignment (breaking a big task into component steps and focusing on completing one step at a time) were used to first help him get to a traveling art exhibit with his wife on the weekend and then put his portfolio together and start to apply for jobs. These simple behavioral experiments were used to test between his belief that he was an "incompetent loser" (Theory A) vs. the notion that he was simply choosing the wrong "behavioral strategy" (Theory B) and getting overwhelmed by the task. This culminated in an incident in which he was able to catch his own automatic negative thoughts and correct them on the fly by using both the alternatives and evidence questions when he found himself stymied by the magnitude of the task involved in organizing his financial records so that he could pay the back taxes that he had ignored for the last 3 years ["I have gotten filing and other stuff done in recent weeks (evidence) when I take a big task and break it down into smaller steps that I can do one at a time (alternatives)"]. Finally, he used the "implications" question to reason that the IRS would be unlikely to send him to jail if he came in voluntarily, something he confirmed with two anonymous phone calls from two separate phone booths in two different twin Minnesota cities.

The second patient was far more complicated, and her issues took far longer to resolve, but therapy progressed through a similar process across a far more extended time frame. She "conned" her way into treatment having gone to *ClinicalTrials.gov* to discover that the particular study in question screened out patients who met criteria for borderline personality disorder and then borrowed a DSM from a graduate student friend to see what she had to deny at intake in order to make it into the study. She was screened in and randomized to CBT and assigned to one of the authors (SDH) for treatment. At her first session she announced that she had been deeply damaged by something that happened to her as a teenager (and that she did not want to talk about in therapy) and as a result had become a "bad" person who invariably tore apart any romantic partner with whom she got involved. She further made it clear that she had no intention of following the study protocol that called for a maximum of 24 sessions over 16 weeks (with an emphasis on

teaching her how to do the therapy for herself so as to make the therapist obsolete); what she wanted instead was for someone to see her four or five times a week for the rest of her life in order to keep her "predatory" relational tendencies in check. She further stated (in response to her therapist's quizzical look) that that should not be that great a burden since she was twenty-nine and did not plan to live past her thirtieth birthday in 6 months. She closed by stating that she was an incorrigible liar, and that the therapist could not believe anything she said, asking if that would be a problem for the therapy. She was somewhat mollified (and bemused) when her therapist told her that it would not be a problem, since his job was not to solve her problems but rather to teach her skills that she could apply to do so if she chose, and that he could teach her those skills as readily working with any fabrications that she made up as with the actual truth. Whether she was honest or not was irrelevant, since there would be by necessity coherence in the stories that she told (her thoughts, feelings, physical reactions, and behavioral impulses would invariably be shaped by evolutionary pressures to form an integrated "whole body" response) and that was all that was needed for the therapist to teach and the patient to learn to apply the skills.

Over the first few sessions the patient and therapist sketched out competing theories regarding what had happened to her and how it had affected her life. Theory A (the one she brought into therapy) was that her father's lack of concern about what had happened to her as a teen taught her that she was worthless and someone that no one would ever love. She responded to this depressogenic schema by adopting a set of compensatory strategies, dissimulating and manipulating her partners in relationships in a desperate effort to secure some small measure of affection before the inevitable rejection, which she forestalled by beating her partner to the punch; she had just run off from her husband of 2 years to join a man she had met over the internet for an affair that lasted less than a week. After some probing of those and other previous relationships (all of which came to a bad end) the therapist developed an alternative Theory B that again started with her father's indifference to her teenage trauma but then proceeded through the notion that she only came to believe that she was unlovable and as a consequence had adopted a series of strategies (manipulate and dissimulate) that she used to compensate for her perceived defects, and it was these strategies, and not any presumed "unlovability" that led to the demise (at her hands) of any relationship she entered. A single-paged two-column depiction of "Theory A vs. Theory B" became the basis for the rest of the therapy, and every behavioral experiment that she ran was cast as a test between the competing formulations (see **Figure 1**). Was the problem that she was defective (a stable trait that would be difficult to change) or that she adopted a set of problematic behavioral strategies in an effort to compensate for her beliefs (that would be easier to change)?

As might have been expected, the traumatic event was a gang-rape by her father's drinking "buddies" in her own home less than a year after she lost her mother to cancer. Her father's total lack of concern when she told him about the rape led her to run away from home and set her off on a several year binge of romantic misadventures (first eloping with her high school boyfriend that his parents quickly got annulled) and then a series of failed relationships that culminated in her deserting her husband and ending up back at the inner-city school where she had done her student teaching. Therapy proceeded through the standard CBT strategies (training in self-monitoring, behavioral activation, and cognitive restructuring) much as it had with the sculptor, but with a few additional twists. The client started making "anonymous" phone calls to the therapist in the middle of the night "just to hear his voice," so he negotiated a deal in which he installed a phone answering machine in his office at work that she could call any time of the day or night on the proviso that he would not check the messages (if she had something that she wanted to discuss she could do it in their nearly daily sessions). She was very suspicious about what other people (including her therapist) were thinking about her (she thought that they thought that she was wild and promiscuous and out sleeping around every night) and often got angry and verbally hostile about those presumed "flights-of-fancy" on the part of the therapist, so he negotiated yet another deal in which he agreed to write down exactly what he was thinking when she became suspicious and show it to her if she chose, which she always did. It was often enough the case that what the therapist was thinking about was innocuous or embarrassing (to him) ("how long is she going to prattle on?" "what should I pick up for dinner on the way home") that she came to trust the honesty of his report and question the accuracy of her own suspicions.

Therapy proceeded for several hundred sessions over the next several years with the frequency decreasing over time from virtually daily sessions to one or two a week and then spacing out to monthly then yearly visits. It took 3 months to persuade the patient to relive the traumatic rape with her therapist, but when she did it became clear that she took two meanings away from the event (and her father's subsequent indifference): first, that she would be of little value (and hence "unlovable") to anyone in whom she had a romantic interest if she revealed what had happened to her (she had lost value as a potential partner because she had been defiled), and, second, that she found it so frightening to think that something so awful could happen to someone who had done nothing to deserve it (the "just world" hypothesis), that she found it more comforting to think of herself as a "bad" person who did the worst to others before they could do the worst to her. It took a series of carefully calibrated disclosures (first to female friend and then to her current and subsequent partners) wrapped around an anonymous survey of "eligible" young male soccer coaches her therapist sampled on her behalf, before she came to realize that others did not share her view of herself as irrevocably damaged as a consequence of the rape. What her romantic partners did take umbrage at was the way that she treated them, the dissimulation and manipulation that she used as compensatory strategies in an effort to preserve her relationships.

She had a particularly difficult time asking for what she wanted from her romantic partners, expecting them to "read her mind" and then getting angry with them and acting out when they did not meet her expectations. Considerable time in therapy was devoted to role playing making such requests in a

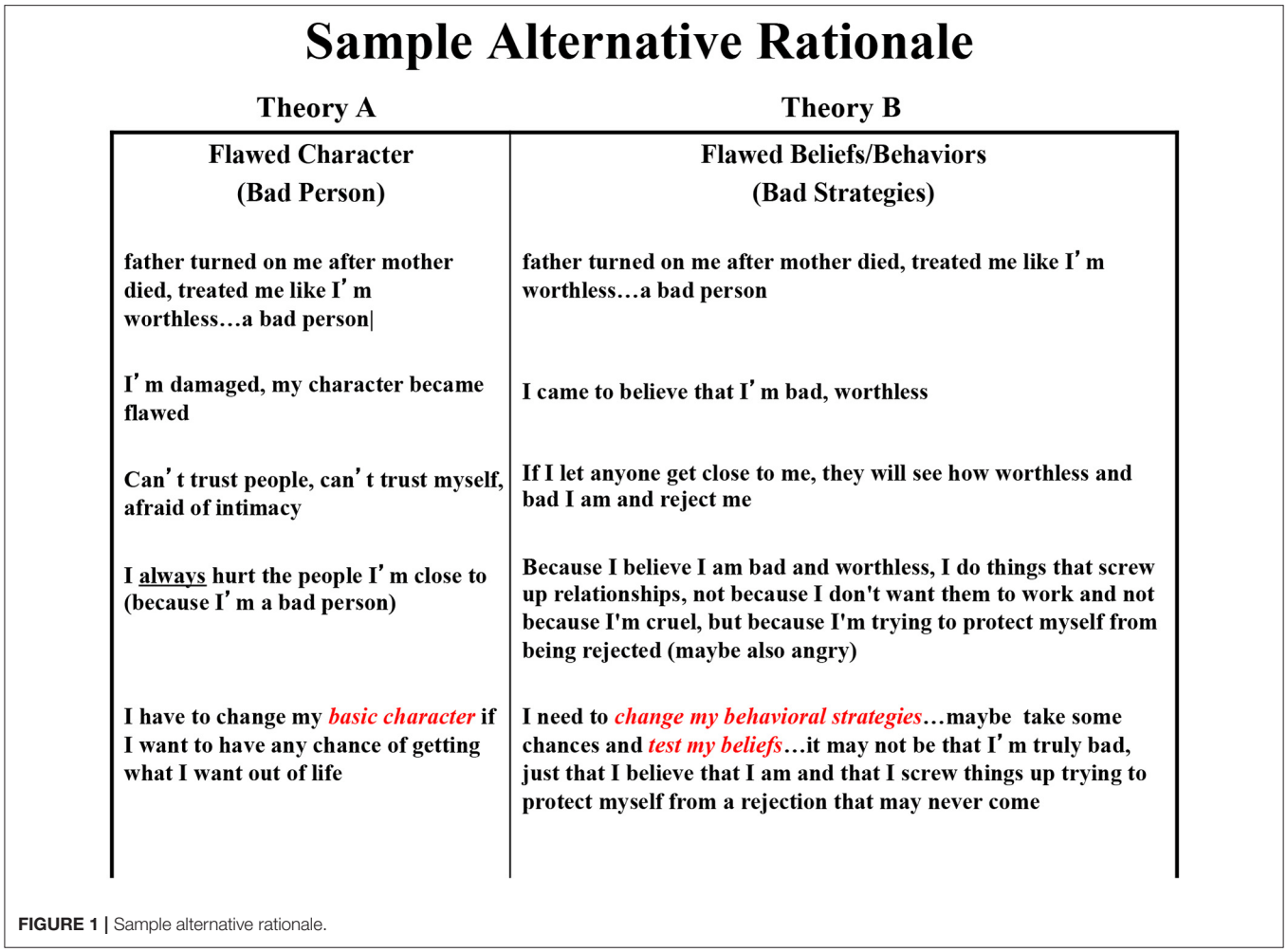


**FIGURE 1 |** Sample alternative rationale.

triadic fashion in which passive non-initiation reflected a respect for her partner's wishes but not her own, aggressive hostility reflected a concern for her own wishes at the expense of her partner's, and finally an assertive request that respected both her wishes and those of her partner and opened the door for compromise in those instances in which their wishes did not coincide. Several years after therapy ended the patient agreed to videotape (shooting over the back of her head to protect her anonymity) her recollections regarding what she did and did not like about therapy for a behavior therapy conference. What she indicated (among other things) was that the aspect of therapy that she disliked the most were the repeated role plays (she found them annoying and anxiety provoking) but that that was the aspect of therapy that she found most helpful (since they let her practice approaching partners as equals).

The question now becomes whether CBT actually works through the process of making rumination more efficient and honing behavioral skills that can be used to help patients get "unstuck." It is easier to detect an effect than it is to explain it. That is because any effort to test for mechanisms of action necessarily involves a three (or more) variable causal chain, and any experimental design can only test the causal impact of the manipulated variable (for example treatment) on either the mechanism or the outcome but not both simultaneously (67). We can and do test for mediation in our designs, but such efforts are by necessity correlational in nature. The link between purported mechanism and the outcome of interest can only be established with any real confidence if we can institute multiple independent manipulations of the mechanism itself [see for example the elegant program of research instituted by Maier and colleagues to specify that it was a descending pathway from the prefrontal cortex to the raphe nucleus that determined whether rats exposed to escapable stress behaved in a helpless or resilient fashion (68)]. By way of analogy, efforts to test for mediation in the context of randomized controlled trials (RCTs) of different treatments are similar to the shadows cast on the wall of Plato's cave; at best they reflect the movements of the people sitting around the fire, but they are not the individuals themselves. Moving the shadows on the wall may not have a causal effect but moving the people will.

There are two steps in the causal chain from intervention to outcome that have been tested with respect to CBT (most of the work to be described has been done with cognitive therapy a particular type of CBT). The first are those components of the treatment manipulation that have a causal impact and are,

in effect, its active ingredients (often referred to as treatment process). The second are the phenomena within the patient that are affected by those active ingredients for which we reserve the term "mechanisms." Both play a causal role but are sequential in their temporal order such that the active ingredients (treatment processes) produce change in the patient mechanisms. Thus, in any efficacious treatment there is at minimum a four-variable sequence; some treatment manipulation (preferably with a randomized comparator) mobilizes active ingredients (processes) that in turn engage phenomena within the patient (mechanisms) that effect changes in the concerns that brought the patient into treatment (outcomes).

It has been shown that CBT works at least as well as ADM and better than pill-placebo (69) and that it has an enduring effect that reduces risk for subsequent symptom return following treatment termination (66). The same appears to be true with respect to acute response for BA (70) and IPT (71), although only BA as of yet has demonstrated an enduring effect that lasts beyond the end of treatment (72). It also appears to be the case that non-specific factors account for the "lions-share" of variance in change among patients with less severe depressions (73); specific effects emerge only among patients who are more severe with respect to both ADM (74) and psychotherapy (75). With respect to CBT, DeRubeis and colleagues have shown that adherence to cognitive and behavioral strategies in early sessions leads to change in symptoms that in turn leads to enhanced quality of the working relationship (76, 77). In effect, the best way to generate a good working relationship in CBT is to bring about rapid symptom change and the best way to do that is to adhere to its specific cognitive and behavioral strategies. With respect to underlying mechanisms, DeRubeis and colleagues found that change in cognition led to change in depression in CBT whereas change in depression led to change in cognition in ADM (78). Tang and colleagues have shown that patients who "get" the cognitive model are more likely to show "sudden gains" in treatment (rapid drops in symptoms) and also are less likely to relapse than patients that show comparable gains in a more gradual fashion (79) and Strunk and colleagues have shown that those patients who best internalize the compensatory cognitive and behavioral skills taught in CBT are those least likely to relapse following termination (80).

This is all consistent with the notion that CBT works "from the top down" with higher cortical processes overriding more emotional processes that emanate from lower limbic regions whereas ADM works "from the bottom up" in the opposite fashion (81). This also is consistent with work by Mayberg and colleagues who found specificity of change in cortical vs. limbic regions following CBT vs. ADM (82). That is wholly consistent with an adaptationist perspective given that energy is deployed to the cortex to facilitate slow and deliberate Type 2 ruminative thinking. CBT requires that patients engage in a careful logical reconsideration of their beliefs and the problems that they face; that is clearly something that they could not do if their "brains were broken." Much in CBT is compatible with an adaptationist evolutionary perspective.

## QUESTION 7: STIGMATIZE VS. VALIDATE?

It is never good to stigmatize the patient and that is one risk that CBT can run. There is an ironic exchange between Aaron Beck and the woman who was roleplaying the patient in the classic Mia videotape. After she described concerns that her son was stealing things in school and that her husband may be having an affair, both of which she attributed to her failure (as a mother and as a wife), Beck started to describe the cognitive model (that her thoughts might be in error) and she slapped her head and said, "So even my thoughts are no good!" As we describe in greater detail in our treatise on "Disordered Doctors or Rational Rats" it is likely preferable to describe depression as a normal (if unpleasant) evolved adaptation in a manner that validates the patient's emotional experience (21). It is possible to differentiate between beliefs that may not serve the patient well and the emotions that they generate, and it is axiomatic to say something along the line of "if you think you are to blame for your son's stealing or your husband's (suspected) infidelities, how could you not feel sad?" Where an adaptationist perspective would separate from a conventional CBT response is in suggesting that even negative self-referential beliefs may play a useful evolutionary role in exploring the possible causes for the problems that the patients face whether they turn out to be accurate or not. One of the authors (JAT) will often say to patients, "Given what you just described, we would be far more worried about you if you were not depressed. We'd be waiting for the other shoe to drop, for you to sink into substance abuse or worse. Your depression did its job. It stopped business as usual amidst this complex calamity and focuses your attention on it." It is "only human" to consider all the possibilities when things go wrong and, from an adaptationist perspective, the opening gambit that motivates a search for a solution.

The essence of root cause analysis is to explore all possible causes whether flattering or not (21). That is neither an instance of disease nor disorder but a step along the process of understanding the causes of the problem as a prelude for coming up with a solution. In CBT, the therapist is schooled against invalidating the patient's affect experience but quick to look for inaccuracies in his or her beliefs. An adaptationist perspective would suggest that recognizing the value of considering all possible explanations, including those not flattering to the self, is what the human brain is designed to do and not an indication of dysfunction. Once that is done patients can proceed to generate a range of alternative explanations and gather evidence to test among them but do so in the knowledge that there is nothing inherently wrong with their brains (20).

## QUESTION 8: IS IT BETTER TO TREAT DEPRESSION WITH ADM OR CBT?

ADM and CBT clearly work and have comparable short-term efficacy (on average). About 30% of patients with more severe depression are more likely to respond to ADM than to CBT and a different 30% of the more severely depressed show the opposite pattern (83). Among patients with less severe

depressions there is little evidence of specificity; neither ADM nor CBT separate from non-specific controls like pill-placebo or supportive psychotherapy (74, 75).

What CBT has that ADM does not is an enduring effect that protects against relapse (the return of symptoms associated with the treated episode) following treatment termination (66) and possibly recurrence (the onset of wholly new episodes) relative to patients kept on ADM to the point of recovery (72, 84). Current convention in psychiatry is to keep patients with a history of chronic or recurrent depression (about 85% of all patients) on ADMs indefinitely. There is no indication that ADMs do anything to reduce future risk once you stop taking them and reason to think they might have an iatrogenic effect that prolongs the life of the underlying episode (22).

Modern psychiatry sees depression as being caused by a malfunction in the brain and this is the basis for the widespread use of ADMs (and especially the SSRIs) (39). However, ADMs are evolutionarily novel drugs and an adaptationist perspective would predict that they cause Wakefieldian disorders by interfering with emotional or physiological adaptations. At the least they should undercut the motivation to resolve the problems that triggered the episode in the first place in a manner akin to anesthetizing the squid so as to minimize the pain of surgery (31). If depression evolved to motivate the search for a resolution to the problem(s) that generated the distress, then simply medicating the distress may undercut that motivation. (One of the authors once had a patient that he had put on medications tell him, "I am no longer depressed but I am still married to the same abusive alcoholic.") The cognitive and behavioral therapies, on the other hand [including both cognitive therapy and problem-solving therapy (PST) and related third-wave behavioral interventions like acceptance and commitment therapy (ACT) and behavioral activation (BA)], are all focused on problem resolution rather than simply dulling the distress.

All antidepressant medications (ADMs) produce an initial increment in the amount of neurotransmitter in the synapse. The older monoamine oxidase inhibitors (MAOIs) do so by inhibiting degradation of all three relevant neurotransmitters (serotonin, norepinephrine, and dopamine) in the presynaptic neuron, whereas the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) do so by blocking reuptake into the presynaptic neuron (85). Because all the different types of ADMs are believed to share a common downstream mechanism (an increment in the amount of neurotransmitter in the synapse that increases the likelihood that an impulse will be propagated along the post-synaptic neuron whatever that may be), it was long believed that depression was a consequence of a deficit in extracellular neurotransmitter that ADMs corrected (86).

In point of fact, no such deficit exists. It is exceedingly hard to measure neurotransmitter levels in the synapse of a living human being, so Barton and colleagues inserted a catheter in the jugular vein to assess serotonin turnover by measuring its principal metabolite exiting the brain. Contrary to expectations, unmedicated depressed patients showed elevated levels of serotonin turnover relative to normal controls, whereas patients stabilized on therapeutic medication doses had returned to the normal range (87). This presented something of a paradox with regard to the widespread belief that ADMs work by correcting a deficit in neurotransmitters in the synapse; if neurotransmitter levels are already elevated in the synapse, how is it that increasing them further (up to four times the levels found in nature) can reverse an existing episode of depression?

The resolution of this paradox requires a more sophisticated understanding of the way that medications work and their interplay with the underlying homeostatic regulatory mechanisms. In a classic monograph published just before the turn of the last century, Hyman and Nestler noted that most medications (ADMs included) do not produce their effects directly, but rather by triggering pushback from the mechanisms that maintain internal homeostasis (88). This principle holds not only for medications with psychiatric properties, but also for drugs of abuse; external administration of opiates suppresses internal synthesis of endorphins leading first to tolerance and then withdrawal when that external supply is cut off. As Andrews and colleagues note, when a patient starts on an ADM, the initial effect is to increment the amount of neurotransmitter in the synapse for the first week or two (during which time there often is an exacerbation of symptoms) before the internal homeostatic regulatory mechanisms kick in and suppress synthesis in the presynaptic neuron and post-synaptic sensitivity (17). As a consequence, neurotransmitter levels are reduced, and the medicated patient returns to "normal" levels as Barton et al. observed (87).

We now return to just what it means to have elevated levels of serotonin in the synapse. Norepinephrine and dopamine are the other two biogenic amines that serve as neurotransmitters that are involved in depression and both are largely modulated by serotonin. Norepinephrine is largely involved in the regulation of the stress response that underlies the BIS, whereas dopamine is largely involved in the pursuit of appetitive rewards that underlies the BAS. As previously described, all the neurons in the brain that use serotonin as a neurotransmitter have their cell bodies in the raphe nucleus (deep in the brain stem) and when they fire, they play a major role in the distribution of metabolic resources across the brain (and the body too). When the raphe nucleus fires, the brain is primed for immune response (if infected), maintenance of vital organs (if starving), or rumination (if melancholic). ADMs provide symptomatic relief, but they do not necessarily resolve the problem that triggered the depression in the first place. In effect, ADMs may anesthetize distress at the expense of leaving the individual more vulnerable to predation.

Moreover, when ADMs suppress symptoms, they may do so at the cost of locking down the very underlying homeostatic regulatory mechanisms that otherwise would have shifted back toward normal baseline levels once the problems were resolved (the process referred to as "spontaneous remission" but that is likely anything but spontaneous). One of the symptoms that ADMs suppress is rumination, and if (as the ARH suggests) its component steps (causal analysis facilitating problem solving) might otherwise have led to a solution, that "natural" healing process will not occur. Moreover, to the extent that ADMs "work" by perturbing the homeostatic mechanisms that regulate

neurotransmitters, there is likely to be "push back" when taken away.

The process of pushing back on those homeostatic regulatory mechanisms has been termed "oppositional perturbation" by Andrews and colleagues and likened by analogy to compressing a coiled spring (89). This leads to the prediction that the more a medication class perturbs the underlying homeostatic regulatory mechanisms, the greater the risk of relapse when the medications are taken away and that is exactly what happens. Risk for relapse following remission on pill-placebo (no direct effect on neurotransmitters) is only about 20%, but doubles to 40% following remission on SSRIs that are serotoninergic only. That risk rises to over 50% for SNRIs and TCAs that also affect norepinephrine and to 75% for MAOIs that also affect dopamine (89). This is impressive accuracy for a prediction derived from adaptationist evolutionary theory.

This leads us to suspect that ADMs may suppress symptoms (a purely palliative effect) at the expense of prolonging the length of the underlying episode (20, 22). It is common practice in psychiatry to keep patients on ADMs for 6–9 months following initial remission to forestall relapse (the return of symptoms of the treated episode) on the presumption that the underlying episode will run its course (that spontaneous remission will proceed). However, if the notion of oppositional perturbation is correct, then the underlying neurobiology will be locked in place and patients will stay at elevated risk for relapse (about 3–5 times greater than the risk of recurrence – the onset of a wholly new episode) for so long as they stay on medications (90). In point of fact, the vast majority of patients are kept on ADMs for over 2 years and at least a quarter for over a decade (91) and current psychiatric guidelines call for keeping patients with a history of chronic or recurrent depression (the vast majority of clinical patients) on ADMs indefinitely (92).

Finally, the long-term consequences of ADM use actually may be deadly (93). The serotonin transporter is expressed in many peripheral organs and tissues (17). Serotonin evolved in the ancestral mitochondrion – the energy powerhouse in cells – and it has mitochondrial functions. What that means is that serotonin may have important effects on the metabolism of peripheral cells outside of the brain and that blockade of the serotonin transporter could cause Wakefieldian dysfunction in those cells. The diffuse set of side effects caused by SSRIs (gastrointestinal, cardiovascular, platelet function, sexual, and developmental) is consistent with that notion. Although SSRIs are presumed to be relative safe over the short run (one of the reasons they are preferred over the TCAs and MAOIs), a meta-analysis by Maslej and colleagues found a 30% increment in "all cause" mortality among patients free from cardiac illness (ADMs are mildly protective for the latter) (94). These findings need to be interpreted with caution since they were based on naturalistic studies that could have been confounded by other factors, but the effect was even stronger when initial levels of depression were controlled. Few industry-funded trials are continued for more than 6–8 weeks and multi-year maintenance trials are uninformative with respect to long-term risks since all patients start on ADMs. We know less about the long-term risks of ADMs than we ought to know, but what we do know is cause for some concern.

## QUESTION 9: WHY DO DEPRESSED PEOPLE OFTEN HAVE INACCURATE BELIEFS?

The ARH posits that depression is an adaptation that evolved to facilitate solving complex (often social) problems by virtue of motivating a switch from quick heuristic-driven Type 1 thinking into a more energy-expensive but carefully deliberative Type 2 thinking (rumination) (16). Cognitive theory suggests that depression is in large part a consequence of inaccurate beliefs and maladaptive information processing and that rumination is, at best, a symptom of depression and at worst a maintaining cause. If depression evolved because it motivates efforts to solve complex (often social) problems and rumination (careful deliberation) is the means by which it achieves that goal, how is it that the beliefs that people hold when depressed seem to be incorrect (at least to their therapist). We think that there are several possible resolutions to this conundrum.

### Intraspecific Competition Occurs in All Species

First, maladaptive mistakes and failures are an integral part of the human condition. Within every species, individuals compete for scarce resources that are important for survival and reproduction (e.g., food, territories, mates). As a result of that competition, it is inevitable that there are winners and losers. Human beings compete for these resources through situationally dependent cognition and behavior (95). For humans, the social world is incredibly complex and constantly in flux, such that the best strategy often changes from one situation to another. As a result, humans have evolved the cognitive capacity to develop *mental models* of human nature in order to predict how best to behave and what to expect from others in response. Due to differences in genes and experience, some people will develop mental models that work relatively well, while others will develop mental models that work more poorly. In other words, we do not need to invoke the concept of a mental disorder to understand why people develop inaccurate beliefs about their social world. It is simply a necessary consequence of the fact that humans compete to develop better mental models of human nature, and some people are less successful than others in this competition.

But this perspective also suggests that natural selection might have favored the evolution of psychological mechanisms that adjust mental models when they fail to function properly. Mental models are not necessarily "maladaptive" just because they are inaccurate; they are maladaptive if they lead to losses or failures to achieve the resources that make reproduction possible (e.g., mates, food, status, social support). Thus, we argue that the reason why depression is often associated with failures and losses in important domains (e.g., romantic relationships) is because these events suggest that one's mental models of the social world are not working well and need to be revised through the employment of careful methodical Type 2 thinking.

## Evolutionary Mismatch

Second, it is possible that what is going on reflects nothing more than ***evolutionary mismatch***. Evolved adaptations are traits that exist now because they were shaped by selective pressures that operated in the past (96). Modern environments may deviate substantially from ancestral ones. If so, then what was adaptive in the past may not be adaptive in the present. Most people crave foods that taste sweet. That was adaptive in our evolutionary past when the primary source of simple carbohydrates were fruits that were also rich in vitamins but serves us less well with the advent of processed sugars that lead to obesity and tooth decay. Similarly, starvation was a recurring risk in our ancestral past leading to a preference for the kinds of high caloric foods that raise the risk for metabolic syndrome for those members of the species who have access to an ample supply of meats and starches. From an evolutionary perspective, people have evolved to pay undue attention to how they are treated by close relatives (those who share your genes) and especially by their parents. If your parents do not love or invest in you, that does not bode well for your future. Most recurrence-prone patients have stable (albeit latent) self-images at the core of their depressotypic schemas that they are flawed in some fashion (usually unlovable or incompetent) that predate adolescence. In many instances these beliefs stemmed from the belief (accurate or otherwise) that their parents did not value them and in our ancestral past that could prove to be highly problematic. It likely still is true that being valued by one's parents helps one survive one's childhood, but it is less likely that retaining those negative beliefs about oneself into adolescence helps one navigate complex social relationships as adults. Moreover, the "nuclear family" is a rather modern invention. Children raised in hunter-gatherer societies were usually surrounded by "allo (other) mothers" who contribute the care and nurturing of the child. "Parental investment" in our ancestral past was more a matter of "tribal investment" than it is today.

## Adaptive Search Strategies Are Imperfect

Natural selection causes a species to incrementally increase its fitness, but it does so without foresight or purpose, and it does not guarantee perfection. As Tooby and Cosmides opined "there is no such thing as an adaptation that can maximize fitness under all possible circumstances" (96). The human eye is a good example. It is one of 40 different kinds of "eyes" that evolved in the animal kingdom to process electromagnetic radiation and it functions to let organisms "see" objects at a distance. The human eye contains a "blind spot" at the back of the retina where the optic nerve exits on its way to the brain. No "intelligent designer" would have "designed" an eye that functioned in that fashion (there is nothing adaptive about having a "blind spot" in the back of one's eye and not all species have one) but natural selection does not double back on itself. If a feature represents an improvement over what came before then it tends to be selected regardless of whether some other solution might have worked better. Search-based optimization techniques are useful and often find a superior solution but that does not guarantee that the optimal solution will be found.

The ARH suggests only that people who are depressed will use a slow deliberate "Type 2" processing style to search for a solution to their problems, not that they will always succeed when they do so. It is quite possible that some will get "stuck" for a period of time at a suboptimal solution. Based on clinical (and personal) experience we suspect that it can be quite useful to carefully examine one's own role when things go wrong since that is the easiest thing to correct in the future, but ascribing blame in the form of a stable trait (unlovable or incompetent) is more likely to keep one "stuck" than focusing on the behaviors that one did (or did not) engage in. Traits are simply harder to correct than actions (20). Clinical experience also suggests that those trait ascriptions are more "conditional" than stable and thus still amenable to change. As previously described, much of what gets done in CBT is focused around getting patients to consider alternative explanations for their problems and to examine the existing evidence for each and to run behavioral experiments to test between those competing beliefs. For example, in the case of the sculptor, it was breaking big tasks down into their component parts and doing them one at a time (graded task assignment) that helped him past his tendency to get so overwhelmed by the magnitude of the task that he did not get started. In effect, gathering evidence and running behavioral experiments allows one to correct misguided assumptions and beliefs (it was not that he was "incompetent" just that he chose the wrong behavioral strategy), and thus correct the residue of unfortunate prior experiences (his belief in his own "incompetence" came from being forced to compete with a younger brother for his father's attention and frequently losing out to a sibling who was more outgoing and more facile). What he learned as a young adolescent was not out-of-line with the competition that he faced and the "failures" he experienced; it just was not all that relevant to the challenges he faced as an adult. That said, depression is needed to motivate one to search for the solution to a problem and without that search there is no solution (21).

## Normal Anxiety Can Disrupt Rumination

Getting "unstuck" from a suboptimal solution may involve doing something different than what one has done in the past and for many people that can involve the perception of risk and its attendant affect anxiety. Anxiety often co-occurs with depression [two-thirds of the patients who met criteria for MDD in the DeRubeis and colleagues in the 2005 Penn-Vandy study also met criteria for one or more anxiety "disorder" (69)] but its effect on cognition is different (42).

Whereas, depression leads the individual to ask, "where did I go wrong" and to carefully weigh paths forward, anxiety tends to promote a "better-safe-than-sorry" approach that is often an adaptive response to an imminently dangerous situation (24, 42). Expressing a romantic interest in someone opens one to the risk of rejection and pursing a goal in an achievement domain leaves one at risk for failure, but neither takes one out of the gene pool. Choosing not to act on either does nothing to further the propagation of one's genes.

Earlier we described a teacher who thought that a prior sexual assault as an adolescent undercut her value as a prospective mate and relied on dissimulations and manipulations as compensatory

strategies (lying about her past and manipulating romantic partners to get what she wanted) to generate a series of troubled and transitory relationships when in fact it was these interpersonal "safety behaviors" that sabotaged the relationships she formed (20). It was not until she took the chance of leveling with a new romantic partner about what had happened to her in the past (something that took great courage on her part) that she learned that he was not the least concerned about what that meant about her (other than he was sorry that she had been assaulted) and that she could drop the safety behaviors (the lies and manipulations) and simply ask for what she wanted from him in the relationship. Fifteen years she had been stuck on a suboptimal peak because of the anxiety that the thought of full disclosure caused her. The process of climbing down off that suboptimal peak was fraught with a sense of dread that took several months in therapy (and a conversation with a girlfriend and an anonymous survey of "eligible" males) to overcome but the outcome was quite gratifying to her, and she got better (and more comfortable) engaging in self-revelation (as needed) across a series of increasingly satisfying relationships.

## Large Fitness Consequences Can Favor Seemingly Unproductive Cognitions

There is nothing so universally depressogenic as the loss of a child. It is not uncommon for parents who have lost a child to ruminate intensely over what they might have done to prevent the child's death even when it seems clear to others (including the therapist) that there was nothing else they could have done. That being said, understanding the causes of a negative event (even one that has already occurred) can be useful in preventing similar negative events in the future (16, 97).

In our ancestral past, women had an average of about six children over their lifetimes of whom several died (98). Effort spent on understanding the causes of one child's death might help prevent the death of another (99, 100). Watching parents engage in self-recriminating rumination might seem cruel, but the fitness costs are so great that natural selection would have favored the expenditure of a great deal of cognitive effort even if it only had a miniscule chance of increasing the odds of survival for the other children. We focused on the loss of a child in this example, but the same principle extends to any situation in which the fitness consequences are great.

As Dawkins describes in his 1976 treatise "*The Selfish Gene,*" we are but "survival machines" engineered by natural selection to propagate our gene lines at all times even if at our own affective expense (101). An evolutionary perspective would suggest that there is little point in trying to convince grieving parents not to engage in a causal analysis in such a situation (or other patients from grieving in the aftermath of a romantic breakup or the loss of a job) but rather to point out that the brain is designed to explore the possible causes of negative life events on the off chance that such events can be prevented in the future. To ruminate in response to loss or failure is an eminently "species-typical" (human) thing to do. The optimal response in CBT is to label it as an attempt to solve a problem (or prevent a future one) and to help the process along.

## Inclusive Fitness Theory

As previously noted, one of the most important insights in evolutionary biology over the last century is that organisms are not designed by natural selection to maximize their own survival or even their own reproductive success but rather to maximize the reproductive success of their gene line (102). This is what Dawkins meant when he labeled us as nothing more than "survival machines" (101). Individuals not only propagate their gene lines through their own reproductive efforts (***direct fitness***) but also via propagating the reproductive success of their biological relatives (***indirect fitness***). The sum of direct and indirect fitness is called ***inclusive fitness*** (103), and it is this sum that best predicts of what kinds of behaviors organisms engage in because that is what is actually maximized by natural selection (102).

The essence of the idea was captured by the iconic quip by the evolutionary geneticist J. B. S. Haldane who was reported to have said that he would not sacrifice his life for his brother, but he would do so for two brothers or eight cousins (104). This phenomenon is easiest to see in the lives of social insects. Only a small percentage of the individuals actually reproduce (the queen and one or more of the male drones) while the vast majority labor to ensure the propagation of a gene line comprised solely of their biological siblings. This concept is crucial in explaining many important biological events including multicellularity, apoptosis and other forms of programmed cell death, as well as the evolution of social systems characterized by family groups and parenting behavior in humans. Where it intersects especially with clinical concerns has to do with self-sacrifice. No one would question a parent's willingness to sacrifice his or her life for the life of his or her child, but not all would see the same genetic mechanism "baked in" to the suicidal ruminations of a person who is concerned about being a burden to biological relatives.

In not-so-distant times amongst peoples who lived on the edge starvation in northern climes (like the Inuit north of the Arctic circle), it would be considered "de rigueur" for post-reproductive elders to walk out into the snow and not come back if the winters were too long and their grandchildren faced starvation as a consequence (105). Such "altruistic" notions might seem misguided in situations in which starvation is not imminent (suicide is the "gift that keeps on giving" to the survivors) but the psychological mechanism would have been selected for in our ancestral past in a manner wholly in keeping with the concept of inclusive fitness.

Many people who die by suicide believe that their families would be better off without them (106). Most patients entertain at least "passive" suicidal ideation, and over half of all people who die by suicide have a history of depression. Self-sacrificial impulses would be favored by natural selection among those individuals who see themselves as defective or impaired and those with a history of childhood abuse (self-esteem is often based on parent's behavior). People with a history of failed relationships also are at risk even during the reproductive years (107–109).

If some of our readers have a visceral response to the use of the word "adaptive" to describe suicide and other forms of self-destructive behavior, this is an indication that the evolutionary

perspective is novel and non-intuitive. ***Clinicians need to understand the naturalistic fallacy.*** *An 'is' is not an 'ought.' Cancer 'is' a collection of cells that are pursuing their inclusive fitness. It is hardly an "ought," but intervention 'is' nevertheless warranted.* Moreover, we should not let moral repugnance bias the scientific study of human behavior. Prolicide (killing one's offspring), the killing of conspecifics, and sexual coercion are common throughout the animal kingdom, and humans are no different. We strongly advocate for clinical intervention in situations in which people are engaging in self-destructive behavior as part of the pursuit of indirect fitness interests. We also think that it is likely to help the patient to identify the evolutionary origins of seemingly maladaptive behaviors, such as rumination and suicide. Not all evolved adaptations need to be implemented if they are not consistent with the patient's current interests (most reproductively capable adults practice birth control from time-to-time). Making treatment more efficacious will require differentiating psychological phenomena that result from some malfunction in the brain from those mechanisms that evolved to maximize inclusive fitness. Any effective and efficient treatment must fit an accurate model of human nature and depression.

## SUMMARY AND CONCLUSIONS

An adaptationist evolutionary theory suggests that depression is an adaptation that evolved because it increases inclusive fitness in response to negative life events and the ARH suggests that it does so by increasing the propensity to ruminate. Whereas, most clinicians see rumination as a symptom of depression, or even worse, a cause, the ARH sees it as a means to move from a careful causal analysis of a complex social problem to a workable solution. Most episodes of depression remit on their own in the absence of treatment, suggesting that whatever adaptation evolved in our ancestral past works well in most instances. CBT is efficacious in the treatment of depression and has an enduring effect that reduces future risk but may only be needed for those among the "recurrence prone" who get "stuck" temporarily making internal stable attributions that provide no clear behavioral path to resolution. ADMs are analgesic at best in that they treat the symptoms but not the problem, and quite possibly iatrogenic with respect to prolonging the underlying episode and worse creating harmful dysfunctions in other areas of the body and brain. CBT might be preferred over ADMs if it facilitates the functions that depression evolved to serve.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SYSTEMATIC REVIEW
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# Virtual Reality-Assisted Cognitive Behavioral Therapy for Anxiety Disorders: A Systematic Review and Meta-Analysis

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**Objective:** We aim to explore the effectiveness of virtual reality-assisted cognitive behavioral therapy (VRCBT) in the treatment of anxiety and depression in patients with anxiety disorders. We further compare the therapeutic effect of VRCBT with that of standard cognitive behavioral therapy (CBT), as well as investigate the long-term efficacy of VRCBT.

**Methods:** As of March 3, 2020, a total of four databases (Web of Science, PubMed, PsycINFO, and Scopus) were retrieved, and two researchers independently conducted literature retrieval and research selection and performed data extraction. Methodological quality assessment was performed using the Cochrane risk of bias tool and Grading of Recommendation, Assessment, Development, and Evaluation tool (GRADE).

**Results:** A total of 11 studies were included ($n = 626$; range, 25.3–43.8), and six randomized controlled trials were quantitatively analyzed. The main outcome was anxiety and depression, and the secondary outcome was the withdrawal rate and long-term effects. Meta-analysis showed that the therapeutic effect of VRCBT on anxiety was better than that of the waiting list group (WLG) (SMD = −0.92; 95% CI: −1.34, −0.50; $p = 0.005$, $I^2 = 66\%$, $n = 276$), while the therapeutic effect of VRCBT on anxiety was similar to that of standard CBT treatment (SMD = −0.26; 95% CI: −0.50, −0.01; $p = 0.77$, $I^2 = 0\%$, $n = 150$). We further found that the therapeutic effect of VRCBT on depression was better than that of the WLG (SMD = −1.29; 95% CI: −2.26, −0.32; $p = 0.09$, $I^2 = 58\%$, $n = 74$), while the effect of VRCBT was similar to that of standard CBT (SMD = −0.30; 95% CI: −0.67, −0.07; $p = 0.39$, $I^2 = 1\%$, $n = 116$). Of the five studies that reported withdrawal rates of patients during the VRCBT and CBT treatment process, the withdrawal rates of the VRCBT group and CBT group did not reach statistical significance (OR = 0.70, 1.48, $p > 0.05$); only two studies reported the long-term effectiveness of VRCBT in anxiety and depression on patients with anxiety disorders.

**Conclusion:** VRCBT treatment has a specific positive effect on patients with anxiety disorders (anxiety and depression). Compared with standard CBT, similar therapeutic

effects can be achieved in the treatment of anxiety disorders. However, limited randomized controlled trials were included, requiring that these results be treated with caution.

**Keywords: cognitive behavioral therapy, virtual reality, anxiety disorder, meta, systematic review**

## INTRODUCTION

Anxiety disorder is the most common mental illness and is characterized by excessive anxiety, fear, and corresponding behavioral disturbance (1). Depressive symptoms often accompany patients with anxiety disorders, and some studies have shown that the anxiety symptoms of patients with depression are more serious (2). A meta-analysis of the results of epidemiological surveys in 44 countries has shown that the prevalence of anxiety disorders is about 7.3% worldwide (2). These diseases are closely related to high social costs (3), social–psychological function, and reduced quality of life (4, 5). Generally, mental illnesses, such as anxiety disorders, are often difficult to detect in time.

Cognitive behavioral therapy (CBT) is an effective method for treating anxiety disorders (6, 7). It is administered in the form of individual or group settings, and therapists are able to reduce patients' psychological pain by changing their way of thinking and behavior (8). Exposure is viewed as a fundamental part of CBT for anxiety disorders, which is very problematic for the treatment process. As part of the therapy, patients can be asked to make a public speech in front of a group of people or be put in awkward and uncomfortable situations (9). Moreover, the situational factors involved in this type of therapy are difficult to control, often making it difficult for therapists to implement CBT (10). Simultaneously, when conducting imaginal exposure, the effects can be limited by the patient's imagination and cognitive function (11).

These weaker aspects of these standard CBTs can be augmented by virtual reality (VR). As a newly developing intervention method, VR has gradually become an adjacent therapy to various disease treatments, such as for cerebral palsy, depression, and Parkinson's disease. VR technology is a human–computer interaction technology based on multisensory perception and has the advantage of creating a sense of immersion while providing timely feedback based on personal performance (11–14). VR was initially widely used in specific phobias, such as arachnophobia (fear of spiders) and aerophobia (fear of flying), and has expanded to more complex anxiety disorders, such as in the treatment of obsessive–compulsive disorder and acrophobia (fear of heights) (10, 15).

For patients with anxiety disorders, virtual exposure can provide multiple advantages compared to standard CBT. In standard CBT, real exposure can be difficult and potentially dangerous (as in the case of posttraumatic stress disorder, for example), or the treatment cost may be too high (phobias in acrophobia) (10, 15). In VRCBT treatment, the therapist no longer needs the patient to carry out exposure therapy in reality, but VR can realize the exposure therapy according to the patient's condition. It can create realistic virtual environments based on different anxiety disorders, accurately shifting to the patient's immersive environment, and expose the virtual environment in different stages according to the needs of the disease. VR therefore allows therapists and patients to fully control the stimulus and exposure. During the course of treatment, therapists can view patients' environment being seen on the screen, and simultaneously observe patients' discomfort and adjust the degree of stimulation (10, 16). Such VR exposure treatment can maximize treatment effectiveness under the condition of complete confidentiality (17) and engage patients to participate in treatment through virtual scenes or *via* direct communication with psychotherapists about potentially uncomfortable subjects.

Because of these advantages, VR therapy has been developed and applied to evaluating and treating various psychological issues. Previous studies have examined the therapeutic effects of using VR therapy alone as well as with traditional treatment options. Powers et al. (18) found in a meta-analysis that VR group patients showed improved effects compared to reality exposure therapy. A further meta-analysis (19) found that VR patients showed moderate to large-scale effects in overall subjective pain, cognitive change, and behavioral measurements of physiological indicators compared to traditional anxiety disorder treatments. It therefore appears that compared to the traditional treatment scheme, VR can achieve similar therapeutic effects. To this effect, a study found that VRCBT seemed to be more conducive to the treatment of anxiety disorders compared to the traditional exposure therapy of CBT (20). In the published meta-analysis, there is no research on the difference between VRCBT and CBT.

In the current study, we conducted a detailed meta-analysis intended to further elucidate the potential benefits of VR therapy. By collecting randomized controlled trials using VRCBT to treat anxiety disorders, we explored the effects of VRCBT on anxiety and depression in patients with anxiety disorders. We further examined the differences in therapeutic effects between VRCBT and standard CBT as well as the long-term effect of VRCBT in order to provide guidance for clinical psychotherapists treating patients with an anxiety disorder.

## METHODS

This study was conducted according to the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (21).

### Literature Search

Electronic searches were conducted using the Web of Science, PubMed, PsycINFO, and Scopus databases from inception through March 3, 2019, to identify all relevant published articles, The search terms included (virtual reality) and (behavior* therap* or cognitive therap* or cognitive behavior* therap*) and

(GAD or generalized anxiety disorder or OCD or obsessive–compulsive disorder or social phobia social or anxiety disorder or specific phobia or simple phobia or PTSD or posttraumatic stress disorder or acute stress disorder), and we searched in the database by "subject" or "title/abstract." To include all relevant research, we further, manually searched relevant research from recently published meta-analyses and review articles.

## Eligibility Criteria

Article screening was independently carried out by two researchers based on the title and abstract, taking into account the research on the therapeutic effect of VRCBT on patients with anxiety disorders. The procedure was intended to eliminate duplicate, irrelevant, and review literature, and then further refine the screening according to the full-text inclusion criteria: (1) Literature type: All the controlled trials compared the effects of VR combined with CBT on patients with anxiety disorders. All the studies were published literature, excluding conference abstracts, and case studies, regardless of whether allocation concealment and blindness were used. (2) Research subjects: The experimental subjects were between 18 and 65 years old, and the structured diagnosis was determined by experienced therapists, which conformed to the features of anxiety disorders in DSM-3, DSM-4, or DSM-5, and all the subjects were assessed for clinical severity through appropriate psychological measurement. (3) Intervention measures: All the studies clearly described the intervention plan and the comparative study between VRCBT and WLG. The study had to specify that an experienced psychotherapist was the one to conduct CBT with patients with anxiety disorders. (4) Result indicator type: In order to be included in this analysis, at least one of the two outcome indicators included in each RCT study had to be anxiety and/or depression symptoms; improvement in the severity of anxiety and depression was measured by an established assessment scale or a scale assessed by a clinical psychologist, and the secondary outcome indicators had to consider the follow-up and withdrawal rate during the intervention. Studies that did not meet the above inclusion criteria were excluded. Disagreements between the two researchers were resolved through discussion with a third reviewer.

## Risk of Bias Within and Across Trials

Two researchers adopted the "bias risk assessment" tool of the Cochrane systematic review to evaluate the quality of six indicators for the included studies: random allocation method, allocation concealment, blinding (investigator-blinded and/or participant-blinded), the integrity of result data, selective reporting of research results, and other sources of bias (21). All studies were scored as possessing (a) low risk of bias, (b) unclear, or (c) high risk of bias (21). Disagreements between researchers were resolved through discussion with a third reviewer.

The GRADE system evaluates the overall quality of the experiment based on the results to provide a transparent and clear interpretation of the study. The table includes five subtraction rules: (a) score of $\leq$40% on the risk of bias assessment; (b) results between studies are inconsistent; (c) studies used indirect measures to test outcomes; (d) questionable accuracy of data collection; and (e) evidence of publication bias. These rules reduced the overall quality of the study, and so three rules were added: (1) one point for large effect size, two points for very large; (2) evidence of a dose response; and (3) confounding variables were accounted for, which can improve the overall quality of the research. According to the evaluation results, the quality of evidence was divided into four levels: (a) high quality—very confident that the real effect value is close to the effect estimate; (b) medium quality—there is a medium degree of confidence in the effect estimates, and the actual values may be close to the estimated value, but there is still the possibility that the two are different; (c) low quality—the degree of confidence in the estimated value is limited, and the real value may be quite different from the estimated value; (d) low quality—there is little confidence in the effect estimate, and the real value is likely to be very different from the estimated value (22). Evaluations were conducted by one researcher and then checked by another; disagreements between the two researchers were resolved through consensus with a third reviewer.

## Data Extraction

Two researchers conducted data extraction by reading the full text to determine the outcome indicators for analysis independently. The primary outcome indicators included anxiety measurement results and depressive symptoms directly related to the target disease, such as the Social Interaction Anxiety Scale (SIAS) used to evaluate social anxiety treatment effect and the measurement results of Beck Depression Inventory (BDI). The secondary outcome indicators included the rate of midpoint withdrawal and follow-up effects. If a 6-month follow-up (or close follow-up) was reported in the study, we extracted the study's follow-up data. If there were no data needed to calculate the magnitude of the effect of the study, we contacted the author. We also extracted descriptive data, according to the following four aspects: literature characteristics, participant characteristics, intervention plan, and anxiety measurement indicators and test tools. Literature characteristics included author, year of publication, and country. Participant characteristics included types and diagnostic criteria of anxiety disorders (diagnostic tools), number of participants (e.g., VRCBT vs. control group number, and sex ratio), and average age. The intervention plan included weekly dose, duration, and follow-up. Anxiety disorder measurement indicators and test tools included testing tools for anxiety and depression in patients with anxiety disorders.

## Data Analysis

To accurately extract the data, a researcher extracted the data, and a second researcher confirmed the extracted data to ensure accuracy. Using Review Manager 5.3 software for meta-analysis, we adopted the random effect model due to different patients and methodological characteristics regardless of heterogeneity. For continuous data, the standardized mean difference (SMD) was selected as the effect scale index for statistics. The magnitude of effect indicates the degree of influence of VR combined with CBT on anxiety disorders. It is classified as follows: 0.2–0.5 = small effect; 0.5–0.8 = medium effect; >0.8 = large effect (21). The effect values are all expressed in a 95% confidence interval (CI).

The heterogeneity between the studies was analyzed using the $I^2$ statistic, classified as follows: $I^2$ = 0–24%, low heterogeneity; $I^2$ = 25–49%, moderate heterogeneity; $I^2$ = 50–74%, high heterogeneity; $I^2$ = 75–100%, very large heterogeneity (21). The "leave-one-out" method was used for sensitivity analysis to determine the source of heterogeneity (21). We contacted the authors of studies by email to obtain relevant information for those studies lacking sufficient detail.

# RESULTS

## Studies Reach

A summary of the results of the literature search and screening process is shown in **Figure 1**. A total of 986 records were retrieved, five records were added manually, and the remaining 822 records were removed. A total of 804 records were excluded through the title and abstract, while 18 studies were included in the full-text review. One (23) study concerned VR exposure therapy for phobias, while the other (24) study was a literature overview of VR in treatment of psychiatric disorders. Two (25, 26) studies had no outcome indicators of interest, and three (27, 28) studies did not provide raw data and were therefore excluded. We performed meta-analysis on 6 of these (9, 10, 29–32).

## Risk of Bias

### Risk of Bias in Individual Studies

Results of bias risk assessment are shown in **Figure 2**. Six (9, 10, 29–32) studies reported the generation of randomized controlled sequences, two studies reported allocation concealment, one (9, 29) study blinded participants, and no studies blinded the evaluation of results. The data of the six (9, 10, 29–32) studies were relatively complete, although, their selective publication was unclear (9, 10, 29–32). One (30) study may have been subject to publication bias due to the use of VR devices with mobile phones as terminals.

### Grade Assessment

The GRADE assessment results for the overall quality of the experiment are shown in **Table 1**. We grouped these studies according to different classifications that assessed the quality of evidence. All studies were initially listed as high quality. Based on a high $I^2$, all groups were removed to indicate inconsistency, and all studies were of medium quality. We have a medium degree of confidence in the effect estimates, and the real value may be close to the estimated value.

## Study Characteristics

A summary of all study characteristics is shown in **Table 2**, where 11 studies on VRCBT treatment of patients with anxiety disorders are summarized and include a total of 6 RCT studies (9, 10, 29–32) published between 2003 and 2019, with a total of 626 patients (age range, 25.3–43.8 years old).

## Data Synthesis

### Effects of VRCBT on Anxiety

Meta-analyses revealed evidence of the impact of VRCBT on anxiety. Five (9, 10, 29–32) studies reported a significant effect of VRCBT treatment on the degree of anxiety compared to

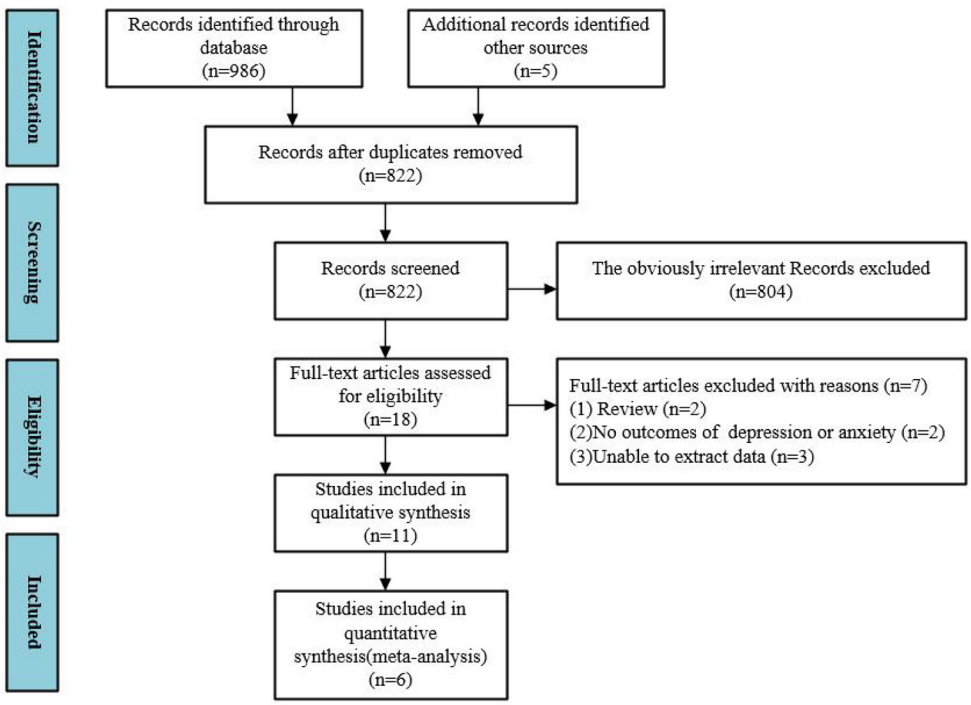


**FIGURE 1 |** The flow of literature search and study selection.

untreated patients, showing a large effect (SMD = −0.92; 95% CI: −1.34, −0.50; $p$ = 0.005, $I^2$ = 66%; **Figure 3**), while four studies (9, 10, 31, 32) reported an effect of VRCBT treatment on the degree of anxiety compared to CBT treatment, showing a small effect (SMD = −0.26; 95% CI: −0.50, −0.01; $p$ = 0.77, $I^2$ = 0%; **Figure 3**). Similarly, there was a group difference in the level of anxiety relief between the untreated group and the CBT-treated group (two RCTs; SMD = −0.59; 95% CI = −0.85, −0.33; $p$ = 0.007; $I^2$ = 53%). A sensitivity analysis of "leave-one-out" was performed on the two groups, and no change in the direction of the effect size was found.

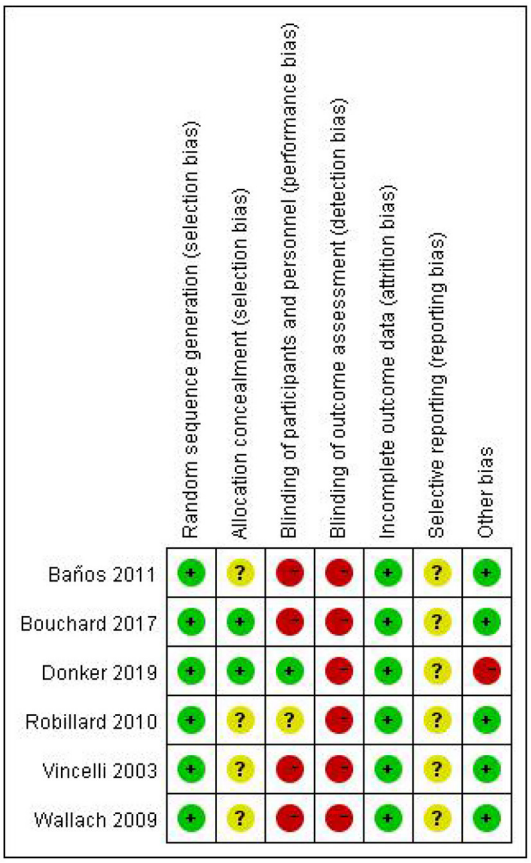


**FIGURE 2 |** Risk of bias in individual studies. +, low risk of bias; ?, unclear risk of bias; –, high risk of bias.

### Effects of VRCBT on Depression

Meta-analysis revealed evidence of the effect of VRCBT on depression. Three (9, 31, 32) studies reported the effect of VRCBT treatment on the degree of depression compared to untreated patients (SMD = −1.29; 95% CI: −2.26, −0.32; $p$ = 0.09, $I^2$ = 58%; **Figure 4**), while four studies (9, 29, 31, 32) reported the effect of VRCBT treatment on the degree of depression compared to CBT treatment (SMD = −0.30; 95% CI:−0.67, −0.07; $p$ = 0.39, $I^2$ = 1%; **Figure 4**). Similarly, there was a group difference in the level of depression relief between the untreated group and the CBT-treated group (two RCTs; SMD = −0.59; 95% CI = 0.85, −0.33; $p$ = 0.007; $I^2$ = 57%). A sensitivity analysis of "leave-one-out" was performed on the two groups, and no change in the direction of the effect size was found.

### Dropout Rates

We only compared the dropout rate of VRCBT treatment to that of CBT treatment. Among them, five (9, 10, 29, 31, 32) studies reported the number of dropouts. Due to the relatively small number of patients, only three (9, 10, 29) studies reported withdrawal in the experiment. Examination of dropout rates showed that the dropout rates of the VRCBT group and CBT group did not reach statistical significance (OR = 0.70, 1.48, $p > 0.05$).

### Long-Term Effects

Of the 11 studies we included, 7 (9, 10, 29, 30) studies followed up patients for 3, 6, and 12 months; however, only 2 (9, 10) studies reported test data for anxiety and depression after follow-up. Since only two studies were included, we did not conduct a meta-analysis on the long-term effectiveness of VRCBT. From the results of these two studies, we found that the effect of the VRCBT group on anxiety and depression levels was maintained after 6 months or 1 year, compared to the post-experiment test, with no statistical significance between VRCBT and standard CBT.

## DISCUSSION

We conducted a meta-analysis on anxiety and depression of anxiety patients treated with VRCBT. This study focused

**TABLE 1 |** GRADE assessment.

| Outcomes | | No. of studies | No. of participants | Quality of the Evidence* | Comments |
|---|---|---|---|---|---|
| Anxiety | VRCBT vs. no treatment | 5 | 276 | Moderate | Quality reduced due to inconsistent results |
| Anxiety | VRCBT vs. CBT | 4 | 150 | Moderate | Quality reduced due to inconsistent results |
| Depression | VRCBT vs. no treatment | 3 | 74 | Moderate | Quality reduced due to inconsistent results |
| Depression | VRCBT vs. CBT | 4 | 116 | Moderate | Quality reduced due to inconsistent results |

*All studies started with high quality of evidence for being RCTs.*

**TABLE 2 |** Study characteristics of eligible studies.

| Reference | | Participant characteristics | | | | Intervention Protocol | | Measurement |
|---|---|---|---|---|---|---|---|---|
| **Author** | **Country** | **Subjects; diagnostic criteria** | ***N*** | **M/W** | **Mean age (years)** | **Intervention dose** | **Follow-up (months)** | **Primary outcome** |
| Vincelli et al. (32) | Italy | Panic disorder; DSM-IV | VRCBT: 4<br>CBT: 4<br>WLG: 4 | 0/12 | 43.8 | VRCBT: 8 sessions of VRCBT therapy<br>CBT: 12 sessions of CBT therapy | Not clear | Anxiety: STAI-S, STAI-T<br>Depression: BDI-2 |
| Anderson et al. (33) | America | Public speaking anxiety; DSM-IV | VRCBT: 8 | 2/88 | Not clear | 4 sessions of anxiety management training; 4 sessions of exposure therapy | 3 | Depression: BDI-2 |
| Wallach et al. (10) | Israel | Public speaking anxiety; structured interview | VRCBT: 45<br>CBT: 34<br>WLG: 33 | 5/23<br>6/24<br>9/21 | 28.2<br>28.6<br>25.3 | 60 h for 12 weeks | 12 | Anxiety: LSAS-F, LSAS-A |
| Robillard et al. (31) | Canada | Social anxiety disorder; DSM-IV | VRCBT: 16<br>CBT: 14<br>WLG: 15 | 13/32 | 34.9 | 16 sessions of therapy | Not clear | Anxiety: LSAS<br>Depression: BDI-2 |
| Baños et al. (29) | Spain | Posttraumatic stress disorder; pathological grief; adiustment disorders; DSM-IV | VRCBT: 25<br>CBT: 25 | 12/27 | 30.9 | Not clear | 3 | Depression: BDI |
| Malbos et al. (34) | Australia | Agoraphobia; DSM-IV | VRCBT: 5<br>VR: 5 | Not clear | Not clear | 15 h for 8 weeks | Not clear | Anxiety: DASS |
| Freedman et al. (17) | Israel | Posttraumatic stress disorder; DSM-IV | VRCBT: 50<br>WLG: 50 | Not clear | Not clear | 16 sessions of therapy | 12 | Depression: BDI-2 |
| Moldovan et al. (35) | Not clear | Social phobia; acrophobia; flight phobia; DSM-IV | VRCBT: 16 WLG:16 | 17/15 | Not clear | 4 to 5 h for 1 week | Not clear | Anxiety: LSAS |
| Bouchard et al. (9) | Canada | Social anxiety disorder; DSM-IV | VRCBT: 22<br>CBT: 17<br>WLG: 20 | 7/15<br>0/17<br>9/11 | 36.2<br>36.7<br>30.6 | 60 h for 14 weeks | 6 | Anxiety: LSAS-SR, SIAS<br>Depression: BDI-2 |
| Donker et al. (30) | Netherlands | Acrophobia; AQ | VRCBT: 96<br>WLG: 97 | 64/129 | 41.3 | Not clear | 3 | Depression: BAI |
| Geraets et al. (36) | Netherlands | Generalized social anxiety disorder; SIAS >25 | VRCBT: 15 | 7/8 | 34.9 | 16-h therapy | 6 | Anxiety: SIAS<br>Depression: BDI-2 |

*M/W, men/women; VR+CBT, Virtual reality-assisted cognitive behavioral therapy; CBT, Cognitive behavioral therapy; WLG: Wait-list Group; BDI-2: Beck Depression Inventory 2; STAI-S: State-Trait Anxiety Inventory for Adults-State anxiety scores; STAI-T: State-Trait Anxiety Inventory for Adults-Trait anxiety scores; LSAS-F: Liebowitz Social Anxiety scale-Fear; LSAS-A: Liebowitz Social Anxiety scale-Avoidance; LSAS: Liebowitz Social Anxiety Scale; DASS: Depression Anxiety Stress; LSAS-SR: Liebowitz Social Anxiety Scale-Self Reported version; SIAS: Social Interaction Anxiety Scale; BAI: Beck Anxiety Inventory; SIAS: Social Interaction Anxiety Scale.*

on variables relevant to clinical practice, given the prior established advantages of standard CBT in treating anxiety disorders. We found that the therapeutic effects of VRCBT on anxiety were greater than those of WLG (SMD = −0.92), while the effects of VRCBT were similar to those of standard CBT treatment (SMD = −0.26). We also found that the therapeutic effects of VRCBT on depression were better than those of WLG (SMD = −1.29), while the effects of VRCBT were similar to standard CBT (SMD = −0.30). We further found that although VRCBT and standard CBT did not reach statistical significance in the intervention of anxiety and depression, they showed a positive trend. Due to the insufficient number of existing studies, performing a meta-analysis on follow-up outcomes was incomplete.

We found evidence to suggest that VRCBT has a potential advantage in treating anxiety disorders, as patients can be treated through VR rather than in a real environment (37). In terms of dropout rates, we found no significant significance between VRCBT and standard CBT treatment rates, and of the six studies included, five (9, 10, 29, 31, 32) reported the dropout of VRCBT and CBT in the course of treatment, and only two (9, 10) studies showed a lower VRCBT treatment dropout rate than CBT treatment. These differences are similar to those found in a previous study (38).

In this meta-analysis, we found no overall differences between VRCBT and standard CBT for treating anxiety and depression, but one (9) study did find VRCBT more effective than standard CBT. As VR technology advances and becomes more affordable, we expect an increase in acceptance of this technology.

One (39) study took a survey of patients with social anxiety disorder following the intervention and found that

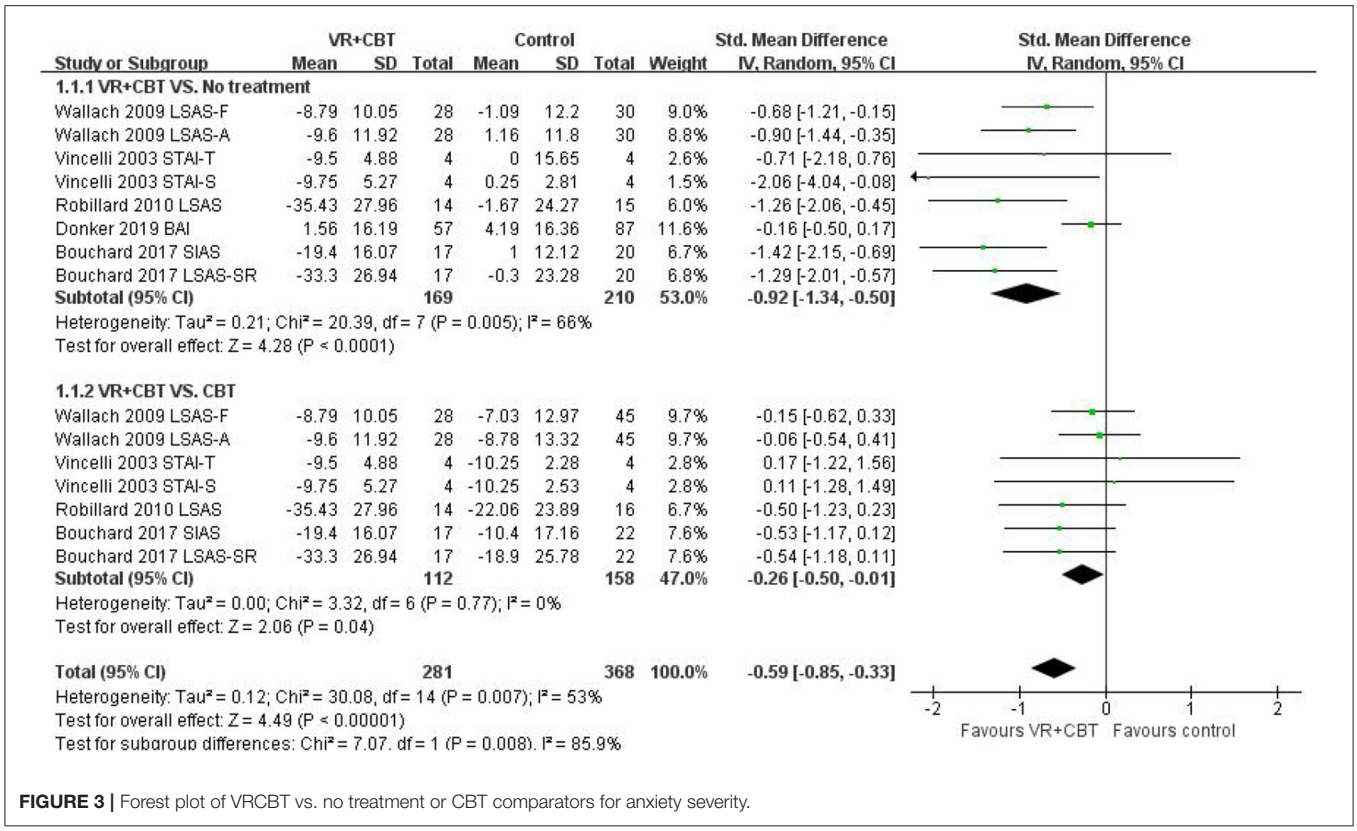


**FIGURE 3 |** Forest plot of VRCBT vs. no treatment or CBT comparators for anxiety severity.

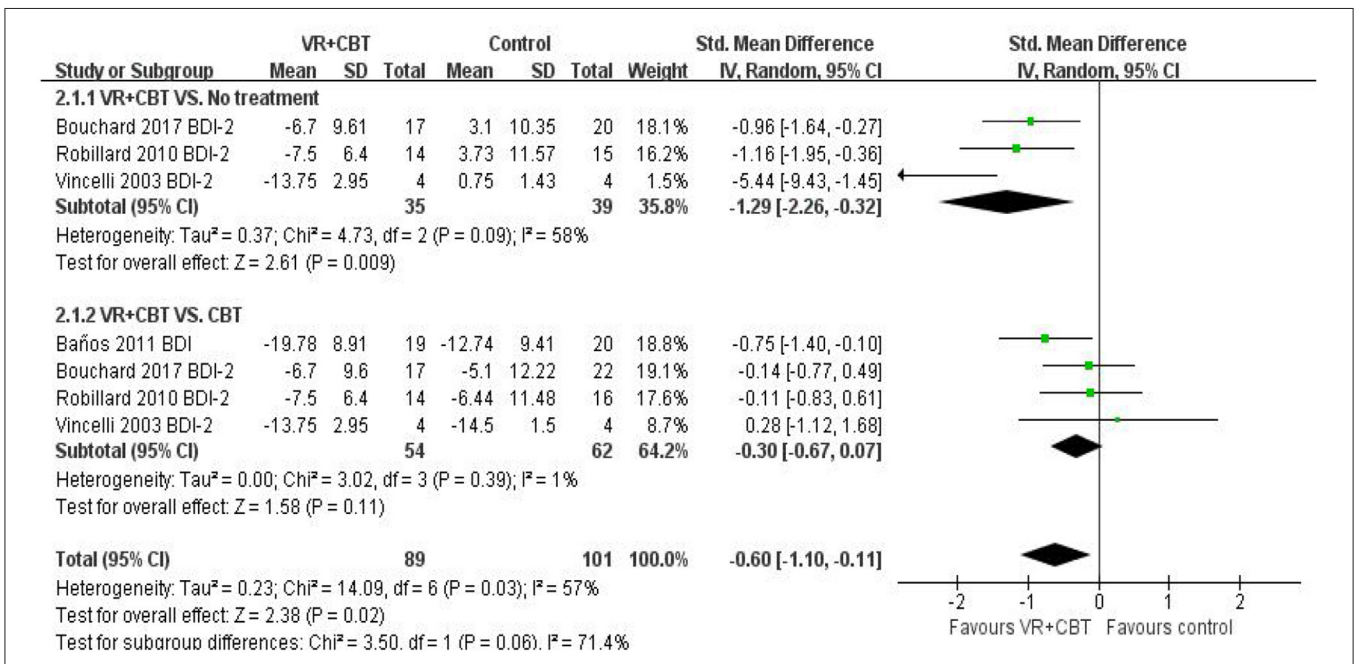


**FIGURE 4 |** Forest plot of VRCBT vs. no treatment or CBT comparators for depression severity.

although the levels of anxiety in VRCBT and standard CBT treatment groups were high, the difference between the two groups was not statistically significant. Another study (31) found similar results in patients with social anxiety. During follow-up, the two groups showed similar efficacy. Despite these results, previous studies have suggested that VR exposure therapy may not be enough for anxiety patients and lacks the cognitive components required to treat psychological function; therefore, combining VR with CBT may be an effective step forward (40). Although, the mechanisms of this are unclear, we found evidence that CBT in a virtual environment shows similar efficacy to standard CBT intervention, and these findings have a particular significance for clinical psychologists who may recommend VRCBT for anxiety disorder treatment (41).

VR technology aims to realize human–machine interaction. While experiencing the simulated environment, human sensation and action can be fed back to the computer using sensor technology and stereoscopic display technology. The basic principle of VR technology exposure is that the virtual environment is set up according to the brain emotional network processing model. When a patient confronts a threatening stimulus resulting in a fearful reaction, the fear network is activated. As new and incompatible information is gradually added to the emotional network, habituation and elimination of fear help patients change their fear structure, rendering the stimulus less threatening. During this procedure, the patient must remain under stimulation until anxiety and fear are reduced to a sufficiently low level to achieve the therapeutic effect (42, 43). At present, the new virtual environment can depict a wide range of tasks and more convenient grading exposure, increasing the body's perceived exposure and providing more inhibitory learning for patients, therefore being conducive to recovery (10). For example, when treating patients with social phobia, virtual people can talk and appear in virtual public places, which is an amicable method. Patients with posttraumatic stress disorder can benefit from this therapy by exposure to virtual elements related to traumatic experiences, being encouraged to reflect on their own experiences and feelings (29). Simultaneously, through the therapist's discovery and guidance, we can identify unreasonable cognition in exposure, find ways to replace it, and identify and correct patients' unreasonable cognition, thereby, achieving a therapeutic effect.

Compared to traditional CBT grading exposure, the therapist can expose patients to different levels according to their condition in the VR environment and provide a sense of security for patients. Since VRCBT can be performed in the therapist's office, the VR environment is confidential, and patients do not have to worry about potentially embarrassing situations or privacy concerns. With the continuous updating of VR technology, the procedure is also more straightforward and less expensive compared to traditional treatments. VRCBT is expected to be used in family therapy in the future, saving time and money. Additionally, VRCBT can be used as an intermediate step for patients who refuse to be exposed to reality, which may increase their likelihood of accepting reality exposure through VR exposure.

## STUDY LIMITATIONS

The most important limitation of this study is the limited number of studies included. This study applied a systematic and rigorous search strategy to retrieve relevant articles according to the research objectives. However, studies on VRCBT for anxiety disorders are too rare. It was impossible to conduct subgroup analysis on the efficacy of treatment on different types of anxiety subtypes. It is difficult to give specific recommendations for certain timings and frequency of the interventions. Second, the latest search of this study was conducted on March 3, 2020, and new research findings published after that date were naturally excluded. Third, we only investigated the effects of VRCBT on the cognitive behavior of anxiety patients but did not investigate research related to neural mechanisms of the disorder. Fourth, although, this study has a single intervention, it does not account for the fact that different VR facilities may bring about different effects on anxiety patients. For example, the virtual environment created by computers and mobile phones may be problematic in evaluating efficacy. Fifth, only six studies were included in this study, so the datasets were individually relatively small, resulting in an overall dataset that was similarly small.

## CONCLUSIONS

The current meta-analysis shows that VRCBT has a positive effect on reducing anxiety and depression in patients with anxiety disorders. Compared to standard CBT, VRCBT can produce similar therapeutic effects but may provide more timely interventions for anxiety disorders. Future research is needed to confirm the benefits of VRCBT for patients with more diverse types of anxiety disorders.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

JW, YS, and ZR contributed to the conception and design of the review. JW, YS, and GZ applied the search strategy. JW, ZZ, and ZR applied the selection criteria. JW and ZR completed assessment of risk of bias. JW and YS analyzed and interpreted the data. JW wrote this manuscript. YS and GZ edited this manuscript. ZR is responsible for the overall project.

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# Cognitive Change and Relaxation as Key Mechanisms of Treatment Outcome in Chronic Pain: Evidence From Routine Care

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Despite effective treatment approaches within the cognitive behavioral framework general treatment effects for chronic pain are rather small to very small. Translation from efficacy trials to naturalistic settings is questionable. There is an urgent need to improve the effectiveness of well-established treatments, such as cognitive-behavior therapy (CBT) and the investigation of mechanisms of change is a promising opportunity. We performed secondary data analysis from routine data of 1,440 chronic pain patients. Patients received CBT in a multidisciplinary setting in two inpatient clinics. Effect sizes and reliable change indices were computed for pain-related disability and depression. The associations between changes in the use of different pain coping skills (cognitive restructuring, activity despite pain, relaxation techniques and mental distraction) and changes in clinical outcomes were analyzed in structural equation models. Pre–post effect sizes range from $g = 0.47$ (disability) to $g = 0.89$ (depression). Changes in the use of cognitive restructuring, relaxation and to a lesser degree mental distraction were associated with changes in disability and depression. Effects from randomized trials can be translated to naturalistic settings. The results complement experimental research on mechanisms of change in the treatment of chronic pain and indicate an important role of cognitive change and relaxation as mechanisms of change. Our findings cautiously suggest that clinicians should optimize these processes in chronic pain patients to reduce their physical and emotional disability.

**Keywords: chronic pain, coping skills, mechanisms of change, naturalistic, multidisciplinary pain treatment, cognitive behavioral therapy, effectiveness**

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## INTRODUCTION

For decades, the Global Burden of Disease Study has ranked chronic pain as the world's greatest cause of disability. Globally, it is the leading cause of years lived with disability [YLD, (1)]. Its negative impact on the quality of life is the highest of all diseases (2, 3) and it brings severe challenges for patients (4, 5): Patients diagnosed with chronic pain sleep worse (6), have an increased suicidal tendency (7), a deteriorated sexuality (8) and an increased probability of a comorbid depression (9), which also represents a major health problem (10). The management of chronic pain is characterized by a range of different treatments e.g., medication, exercise or cognitive behavioral therapy [CBT, (11)]. To date, a biopsychosocial perspective is broadly accepted and is best reflected by a multidisciplinary treatment approach (12, 13). There is ample evidence that psychosocial factors such as pain-related fear are more important in explaining disability than pain itself (14). The cognitive-behavioral perspective explicitly targets these factors and includes a variety of well-established psychological treatment options for chronic pain (15).

The main goal of CBT in treating chronic pain is to increase the patient's functionality (16). Turk and Flor (17) categorize three CBT-specific treatment approaches for chronic pain—operant, cognitive, and respondent—each targeting different mechanisms of change. The operant approach focuses on operant learning mechanisms by reducing maladaptive pain behavior (e.g., avoiding activity due to fear of injury) and building up positive activities. In the cognitive approach, cognitive restructuring is performed to change evaluative aspects of pain (e.g., "I can't do anything about my pain") and generate more positive pain-related expectations. The respondent approach intends to directly modify the response to pain-related stimuli—muscle tension and anxiety—by means of relaxation techniques (11). In CBT, patients are taught to target these three response systems by adaptive pain coping skills (18, 19). There is a large body of research focusing on different pain coping skills that target one of the three different response systems (17): Being active despite one's own pain is important and can improve pain symptoms via the operant response system (20, 21). Cognitive restructuring improves pain coping by targeting the cognitive response system (22, 23) and applying relaxation techniques targets the respondent system (24, 25). Evidence on mental distraction, another pain coping skill routinely used and originally included in the cognitive approach (17), is mixed: mental distraction may be considered helpful by patients (26) but could aggravate the experience of pain in the long run (27, 28). Coping self-affirmations may also not have any positive effect on pain coping (29). In summary, different coping skills seem to be heterogeneously effective in managing pain (29, 30).

Despite effective treatment approaches within the cognitive behavioral framework (31–33) general treatment effects are rather small to very small (34). Furthermore, long-term stability is questionable (35, 36) as well as the generalizability of efficacy trials on the effects on everyday clinical practice (37). There is an urgent need to improve the treatment for patients with chronic pain. Since an effective treatment of chronic pain remains a challenge, Morley et al. call for a paradigm shift in research (38). They promote complements to efficacy trials (e.g., randomized controlled trials, RCTs) and emphasize, among others, secondary data analysis. Accordingly, practice-based evidence (PBE) research methods can make an important contribution to treatment improvement (39). Although observational PBE studies do not allow to draw causal conclusions (40), they can identify treatment elements associated with better clinical outcomes for a wide range of patients (41). In addition, they usually incorporate a high sample size of patients, yield a high external validity and are cost-efficient (42). PBE should therefore have a firm place in research (39) and can also be successfully implemented in the field of chronic pain (43).

In order to enhance the effectiveness of CBT in the treatment of chronic pain, research on the driving mechanisms of change is vital (44). Routine clinical data can contribute to this (45–47). The effectiveness of coping skills has been assessed experimentally or in RCTs. While experiments usually have a high internal validity, they often only provide short-term results on acute pain. These results are difficult to transfer to clinically relevant outcomes like pain-related disability. Clinical RCTs do have the potential to test causal assumptions on clinically relevant outcomes. However, usually treatment arms consist of a bundle of interventions (48) and thus questions about the impact of specific pain coping skills remain unanswered. A direct comparison of the impact of different pain coping skills on clinical outcomes such as pain-related disability could therefore provide valuable information for possible treatment improvements. Assessing the impact of changes in mechanisms on changes in outcomes is a common technique to draw conclusions about their importance (44) and it is vital to compare multiple potential mechanisms of change in the same study (48). As different pain coping skills are thought to target different mechanisms of change, the investigation of associations between changes in the use of coping skills and changes in outcomes could help to answer the important question, which mechanisms of change are most essential in routine clinical care thereby increasing the effectiveness of CBT in the long run.

Analyzing a large routinely collected pre-post-data set from two large clinics specialized in chronic pain implementing a multidisciplinary pain treatment program, the first aim of this study is to investigate the effectiveness of routine clinical care in reducing pain-related disability and depression in chronic pain patients. The second goal of this study is to examine the associations between changes in the use of different pain coping skills and changes in clinical outcomes (pain-related disability and depression). We believe that a focus on the change in the use of pain coping skills can provide valuable insights into mechanisms of change involved in the treatment of chronic pain. The coping skills selected are based on the three approaches of Turk and Flor (17). We investigate the change of activity despite pain (operant approach); cognitive restructuring and mental distraction (cognitive approach); and relaxation (respondent approach). Based on the previous literature we expect that an improved use of cognitive restructuring, relaxation and activity despite pain are equally related to changes in clinical outcome measures. Furthermore, we hypothesize that an improvement in

the use of mental distraction is to a lesser extent positively related to our outcomes.

# METHOD

## Procedure

Routine pre-post data from two large psychotherapeutic clinics in Germany were analyzed. Data was collected between 2013 and 2017. Patients completed self-report questionnaires immediately before and after treatment. Pain coping skill use and depression was measured in both clinics, while pain related disability was only routinely measured in clinic A.

## Patient Sample

Patients were included who had been treated for at least 4 weeks for chronic pain, who were diagnosed with F45.41 according to the ICD-10-GM (49) by trained clinical practitioners and who filled out the Questionnaire for the assessment of pain processing ["Fragebogen zur Erfassung der Schmerzverarbeitung," FESV, (50)] at the beginning of the treatment. This led to a total sample size of $N = 1{,}440$, with $n = 754$ patients treated in clinic A and $n = 686$ in clinic B who were included in the analyses. All patients gave informed consent for their anonymous data to be used for research purposes. There were $n = 661$ (87.7%) complete cases for the analysis of associations between changes in pain coping skills and pain related disability in clinic A and none in clinic B, because pain related disability was only assessed in clinic A. There were $n = 668$ (88.6%) complete cases for the analysis of associations between changes in pain coping skills and depression in clinic A and $n = 570$ (83.1%) in clinic B. Full missing data specifications are included in **Table 1**.

## Multidisciplinary Treatment Program

Patients received a multidisciplinary treatment in one of two clinics specialized for chronic pain. Both clinics offered acute care and rehabilitative routine care. In Germany, rehabilitative care follows the goals of tertiary prevention and acute care of secondary prevention. The treatment was based on CBT for chronic pain intended to last for 5 weeks (rehabilitative care, $n = 556$) or 6 weeks (acute care, $n = 884$). In some cases, the duration of treatment has been extended in agreement with the healthcare provider. Patients received treatment for 28–84 days with a median of 41 days ($SD = 8.1$). Twice a week (on average 200 min per week) all patients participated in manualized CBT group therapy for chronic pain, in which they received pain-related psychoeducation and training for pain coping skills. Patients also received individual non-manualized CBT for at least 50 min per week. Patients received additional non-manualized CBT, depending on the ward in either a group setting or an individual setting. All CBT treatments were administered by trained therapists. There were medical visits at least once a week by a medical doctor and the head of the ward, group visits multiple times per week and daily contact with co-therapists. An individual treatment plan was tailored to each patient by a multidisciplinary team. Optional treatment components consisted of general group therapy; social competence training; group therapy for psychological comorbidities; physiotherapy; sport and movement therapy; mindfulness and relaxation group training; biofeedback; social counseling; arts and craft therapy; and body therapy. While psychological interventions were the main treatment focus, medication was administered according to the current national and international guidelines.

## Measurements

### Pain Coping Skills

The FESV (50) is a well-established self-rating questionnaire that measures pain coping skills. It was specifically designed to assess the coping repertoire for chronic pain. The FESV has been found suitable for multipoint surveys (51). The FESV is based on empirical research about pain processing. It consists of three scales (cognitive pain coping, behavioral pain coping, and pain-related psychological impairment). Each scale has three subscales. For the present study, we used the cognitive pain coping scale and behavioral pain coping scale. Of their six subscales two were excluded because they are conceptually too close to the evaluated outcomes (*coping self-efficacy*, "When I feel pain, I am sure that I can deal with it" and *action planning*, "When I feel pain, I have a number of possibilities to fight it"). The remaining four scales measure the usage of active coping skills during the occurrence of pain: *cognitive restructuring* (e.g., "When I feel pain, I weigh it against the good sides of life," Cronbach's $\alpha = 0.75$ in the current study), *mental distraction* (e.g., "When I feel pain, I distract myself by listening to pleasant music," $\alpha = 0.74$), *activity despite pain* (e.g., "When I feel pain, I conceal them by just continuing with my work," $\alpha = 0.77$) and *relaxation techniques* (e.g., "When I feel pain, I apply a relaxation technique (e.g., autogenic training, progressive muscle relaxation)," $\alpha = 0.79$). All items are formulated as statements to be answered on a six-point response scale ranging from 1 (not agree) to 6 (completely agree).We tested the factor structure of the subscales in the current dataset. Parallel analysis resulted in four components. All items but one loaded with at least 0.6 on their theoretically assumed factor. The item that did not sufficiently load on any factor originally belonged to the subscale *activity despite pain* ("When I feel pain, I actively seek contact with other people to distract myself.") and was excluded from further analysis, which led to an increased Cronbach's $\alpha = 0.83$. In order to avoid a logical tautology, we excluded one of the four items of the cognitive restructuring scale that implied a positive therapy outcome ("When I experience pain, I tell myself that I can cope with it much better than before"). This led to a reduced Cronbach's $\alpha = 0.67$. Overall, Cronbach's $\alpha$ was slightly lower than in comparable studies where it ranges from Cronbach's $\alpha = 0.78$ (*cognitive restructuring*) to Cronbach's $\alpha = 0.85$ (*mental distraction and activity despite pain*) (52). The reliabilities of the difference scores as calculated in the sample using the formula in Gollwitzer et al. (53) were between $\alpha = 0.40$ (*cognitive restructuring*) and $\alpha = 0.65$ (*activity despite pain*).

### Pain Related Disability

The Pain Disability Index [PDI, (54)] is a well-established seven-item self-rating questionnaire that assesses patients' current perceived level of disability in seven life domains (e.g., social activity; occupation; or self care) with one item each (55).

**TABLE 1 |** Missing data in both clinics.

| | FESV T1 *n* (%) | FESV T2 *n* (%) | PDI T1 *n* (%) | PDI T2 *n* (%) | PHQ T1 *n* (%) | PHQ T2 *n* (%) |
|---|---|---|---|---|---|---|
| Clinic A ($N = 754$) | 0 (0.0) | 54 (7.2) | 5 (0.7) | 55 (7.3) | 7 (0.9) | 58 (7.7) |
| Clinic B ($N = 686$) | 0 (0.0) | 115 (16.8) | 686 (100) | 686 (100) | 0 (0.0) | 97 (14.1) |

*PHQ-9, Patient Health Questionnaire; PDI, Pain Disability Index; FESV, Pain Management Questionnaire.*

The seven items are assessed on a 0 (no disability)–10 (worst disability) numeric rating scale, with the sum score ranging from 0 to 70. The internal consistency in this sample was Cronbach's $\alpha = 0.81$ which is consistent with the results in comparable samples (56). The reliability of the difference score in the sample was $\alpha = 0.68$.

### Depression

Depression was measured with the German version (57) of the Patient Health Questionnaire-9 [PHQ-9, (58)], which has been successfully validated for the purpose of measuring treatment outcomes in depression (59). The self-rating questionnaire consists of 9 items (e.g., "Feeling tired or having little energy.") each with four possible answers ranging from 0 (not at all) to 3 (nearly every day). The sum score (0–27) indicates the level of depression with a higher score indicating greater severity of depression. The internal consistency in this sample was $\alpha = 0.85$ which is comparable with other studies (60). The reliability of the difference score in the sample was $\alpha = 0.75$.

## Statistical Analysis

All statistical analyses were performed in R (61) using the packages tidyverse, lavaan and psych (62–64). We conducted *t*-tests between the two clinics for all continuous variables and chi-squared tests between the two clinics for all nominal variables.

### Effect Sizes and Clinical Significance

Pre–post effect sizes (Hedge's g) were computed for all outcomes and pain coping skill variables for completers using the package effectsize (65). Additionally, last observation carried forward effect sizes (LOCF) were computed for the same variables in order to provide a more conservative effect size estimation based on the assumption that individuals with missing data did not show any improvement. Clinical significance and reliable change indices (66) were computed using the R package JTRCI (67). The reliabilities were based on German validation studies [PHQ-9: $\alpha = 0.88$; PDI: $\alpha = 0.88$, (57, 68)]. A PHQ-9 value of $M = 3.3$ [$SD = 3.7$, (60)] for depression was used as a norm for the healthy population, resulting in a cutoff for recovery of $c = 7.2$ where individuals were equally likely to belong to a healthy population and the pre-treatment sample in this study (69). A PDI score of $M = 9.0$ [$SD = 12.6$, (70)] reported in a German sample with at least one physical complaint was used as a norm for the healthy population for disability ($c = 24.9$).

### Modeling the Associations Between Changes

We used structural equation modeling (SEM) to model associations between changes from pre-treatment to post-treatment. We modeled a single indicator latent change score (53, 71) for each of the four pain coping skill use scales and the two outcomes PDI and PHQ-9 using their sum scores. Latent change scores seperate the part of the variance that remains constant between two points of measurement from the part that changes (71). Latent change scores offer advantages over manifest difference scores or residual change scores (53) and have been used in previous studies in which associations between changes over time were modeled (72, 73). Gollwitzer et al. (53) advocate the use of latent change scores with multiple indicators. However, we believe that the pain coping skill scales represent composites rather than single latent factors (74). In this case using a miss-specified measurement model with multiple indicators can lead to more biased estimates than using sum scores, even when measurement error is present (74) which is why we use sum scores as single indicators when modeling latent changes.

All latent change scores were included in the same model. To estimate the total associations between variables, we first created a model in which all correlations between pre-treatment variables and latent change variables were allowed. In a second step we checked whether the pain coping skills scores uniquely explained variance in the change scores of the outcomes. Therefore, in these models, each of the pain coping skill use change scores was regressed on each available outcome change score.

### Comparison of the Models Between Clinics

A first SEM model was fitted using the data from clinic A. Here, both outcomes were available: PDI and PHQ-9. The data from clinic B was used for a partial replication: Model 2 was fitted using all data from clinic B and the PHQ-9 as the outcome.

In order to test for differences in the associations between changes between the two clinics, all data available was grouped by clinic. Here the PHQ-9 was used as the only outcome, as it was available in both clinics. Four models were fitted that varied in which parameters were fixed to be equal in both clinics: In Model A, the null model. all parameters could vary freely between the clinics. In Model B all regression coefficients were fixed to be the same between clinics. In Model C all regression coefficients and all covariances between latent variables were fixed to be the same between clinics and in Model D all parameters were fixed to be the same between clinics.

Model fit indices Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Tucker-Lewis Index (TLI), Comparative Fit Index (CFI), Standardized Root Mean Residual (SRMR) and Root Squared Mean Error Average (RMSEA) were computed for all models. Additionally, nested model comparisons were performed.

### Computation of SEM Models

All SEM models were fitted using lavaan (63) using full information maximum likelihood estimation to deal with missing data.

Sensitivity analyses were performed by using a robust maximum likelihood estimator with Huber-White standard errors and by using a different method for dealing with missing data: multiple imputation with the package MICE (75). Estimates from estimations on 100 imputed datasets were pooled using the package SEMTools (76).

# RESULTS

## Sample Description

Patients were between 19 and 87 years old ($M = 52.4$; $SD = 10.2$). Of $N = 1{,}440$ patients, 1,070 (74.3%) were female. Patients were diagnosed with an average of 2.9 ($SD = 1.2$) mental disorders according to the ICD-10. A total of 333 patients (24.4%) were able to work before the treatment; 754 patients (52.4%) were treated in clinic A and 686 patients (47.6%) were treated in clinic B. Patients in clinic B differed from patients in clinic A in a number of variables: They were treated more often in rehabilitative care, were diagnosed with fewer mental disorders, were more often treated in an inpatient ward for the first time, were treated for a shorter period of time and had lower scores of depression at intake. An extended summary of patient characteristics in comparison between Clinics A and B are presented in **Table 2**.

## Effectiveness

Across both clinics, effect sizes were large for depression [$g = 0.89$, 95% CI = [0.82, 0.95]] and medium for pain-related disability [$g = 0.47$, 95% CI = [0.39, 0.55]]. Using the more conservative LOCF estimates, effect sizes were still large for depression [LOCF $g = 0.81$, 95% CI = [0.75, 0.87]] and medium on pain-related disability [LOCF $g = 0.45$, 95% CI = [0.37, 0.52]]. Out of $n = 754$ patients available for the reliable change analysis in pain related disability, 65 (8.6%) recovered, 74 (9.8%) reliably

**TABLE 2 |** Sociodemographic and clinical characteristics as well as self-rating scores of the sample ($n = 754$ clinic A and $n = 686$ clinic B) at baseline.

| Characteristics | Clinic A ($n = 754$) | Clinic B ($n = 686$) | $p$[f] |
|---|---|---|---|
| Age (years) *M* (SD) | 52.1 (10.2) | 52.6 (10.2) | <0.001 |
| Sex *n* (%) | | | 0.05 |
| Male | 177 (23.5) | 193 (28.1) | |
| Female | 577 (76.5) | 493 (71.9) | |
| Educational score *M* (SD)[a] | 2.8 (0.9) | 2.4 (1.1) | <0.001 |
| Number of mental Disorders *M* (SD) | 3.1 (1.2) | 2.7 (1.1) | <0.001 |
| Frequent comorbidities *n* (%)[b] | | | |
| Depressive episode (F32) | 160 (21.2) | 122 (17.8) | 0.12 |
| Recurrent depressive disorder (F33) | 570 (75.6) | 487 (69.7) | 0.01 |
| Personality Disorder (F60) | 104 (13.8) | 63 (9.2) | 0.008 |
| Married *n* (%) | 473 (63.4) | 374 (60.7) | 0.65 |
| In a relationship *n* (%) | 625 (83.8) | 487 (79.1) | 0.03 |
| First inpatient treatment *n* (%) | 399 (74.3) | 499 (85.2) | <0.001 |
| Occupational status *n* (%) | | | <0.001 |
| Unemployed | 104 (13.9) | 115 (18.7) | |
| Retired | 288 (38.6) | 184 (29.9) | |
| Working at least part time | 288 (38.6) | 386 (46.5) | |
| Other | 46 (6.2) | 17 (2.8) | |
| Working ability *n* (%) | 178 (23.8) | 155 (25.2) | 0.61 |
| Outpatient psychotherapy *n* (%) | 359 (48.1) | 244 (39.6) | 0.002 |
| Outpatient psychiatric treatment *n* (%) | 440 (59.0) | 441 (71.6) | <0.001 |
| Duration of treatment (in days) | 44.9 (8.8) | 39.7 (6.2) | <0.001 |
| PHQ-9 score *M* (SD)[c] | 15.4 (5.6) | 13.9 (5.7) | <0.001 |
| PDI score *M* (SD)[d] | 40.6 (12.6) | -[g] | |
| FESV Cognitive Restructuring *M* (SD)[e] | 3.2 (1.1) | 3.3 (1.2) | 0.03 |
| FESV Mental Distraction *M* (SD)[e] | 2.8 (1.1) | 2.8 (1.2) | 0.65 |
| FESV Activity Despite Pain *M* (SD)[e] | 2.8 (1.1) | 3.0 (1, 2) | 0.008 |
| FESV Relaxation Techniques *M* (SD)[e] | 2.9 (1.2) | 3.1 (1.2) | <0.001 |

*[a]Based on the German school system; scale from 0 (no degree) to 4 (general qualification for university entrance); [b]Diagnosis as given by practitioners according to ICD-10; [c]PHQ-9, Patient Health Questionnaire, 9 items scale 0–3 per item; [d]PDI, Pain Disability Index, seven items scale 0–10 per item, range 0–70; [e]FESV, Pain Management Questionnaires, 1–6 per item; [f]p-values derived from t-tests for continuous variables and chi-squared tests for categorical data for differences between clinics; [g]this questionnaire was not routinely administered in clinic B.*

improved, 83 (11.0%) recovered non-reliably, 446 (60.2%) remained unchanged, 28 (3.7%) deteriorated and 64 (8.5%) did not complete the post-treatment questionnaire. Examining reliable change in depression, 222 (15.4%) recovered, 256 (17.7%) improved reliably, 231 (16.0%) recovered non-reliably, 549 (38.1%) remained unchanged, 22 (1.5%) deteriorated and 160 (11.1%) did not complete the post-treatment assessment.

## SEM Models

### Associations Between Changes in Pain Coping Skill Use

In clinic A all changes in pain coping skill use were positively correlated. Changes in the use of cognitive restructuring and relaxation were correlated with a large effect size ($r = 0.49$, 95% CI = [−0.43, 0.54]]. Changes in the use of mental distraction were correlated with medium effect sizes with changes in the use of cognitive restructuring [$r = -0.32$, 95% CI = [0.25, 0.38]] and relaxation [$r = 0.36$, 95% CI = [0.30, 0.43]]. There were small correlations between changes in the use of activity despite pain and the other pain coping skills ($0.09 \leq r \leq 0.22$). All bivariate correlations between baseline variables and change scores are presented in **Appendix A**.

### Associations With Changes in Pain-Related Disability

In clinic A, higher reductions in pain-related disability were correlated with positive changes in the use of cognitive restructuring [r = −0.22, 95% CI = [−0.29, −0.15]], with positive changes in the use of relaxation technique [r = −0.24, 95% CI = [−0.31, −0.17]], and with positive changes in the use of mental distraction [r = −0.16, 95% CI = [−0.23; −0.09]]. All effect sizes were small to medium. Changes in activity despite pain were not correlated with changes in pain-related disability [r = −0.04, 95% CI = [−0.11, 0.03]].

Only changes in the use of cognitive restructuring [$\beta$ = −0.12, 95% CI = [−0.20, −0.04]] and relaxation technique [$\beta$ = −0.16, 95% CI = [−0.25, −0.08]] were independently associated with changes in pain related disability. The independent associations between latent changes in clinic A are depicted in **Figure 1**.

### Associations With Changes in Depression

In clinic A, higher reductions in depression were correlated with positive changes in the use of cognitive restructuring [r = −0.28, 95% CI = [−0.35, −0.21]], relaxation technique [r = −0.26, 95% CI = [−0.33, −0.19], and positive changes in the use of mental distraction [r = −0.21, 95% CI = [−0.28; −0.14]] with small to medium effect sizes. Changes in activity despite pain were not correlated with changes in depression [r = 0.05, 95% CI = [−0.03, 0.12]].

Higher reductions in depression were independently associated with positive changes in the use of cognitive restructuring [$\beta$ = −0.19, 95% CI = [−0.27, −0.11]], relaxation technique [$\beta$ = −0.13, 95% CI = [−0.22, −0.05]], and mental distraction [$\beta$ = −0.13, 95% CI = [−0.21, −0.05]] but with negative changes in activity despite pain [$\beta$ = 0.11, 95% CI = [0.04, 0.18]].

### Model Comparisons Between Clinics

In nested model comparisons using only depression as an outcome, constraining regression coefficients to be equal between clinics (Model B) did decrease the performance of the model [$X^2$diff(dfdiff = 4, $N$ = 1,440) = 10.7, $p$ = 0.03]. Further constraining covariances to be equal between clinics (Model C) did not further decrease the performance of the model either [$X^2$diff(dfdiff = 45, $N$ = 1,440) = 59.4, $p$ = 0.19] but constraining all parameter to be equal across clinics did [Model D; $X^2$diff(dfdiff = 65, $N$ = 1,440) = 118.7, $p < 0.001$]. According to fit indices, the model with equal regression coefficients and covariances between both clinics showed the best fit overall of all constrained models (see **Table 3**).

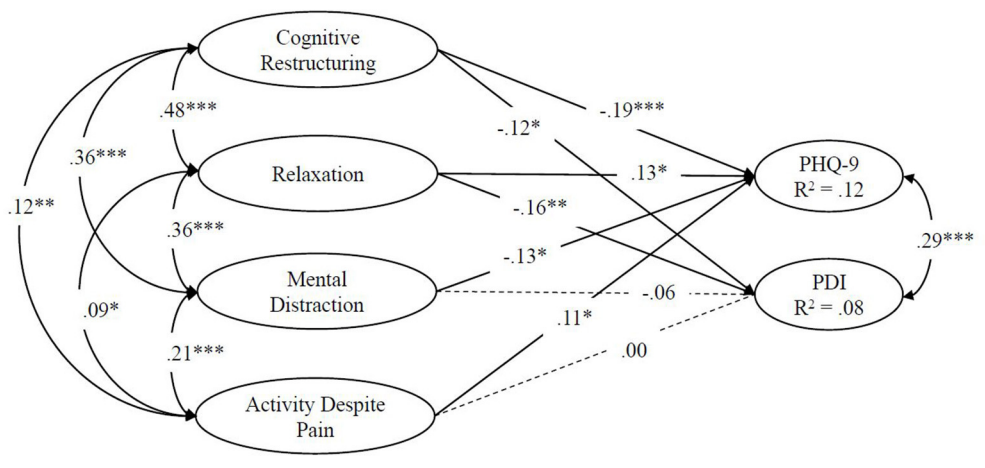


**FIGURE 1 |** Regressions in a structural equation model on the associations between single indicator latent changes in pain coping skills and changes in disability in Model 1 (clinic A); PDI, Pain Disability Scale; *$p < 0.05$, **$p < 0.001$, ***$p < 0.00001$; estimation with full maximum likelihood; $n = 754$.

### Replication of the Associations With Changes in Depression in Clinic B

In clinic B and when data from both clinics were used simultaneously (Model C) most of the effects in clinic A were replicated. However, when only data from clinic B were used, there was a correlation between changes in the use of activity despite pain and changes in depression [r = −0.10, 95% CI = [−0.18, −0.02]] but no direct association [$\beta$ = −0.03, 95% CI = [−0.11, 0.05]]. The same was true when data from both clinics were used. Additionally, in clinic B higher reductions in depression were not independently associated with positive changes in the use of mental distraction [$\beta$ = −0.09, 95% CI = [−0.18, 0.00]]. All regression coefficients on either change in disability or depression are shown in **Table 4**.

### Sensitivity Analyses

Using multiple imputation instead of full maximum likelihood estimation did not affect whether effects were significant or not. However, using robust maximum likelihood estimation, the independent association of positive changes in the use of mental distraction [$\beta$ = −0.09, 95% CI = [−0.18, 0.00]] on pain-related disability in Model A became significant whereas the coefficient did not change.

The pattern of results did not change when age, gender or duration of treatment were introduced into the models as predictors of latent changes.

## DISCUSSION

The first aim of this study was to evaluate the effectiveness of a multidisciplinary pain treatment based on CBT in a large naturalistic sample. Pre–post effect sizes were large to medium and support the effectiveness of inpatient routine care in the treatment of chronic pain. One in three patients reliably improved or recovered from depression and one in five did so for pain-related disability. Second, we investigated the associations of changes in pain coping skills and reductions in pain-related disability and depression. Our data demonstrate small to moderate associations between coping skills for chronic pain and a decrease in both outcomes. Further, we were interested which coping skills in particular are associated with reduced severity of pain-related disability and emotional distress (depression). Cognitive restructuring and relaxation as specific coping skills showed small to moderate associations with improvements in both pain-related disability and depression. The independent association between mental distraction and depression proved to be small but could only be found in one clinic. We found a small negative independent association for the coping skill activity despite pain with respect to depression. However, this could not be replicated in clinic B.

General effect sizes ranged from medium (disability) to large (depression), which is encouraging since current reviews only found small to medium effects for CBT (34). However, the medium to large effect sizes are in line with benchmarks for pre–post effects of randomized CBT trials (77). Since we investigated a multidisciplinary intensive treatment program, slightly higher effect sizes than with CBT alone can be expected (78). In addition, the fact of inpatient treatment may also have contributed to the higher effect sizes, since, for example, patients are not confronted with everyday problems and receive support from fellow patients. In summary the effectiveness in this sample is slightly higher than to be expected from psychological interventions alone,

**TABLE 3 |** Model fit indices for path models across two clinics.

| Model | CFI | TLI | BIC | RMSEA | SRMR |
|---|---|---|---|---|---|
| All coefficients free (Null model) | - | - | 35434.1 | - | - |
| Regression coefficients equal in both clinics | 0.999† | 0.968 | 35415.6 | 0.048 | 0.005† |
| Regression coefficients and correlations equal | 0.997 | 0.994† | 35166.2 | 0.021† | 0.033 |
| All parameters equal | 0.976 | 0.967 | 35139.5† | 0.049 | 0.055 |

*Full maximum likelihood estimation of information in structural equation models across two clinics (clinic A with n = 754 and clinic B with n = 686); CFI, comparative fit index; TLI, Tucker–Lewis index; BIC, Bayesian information criterion; SRMR, standardized root mean residual; RMSEA, root mean squared error average; †most favorable value for respective fit index within the block of models for clinic A and B combined; In the combined analyses all parameters were allowed to vary freely by default between the two clinics except for regression coefficients.*

**TABLE 4 |** Standardized regression weights of pain coping skill changes on temporally concurrent changes in outcomes in clinic A (*n* = 754) clinic B (*n* = 686) and in a model with both datasets combined (*N* = 1,440).

| | Clinic A | | Clinic B | Combined |
|---|---|---|---|---|
| Predictor | PDI change | PHQ 9 change | PHQ 9 change | PHQ 9 change |
| Cognitive restructuring change | −0.12* | −0.19*** | −0.12* | −0.16*** |
| Mental distraction change | −0.06 | −0.13* | −0.09 | −0.11** |
| Activity despite pain change | 0.00 | 0.11* | −0.03 | 0.05 |
| Relaxation techniques change | −0.16** | −0.13* | −0.18** | −0.16*** |

** p < 0.05, ** p < 0.001, *** p < 0.00001; Full maximum likelihood estimation of information in structural equation models across two clinics (clinic A with n = 754 and clinic B with n = 686). Changes were modeled as single indicator latent changes.*

but comparable to similar multidisciplinary interventions and results of randomized CBT trials (78–80). Of note, baseline levels of pain-related disability and inability to work were higher in our study than in these studies. Thus, our data demonstrate promising effects for treating highly disabled pain patients in a multidisciplinary treatment program for chronic pain. However, naturalistic trials often vary in multiple important variables, such as setting, intensity, duration of treatment and symptom severity at baseline. For a more nuanced benchmarking of effect sizes, more data and meta-analytic analyses are needed.

According to our data, both the cognitive approach (cognitive restructuring and mental distraction) and the respondent approach (relaxation) but not the operant approach (activity despite pain) seem to be important for the treatment of chronic pain.

More specific, our results indicate an association between cognitive restructuring and reductions in pain-related disability and depression. This result is in line with a large body of research that highlights the relevance of changing cognitions—especially catastrophizing—in the treatment of chronic pain (81, 82), as they might even have positive effects on pain intensity (83). Even in exposure-based treatments changes in maladaptive thoughts—for example, harm expectations—are of particular importance (84).

Further, the results suggest that changes in relaxation coping skills were associated with changes in disability and depression. Improvements in the use of relaxation were directly associated to a small effect with reductions in pain-related disability and depression. This result supports the fact that relaxation has long been an integral part of the treatment of chronic pain in CBT (85). Furthermore, there is evidence that an increased use of relaxation leads to positive pain-related outcomes (24, 86, 87). Using relaxation as a coping skill may help to reduce pain by reducing muscle tension in affected regions, at least for some forms of pain (88).

The small independent effect of mental distraction on the two outcomes is consistent with our hypothesis and matches with parts of the literature (89), as mental distraction (or attention shifting) is a common treatment component of cognitive therapies (90). However, evidence seems to be heterogeneous (28), with studies supporting possible benefits of distraction from pain (91) and evidence indicating no benefit in a sample similar to the one presented here (30). Given that mental distraction and cognitive restructuring are originally intended to target the same mechanism of change (17), the discrepancy between the associations of these pain coping skills may suggest further differentiation within the cognitive approach.

Contrary to our hypothesis, however, we found no consistent associations between the operant coping skill (e.g., continuing to be active despite pain) and changes in the outcomes. This finding was surprising as operant approaches like graded activity and exposure-based treatments clearly reduce pain-related disability (31, 92) and are associated with a positive mood (93). In addition, positive exposure experiences can be particularly valuable if they lead to cognitive changes, such as may be the case with self-efficacy (94), which is an important protective factor (95). One explanation might be the subscale itself. The items which are intended to measure behavioral coping mainly include a behavioral distraction from pain. It is reasonable to assume that this describes more a reaction to chronic pain like endurance responses including task/pain persistence behavior (96) than actively approaching situations where pain is expected to reduce avoidance behavior like in exposure based treatments (97). Thus, it is possible that the missing association, especially with pain-related disability, is mainly related to the questionnaire's conceptualization of the pain skill activities despite pain.

## Strengths

Main strengths of this study are the large sample size and the use of SEM models for analysis. The results of this study were confirmed by two large, independent and heterogeneous samples of highly disabled chronic pain patients. The use of routine data in a naturalistic setting contributes to a high external validity. The current work identified differences in the associations of changes of different pain coping skills with changes in clinically relevant outcomes. This may provide valuable information on mechanisms of change that are clinically relevant in the treatment of chronic pain. It complements more mechanistic experimental studies by providing information on which pain coping skills might be most relevant for clinical practice. A sufficient discrimination of the pain coping skills and outcome constructs was ensured by asking about pain coping skill use at the level of behavior and by excluding pain coping skill items that implicated positive therapy outcomes. Sensitivity analyses on the sensitive issue of modeling missing data and response distributions were provided.

## Limitations

Because there are only two points of measurement available in the data and the changes happen simultaneously, no conclusions can be drawn on the causal direction of the associations between the changes of pain coping skill use and changes in the outcomes. For example, spontaneous improvements in depressive symptom severity might have induced generally increased levels of activity and therefore increased coping skill use. Implementing more than two points of measurement in routine care would enable researchers to better disentangle the effects and draw stronger causal claims (48) as well as to perform more sophisticated statistical analysis to identify the mechanisms of change (98, 99). In addition, the low and differing reliabilities of the temporal differences in the pain coping skills scales may have reduced the statistical power of the analyses and resulted in a biased pattern of associations between changes. Furthermore, individual therapy was not manualized and treatment plans differed between wards in the weighting of different therapeutic groups apart from the pain-specific group therapy. Patients therefore were likely exposed to different doses of training for the different pain coping skills examined in this work. Unfortunately, information on the medication administered was not available in this data set. The data additionally consist of a mixed pain sample and mechanisms of change might differ between different forms of pain. The emotional and depressive states at the measurement points might not only have influenced depression ratings but also have led to biases in reporting of pain coping skill use. Electronic

momentary assessment and electronic diaries might be important tools that could be integrated into routine clinical care to measure pain coping skill use more accurately in future studies (100). Event sampling of coping skill use experiences might also enable researchers to assess the causal effects of different pain coping skills in a naturalistic setting in a similar way to research done on the effect of coping skill use in the context of borderline personality disorder (101).

## Conclusion

We found medium to large effects for a CBT-based multidisciplinary treatment in highly disabled pain patients. The present study supports the importance of coping strategies for reducing pain-related disability and depression. In particular, an increased use of the skills cognitive restructuring, relaxation, and mental distraction appear to be associated with positive treatment outcomes. The focus on the associations of changes in the use of these skills and relevant clinical outcomes in a naturalistic setting complements small-scale experimental studies in identifying the driving mechanisms of change in CBT. Based on our findings, both respondent and cognitive coping skills seem to be relevant mechanisms of change in the treatment of chronic pain. Overall, our findings suggest that not all coping skills might be equally effective. More research is needed to further investigate the important question which skills or mechanisms of change are most effective for pain patients with different sets of characteristics.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data sharing is not applicable to this article as only secondary analyses were performed on a routinely collected data set with permission to use for research purposes but without explicit permission of data sharing by the patients. Requests to access these datasets should be directed to Matthias Feldmann, matthias.feldmann@uni-marburg.de.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MF: conceptualization, methodology, statistical analysis, writing—original draft methods and results, review, and editing. HH: conceptualization, methodology, visualization, writing—original draft introduction and discussion, review, and editing. UV: resources, data curation, writing—review and editing, and project administration. RD, TH, and GL: resources, data curation, and writing—review and editing. PH and TK: writing—review and editing. WR: writing—review and editing and supervision. JR: conceptualization, methodology, writing—review and editing, and supervision. E-LB: conceptualization, methodology, writing—review and editing, supervision, and project administration. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.617871/full#supplementary-material

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