

# Mechanisms of change in psychotherapy for depression

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Review

# Mechanisms of change in psychotherapy for depression: An empirical update and evaluation of research aimed at identifying psychological mediators



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HIGHLIGHTS

- Little is known about the psychological mechanisms of psychotherapy for depression.
- The *mechanism question* has motivated dozens of investigations of mediation.
- We provide an empirical update and critical evaluation of this body of research.
- Research is heterogeneous and unsatisfactory in methodological respect.
- Psychotherapy might be too complex to be explained in simple models of psychological change.

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ABSTRACT

We present a systematic empirical update and critical evaluation of the current status of research aimed at identifying a variety of psychological mediators in various forms of psychotherapy for depression. We summarize study characteristics and results of 35 relevant studies, and discuss the extent to which these studies meet several important requirements for mechanism research. Our review indicates that in spite of increased attention for the topic, advances in theoretical consensus about necessities for mechanism research, and sophistication of study designs, research in this field is still heterogeneous and unsatisfactory in methodological respect. Probably the biggest challenge in the field is demonstrating the causal relation between change in the mediator and change in depressive symptoms. The field would benefit from a further refinement of research methods to identify processes of therapeutic change. Recommendations for future research are discussed. However, even in the most optimal research designs, explaining psychotherapeutic change remains a challenge. Psychotherapy is a multi-dimensional phenomenon that might work through interplay of multiple mechanisms at several levels. As a result, it might be too complex to be explained in relatively simple causal models of psychological change.

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## 1. Introduction

Many researchers in the field of clinical psychology agree that gaining a better understanding of the mechanisms underlying psychotherapeutic change is crucial for optimizing treatment outcomes for patients suffering from psychiatric disorders such as depression (Kazdin & Nock, 2003; Kraemer, Wilson, Fairburn, & Agras, 2002). Knowledge about active ingredients of therapy can assist in the verification and refinement of theories of the disorder, and allows enhancement of elements that are crucial for therapeutic change, while dismissing those found to be redundant (Garratt, Ingram, Rand, & Sawalani, 2007; Longmore & Worrell, 2007).

An important first step towards examination of mechanisms of change is the identification of mediators (Kazdin & Nock, 2003; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001; Kraemer et al., 2002). A mediator is a variable that statistically explains why and in what way a treatment has an effect on outcome, and can be seen as a potential mechanism: the actual process or event that is responsible for change (Baron & Kenny, 1986; Kazdin, 2007, 2009; Kraemer et al., 2001; MacKinnon, Fairchild, & Fritz, 2007). In other words, the mechanism is the phenomenon to reveal, the mediator can be the mean to this end. Mediators can be distinguished from moderators in the sense that they *explain* the relationship between an independent and dependent variable (i.e. they indicate whether treatment has an effect on outcome via the mediator), whereas moderators *influence* that relationship (i.e. they indicate when or under what conditions the relationship between treatment and outcome can be expected: Hayes, 2013).

### 1.1. Requirements for a mediator

Establishing a mediator involves several requirements. For a long time, mediation solely referred to statistical mediation: to statistically demonstrate that the effect of treatment on outcome is explained by a third variable: the mediator. The most well-known method to determine statistical mediation is indubitably Baron and Kenny's (1986) causal step method. With almost 60.000 citations, their paper is one of the most frequently cited articles in the field of psychology. According to Baron & Kenny, mediation is established when 1) there is a main effect of treatment (efficacy test), 2) treatment is related to change in the mediator (intervention test), 3) change in the mediator and change in outcome are related (psychopathology test), and 4) the effect of treatment on outcome is absent (full mediation) or significantly weakened (partial mediation) when statistically controlling for the mediator (mediation test). Subsequently, a Sobel test (Sobel, 1982) determines the amount of mediation – also called the indirect effect.

Influential as it has been, the Baron and Kenny (1986) model has significant limitations for application in social sciences and therefore also in clinical process research for disorders such as depression. For example, the method has low type I error rates and, in order to have sufficient power, requires large sample sizes and large treatment effects, both of which are not always available in this type of research (Hoyle & Kenny, 1999; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002;

MacKinnon, Lockwood, & Williams, 2004; Shrout & Bolger, 2002). The applicability of the model in this field is further limited by restrictions resulting from the first and fourth criterion. The first criterion (efficacy test) is formulated in a way that the ability to perform mediation analysis strongly depends on the presence of differential treatment effects. When two treatments turn out to be equally effective – a phenomenon that is not uncommon in the field of psychotherapy for depression (for more details see e.g. Cuijpers & van Straten, 2011; Cuijpers, van Straten, Andersson, & van Oppen, 2008; Wampold et al., 1997) – this type of mediation analysis is not possible. This is an important drawback, because especially when two treatments turn out to be equally effective it is important to examine processes of change, since this can tell us more about whether the change that is observed is reached through similar or differential pathways (MacKinnon, 2008). Moreover, given the population (depressed patients) and the nature of treatments (psychotherapy), it is ethically and practically very difficult (if not impossible) to include a substantially less powerful treatment (such as a full waiting-list control group, or a placebo intervention) to increase the contrasts between groups. And even if a third ineffective control condition would be added, it is still not possible to test differential pathways between the two equally effective treatments. The fourth Baron and Kenny (1986) criterion (mediation test) has been criticised because the tests that have to demonstrate the reduction of the effect after statistically controlling for the mediator have shown to be underpowered (MacKinnon et al., 2007).

As a result of these limitations, the criteria for statistical mediation have been modified over time to make them more applicable and suitable for treatment research. For example, the MacArthur group (Kraemer et al., 2001, 2002) toned down the importance of the first criterion by stating that differential treatment effects are not required to establish mediation as long as there is an interaction between treatment and the mediator. This is particularly useful in clinical trials comparing two (equally) effective treatments that are likely to operate through different mechanisms. With regard to step 4, it was decided that it was sufficient to show that treatment has an effect on the mediator and that the mediator has an effect on the outcome, even after controlling for treatment, a procedure known as joint significance testing (MacKinnon et al., 2007). Furthermore, advances have been made in statistical methods to test the various mediation models (see developments by e.g. Arbuckle, 1999, 2005; Kraemer et al., 2001, 2002; MacKinnon et al., 2002, 2004, MacKinnon et al., 2007, MacKinnon, 2008; Muthén & Muthén, 2001, 2007; Preacher & Hayes, 2004).

#### 1.1.1. Statistical mediation is important but not sufficient

Although statistical mediation still plays a central role in addressing whether a particular construct accounts for change (Hollon & DeRubeis, 2009; Kazdin, 2007, 2009), it is not sufficient to make a case for the operation of a mediator (e.g. Johansson & Høglend, 2007; Kazdin, 2007, 2009; Laurenceau, Hayes, & Feldman, 2007). Probably the most important addition to statistical mediation is demonstrating the direction of causality. Conditions for inferring causal relations in scientific research have been outlined by e.g. Hill (1965), Kenny (1979), Schlesselman

(1982), and brought to the psychotherapy literature by Kazdin (2003, 2007, 2009). Apart from a strong statistical association between treatment, mediator and outcome, Kazdin describes six requirements for adequate evidence for causal temporal relationships. First of all, it has to be demonstrated that the treatment causes the mediator variable to change, which in turn causes the outcome, and not the other way around (Kazdin & Nock, 2003; Kraemer et al., 2002). In order to get a clear view of the shape of change and the relation between mediator and outcome, it is important that both the mediator and outcome measure are assessed at multiple time points during treatment. The importance of demonstrating *temporality* is supported by many research groups (e.g. Collins & Graham, 2002; Hollon & DeRubeis, 2009; Johansson & Høglend, 2007; Kazdin, 2007, 2009; Kazdin & Nock, 2003; Kraemer et al., 2002; Laurenceau et al., 2007; Murphy, Cooper, Hollon, & Fairburn, 2009), and has even been called the fifth step of statistical mediation analysis (Johansson et al., 2010). Second, alternative explanations for the observed relation between mediator and outcome should be ruled out. This can be done by using an *experimental approach* in which all variables are held constant across individuals in various conditions while changing only the proposed mechanism of change (Kazdin, 2007, 2009). Furthermore, Kazdin emphasizes the importance of *specificity* of the association among the intervention, proposed mediator and outcome. This means that it has to be demonstrated that the mediator plays a crucial role in one treatment, but not (or less so) in the other. In addition, inclusion of *plausible processes*, *consistency* across studies, and a *gradient*, in which larger changes in the mediator are associated with larger changes in outcome, should further enhance the evidence.

Kazdin (2007) emphasizes that each criterion is important, but that interpretations should be made based on their convergence. Examination starts with statistical tests for mediation. After that, one determines the value of the results by examining the extent to which a study meets the other criteria. Even though the satisfaction of each criterion increases the strength of the argument for the operation of a mediator – or even a mechanism – not all criteria are weighted equally important. According to Kazdin and Nock (2003), *statistical association*, *temporality*, *specificity*, and *experiment* are considered to be the most important, whereas the remaining three should further enhance the evidence.

### 1.1.2. Requirements for study designs

The extended requirements and possibilities for identifying mediators also called for additional features of study designs. According to the latest standards, the extent to which a process meets the requirements for mediation can only be examined properly in a theoretically well planned RCT with carefully spaced repeated measures, sufficient power and an appropriate control group (Kazdin, 2007; Kazdin & Nock, 2003; Kraemer et al., 2002; Laurenceau et al., 2007). Furthermore, it is important to experimentally manipulate the proposed mediators, which requires an experimental study design. In addition, mediation analysis should be performed using up-to-date definitions and state-of-the-art statistical analyses techniques (Collins & Graham, 2002; Haaga & Stiles, 2000; Haubert & Dobson, 2007; Kraemer et al., 2002; Laurenceau et al., 2007; MacKinnon et al., 2007). Moreover, depending on what the theory stipulates about processes, assessment of a single mediator might not be sufficient. It is therefore recommended to include multiple mediators to examine rival hypotheses, test alternative explanatory models, and map out interactions between theorized processes.

### 1.2. Research studying mediators in psychotherapy for depression

The past decades, the interest for mediators in mechanism research in depression has grown, and several research groups worldwide have studied mediators of psychotherapy. In 2007, Johansson and Høglend identified 61 studies that performed mediational analyses to identify the active ingredients of psychotherapy for several psychiatric

disorders. A closer look at the literature specific for depression indicates that the majority of studies has focused on the mediational role of cognitive processes, such as automatic thoughts, dysfunctional attitudes, attributional style, and other cognitive distortions. The cognitive mediation hypothesis was also the focus of the influential systematic review by Garratt et al. (2007). Garratt and colleagues summarized results of 31 studies on the role of cognitive change and concluded that research generally supports the cognitive mediation hypothesis, but that this does not necessarily need to be specific for interventions in which cognitions are actively targeted. This indicates that cognitive change, no matter how it occurs, might play a role in various treatment modalities. Even though Garratt et al. acknowledged that these findings increased knowledge about the relation between cognition and depression, they emphasized that their findings did not permit clear-cut answers about the exact role of cognitive change as a process that facilitates psychotherapeutic change in the context of psychotherapy. They provided several reasons for this. First of all, there was a large variety in research questions and methodology across studies, which made it difficult to compare results across studies and to integrate findings into broader knowledge. Second, many studies did not meet the criteria for reputable mechanism research, hereby limiting the interpretability of study findings. More specifically, Garratt et al. concluded that none of the studies that were identified in their review addressed the criteria for mediation in methodologically sound ways. Garratt and colleagues expressed their hope that this would change in subsequent years, in studies with e.g. larger sample sizes, up-to-date-statistical methods, and a broader array of measures. These issues are acknowledged by others in the field as well (e.g. Johansson & Høglend, 2007; Kazdin, 2007; Kraemer et al., 2001; Laurenceau et al., 2007). A third difficulty in interpreting results from studies in this field – not mentioned by Garratt et al. – is the fact that not every study that makes claims about mediators, actually performed statistical mediation analyses. Instead, some studies present correlations between changes in hypothesized process measures and depressive symptoms from pre- to post-treatment as evidence for mediation. Others make claims about mediators based on prediction analyses. This does not only further increase the heterogeneity in the field, but also leads to conclusions about mediators in studies where no statistical mediation analyses were performed. Garratt and colleagues did not differentiate between this in their review. Fourth, since most studies so far mainly focused on the role of cognitive factors, the influence of non-cognitive factors is still largely unknown.

### 1.3. Aim of the current review

Almost ten years have passed since the Garratt et al. (2007) review, and the question is whether and how the field has changed. The aim of the current review was therefore to provide an update and critical methodological evaluation of the current body of research on this topic. In a systematic literature search, we selected studies aimed at identifying psychological mediators in psychotherapy for depression. To get a comprehensive overview of the field, we included various forms of psychotherapy and included both cognitive and non-cognitive processes. We only selected studies that included an actual test of statistical mediation (Baron & Kenny (1986) or one of the more advanced methods). We summarize study characteristics and results of 35 studies and discuss the extent to which these studies meet the most important requirements for mechanism research that were mentioned earlier. With this we hope to learn more about the magnitude and relevance of the existing body of research and map out necessities for future research.

## 2. Method

### 2.1. Data sources and data reduction

Three different approaches were used to identify relevant studies. First, five databases (i.e. PubMed, PsychInfo, Embase, Cochrane, and

Cinahl) were systematically searched for potentially relevant papers that were published in English in peer reviewed journals until spring 2016. Key terms were Depression, Psychotherapy, Mechanisms and Mediation (a full key-term scheme can be found in [Appendix A](#)). The data search yielded a total of 617 unique studies. One of us (VM) carefully read through all abstracts<sup>1</sup> and retained those articles that met a set of a priori generated inclusion and exclusion criteria. LL checked the generated table entries for accuracy.

To be included in the review articles needed to be empirical research reports (no reviews, theoretical essays or commentaries) examining psychological mediators over the course of treatment of various forms of evidence-based psychotherapy for patients (adults and adolescents) with (subclinical) depression. Furthermore, studies needed to actually include statistical mediation analyses in their analysis plan (in the sense of Baron and Kenny or one of the modern alternatives). Studies including patients diagnosed with bipolar depression were excluded, as were those that focused on other forms of psychopathology<sup>2</sup> and/or (relapse) prevention. A complete overview of the in- and exclusion criteria can be found in [Appendix B](#).

Of the 617 articles that were identified in the literature search, 584 did not meet our inclusion criteria and were therefore excluded. The majority of studies were excluded because they did not focus on psychological mechanisms of treatment for depression ( $n = 356$ ). Other papers were excluded because they were theoretical papers (e.g. reviews, commentaries) instead of empirical research reports ( $n = 90$ ), or because they did not focus on an (evidence-based) psychological intervention ( $n = 135$ ). Two papers were excluded because after careful reading they did not perform statistical mediation analysis ([Backenstrass et al., 2006](#); [Sasso, Strunk, Braun, DeRubeis, & Brotman, 2015](#)), and one because it did not include a clinical outcome measure ([Johansson et al., 2010](#)).<sup>3</sup> A total of 33 articles met all inclusion criteria and were selected for further review. Subsequently, we hand searched reference lists of the 33 articles that met all inclusion criteria, and asked several experts (3 psychologists, 1 psychiatrist) with longstanding experience in the research field and clinical practice of depression to check the list that was generated. Two additional papers were added, resulting in a total of 35 studies that were further explored.

## 2.2. Data assessment

Two researchers (LL and VM) carefully read the 35 articles that were selected and tabulated study characteristics and results. To answer our main research question, all papers were assessed by means of several important requirements for mediation research that were discussed earlier: the use of an RCT design and inclusion of a control group, a sufficient sample size (defined as  $n \geq 40$ ), examination of multiple potential mediators within one study, the assessment of temporality (as defined by 3 or more assessments in the treatment phase), and direct experimental manipulation of the mediator. Each study was rated with respect to meeting (+) or not meeting (–) each of these criteria. Differences in scoring were resolved by consensus. A qualitative analysis was conducted by summarizing, comparing and contrasting the data.

It has to be noted that *specificity* is not included in the list of features that was described above. This does not mean that we think that examining specificity is not important (in fact, as was stated in the [Introduction](#), we think it is very important to examine whether change in two treatments is achieved through similar or differential pathways). However, we think that conceptually it does not make sense to include this as a first-order requirement for a mediator. In our view, the primary

goal in process research is to identify any factors that facilitate symptom change, regardless of their specificity to one treatment. A first priority is therefore to identify process factors that are a linking pin between treatment and outcome. A subsequent specificity analysis could then show whether this factor plays a role in only this treatment or also in other treatments. By requiring specificity as a (testable) criterion for mediation, basic information about whether or not a process facilitates symptom change is discarded when it turns out that the specificity criterion is not met. Since we consider this information important, we decided not to include specificity in our evaluation.

## 3. Results

### 3.1. Study characteristics and results

[Table 1](#) (left panel) gives an overview of study characteristics and results of 35 studies that were included in the review. The majority of studies was conducted in the USA (57.1% vs. 28.6% in Europe, and 14.3% in other parts of the world), and 48.6% was published in the past five years (2012–2016). Sample sizes ranged between  $n = 4$  and  $n = 523$ , with a mean of  $n = 173$  ( $SD = 145.3$ ). Patients were adults (in 26 studies) and adolescents (in 9 studies) ranging in age from 12 to 68 years ( $M = 40.2$   $SD = 8.2$  for studies in adults<sup>4</sup> and  $M = 15.1$   $SD = 0.5$  for studies including adolescents<sup>5</sup>). In 90.9% of the studies the majority (> 50%) of participants were female.<sup>6</sup>

Cognitive (Behavioural) Therapy (C(B)T) was the most frequently researched intervention (examined in 21/35 studies), followed by Mindfulness Based Cognitive Therapy (MBCT, included in 5 studies). Other treatments were Acceptance and Commitment Therapy (ACT,  $k = 3$ ), Behavioural Activation (BA,  $k = 1$ ), Cognitive Behavioural Analysis System of Psychotherapy (CBASP,  $k = 1$ ), Interpersonal Psychotherapy (IPT,  $k = 2$ ), Non-Directive Supportive Therapy (NST,  $k = 2$ ), Problem Solving (Couples) Therapy (PST,  $k = 2$ ), Psychodynamic Therapy ( $k = 1$ ), Psychoanalytic Therapy ( $k = 1$ ), and Systematic Behavioural Family Therapy (SBFT,  $k = 2$ ). Three studies included a combined treatment.

Common measures of depression severity were the (second edition of the) Beck Depression Inventory (BDI(-II); [Beck, Steer, & Brown, 1996](#); [Beck, Ward, Meldelson, Mock, & Erbauch, 1961](#)), which was implemented in 18 studies, and the Hamilton Rating Scale for Depression (HRSD; [Hamilton, 1960](#)), used in 7 studies. Nine studies (e.g. [van Aalderen et al., 2012](#); [DeRubeis et al., 1990](#); [Vittengl, Clark, Thase, & Jarrett, 2014](#); [Warmerdam, van Straten, Jongma, Twisk, and Cuijpers, 2010](#)) used them both, thereby obtaining a self-report and an observer-based measure of depression.

The identified studies examined 39 different potential mechanisms. Given the substantial number of studies that examined C(B)T, mediators were predominantly the theorized processes of this intervention, such as Negative (Automatic) Thoughts (7 studies), Dysfunctional Attitudes (7 studies), Attributional style (3 studies) and other cognitive constructs (9 constructs in 7 studies). Furthermore, six studies assessed the behavioural component of CBT. In studies in which Mindfulness-Based interventions were the choice of treatment Rumination, Mindfulness, and Worry were common process measures (included in 5, 4, and 3 studies respectively). The potential mediational role of Therapeutic Alliance was examined in 3 of the 35 identified studies. As can be seen in [Tables 1 and 2](#), dysfunctional attitudes, negative (automatic) thoughts, rumination, worry and mindfulness skills were found to be associated with change in the majority of studies. Findings on the mediational role of the other constructs that were investigated across studies are more mixed. In general, approximately half of the studies examining a

<sup>1</sup> If the abstract did not provide all the information necessary to assess in- and exclusion criteria, the full article was consulted.

<sup>2</sup> If a study used a mixed sample (e.g. depression and anxiety) but the main focus was on depression and the majority of the sample was depressed, the study was included.

<sup>3</sup> Because we excluded studies as soon as they did not meet one of the inclusion criteria, the number of studies meeting multiple exclusion criteria is unknown.

<sup>4</sup> Based on 24 studies; two studies did not report on this ([Webb et al., 2013](#); [Zettle et al., 2011](#)).

<sup>5</sup> Based on 8 studies; one study did not report on this ([Smith et al., 2015](#)).

<sup>6</sup> Based on 33 studies; two studies did not report on this ([Webb et al., 2013](#); [Smith et al., 2015](#)).

**Table 1**

Characteristics and results of 35 identified studies aimed at identifying psychological mediators for (subclinical) depression, and the extent to which they meet requirements for process research.

Study characteristics and results					Requirements for process research					
Authors	Intervention(s)	Measure(s) of Depression	Statistical Method	Potential Mediator(s) & Results	RCT	Control	$n \geq 40$	Multiple Mediators	Temporality ( $\geq 2$ ass.)	Manipulation
- v. Aaldere et al. (2012)(NL)	- MBCT + TAU ( $n = 102$ ) vs. - TAU only ( $n = 103$ )	- HRSD - BDI	- Preacher & Hayes (2008) - MacKinnon (2008)	- $\downarrow$ Rumination <sup>(+)</sup> - $\downarrow$ Worry <sup>(+)</sup> - Mindfulness skills <sup>(-)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Allart-v. Dam et al. (2003)(NL)	- Group CBT ( $n = 68$ ) vs. - Advice only ( $n = 42$ )	- BDI	- Baron & Kenny (1986) - MacKinnon et al. (2002)	- $\downarrow$ Negative Thoughts <sup>(+)</sup> - $\uparrow$ Self-esteem <sup>(+)</sup> - Pleasant activities <sup>(-)</sup> - Social skills <sup>(-)</sup> - Perceived support <sup>(-)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Batink et al. (2013)(NL)	- MBCT ( $n = 64$ ) vs. - TAU: WLC ( $n = 66$ )	- IDS-SR - HRSD	- Goodman (1960) - Sobel (1982) - MacKinnon et al. (2007)	- $\Delta$ in Mindfulness skills <sup>(+)</sup> - $\Delta$ Positive affect <sup>(+)</sup> - $\Delta$ Negative affect <sup>(+)</sup> - $\Delta$ Worry <sup>(+ via pos. and neg. affect)</sup> - $\Delta$ Rumination on sadness <sup>(-)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Beevers et al. (2007) (USA)	- PHT + various forms of Psychological Treatment ( $n = 121$ )	- MHRSD	- Curran & Hussong (2002)	- Negative Cognition <sup>(+ in relation between depression history and outcome)</sup> - Family impairment <sup>(predicts slower change in depression)</sup>	(-) <sup>a</sup>	(-) <sup>a</sup>	(+)	(+)	(-)	(-)
- Blalock et al. (2008) (USA)	- CBASP+PHT ( $n = 179$ ) vs. - PHT only ( $n = 165$ ) vs. - CBASP only ( $n = 173$ )	- HRSD	- Baron & Kenny (1986) - MacKinnon (1994)	- Attributional style <sup>(+)</sup> - Coping style - Escape/Avoidance <sup>(+)</sup> - Problem solving <sup>(+)</sup> - Distancing <sup>(-)</sup> - Accepting - Responsibility <sup>(-)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Cohen et al. (2014) (USA)	- Brief Problem Focused Therapy ( $n = 18$ ) vs. - WLC ( $n = 17$ )	- BDI-II	- Baron & Kenny (1986) - Pitariu & Ployhart (2010) - MacKinnon (2008)	- Negative behaviour/attitude towards depression <sup>(+)</sup> - Empathic communication <sup>(-)</sup> - Support <sup>(-)</sup>	(+)	(+)	(-)	(+)	(-)	(-)
- DeRubeis et al. (1990) (USA) <sup>b</sup>	- CT + PHT ( $n = 32$ ) vs. - PHT only ( $n = 32$ )	- Composite score of 3 measures of depression <sup>c</sup>	- Baron & Kenny (1986) - Temporal correlations <sup>d</sup>	- $\Delta$ Attributional style <sup>(-)</sup> - $\Delta$ Neg. auto. thoughts <sup>(-)</sup> - $\Delta$ Dysfunctional attitudes <sup>(-)</sup> - $\Delta$ Hopelessness <sup>(-)</sup>	(+)	(+)	(-)	(+)	(+)	(-)
- Dietz et al. (2014) (USA)	- CBT ( $n = 25$ ) vs. - SBFT ( $n = 20$ ) vs. - NST ( $n = 18$ )	- BDI - K-SADS-P	- MacKinnon et al. (2002)	- $\Delta$ in Interpersonal Behaviour - $\Delta$ in problem solving <sup>(+ but only in CT and only when maternal depressive symptoms were low or moderate)</sup> - $\Delta$ in involvement <sup>(-)</sup> - $\Delta$ in dyadic conflict <sup>(-)</sup>	(+)	(+)	(-)	(+)	(-)	(-)
- Fledderus et al. (2013) <sup>e</sup> (NL)	- Self-help ACT ( $n = 250$ ) vs. - WLC ( $n = 126$ )	- CES-D	- Preacher & Hayes (2008)	- $\uparrow$ psychological flexibility <sup>(+ in ACT)</sup>	(+)	(+)	(+)	(-)	(+)	(-)
- Forman et al. (2012) <sup>e</sup> (USA)	- CT ( $n = 90$ ) vs. - ACT ( $n = 84$ )	- BSQ	- Krull & MacKinnon (2001); - MacKinnon et al. (2002, 2004, 2007)	- Cognitive and Affective Change <sup>(+ CT only)</sup> - Acceptance <sup>(+ ACT only)</sup> - Cognitive defusion <sup>(+ both)</sup> - Dysfunctional Thinking <sup>(+both)</sup> - Willingness to engage in behavioural activity <sup>(+both)</sup>	(+)	(+)	(+)	(+)	(+)	(-)

(continued on next page)

Table 1 (continued)

STUDY CHARACTERISTICS AND RESULTS					REQUIREMENTS FOR PROCESS RESEARCH					
Authors	Intervention(s)	Measure(s) of Depression	Statistical Method	Potential Mediator(s) & Results	RCT	Control	n ≥ 40	Multiple Mediators	Temporality (≥2 ass.)	Manipulation
- Gaynor & Harris (2008) (USA)	- BA (n = 4)	- BDI-II	- Mueser, Yarnold, & Foy, (1991)	- ↑ Activation level <sup>(+ in 2/4 patients)</sup> - ↓ Dysfunctional thoughts <sup>(-)</sup>	(-)	(-)	(-)	(+)	(+)	(-)
- Jacobs et al. (2009) (USA)	- CBT (n = 111) vs. - PHT (n = 109) vs. - CBT + PHT (n = 107) vs. - Pill placebo (n = 112)	- CDRS-R	- Kraemer et al. (2002)	- Perfectionism (DAS) <sup>(+ partial)</sup>	(+)	(+)	(+)	(-)	(+)	(-)
- Jacobs et al. (2014) (USA)	- CBT (n = 95) vs. - PHT (n = 99) vs. - CBT + PHT (n = 97)	- CDRS-R	- Kraemer et al. (2002)	Δ in 4 Cognitive Constructs - in Cognitive distortions <sup>(+)</sup> - in Cognitive avoidance <sup>(+)</sup> - in Positive outlook <sup>(+ strongest)</sup> - in Solution-foc. thinking <sup>(-)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Kaufmann et al. (2005) (USA)	- Group CBT (n = 45) vs. - Life skills control (n = 48)	- BDI-II - HRSD	- Baron & Kenny (1986); - MacKinnon et al. (2002); - Muthén & Muthén (2001)	- Δ Automatic Thoughts <sup>(+)</sup> - Relaxation <sup>(-)</sup> - Social Skills <sup>(-)</sup> - Pleasant Activities <sup>(-)</sup> - Problem Solving <sup>(-)</sup> - Working Alliance <sup>(-)</sup> - Group Cohesion <sup>(-)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Klug et al. (2012) (GER)	- Psychoanalytic (n = 35) vs. - Psychodynamic (n = 31) vs. - CBT (n = 34)	- BDI - SCL-90-R	- Baron & Kenny (1986)	- Positive Introject <sup>(+)</sup> - Therapeutic relationship <sup>(-)</sup>	(-)	(+)	(-)	(+)	(-)	(-)
- Kolko et al. (2000) (USA)	- CBT (n = 36) vs. - SBFT (n = 32) vs. - NST (n = 35)	- BDI	- Baron & Kenny (1986); - Holmbeck (1997)	- Cognitive distortion <sup>(-)</sup> - Family dysfunction <sup>(-)</sup>	(+)	(+)	(-)	(+)	(+)	(-)
- Kuyken et al. (2010) (USA)	- Group MBCT (n = 61) vs. - Maintenance PHT (n = 62)	- HRSD	- Kraemer et al. (2002)	- ↑ Mindfulness <sup>(+ in MBCT)</sup> - ↑ Self-compassion <sup>(+ in MBCT)</sup> - Cognitive reactivity <sup>(+ in MBCT)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Kwon & Oei (2003) (AUS) <sup>b</sup>	- Group CBT (n = 35)	- BDI	- SEM - Arbuckle & Wothke (1999)	- ↓ Neg. automatic thoughts <sup>(+)</sup>	(-)	(-)	(-)	(-)	(+)	(-)
- Lewis et al. (2009) (USA)	- CBT (n = 79) vs. - PHT (n = 85) vs. - CBT + PHT (n = 86) vs. - Pill placebo (n = 82)	- CDRS-R	- Kraemer et al. (2002)	- 4 stages of readiness to change - Action <sup>(+)</sup> - Pre-contemplation <sup>(-)</sup> - Contemplation <sup>(-)</sup> - Maintenance <sup>(-)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Lo et al. (2013) <sup>e</sup> (CHI)	- C-MBCT (n = 41) vs. - WLC (n = 41)	- BDI-II	- Baron & Kenny (1986) - Sobel (1982) <sup>f</sup>	- Stagnation <sup>(+)</sup>	(+)	(+)	(+)	(-)	(-)	(-)
- Quilty et al. (2014) (CAN)	- CBT (n = 54) vs. - PHT (n = 50)	- BDI-II - HRSD	- Kraemer et al. (2002)	- Cognitive Organisation - Distancing <sup>(+ negative subscale)</sup> - Attribute Redundancy <sup>(-)</sup> - Cognitive Processing - Encoding <sup>(+ negative subscale)</sup>	(+)	(+)	(+)	(+)	(+)	(-)

Table 1 (continued)

STUDY CHARACTERISTICS AND RESULTS					REQUIREMENTS FOR PROCESS RESEARCH					
Authors	Intervention(s)	Measure(s) of Depression	Statistical Method	Potential Mediator(s) & Results	RCT	Control	n ≥ 40	Multiple Mediators	Temporality (≥2 ass.)	Manipulation
- Quilty et al. (2008) (CAN)	- CBT (n = 45) vs. - IPT (n = 46) vs. - PHT (n = 41)	- BDI-II - HRSD	- Arbuckle (2005) - Shrout & Bolger (2002) - Kline (2005)	- Dysfunctional Attitudes (+ only in CT)	(+)	(+)	(+)	(-)	(-)	(-)
- Ryba et al. (2014) (USA)	- BA (n = 23)	- BDI-II	- Selig & Preacher (2009) - Muthén & Muthén (2007)	- ↑ Environmental Reward <sup>(c)</sup> both in relation between 1) proportion- and 2) quantity of activities completed and outcome depression	(-) <sup>a</sup>	(-) <sup>a</sup>	(-)	(-)	(+)	(-)
- Shahar et al. (2004) (USA)	- Combined sample: CBT, IPT & PHT (n = 144)	- Composite score of 5 clinical measures <sup>g</sup>	- SEM - Hoyle & Smith (1994) - Arbuckle (1999)	- Social Network <sup>(+ in relation between perfectionism and depression)</sup> - Working Alliance <sup>(+ in relation between perfectionism and depression)</sup>	(-) <sup>a</sup>	(-) <sup>a</sup>	(+)	(+)	(-)	(-)
- Shahar et al. (2010) (USA)	- Group MBCT (n = 26) vs. - WLC (n = 19)	- BDI	- Preacher & Hayes (2004, 2008)	- Mindfulness <sup>(+)</sup> - Rumination: Brooding <sup>(+)</sup> - Rumination: Reflection <sup>(-)</sup>	(+)	(+)	(-)	(+)	(-)	(-)
- Smith et al. (2015) (UK)	- Online CBT (n = 55) vs. - WLC (n = 57)	- MFQ-C	- Baron & Kenny (1986); - Preacher & Hayes (2004); - Hayes (2013)	- Rumination <sup>(+; partial mediation)</sup>	(+)	(+)	(+)	(-)	(-)	(-)
- Stice et al. (2010) (USA)	- Group CBT (n = 89) vs. - Group SE-CBT (n = 88) vs. - Bibliotherapy (n = 80) vs. - Control (n = 84)	- BDI	- Stice, Presnell, Gau, & Shaw (2007)	- Negative cognitions <sup>(-)</sup> - Pleasant activities <sup>(-)</sup> - Emotional expression <sup>(-)</sup> - Loneliness <sup>(-)</sup>	(+)	(+)	(+)	(+)	(+)	(-)
- Toth et al. (2013) (USA)	- IPT (n = 99) vs. - ECS (n = 29)	- BDI-II - HRSD	- Cheong, MacKinnon & Khoo (2001, 2003) - Jo (2008)	- ↓ Perceived Stress <sup>(+ on both BDI-II and HRSD)</sup> - ↑ Family Social Support <sup>(+ on HRSD)</sup> - ↑ Friends Social Support (-) - ↑ social adjustment (-)	(+)	(+)	(-)	(+)	(-)	(-)
- Vittengl et al. (2014) (USA)	- CT (n = 523)	- BDI-II - HRSD	- series of cross-lagged SEM	- Hopelessness <sup>(-)</sup> - Dysfunctional attitudes <sup>(+)</sup> - Attributional style <sup>(-)</sup> - Self-Control <sup>(-)</sup>	(-)	(-)	(+)	(+)	(+)	(-)
- Warmerdam et al. (2010) (NL)	- Online CBT (n = 88) vs. - Online PST (n = 88) vs. - WLC (n = 87)	- CES-D	- Baron & Kenny (1986)	- Dysfunctional attitudes <sup>(+ CBT and PST)</sup> - Worrying <sup>(+ CBT and PST)</sup> - Negative problem orientation <sup>(+ CBT and PST)</sup> - Other problem solving orientations <sup>(-)</sup> - Perceived control <sup>(+ CBT and PST)</sup>	(+)	(+)	(+)	(+)	(+)	(-)

(continued on next page)



Table 1 (continued)

STUDY CHARACTERISTICS AND RESULTS					REQUIREMENTS FOR PROCESS RESEARCH					
Authors	Intervention(s)	Measure(s) of Depression	Statistical Method	Potential Mediator(s) & Results	RCT	Control	n ≥ 40	Multiple Mediators	Temporality (≥2 ass.)	Manipulation
- Watkins et al. (2011) (UK)	- R-CBT + TAU (n = 21) vs. - TAU only (n = 21)	- HRSD - BDI-II	- Baron & Kenny (1986)	- Δ Rumination <sup>(+)</sup>	(+)	(+)	(-)	(-)	(-)	(-)
- Watson et al. (2014) (USA)	- Combined sample: CBT & EFT-PE (n = 55)	- BDI	- Baron & Kenny (1986)	- ↓ insecure attachment <sup>(+ in the relation between therapists' empathy and outcome)</sup> - ↓ negative self-treatment <sup>(+ in the relation between therapists' empathy and outcome)</sup> - ↑ secure attachment <sup>(+ in the relation between therapists' empathy and outcome)</sup> - ↑ positive self-treatment <sup>(-)</sup>	(-) <sup>a</sup>	(-) <sup>a</sup>	(+)	(+)	(-)	(-)
- Webb et al. (2013) <sup>e</sup> (USA)	- CBT (n = 420)	- CES-D - BASIS	- Preacher & Hayes (2008)	- Cognitive skills <sup>(+ in expectancy outcome relation)</sup> - Behavioural skills <sup>(+ in expectancy outcome relation)</sup>	(-)	(-)	(+)	(+)	(-)	(-)
- v/d Zanden et al. (2014) (NL)	- Online CBT (n = 121) vs. - WLC (n = 123)	- CES-D	- Baron & Kenny (1986) - MacKinnon (2008)	- Δ in Anxiety <sup>(+)</sup> - Δ in Mastery <sup>(+)</sup>	(+)	(+)	(+)	(+)	(-)	(-)
- Zettle et al. (2011) (USA)	- CT (n = 13) vs. - ACT (n = 12)	- BDI	- Baron & Kenny (1986) - Preacher & Hayes (2004, 2008)	- Cognitive defusion <sup>(+ in ACT)</sup> - Depressogenic thoughts <sup>(-)</sup> - Dysfunctional attitudes <sup>(-)</sup>	(+)	(+)	(-)	(+)	(-)	(-)

ABBREVIATIONS: Column Headings: RCT = Design is Randomized-Controlled Trial (yes/no); n ≥ 40 = Sample size per treatment arm is at least 40 (yes/no); Control = Control Group (yes/no); Multiple Mediators = Study included more than 1 potential mediator (yes/no); Temporality (ass n > 2) = Number of assessment in treatment phase (FU assessments are not included in count); Manipulation of mediator = Manipulation of Mediator (yes/no); (+) = Present/Yes; (-) = Absent/No. Countries: AUS = Australia; CAN = Canada; CHI = China; GER = Germany; NL = the Netherlands; UK = United Kingdom; USA = United States of America Interventions: ACT = Acceptance and Commitment Therapy; BA = Behavioural Activation; CBASP = Cognitive Behavioural Analysis System of Psychotherapy; CBSM = Cognitive Behavioural Stress Management Treatment; CBT = Cognitive Behavioural Therapy; CM = clinical management; C-MBCT = Compassion focused MBCT; CT = Cognitive Therapy; DT = Dynamic Therapy; ECS = Enhanced Community Standard; EFT-PE = Emotion-Focused Therapy, Process Experiential approach; IPT = Interpersonal Psychotherapy; MBCT = Mindfulness Based Cognitive Therapy; MBSR = Mindfulness Based Stress Reduction; NST = Non-Directive Supportive Therapy; PHT = Pharmacotherapy; PST = Problem Solving Therapy; R-CBT = Rumination focused CBT; SBFT = Systematic Behavioural Family Therapy; SE-CBT = Supportive-Expressive Cognitive Behavioural Therapy; TAU = Treatment-as-usual; WLC = Waiting-List Control. Outcome measures: BASIS = Behaviour and Symptom Identification Scale; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory II; BSI = Brief Symptom Inventory; BSQ = Before Session Questionnaire (items: symptom intensity and progress towards goal); CDRS-R = Children's Depression Rating Scale Revised; CES-D-(10) = Centre for Epidemiological Studies Depression Inventory (10 item version); HRSD = Hamilton Rating Scale for Depression; IDS-SR = Inventory of Depressive Symptoms, self-rating; K-SADS-P = Schedule for Affective Disorders and Schizophrenia for School-Age children, Present Episode Version; MFQ-C = Mood and feelings Questionnaire Child; MHRSD = Modified Hamilton Rating Scale for Depression; PFS-IF = Psychodynamic Functioning Scale – Interpersonal Functioning Subscales; SCL-90-(R) = Symptoms Checklist 90 (Revised). Statistical Method: SEM = structural equation modeling. Mediator variables: DAS = Dysfunctional Attitudes Scale. NOTES: <sup>a</sup> = Data come from RCT's, but studies do not make use of RCT design in analyses; Beavers et al. (2007), Shahar et al., 2004 and Watson et al. (2014) use a combined sample, and Ryba et al. (2014) only select patients allocated to BA. Therefore there is no control/comparison group available in these studies; <sup>b</sup> = study was also included in the review by Garratt & Ingram (2007); <sup>c</sup> = Composite score of BDI, HRSD, Raskin Depression Scale; <sup>d</sup> = Used residualized change scores; <sup>e</sup> = study sample consisted of patients diagnosed with depression (> 50%) and anxiety disorders; <sup>f</sup> = Description of the exact statistical procedure used in this study is lacking. Based on reading the method section one could conclude that this is Baron & Kenny (1986) and Sobel test (1982); <sup>g</sup> = Composite score of BDI, SCL-90, HRSD, Global Assessment Scale (GAS) and Social Adjustment Scale (SAS), as described by Blatt et al. (1996).

construct found evidence for mediation, whereas the other half did not find a relation between the mediator and outcome. When only focusing on findings of C(BT) studies that examined treatment specific mediators (n = 16), support for (partial) mediation was found in 63.3% of the cases.

Exploration of the statistical methods of the 35 identified studies indicated that early papers mainly examined the four basic steps of the mediational model using linear regressions. The size of the indirect effect was often examined with a Sobel (1982) test. However, as time passed, a range of new (more sophisticated) statistical analyses techniques was observed. For example, mediational effects were now estimated using multiple regression (ordinary least squares), logistic regression, multilevel regression and structural equation modeling (SEM). The Sobel test was replaced with joint-significance testing (MacKinnon et al., 2007) and bootstrapping (Preacher & Hayes, 2004, 2008). A closer look at the statistical methods showed that two studies (DeRubeis et al., 1990; Kolkko, Brent, Baugher, Bridge, & Birmaher, 2000) could not finish their mediation analyses because the treatment conditions that were compared did not differ significantly with regard to outcome. However, while DeRubeis et al. (1990) concluded that mediation analysis was not possible because group differences were absent, Kolkko et al. (2000) concluded that mediational effects of the proposed mediators were lacking. Re-analysing these data using the adapted guidelines

as proposed by the MacArthur group (discussed in the Introduction) could have been a solution here.

### 3.2. A closer look at the value of these results

As discussed by Kazdin (2007), after completing statistical mediation analysis, one should return to the other criteria to assess the extent to which they are met. The results of the assessment of requirements for process research are presented for each individual study in the right panel of Table 1 and summarized in Table 3.

The majority of studies (74.3%) used an RCT design, and consequently included one or more comparison groups. Interventions of interest were compared to a) other active treatments (psychological and/or pharmacological; e.g. Blalock et al., 2008; DeRubeis et al., 1990; Forman et al., 2012; Jacobs et al., 2009, Jacobs et al., 2014); b) treatment as usual (e.g. Watkins et al., 2011); or c) non-active waiting-list control conditions (e.g. Fledderus, Bohlmeijer, Fox, Schreurs, & Spinhoven, 2013; Lo, Ng, Chan, Lam, & Lau, 2013; Shahar, Britton, Sbarra, Figueredo, & Bootzin, 2010; Smith et al., 2015). Since studies with an active control condition and those with a non-active (wait-list) comparison group present different types of testing the significance of mediators, we compared the results of studies with an active control

**Table 2**  
Selection of significant mediators in the identified studies.

	All studies (n = 35)		Studies meeting 4 or more criteria (n = 17)	
	Examined	Significant	Examined	Significant
- Dysfunctional attitudes	7	4	3	2
- Negative (automatic) thoughts	7	4	4	2
- Attributional style	3	1	2	1
- Behavioural concepts	6	3	4	3
- Mindfulness skills	4	3	3	2
- Rumination	5	4	2	1
- Worry	3	3	3	3
- Therapeutic alliance	3	1	1	1
Total	38	23 (61%)	22	15 (68%)

group ( $n = 16$ ), with those including a non-active control group ( $n = 11$ ). Studies with a non-active control group showed relatively more statistically significant mediators as compared to studies with an active contrast group (69.0 vs 41.3%).

Four studies used data that originally came from RCTs, but did not make use of the RCT design in their mediational analyses. They either only selected patients allocated to one particular condition (Ryba, Lejuez, & Hopko, 2014), or merged the various intervention groups into one combined sample (Beevers, Wells, & Miller, 2007; Shahar, Blatt, Zuroff, Krupnick, & Sotsky, 2004; Watson, Steckley, & McMullen, 2014). As a result, there was no control/comparison group available. In addition, as can be seen in Table 3, the number of studies including a control group is higher than the number of studies with an RCT design. This can be explained by the fact that one study compared two treatments in a non-randomized design (Klug, Henrich, Filipiak, & Huber, 2012).

Table 3 furthermore shows that two thirds of the selected studies included sample sizes of >40 participants per condition. This was even the case in several RCTs with three or four arms (e.g. Jacobs et al., 2009; Jacobs et al., 2014; Stice, Rohde, Seeley, & Gau, 2010). However, the small sample sizes in various other studies show that power can still be an issue in this type of research, also in relatively recent studies (e.g. Ryba et al., 2014; Watkins et al., 2011; Zettle, Rains, & Hayes, 2011). The smallest sample was found in a study by Gaynor and Harris (2008), who conducted single participant assessment of mediators in four depressed adolescents. One study explicitly compensated for the small sample size and low power by conducting mediation analyses with the therapy groups combined (Watson et al., 2014).

Almost 80% of studies included more than one mediator in their design. Some studies included several separate potential processes of change (e.g. Allart-van Dam, Hosman, & Hoogduin, 2003; Kaufman, Rohde, Seeley, Clarke, & Stice, 2005; Warmerdam et al., 2010), whereas others examined subscales of the same construct (Blalock et al., 2008; Lewis et al., 2009). However, even when multiple mediators were included in a study, they were often analysed individually. Only a small number of studies looked at the relative importance and collaboration between several potential mechanisms. For example, the study by Batink, Peeters, Geschwind, van Os, & Wichers (2013) indicated that even though both positive affect, as well as negative affect played a substantial mediating role in the reduction of depressive symptoms during MBCT, the effect of the first was larger compared to the latter. Shahar et al. (2010) also included several potential mediators in one model and showed that changes in mindfulness and changes in brooding both

mediated the effect of MBCT on depression severity, and that they did so to the same extent.

A closer look at the aspect of temporality identified three categories of studies. First of all, there were 12 studies that assessed mediator(s) and outcome more than twice during treatment, and were therefore able to make some kind of judgment about the temporal order of change (e.g. DeRubeis et al., 1990; Fledderus et al., 2013; Jacobs et al., 2009; Kwon & Oei, 2003; Warmerdam et al., 2010). Two of these twelve studies even assessed mediators and outcome on a session-by-session basis (Forman et al., 2012; Ryba et al., 2014). The second group consisted of studies that only included pre- and post-treatment assessments. By assessing processes and outcomes only at pre- and post-treatment one can say that change in a mediator indeed correlates with, explains a certain amount of variance, or predicts change in outcome, but not whether one process precedes the other. For example, Quilty, McBride, and Bagby (2008) found in their study that a decrease in dysfunctional attitudes was associated with a decrease in depression severity in CBT. This is in line with cognitive theory of depression. However, no conclusions about temporality could be drawn because mediators and outcome measures were only measured twice at the same assessments. Similarly, the fact that Allart-van Dam et al. (2003) found that changes in depressive cognition and self-esteem were significant mediators of depressive symptoms following a coping with depression course, is of less value because they only used two assessment points. Other examples can be found in Table 1. A third category consisted of studies that did include more than two assessment points, but not within the active phase of treatment. For example, Kuyken et al. (2010), included a total of three assessment points, but one of them was at 15 month follow-up, leaving only 2 assessments during treatment (baseline and post-treatment). A similar approach was used by Toth et al. (2013). Even though this is very informative regarding to the knowledge on mediators of sustained treatment effects, it will not help to reveal mechanisms during treatment. Lastly, none of the identified studies used an approach in which the proposed mediator was experimentally manipulated.

### 3.2.1. The criteria in concert

Since satisfaction of each criterion increases the strength of the argument for the operation of a mediator, further interpretation of findings should be based on concerted action between these criteria. We therefore also looked at the total number of criteria met by each study. An overview is given in Fig. 1. As can be seen in the figure, not one study meets all criteria.

Four studies scored 5 out of 6 and seem to be the most promising with regard to meeting the various criteria. Forman et al. (2012) examined the mediating role of theorized mechanisms in ACT and CT (utilization of cognitive acceptance vs. change, utilization of affective acceptance vs. change, dysfunctional thinking, cognitive defusion and committed action). They found that treatment group moderated the mediating effects of both cognitive and affective changes. More specifically, cognitive techniques facilitated outcome for those receiving CT, whereas utilization of psychological acceptance strategies facilitated

**Table 3**  
Number (%) of studies meeting requirements for process research ( $n = 35$ ).

Requirement	n studies (%)
- RCT, yes, n (%)	26 (74.3)
- Control group, yes, n (%)	27 (77.1)
- Sample size per condition $\geq 40$ , yes, n (%)	23 (65.7)
- Multiple mediators, yes, n (%)	27 (77.1)
- Assessment of temporality, yes, n (%)	12 (34.3)
- Manipulation of mediator/experiment, yes, n (%)	0 (0.0)

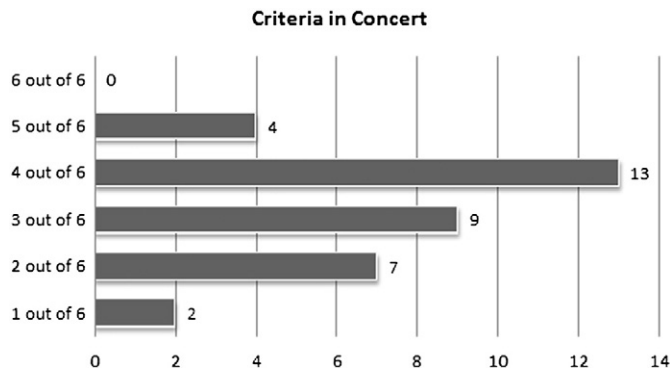


Fig. 1. The criteria in concert: number of studies per number of criteria met.

outcome in ACT. Results of this study are promising since they are obtained in a large RCT ( $n = 174$ ) with repeated assessments (before each session) of multiple mediators and outcomes. It has to be noted however, that they included a mixed sample of patient with anxiety and depression, and did not control for the influence diagnosis. [Stice et al. \(2010\)](#) randomized 341 teens with elevated levels of depression to group CBT, Group Supportive Expressive therapy (SET), Cognitive Behavioural Bibliotherapy or assessment-only control, and examined the mediating role of theorized processes of change of CBT (negative cognitions/pleasant activities) and SET (emotional expression/loneliness). Separate analyses were conducted for each of the active treatments, in which each treatment was contrasted to the non-active control. The results on the Group CBT intervention indicated the presence of a mediator: the treatment reduced depressive symptoms, negative cognitions, and increased pleasant activities. Furthermore, change in these processes predicted change in depression, and intervention effects became weaker when controlling for change in the processes. However, after examination of the sequence of changes, it was found that change in depression occurred before change in the mediator. Therefore it was concluded that changes in theorized processes did not mediate the intervention effects. This illustrates the importance of including the aspect of temporality. A similar (but less strong) pattern was found for SET. [Quilty, Dozois, Lobo, and Bagby \(2014\)](#) examined the temporal dynamics and causal role of cognitive structure and processing in CBT ( $n = 54$ ) vs. pharmacotherapy ( $n = 50$ ) for depression. The authors included multiple mediator measures and outcomes that were assessed at various points before, during and after treatment. Data were analysed using modern statistical methods. In spite of a well-considered design, the evidence for the mediational role of the investigated constructs was weak. Only two out of 14 subscales exhibited (partial) mediation on one of the outcome measures. Effects did not seem to be specific for CBT. [Warmerdam et al. \(2010\)](#) studied the mediating role of dysfunctional attitudes, worry, negative problem orientation, and feelings of control in online CBT and PST for depression. A total of 263 participants were randomly allocated to one of the two active treatment conditions, or to a waiting-list condition. Measures were taken at three points over the course of treatment. Similarly to [Stice et al. \(2010\)](#) active conditions were contrasted to the WLC condition. Warmerdam and colleagues found support for the notion that the mechanisms of interest played a mediating role in both CBT as well as PST. Multiple mediation analysis showed that – in both groups – reduction in depression was mostly explained by improvement in worrying, perceived control and a negative problem orientation. However, since most of the total improvement had already taken place before the mid-treatment assessment (5 months) – leaving only little room for later change – the authors were not able to differentiate between cause and effect. So in spite of a suitable repeated measures design, and promising results, they were not able to discern the temporal relation necessary to identify a mechanism of change.

In addition, 13 studies met 4 out of 6 criteria. As can be seen in [Table 1](#), the combination of criteria that were met was different for the various studies. Apart from the manipulation criterion, many studies did not meet the requirement of temporality. The remaining 18 studies met <4 criteria. Remarkably, the two studies meeting only one criterion ([Kwon & Oei, 2003](#); [Ryba et al., 2014](#)), met the temporality criterion, which was lacking in many of the other studies.

The question that remains is what is left of the evidence when only taking 'high quality' studies into consideration (i.e. studies that meet  $\geq 4$  criteria). Results of studies meeting 4 or more criteria ( $n = 17$ ) are displayed in the right panel of [Table 2](#). As can be seen in the table, the relative percentage of studies finding significant mediators is slightly higher than when all studies are taken into account (68% vs 61%). However, results should be interpreted with caution given the relatively small number of studies per potential mechanism.

#### 4. Discussion

We provided a systematic empirical update and critical evaluation of the current status of research aimed at identifying a variety of psychological mediators in various forms of psychotherapy for depression. With this we wanted to learn more about the magnitude and relevance of the existing body of research and map out necessities for future studies. We summarized study characteristics and results of 35 relevant empirical studies that were identified in a systematic literature search, and discussed the extent to which these studies meet several important requirements for mechanism research. The selected studies examined a total of 39 potential mediators in 12 different treatment modalities. Conclusions about the mediational role of the various constructs that were examined across studies were mixed, potentially due to a large variation in research questions, methodology and quality of studies. However, despite this variation, several processes (e.g. dysfunctional attitudes, negative (automatic) thoughts, rumination, worry and mindfulness skills) were associated with change in the majority of studies reviewed, and therefore warrant further examination. In doing this, it would be important to also take the specificity-hypothesis into account. Not so much as a requirement for mediators, but in order to broaden our overall knowledge about the processes associated with therapeutic change. Studies with a non-active control group showed relatively more significant mediators than studies with an active control group. None of the identified studies met all requirements for tests of treatment mediation, mainly because studies were unable to assess the temporal relationship between change in the mediator and change in outcome, and because none of the studies used an approach in which the proposed mediator was experimentally manipulated. Of course, one can question the prominence of this latter criterion, as the external validity of experiments that manipulate a proposed mechanism in isolation, keeping everything else constant, might be limited.

When comparing our findings to those of previous reviews in the field (e.g. [Garratt et al., 2007](#); [Johansson & Høglend, 2007](#)), it can be concluded that some advances have been made in theoretical consensus about necessities for this type of research, and in the degree of sophistication that researchers bring to research on mediators. More and more attention is paid to the aspect of temporality, sample size, and the inclusion of multiple processes in one study. Nevertheless, the empirical state of affairs has only shown little progress in the past decade. Research is still heterogeneous and often unsatisfactory in methodological regard. Probably the biggest challenge in research aimed at identifying mediators is demonstrating the causal relation between change in the mediator and change in depression severity. As a result, after more than three decades of process research focused on depression treatment, there is still no clear-cut empirical explanation for psychotherapeutic change.

Demonstrating causality is difficult though, even in studies that are designed to explain therapeutic change in terms of causal processes. First of all, determining the best timing and spacing of observations to capture the critical point of change is a difficult and delicate matter,

especially when there is no prior information available about the speed and shape of change. One needs to balance the most optimal study design, with the burden for patients, and the risk of measurement artefacts when making too many demands for data (Longwell & Truax, 2005). Furthermore, research designs are often based on the assumption that change is gradual and linear. However, various studies have shown that change often happens sudden, rather than gradually over the course of treatment (see review of Aderka, Nickerson, Bøe, & Hofmann, 2011 for more details). If therapeutic change indeed occurs suddenly (e.g. the ‘aha-experience’) it might be very difficult to capture this moment, let alone to assess the temporal relation between change in the mechanism and change in symptoms.

Research aimed at identifying the active ingredients of psychotherapy for depression would benefit from a further refinement of research methods to disentangle mechanisms of change. Table 4 gives an overview of several recommendations for future research. In short, future studies should focus on establishing a more fine-grained analysis of the exact shape of change. Studies should include multiple measures of potential (specific and non-specific) process measures and outcomes in well-planned temporal research designs paying special attention to the timing of assessments and within-patient variances. This is not only relevant in the light of examining the causal relation between change in the mediator and change in outcome, but could also provide more insight in the differential patterns of change of two treatments that overall have comparable effects. Experience Sampling Methods (ESM) might be promising in this regard. With regard to the choice of mediator variables it is important to examine the role of both theorized (specific and non-specific) processes, as well as of processes that theoretically might not mediate the relation between treatment and outcome since this can serve as an important tool to further examine whether treatments work for the hypothesized reasons, or due to other processes. Furthermore, researchers should invest in the development and evaluation of mediator measures. In particular, fundamental research on the validity of process measures should progress. In addition, it is important that researchers use sophisticated statistical methods for the analysis of change and pay attention to the potential

influence of the choice of the contrast group. Moreover, apart from traditional designs to examine processes of change, alternative designs – including e.g. experimental manipulations, component analyses, and Sequential Multiple Assignment Randomized Trials (SMART) designs – should be considered as well. After the identification of processes that are a linking pin between treatment and outcome, further analyses should examine whether these processes play a role in only one treatment, or are relevant for other treatments as well. In doing all of this, it is important that researchers invest in the development of a uniform research language, and standardized assessment- and research protocols. This will make it easier to compare results across studies, and integrate findings into broader knowledge.

Furthermore, identifying and understanding mediators relies on theory about mechanisms of change. Statistical tests of mediation are tools, silent as to content, and without theory we cannot answer the questions that we are still confronted with despite multiple decades of research. Without theory, we do not know which mechanisms might play a role and should be tested. Theories on mechanisms of change do exist, but often do not specifically account for the interplay between multiple (specific and non-specific) processes. Furthermore, little progress has been made during the last decades on the theoretical level: basically, we are still testing the same mechanisms that were proposed 20 years ago. It is rather disappointing that almost two decades after these points were raised (e.g. Kazdin, 1999; Kurtines & Silverman, 1999) we see very little progress in the field. Therefore, apart from advances in research methods, the field urgently needs further development of theories of therapeutic change. When constructing and evaluating theoretical models of change, it would be useful to not only look at the theoretical mediators of a particular treatment, but also to consider how other treatments would be expected to affect these mediators and how the mediators would be expected to affect the outcome.

However, even with well-considered theoretical frameworks and optimal research designs, explaining psychotherapeutic change remains a challenge. Psychotherapy for depression is a complex, multi-dimensional phenomenon that might work through interplay of multiple mechanisms on several levels (physiological, affective, behavioural and cognitive aspects). Psychotherapeutic change might therefore consist of a complicated chain of events on these different levels. In addition, it is possible that active components of therapy and their associated mechanisms of change work differently at different points in time and differ between (subgroups of) depressed patients. With this in mind, psychotherapeutic change might even be too complex to be explained in relatively simple causal models of psychological change. If this is the case, psychological research designs might never be able to explain all aspects of therapeutic change. However, it would make it a lot easier to understand why research so far has not led to clear-cut empirical explanations of how psychotherapy for depression works.

**Table 4**  
Recommendations for future research aimed at identifying mediators.

#### Potential mediators

- Invest in further development of theories of therapeutic change.
- Use theory to select multiple specific and non-specific potential mediators.
- Include processes that would falsify the theory as well.
- Provide a clear description of each process that is included.
- Use mediator measures that have shown to be psychometrically valid.
- Invest in the evaluation and further development of (implicit) mediator measures.
- Use multiple sources of information (self-report, clinician rated, independent rater, and behavioural and biological measurements).

#### Study design

- (Multi-site) RCTs with a control group, preferably also including a non-active arm.
- Include a fine grained temporal design, especially in the early phase of treatment.
- Justify the timing and spacing of observations
- Invest in development of alternative research designs including experimental manipulations and component analyses.

#### Analyses

- Use modern statistical analysis methods to examine change over time and mediation.
- Focus on statistical significance but also on the clinical meaning of changes.
- Examine the unique influence of each mediator, as well as their interactions.
- Perform analysis on group level; but also examine subgroups, and individual trajectories.

#### Reporting

- Invest in 1 research language and standard guidelines for reporting mechanisms.
- Replicate studies and publish negative data as well.

#### Appendix A. Key-term scheme for database search

‘Psychotherapy’, ‘Psychotherapies’, ‘Psychological Treatment(s)/ Intervention(s)’, ‘Interpersonal (Psycho)therapy’, ‘(Mindfulness-based) Cognitive (Behavio(u)ral) Therapy’, ‘Psychodynamic/analytic Therapy’, ‘Client-Centered Therapy’, ‘Behavio(u)ral Activation’, ‘Acceptance Commitment Therapy’, ‘Mechanisms of Change/Action’, ‘Working Mechanisms (of psychotherapy)’, ‘Processes of therapy’, ‘Process Research’, ‘Change’, ‘Mediation’, ‘Mediator’, ‘Mediating effects’, ‘Depression’, ‘Major Depressive Disorder’, ‘Dysthymia’, ‘Dysthymic Disorder’

#### Appendix B. In & exclusion criteria

- Published in English in Peer-reviewed Journal
- Empirical Research report (no review/theoretical paper/commentary)

- Focus = Psychological mechanisms of treatment for Depression
- Population = Diagnosis/Symptoms of Depression
- Intervention = (Evidence-based) psychotherapy
- Including clinical outcome measure for depression
- Performing Statistical Mediation analysis

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