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HONORARY PAPER

Major developments in methods addressing for whom psychotherapy may work and why

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Abstract

Significant progress has been achieved in the last decades in studying two central questions in psychotherapy research: what treatment works for which patient and why does treatment work. This paper delineates central developments in the methods used to study each of these questions. Through targeted examples, the paper discusses several phenomena and trends in psychotherapy research. Regarding the question of what works for whom, the discussion focuses on the progress from the search for one moderator to guide clinical decision-making to the search for a set of such moderators and their interactive effects, to best answer this question. To answer the question why treatment is effective, the paper reviews the progress from a single snapshot of a process variable to approaching causality, that is, temporal relationships, higher dependability, and closer attention to the dynamics of change in process variables. Finally, methodological developments made it possible to combine these two questions so as to better capture the richness and complexity of therapeutic work. Two central products of this integration are discussed and demonstrated through the case of the working alliance.

Keywords: psychotherapy research; process–outcome research; moderators; process variables; personalized treatment; working alliance

Clinical or methodological significance of this article: Progress achieved in research regarding the methods used to examine which treatments work for which patients and why is reviewed, and some of the most promising paths toward personalized treatment integrating research on these two questions are suggested.

1. Introduction

Psychotherapy research has changed dramatically since its inception, at the beginning of the twentieth century (Norcross, VandenBos, & Freedheim, 2011). It has reached the point where it actually supplements the theory-based activities of therapists and serves as basis for treatment guidelines and best practice statements, alongside clinical experience (Lambert, 2013). More than ever, psychotherapy research begins to realize its potential to improve the lives of people worldwide. Historically, psychotherapy research has focused mainly on *outcome research*, examining the efficacy or effectiveness of a particular therapy. Outcome research has produced empirical findings on effective treatments for many forms of mental health disorders (Lambert, 2013).

These studies generally suggest that at the sample level, ignoring individual differences, many treatments are more effective than receiving no treatment. Over the years, the number of psychotherapy approaches has expanded dramatically, each new approach sharing some commonalities with others, while making its unique contribution. This development has stressed the need to understand what works for whom, and whether, similarly effective therapies have identical or distinct mechanisms of change. New methods that emerged in the last decades have dramatically enriched the research on *why* and *for whom*, bringing it closer to the complexity of human life.

Initial interest in questions of *why* and *for whom* can be traced back to the early years of psychotherapy.

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Freud and his followers sought to identify patients who were suitable for psychoanalysis (“analysable,” 1905/2000). Rogers’s research groups used sound recordings of sessions (1942) and learning-based approaches to examine the association between therapists’ interventions and treatment response (for a historical review, see Lambert, Garfield, & Bergin, 2004). It is in the last 70 years that outcome research has become largely complemented by extensive research on these two questions. With the development of advanced study designs and methods of inquiry, psychotherapy research has become increasingly personalized, interested in the best practice that may be adapted to a subset of individuals who share similar characteristics. This development goes hand in hand with movements towards more cost-effective treatments, influenced by demands from the reimbursement systems. The present paper delineates two research paths, each focusing on one of these two questions, which for decades have developed separately, and in recent years, started to converge. Rather than provide an exhaustive review of the literature, the paper illustrates, through targeted examples, several phenomena and trends taking place in psychotherapy research.

2. What Works for Whom? Towards the Best Treatment for Subpopulations of Patients with Similar Characteristics

The literature describes several evidence-based treatments for each mental health disorder, such as depression, which are not significantly different from one another in their efficacy and are all more effective than controls (Wampold & Imel, 2015). Decades of empirical research have supported the finding that treatments based on substantially different theoretical assumptions can produce similar patterns of change. Does this mean that all treatments are likely to be similarly effective for all patients? The literature suggests that this is not the case. Although *at the sample level*, no evidence-based treatment appears to be consistently more effective than another, *at the individual patient level*, one treatment fits best (Cohen & DeRubeis, 2018). Researchers argue that it is crucial to custom-tailor the treatment to the individual patient at any given time (Fisher & Boswell, 2016). Clinicians also argue that it is important to tailor psychotherapy to individual patients’ needs and characteristics (Kazdin, 2008). Rather than adjusting themselves to the therapist’s templates and agenda, patients would prefer it if the therapist adjusted the treatment to their personal characteristics and needs (Maslow, 1966). Although there is general agreement between researchers, clinicians,

and patients about the importance of personalized treatment, only in recent decades has research started to catch up with this concept.

The need to tailor treatment to the individual patient and not only to the patient’s general diagnosis rests on the evidence that there is great diversity within diagnostic categories. There are, for example, more than 32,000 combinations of symptoms that meet the criteria for conduct disorder (Kazdin, 2008). The same is true for other disorders, such as agoraphobia, where two individuals can have the same diagnosis without sharing a single symptom. It is not surprising, therefore, that after completing an evidence-based, diagnosis-specific treatment for their mental health disorders, a substantial portion of patients still retain their diagnosis and suffer from many adverse symptoms. Clearly, to improve treatment, it is necessary to determine the conditions that dictate when a treatment is most effective. Therefore, psychotherapy research has become increasingly focused on what works for whom, aiming to develop rules for treatment decision-making and methods to enhance outcomes for individual patients.

This shift from searching for the best diagnosis-specific treatment to searching for treatments that show the best results for a subset of patients within diagnosis is supported by research showing that patient characteristics are a better predictor of treatment outcome than is the putative effect of a particular type of intervention (e.g., studies on the TDCRP project: Ablon & Jones, 1999; Blatt, Quinlan, Pilkonis, & Shea, 1995; Zuroff et al., 2000). Identifying the premorbid clinical and personality characteristics that predict differential outcomes for different treatment conditions can help guide clinicians in their treatment choices and adapt treatments to the needs of different patients (Clarkin & Levy, 2004). With the shift from focus on diagnosis-specific to patient-specific treatment, psychotherapy research and practice have started moving closer to each other, with a view to intersecting at a junction called “personalized treatment.”

2.1. The Best Treatment for a Subpopulation of Patients: Searching for the Single Best Moderator of Treatment Outcome

Decades of research suggest that some subpopulations of patients may benefit more from one treatment than other subpopulations. What works for whom is usually investigated using moderators, namely, variables that describe for whom and under which conditions a given intervention is most strongly related to better outcomes. Moderators are

often referred to as *prescriptive variables* because they predict different outcomes depending on the type of treatment, as opposed to *prognostic variables* that predict treatment outcome irrespective of the type of treatment (Hollon & Beck, 1986). Treatment moderators (statistically, interaction effects) can provide valuable information to guide decision-making by clinicians, match patients with treatments, and improve clinical outcomes (Kazdin, 2007; Kraemer, Wilson, Fairburn, & Agras, 2002), progressing towards personalized treatment.

Studies focusing on a single moderator produced important results, revealing comorbidity as an important factor on which treatment decision may be based, rather than being ignored. For example, cognitive behavioral therapy (CBT) was found to be more effective in depressed patients with elevated levels of avoidant personality disorder symptoms, whereas Interpersonal Therapy was more effective in patients with elevated levels of obsessive-compulsive personality disorder symptoms (Barber & Muenz, 1996). Over the years, many variables were identified as potential single moderators, including genes. Other examples are patient's pretreatment interpersonal functioning (Dolev & Zilcha-Mano, 2018), attachment style (McBride, Atkinson, Quilty, & Bagby, 2006; Newman, Castonguay, Jacobson, & Moore, 2015), expectation from treatment (Constantino, 2012) and from the relationship with the therapists (Zilcha-Mano, Keefe, et al., 2016), variation in the promoter region of the serotonin transporter gene (i.e., 5-HTTLPR; Eley et al., 2012), and more. Although the search for a single factor to explain variability in patient's response to treatment helped identify important moderators, as documented in more than a dozen reviews (e.g., Consoli, Beutler, & Bongar, 2016; Norcross & Wampold, 2011), it produced little consistency and many mixed results across studies (for review, see Bohart & Wade, 2013; Clarkin & Levy, 2004), where few consistent single moderators can be detected.

The mixed results reflect a flaw in the methods seeking to identify a single best moderator that predicts outcome: it relies on the assumption that a single variable is adequate to inform clinical decisions on treatment assignment. The search for a single moderator treats all other variables as merely noise. Personalized treatment assumes the opposite, that variability in treatment outcomes between individual patients is of great importance and that identifying finer-grained individual differences, based on more than one moderator, can produce actionable, prescriptive information about which interventions are best suited for which patients. It is reasonable to assume that no single factor is as important to

treatment outcome as a set of interrelated ones (Norcross & Wampold, 2011). Human beings are complex, multifaceted entities. Focusing on a single moderator at a time is a reductionist approach that may be responsible for the inconsistent findings across studies. Traditional approaches to subgroup analysis that test each moderating factor as a separate hypothesis can lead to erroneous conclusions because of problems related to multiple comparisons (inflated type I errors), model misspecification, and multicollinearity. Findings may also be affected by publication bias, because statistically significant moderators have better chances of being reported.

2.2. The Best Treatment for a Subpopulation of Patients: Searching for a Set of Moderators

As we move away from the single moderator approach, we are faced with an overwhelming number of patient, therapist, and setting factors to consider. It is impossible to adequately test all relevant variables one by one, either in a *post hoc* analysis or in planned prospective studies. The solution lies in novel, systematic approaches to subgroup analysis. In the last decades, there has been a growing recognition that expertly conducted hypothesis-generating activities are needed to produce stronger hypotheses for the next generation of hypothesis-testing studies and to provide the background information necessary for designing powerful randomized controlled trials (RCTs) (Kraemer et al., 2002). Better tools for maximizing treatment efficacy for individuals are emerging, showing differential effects for *subgroups of patients*, where the main outcome analyses of the same data failed to find any differences between conditions *at the sample level*. Various types of novel methods have all shown that when no single moderator can explain sufficient variance in treatment outcome to guide the choice of treatment, a set of variables can do so quite well. Although the value of the new methods still awaits validation in prospective research that tests the benefit of assigning patients to their expected optimal treatment (Cohen & DeRubeis, 2018), their revolutionary effect on the study of moderators cannot be overestimated.

One such method is to collapse several moderators into one factor (Wallace, Frank, & Kraemer, 2013), based on the rationale that it is necessary to combine weak individual measures to create a single strong moderator to predict differential outcome across treatments. For example, Wallace et al. (2013) collapsed eight potential baseline moderators from an RCT comparing acute-phase interpersonal psychotherapy vs. pharmacotherapy for major

depressive disorder (MDD) into a single index. No significant differences had been found between treatment conditions for the average patient. With this method, the number of moderators was reduced from 32 to 8. Weights were calculated for each of the eight moderators to form a combined moderator score, which has been shown to discriminate between the outcomes of various treatment options. This analytic strategy is relevant also to genetic studies. For example, cumulative genetic score analysis, which aggregates genetic effects across polymorphisms and/or genes (Beevers & McGeary, 2012), combines contributions from multiple polymorphisms into a single parameter to increase the explained variance. Another important promising method is the nearest neighbour approach, in which the response curves of individuals who are most similar to a new patient and who have already been treated are used to derive predictions for individual new patients (Lutz et al., 2005; for a review, see Rubel & Lutz, 2017).

Recently, DeRubeis, Cohen, et al. (2014) proposed a method for identifying moderators that leverages the power of a set of moderators to predict the response of each individual to each treatment option. Comparison of the predictions for each treatment produces a Personalized Advantage Index (PAI), which identifies the treatment expected to result in the best outcome for a given patient, and provides a quantitative estimate of the predicted advantage (DeRubeis, Gelfand, German, Fournier, & Forand, 2014; Huibers et al., 2015). In one implementation of the PAI method, nine pretreatment variables that predicted or moderated treatment response in a full sample of patients receiving treatment for MDD were combined through linear multiple regression models to estimate individual patients' advantage if they are assigned to the optimal vs. non-optimal treatment. Based on the PAI, 60% of patients were forecast to have a clinically significant advantage if assigned to their optimal treatment. Using the PAI, Zilcha-Mano, Keefe, et al. (2016) found that when patients were divided into those randomly assigned to their optimal treatment and those assigned to their least-optimal treatment, dropout rates in the optimal treatment (24.4%) were significantly lower than those in the least-optimal treatment (47.4%).

It is possible to differentiate between two aims pursued by advanced, machine-learning approaches in the search for moderators of treatment efficacy. The first is to produce the best prediction for the individual patient. For example, using a random forest algorithm, it is possible to search for the optimal treatment for a given patient based on the patient's pretreatment characteristics. Such methods can produce a "black box" algorithm, into which the

clinician feeds all the required baseline information about the patient and obtains the expected optimal assignment for that patient. The method of Wallace et al. (2013), described above, is an excellent example of this aim: the results reflect the optimal assignment for the patient based on the integration of the patient's unique combination of pretreatment characteristics, but they do not provide a meaningful description of how the black box algorithms made a given assignment decision.

The second aim is to further delineate the ways in which different moderators interact to affect treatment efficacy for given subpopulations of patients. Contrary to the black box approach, with this method, the clinician actually can see a decision tree of the variables predicting that a certain treatment will be optimal for a given patient. For example, in one of our studies, we found that patients with better expectations regarding the alliance before the start of treatment were at lower risk of dropping out from supportive-expressive treatment than from dropping out of antidepressant treatment (Zilcha-Mano, Keefe, et al., 2016). Another example of a decision tree with two splits, from the field of geriatric psychiatry, shows that antidepressant citalopram was more effective than placebo among the elderly only when the patient had less than 12 years of education and at the same time suffered from MDD for more than 3.47 years (Zilcha-Mano, Roose, Brown, & Rutherford, 2018). More splits can yield more nuanced differentiation between patients, based on additional baseline characteristics. Such an approach may help explain why each variable is selected and pave the way for future studies searching for the mechanisms underlying these moderating effects. For example, some of the questions that may be answered in this way are: Why do positive expectations about the relationship with the therapist help a patient stick with the psychotherapeutic treatment even in difficult times, when the patient may not do so in a psychopharmacological treatment? What is unique about the subset of elderly patients who are less educated and suffer from depression for a longer duration? It is also possible to integrate the two approaches into a third one by selecting the strongest moderators using a black box approach, like the random forest algorithm, then delineating the interactions between variables using decision-tree approaches, such as model-based partitioning for condition assignment (Zilcha-Mano et al., 2018; Zilcha-Mano, Keefe, et al., 2016).

In future studies of moderators in psychotherapy, greater efforts may be invested in replicability and in integrating advanced analytic methods with theoretical conceptualizations and with clinical experience pointing to who may benefit most from each

treatment. Integrating theory- and data-driven approaches, potential moderators can be first identified based on theory and previous empirical findings, then tested together with the potential interacting effects between them, using powerful machine-learning approaches. The richness of the new methods applied to answer the question what works for whom, should bring us closer to, rather than farther away from clinical knowledge and understanding. Additionally, applying the new methods to answer the question what works for whom to within-patient decision-making, rather than only to between-patients treatment assignment, may make research on moderators even more relevant for clinical work. For example, the new methods can be used to examine which technique is most effective for the individual patient in case of a confrontational rupture between patient and therapist. Data on between-patients characteristics (e.g., Did the patient seek treatment because of interpersonal problems? Is the patient always too withdrawn, so that being confrontational is a good sign?) as well as on within-patient data (e.g., Has the patient been making any progress in treatment? What types of alliance trajectories are evident so far?) can serve as predictors in models of within-patient decision-making for the techniques to be used at the next session or even the next talking turn within a session.

3. Why Is Treatment Effective and How Does It Work?

What makes people feel better following psychotherapy? For decades, theoreticians and researchers sought to understand the processes by which psychotherapy achieves its results, garnering important knowledge. Advances in recent decades in the study design and in the methods used to examine the process of change in psychotherapy facilitated even further the progress in the investigation of the process by which treatments produce change and the factors involved in these processes (Kazdin, 2007; Kraemer et al., 2002). A better understanding of what makes change happen in psychotherapy can help us devise and deliver better treatments, intensify and refine active therapeutic components, and discard inactive or redundant ones.

Well-designed RCTs have been conducted to determine whether a given hypothesized active ingredient has a causal effect on the outcome. RCTs comparing treatment conditions can establish a causal relation between an intervention and therapeutic change. Yet demonstrating a causal relation does not necessarily provide the construct required to explain why the relation was obtained (Kazdin,

2008). To achieve this, research focusing on process variables is needed. Different types of change-related constructs have been the focus of process research throughout the decades: mechanisms, mediators, process mechanisms, active ingredients, and others. Much has been written about the differences and the relations between them (e.g., Kazdin, 2007; Kraemer et al., 2002). It is not the objective of the present paper to clarify these distinctions, but rather to argue that several important developments in the field are relevant to most, if not all, of them. Therefore, the paper follows the broad concept of “process variables” (Crits-Christoph, Gibbons, & Mukherjee, 2013), according to which, mediation models, inherently based on experimental designs (e.g., random assignment), are only one way of examining process variables. It is important not to confuse process variables with causal influences: most findings collected over decades of process research are not based on random assignment, and the direction of influence as well as the roles of potential third variables are not always clear. Nevertheless, developments in the methods used to study process variables, such as the test of correct temporal relationships between the process variable and treatment outcome, may at times be more important than studying mediation models, which do not adequately account for the temporal relationship. As noted before, accounting for temporal order even with respect to a single link in the mediation chain may provide stronger evidence in support of a causal hypothesis than a test of mediation models in which the temporal order has not been accounted for (Lorenzo-Luaces, German, & DeRubeis, 2015).

3.1. A Single Session Process Variable as a Predictor of Treatment Outcome

Since the 1950s, process research has expanded exponentially (Orlinsky, Ronnestad, & Willutzki, 2004), much of it examining the ability of process variables, estimated based on a single session, to predict outcome from pre- to post-treatment. A range of studies found that technique adherence and competence, evaluated at a single session (mostly early in treatment), can predict change in several types of outcomes from pre- to post-treatment, for example: adherence to CBT techniques (e.g., Ablon & Jones, 2002); adherence to concrete cognitive therapy (CT) techniques (Feeley, DeRubeis, & Gelfand, 1999); interventions focused on exploration of early experiences with parents (Hayes, Castonguay, & Goldfried, 1996); use of cognitive behavioural and psychodynamic techniques, as

reported by the patient (DeFife, Hilsenroth, & Gold, 2008); and adherence to psychodynamic-interpersonal techniques (Slavin-Mulford, Hilsenroth, Weinberger, & Gold, 2011), to name only a few. These findings were not consistent across studies, however, and in most single studies, the findings were more complicated than a simple strong association between techniques and outcome (Crits-Christoph et al., 2013; Lorenzo-Luaces et al., 2015; Webb, DeRubeis, & Barber, 2010).

3.2. Towards Causality: From a Single Snapshot to a Frequent Assessment of Process Variables

Despite many valuable developments over the decades in the study of process variables (more adequate training of raters, improved inter-judge reliability, better control over patient and therapist variability, examination of several perspectives of the same process construct, reduced association inflation due to shared method variance, etc.), the key breakthrough in the field was the progress towards serial assessment of process data. Session-by-session data measurement of process variables has become the state of the art for data collection, making it possible to examine the process variables as they develop over the course of treatment. This change in design brings us closer than ever to establishing causal relationships, by letting us: (a) better represent process variables, without being affected by random errors; (b) treat process variables as dynamically changing factors across treatment, rather than fixed entities; and (c) test the appropriate temporal relation between process variables and outcome.

3.2.1. From a single snapshot of a process variable to a dependable measure. It is unlikely that one early session assessment is enough to provide a dependable estimate of the effect of process variables on treatment outcome (Messer, Tishby, & Spillman, 1992). Higher dependability of a measure in psychotherapy research means that the assessment of the measure is based on an adequate sample of sessions, making possible the generalization of the findings based on that measure (Crits-Christoph, Gibbons, Hamilton, Ring-Kurtz, & Gallop, 2011; Cronbach, Rajaratnam, & Gleser, 1963). Reliance on a single session may reduce the ability to estimate the association between process variables and outcome because of the error added to each sampled session. Focusing on alliance as a process variable, Crits-Christoph et al. (2011) have shown that at least four treatment sessions must be aggregated per patient to fully understand the size

of the effect of the alliance as a process variable on the outcome. We do not currently know how many sessions are needed to create dependable measures of other process variables; an empirical examination of this issue is an important task for the future.

Outside of the literature on alliance, several previous studies were not satisfied with the estimation of process variables based on a single session and used aggregated scores across at least several sessions, the number of sessions changing from one study to the next because of lack of empirical evidence concerning the required number for process variables other than alliance. Several studies that used aggregated levels of technique adherence and competence across sessions showed promise in their ability to predict the outcome. For example, such studies used the aggregated level of CT competence across four sessions (Strunk, Brotman, DeRubeis, & Hollon, 2010) or nine sessions (Shaw et al., 1999); aggregated level across sessions of frequencies of interpretation connecting feelings toward persons in the past with feelings towards the therapist (Marziali, 1984); adherence to psychodynamic-interpersonal techniques for seven sessions (Hilsenroth, Ackerman, Blagys, Baity, & Mooney, 2003); and aggregated levels of adherence rating across four sessions (Goldman & Gregory, 2009), to name several of the available studies.

3.2.2. From a single snapshot of a process variable to a dynamically changing process variable. Estimating process variables based on a single session precludes observing both their development across the treatment and the effect of their development on the outcome. Based on a single snapshot, we cannot know whether the estimated level of the process variable is a fixed characteristic of the patient or a feature that has changed during the treatment, presumably as a result of it, and whether or not the process variable develops according to the expectation. At first, researchers started examining process variables at two time points, calculating the change from one to the other. Several studies found that the change scores were significant predictors of outcome, such as early change in hopelessness (Kuyken, 2004), change in attributional style (Seligman et al., 1988), change in dysfunctional attitudes (Quilty, McBride, & Bagby, 2008), and change in compensatory skills (Connolly Gibbons et al., 2009).

But the change in process variables during psychotherapy is not always linear, and the magnitude of change may differ at different phases of treatment. Therefore, in recent decades, researchers began measuring process variables at several time points

during the treatment to capture the dynamics in the change of process variables over the treatment and their effect on the outcome (Hayes, Laurenceau, Feldman, Strauss, & Cardaciotto, 2007). Similarly to trajectories of change in outcome, such as sudden reductions in symptoms (sudden gains) between consecutive sessions (Tang & DeRubeis, 1999), early rapid response (Ilardi & Craighead, 1994), and depression spikes (Hayes et al., 2007), trajectories in process variables also show great promise. For example, the literature focusing on trajectories of alliance development has identified several patterns, such as rupture-resolution (Eubanks-Carter, Gorman, & Muran, 2012) and U-shaped alliance (Gelso & Carter, 1994) showing differential associations with outcomes (Stiles & Goldsmith, 2010).

3.2.3. From an overlap between process variable and outcome to temporal precedence.

DeRubeis and colleagues (DeRubeis & Feeley, 1990; DeRubeis, Brotman, & Gibbons, 2005) and Barber (2009) have stressed the importance of establishing an appropriate temporal relationship between process variables and outcome to rule out reverse causation. Studies have addressed reverse causation by examining the ability of a single session process variable to predict outcome from the single session to post-treatment, often controlling for early change in outcome (until the given single session). Several studies have shown that a single assessment of the process variable significantly predicted subsequent treatment outcome, such as the level of competence in delivering psychodynamic techniques (Barber, Crits-Christoph, & Luborsky, 1996), adherence in delivering CT technique (DeRubeis & Feeley, 1990; Feeley et al., 1999), competence in delivering CT technique in the early phase of treatment (Strunk et al., 2010), and levels of accuracy in therapist interventions addressing the patient's central interpersonal wish (Crits-Christoph, Gibbons, Temes, Elkin, & Gallop, 2010). Although these studies marked a great progress in the research of process variables, mixed findings remained common (Barber, 2009; Crits-Christoph et al., 2013).

In recent decades, researchers started to collect several time points for each process variable, which made it possible to examine the question whether *changes* in process variables precede changes in outcome. Accumulating findings started to indicate that change in several types of process variables predicted subsequent change in several types of outcomes, for example, it was true in cases of dysfunctional attitudes and hopelessness (DeRubeis

& Feeley, 1990), compensatory skills (Connolly Gibbons et al., 2009), cognitions (Neimeyer & Feixas, 1990; Powers, Thompson, & Gallagher-Thompson, 2008; Shirk, Crisostomo, Jungbluth, & Gudmundsen, 2013), process variables specific to dialectical-behaviour therapy (Neacsiu, Rizvi, & Linehan, 2010), and relational representations (Zilcha-Mano, Chui, et al., 2016).

Recently, researchers started examining whether session-to-session changes in process variables temporally precede session-to-session changes in outcome, achieving a higher resolution of the process of change. For example, accounting for temporal precedence session-to-session early in treatment, Strunk et al. (2010) found that CT competence predicted subsequent change in treatment outcome, and Kivlighan, Multon, and Patton (2000) found that independent judges' ratings of gains in insight at one session were significantly associated with improvements in target complaints at the next session for patients who had received 20 sessions of psychotherapy for relationship problems.

To date, studies have addressed one or at most two of the above three bases for establishing a causal relationship between process variables and outcome: dependability, capturing the dynamic of change across treatment, and establishing correct temporal relationship. Future process studies may address all three within the framework of well-designed RCTs, isolating the process variables that lead to symptom change (Crits-Christoph et al., 2013; Lorenzo-Luaces et al., 2015), using powerful tests such as mediation analyses. Crucial in the design and implementation of future research is the session-by-session assessment of several theoretically relevant process variables. Designs of this type would allow assessing important clinical phenomena like therapist responsiveness (Silberschatz, 2015; Stiles, 2013). For example, examining the interrelation between alliance and supportive techniques based on a single assessment of each, measured at session 5, may lead to the conclusion that supportive techniques are associated with poorer alliance, when in reality the attuned therapist sensed a rupture in the alliance and adequately responded to it using supportive techniques (Wachtel, 2011). The interplay between alliance and supportive techniques, and its effect on theoretically relevant outcome illustrate how in a successful treatment the decline in alliance was followed by the use of supportive techniques, which in turn was followed by an increase in alliance levels. The methods delineated here can be integrated with other important methods (e.g., Greenberg, 2007), progressing towards more precise conceptualizations of process variables with reference to such constructs as therapist responsiveness

(Silberschatz, 2015; Stiles, 2013), yielding a rich understanding of the process of change in psychotherapy.

4. Why Treatments Work, and for Whom, Are Not Necessarily Unrelated Questions

The two most researched questions in psychotherapy, *why* treatment works and *for whom*, have evolved over time mostly as separate entities. In recent decades, the two research questions have started to converge, leading to high-resolution psychotherapy research that can better capture the complexity and richness of the process of therapeutic change for given individuals.

4.1. Moderators Guide the Search for Process Variables

Although they are usually examined separately, moderators and process variables are theoretically closely related because moderators suggest that different processes may be involved for different subpopulations that benefit differently from the intervention (Kazdin, 2007). The fact that a treatment is most effective for a certain subpopulation may help investigate how it works by pointing to processes unique to those who benefit most from it. Moderators identify different subpopulations with different abilities to benefit from a given treatment, highlighting differences in the process variables at work (Kraemer et al., 2002) and guiding the search for process variables that predict treatment outcome for each subpopulation.

For decades, empirical studies of process variables have been conducted almost exclusively with data aggregated across many individuals, masking inter-individual variability in the association between a process variable and outcome (Fisher, 2015; Forand, Huibers, & DeRubeis, 2017). Using aggregated data in the face of such variability has two negative effects. First, in individual studies, powerful process variables may go undetected if they are sought in the aggregated data of subpopulations with different associations between the process variable and outcome, and not in the subpopulation for which they are relevant, as identified based on moderators. Second, replicating findings across studies may be hampered by the use of unspecified samples (with different percentages of representations of each subpopulation), preventing the discovery of consistent process variables across studies. A good example is the meta-analysis by Webb et al. (2010) of the effect of techniques on treatment outcome. The great heterogeneity in findings made it

impossible to reach any firm conclusions. For example, of the two process variables that have received theoretical and empirical support in specific subpopulations, in a group including another mix of subpopulations, only one received support (Feeley et al., 1999 vs. Castonguay, Goldfried, Wiser, Raue, & Hayes, 1996; for review, see Crits-Christoph et al., 2013). It is, therefore, best to examine the effect of process variables within the subpopulations for which they are expected to be relevant, as indicated by moderation analysis. One way to accomplish this is to use moderated mediation models (Muller, Judd, & Yzerbyt, 2005), in which the mediating process that intervenes between the treatment and the outcome is different for different levels of the moderator, such as specific subpopulations grouped according to the trait-like characteristic of the patient.

It makes no sense to seek a process variable to explain the effect of treatment in a subpopulation in which moderator studies showed no effectiveness for that treatment. A process variable that may not be related to outcome at the whole cohort level (if we ignore individual differences) may have a significant strong effect on treatment outcome for a specific subpopulation of patients who share similar characteristics. For example, if moderator studies reveal that a given treatment for MDD is effective for patients with personality disorders but not for others, it makes sense to seek the effect of techniques (and other process variables specific for that treatment) on the outcome in the subpopulation of patients with personality disorders. In this way, comorbidity becomes an important factor to consider, rather than ignore, when examining process variables.

It follows that the best studies to evaluate process variables are those designed for this purpose from the outset, rather than that derived from data collected for a high-quality study of treatment effectiveness. Achieving good integration of the two questions begins at the planning stage. To examine a given process variable that is theorized to be at the basis of a certain intervention, we must recruit the subpopulation that shows the strongest ability to benefit from the intervention. Similarly, to compare two process variables, one for each of two distinct treatment conditions, we must recruit two subpopulations, each benefitting most from one of the two interventions according to the results of moderation analyses. This reduces the undesirable heterogeneity of the effect of the process variable on the outcome by focusing only on the relevant subpopulations that are expected to benefit from the treatment.¹ It also enables researchers to focus their efforts on recruiting sufficient patients to achieve highly desirable variability within the process variables. In other words, if

researchers can focus only on subpopulations for which the correlation between a given process variable and outcome is predicted to be high based on previous findings, they can achieve sufficient variability in the process variable. Consider a study with a budget for recruiting 150 patients, half for each of two treatment conditions. Without focusing on a sample known to benefit from the intervention, only a portion of participants may actually belong to the relevant population that benefits from it (e.g., 60% for each condition results in a relevant sample size of $n = 45$ in each), making it less likely to achieve the desired greater variability in the process variable in this small sample. But if the entire sample in each condition belongs to each relevant subpopulation ($n = 75$), it is more likely to achieve the desired greater variability in the process variable in that larger sample.

As illustrated by DeRubeis, Gelfand, et al. (2014), having sufficient variability among patients in the levels of process variables is crucial for identifying the effects of the process variable on treatment outcome. When focusing only on the relevant subpopulation, there is a better chance that a greater range in the process variable is found because the *relevant* sample size is larger. In this way, the undesirable variability (in the relationship between the process variable and outcome, resulting from seeking the process variables in irrelevant subpopulations) is washed out, and a desirable variability is introduced, achieving sufficient variability in the process variable for the subpopulations in which it should be tested.²

In addition to increasing the relevant sample size and, therefore, the chances of detecting process variables, the integration of research on moderators with that on process variables has other important implications. The first one is a clinical implication that advances psychotherapy towards personalized treatment. Integrating the two fields of research can help clinicians eschew unnecessary or irrelevant therapeutic elements and focus on more efficient treatment delivery, adapted to the individual patient. If a process variable that is most likely to stimulate change for an individual is identified, then a corresponding treatment most likely to address that particular process can be chosen. It is the goal of psychotherapy research to identify interventions that are most effective for a given individual, by recognizing the process variables most related to change for that individual. The second implication of the integration of the two fields of research is that it helps identify certain subpopulations within populations with the same diagnosis or within trans-diagnostic populations. Identifying unique process variables specific to given subpopulations of patients may

advance our understanding of the nature of clinical disorders and isolate the differences between subtypes of disorders. For example, different subpopulations of patients with depression show different characteristics and predispositions, and eventually may respond better to certain process variables than to others. The search for process variables that are most relevant for a subpopulation of patients, as identified by known moderators, can also help us understand the risks and protective factors of disorders, such as depression, and produce warning signals before relapse. Certain moderators of treatment efficacy (e.g., baseline levels of emotion regulation, abstract reasoning, problem-solving, attributions) could identify subpopulations benefiting from different process variables (e.g., certain emotional regulation work, particular cognitive processes), which in turn may identify a given subpopulation with a specific disorder (subpopulations within the population of patients suffering from MDD).

4.2. Can the Same Theoretical Construct Answer Both Questions?

It has been argued that it is critical to determine whether a certain patient characteristic operates as a moderator or as a process variable (Clarkin & Levy, 2004). But could the same variable be used for both treatment selection (as a moderator) and also act as a process variable? Conceptually, between-patients variables (trait-like characteristics of each patient or dyad) can serve as moderators, whereas within-patient variables (state-like characteristics of each patient) as process variables (Kraemer et al., 2002). Statistically, the effect of each potential process variable on treatment outcome is the product of the combination of both a between-patients trait-like effect and a within-patient state-like effect of the process variable on treatment outcome (Curran & Bauer, 2011; Wang & Maxwell, 2015). Thus, trait-like and state-like characteristics of the same construct may play different roles in treatment; the former can act as a moderator, the latter as a process variable. For example, Kraemer et al. (2002) has argued that the lack of social support before treatment is not the same variable as change of social support during treatment, and whether one is a moderator has nothing to do with whether the other is a process variable. It follows that when studying the effect of process variables on treatment outcome, we should consider only the state-like elements that are changing in treatment, and their effect on the outcome, and wash out the between-patients trait-like elements.

Progress in clinical trial design to session-by-session assessment makes it possible to disentangle the state-like aspects of a process variable from the trait-like aspects of the same variable (Curran & Bauer, 2011; Wang & Maxwell, 2015), which is essential for isolating the aspects of the variable that can play the role of a process variable. Disentangling the two aspects is critical for understanding the effect of the process variable on the outcome, without it being contaminated by the effects of the between-patients aspects of the variable (Falkenström, Ekeblad, & Holmqvist, 2016; Zilcha-Mano, 2016). Because within-patient and between-patients effects may pull in opposite directions, a powerful process variable may go undetected when the two aspects are not disentangled. For example, the state-like and trait-like aspects of the effect of anxiety on depression were demonstrated to work in opposite directions (Fisher & Boswell, 2016): as a between-patients effect, anxiety was positively associated with depression (patients with higher levels of depression tend to show also higher levels of anxiety), but as a within-patient effect, it was negatively associated with depression (as levels of depression increase at one session, levels of anxiety are likely to decrease in successive ones). When looking for process variables, only the state-like changes in anxiety are of interest.

The role of the within-patient effects is clear: we need to focus only on these aspects when examining processes of change. What, then, is the function of the between-patients effect? The answer to this question depends on the ways in which within- and between-patients effects are disentangled. To the extent that it is possible to assess the between-patients effect in a way that is less contaminated by the process of treatment, it may serve as a moderator (e.g., the patient's trait-like level of attributional style, as assessed before the beginning of treatment). For some constructs, however, this is not possible, and the between-patients effects also reflect the type of treatment and the circumstances under which it is being delivered (e.g., when it is tested at an aggregated level of the potential process variable across treatment). If the between-patients effect cannot be separated from the effect of treatment, as at times it is the case (for example, in the case of alliance, when it makes no sense to examine the process variable before treatment begins), it may serve as a prognostic variable (Hollon & Beck, 1986). In these instances, the between-patients effect may single out those for whom, under the specific circumstances, the given treatment may have the most clinically significant effect.

5. Alliance as an Example of the Integration of the Two Questions

5.1. Delineating Methodological Developments in the Study of the Therapeutic Alliance

There is consistent evidence supporting the ability of only very few variables to act as process variables across studies and to predict treatment outcome with the correct temporal relationship; the clearest example is that of working alliance. Alliance is most commonly defined as the emotional bond established in the therapeutic dyad, and the agreement between patient and therapist concerning therapy goals and the tasks necessary to achieve them (Bordin, 1979; Hatcher & Barends, 2006). The strength of the alliance is one of the most consistent predictors of outcome in psychotherapy, with stronger alliance predicting better therapeutic outcomes (Horvath, Del Re, Flückiger, & Symonds, 2011). In a way, alliance is the exception to not finding significant process variables across studies.

Research on alliance as a process variable followed the historical development described above. Decades of research have shown that alliance assessed at a single time point in treatment (commonly week 3 or 5) predicts change from pre- to post-treatment. Recent advances in study design and statistical analysis produced three important advancements in the research on alliance: (a) determining the need to examine at least 4 sessions to adequately assess the effect of alliance on the outcome (e.g., session 3 alliance scores explained 4.7% of outcome variance, but the average of sessions 3–9 explained 14.7%; Crits-Christoph et al., 2011); (b) identifying distinct trajectories of change in alliance (e.g., rupture-resolution and U-shaped patterns) that show differential association with outcome (e.g., Kivlighan & Shaughnessy, 2000; Stiles & Goldsmith, 2010; Strauss et al., 2006), even when assessed as early as the first four sessions of treatment (Zilcha-Mano & Errázuriz, 2017); and (c) demonstrating temporal precedence (Barber, 2009; Crits-Christoph et al., 2013; Zilcha-Mano, Dinger, McCarthy, & Barber, 2014), even in a session-to-session manner (e.g., Falkenström, Granström, & Holmqvist, 2013; Zilcha-Mano & Errázuriz, 2015).

The question arises whether the integration of the two fields of research is still needed when several process variables, most notably alliance, significantly predict outcome across studies. The answer is affirmative for two reasons. First, other process variables may not show such robust effects as does alliance. Alliance is unique in acting as a common mechanism across subpopulations and treatments, and its effect remains significant even when tested in different

subpopulations of patients (Horvath et al., 2011). Second, although several process variables, like alliance, show a consistent effect on treatment outcome, this effect may not be reliable. Almost all studies on the ability of process variables to predict outcome, including those on alliance, are based on data in which the trait- and state-like elements of the variable are not separated. In this body of research, two different aspects of alliance are treated as if they were one. Similarly to other process variables, alliance can be disentangled into aspects that make it a process variable (its state-like component, which statistically consists of within-patient effects) and its between-patients trait-like aspects, which can be treated best as semi-moderators or prognostic variables (Zilcha-Mano, 2017). The trait-like aspects of alliance (patients' general predisposition or capability to form satisfactory relationships with others, their internal representations of self and others, and expectations from interpersonal relationships) may affect their capacity to form a satisfactory relationship with the therapist, which manifests in a strong alliance and also influences their capacity to benefit from treatment (DeRubeis et al., 2005). Thus, the alliance-outcome association is at least partly due to existing traits of the patients rather than to the interaction with the therapists, therefore the trait-like elements are not the ones that make alliance a process variable. By contrast, the state-like aspects of alliance, which reflect the changes in alliance during treatment (e.g., time-specific strengthening of the alliance) are the aspect that brings into focus the therapeutic nature of alliance, an active ingredient sufficient in itself to bring about therapeutic change, and can serve as a process variable.

Disentangling the two elements of the effect of alliance on treatment outcome is crucial because it may reveal different functions that alliance *as a process variable* plays in different treatments. For example, CBT traditionally emphasizes the trait-like component of alliance, where the patients' general trust that the therapist is acting in their best interest makes it possible to use specific techniques effectively in a collaborative atmosphere (Beck, Rush, Shaw, & Emery, 1979; Castonguay, Constantino, McAleavey, & Goldfried, 2010). By contrast, alliance-focused therapy (AFT) emphasizes the state-like changes in alliance negotiations as a curative process (Safran & Muran, 2000). Disentangling the two elements may elucidate the distinct functions of alliance in different treatments. A recent study examining the effect of alliance on the outcome in a sample of 241 patients receiving either CBT or AFT supports this claim. The study found a significant association between alliance and outcome at the sample level, but the ability of the state-like effect of alliance to predict

outcome was significantly more profound in the AFT than in the CBT condition (Zilcha-Mano, Muran, et al., 2016). Further support comes from a study demonstrating how in conditions that actively draw therapists' attention to the alliance, the effect of the state-like element of alliance on the outcome is stronger (Zilcha-Mano & Errázuriz, 2015). The distinction between the state and trait elements of alliance means that only part of it can be treated as a common mechanism that is shared by most forms of psychotherapy and populations, whereas the other part is unique to certain forms of treatment.

Assessing the aggregated levels, which combine the trait- and state-like elements of the effect of alliance on treatment outcome, may also lead to the false conclusion that alliance is a significant process variable across subpopulations, when in practice this may not be so. When we segregate the state- and trait-like elements, it becomes clear that some subpopulations benefit from the state-like effect of alliance on the outcome and others do not. For example, patients presenting less severe symptoms (Zilcha-Mano & Errázuriz, 2015) or fewer personality problems (Falkenström et al., 2013) may benefit less from changes in the state-like alliance, to the point where the effect of alliance on the outcome is insignificant.

Future studies evaluating the state-like effect of alliance on treatment outcome should focus on the subpopulations that benefit most from alliance as a process variable, as demonstrated by known moderators (see also Lorenzo-Luaces, DeRubeis, & Webb, 2014; Lorenzo-Luaces, et al., 2017). Although these subpopulations are expected to be homogenous in the effect of alliance on the outcome, studies should seek as much variability as possible in the levels of alliance in their samples (DeRubeis, Gelfand, et al., 2014). Studies that are interested in comparing different subpopulations with different levels of state-like effect of alliance on treatment outcome should actively manipulate the effect of alliance on the outcome (e.g., Zilcha-Mano & Errázuriz, 2015; Zilcha-Mano, Muran, et al., 2016). Therefore, a high-quality process study design should make possible the adequate examination of the process variable that is the focus of the study, rather than be based on well-designed efficacy or effectiveness studies.

5.2. Clinical Demonstration Based on the Therapeutic Alliance

To demonstrate the clinical importance of disentangling the between- and within-patient effects of alliance on treatment outcome, I would like to conclude by briefly quoting two letters I received from

two of my patients at the end of their treatments (after obtaining their approval and disguising their personal details). These examples demonstrate how alliance may fulfil distinct roles for different patients. The first patient described how insightful the treatment was, writing that

I found out how time and again I keep doing the same things, which made my life really miserable. What was most helpful for me was to see why I'm doing that. I think this is really what made this therapy so meaningful for me.

The patient also mentioned that from very early in the course of treatment, he felt that I was there for him, and whatever I said (my interpretations) were said not as a criticism but for his benefit. For this patient, the alliance was what made possible the effective use of techniques (interpretation). With a second patient, however, the alliance seemed to be therapeutic on its own. The patient described in her letter how meaningful our relationship was for her. She explained that before treatment she would not believe that anyone could really be for her and with her, that anyone could understand what she called "my scrapes" and accept her for who she was. She mentioned also how ironic it was that her feeling that I loved and appreciated her for who she really was gave her the will and the strength to make changes in her life.

The two examples demonstrate how alliance can serve different roles in different treatments delivered by the same therapist. In the first example, the alliance mainly played the role of enabling the process of effective treatment to happen. In this case, because of the strong alliance the patient was able to form early in the course of treatment, he received my interpretations concerning repetition compulsion patterns as having been for his benefit, and not as criticism. In the second case, the alliance acted mainly as a therapeutic ingredient in and of itself, bringing about therapeutic change. In this second example, a corrective experience occurred between the patient and me, and the patient could feel accepted and loved for who she was, actualizing her unfulfilled wish for a close interpersonal relationship (to borrow a Core Conflictual Relationship Theme term). By actualizing this wish in the therapy room, the therapeutic alliance becomes not only what enables the therapeutic work, but the therapeutic work itself. It is possible to speculate about what made the alliance play these distinct roles in the treatment of the two patients. For example, an early trauma experienced by the second patient but not by the first one may have been a contributing factor.

It is important to stress that although I offer a distinction between the two functions of alliance, often a dialectical interplay takes place between the two distinct forms of influence that the therapeutic alliance exercises over the course of treatment. A closer look at the process of each of the two treatments shows that although a specific role of alliance was more dominant than the other for each of the patients, a dialectical interplay was evident between these two distinctive forms of influence of the alliance. In some of the sessions of the first patient, especially at the beginning of the treatment, the alliance played a therapeutic role in itself, and in some of the sessions of the second patient, especially toward the end of the treatment, the alliance served to enable the patient to benefit from interpretations focusing on interpersonal patterns.

6. Summary

Much progress has been made over the decades in identifying who may benefit most from which intervention and why. The developments reviewed in this paper, translated into policy and practice, hold promise to continue delivering benefits to patients in the short and long terms. Identifying exactly how change occurs in psychotherapy for any individual can help refine personalized therapies and introduce them into community settings through appropriate training of community clinicians. Much work is still ahead on replications and on identifying process variables that are most effective for given subpopulations of patients. New trends in statistical analysis promise to make clinical research more relevant to practice.

The developments reviewed here rely on more complex statistical analyses than have been used in psychotherapy research ever before. On one hand, this addresses previous claims that psychotherapy research reduces human experience to a single variable, fixed in time (Kazdin, 2008). Today we are better able to generalize findings from research to real-world clinical settings. On the other hand, the added complexity makes it more difficult for people who are not experienced or interested in these statistical analyses to follow this type of research. Thus, it is critical to translate the findings into a language relevant to all those who can benefit from it. Finally, although the controversy concerning theory-driven vs. data-driven research in psychotherapy (Kraemer et al., 2002) is an old one, the present paper took for granted the fact that for any finding to affect the lives of millions of people worldwide, it should make sense to both clinicians and patients, regardless of whether or not this rationale was the starting point.

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Notes

- ¹ There is less concern with the restriction of range in process variable levels when examining the association between the process variable and outcome for those that benefit from the treatment, because when the process variable does not improve across treatment, not much within-patient variability exists anyway.
- ² Efforts to increase variability in the process variable and reduce variability in the association between the process variable and outcome may be challenging in certain cases of piecewise association, in which the association may be stronger at specific levels of the process variable.

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