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Combining baseline characteristics to disentangle response differences to disorder-specific versus supportive psychotherapy in patients with persistent depressive disorder

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ABSTRACT

Does the pre-treatment profile of individuals with persistent depressive disorder (PDD) moderate their benefit from disorder-specific Cognitive Behavioral System of Psychotherapy (CBASP) versus supportive psychotherapy (SP)? We investigated this question by analyzing data from a multi-center randomized clinical trial comparing the effectiveness of 48 weeks of CBASP to SP in n = 237 patients with early-onset PDD who were not taking antidepressant medication. We statistically developed an optimal composite moderator as a weighted combination of 13 preselected baseline variables and used it for identifying and characterizing subgroups for which CABSP may be preferable to SP or vice versa. We identified two distinct subgroups: 58.65% of the patients had a better treatment outcome with CBASP, while the remaining 41.35% had a better outcome with SP. At baseline, patients responding more favorably to CBASP were more severely depressed and more likely affected by moderate-to-severe childhood trauma including early emotional, physical, or sexual abuse, as well as emotional or physical neglect. In contrast, patients responding more favorably to SP had a higher pre-treatment global and social functioning level, a higher life quality and more often a recurrent illness pattern without complete remission between the episodes. These findings emphasize the relevance of considering pre-treatment characteristics when selecting between disorder-specific CBASP and SP for treating PDD. The practical implementation of this approach would advance personalized medicine for PDD by supporting mental health practitioners in their selection of the most effective psychotherapy for an individual patient.

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1. Introduction

Approximately one-third of all individuals with a lifetime depressive disorder develop a chronic course that lasts two years or longer (Murphy & Byrne, 2012), also referred to as persistent depressive disorder (PDD). PDD often begins early in life (i.e., before the age of 21), and is commonly associated with childhood trauma, mental comorbidities, as well as a low interpersonal and occupational functioning level (Arnow & Constantino, 2003; Berndt et al., 2000; Klein et al., 1999). A large number of patients with PDD experience side effects, relapses or resistances when treated with antidepressant medication (Arnow & Constantino, 2003; Kocsis, Gelenberg, et al., 2009; Schramm et al., 2017) and many report a preference for psychological over pharmacological treatments (McHugh, Whitton, Peckham, Welge, & Otto, 2013). For these reasons, psychotherapy is an indispensable tool in the treatment of many patients with PDD.

So far, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP; McCullough, 2003) is the only psychotherapy model specially designed for treating PDD. As a manualized cognitive-behavioral-oriented therapy, CBASP uses techniques including situation analysis, interpersonal discrimination exercises, and behavioral skills training to improve the patients' social functioning and recovering from PDD (McCullough, 2003; Neudeck, Walter, & Schoepf, 2012). There is strong empirical evidence of the effectiveness of CBASP for the treatment of PDD (e.g. Furukawa et al., 2018; Jobst et al., 2016; Schramm et al., 2011; Wiersma et al., 2014).

Due to the body of evidence that indicates its general superiority over alternative psychotherapeutic approaches, CBASP has been recommended as first-choice psychotherapy for treating PDD (Jobst et al., 2016). However, CBASP is poorly accessible in many communities where it is not routinely implemented in the mental health care system (Schramm et al., 2017).

Supportive psychotherapy (SP), which is more widely used, emphasizes non-specific, common core therapeutic factors like empathic listening, building a therapist-patient alliance, and therapeutic optimism (Markowitz, 2014). Unlike CBASP, SP does not use specific techniques like problem-solving or exposure exercises (Markowitz, 2014). In a meta-analysis, Cuijpers et al. (2012) found that SP has a considerable effect on mild to moderate depression in adult patients and is equally effective as cognitive-behavioral-oriented psychotherapies when controlling for investigator allegiance. Moreover, the authors concluded that non-specific factors account the most for the effectiveness of all investigated psychotherapies, while the contribution of specific techniques was limited at best. This may suggest that for some patients with PDD, SP might be equally or even more effective than CBASP. For others, disorder-specific CBASP might be more beneficial than a supportive approach. However, so far, little has been understood about which psychotherapeutic approach works for which patients with PDD (Cuijpers, Huibers, & Furukawa, 2017; Jobst et al., 2016).

In randomized clinical trials, an essential step in understanding who benefits from which treatment is to identify moderators of treatment response, i.e. pretreatment or baseline characteristics that are independent of the assigned treatment and show a different treatment effect depending on their value (Kraemer, 2013). For example, Nemeroff et al. (2003) found that for chronically depressed patients with a history of childhood trauma (i.e., early loss of parents, physical or sexual abuse, or neglect), CBASP was superior to monotherapy with nefazodone. Another analysis revealed that the effectiveness of CBASP and nefazodone varied depending on the patients' preference, in that they responded better to their preferred treatment (Kocsis, Leon, et al., 2009). The results of a meta-analysis of individual participant data (Furukawa et al., 2018) indicated that for PDD patients with severe depression and anxiety, the combination of CBASP and antidepressant medication was more effective than monotherapy with CBASP or antidepressant medication.

Although relevant for theory and treatment development, research emphasizing individual moderators often produces inconsistent results across different trials (Kraemer, 2013; Wallace & Smagula, 2018). For example, Bausch et al. (2017) failed to replicate the moderating role of childhood trauma (Nemeroff et al., 2003) in a comparison trial of CBASP and escitalopram in patients with PDD. Moreover, the isolated examination of individual moderators can lead to contradictory treatment recommendations. For instance, for a patient who prefers antidepressant medication and who has a history of early trauma, one might indicate medication over CBASP based on the treatment preference (Kocsis, Leon, et al., 2009), and at the same time, CBASP over medication with regard to the early trauma history (Nemeroff et al., 2003). Another issue with individual moderators is that they often have weak effects (Kraemer, 2013), and many studies do not report effect sizes that capture their moderation effect. To address these issues, Kraemer (2013) developed the optimal composite moderator approach, in which multiple individual moderators are combined to an optimal composite moderator 'M*', which is used to identify and subsequently characterize patients who benefit more from one treatment than from another. This approach was applied to a number of randomized clinical trials examining interventions for episodic depression (Wallace, Frank, & Kraemer, 2013), late-life depression (Smagula et al., 2016), bipolar disorders (Frank et al., 2014) and anxiety disorders (Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor, Arch, & Craske, 2017; Wallace et al., 2017). In all of these studies, the effect size of M* was larger than any effect size of an individual moderator. So far, no previous work has applied this approach to a trial conducted in patients with PDD.

In a multi-center randomized clinical trial, Schramm et al. (2017) compared the effectiveness of 48 weeks of CBASP to SP in outpatients with early-onset PDD who were not taking antidepressant medication. The findings suggested that both interventions were associated with pre- to post-treatment reductions in depression severity, but that CBASP was modestly superior to SP. The present exploratory study used data from the trial conducted by Schramm et al. (2017) to identify and characterize subgroups of patients for whom CBASP was more likely to result in symptom reduction than SP, and vice versa. By addressing the question of what worked for whom, we aimed to generate findings that may be validated in future independent clinical populations, serve for developing treatment recommendations, and thus meet the need to advance personalized medicine for chronic forms of depression (Cuijpers et al., 2017).

2. Method

The data used had been collected as part of an evaluator-blinded, prospective, parallel-group randomized clinical trial conducted at eight university centers throughout Germany (ClinicalTrials.gov identifier NCT00970437). The trial was carried out following the latest version of the Declaration of Helsinki and was separately approved by the ethics committees of all study centers. Patients provided written informed consent after receiving explanations of all procedures. Detailed information on the study trial can be found in the published protocol (Schramm, Hautzinger, et al., 2011) and the published main results of the trial (Schramm et al., 2017).

2.1. Participants

Among 622 patients assessed for eligibility, 268 were randomized to either CBASP (n = 137) or SP (n = 131). Study participants were outpatients aged 18–65 years who met the DSM-IV (American Psychiatric Association, 1994) criteria for a current major depressive disorder (MDD) of at least two years duration (chronic MDD; 31.5%), MDD superimposed on a pre-existing dysthymic disorder (double depression; 45.8%), or recurrent MDD without complete remission between episodes (22.7%), all with an early illness onset (before age 21). At the screening, patients scored at least 20 points on the 24-item

Hamilton Rating Scale for Depression (HRSD-24; Hamilton, 1967). Exclusion criteria included: an acute risk of suicide; a primary diagnosis of another Axis I disorder; a lifetime history of psychotic symptoms; a diagnosis of bipolar disorder, antisocial, schizotypal, or borderline personality disorder; a severe medical condition; an organic brain disorder; severe cognitive impairment; no response to a previous trial with CBASP or SP; or an ongoing treatment with a psychotherapy or antidepressant medication. The intake of any antidepressant medication was prohibited during the entire trial.

2.2. Interventions

The CBASP is a highly structured, theory-driven psychotherapy from the third generation of behavioral therapy models specially designed to treat PDD. During the therapy, the patients are trained to develop a better understanding of the consequences of their behavior on others. The therapist uses techniques such as situation analysis, interpersonal discrimination exercises, and behavioral skill training to facilitate this (McCullough, 2003). Supportive psychotherapy is a disorder non-specific psychotherapy that emphasizes "common" factors that are supposed to be relevant tools across all psychotherapies including empathic listening and therapeutic optimism (Markowitz, 2014). In our trial, treatments were delivered by trained and experienced therapists who followed standardized CBASP and SP manuals. Sessions of CBASP and SP were held twice weekly for the first four weeks and weekly for the next 16 weeks in the acute treatment phase, followed by eight continuation sessions during the next 28 weeks, resuming to 32 sessions.

2.3. Baseline variables examined as potential individual moderators

Before treatment randomization, study participants completed several diagnostic interviews, psychological questionnaires, and rating scales related to socio-demography, clinical characteristics, and treatment history. In our exploratory analysis, we considered 36 baseline variables as potential individual moderators and calculated moderator effect sizes as developed by Kraemer (2013) for each of them. Details on the assessment of all analyzed baseline variables are provided in Supplemental Table 1 in the supplemental materials (SM).

Demographic characteristics: Gender, age at randomization (years), being single, married or cohabiting, separated, divorced, or widowed, having a high educational level (= at least 12 years), being employed and the presence of morbidities were each considered as a potential moderator.

Questionnaires administered at baseline: We considered the baseline sum scores of the following questionnaires: HRSD-24 (Hamilton, 1967), self-rated Inventory of Depressive Symptomatology (IDS-SR; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996), the sum scores of the anxiety and phobic anxiety subscales of the Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983), Generalized Anxiety Disorder Scale-7 (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006), Beck Scale for Suicidal Ideation (BSSI; Beck, Kovasac, & Weissman, 1979), Inventory of Interpersonal Problems (IIP-64; Horowitz, Strauβ, & Kordy, 2000), Global Assessment Functioning Scale (GAF; Endicott, Spitzer, Fleiss, & Cohen, 1976), Quality of Life in Depression Scale (QLDS; Hunt & McKenna, 1992), and Social Adaptation Self-Evaluation Scale (SASS; Duschek, Schandry, & Hege, 2003).

Mental comorbidities: We examined the presence of any comorbid Axis I disorders (diagnosed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, SCID-I; First, Spitzer, Gibbon, & Williams, 2002) as well as the presence of any comorbid Axis II personality disorders (diagnosed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, SCID-II; First, Gibbon, Spitzer, & Williams, 1997).

Illness characteristics and history: We examined the three subtypes (chronic MDD, double depression, and recurrent MDD without complete remission between episodes), the illness duration (in years), the age of illness onset (in years), and the history of at least one previous suicide attempt.

Early trauma: Early trauma was assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein, Stein, & Newcomb, 2003). The CTQ assesses five types of early trauma that happened before the age of 18: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. In our analysis, the presence of each type was defined as at least moderate-to-severe, corresponding to a specific cut-off on the respective scale (for details, please refer to Supplemental Table 1 in the SM).

Treatment history and preference for psychotherapy: The examined variables included a history of at least one previous psychotherapy (with a duration of at least eight sessions) to treat depression, a history of at least one treatment with antidepressant medication (taken for at least four weeks), a history of combination treatment of psychotherapy with antidepressant medication, and a history of inpatient treatment for depression. Lastly, because we compared the effectiveness of two forms of psychotherapy, we analyzed the patients' preference for psychotherapy over other treatments for depression as a potential moderator.

2.4. Outcome

In the present analysis, we used the percentage change in HRSD-24 scores from baseline to week 48 as an outcome. Negative scores reflect a reduction in depression severity, a score of zero reflects no change and positive scores indicate an increase in depression severity from baseline to week 48. The HRSD-24 ratings were performed by trained and experienced evaluators who were blind to treatment assignment. The interrater reliability of the HRSD-24 ratings was calculated based on data from 21 evaluators' ratings of nine audio- or videotaped interviews and had an intra-class correlation coefficient of 0.973 (95% CI, 0.889–0.999). Missing HRSD-24 data at week 48 (n = 59; 22.0%) were replaced by the last observation carried forward method, as specified in the study protocol (Schramm, Hautzinger, et al., 2011).

2.5. Statistical analyses

Individual moderator effect sizes: First, we used the method described by Kraemer (2013) to examine moderator effect sizes for all 36 candidate variables. We started by pairing each patient assigned to CBASP to each patient assigned to SP. Next, for each pair in this dataset, we calculated the difference in the outcome (i.e., the percentage change in HRSD-24 scores) and the average value of each baseline variable. Next, to obtain the effect sizes, we computed non-parametric Spearman correlations between the difference in the outcome and each average, and estimated their 95% bootstrap confidence intervals (CI) based on 100 replications. Effect sizes obtained after this method are invariant over linear transformations of the baseline variable or the outcome, varying between -1 and $+1$, with higher magnitudes indicating a stronger moderation and 0 indicating the absence of a moderation effect (Kraemer, 2013). Variables were considered to be moderators if their effect size was $\geq |0.10|$ (i.e., at least small). This cutoff is similar to those used in previously published applications of Kraemer's composite moderator method (e.g., Smagula et al., 2016; Wallace et al., 2017). Given the exploratory character of this analysis, we abstained from including the statistical significance of interaction effects between the treatment and the moderator as a selection criterion (Wasserstein & Lazar, 2016).

Model selection of the composite moderator: Next, we wanted to identify which of the variables with effect sizes $\geq |0.10|$ to include in the composite moderator (M*) and to determine their weights contributing to M*. According to Kraemer (2013), in the paired dataset, the weights of the single moderators have to be estimated by a multivariable regression model, in which the difference in outcome is

predicted by the averages of all preselected individual moderators. Similar to previous applications of the composite moderator approach (e.g., Smagula et al., 2016; Wallace et al., 2017; Wallace et al., 2018), we chose to perform least absolute shrinkage and selection operator (lasso) regression (Tibshirani, 1996) in the multivariable model. In principle, lasso regression selects the most useful independent variables and shrinks the regression weights of the least useful variables (e.g., those with little predictive power or correlated with other predictors) to zero, thereby removing them from the model (Tibshirani, 1996). Moreover, to optimize the model's predictive performance and to avoid overfitting, we combined lasso regression with *k*-fold cross-validation (James, Witten, Hastie, & Tibshirani, 2013). Other recent applications of the composite moderator approach have discussed the advantages of combining *k*-fold cross-validation with Kraemer's method, and have successfully applied it to develop composite moderators of continuous and dichotomous outcomes (refer to Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor et al., 2017). In *k*-fold cross-validation, the data is randomly sampled into *k* folds: (*k*-1) folds are used as the training dataset, and the *k*th fold constitutes the validation dataset. The model is estimated within the training dataset, and its predictive performance is assessed within the held-out validation dataset (James et al., 2013). The entire procedure is repeated *k* times so that each fold is used for validation once. When applied to lasso regression, *k*-fold cross-validation can be used to identify the value of the tuning parameter (λ) that minimizes the estimated mean-squared prediction error (MSPE) in the validation dataset. Thus, *k*-fold cross-validation enables to select a model that is more likely to have a good predictive performance in future new data, than a model that was trained *and* tested within the same data. In our analysis, for defining the tuning parameter that yields the smallest MSPE, we applied 10-folds cross-validation as described by Ahrens, Hansen, and Schaffer (2019) and implemented in their package *lassopack* developed for use in STATA. Within the paired dataset, we ran the 10-folds cross-validation by using the command "*cvlasso*", which internally repeats lasso regression and finally selects the model with the optimal tuning parameter (λ_{opt}) that yields the smallest MSPE.

Identification of subgroups: After selecting the optimal model based on the procedure described before, we extracted the weights from each of the moderators selected by this model and calculated the value of M* for each patient as described by Kraemer (2013). Finally, in the unpaired full dataset, we conducted a regression analysis predicting the outcome (i.e., percentage change in HRSD-24 scores) from the composite moderator M*, the treatment group, and their interaction, and computed the effect size of M* together with the 95% bootstrap CI. We calculated the value of M* at which the predicted outcomes for CBASP and SP group crossed one another. When they crossed, we divided the sample into two subgroups, one below and one above the cross-point, each with a different treatment associated with a more favorable outcome. Within both subgroups, we calculated Cohen's *d* treatment effect sizes with 95% CI. Finally, we characterized the baseline profiles of each subgroup. Analyses were conducted in STATA version 15.1 (StataCorp, 2017).

3. Results

Effect sizes of individual moderators: Table 1 displays effect sizes with 95% CI for each of the 36 baseline variables. Effect sizes ranged from −0.209 (IDS-SR; self-rated depression severity) to 0.084 (past psychotherapy). Negative values indicate a better outcome (i.e., a greater reduction in HRSD-24 scores from pre-to post-treatment) with CBASP than with SP for higher values of the moderator. Positive values indicate a better outcome with SP than with CBASP for higher values of the moderator. In total, we identified 13 baseline variables with an effect size ≥ |0.10|. These were self-rated depression severity (IDS-SR), clinician-rated depression severity (HRSD-24), having at least one comorbid Axis I disorder, early moderate-to-severe emotional neglect, early moderate-to-severe physical neglect, quality of life (QLDS, with higher values indicating lower quality of life), being divorced, separated, or widowed, illness duration (years), chronic MDD as subtype, recurrent MDD without complete remission between the episodes as subtype, having at least one comorbid Axis II disorder, social functioning (SASS), and global functioning (GAF).

Optimal composite moderator M*: By using 10-fold cross-validation as described in the methods, we selected an optimal model that contained all 13 moderators with an effect size ≥ |0.10|. Supplemental Fig. 1 of the SM provides a plot of the estimated MSPEs as a function of the tuning parameter resulting from the 10-fold cross-validation. The estimated weights for the composite moderator M* are provided in Table 1. They represent the extent to which each moderator distinguishes differences in the outcome between patients from CBASP and those from SP in the context of the other selected moderators. The effect size of the composite moderator M* was r = 0.34 (95% CI, 0.32; 0.36). In comparison, the effect size of the largest individual moderator, self-rated baseline depression severity (IDS-SR), was r = −0.209 (95% CI of −0.227 to −0.190).

Identified subgroups: Values of M* were calculated for n = 237 patients who had complete data on all 13 moderators. Next, in the unpaired dataset, we performed the regression analysis explained in the methods. Fig. 1 illustrates the predicted pre- to post-treatment percentage change in HRSD-24 scores for CBASP and SP across the range of M*. The lines cross at M* = 8.40. Below this cross-point (M* < 8.40), CBASP was moderately preferable to SP (Cohen's d = −0.57; 95% CI: 0.91; −0.23) for n = 139 (58.65%) patients. Above this cross-point (M* > 8.40), SP was little preferable to CBASP (Cohen's d = 0.29; 95% CI: 0.11; 0.68) for n = 98 (41.35%) patients.

Table 2 provides descriptive statistics to characterize patients in both subgroups. Patients responding more favorably to CBASP had a more prolonged illness duration, were more often divorced, separated, or widowed, and more likely diagnosed with chronic MDD. More often, they had at least one comorbid Axis I disorder as well as higher initial self- and clinician-rated depression severity. All five forms of moderate-to-severe childhood trauma (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse) were more often reported by these patients. Conversely, patients responding more favorably to SP tended to have higher baseline general and social functioning levels. Their baseline quality of life was less affected by PDD. They were also more likely to have recurrent MDD without complete remission between the episodes as well as at least one Axis II disorder. Note that, because of the explorative character of this analysis, we abstained from testing any of these subgroup differences.

4. Discussion

The aim of this study was to identify and characterize subgroups of patients with early-onset PDD who responded more favorably to 48 weeks of CBASP versus SP and vice versa. By using the approach described by Kraemer (2013) and two statistical learning methods (lasso regression and *k*-fold cross-validation), we preselected and combined single baseline variables into an optimal composite moderator to predict whether a patient will be more likely to benefit from CBASP or SP. In line with previous applications of the composite moderator approach (e.g. Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor et al., 2017; Smagula et al., 2016; Wallace et al., 2017), the effect size of M* was larger than the effect size of any individual moderator. We found two subgroups: one comprising approximately 59% of patients for whom CBASP was preferable to SP, and another comprising 41% of patients for whom SP was preferable to CBASP. We finally characterized and compared both subgroups in terms of their pre-treatment profiles.

The CBASP was associated with a better outcome than SP for more severely depressed patients who had higher rates of early trauma in the form of sexual, emotional or physical abuse, or emotional or physical neglect. Importantly, CBASP was specially developed to treat early-trauma-driven behavioral and cognitive deficits in chronically

Table 1
Moderator effect sizes for analyzed baseline variables and weights for the composite moderator.

Baseline variable	Moderator effect size (95% CI)	Weight in the final model
Included in the final model		
IDS-SR	−0.209 (−0.227; −0.190)	−1.610
HRSD-24	−0.162 (−0.180; −0.144)	0.124
At least one comorbid Axis-I disorder	−0.141 (−0.155; −0.127)	−18.821
Early emotional neglect	−0.121 (−0.136; −0.106)	−6.326
QLDS	−0.118 (−0.132; −0.103)	0.674
Separated, divorced or widowed	−0.114 (−0.128; −0.100)	−15.680
Illness duration	−0.108 (−0.121; −0.095)	−0.034
Chronic major depression	−0.108 (−0.122; −0.094)	−9.941
Early physical neglect	−0.102 (−0.116; −0.089)	−6.518
Recurrent major depression without complete remission between episodes	0.100 (0.084; 0.117)	20.919
At least one comorbid Axis-II disorder	0.106 (0.092; 0.119)	30.943
SASS	0.113 (0.098; 0.127)	0.456
GAF	0.144 (0.126; 0.163)	0.744
Not included in the final model		
GAD-7	−0.098 (−0.115; −0.081)	
Age at randomization	−0.095 (−0.108; −0.081)	
At least one lifetime suicide attempt	−0.086 (−0.102; −0.071)	
At least 12 years of education	−0.075 (−0.089; −0.061)	
Early physical abuse	−0.069 (−0.084; −0.055)	
BSI, subscale anxiety	−0.064 (−0.080; −0.047)	
Past treatment with antidepressant medication	−0.060 (−0.074; −0.046)	
Having at least one morbidity	−0.047 (−0.062; −0.032)	
IIP-64	−0.042 (−0.058; −0.027)	
Gender (= female)	−0.027 (−0.042; −0.011)	
Early emotional abuse	−0.026 (−0.040; −0.011)	
Past inpatient treatment	−0.009 (−0.023; 0.005)	
BSSI	−0.003 (−0.018; 0.013)	
BSI, subscale phobia	−0.001 (−0.014; 0.013)	
Past combination treatment	0.003 (−0.012; 0.019)	
Early sexual abuse	0.013 (−0.005; 0.031)	
Double depression	0.017 (0.002; 0.032)	
Preference for psychotherapy	0.029 (0.015; 0.043)	
Being single	0.034 (0.020; 0.049)	
Married or cohabiting	0.052 (0.037; 0.068)	
Employed	0.061 (0.050; 0.073)	
Age at illness onset	0.072 (0.056; 0.087)	
Past psychotherapy	0.084 (0.068; 0.100)	

Abbreviations: BSI = Brief Symptom Inventory; BSSI = Beck Scale for Suicidal Ideation; CI = confidence interval; GAD-7 = Generalized Anxiety Disorder Scale-7; GAF = Global Assessment Functioning Scale; HRSD-24 = 24-Item Hamilton Rating Scale for Depression; IDS-SR = Inventory of Depressive Symptomatology, self-rated; IIP-64 = Inventory of Interpersonal Problems; QLDS = Quality of Life in Depression Scale; SASS = Social Adaptation Self-Evaluation Scale.
Notes: Negative values indicate a better outcome with CBASP than with SP for higher values of the moderator. Positive values indicate a better outcome with SP than with CBASP for higher values of the moderator.

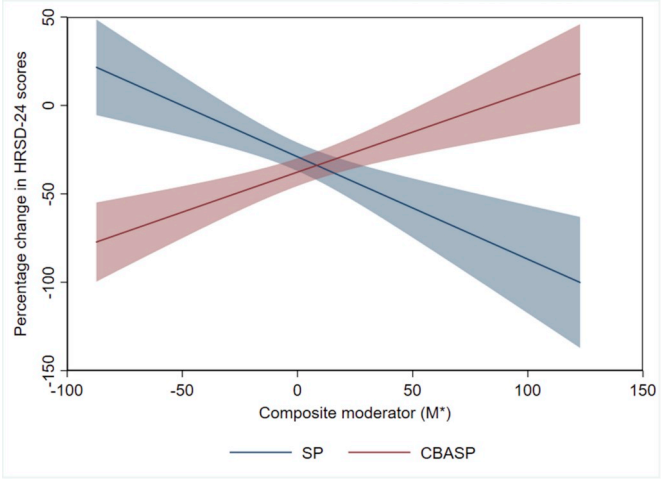

Fig. 1. Predicted percentage change in HRSD-24 scores with 95% confidence intervals for CBASP and SP across the observed range of the composite moderator M*.
Abbreviations: CBASP, Cognitive Behavioral Analysis System of Psychotherapy; HRSD-24, 24-Item Hamilton Rating Scale for Depression; SP, supportive psychotherapy.

depressed patients (McCullough, 2003). The CBASP therapist seeks to help his clients to recognize the negative consequences of their dysfunctional behavior on others, as well as to improve their stress management skills and emotional control over depression by applying bottom-up and top-down techniques to encourage formal operative thinking and behavior (McCullough, 2003; Neudeck et al., 2012; Schramm et al., 2017). Thus, it is plausible that this approach was more useful than non-structured SP for those patients with a lower social and global functioning level at baseline, who were also more early traumatized and who had a higher initial depression severity. Their baseline profile corresponds more to the picture of the chronically depressed patient portrayed by McCullough in the early years of the development of CBASP (McCullough, 2003) than the pre-treatment characteristics dominating in the subgroup benefiting more from SP. Patients who responded more favorably to SP had a higher initial social and global functioning level, less early trauma, and a lower baseline depression severity. According to Markowitz (2014), SP bypasses the confrontation with biographical aspects while offering a more liberal and supportive therapeutic setting that focuses on activating available resources. Given the constellation of more beneficial baseline features, this subgroup might have benefited from the resources that were activated through the approach of SP. The lower rates of early traumatic experiences in this subgroup might also explain why the early-trauma emphasizing approach of CBASP was less beneficial for these patients. Given the

Table 2
Baseline profiles of patients within the two subgroups above and below M* = 8.40

Baseline characteristics	CBASP is preferable to SP (M* < 8.40; n = 139)	SP is preferable to CBASP (M* > 8.40; n = 98)
Illness duration, y, mean (SD)	34.1 (13.2)	28.7 (13.4)
Separated, divorced or widowed (%)	25.2	8.2
Chronic major depression (%)	46.8	12.2
Recurrent major depression without complete remission between episodes (%)	10.1	39.8
Any Axis I disorder (%)	53.2	23.5
Any Axis II disorder (%)	26.6	53.1
CTQ emotional neglect (%)	74.8	52.0
CTQ emotional abuse (%)	66.9	48.0
CTQ physical neglect (%)	41.7	15.3
CTQ sexual abuse (%)	29.0	15.5
CTQ physical abuse (%)	28.8	10.2
Self-rated depression severity, IDS-SR, mean (SD)	43.1 (8.4)	33.3 (8.1)
Clinician-rated depression severity, HRSD-24, mean (SD)	27.0 (6.7)	21.7 (6.3)
Quality of life, QLDS, mean (SD)	20.7 (7.1)	16.6 (7.8)
Social functioning, SASS, mean (SD)	28.6 (6.5)	32.0 (5.9)
Global functioning, GAF, mean (SD)	51.1 (8.1)	58.5 (8.5)

Abbreviations: CBASP, Cognitive Behavioral Analysis System of Psychotherapy; CTQ, Childhood Trauma Questionnaire; GAF, Global Assessment Functioning Scale; HRSD-24, 24-Item Hamilton Rating Scale for Depression; IDS-SR, self-rated Inventory of Depressive Symptomatology; QLDS, Quality of Life in Depression Scale; SASS, Social Adaptation Self-Evaluation Scale; SD, standard deviation; SP, supportive psychotherapy; y, years.
Notes: Higher values of the QLDS indicate a lower quality of life due to depressive disorder.

greater availability of SP in clinical practice (Markowitz, 2014), future research should investigate its potential to treat PDD in patients with such pre-treatment characteristics.

Importantly, we want to emphasize that these subgroup effects apply, so far, only to the here investigated population of outpatients with PDD who were not taking antidepressant medication. Although we performed cross-validation, the replicability of the model generated to calculate M*, as well as the effect size of M*, have to be tested in a rigorous external validation before these findings can be generalized and applied to clinical practice. Besides the validation of the model provided in this work, one might also select prominent baseline differences that differed (e.g., early trauma, PDD subtype) between both subgroups and stratify new populations according to them in order to test specific hypotheses or new treatment combinations. For the prediction of treatment response, models based on integrating several multi-domain characteristics might, however, be more realistic and useful than the traditional approach of examining one moderator per model (for a discussion, refer to Cohen & DeRubeis, 2018 and Wallace & Smagula, 2018).

4.1. Limitations and outlook

Our findings should be considered in the context of some limitations. First, we want to emphasize that our study was a hypothesis-generating one. As already mentioned, the predictive performance of the developed composite moderator must be externally validated in a new population. Also, mediator analyses are further necessary to identify the factors that have influenced the process between randomization and post-treatment within each subgroup. Second, the psychotherapies compared here (i.e., CBASP and SP) are two out of many possibilities to treat PDD. Future studies might develop composite moderator approaches that rank the effectiveness of several treatments. Another necessity is to develop more sophisticated models that consider the benefits and the side effects of treatments. Third, we only had a limited number of variables, with which to develop the composite moderator. It is likely that other moderators, which were not assessed, would have enhanced the effect size of M* if included. Forth, in order to restrict the model's complexity, we did not examine interactions between single variables or non-linear moderator effects. Due to the many possible models, sophisticated machine learning methods might represent a more useful alternative for testing this diversity. Finally, further analyses should be performed to determine whether the composite moderator is also reflective of outcomes at a given follow-up time point.

5. Conclusion

By using the composite moderator methodology, we have identified two subgroups with differential benefits from disorder-specific CBASP compared to SP. These results emphasize the relevance of detecting subgroups with differential treatment benefits in randomized clinical trials by methods such as the one applied here. After validation in an independent sample, algorithms based on this method could help mental health practitioners select the most promising psychotherapy for patients in the community. Further progress in this research field is urgently needed to personalize treatment selection for patients suffering from PDD.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2019.103512.

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