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Research paper

Inpatient psychotherapy for depression in a large routine clinical care sample: A Bayesian approach to examining clinical outcomes and predictors of change

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ABSTRACT

Background: A routinely collected dataset was analyzed (1) to determine the naturalistic effectiveness of inpatient psychotherapy for depression in routine psychotherapeutic care, and (2) to identify potential predictors of change.
Methods: In a sample of 22,681 inpatients with depression, pre-post and pre-follow-up effect sizes were computed for various outcome variables. To build a probabilistic model of predictors of change, an independent component analysis generated components from demographic and clinical data, and Bayesian EFA extracted factors from the available pre-test, post-test and follow-up questionnaires in a subsample ($N = 6377$). To select the best-fitted model, the BIC of different path models were compared. A Bayesian path analysis was performed to identify the most important factors to predict changes.
Results: Effect sizes were large for the primary outcome and moderate for various secondary outcomes. Almost all pretreatment factors exerted significant influences on different baseline factors. Several factors were found to be resistant to change during treatment: suicidality, agoraphobia, life dissatisfaction, physical disability and pain. The strongest cross-loadings were observed from suicidality on negative cognitions, from agoraphobia on anxiety, and from physical disability on perceived disability.
Limitations: No causal conclusions can be drawn directly from our results as we only used cross-lagged panel data without control group.
Conclusions: The results indicate large effects of inpatient psychotherapy for depression in routine clinical care. The direct influence of pretreatment factors decreased over the course of treatment. However, some factors appeared stable and difficult to treat, which might hinder treatment outcome. Findings of different predictors of change are discussed.

1. Introduction

Depression is a highly prevalent and disabling mental disorder that is listed among the top ten causes of years lived with disability (Vos et al., 2015). Encouragingly, patients suffering from depression can be treated effectively: Many randomized controlled trials (RCTs) and meta-

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analyses have demonstrated the general efficacy of psychotherapy for depression on average (Lepping et al., 2017), although effect sizes (ES) vary greatly depending on the population under investigation, the treatment setting and the particular methodological approach. Overall, large short- and long-term effects can be observed for cognitive behavioral therapies (CBT) and interpersonal psychotherapy (IPT) in episodic depression (Lemmens et al., 2015; Lemmens et al., 2019); however, ES are considerably low for the treatment of persistent depressive disorder (Cuijpers et al., 2010b; Schramm et al., 2017, 2019), treatment-resistant depression and inpatient settings (Schefft et al., 2019). When considering all forms of psychotherapies and depressive subtypes, a new network meta-analysis suggests that the combination of psychotherapy and pharmacotherapy might be superior to monotreatment for patients with moderate depression in terms of short-term effects (Cuijpers et al., 2020) without investigating long-term effects. Although psychotherapy for depression thus seems to be effective on average, psychotherapy research on the treatment of depression has to face several challenges.

A critical issue in psychotherapy research is the research-practitioner gap, that is, the lack in the translation of what is known of effective depression treatments (evidence-based treatments) and what is provided to patients in routine clinical care (nonacademic community-based practice) (Kilbourne et al., 2012). Notwithstanding some controversies about the precise ES of previous RCTs (Cuijpers et al., 2019a,b), only recently, studies examined the effectiveness of treatments for depression under routine clinical care conditions, that is, how effective current treatments in the "real world" are (Delgadillo et al., 2020; Flückiger et al., 2020; Forgeard et al., 2018; Robinson et al., 2020; Wakefield et al., 2020). Methodologically, this refers to clinical effectiveness studies under day-to-day circumstances (Phase IV-studies) with high external validity, as investigated in recently published practice-based studies (Herzog et al., 2021, 2020a,b). Within the framework of practice-oriented research (Castonguay et al., 2013), an estimation of this effectiveness of depression treatments can serve as both an indicator for the implementation of evidence-based treatments for depression and a benchmark for depression treatment (Merrill et al., 2003; Minami et al., 2008, 2007). To date, such benchmark studies in this respect are rare, however (Barkham et al., 2010; Wampold and Imel, 2015). Therefore, our first objective was to determine the naturalistic effectiveness of psychotherapy for depression under naturalistic conditions in a large, routinely collected dataset of German psychotherapeutic clinics that might serve as a benchmark.

Moreover, an important second challenge refers to the large heterogeneity of patients suffering from depression and their individual response to the treatment delivered. In fact, despite extensive research and the development of countless new treatment approaches (Goldfried, 2019), the efficacy of depression treatment seems to stagnate: One-third to half of depressed patients do not benefit from the treatment, both in terms of non-response and/or relapse (Lambert, 2017; van Bronswijk et al., 2019a). For example, about 65–80% of the patients still report clinically significant residual symptoms at posttreatment (Lemmens et al., 2015). Thus, since the response to specific psychological treatments for depression varies greatly among individuals, a better understanding of the predictors of symptom change would be of great value enabling to optimize the depression treatments delivered (Grant et al., 2014; Simon and Perlis, 2010). As such, the ability to identify patients at risk for not benefitting from treatment yields some promising advantages (Webb et al., 2020), i.e., a treatment tailored to important predictors of change in the short and long run might be able to reduce the potential of a chronic course of depression, possibly preventing treatment-resistance and its associated factors: reduce morbidity and mortality; shorten suffering; reduce rates of treatment dropouts; and reduce the cost burden for the patient and society (Bergfeld et al., 2018; Cepeda et al., 2018; Johnston et al., 2019; Reutfors et al., 2018), which usually allocates those patients to a difficult-to-treat population from a practitioner's perspective. In the context of personalizing treatments, the identification of prognostic variables by single-treatment studies[1] might enable to better tailor treatments to the individual patient (Cohen and DeRubeis, 2018; Webb et al., 2020). Promisingly, a few variables could be consistently identified as robust negative general predictors of treatment outcome across studies: high baseline depressive symptom severity; persistent or recurrent depressive disorder; early onset of depression; and comorbid Axis I disorders (Blom et al., 2007; Carter et al., 2011; Constantino et al., 2008; Frank et al., 2011; Jarrett et al., 1991; Mynors-Wallis and Gath, 1997). Those general predictors as prognostic variables have guided research so far and might be useful as indicators of patients who are difficult to treat (Frank et al., 2011). Nevertheless, the prediction of treatment outcome appears an ongoing challenge as studies examining predictors often produce inconsistent results. In fact, these partially inconsistent findings were mainly traced back to methodological issues (Lee et al., 2018; Simon and Perlis, 2010). In particular, some major limitations of previous studies result from their lack of power due to small sample sizes, the separate inclusion of sociodemographic or clinical or psychological data and statistical issues. Naturalistic studies with larger and super-regionally representative case numbers in the context of a practice-research network (Castonguay and Muran, 2015; Castonguay and Muran, 2016) might thus help address such statistical problems and to overcome the research-practice gap. Furthermore, some researchers call for new statistical models that use multiple resources of data by combining clinical and demographic data (Chekroud et al., 2016; Cipriani and Geddes, 2016) and the advantages of Bayesian statistics (Høifødt et al., 2015; Wagenmakers et al., 2018).

Aiming to addressing some of the aforementioned shortcomings, the current study has two objectives: (1) to determine the naturalistic short- and long-term effectiveness of specialized inpatient psychotherapy for depression, that is, benchmarking inpatient psychotherapy for depression in routine clinical care; and (2) to identify its predictors of change, that is, the underlying processes by which this treatment works in the short and the long run. Therefore, this study tries to shift the focus on candidates for predictors of change by combining a theory- and data-driven approach and applying Bayesian statistics (cf., Høifødt et al., 2015) with the superior goal of informing feature selection for treatment development and refinement.

2. Methods

This study was conducted in accordance with the ethical standards as laid out in the 1964 Declaration of Helsinki and its subsequent amendments. All patients gave informed consent to anonymous evaluations of their routinely collected data. However, ethical approval was not obtained for this retrospective study because data was routinely collected as a standard clinic diagnostic procedure to ensure quality assurance and did therefore not involve prospective evaluation.

2.1. Sample

For the current study, we were able to analyze data routinely and consecutively collected between 2013 and 2017 from depression inpatients treated in five German acute psychotherapeutic clinics with specialized inpatient depression treatment as recommended in international and national guidelines for the treatment of complex and severe depression (DGPPN et al., 2017; NICE, 2018). In the German mental healthcare system, specialized inpatient treatment is given to patients when outpatient treatment not sufficiently reduce symptom severity. Inclusion criteria were: primary diagnosis of depression (F32 or F33 according to ICD-10); age of at least 18 years; and a focus of the treatment delivered mainly on depression. Taking into account the

[1] Sometimes referred to as general predictors.

complexity and heterogeneity of patients suffering from depression, no further exclusion criteria were defined a priori (such as medication status, comorbid diagnoses, etc.). In total, 22,681 patients met these inclusion and exclusion criteria.

2.2. Specialized inpatient treatment for depression

The psychotherapeutic clinics offer multimodal modern CBT treatment programs for depression based on national and international guidelines (DGPPN et al., 2017; NICE, 2018). The multiple sites (i.e. clinics) are part of one large clinic group. Inpatient psychotherapy of depression in German psychotherapeutic clinics aims to deliver a maximum of symptom-specific therapy for depression with a focus on behavioral activation and cognitive interventions based on Beck's CBT manual (Beck, 1979) for major depressive disorder (MDD) and – meanwhile in most of the clinics – CBASP for persistent depressive disorder (PDD) augmented with multimodal groups being based on modern approaches of depression treatment such as ACT and other mindfulness-based interventions. Since inpatients generally suffer from more severe and more complicated illnesses than outpatients and often have no direct follow-up treatment after discharge, the following stages of the therapeutic process are of particular importance: motivational training and psychoeducation, behavioral training and cognitive interventions, transfer into daily routine and relapse prevention. The therapeutic elements of the routine treatments of the five clinics are outlined in the Supplemental material (see Supplemental Material 1).

In total, inpatients in these five psychotherapeutic clinics receive a minimum of 1 h per week of individual psychotherapy, 8–12 h per week of group therapy plus access to an average of 6–10 h per week of multimodal interventions over an average of 6–8 weeks, leading to a total of 78–184 therapy hours according to individual indication and depending on comorbidities. In our sample, the average length of stay was $M = 43.3$ days ($SD = 14.8$). For the patient-staff ratio on each depression ward, a minimum of two licensed psychotherapists are available (3–5 years of training in CBT, one medical doctor and one certified clinical psychologist); 1–2 therapists in CBT training; and at least 1,5 certified nursing staff members. These training levels and regular supervision guarantee the adherence to the CBT-based treatment program, including elements of CBASP and ACT. During the weekends, emergency care in the clinic with medical, psychological and nursing personal is warranted.

Psychopharmacological treatment is administered when indicated according to current national and international guidelines (DGPPN et al., 2017; NICE, 2018), based on the informed consent of the patients. In the dataset for our analysis, data from the medication status at discharge were included. Notably, the major treatment focus in these psychotherapeutic clinics is placed on psychotherapeutic work in individual and group settings.

2.3. Assessment/Measures

Concerning naturalistic effectiveness, change in depression was the primary outcome assessed at admission and discharge using the following measures: the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) and the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). Both instruments were used in order to enhance comparability with previous studies (Gyani et al., 2013; Knapstad et al., 2018). The secondary outcomes, which were also assessed at admission and discharge, capturing psychological distress, (health-related) and general quality of life, were assessed by the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983), the Short-Form-36 (SF-36) (Ware et al., 1993) and the Satisfaction with Life Scale (SWLS) (Diener et al., 1985). Medication in eight classes of substances (namely, antidepressants, neuroleptics, tranquilizers, anticonvulsants, narcotics, substitution, analgesics, other medication) was assessed only at discharge. At follow-up (six months after discharge), only the BDI-II, PHQ-9 and SWLS were assessed. This data collection was part of the follow-up routine outcome management of some hospitals, which is why only a limited number of questionnaires were collected.

2.4. Other measures for computing path models

Sixteen clinical and sociodemographic variables were asked about at intake via a self-report and therapist-rated questionnaires. Sociodemographic data included age, sex, education level and marital status, among others (see sample characteristics in the Results section). Clinical characteristics were assessed at intake, including diagnosis and previous psychotherapeutic and psychiatric treatments. In addition to the aforementioned questionnaires, a self-report questionnaire assessing social and work-related adjustment (Mundt et al., 2002) was applied at intake and discharge. In addition, as two other modules of the PHQ-D, the General Anxiety Disorder-7 (GAD-7) was used as a self-administered questionnaire measuring generalized anxiety disorder, and the Patient Health Questionnaire-15 (PHQ-15) was used as a questionnaire administering somatic symptoms. Furthermore, the Global Assessment of Functioning (GAF) (Endicott et al., 1976) was used as an observer-rated index to determine psychological, social and occupational functioning levels on a continuum ranging from severe mental illness (0) to mental health (100).

2.5. Statistics

All analyses were performed using the statistical processing language R (R Core Team, 2018). To determine the naturalistic effectiveness of the inpatient depression treatment, the corrected Hedge's g unstandardized pre-post and, where data was available, pre-FU effect sizes (ES) were used for the primary and secondary outcomes. To set an upper limit on the potential impact of treatment discontinuation on effect size estimation, we also calculated last observation carried forward (LOCF) effect sizes.

In order to gain new insights into (Granger-) causal pathways of depression course in the short run directly after treatment and in the long run after completing treatment in a 6-month follow-up, and to assess model selection uncertainty, we decided to choose Bayesian path analysis, which is described in more detail below.

2.5.1. Dimensionality reduction

In total, 16 variables were available from demographic and clinical variables ('trait'). Parallel analysis was performed to estimate the optimal number of components in the R package *psych* (Revelle, 2017). Afterwards, missing data were imputed using the algorithm *missForest* (Stekhoven, 2013; Stekhoven and Bühlmann, 2012) and independent components were constructed using independent component analysis (ICA) with the function *fastICA* from the R package *ica* (Helwig, 2015). All hypothesized 'trait' variables were entered into one to build unrelated components, leading to a total number of 8 components.

For self-report data as 'state' variables, 6 questionnaires with a total of 148 individual items were available at T1 and T2, with less than 80% missing data.

Due to the overlap of constructs in the original 23 subscales, a Bayesian exploratory factor analysis was performed using the function *befa* from the R package *BayesFM* (Piatek, 2017). The *befa* function produces an identified factor structure and simultaneously selects the optimal number of identified factors (Conti et al., 2014). By doing so, a lower-dimensional representation of the data could be found. Due to computational constraints of the algorithm, Conti et al. (2014) recommend an approximation in two steps: In the first step, starting from the original factor model with 23 subscales, there were no restrictions on the identification of factors. A solution without constraints for the number of items per factor was generated, yielding a model with 21 factors. In the second step, the results of the first step were used as a starting point to find an identified solution. However, here a restriction of at least five

items per factor was applied to filter out the most important factors, resulting in 15 factors. Priors were based on the largest naturalistic example of another study (Conti et al., 2014). The factor loadings of the initial item pool comprising 130 items are presented in Supplemental Material 2. The factors were interpreted and named based on the content of their items. Confirmatory factor analysis was conducted in the R package *lavaan* (Rosseel, 2012) using the 23-factor model and the 15-factor model, and a difference in Bayesian information criterion (BIC) was computed to ensure the superiority of the smaller model.

2.5.2. Model selection

All available factors were clustered into 5 blocks of factors: the 8 sociodemographic-clinical factors assessed at pretreatment; medication assessed at posttreatment; the 15 self-report factors, assessed at pretreatment and posttreatment; as well as 4 of the 15 self-report factors at follow-up (because only for these 4 factors were data available, see above). Ten maximum likelihood path models with full maximum likelihood imputation were constructed using the R package *lavaan* (Rosseel, 2012), in which associations between factors were enabled or disabled in blocks, in order to test the basic structure of the data and to build probabilistic models of change in depression. Block-wise path coefficients were estimated by computing the average of the absolutes of all path-coefficients from one block to another. Due to the missing data structure of the dataset, there were strong statistical artifacts when using the data from all clinics. These artifacts could be replicated when artificially imposing the same pattern of missing data in the data from just one clinic, where missing data was minimal. Thus, in order to avoid these artifacts, the subsequent path analysis was based on the data of only one hospital ($N = 6377$). Comparative fit measures (that is, BIC, BIC2, AIF, CFI, GFI) were calculated for all 10 path models, and the best model was selected.

2.5.3. Coefficient estimation

In order to gain more robust estimates for the individual path coefficients, the best path model was re-computed using a Bayesian path model with the R package *blavaan* (Merkle and Rosseel, 2015), which used the Bayesian statistical programming language *stan* in the background. A normal prior with a standard deviation of 0.05 was placed on each standardized path coefficient in order to enforce a slight ridge-like regularization and reduce false positives (Jacobucci and Grimm, 2018).

3. Results

3.1. Patient characteristics

The full sample consisted of 22681 inpatients with a mean age of $M = 47.3$ years ($SD = 12.7$), 58.1% of whom were female and 78.5% in a relationship. More than half of the patients (54.5%) were married; 49.9% were fully employed, 13.3% were unemployed, and only 33.6% were able to work. For most of the patients (81.5%), the treatment received in the respective hospital was their first inpatient treatment; however, 58.1% had already been treated with outpatient psychotherapy, and 61.2% of the patients had received outpatient psychiatric treatment in the past.

According to the ICD-10 and regarding the depression subtype, 36.7% of the sample met the criteria of a depression with a single episode (F32), whereas the majority (63.1%) was diagnosed with recurrent depression (F33); only a few patients met the criteria of a persistent mood [affective] disorder (0.2%). On average, patients had 1.9 ($SD = 1.1$) comorbid mental disorders, with neurotic, stress-related and somatoform disorders (F4) being among the most frequent comorbidities (together accounting for 39.2%). A post-hoc analysis revealed that phobic anxiety disorders (F40) with n = 2406 (10.6%) and somatoform disorders (F45) with n = 4669 (20.6%) accounted for the high percentage of disorders within the F4-spectrum. The majority of the sample (83.7%) was discharged as normal.

The mean BDI-II sum score at baseline was $M = 28.2$ ($SD = 11.0$), and the mean PHQ-9 sum score at baseline was $M = 14.5$ ($SD = 5.6$), indicating moderate to severe depressive symptoms on average. Concerning functioning, the mean GAF score at baseline was $M = 48.5$ ($SD = 8.9$), and the mean BSI score at baseline was $M = 1.3$ ($SD = 0.7$), indicating moderate to high general psychological distress and impairment in psychosocial adaptation. In terms of life satisfaction, the SWLS was rather low ($M = 16.8$; $SD = 6.9$).

Table 1 depicts the relevant sociodemographic and clinical characteristics of the full sample ($N = 22681$).

3.2. Naturalistic effectiveness of the inpatient treatment

In the full sample, the corrected Hedge's g unstandardized pre-post and pre-FU effect sizes (ES) for relevant outcomes were as follows: For the primary treatment outcome, Hedge's g of the pre-post ES in the BDI-II was 1.32 (95% CI [1.29, 1.34]), whereas the LOCF-corrected Hedge's g was 1.14 (95% CI [1.12, 1.16]), indicating large effects. Hedge's g of the pre-post ES in the PHQ-9 was 1.15 (95% CI [1.13, 1.17]), and the LOCF-corrected ES was 1.04 (95% CI [1.02, 1.06]). For general psychopathological distress, Hedge's g of the pre-post ES in the BSI was 0.99 (95% CI [0.97, 1.02]), and the LOCF-corrected Hedge's was 0.91 (95% CI [0.89, 0.94]). For quality of life, Hedge's g of the pre-post ES in the SWLS was 0.49 (95% CI [0.47, 0.51]), its LOCF-corrected ES was 0.40 (95% CI [0.38, 0.42]); Hedge's g for the SF-36 was 0.81 (95% CI [0.77, 0.85]), whereas its LOCF-corrected ES was 0.77 (95% CI [0.73, 0.80]).

For the primary outcome in patients, where data was available, Hedge's g of the pre-FU ES in the PHQ-9 was 0.74 (95% CI [0.72, 0.76]), and the ES for the SWLS was 0.31 (95% CI [0.29, 0.33]).

3.3. Testing different path models

Ten path models were computed as plausible candidate models on the temporal structure of the data, based on research findings concerning risk factors of depression and predictors of treatment outcome (see Supplemental Material 3), and their comparative fit indices were computed. The comparative fit indices are displayed in Supplemental Material 4. By 'comparative fit index' we refer to the fit index relative to the best model, i.e., the best model has comparative fit indices of zero. In other words: lower fit indices indicate a better fit of the model to the data. The BIC, BIC2, AIC, and CFI of Model 2 were the lowest of the reported models, hence its comparative fit indices are zero, indicating the best model fit. The next best models are Model 8 and Model 1; therefore, based on these criteria, Model 2 was selected for further analysis.

3.4. Selecting a path model

The averaged block-wise path-coefficients of Model 2 are highlighted in Fig. 1. The strongest influence was exerted by the block 'sociodemographic and clinical pretreatment characteristics' (abbreviated: 'DemoClinPreTreatment') on clinical baseline data (abbreviated: 'clinical T1 data') with $\beta = 0.09$, followed by the influence of clinical baseline data (T1) on clinical data at discharge (abbreviated: 'clinical T2 data') with $\beta = 0.08$ and further from clinical data at discharge (T2) on clinical data at a 6-months follow-up (abbreviated: 'clinical T3 data') with $\beta = 0.05$. Notably, the medication at discharge (abbreviated: 'Medication T2') was only moderately influenced by sociodemographic and clinical pretreatment characteristic ($\beta = 0.03$) and clinical baseline data (T1) ($\beta = 0.04$), and medication itself exerted no important influence on clinical data at a 6-month follow-up (T3).

3.5. Examining the role of pretreatment factors on symptomatology

The path-coefficients of sociodemographic and clinical pretreatment characteristics on clinical baseline data (T1), clinical data at discharge

Table 1
Sample characteristics of the full sample (N = 22681).

Characteristics	Full sample	n
Age at admission *M* (SD)	47.3 (12.7)	22681
Sex *n* (%)		22681
Female	13174 (58.1)	
Male	9507 (41.9)	
Educational score *M* (SD)[a]	3.2 (0.8)	21792
Depression subtype *n* (%)[b]		22681
Major depressive disorder, single episode (F32)	8305 (36.7)	
Major depressive disorder, recurrent (F33)	14335 (63.1)	
Persistent mood [affective] disorders (F34)	41 (0.2)	
Number of mental comorbidities *M* (SD)[b]	1.9 (1.1)	22681
Most frequent mental comorbidities *n* (%)[b]		22681
Mental and behavioral disorders due to psychoactive substance use (F1)	1866 (8.2)	
Schizophrenia, schizotypal and delusional disorders (F2)	47 (0.2)	
Other mood (affective) disorders (F3)	1640 (7.3)	
Neurotic, stress-related and somatoform disorders (F4)	8894 (39.2)	
Behavioral syndromes associated with physiological disturbances and physical factors (F5)	1928 (8.5)	
Disorders of adult personality and behavior (F6)	2384 (10.5)	
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F9)	884 (3.9)	
Discharge type *n* (%)		11024
Scheduled discharge	9230 (83.7)	
Prematurely discontinued by patient	499 (4.5)	
Prematurely discharged by the team	91 (0.8)	
Prematurely by mutual agreement	967 (8.8)	
Transfer	192 (1.7)	
Marital status *n* (%)		22658
Married	12341 (54.5)	
Divorced	2866 (12.6)	
Widowed	782 (3.5)	
Single	6666 (29.4)	
In a relationship *n* (%)	17751 (78.5)	22626
Occupational status *n* (%)		22650
Unemployed	3018 (13.3)	
Retired	3050 (13.5)	
Student, in training, home care	1333 (5.9)	
Working full time	11297 (49.9)	
Working half time	3036 (13.4)	
Working occasionally	527 (2.3)	
Ability to work *n* (%)	7593 (33.6)	22631
First inpatient treatment *n* (%)	13252 (81.5)	16265
Outpatient psychotherapy *n* (%)	13156 (58.1)	22641
Outpatient psychiatric treatment *n* (%)	13841 (61.2)	22622
BDI-II score at baseline *M* (SD)[c]	28.2 (11.0)	20111
PHQ-9 score at baseline *M* (SD)[d]	14.5 (5.6)	20976
GAF score at baseline *M* (SD)[e]	48.5 (8.9)	22038
BSI mean score at baseline *M* (SD)[f]	1.3 (0.7)	17395
SF-36 mean score at baseline *M* (SD)[g]	45.6 (16.4)	5889
SWLS score at baseline *M* (SD)[h]	16.8 (6.9)	20722

Note. M = mean, SD=Standard deviation, n = number.

[a] Based on the German school system; scale from 0 (no degree) to 4 (general qualification for university entrance).
[b] Diagnosis as given by practitioners according to ICD-10.
[c] BDI-II = Becks Depression Inventory – II: 21 Items scale 0–63.
[d] PHQ-9 = Patient Health Questionnaire-9: 9 items scale 0–27.
[e] GAF = Global Assessment of Functioning: Scale 0–100.
[f] BSI = Brief Symptom Inventory: 53 items, scale 0–4.
[g] SF-36 = Short Form-36 Health Survey.
[h] Satisfaction With Life Scale: 5 Items, scale 5–35.

(T2) and on clinical data at a 6-month follow-up (T3) are presented in Table 2.

Almost all pre-treatment factors (except for "Wish for retirement") significantly influenced different factors at baseline, whereas their direct influence weakened over the course of the treatment. Specifically, a younger age had a positive influence on negative cognitions (β = 0.14), suicidality (β = 0.15) and life dissatisfaction (β = 0.24) at baseline and aggressiveness at discharge (β = 0.12). Lower education levels had positive effects on paranoia (β = 0.12), agoraphobia (β = 0.13) and physical disability (β = 0.16) at baseline. The degree of chronicity was associated with suicidality (β = 0.13) and physical disability (β = 0.22) at baseline. Furthermore, work-related problems were strongly positively related to negative cognitions (β = 0.13), paranoia (β = 0.12), concentration difficulties (β = 0.12), agoraphobia (β = 0.13), perceived disability (β = 0.15) and life dissatisfaction (β = 0.18) at baseline and concentration difficulties (β = 0.12) at discharge. Treatment resistance was positively correlated with anxiety (β = 0.12), concentration difficulties (β = 0.12) and perceived disability (β = 0.13) at baseline. Moreover, interpersonal dysfunction exerted a strong positive influence on negative cognitions (β = 0.15), aggressiveness (β = 0.12), paranoia (β = 0.14) and agoraphobia (β = 0.12) at baseline. Female gender was strongly positively correlated with negative cognitions (β = 0.15), loss of interest (β = 0.12), rumination (β = 0.13), somatic anxiety symptoms (β = 0.14), feeling of weakness (β = 0.19), physical disability (β = 0.14) and pain (β = 0.22). Interestingly, the wish for retirement only had a positive influence on physical disability at baseline (β = 0.19) and discharge (β = 0.12).

3.6. Investigating the stability of psychopathology

The autoregressive coefficients and explained variance of the self-report data from clinical baseline data (T1) on clinical data at discharge (T2) and on clinical data at follow-up (T3) are displayed in Table 3.

Notably, for factors with autoregressive coefficients over β = 0.5 and at least R^2 = 0.35, suicidality (β = 0.52), agoraphobia (β = 0.56), life dissatisfaction (β = 0.60), physical disability (β = 0.65) and pain (β = 0.52) seem to be among the most stable factors from T1 to T2, despite the treatment received, and can therefore be considered as treatment-resistant factors. In the long run, the influence of psychopathological factors at baseline and discharge on the same factors at follow-up diminished to some extent for life dissatisfaction (T1 on T3: β = 0.28, and T2 on T3: β = 0.32, respectively) and pain (T1 on T3: β = 0.32, and T2 on T3: β = 0.25, respectively); and almost vanished for loss of interest (T1 on T3: β = 0.13, and T2 on T3: β = 0.15, respectively) and rumination (T1 on T3: β = 0.18, and T2 on T3: β = 0.21, respectively).

3.7. Unveiling underlying predictors of change

The cross-loadings are delineated in Fig. 2. Remarkably, the strongest influence can be observed from suicidality at T1 on negative cognitions at T2 (β = 0.14); from agoraphobia at T1 on anxiety at T2 (β = 0.15); and from physical disability at T1 on perceived disability at T2 (β = 0.13). Interestingly, the cross-loadings of clinical T2 data on clinical follow-up data (T3) seem to be rather small overall. All coefficients range between $-0.09 \leq \beta \leq 0.09$. However, to gain some insights in an

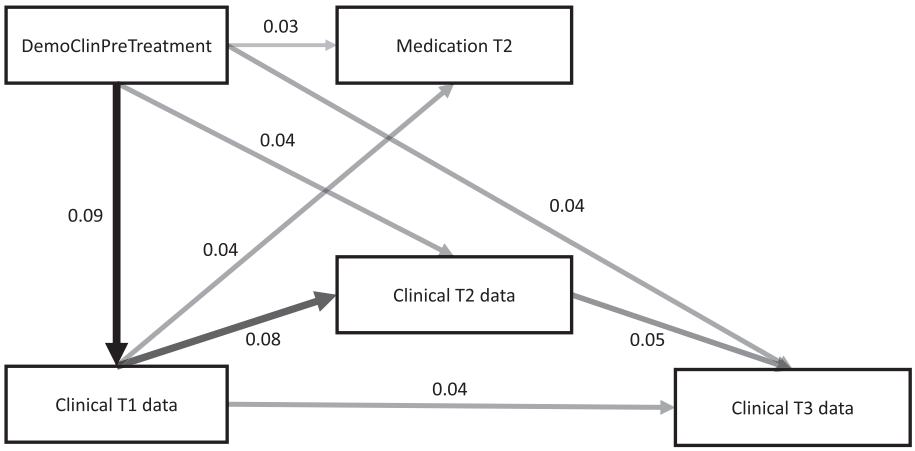


Fig. 1. Selected path model (Model 2) with averaged blockwise path coefficients.

exploratory manner of the psychopathological state at discharge on the follow-up state beside the autocorrelations, these coefficients revealed small relationships of physical disability on pain, rumination and loss of interest. Furthermore, both perceived disability and concentration difficulties had effects on rumination and loss of interest; somatic anxiety symptoms influenced pain; and suicidality had an influence on rumination and loss of interest.

4. Discussion

This study aimed: (1) to examine the naturalistic effectiveness of inpatient psychotherapy for depression in a routine clinical care setting; and (2) to unravel some possible causal pathways through which treatment effects in depression are achieved, both at discharge and at a 6-month follow-up.

With regard to the first objective, we added to current discussions related to the absolute effectiveness of psychotherapy for depression (Cuijpers et al., 2019a,b; Munder et al., 2019a,b) by using a large inpatient sample (N = 22,681) to compute unstandardized effect sizes (ES) for treatment according to routine clinical care. In our sample, we found large raw pre-post and pre-follow-up changes across several important symptom-specific and more global outcomes. This is in line with other findings, for example, the Norwegian IAPT showed pre-post-changes of ES = 1.1 for depression using PHQ-9 in large multicenter cohort study (Knapstad et al., 2018). Moreover, another German routine clinical care study reported changes from baseline to 4 weeks after discharge of ES = 1.11 in the ITT sample following 8-weeks of inpatient psychotherapy for depression (Dinger et al., 2014). In our study, we used the BDI-II in addition to the PHQ-9 in order to enhance comparability with previous studies (Gyani et al., 2013; Knapstad et al., 2018). Notably, the scores obtained from self-report measures such as BDI-II are always somewhat lower than data obtained from clinician-rated measures such as the Hamilton Rating Scale for Depression (HRSD) (Cuijpers et al., 2010a,b; Lambert et al., 1986). Therefore, speculatively, the ES found in our analysis might be somewhat underestimated, such that the real ES could actually have been even higher if observer-rated measures such as the HRSD had been used. Nevertheless, these (unstandardized) ES estimations based on the large dataset might serve as a benchmark of naturalistic short- and long-term effectiveness of specialized inpatient depression treatment in routine clinical care in Germany (cf., Schefft et al., 2019). Since the large raw effects found in our analyses speak to a generally high real-world clinical effectiveness of psychotherapy for depression in this naturalistic inpatient setting, one can conclude that the so-called research-practice gap appears to be not as large as expected (Kilbourne et al., 2012). To note in this practice-based study (Barkham et al., 2021), we used a single-treatment pre-post design to determine the naturalistic effectiveness of psychotherapy delivered routinely in this real-world clinical setting and thus provide rather moderate-level evidence compared to more rigorous study designs, e.g., prospective quasi–experimental naturalistic studies (Leichsenring, 2004).

To address the second objective of our study, three key findings in respect to predictors of change in depression treatment can be obtained from our analyses using Bayesian statistics: First, we found that reducing the level of physical disability through inpatient psychotherapy had positive effects on perceived disability. This finding is consistent with the traditional focus of CBT on behavioral activation, which is thought to increase patients' levels of activation and participation through encouraging them to re-engage in behaviors such as social interactions and physical activation, which patients with depression used to avoid or withdraw from (Dimaggio and Shahar, 2017). Here, we demonstrated in a large naturalistic sample that such a focus of depression treatment on physical disability indeed had positive effects on the level of perceived disability, which is arguably important for patients to participate in everyday life, work and social interactions. Second, reducing agoraphobia tendencies in depression had general positive effects on anxiety levels at posttreatment. While anxious depression is well known as a more difficult-to-treat population of depression subgroup in practice (Ionescu et al., 2013), the specific inpatient context including group therapy might have had positive effects on this relationship. In general, mindfulness-based interventions showed beneficial effects for both anxiety and depression (Hofmann et al., 2010) and therefore might also have addressed anxiety issues in our sample. Interestingly, anxiety and depression appear to be bidirectional risk factors for one another (Jacobson and Newman, 2017). Third, and perhaps most importantly, our results indicate an influence of suicidality on negative cognitions at posttreatment. Indeed, cognitive distortions, that is, hopelessness and helplessness (Ellis and Rutherford, 2008; Lester, 2012), for example, have been found to have a direct influence on suicidal ideation (Fazakas-Dehoog et al., 2017), and cognitive theory in general played also an important role in suicide theory (Rudd et al., 2001). Yet, our data also suggests the reciprocal influence, that is, that reducing suicidal thoughts might indeed positively influence negative cognition in a more general manner at posttreatment, highlighting once more the role of changing dysfunctional cognitions in depression treatment. For example, changing the attributional style has been shown to be significantly related to the resolution of suicidal ideation in an inpatient sample of children and adolescents (Wagner et al., 2000), which might also have been the underlying mechanism of change in our sample of depressed adults. At follow-up, the current results provide some initial indications for the predictors of change in the long run. Physical and perceived disability, suicidality and concentration difficulties at discharge all predicted rumination and loss of interest at follow-up, while physical disability

Table 2
Coefficients of sociodemographic and clinical pretreatment characteristics on self-report factors at baseline/intake (T1), discharge (T2) and 6-months follow-up (T3).

	Younger age			Lower education			Chronicity			Work related problems			Wish for retirement			Treatment resistance			Interpersonal dysfunction			Gender female		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Negative cognitions	**0.14**	0.05	–	0.04	0.03	–	0.08	0.03	–	**0.13**	0.12	–	0.02	0.04	–	0.11	0.08	–	**0.15**	0.09	–	**0.15**	0.04	–
Loss of interest	0.04	0.03	−0.05	0.03	0.03	0.07	0.08	0.02	0.06	0.10	0.11	0.03	0.06	0.06	0.03	0.10	0.08	0.01	0.08	0.06	−0.03	**0.12**	0.01	−0.04
Suicidality	**0.15**	0.06	–	0.02	0.02	–	**0.13**	0.04	–	0.11	0.09	–	0.04	0.03	–	0.09	0.06	–	0.11	0.08	–	0.06	−0.02	–
Rumination	0.04	0.06	−0.05	0.01	0.03	0.08	0.06	−0.01	0.06	0.07	0.11	0.05	0.02	0.03	0.03	0.11	0.08	–	0.09	0.09	−0.01	**0.13**	0.03	−0.03
Aggressiveness	0.06	**0.12**	–	0.04	0.04	–	–	0.01	–	0.07	0.09	–	−0.02	0.02	–	0.06	0.05	–	**0.12**	0.08	–	0.05	−0.01	–
Anxiety	0.03	0.03	–	0.07	0.05	–	0.11	0.01	–	0.09	0.1	–	0.06	0.03	–	**0.12**	0.07	–	0.1	0.07	–	0.11	0.02	–
Somatic anxiety symptoms	0.01	0.01	–	0.08	0.04	–	0.10	0.02	–	0.06	0.07	–	0.08	0.04	–	0.06	0.04	–	0.05	0.04	–	**0.14**	0.03	–
Paranoia	0.11	0.04	–	**0.12**	0.05	–	0.03	0.05	–	**0.12**	0.11	–	0.02	0.04	–	0.07	0.05	–	**0.14**	0.07	–	0.08	−0.01	–
Concentration difficulties	0.08	0.04	–	0.04	0.04	–	0.06	0.03	–	**0.12**	**0.12**	–	0.02	0.06	–	**0.12**	0.07	–	0.1	0.06	–	0.10	–	–
Agoraphobia	0.08	–	–	**0.13**	0.03	–	0.08	0.05	–	**0.13**	0.07	–	0.06	0.03	–	0.09	0.05	–	**0.12**	0.06	–	0.08	0.01	–
Feeling of weakness	−0.03	−0.01	–	0.1	0.05	–	0.11	0.02	–	0.09	0.08	–	0.09	0.04	–	0.07	0.03	–	0.05	0.03	–	**0.19**	0.03	–
Perceived disability	0.07	0.03	–	0.01	0.04	–	0.08	0.03	–	**0.15**	0.12	–	0.06	0.09	–	**0.13**	0.07	–	0.08	0.07	–	0.09	0.01	–
Physical disability	−0.11	−0.04	–	**0.16**	0.06	–	**0.22**	0.06	–	0.11	0.06	–	**0.19**	**0.12**	–	0.07	0.04	–	0.02	0.01	–	**0.14**	0.03	–
Life dissatisfaction	**0.24**	0.08	–	0.09	0.03	0.09	0.11	0.01	0.03	**0.18**	0.10	0.03	0.05	0.03	0.04	0.06	0.03	0.02	0.07	0.05	–	0.03	0.01	−0.01
Pain	−0.01	0.01	−0.04	0.09	0.04	0.04	0.11	0.02	0.05	0.05	0.05	0.01	0.08	0.05	0.03	0.05	0.04	0.02	0.05	0.03	–	**0.22**	0.04	0.01

Note. Standardized regression coefficients in a Bayesian path model with small variance prior (SD = 0.05). Bold numbers signify 95% highest posterior density interval > 0.09 (small effect). T1 = clinical baseline data at intake, T2 = clinical data at discharge, T3 = clinical data at follow-up.

Table 3
Autoregressive coefficients and explained variance for clinical data at baseline (intake), discharge and follow-up.

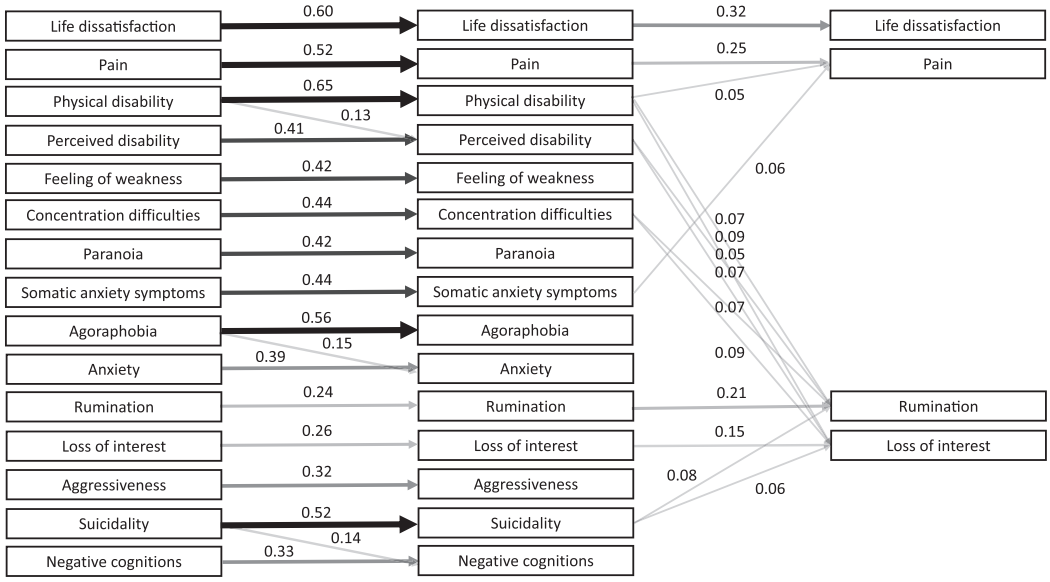
	Coefficient T1	Coefficient T2	Residual variance	R^2
Negative cognitions T2	0.33	–	0.69	0.31
Loss of interest T2	0.26	–	0.76	0.24
Suicidality T2	0.52	–	0.63	0.37
Rumination T2	0.24	–	0.77	0.23
Aggressiveness T2	0.32	–	0.77	0.23
Anxiety T2	0.39	–	0.69	0.31
Somatic anxiety symptoms T2	0.44	–	0.69	0.31
Paranoia T2	0.42	–	0.67	0.33
Concentration difficulties T2	0.44	–	0.66	0.34
Agoraphobia T2	0.56	–	0.58	0.42
Feeling of weakness T2	0.42	–	0.69	0.31
Perceived disability T2	0.41	–	0.65	0.35
Physical disability T2	0.65	–	0.43	0.57
Life dissatisfaction T2	0.6	–	0.5	0.5
Pain T2	0.52	–	0.6	0.4
Loss of interest T3	0.13	0.15	0.74	0.26
Rumination T3	0.18	0.21	0.74	0.26
Life dissatisfaction T3	0.28	0.32	0.59	0.41
Pain T3	0.32	0.25	0.58	0.42

Note. Standardized autoregressive regression coefficients in a Bayesian path model with small variance prior ($SD = 0.05$); predicted variables in rows; T1 = clinical baseline data at intake, T2 = clinical data at discharge, T3 = clinical data at follow-up.

and somatic anxiety symptoms predicted pain at follow-up. This indicates at least that a better end-state functioning on the aforementioned factors at posttreatment predicted better outcomes at follow-up. However, these results must be interpreted more cautiously because of the reduced data and weaker relations. Finally, medication at discharge was not associated with additional symptom change at a 6-month follow-up. The most commonly used long-term treatment is maintenance antidepressants despite the uncertainty of its long term efficacy (Hengartner, 2020; Pies, 2012; Uher and Pavlova, 2016). In line, a meta-analysis found no significant difference in relapse after the acute phase CBT versus continuation of pharmacotherapy after remission (Cuijpers et al., 2013), i.e. discontinued CBT might be as effective as continued antidepressant treatment and more effective than discontinued antidepressants. A more detailed discussion of main factors contributing to persistent psychopathology and the role of pretreatment factors on symptomatology at baseline can be found in the Supplemental Material (see Supplemental Material 5).

4.1. *Limitations and future research directions*

Due to the naturalistic design of our practice-based study (Barkham et al., 2008), a major inherent limitation is that there is no control group, nor a randomization to different treatments, leading to a lack of internal validity. When interpreting the naturalistic effectiveness results, it is important to take into account the fact that we reported unstandardized pre-post effect sizes that heavily depend on the case mix, the setting, and the specific psychotherapeutic treatment. Further, the predictors of change as suggested by our analyses should be replicated under more controlled circumstances, that is, in prospective studies (e.g. in RCTs), and also in an outpatient setting to enhance generalizability. In doing so, future research may examine multiple treatments to determine differential predictors (i.e. moderators or prescriptive variables) of treatment response in order to guide treatment selection (Cohen and DeRubeis, 2018; van Bronswijk et al., 2019a,b), by using different machine learning algorithms (Webb et al., 2020), for example, the personalized advantage index (PAI) (DeRubeis et al., 2014). Moreover, it must be considered that the specific characteristics of the treatment received (which is a peculiarity in the German mental health care system) might



Note. Only edges from T1 to T2 with a 95 % highest posterior density interval > 0.09 (small effect) included; Only edges from T2 to T3 with a 95 % highest posterior density interval > 0 included. For detailed information regarding the underlying scales of the factors, we refer to the Supplemental Material 2.

Fig. 2. Bayesian path model using a small variance prior ($SD = 0.05$) with standardized regression coefficients of the relations between clinical T1, T2 and T3 data.

limit at least partially the external validity to other settings that are more commonly used worldwide (e.g., outpatient treatment programs). However, for example, psychological treatments for depression also seem to be effective in institutional settings up to one year follow-up with small to moderate ES (Cuijpers et al., 2021). In addition, note that with the analysis of the cross-lagged panel data available, no causal conclusions can be drawn directly from our results – only Granger causal conclusions. By taking multiple repeated measures and incorporating them in the cross-lagged model, two requisites for establishing causal relations are fulfilled, namely, establishing an association between the variables studied and taking into account the time order of the processes (e.g. the cause has to occur before the result). Such an association between variables, in which a variable *X* predicts future values of another variable *Y*, is referred to as Granger-causal: Variable *X* "Grangercauses" variable *Y* (Granger, 1969; Schuurman et al., 2016). Of note, unmeasured constructs might be related to the factors measured in this study and act as confounders and true causes of change in other factors. Other variables that have been found to contribute to treatment outcome but were not measured routinely in the clinics include, for example, depression-specific expectations (Kube et al., 2018) and childhood maltreatment (R.-Mercier et al., 2018), and should be assessed in future studies. A further limitation of ES estimation is that we exclusively used self-report data, that is, the BDI-II and PHQ-9 as the primary treatment outcome measure; accordingly, we could not include a clinician-rated measure of depressive symptoms, such the HRSD, in our analysis. Furthermore, the results of our Bayesian analyses rely solely on clinician- and patient-report data. Notably, a recent study has found that models with multiple data sources (i.e. neuroimaging and genetic data) are more accurate and adequate than models with single, lower-dimension data types (i.e. exclusively phenomenological data) (Lee et al., 2018), and should therefore be considered in future (prospective) studies. Lastly, due to technical limitations, the runtime of a full Bayesian analysis of all models would have been infeasibly long. Thus, we used maximum likelihood estimation in model selection, but refit the final model with the Bayesian approach. We are aware that this procedure can only yield an approximate answer to our research questions. However, we are confident that these problems will be solved in the near future, and that we will then be able to give a more precise answer.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.02.057.

Statement of ethics

Hereby, we confirm that we complied with the guidelines for human studies and that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki of 1975, as revised in 2008. Yet, ethical approval was not obtained for the present retrospective study because the data was routinely collected as a standard clinic diagnostic procedure to ensure quality assurance and did therefore not involve prospective evaluation. Nevertheless, all patients gave informed consent to anonymous evaluations of their routinely collected data.

Authorship contribution statement

PH and ELB conceptualized the study. PH originally drafted and edited the manuscript, ELB supervised, reviewed and edited the manuscript, MF computed the statistical analyses, DE supervised the statistical analyses, TK revisited the manuscript critically for important intellectual content, WR gave substantial feedback for the conception and design of this study and GL, TG, ER, RD, AH and UV routinely collected data and were significantly involved in the acquisition of this routine data for the present work. All authors have approved the final article.

Declaration of competing interest

The authors report no conflict of interest.

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